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THE EPIDEMIOLOGY AND MANAGEMENT OF HYPOTHYROIDISM IN GENERAL PRACTICE

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ABSTRACT

Background

Hypothyroidism is a common condition in general practice. Evidence of long-term outcomes and the effectiveness of treatment for subclinical hypothyroidism are lacking. This thesis provides new knowledge to support practice in relation to subclinical hypothyroidism.

Methods and Results

Several research methodologies were utilised:

- A cross-sectional study in general practice showed that prevalence of hypothyroidism in Hamilton City was 2.5%, with an overall level of thyroid dysfunction at 3.2%.
- Examining retrospective laboratory data of thyroid function tests showed that 1 in 6 patients without known thyroid disease are tested within a 12-month period.
- Focus groups of general practitioners found that patients with a raised thyroid stimulating hormone (TSH) assay posed a dilemma for general practitioners.
- Retrospective laboratory data and note review of the management of patients with raised TSH found that two percent of patients were managed according to New Zealand Best Practice Advocacy Centre (BPACnz) recommendations.
- Note review and interviews with patients with central hypothyroidism showed that a first-line TSH strategy was not the cause of delayed diagnosis but indicated a reliance on biochemical results over manifest signs and symptoms.
- Survival analysis comparing patients with thyroid dysfunction against cardiovascular events and all-cause mortality found that patients with both subclinical and overt hypothyroidism had an increased risk of cardiovascular events [Hazards ratios 1.22 (1.12-1.33) and 1.58 (1.44-1.73)] and death [1.29 (1.17-1.42) and 1.45 (1.31-1.62)] compared to euthyroid individuals after adjusting for age, gender, ethnicity and social deprivation. The increased cardiovascular event risk was greatest in those under 65 years of age with subclinical hypothyroidism [1.26 (1.07-1.49)] compared with those 65+ years [1.14 (1.03-1.27)].

- A systematic review of patients with subclinical hypothyroidism treated with thyroxine found that treatment had a positive effect on lipids, BMI, cardiac function and systolic blood pressure in individuals less than 65 years of age with stable subclinical hypothyroidism.

Conclusions

Subclinical- and overt hypothyroidism are associated with increased cardiovascular morbidity and all-cause mortality with the greatest excess risk in patients with subclinical hypothyroidism who are less than 65 years of age. Treatment with thyroxine should be considered in these patients to reduce cardiovascular risk.

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ABBREVIATIONS

Abbreviation	Description
Anti-Tg	thyroglobulin antibodies
Anti-TPO	thyroid peroxidase antibodies
BMI	Body Mass Index
BP	blood pressure
BPACnz	Best Practice Advocacy Centre (New Zealand)
DHB	District Health Board
E/A	Early (E)/Atrial (A) ventricular filling velocity
FT_3	free T_3
FT_4	free T_4
GATE	Graphic Appraisal Tool for Epidemiology
HDL	high-density lipoprotein
ICD	International Classification of Diseases
LDL	low-density lipoprotein
LT_4	levo-thyroxine
MORT	Mortality Collection
NHANES	National Health and Nutrition Examination Survey
NACB	The National Academy of Clinical Biochemistry
NHI	National Health Index
NMDS	National Minimum Data Set
NZDep	New Zealand Deprivation Index
OH	overt hypothyroidism
OHe	overt hyperthyroidism
RCT	randomised controlled trial
SCH	subclinical hypothyroidism
SCHe	subclinical hyperthyroidism
T_1	mono-iodotyrosine
T_2	di-iodotyrosine
T_3	3,5,3’-triiodothyronine, liothyronine
T_4	tetraiodothyronine, thyroxine

TBG	thyroxine-binding globulin
TC	total cholesterol
TD	thyroid dysfunction
TG	triglycerides
Tg	thyroglobulin
TPO	thyroid peroxidase
TRH	thyrotropin-releasing hormone
TRT	thyroid hormone replacement therapy
TSH	thyroid stimulating hormone, thyrotropin

CHAPTER 1 – THE EPIDEMIOLOGY AND MANAGEMENT OF HYPOTHYROIDISM IN GENERAL PRACTICE

INTRODUCTION

Thyroid dysfunction is one of the commonest conditions found in New Zealand general practice. The most common clinical disorder of the thyroid gland is hypothyroidism [1-3]. The prevalence of hypothyroidism increases with age and there are marked gender differences [4]. It is predominantly a condition of post-menopausal women [3, 5, 6] affecting up to 20% of this population as they age; men are affected at a lower rate. For the purpose of this examination of hypothyroidism, we define hypothyroidism to include both overt- and subclinical hypothyroidism. Both of these conditions are characterised by a sustained elevation of thyroid stimulating hormone (TSH, thyrotropin) with overt hypothyroidism consisting of a TSH $\geq$10 mIU/L together with reduced levels of free thyroxine (FT_4); and subclinical hypothyroidism, in this instance, defined by a TSH result between 5 – 9.9 mIU/L with normal levels of FT_4 [1, 7].

Thyroid function tests, used in the diagnosis of hypothyroidism, are one of the more frequently requested tests in general practice [8]. Traditionally when investigating suspected thyroid dysfunction, thyroid hormone levels of thyroxine (T_4) and tri-iodothyronine (T_3) were assessed to aid diagnosis. More recent recommendations have shifted to the use of TSH assay alone as a first-line test in the investigation of thyroid dysfunction. However, controversy still exists with specialists arguing that pituitary disease will be missed [9, 10]. In addition, debate surrounds the clinical usefulness of the upper reference interval for TSH; with many believing there is compelling evidence for a narrower range due to an increased prognosis of adverse outcomes in patients with thyroid function within normal limits [11-13]. A reduction in the upper reference interval would effectively make hypothyroidism the most common endocrine disorder, outstripping diabetes mellitus, with approximately 20% of the population being classified as hypothyroid [14]. Diabetes mellitus is of concern at a population level because it is common and the health effects are severe, for example, the odds ratio of myocardial infarction in patients with diabetes is 3.0 [15]. In comparison, the odds of cardiovascular disease in patients with hypothyroidism are 2.3 when compared with healthy controls [15, 16].

The main reason for treating hypothyroidism with thyroid hormone replacement therapy (TRT) is to normalise thyroid function to ensure continued regulation of metabolism and thermogenesis [3]. Several studies have suggested that treatment with TRT can attenuate cardiovascular disease by reducing certain key risk factors [17-19]. Cardiovascular disease

accounts for 40% of all deaths in New Zealand [20] and cardiovascular risk factors relating to lipids, exercise tolerance and cardiac function are altered in hypothyroidism [21]. Cholesterol metabolism is slowed leading to a rise in cholesterol levels (particularly total (TC) and low-density lipoprotein (LDL) and an increased risk of atherosclerosis [2]. Patients with hypothyroidism have significantly increased cardiovascular morbidity and it is argued that this extends to those with subclinical hypothyroidism (SCH) where TSH is raised while thyroid hormone levels remain within normal limits [6, 22, 23].

However, a recent Cochrane Review showed no difference in treatment outcomes in patients with SCH; suggesting that general practitioners use clinical judgement and patient preference in deciding whether to treat [24]. General practitioners are therefore faced with uncertainty with regard to the prognosis and management of patients identified with SCH. In the past decade there have been a number of studies addressing the relationship between SCH and cardiovascular disease, yet these fail to provide evidence that can be directly translated to knowledge needed by general practitioners [25-29]. As well as this, international guidelines on managing SCH differ in relation to target populations and the role of screening and although available guidelines have expressed a strong opinion, evidence in support of these recommendations is lacking [30-34]. Studies focussing on the role of general practitioners in the diagnosis and management of hypothyroidism are absent.

This introduction section has touched on key areas which will be detailed in the rest of this chapter. A brief introduction to the anatomy of the thyroid gland and the physiology of thyroid function is presented. This may appear complex but is a mere snapshot of a dynamic system which impacts on the diagnosis and management of hypothyroidism. The physiological effects of hypothyroidism with a focus on the association with the cardiovascular system are outlined and signs and symptoms of hypothyroidism and subclinical hypothyroidism are described. The epidemiology of hypothyroidism is detailed, followed by controversies in relation to diagnosing and investigating thyroid dysfunction and the role of general practitioners in hypothyroidism.

BACKGROUND

The thyroid gland is part of the endocrine system, a system of ductless glands that secrete hormones (chemical messengers) to regulate body functions. The function of the thyroid gland is to produce sufficient amounts of thyroid hormone to meet the daily requirements of

the body [35]. The thyroid gland synthesises both thyroid hormones, tetra-iodothyronine (thyroxine or T_4) and tri-iodothyronine (T_3), although a significant portion of T_3 is produced by peripheral conversion of T_4 to T_3 [36, 37]. Although the effects of thyroid hormone are pleiotrophic, and poorly understood, the principal effects of the thyroid hormones appear to be to regulate general metabolism, increase energy expenditure and thermogenesis [3, 37].

Iodine is an essential element trapped by the thyroid gland and incorporated into the thyroid hormone molecules [36]. Under normal circumstances, the thyroid gland is regulated by the secretion of thyroid stimulating hormone (TSH or thyrotropin) from the pituitary gland which itself is controlled by the release of thyrotropin-releasing hormone (TRH) by the hypothalamus. The release of both TRH and TSH are controlled by negative feedback inhibition by T_3, such that, with normal pituitary function, when there is insufficient thyroid hormone detected by the tissues the level of TSH increases to correct the thyroid hormone deficiency [3, 36-38]. When the thyroid produces insufficient thyroid hormone due to structural or functional changes in the thyroid gland (primary hypothyroidism), the low levels of thyroid hormone in the blood are detected by both the hypothalamus and pituitary gland, with increased levels of TSH signalling the thyroid gland to increase the production of T_4 and T_3. Hypothyroidism may be caused by alterations in the structure or functioning of the thyroid gland, (primary thyroid disease) or less commonly inadequate production of TSH due to pituitary or hypothalamic disorders (secondary thyroid disorders).

The commonest cause of primary hypothyroidism worldwide is iodine deficiency, although in developed countries such as New Zealand that have sufficient iodine exposure, the leading aetiology is reported as chronic autoimmune thyroiditis (Hashimoto's disease, and primary atrophic myxoedema) [39]. Reported estimates of prevalence from international studies suggest up to 10% of the adult population, rising to 20% in certain populations, may have thyroid dysfunction [40-47]. The variability in reported prevalence and incidence has been attributed to a number of external factors including differences in patient characteristics (age, gender, menopausal status, weight, genetics, smoking status) [48-55], diet (iodine exposure, goitrogens, selenium) [56-61], environmental factors (seasonality, living in close proximity to factories that expel substances, such as prolybrominated biphenyls and polychlorinated biphenyls, into the air, which have been reported to cause hypothyroidism in exposed workers)[49, 62, 63] and differences in laboratory indices due to monoclonal antibody contamination in referencing groups or reagents [6, 64].

Hypothyroidism is due to an under-functioning thyroid gland (primary hypothyroidism) [5]. Primary hypothyroidism can be readily detected by raised levels of TSH in the presence of either low or normal levels of thyroid hormone. Over the past several decades, significant improvements have been made in detecting hypothyroidism through highly sensitive and specific assays of TSH. This has led to the development of subclasses of thyroid dysfunction, namely subclinical disease where the TSH is raised but thyroid hormone levels remain normal [65]. Patients with subclinical hypothyroidism may have subtle symptoms, or be asymptomatic with the definition of these subclasses being solely biochemical [64]. It has been questioned whether subclinical hypothyroidism represents actual disease with associated outcomes, or whether it has no immediate or long-term sequelae [66, 67].

Several endocrine organisations have recommended using TSH assay as a first-line strategy in assessing thyroid function [14, 30, 33, 68]. The log-linear relationship between TSH and T_4 is such that a 2-fold change in FT_4 represents a 100-fold change in TSH, due to a highly attuned pituitary, sensitive to both minimal decreases and increases in thyroid hormone concentration [69]. As such TSH becomes elevated as the first indication of thyroid hormone insufficiency. In addition, the elevated levels of TSH stimulate the failing thyroid gland to increase its production of thyroid hormone and correct the deficiency. The sensitivity of the TSH assay in detecting primary hypothyroidism has led to TSH being the investigation of choice by policy-makers when initiating the investigation of thyroid function [30, 68, 70].

In New Zealand, over 850,000 TSH tests were collected in 2007 alone, making it one of the more commonly requested biochemical investigations (behind glucose and lipids) [8]. In line with greater emphasis on the use of TSH as a first-line strategy in detecting thyroid dysfunction [30, 33, 71], the simultaneous request for both TSH and FT_4 to assess thyroid function has lessened in the past decade. For example, in Waikato (New Zealand) the ratio of FT_4 to TSH was 1:1.2 in 1997 compared with 1:3 in 2006 [72]. This strategy of using the TSH assay alone has been criticised for its failure to provide a complete picture of thyroid function [10]. For instance, in central hypothyroidism, in which either pituitary or hypothalamic disease may affect thyroid function, a TSH result within the reference interval may falsely reassure a general practitioner that the thyroid gland is functioning well [73].

General Practice is the key to primary health care in the New Zealand health system [74]. General practitioners have a central role in the initiation of investigations into thyroid dysfunction. The prevalence of hypothyroidism increases with age [40, 43] and with an ageing

population, the numbers of people with hypothyroidism will increase. In addition, as many as 50% of patients treated for hyperthyroidism will have subclinical hypothyroidism within one year of treatment; with a 2-6% annual rate of progression to hypothyroidism after this time [23]. This will increase the burden for general practitioners in managing hypothyroidism.

While the management of primary hypothyroidism is unambiguous for general practitioners the management of a greater number of patients identified with SCH is contentious. In addition, general practitioners knowledge when managing thyroid dysfunction may be less than optimal. A study that gauged whether general practitioners had the ability to assess their own learning needs in relation to thyroid disorders showed poor correlation between self-assessment and test score [75], indicating that general practitioners may feel confident in managing thyroid disorders without the necessary skills to do so. Currently there are clear guidelines relating to hypothyroidism. However, general practitioners need comprehensive evidence on both the diagnosis and management of subclinical hypothyroidism in relation to long-term sequelae because current guidelines are ambiguous about this.

Diagnosis of hypothyroidism (either primary or secondary) is suggested by assessing an individual's symptoms and confirming suspicions by testing thyroid function (TSH followed by FT_4 if raised) [30]. Two pertinent factors impact on general practitioners in the decision-making processes for thyroid investigation: firstly, there are guidelines to recommend testing protocols in general practice [68, 70, 71, 76, 77]; and second, guidelines on how hypothyroidism should be managed are also debated [14, 31, 33, 34]. The adoption and impact of both these sets of guidelines continues to be a source of discussion.

Cholesterol metabolism is altered in hypothyroidism leading to a rise in cholesterol levels (particularly total (TC) and low-density lipoprotein (LDL) cholesterol) and with an increased risk of atherosclerosis [2]. The management of hypothyroidism involves the prevention of cardiovascular-related morbidity associated with an under-functioning thyroid gland. It is clear that as well as restoring an individual to euthyroidism, reducing the risk of cardiovascular-related morbidity should be an aim of treatment. Treating hypothyroidism has been shown to improve lipid parameters [66, 78]. Whether the positive correlation between overt hypothyroidism and cardiovascular complications extends to subclinical hypothyroidism, and at which level of TSH, is yet to be established.

Treatment for hypothyroidism is with thyroid hormone replacement therapy (TRT), usually synthetic thyroxine such as levo-thyroxine. Initiation and adjustments to treatment are made

according to age, pre-existing co-morbidities such as coronary heart disease, evidence of related symptoms and laboratory results. Despite prescribed treatment with thyroxine, as many as 50% of patients on TRT will be under- or over-treated [43, 79, 80]. The use of thyroxine in patients with subclinical hypothyroidism has been questioned due to the potential risks of over-treatment and the lack of beneficial evidence [66, 81].

A decision to treat patients who have SCH is also not without controversy. Arguments arise around the necessity of TRT in SCH patients with a serum TSH between 5 and 10 mIU/L, in which the progression to overt hypothyroidism may be slow (up to 20 years) [66]. In addition, the presence or absence of anti-thyroid antibodies has been shown to have a bearing on disease progression [82], although up to 12% of the general population have detectable levels of anti-thyroid antibodies without coexisting thyroid disease [39]. Therefore a 'wait and see' approach has also been advocated to avoid unnecessary treatment and potential harm from over-treatment resulting in the effects of hyperthyroidism [66]. Inherent risks in over-treatment and hyperthyroidism include a reduction in bone mineral density [83], cardiac arrhythmias, and the precipitation or exacerbation of existing acute coronary syndromes in older individuals [84, 85]. On the contrary, a slightly raised TSH has been reported to be beneficial in older patients with severe coronary artery disease since a lowered basal metabolic rate may be considered cardio-protective [22].

Current international guidelines have promoted the cost-effectiveness of targeting women to screen for raised TSH levels: however, there is no consensus on the earliest age for screening or on the health outcomes of screening [14, 31]. Screening for thyroid dysfunction is not recommended in New Zealand [30]. The variability of international guidelines and continued debate within the literature regarding the diagnosis and management of subclinical hypothyroidism adds to the confusion that general practitioners face in providing evidence-based care for these patients. A recent Cochrane review recommends that in the absence of evidence, the management of SCH in general practice can be based on the clinician's experience and patient preference [24].

The rationale for the use of TRT in subclinical hypothyroidism needs clarifying [66, 67, 86-92]. Population studies have identified a positive correlation between SCH and TC and LDL levels compared with those subjects whose TSH levels are within the normal reference interval [93-95]. Therefore, treatment is believed to be an important protector of cardiovascular health [16, 67, 78, 86, 89, 96-99]. Despite several randomised controlled trials (RCTs), the benefits of

treating SCH with TRT to reduce cardiovascular morbidity remains unclear [24]. Furthermore, published studies of the effects of SCH on cognition, anxiety and depression [100-104] are not conclusive on the benefits of TRT in minimising the effects on neuropsychiatric characteristics [102, 103, 105, 106]. A further consideration is in the prevention of the progression to overt hypothyroidism [47, 107, 108]; although, the rate of progression from SCH to overt hypothyroidism, at 2-4% per annum, is reported to be less than the rate of reversion back to euthyroidism (37-50% in 1-5 years) [107, 109, 110]. More recently, arguments have concentrated on the benefit of TRT in reducing cardiovascular risk factors by recommending the timely treatment of patients with SCH to prevent cardiovascular complications, such as: an increased incidence of ischaemic heart disease [17, 22, 27, 111]; a greater likelihood of heart failure progression [26, 112]; and, an increase in cardiovascular mortality [27]. Currently the strength of evidence remains weak on whether there is an increased risk of morbidity and mortality in patients with SCH and on the benefits of TRT in reducing cardiovascular mortality in this group of patients.

What is known is that SCH is prevalent in 6.4-10% of the adult population [39, 43, 46, 113]. In particular, the prevalence increases with advancing age at a greater rate in women than in men [39, 40, 43, 47]. Conclusive rationale for testing and evidence for the benefit for treatment are lacking. The evidence that is available appears confused [66, 67, 86, 87, 89]. Adding evidence to the body of knowledge around SCH will provide general practitioners with clearer rationale for the management of their patients.

The overall aims of this thesis are to investigate the epidemiology and management of hypothyroidism in general practice and to provide new knowledge to support practice in relation to subclinical hypothyroidism.

STRUCTURE AND FUNCTION OF THE THYROID GLAND

STRUCTURE

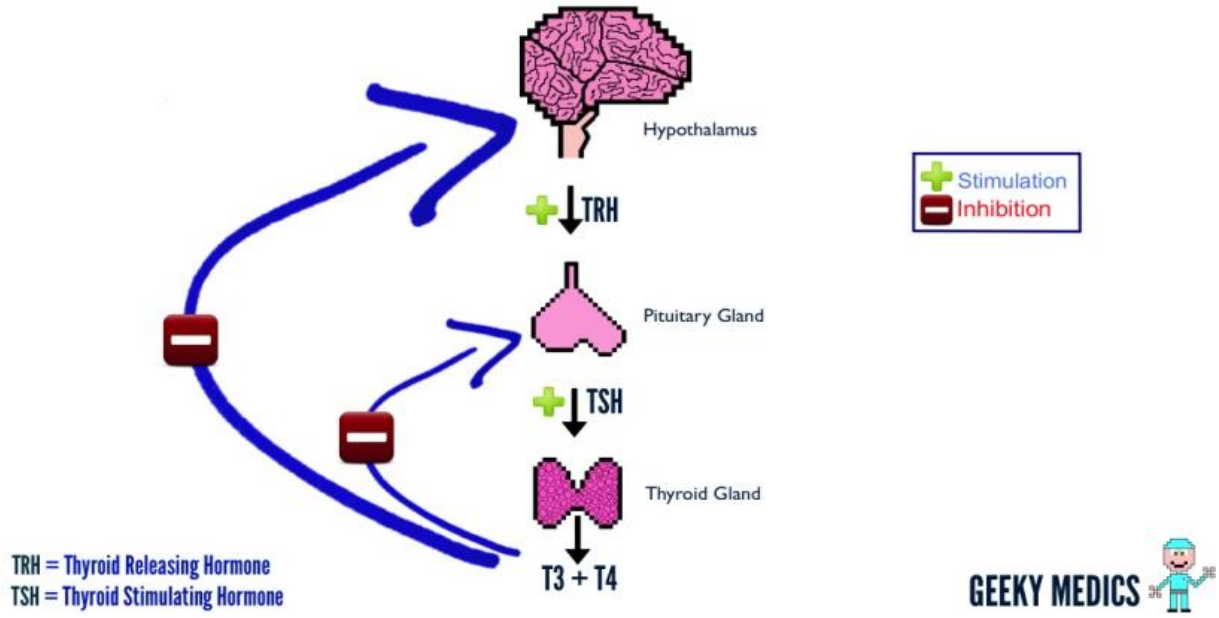
The thyroid gland is the largest endocrine gland in adults. It is situated in the neck, anterior and caudal to the larynx [114]. Thyroid development commences at day 24 in the human embryo as a midline thickening in the pharyngeal floor. The foetal thyroid gland can synthesize thyroxine by week 11, but does not respond to pituitary secretion of TSH until about gestational week 22 [3].

The naming of the thyroid gland (Greek *thyreos*, shield, plus *eidos*, form) is credited to Thomas Wharton (1614-1673), a physician at St Thomas Hospital [115], who described its shield shape; a structure consisting of two lobes that are connected by an isthmus [3]; however, this shape relates more to the nearby thyroid cartilage [116]. The two lobes of the thyroid are asymmetrical with the right lobe often larger than the left. The normal thyroid weighs 12-20g dependent on body size and iodine supply [48]. In addition, there are gender differences; women usually have larger thyroid glands than men. There are also variations between women; as the thyroid gland enlarges during puberty, in pregnancy, during lactation, and in the latter part of the menstrual cycle. [3] Seasonal variation has been reported with an increase in thyroid volume (up 23%) during winter compared with summer [48].

FUNCTION

Thyroid hormones have effects on almost all tissues in the body. The primary function of the thyroid gland is to secrete an appropriate amount of T_4 and to a lesser degree T_3 to maintain the thyroid hormone levels within the body that are sufficient to meet the metabolic needs of the tissues. The levels of thyroid hormones are controlled by means of a negative feedback loop on the anterior pituitary and hypothalamus, whereby if the level of T_3 is low the pituitary secretes TSH which stimulates further thyroid hormone production and secretion. Conversely if the level of T_3 is raised, TSH secretion is inhibited and thyroid hormone synthesis by the thyroid gland decreases (Figure 1).

FIGURE 1: HYPOTHALAMIC-PITUITARY-THYROID AXIS



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Thyroid hormones promote a number of actions within the body, all necessary to maintain life. Normal foetal and childhood growth and development requires thyroid hormones, as does the regulation of heart rate and myocardial contractility; gastrointestinal motility and water clearance; and modulation of the body's energy expenditure, thermogenesis and weight [117].

Dietary iodine is essential to the manufacture of thyroid hormones. Iodide, iodine in its ionized form, is bound to serum proteins, particularly albumin for transportation to the thyroid gland [114]. Because the plasma concentration of iodide is so low the thyroid gland requires a mechanism to concentrate this element, within its cells. The thyroid gland is capable of concentrating iodide against an electro-chemical gradient, some 20 to 40-fold above its level in the plasma [36]. Iodide is taken up by active transport into the thyroid cell by the sodium/iodide symporter, a membrane bound protein, a first and vital step in the process of iodide supply for thyroid hormone synthesis [36]. The sodium/iodide symporter is highly regulated, allowing for adaptation to variation in dietary supply [114].

The pituitary gland secretes trophic hormones which control the production of hormones by its various target organs. The thyroid gland is regulated by TSH, which itself is produced by the anterior pituitary gland. In the case of the thyroid gland, the pituitary secretes TSH which is a trophic hormone regulating both the secretion of thyroid hormones and the growth of the thyroid gland. Under normal circumstances the production of TSH is itself controlled by the level of thyroid hormones (by negative feedback inhibition), such that, in the absence of hypothalamic or pituitary disease, illness or drugs, when the thyroid gland is overproducing thyroid hormones, the TSH level is suppressed; the converse occurs when the thyroid gland is not producing sufficient thyroid hormone (primary hypothyroidism) [69].

The synthesis and release of TSH is stimulated by thyrotropin-releasing hormone (TRH) a tripeptide released into the hypothalamic-hypophyseal portal system from the hypothalamus. TSH is inhibited by thyroid hormone in a negative feedback system. TSH is a glycoprotein composed of α and β subunits, the α subunit being common to the other glycoprotein hormones (luteinising hormone, follicle stimulating hormone and human chorionic gonadotropin), whereas the β subunit is unique to TSH. The set-point for the TRH/TSH axis (also referred to as the hypothalamic-pituitary axis) is established by TSH [114]. This is evident

in older adults where the TSH response to decreasing FT_4 levels are considered inappropriately low, suggestive of a resetting of the thyroid hormone feedback regulation threshold of TSH secretion [118].

The thyroid gland consists of a highly organised collection of follicles; the functional units of the gland. These follicles consist of a single layer of epithelial follicular cells resting on a basement membrane, and surrounding a closed cavity or central lumen filled with colloid. The colloid is composed primarily of thyroglobulin (Tg), a glycoprotein on which the thyroid hormones are synthesized. Thyroid follicular cells can be recognised by the presence of sets of proteins. Unlike some other thyroid proteins such as TSH receptor, the sodium/iodide symporter and pendrin, which are found in a few other tissues: both Tg and an enzyme called thyroid peroxidase (TPO) are highly specific and detectable exclusively in thyroid follicular cells [119]. Thyroid hormone synthesis requires that Tg, the sodium/iodide symporter and TPO all be present, functional and uninhibited [117].

Thyroid hormone synthesis begins with uptake of iodide molecules from the plasma by the sodium/iodide symporter in the basolateral aspect of the follicular cell by a process called 'trapping'. Trapping of iodide requires active transport because the concentration gradient of iodide is higher within the cell than in the extracellular fluid. Once inside the follicle, the iodide molecules are oxidised to an unknown 'activated' form of reactive iodine by TPO attached to the apical or luminal side of the follicular cell. The amino acid, tyrosine, a component of the thyroglobulin molecule, plays a key role in thyroid hormone synthesis. The 'activated' iodide molecules are then catalysed by TPO to bind to various tyrosine residues within the thyroglobulin molecule in a process called 'organification'. This produces mono-iodotyrosine (T_1) and di-iodotyrosine (T_2) which, when also catalysed by TPO, couple together to form the thyroid hormones, 3,5,3',5'-L-tetraiodothyronine (T_4, thyroxine) and 3,5,3'-L-triiodothyronine (T_3) (Figure 2) [114].

FIGURE 2: MOLECULAR CONFIGURATION OF T_4 AND T_3

3,5,3',5'-L-tetraiodothyronine (T_4, thyroxine) **3,5,3'-L-triiodothyronine (T_3)**

T_4 has 4 iodine molecules attached; T_3 has 3 iodine molecules attached.

Thyroid hormones are stored within the colloid of the follicles. The thyroid is unique amongst endocrine glands, in that it can store its hormones for weeks at a time, unlike most other endocrine glands which synthesize and secrete their hormone as needed [2]. It is estimated that thyroglobulin can store approximately a two-month supply of preformed T_4 in the normal human thyroid, allowing an individual to remain euthyroid should conditions of iodine deficiency occur [3]. Unused T_1 and T_2 are rapidly de-iodinated and the iodide is liberated to be excreted in urine or returned to the follicle via the iodide trapping mechanism as described [120]. Newly synthesized T_4 and T_3 are released from the thyroglobulin complex, which is absorbed (through endocytosis) from the colloid, back into the follicular cell. From here, thyroid hormone is cleaved in lysozomes, yielding T_4 and T_3 molecules which are then secreted into the bloodstream [2].

The amount of reactive iodine incorporated into thyroglobulin is directly related to the concentration of iodide reaching the thyroid gland from the circulation [3]. Under normal conditions of dietary iodine sufficiency, thyroglobulin will contain more T_2 than T_1. When the T_2 levels are high, thyroglobulin will contain two to four molecules of T_4 with little T_3 formed within it, due to insufficient availability of T_1 to couple with T_2 [3]. When dietary iodine is limited or deficient, there will be less iodide incorporated into thyroglobulin. This results in thyroglobulin containing more T_1 than T_2. As a consequence, under these circumstances thyroglobulin will contain more T_3 than T_4.

In conditions of iodide deficiency TSH is secreted and binds to the TSH receptor, stimulating both the function and growth of the thyroid gland. TSH increases the rate of iodide uptake (trapping) as well as the synthesis and release of thyroid hormone by the thyroid gland. In addition, TSH stimulates the growth of the thyroid gland which may result in a clinically enlarged thyroid (goitre)[120]. This causes compensatory change in adults where the thyroid secretes T_3 in preference to T_4 [114]. Furthermore, changes in thyroid function can be observed in the shape of the follicular cells which alter according to the level of thyroid function. Under the microscope, depending on TSH stimulation, where there is less T_4 as in hypothyroidism, the follicles are distended with colloid and the follicular cells appear flatter; in hyperthyroidism, the follicular cells become columnar [3, 119].

T_3 is the biologically active form of thyroid hormone that binds to the thyroid hormone receptor, which acts as a ligand-bound transcription factor. T_4 is a prohormone which must be converted in the peripheral tissues to T_3 to be biologically active. The ratio in serum of T_4:T_3

is usually about 20:1. T_4 is recognised to be a prohormone or precursor to T_3 as most of the thyroid hormone bound to receptors is in the form of T_3 [121].

T_4 is converted into T_3 by deiodinase enzymes of which there are three types (Type I, II and III) [114]. These deiodonases are tissue specific – Type I located primarily in the thyroid, liver and kidney has a low affinity for T_4, Type II has a higher affinity for T_4 and is found primarily in the pituitary gland, thyroid, brain and brown fat. Its presence allows regulation of T_3 concentrations locally, that is, T_4 is deiodinated peripherally to biologically active T_3 [114]. The thyroid gland allows for storage of T_4; acting as a reservoir for later conversion to T_3. 90% of T_3 available to the tissues is produced by the peripheral deiodination of T_4, with only approximately 10% of T_3 being directly secreted by the thyroid gland [120]. The serum half-life of T_3 is approximately one day compared to seven days for T_4 [120]. Type III deiodinase inactivates both T_4 and T_3, converting T_4 to reverse T_3, a biologically inactive iodothyronine, and converting T_3 to T_2.

Thyroid hormones are poorly soluble in water and are transported in the bloodstream by specific carrier proteins (thyroxine binding globulin (TBG), transthyretin and albumin). Of these, TBG has the highest affinity to T_4 and T_3, although has the lowest concentration in serum, whereas albumin has relatively low binding affinity for T_4 and T_3 but is present in high concentration. When T_4 is bound to a carrier protein it is inactive, that is, it is not available to be taken up by the tissue and exert its effects. A small portion of thyroid hormone is unbound (free) and considered biologically active. The free and bound hormones are in equilibrium, such that removal of the free form leads to increased dissociation of the bound hormone from its binding protein until the equilibrium and concentration of free hormone is re-established. Some conditions or medications (e.g. oestrogen containing contraceptives) affect the concentration or the ability of carrier proteins to bind to thyroid hormones. This does not affect the level of free hormones but can have a direct effect on measurement of total thyroxine (free + bound) [2].

Protein, carbohydrate and lipid metabolism are affected by the amount of circulating thyroid hormone due to changes in metabolic clearance of these metabolites [2]. In particular, low thyroid hormones promote glycogen synthesis and high thyroid hormones promote glycogen breakdown. Cholesterol metabolism is also decreased in thyroid hormone deficiency leading to a rise in cholesterol levels and an increased risk of atherosclerosis. [2].

RELATIONSHIP BETWEEN THYROID FUNCTION AND THE CARDIOVASCULAR SYSTEM

The pathophysiological effects of thyroid function on the cardiovascular system are directly related to the consequences of thyroid hormone on the heart and vascular system [122, 123]. Changes in cardiovascular function in patients with hypothyroidism include: an increased systemic vascular resistance; decreased heart rate; slight reduction in cardiac output; an increase in isovolumic relaxation time; and, a decreased percentage of blood volume [122]. These cardiovascular manifestations may not produce overt clinical symptoms in patients with hypothyroidism due to internal compensatory mechanisms.

A study of 14 patients with SCH assessed vascular reactivity in relation to their lipid profiles [124]. Vascular function is maintained mostly by the endothelium, which produces vasodilator and vasoconstrictor substances; the most important being nitrous oxide. Breakdown of nitrous oxide can occur as a result of increases in cardiovascular risk factors that result in oxidative stress [125]. Lipid abnormalities were found to appear as a result of increased oxidative stress or disturbances in substances that regulate vasomotor tone [124]. Hypothyroidism is a common secondary cause of dyslipidaemia manifesting as elevations in both triglyceride and LDL cholesterol [2]. A raised TSH is significantly associated with increased serum LDL cholesterol concentrations after adjustments for age and gender [94, 126]. There is a linear association with serum lipids across the entire reference range of TSH [127-129]. This suggests that with increasing TSH there are subtle changes in lipid levels well before the threshold at which overt hypothyroidism is diagnosed and treated.

In patients with hypothyroidism, there are 50-60% increases in peripheral vascular resistance accompanied by 30-50% decreases in resting cardiac output [123]. The resultant decrease in blood flow and tissue oxygen consumption manifests in vascular oxygen extraction across major organs that are no different between hypothyroid patients and normal subjects. Increased peripheral vascular resistance is considered an early sign of atherosclerosis [124].

There is a positive correlation between diastolic and systolic blood pressure in relation to increasing TSH levels [29, 130]. The most common noticeable signs of hypothyroidism are bradycardia, and mild hypertension, in particular diastolic hypertension in 10- 25% of patients [114, 123]. In a cross-sectional survey of 1319 subjects that investigated the relationship between serum TSH level and blood pressure, the prevalence of hypertension was higher in the group with raised TSH than those that were euthyroid [131]. In another study from a primary

care setting, no association was found between hypertension and hypothyroidism in 122 patients between 75-85 years of age who were grouped by a single TSH level >5 mIU/L compared with 122 controls (less than 5 mIU/L). However, in the hypothyroid group 55.7% were on thyroid replacement therapy (TRT) suggesting that treatment may underestimate an association between hypertension and hypothyroidism and furthermore, that a single TSH may overestimate the prevalence of hypothyroidism by including one-off variations and transient non-thyroidal illness. No univariate or multivariate analysis in this reported study took into account TRT use. Mean diastolic blood pressure while still within the normal range was found to be significantly higher when comparing those with subclinical hypothyroidism with euthyroid controls [19, 132].

Reflex changes in cardiac function, such as a small decrease in heart rate, alongside a decrease in left ventricular ejection fraction result in decreased cardiac output characteristic of hypothyroidism [122]. In subclinical hypothyroidism, impaired left ventricular diastolic function, characterised by impaired ventricular filling and slowed myocardial relaxation, is a consistent cardiac abnormality [96, 133]. Recent studies have indicated that impaired vascular function is present in subclinical hypothyroidism, resulting from an increase in systemic vascular resistance and arterial stiffness and by impaired endothelial function; predisposing these patients to diastolic hypertension [22, 124, 129, 132, 134, 135]. Furthermore, diastolic dysfunction in the general population is reported to have a negative impact on cardiovascular morbidity and mortality [136].

Increased lipids appear to be an acceptable marker of cardiovascular risk but not all measures are a reliable marker of disease. A study of 794 hyperlipidaemic patients and 1588 controls enrolled in an outpatient clinic showed no association between carotid atherosclerosis and hypothyroidism when using intima-media thickness as a marker [25]. However, the authors further comment that observing carotid intima-media thickness may not be useful due to possible non-atherosclerotic infiltration of arteries as a result of the hypothyroid state. Another study supports this, identifying increases in arterial stiffness but not intima-media thickness in women with Hashimoto's thyroiditis [137]. This expresses evidence of internal compensatory mechanisms making it difficult to distinguish between direct effects of hypothyroidism against those which are modified as a result of them.

HYPOTHYROIDISM

Hypothyroidism relates to under activity of the thyroid gland but the definition extends to the effects on physiology of signs and symptoms (See Table 1). The diagnosis is usually confirmed by laboratory findings, usually distinguished by low FT_4 and raised TSH in the serum. There are no universal reference intervals as these are dependent on the assays used. Hypothyroidism is classified on the time of onset (congenital or acquired) as well as on the level of endocrine dysfunction, whether the failure is within the thyroid gland itself (primary) or whether activity of the gland is due to failure of the pituitary or hypothalamus (central).

The onset of hypothyroidism in adults may be insidious. Some patients may be unaware they have had hypothyroidism until euthyroidism is restored [114]. The effects of hypothyroidism in adults are as a result of a lowered metabolic rate [3]; a collection of signs and symptoms, none of them alone are a sensitive or specific indicator of the presence of hypothyroidism, although several symptoms together may be suggestive [1].

TABLE 1: SIGNS AND SYMPTOMS OF HYPOTHYROIDISM

Symptoms	Signs
Tiredness, weak, fatigued, lethargic, sleepy	Dry coarse skin; cool peripheral extremities
Dry skin	Peripheral oedema (non-pitting in myxoedema)
Feeling cold	Diffuse alopecia
Hair loss	Bradycardia, reduced cardiac output
Difficulty concentrating and poor memory	Delayed tendon reflex relaxation
Constipation	Carpal tunnel syndrome
Weight gain	Serous cavity effusions
Dyspnoea	Slow movements
Hoarseness of voice	Slow speech
Menorrhagia	
Paresthesia	
Impaired hearing	
Decreased appetite	
Depression	
Decreased perspiration	

Weight gain and tiredness are common symptoms which set in motion the request for thyroid function testing [1, 63, 83]. Weight gain, however, is considered modest and due mainly to fluid retention as a result of long-standing hypothyroidism [114, 123]. Nevertheless, in determining the

relationship between symptoms and biochemical disease, subjects who reported no symptoms were about twice as likely to be euthyroid as hypothyroid subjects [138].

In screened populations the diagnostic accuracy of clinical findings is low. In a study of 67 newly diagnosed subjects with overt hypothyroidism matched with 147 controls, the likelihood of hypothyroidism increased in a graded manner as the number of reported symptoms increased, particularly a change in symptoms [138]. The positive predictive value of individual hypothyroid symptoms was 8-12%. The most frequent symptoms of hypothyroidism relate to appearance, disposition, neuromuscular function, cardiac function and menstrual irregularities in women due to impaired oestrogen metabolism [1].

SUBCLINICAL HYPOTHYROIDISM (SCH)

SCH is defined as an elevated serum TSH level combined with normal FT_4 and FT_3 levels in patients who have mild or minimal symptoms. Classical signs and symptoms may be rare or absent except for a raised TSH level [139]. SCH is a condition found in areas of sufficient rather than deficient iodine intake [140]. A further consideration is that TSH concentrations increase with age, making the prevalence of SCH more likely with time [141].

Making the diagnosis of SCH can be complex especially in older populations where there may be difficulty in distinguishing between physiological abnormalities and pathological increases in TSH as a result of ageing. SCH is diagnosed by a set of tests demonstrating elevated levels of serum TSH with a FT_4 level within the normal reference range [140]. FT_3 levels, if measured, are also within the normal reference range [47]. A diagnosis of SCH should, by definition, be based on laboratory findings rather than on references to symptoms in the patient. The literature, however, is unclear over the inclusion or exclusion of symptoms in the definition [14, 47, 140, 142]. If symptoms are considered part of the presentation of SCH they are invariably vague and are a poor indicator of abnormal laboratory tests [143].

Recent data suggests impaired left ventricular diastolic dysfunction is the most consistent cardiac abnormality in patients with subclinical hypothyroidism [96]. In patients with cardiac disease, a mildly altered thyroid status is associated with an increased risk of mortality [144]. However, this is contradicted where subjects with subclinical hypothyroidism, in whom the mean serum TSH level is slightly above the reference range, appear to have normal cardiac function [145]. While the effects of overt hypothyroidism are known, the effects of subclinical hypothyroidism are more subtle. Subclinical hypothyroidism has been linked with increased

morbidity, particularly with cardiovascular disease. Effects have been studied on serum lipid levels, atherosclerosis and coronary heart disease [16, 146].

Subclinical hypothyroidism has also been studied in association with depression, memory, and mood, including anxiety and somatic symptoms with contradictory results [24, 100, 147]. Furthermore, a suggested link has been made with subclinical hypothyroidism and cognitive decline [148-150]. Conflicting results emerge from these studies and in particular, any changes brought about by treatment with thyroid hormone replacement therapy (levo-thyroxine) [64].

EPIDEMIOLOGY OF HYPOTHYROIDISM

Hypothyroidism is reported to be common within the community [46], with wide variation in the reported incidence and prevalence [43, 151]. Prevalence estimates of hypothyroidism range from 1% to 10.3% [6, 41, 43, 46, 47, 151, 152]; however, these studies differ by the age of the population studied and in the variability in laboratory cut-offs for TSH in diagnosing thyroid disease. Some studies encompass all individuals with a raised TSH; hence subclinical hypothyroidism is included in prevalence estimates.

PREVALENCE

The Whickham study, undertaken in northeast England between July 1972 to June 1974, was the first study to have used a whole population-based sample in establishing the prevalence of thyroid disorders in the community [40]. Eighty-two percent of the available sample (2,779 individuals) participated in the survey. Personal details were obtained in addition to family history relating to goitre and thyroid dysfunction. Signs and symptoms relating to hyper- and hypothyroidism were sought, as well as evidence of vascular disease from personal and family history. Investigations included blood pressure, 12-lead electrocardiogram, and a fasting blood sample (TSH, T_4, T_3, free T_4, thyroglobulin antibodies, microsomal antibodies, and lipids). A subset of the sample (n=197) was also asked to provide a single casual urine sample and serum for iodine estimations. The population sample was similar in age distribution to that of Great Britain but the socio-economic position was towards the more affluent social classes I-III over the less affluent social classes IV and V (similar to New Zealand quintiles) compared to Great Britain as a whole.

The definition of overt hypothyroidism was based on clear clinical findings as well as biochemical criteria [79]. The prevalence of overt hypothyroidism was 1.4-1.9% in women and

less than 0.1% in men. TSH distribution was similar in both sexes below age 45 years but increased markedly in women above this age. A similar pattern was found in men and women with subclinical hypothyroidism. Analysis of data excluding individuals with a past or family history of thyroid disease, presence of goitre or thyroid antibodies, demonstrated that gender differences between men and women over 45 years of age were almost abolished [40].

The frequency of thyroglobulin antibodies remained constant with age in men but increased from 1% in women below 45 years of age to 4.6% in 45-54 year age group rising to 7.4% in aged 75 years and above. Similarly, microsomal antibodies remained steady in men across the age groups but rose from 6.9-9.7% in women under 45 years of age, to 13.7% at age 45-54 years and fell to 8.8% after 75 years of age.

Having thyroid microsomal antibodies and an elevated TSH level (>6mIU/L) was twice as likely in women over 45 years of age compared with women under 45 years of age. In the Whickham survey, there was evidence of autoimmune thyroiditis and a minor degree of hypothyroidism in 10% of women over 45 years of age, while overt hypothyroidism was diagnosed in only 0.5% of this age group.

Of the 1877 known survivors from the Whickham study, 96% participated in a 20-year follow-up study [79]. Overt hypothyroidism was defined on an intention-to-treat basis by the general practitioner. The mean annual incidence of spontaneous hypothyroidism was 3.5/1000 per year in surviving women and 0.6/1000 in men [79]. The hazard ratio showed an increase in hypothyroidism with age. The presence of goitre was not associated with any clinical or biochemical evidence of thyroid dysfunction nor was a positive family history of any form of thyroid disease from the first survey likely to increase the risk of developing hypothyroidism. The odds of developing hypothyroidism were greater in women than men especially when both raised serum TSH and positive thyroid antibodies (thyroglobulin and microsomal antibodies) were present (Table 2).

TABLE 2: THE RISK (ODDS RATIO) OF DEVELOPING HYPOTHYROIDISM FROM WHICKHAM SURVEY [40]

	Women	**Men**
a) raised TSH alone	8	44
b) positive thyroid antibodies alone	8	25
c) both raised serum TSH and anti-thyroid antibodies	38	173

The probability of developing hypothyroidism was higher for values of TSH which were above 2 mIU/L at the first survey, independent of age and anti-thyroid antibody status. This was further increased if anti-thyroid antibodies were present. The annual risk of developing hypothyroidism for women was 4.3% per year if both raised TSH and anti-thyroid antibodies were present, 2.6% per year if a raised TSH alone was present and 2.1% per year if anti-thyroid antibodies alone were present.

In another community survey, 'The Colorado Thyroid Disease Prevalence Survey' (the Colorado study, 2000), the prevalence of abnormal thyroid function as well as its relationship to lipid levels and to symptoms was determined [43]. This study was the largest of its type with 25,862 participants recruited from a state-wide health fair in Colorado, United States. The main outcomes measured were serum TSH, total T_4, serum lipid levels and responses to a hypothyroid symptom questionnaire. The population, when compared with the general population of Colorado, was older, had more women, a greater proportion who were white and more high school and university graduates.

An abnormal serum TSH concentration was found in 11.7% of participants, with 2.4% having a TSH >10 mIU/L. A further 7% had a TSH between 5.1 and 10 mIU/L classed as subclinical hypothyroidism. Elevated TSH raised in decades of age from 4% (18-24yrs) to 21% (>74yrs) in women and 3% to 16% respectively in men.

The impact of oestrogen was evaluated only with those participants who identified using oestrogen supplementation and were also on thyroid replacement therapy. The relationship of oestrogen to thyroid dysfunction lies in the interpretation of tests, where oestrogen has a direct effect on total T_4 measurements due to the ability of serum proteins to bind to T_4. Therefore, the use of total T_4 in the Colorado study will not accurately reflect the free level (unbound T_4) and errors in diagnosis and management may result [2]. Using total T_4 instead of free T_4 leads to an incorrect estimation of overt and subclinical hypothyroidism: due to the increase in thyroid binding proteins in individuals who receive oestrogens. It was important to show whether those on oestrogen supplementation would have an effect on the categorisation within the study. However, in another United States study, the NHANES III study described below, no significant difference was found between the oestrogen group and those not taking it [39].

In the Colorado study, a higher proportion of hypothyroid participants had elevated total cholesterol (TC) and low density lipoprotein (LDL) compared with the euthyroid participants. Furthermore, a higher proportion of subclinically hypothyroid participants also had elevated TC when compared with the euthyroid group. Mean TC and LDL progressively increased as TSH levels increased. No significant changes were evident with triglycerides or high density lipoprotein (HDL).

Using a symptom score, a greater percentage of symptoms were reported by the overt hypothyroid group compared with the subclinically hypothyroid group. Both hypothyroid groups reported more symptoms than the euthyroid group. Positive predictive values of symptoms were low (8 – 12%). Multiple regressions based on disease state and 14 changed symptoms found only two symptoms were significant for individuals with hypothyroidism – current constipation and feeling colder – compared with their symptoms the year before. Previous use of the symptom score were in populations suspected of having hypothyroidism [153], therefore the sensitivity in an unselected population is expected to be lower.

The National Health and Nutrition Examination (NHANES) III (1988-1994) study evaluated for the first time the prevalence of thyroid function to provide reference data for TSH, T_4, and thyroid antibodies in the United States population using a population sampling method – a stratified, multistage probability design [39]. Oversampling took place to ensure sufficient numbers for studies of minority groups. Extending the NHANES study to establish the prevalence of thyroid dysfunction was in response to a reduction in median urinary iodine concentrations over a 20 year period (320 µg/L to 145 µg/L) since NHANES I (1971-74) and awareness that subclinical and clinical forms of hyper-and hypothyroidism in the United States may be potential contributors to morbidity for various cardiovascular and neuropsychiatric diseases [39]. Urinary iodine measures are discussed in more detail in the section on iodine on page 24.

The sample of 17,353 participants aged ≥12 years represented the geographic and ethnic distributions of the United States population. Separating 820 participants with self-reported thyroid disease or on thyroid medications left a disease-free population of 16,533 people. Undiagnosed hypothyroidism was evident in 4.6% of the disease-free population (0.3% was overt and 4.3% subclinical). In addition, there were significantly more females than males with hypothyroidism in the 40-49, 50-59 and 60-69 year age bands. A reference population of 13,344 was created after further excluding those with a goitre and individuals with conditions

that may affect thyroid function such as pregnancy, usage of oestrogen, androgens or lithium, those who had detectable anti-thyroid antibodies or had laboratory evidence of hyper- or hypothyroidism.

The difference in hypothyroidism rates to those found in the Colorado study may relate to sampling method and regional differences. When rates of thyroid disease were studied using only white women, NHANES III rates were similar to Colorado study rates.

Subclinical hypothyroidism is a common condition occurring in 8.5% of an adult population not taking thyroid medication [43]. Women have two to three times the prevalence of SCH than men [40, 152]. Prevalence varies with age, genetic factors such as presence of thyroid autoimmunity, iodine intake and tobacco smoking, occurring in as many as 15% to 20% of women over the age of 60yrs [40, 43, 83]. The condition may progress to overt hypothyroidism in 2% to 3% of patients per year but the incidence may increase to 4% to 5% per year where thyroid auto-antibodies are present [24, 79].

Further epidemiological studies have been undertaken on the prevalence of hypothyroidism in Norway [41], Scotland [45], Australia [46] and Japan [154] and are tabled over the page (Table 3).

TABLE 3: PREVALENCE OF HYPOTHYROIDISM AND THYROID ANTIBODIES FROM INTERNATIONAL STUDIES[41, 45, 46, 154]

Author	Method	Hypothyroidism	Antibodies
Bjoro T et al, 2000. [41]	Cross sectional questionnaire and blood sample (N=65,263) Blood sample alone (N=30,297)	Self-reported thyroid disease: men 0.9% (271/30519), women 4.8% (1666/34744) Population without self-reported thyroid disease from questionnaire: overt hypothyroidism: men 0.4% (38/10165), women 0.9% (182/20132). Subclinical hypothyroidism (TSH >4 - <10mIU/L): men 3.7% (372/10165), women 5.1% (1019/20132)	Sub-sample of population over 40 years of age: men 2.8% (10/360), women 13.9% (81/582) Gender and age differences in median TSH and 97.5 percentile disappeared when the positive microsomal antibodies were excluded.
Flynn RWV et al, 2004. [45]	Data linkage using 6 principal databases based on subjects receiving T_4 replacement	All cause prevalence rose from 2.2% in 1993 to 3.0% in 1996.	Not reported
O'Leary PC et al, 2006. [46] 'The Busselton Study'	Cross sectional health survey involving questionnaire and blood sample. (N=2,026)	Population without prior thyroid disease - prevalence of: overt hypothyroidism 0.5% (11/2026) (4 men, 7 women); subclinical hypothyroidism 5.1% (34 men, 70 women)	Prevalence 12.4% (251/2026) or 11.6% without history of thyroid disease Elevated TPO antibodies 10.7% Elevated thyroglobulin antibodies 5.5% 35.9% with elevated microsomal also had raised thyroglobulin antibody – 3.9% of study population
Kasagi K et al, 2009. [154]	General health check up (N=1818)	Population includes patients with prior disease: prevalence of overt hypothyroidism 0.7% (12/1818); subclinical hypothyroidism 5.8% (105/1818).	Positive TgAb 22.2% (Male 13.1%, Female 29.4%) Positive TPOAb 11.6% (Male 7.2%, Female 15%)

AETIOLOGY OF HYPOTHYROIDISM

World-wide, the most common cause of hypothyroidism is a lack of dietary iodine, termed iodine deficiency disorders by the World Health Organisation. A lack of iodine precludes the thyroid from manufacturing thyroid hormone. Iodine deficiency is more prevalent in developing rather than in developed countries. In developed countries, auto-immune disease is the most frequent cause of hypothyroidism. Other causes of thyroid under activity include medicines (both prescribed and over-the-counter), surgery, infection, and radioactive iodine therapy or possibly environmental effects such as exposure to radiation. The inhalation of toxic agents that affect thyroid function or the ingestion of naturally occurring goitrogens (goitre-causing agents) will not be discussed here as these are rare occurrences in New Zealand. In less than 1% of patients, hypothyroidism is caused by diseases of the pituitary or hypothalamus.

IODINE

Prevalence of thyroid disease is strongly influenced by dietary iodine. Without iodine [or iodide in its ionized form] there would be no biosynthesis of thyroid hormones and thyroid function, which is dependent on an adequate supply of iodine to the thyroid gland, will be compromised [36]. Iodine deficiency affects over one billion people worldwide [155], and is the main cause of hypothyroidism in developing countries such as South Asia and sub-Saharan Africa [156].

The required daily intake of iodine as recommended by the World Health Organisation is at least 150 micrograms (mcg) for adults, 200 mcg for pregnant women, 90-120 mcg for children aged 2 to 11 years and 50 mcg for infants less than 2 years of age [157 158]. Lower iodine intakes are associated with goitre and hypothyroidism. Severe iodine deficiency increases the risk of thyroid hormone deficiency in infants, and when a mother has an inadequate intake of iodine during pregnancy, thyroid hormone deficiency results in cretinism. Cretinism is characterised by developmental delay, both mentally and physically, in children who have not been treated with iodine or with thyroid hormone replacement to restore normal thyroid levels early in childhood [4].

Iodised salt was first introduced in parts of Switzerland in 1924 with a few other countries following its lead [159]. New Zealand has a naturally low iodine environment and endemic goitre was prevalent at the beginning of last century [160]. Iodised salt was introduced into New

Zealand in 1924 as a voluntary scheme. The recommended dose for supplementation based on the Swiss experience was 4 mg of iodine per kilogram (mgI_2 /kg) of salt. Initially this level of iodine supplementation was not met in New Zealand but was later increased to the current level of 40-80 mgI_2/kg salt by 1939 [159]. In 1953 the World Health Organization Study Group on Endemic Goitre recommended that iodised salt should be used compulsorily in any country or area where goitre was endemic [160]. A 2009 report on the levels of iodine in retail salt showed that the mean concentration of iodine in iodised table salts ranged from 32-64 mgI_2/kg salt, which is within the required standards of the Food Standards Australia New Zealand code. Sea, rock and 'other' salt products contained about 30 times less iodine than iodised salts; between 1-5 mgI_2/kg of salt – not sufficient to meet the Food Standards Australia New Zealand standards [161].

Iodine intake was further increased as a result of the use of iodine-containing iodophors in the dairy industry. Iodophors are sanitizers in which iodine is bound to a surface active agent in a concentrated form and then released when diluted with water. They have been extensively used to control micro-organisms in dairy processing premises. The increase in iodine content of bovine milk as a result of iodophors usage is well known [160]. The use of iodophors in the dairy industry reached a peak in 1976-78 but has since declined on subsequent testing in 1978-79 and 1987-88 [162]. Since the introduction of iodised table salt and the use of iodophor detergents in the dairy industry,[163] adequate levels of iodine intake have been reported [142].

On its own, the amount of iodine naturally found in milk (background iodine content) is small and the amount varies for a number of reasons such as the time of year, stage of lactation, pregnancy, breed of cattle, time interval between milkings, stress and disease [160]. The background iodine content in raw milk products tested in 1973 in the absence of adventitious sources such as iodophors was found to be 0.03-0.11 mgI_2/kg. In a 1998 survey, standard milk was found to contain 0.04-0.25 mgI_2/kg [160]. In comparison to the United Kingdom and the United States, New Zealand has lower mean iodine content in standard milk. Fresh milk is unlikely to be the primary determinant of human iodine status in New Zealand [164].

Most iodide is excreted by the kidney making urinary iodine excretion an excellent index of dietary intake [117]. Although, urinary iodine concentrations are a prime indicator of an individual's current nutritional iodine status, a single measurement is not representative due to reported day-to-day and within-day variation [165]. Urinary iodine concentrations are a validated use in prevalence studies when measuring urinary iodine concentrations in

population samples [157, 164, 166, 167]. In addition, because of significant circadian rhythmicity, studies comparing urinary iodine concentrations should ideally compare samples that have been taken at the same time of day [168]. Median iodine concentrations, as recommended by the World Health Organisation (WHO), relate to community measures in which those suffering moderate to severe iodine deficiency would account for 20% of the population [169]. Therefore, median rather than mean are recommended as the measure of central tendency due to the population measures of urinary iodine concentrations not being normally distributed [158]. Recommended epidemiological criteria for assessing median urinary iodine concentrations are: <20 micrograms/L (mcg/L) = severe iodine deficiency, 20-49 mcg/L = moderate iodine deficiency, 50-99.9 mcg/L = mild iodine deficiency and ≥100 mcg/L = no iodine deficiency [157, 158]. In countries where dietary iodine intake appears to be sufficient, there are risks of adverse health outcomes with excessive iodine intake [166]. The risks of excessive iodine intake measured in terms of urinary iodine concentrations, added to international recommendations, include: 200-299 mcg/L = risk of iodine-induced hyperthyroidism in susceptible groups, mainly older subjects with pre-existing nodular goitres, and ≥300 mcg/L = risk of adverse health consequences (iodine-induced hyperthyroidism, autoimmune thyroid disease) [158]. Population-based criteria are required for measuring iodine status since there are no reference ranges for urinary iodine [170].

Measurements of 24-hour urinary iodine concentrations from the Whickham study (1977) demonstrated a mean ± standard error urinary iodine output of 81.1±5.3 mcg/24h which the authors reported was of an iodine-replete population [40]. 24-hour urine excretion criteria are: low (<60 mcg/day); medium (60-90 mcg/day), and high (>90 mcg iodide/day). This indicates that the Whickham population had medium iodine status at that time of the study [171].

The NHANES III study (1988-1994) reported the median urinary iodine concentration had reduced from the NHANES I (1971-1974) level of 320 mcg/L to 145 mcg/L over 20 years [39]; both levels within the 'no iodine deficiency' criterion. The NHANES III study also describes no significant difference in TSH in individuals with normal urinary iodine levels compared with those with either low or high urinary iodine. The authors report that TSH was not a sensitive indicator of iodine deficiency in this population.

Reports within the past decade on the iodine status of New Zealanders suggest urinary iodide levels are declining, indicating reduced dietary iodine intake, to the point where intervention is required to ensure that iodine deficiency does not once again affect the health of our

population [163, 164, 167, 172]. A New Zealand study in 1997-1998 assessed the clinical significance of low iodine excretions in terms of thyroid hormone status and thyroid volume and was conducted in an adult population in a low soil iodine area of the South Island [167]. Mean urinary iodine concentrations were 59±33 mcg/L and 24-hour concentrations were 86±49 mcg/day. Both of the results from this New Zealand study demonstrate that iodine levels are below the level of optimal iodine intake. Falls in iodine status were demonstrated to be reflected in clinical measures of thyroid status, however, despite TSH immunoassay being described as the most appropriate diagnostic test for determining hypothyroidism, in individuals over 30 years of age TSH is reported as an unreliable indicator of current iodine intake [173]. Furthermore, the authors report no relationship between thyroid hormone status and iodine excretion exists after this age. With the threat of recurrence of endemic goitre and associated health risks, Food Standards Australia New Zealand has proposed to fortify food with iodine to ensure that dietary iodine intake is adequate at a population level [174]. This strategy has the potential to alter patterns of thyroid disease in New Zealand. Fortifying food with iodine is expected to have a positive effect on the health of most New Zealanders by preventing the associated risks of hypothyroidism.

The risk of having a strategy that provides an increase in dietary iodine intake to the population may contribute to a negative impact on health for some individuals [174]. This risk of harm as a result of mandatory iodine fortification of food is highest in groups more sensitive to increases in iodine intake, such as individuals with existing thyroid conditions. A study of 30 newly-diagnosed patients with hyperthyroidism were recruited over a 12-14 month period (November 1970 – December 1971) in Tasmania [56]. The diagnosis of hyperthyroidism was based on clinical features supported by investigative results – serum assays and radionuclide thyroid uptake scans. An increased incidence of hyperthyroidism in Tasmania was directly linked to the increased intake of iodine, particularly in individuals with thyroid-stimulating auto-antibodies or with existing thyroid nodules. The health risks to these individuals as a result of the population-wide mandatory dietary iodine supplementation supports the notion that this occurrence is consistent with iodine-induced hyperthyroidism [117], resulting from an increased supply of iodine to unregulated thyroid tissue [56]. A New Zealand study indicated that this increase in hyperthyroidism was temporary (although lasting several decades) and was compensated by long-term benefits to the population [159].

In China, an increase in dietary intake of iodine, as a result of iodination in 1996, led to an increased prevalence of overt hypothyroidism, subclinical hypothyroidism, and autoimmune

thyroiditis [175]. The rise in hypothyroidism in China resulting from the introduction of iodination to salt occurred in all areas irrespective of prior iodine sufficiency: contrary to the Tasmanian experience where there was a rise in hyperthyroidism following iodination. Other internal and external mechanisms may have contributed to the differing outcomes between China and Tasmania. These mechanisms are described in more detail in this chapter (see Patient Characteristics on page 33 and Environment on page 38).

The administration of iodine has been shown to reduce goitre prevalence and, as expected, increased the excretion of urinary iodine after treatment [176]. A study of 2316 school children given iodised oil reported the development of microsomal in a small number of subjects receiving 1 ml of iodised oil either orally or intramuscularly compared with 2393 untreated school children who acted as controls [176]. Further epidemiological evidence points to the development of autoimmune thyroid antibodies following iodination and its contribution to hypothyroidism [177]. A study in 40 euthyroid patients with simple nontoxic goitre, adequate iodine intake and an absence of thyroid antibodies were each given intramuscularly 1 millilitre of iodised oil containing 480 mg of iodine [178]. The aim of the study was to evaluate the effect of iodine on thyroid function and on the development of indices of autoimmunity through measures of thyroid antibodies and lymphocytic infiltration. The findings identified the development of abnormal levels of thyroid antibodies in some cases and an increase in thyroid lymphocytic infiltration as a result of the administration of iodised oil to patients with small nontoxic goitre in an iodine-replete area. The evidence of iodine-induced autoimmunity concurs with the greater prevalence rates of autoimmune thyroid disease found in iodine-replete countries [5, 6, 39 177].

There are routine surveys of iodine intake in New Zealand but there are currently no prevalence studies of thyroid dysfunction in New Zealand [155, 164, 167, 179, 180]. Enabling an initial local examination of thyroid dysfunction will allow identification of changes over time that may develop as result of the forthcoming fortification of foodstuffs with iodine in New Zealand.

AUTOIMMUNE THYROID DISEASE

In general, diseases in which the pathology is caused by an adaptive immune response to self antigens are called autoimmune diseases [181]. A combination of genetic and non-genetic factors are implicated in the failure of T-cell tolerance leading to autoimmune disease [182].

Chronic autoimmune thyroiditis, the most common cause of endogenous primary hypothyroidism, results from lymphocytic destruction of the thyroid and thyroid inhibitory auto-antibodies [2, 4, 5].

The two most common thyroid autoantibodies measured by general practitioners are thyroglobulin (anti-Tg) and thyroid peroxidase (anti-TPO, also known as microsomal antibodies) [182]. As with Tg and TPO, these antibodies are specific to thyroid follicular cells, that is, they are not found in cells elsewhere in the body. Anti-Tg and anti-TPO autoantibodies indicate the possibility of autoimmune thyroid disease whether that be hypothyroidism or thyrotoxicosis [46, 183]. In autoimmune hypothyroidism these specific anti-Tg and anti TPO antibodies are not pathogenic but are markers of an immune process which can be directed towards the thyroid [184]. The destruction of thyroid cells may be gradual with the subsequent development to hypothyroidism [185].

Anti-TPO is present in 95% of individuals with hypothyroidism, whereas anti-Tg is present in only 60% [114]. Anti-TPO and anti-Tg are found in 10-15% of the healthy population [39, 186]. Factors that determine autoimmune thyroid disease and their interrelationships remain unclear with respect to cause and progression [4, 182].

Chronic autoimmune thyroiditis is divided into two predominant types: chronic atrophic thyroiditis and chronic goitrous thyroiditis [182]. Chronic atrophic thyroiditis was first described in the late 1890's by William Ord (1834-1902), a general practitioner and physician to St Thomas' Hospital, London [115], as dependent on the presence of anti-TPO, which is associated with gradual infiltration of the follicular cells by lymphocytes in the thyroid gland [186]. Chronic goitrous thyroiditis, also known as Hashimoto's thyroiditis or hypertrophic autoimmune hypothyroidism, was first described in 1912 by Hakuru Hashimoto (1881-1934), a surgical registrar, as part of his MD thesis [115]. The pathology of Hashimoto's thyroiditis consists of varying degrees of lymphocytic infiltration of thyroid tissue with leukocytes, fibrosis and gradual destruction of the follicular epithelium in the thyroid gland; goitre is also present.

Studies have questioned whether atrophic hypothyroidism and Hashimoto's thyroiditis are variants of the same disease [187, 188]. The variants of chronic autoimmune thyroiditis share many clinical and biochemical features, which suggest that the pathogenesis of atrophic and goitrous forms of hypothyroidism overlap [182]. There are no strict criteria to separate atrophic and goitrous forms of hypothyroidism; classification is often based on the presence or

absence of goitre on clinical examination [186, 189]. A transient hyperthyroid state, which may include loss of weight, palpitations, feeling hot, diarrhoea; the opposite of what would be expected of hypothyroidism, known as "hashitoxicosis", is a recognised acute phase of Hashimoto's thyroiditis: this phase is rare in atrophic hypothyroidism [5]. A prospective study examining the thyroid volumes in 144 patients with newly diagnosed overt autoimmune hypothyroidism found that log-transformed thyroid volumes followed a Gaussian (normal) distribution for both males and females with no bimodal pattern suggesting that atrophic and goitrous hypothyroidism are the same disease at opposite ends of a spectrum[189]. This Danish study, in agreement with a prior study, proposes a combined term "Ord-Hashimoto's" disease to describe chronic autoimmune hypothyroidism collectively [187, 189]. The idea that Hashimoto's thyroiditis precedes atrophic hypothyroidism is not universally shared with some believing that there is no good evidence for this [182, 186].

Another type of autoimmune thyroiditis exists and is implicated in a further 5-10% of autoimmune hypothyroidism. This variant is a result of thyroid stimulating hormone-receptor blocking antibodies, which blocks the action of TSH, where no evidence of anti-TPO, anti-Tg or thyroid stimulating immunoglobulin antibodies exist [186]. These are all termed within the classification of autoimmune thyroid antibodies.

The NHANES III study found the prevalence of autoimmune thyroid antibodies to be approximately 10.4% for anti-Tg and 11.3% for anti-TPO [39]. In addition, those with anti-Tg alone in the absence of anti-TPO were not significantly associated with thyroid disease. The presence of thyroid autoantibodies is not synonymous with having autoimmune thyroid disease, that is, not all individuals with thyroid autoantibodies will develop hypothyroidism. Many individuals labelled with autoimmune thyroid disease who have antithyroid antibodies are euthyroid (normal thyroid function) [21]. Histological changes in goitrous chronic lymphocytic thyroiditis changes little over time in many patients regardless of the administration of thyroxine replacement therapy [188], as opposed to thyroid autoantibodies which decreased significantly with thyroid hormone administration. Thyroid autoantibodies are a marker for thyroid autoimmune disease [186].

Several hypotheses have been formulated regarding the pathogenesis of chronic autoimmune thyroiditis. These include the possible role of iodine, pesticides, by-products of industry and infection in triggering a thyroid autoimmune response [190]. There is some plausibility that infectious agents such as viruses cause autoimmunity, although it is difficult to prove

particularly where hypothyroidism may develop after a long preclinical course of disease [182]. The various modes of action for the induction of an autoimmune response are said to be: via a bacterial or viral agent that is structurally similar to a thyroid protein, termed molecular mimicry; by involvement of abnormal major histocompatibility complex class II protein expression on thyroid follicular cells, which are not normally expressed in thyroid cells from healthy individuals; or through thyroid cell apoptosis induced by Fas ligand-Fas system in association with interleukin-1, with Fas expressed on thyroid follicular cells ultimately causing cell death, again not normally expressed on healthy thyroid cells [4].

Another theory is that of prenatal nutrition and its effect on chronic conditions in later life, entitled the 'thrifty phenotype hypothesis', or more commonly as 'Barker's Hypothesis' [191, 192]. A study determining whether a relationship existed between foetal and infant development and susceptibility to thyroid antibodies and chronic autoimmune thyroiditis took place in six districts in Hertfordshire in the United Kingdom [191]. In total, 305 women, aged 60-71 years, who were born and raised in East Hertfordshire, and who had complete midwifery and health visitor records from infancy, participated. Anti-Tg and anti-TPO antibodies were found in 37% and 41% of women respectively. Of the 17 women with hypothyroidism, 16 were positive for anti-TPO and 1 was positive for anti-Tg. The study showed that adults who developed thyroid autoantibodies have a lower prenatal weight gain. One explanation for the association between reduced foetal growth and autoantibody production in middle age relates to development and maturation of the thymus in utero. The thymus reaches its maximum weight at birth and plays a central role in the preservation of immunological tolerance [193]. The effect of reduced foetal growth as a result of prenatal influences may contribute to the size and function of the thymus at birth, thus, making adults with low birth weight more susceptible to thymic involution and the earlier emergence of autoimmune antibody production than those of greater birth weight [191].

In addition, there appears to be a genetic component to autoimmune thyroid disease. The risk is greater in siblings and it is reported that in those with autoimmune thyroid disease up to 50% of first-degree relatives will also have autoimmune thyroid disease [114 186]. Euthyroid women with a first or second degree relative with documented autoimmune thyroid disease participated in a nested case-control study within a prospective cohort study of autoimmune thyroid disease in Amsterdam [185]. A total of 790 healthy euthyroid women were followed for 5 years to evaluate the time of progression from euthyroidism to overt autoimmune hypothyroidism. Data suggested progression towards overt hypothyroidism was a gradual

process taking several years. While family and twin studies suggest a genetic contribution to autoimmune thyroiditis, environmental factors are of aetiological importance [194]. Barker's Hypothesis would argue that environmental factors such as maternal nutritional affecting prenatal growth may in part explain familial clustering [191]. A Danish study of 512 same-sex twin pairs (1024 participants) aimed to study the relationship between low-birthweight and development of thyroid autoimmunity found no evidence to support Barker's Hypothesis in the role in the aetiology of thyroid autoimmunity [195].

Other factors relating to an increased risk of developing autoimmune thyroid disease include patients with previous history of head and neck or thyroid irradiation or surgery; other autoimmune endocrine conditions, such as type 1 diabetes mellitus, adrenal insufficiency, ovarian failure; and, other non-endocrine autoimmune disorders; for example, coeliac disease, vitiligo, and pernicious anaemia [63]. Autoimmune thyroid disorders have frequently been accompanied by other organ specific and non-organ specific diseases [196]. Additionally, a previous history of silent thyroiditis or postpartum thyroiditis is considered to be a manifestation of chronic autoimmune thyroiditis and is a risk factor for future hypothyroidism [197], although, a history of subacute thyroiditis as a result of a post-viral inflammation of the thyroid, is not a form of autoimmune thyroiditis [186].

The higher rate of autoimmune disease in women is likely due to the effects of sex steroids on the immune response [114, 182]. As with most autoimmune diseases; women are affected at a greater rate than men [39]. In particular, the difference in sex ratio between autoimmune diseases is greatest between the menarche and the menopause, when levels of such hormones are highest [181]. Women in the postpartum period have an increased risk of developing hypothyroidism [182 185]. Nearly 25% of women who develop postpartum thyroiditis becoming overtly hypothyroid within 3-4 years [198].

Thyroid autoantibodies are believed to be associated with the progression of mild or subclinical thyroid failure to overt hypothyroidism [6, 199]. In the United States, thyroid autoantibodies have been reported in as many as 18% of adults without a reported thyroid disorder and in 25% of women over 60 years of age [39]. The NHANES III study found concentrations of TSH >4.5 mIU/L were linearly and logistically associated with positive anti-TPO ($p<0.01$; OR 8.4, 5.8-12.1). A linear relationship between TSH and positive anti-Tg was not evident but a logistic association was less strongly associated with positive anti-Tg ($p=0.6$; OR 1.8, 1.3-2.7 respectively). The mean annual incidence rate of autoimmune

hypothyroidism is approximately 4 per 1000 women and 1 per 1000 men per year [114]. A cross-sectional investigation in an iodine-sufficient area examined the relationship between anti-TPO and TSH in 2394 euthyroid subjects [200]. After 9.1 years follow-up, anti-TPO and TSH remained independent predictors of future development of hypothyroidism [200]. In another longitudinal study (13 years) in an iodine-sufficient area, the risk of hypothyroidism in anti-TPO positive subjects was found to be highest in those in the highest range of anti-TPO concentrations (≥350 IU/ml), over 10 times the cut-off, whereas the risk in those with three-times the normal cut-off limit has no independent predictive value after adjusting for age, gender and TSH [183].

Having positive thyroid antibodies is not a pre-requisite for thyroid dysfunction but remains a strong risk factor. Lymphocytic infiltration of the thyroid gland is present in up to 40% of healthy women with anti-thyroid antibodies but who are euthyroid [64]. Only in the presence of a raised TSH and with very high levels of anti-TPO antibody are antibodies an independent predictor of hypothyroidism risk [183].

A 20-year follow-up study of the Whickham study investigated whether evidence of autoimmune thyroid disease, independent of having a raised serum TSH, was associated with the subsequent development of ischaemic heart disease [111]. The findings did not support an association between evidence of autoimmune thyroid disease as documented at the first survey with the development of ischaemic heart disease.

PATIENT CHARACTERISTICS

Patient characteristics such as age, gender, ethnicity, and weight have been cited as risk factors for hypothyroidism. Environmental factors including diet, smoking and seasonal variation, all of which can impact on the epidemiology of hypothyroidism have also been cited. Each of these will be discussed in more detail. Contradictory prevalence estimates within and between countries have been found. For example, in Sweden, two community studies on women aged over 60 years of age with similar participant numbers had opposing prevalence of hypo- and hyperthyroidism (1.3% vs. 0.5% hypo; 0.2% vs. 1.9% hyper) [201, 202]. Factors which may contribute to these differences include the methods of detection such as screening [202] versus random population sampling [201] and the focus of enquiry – undiagnosed thyroid dysfunction [202] versus effects of age and/or smoking [201]. Likewise, in a Spanish urban community, prevalence of hypothyroidism was reported in adults over 60 years of age

at 2% compared with 6.5% hyperthyroid [44], while in a study of an urban community in America over 55 years of age the overall prevalence of thyroid dysfunction was similar but found 6.9% were hypothyroid compared with 2% hyperthyroid [152]. Geography and time between studies may affect the outcome of these age-comparative studies. Many other studies have corroborated the findings of the Whickham study indicating their applicability to other regions of the world with the exception of areas with iodine deficiency, water-borne goitrogens, and radiation [203].

AGE

The underlying assumption up to the late nineteenth and early twentieth century was that hypothyroidism was a natural consequence of age [204]. Several epidemiological studies have demonstrated an increase in TSH and in hypothyroidism with age. In the Whickham study, the incidence of spontaneous hypothyroidism increased steadily from 1.4/1000/year in female survivors aged 18-24 years at first survey to 6.7/1000/year if aged 65 – 74 at first survey [40, 79]; the hazard ratio showed an increase with age in hypothyroidism [79]. The prevalence of hypothyroidism was also found to increase with age in Norway, another iodine-sufficient area [41]. Secondary analysis of data from the third NHANES study (1998 – 2004) showed that individuals aged 80 years and older had a five times greater odds of hypothyroidism compared to 12- to 49-year-olds [205]. The Colorado Study showed elevated TSH by decades of age from 4% (18-24yrs) to 21% (>74yrs) in women and 3% and 16% respectively in men [43]. Likewise, a community study from Australia, the 'Busselton study' showed an increase in TSH levels from 2.5% in women and 1.6% in men under 50 years of age to 12.8% and 3.6% respectively when over 50 years of age [46].

An increased prevalence of hypothyroidism with advancing age may be due to several factors. Animal models indicate age-related changes within the hypothalamic-pituitary-axis, which suggest a defect at the hypothalamic level [114 206]. While serum T_4 concentrations remain relatively stable from birth through adulthood, in healthy older adults, defective peripheral metabolism of thyroid hormones, decreased thyroid hormone secretion and reduced output of TRH and TSH with age further supports the possibility of a resetting of the hypothalamic-pituitary-axis [119, 204]. The physiological adjustments with age that take place within the thyroid gland contribute to the maintenance of FT_4 at equilibrium with free hormone and binding proteins concentrations being re-established [118, 151].

There is a linear relationship between age and the presence of autoimmune antibodies [39, 79 46]. In addition to the relationship between age and hypothyroidism [182 40, 43], up to 25% of euthyroid women over 60 years of age in the NHANES III study were found to have thyroid antibodies [39]. Ageing is positively correlated with concurrent non-thyroidal illness and drug administration, both having an effect on thyroid function [114]. The difficulty in studying thyroid dysfunction in the elderly is in distinguishing between normal changes of ageing and changes as a result of co-morbidities and medication [207]. Furthermore, there is evidence of raised TSH levels and low FT_4 levels being associated with better survival in elderly subjects [22, 208].

There is difficulty in answering whether thyroid dysfunction is a natural process of ageing or as a function of disease [204]. Increasing age is a non-modifiable risk factor in the development of hypothyroidism as well as in increasing cardiovascular risk. As the number of older people increases in most developed countries, age-related changes in thyroid function that affect quality or quantity of life is important to examine.

GENDER

Hypothyroidism is more common in women. The Colorado study demonstrated the percentage of women with an elevated TSH concentration was greater than men in each decade of age, reaching statistical significance for each decade after the age of 34 years ($p<0.1$) [43]. The female to male ratio for hypothyroidism is 5:1 in a Norwegian study [41]. The Whickham study also found a higher prevalence of hypothyroidism in women [40]. In New Zealand, the prevalence of self-reported thyroid conditions affects 5 women for each man [209] .

Epidemiological studies which addressed the higher prevalence of hypothyroidism in women have tested associations with thyroid antibodies [39, 46], sex hormones [182, 210], and inherent gender differences in the hypothalamic-pituitary-axis [211]. Any gender differences between men and women as a result of having a raised TSH disappeared when anti-TPO was controlled for in multivariate analysis in the NHANES III study [39]. Furthermore, when the probability of developing hypothyroidism is plotted against increasing serum TSH levels, the increased risk in men is more pronounced than in women [203]. Autoimmune antibodies peak in women at menopause [76, 181].

Seldom have studies assessed thyroid status and menopause [210]. The Study of Women's Health Across the Nation (SWAN), a United States community-based multiethnic study of

menopause transition, enrolled 3,302 women aged 42-52 years with the aim to evaluate menopausal symptoms, menstrual cycle characteristics and reproductive hormones against TSH concentrations [210]. Women were pre- and perimenopausal. TSH values were lower in untreated perimenopausal women compared with untreated premenopausal women (1.89 vs. 2.3 mIU/L) but there was no significant difference between the two groups [210]. Overall, 7.6% of untreated women had TSH values outside the range of 0.5-5.0 mIU/L. Of these, 4.1% were within the 5.0-10.0 (subclinical hypothyroidism) range. There was no relationship found between oestradiol concentrations and TSH [210].

A study of 46 subjects (24 were male) aimed to analyse TSH profiles in healthy men and women to identify gender differences in the hypothalamic-pituitary-axis [211]. They found basal and pulsatile TSH secretions were indistinguishable between the two genders and no differences in diurnal variation. There was an association between TSH and age in women but not in men [211].

WEIGHT

The relationship between body weight and thyroid function has been examined in several different contexts: to evaluate the involvement of the thyroid gland in overweight and obese children (using BMI SDS, a measure of BMI for children comparing how many standard deviations a measurement is above and below the median of the distribution for weight and height) [55], the relationship between thyroid function and weight gain [212], the impact of diet and activity in relation to thyroid function and weight [213], and thyroid function in morbidly obese (BMI ≥40, measured as kg/m^2 = weight in kilograms divided by (height in metres x height in metres) [214].

A study of 186 overweight and obese children in Italy demonstrated that obese children frequently showed alterations of thyroid structure and function; however, this was not explained by autoimmune involvement [55]. Another study of 3,654 adults over 49 years of age showed that increasing TSH was associated with a 50% higher likelihood of having a >2kg weight gain after adjusting for age, baseline body weight and smoking in women but not in men [213].

In a study of 350 morbidly obese individuals, 20 subjects (5.7%) had previous treatment for hypothyroidism [214]. A further 8% had raised TSH greater than 4.0 mIU/L. Two hundred and eighty subjects had thyroid parameters within the reference range and were negative for

thyroid antibodies. When compared with an age- and sex-matched control group, thyroid hormones were significantly lower and TSH was significantly higher in the morbidly obese group while remaining within the reference intervals, although FT_4/FT_3 ratios were similar between the two groups [214].

Further studies have identified a linear relationship between TSH and obesity with TSH levels reducing following weight loss, while remaining within the reference interval [215]. Abnormalities in thyroid function and TSH have been found to normalise after weight loss [216]. This has been shown to be independent of whether the loss was from diet or by surgery, suggesting reversibility of biochemical alterations from weight gain [217]. It is believed that there is a relationship between adiposity and mechanisms causing thyroid dysfunction and morphological thyroid changes [55].

Not all studies have supported the relationship between thyroid function and obesity [64]; however, increasing weight (BMI >25) is an independent risk factor for heart failure, coronary heart disease and cardiovascular morbidity and mortality [20].

ETHNICITY

Several studies have shown differences relating to TSH levels by ethnicity. The NHANES III study showed differences in TSH between the White, non Hispanic population when compared with the Black, non Hispanic population (1.57 mIU/L vs. 1.18 mIU/L) [39]. One suggestion for this has been the higher rate of thyroid autoantibodies in White vs. Black populations.

In contrast, African-American and Japanese women, who were not being treated for thyroid dysfunction, were proportionately more likely to have TSH levels <0.5 mIU/L, while Caucasian, Hispanic and Chinese women were more likely to have values greater than 5.0 mIU/L [210]. It is possible lifestyle factors which could include dietary intake of iodine may exert change in thyroid physiology, however, as this study was conducted within the United States, it is possible that the role of traditional foods may be different than if this study was conducted in populations residing in their countries of ethnic origin.

Thyroid antibodies are reported to differ by ethnicity and these may also influence the epidemiology of hypothyroidism. The incidence and prevalence of unsuspected spontaneous hypothyroidism is increased eightfold with the presence of either an elevated TSH level or

positive antibodies alone [203]. The NHANES III study found that Blacks were likely to have lower levels of thyroid antibodies compared with Whites (4.5% vs. 12.3%) [39]. After adjustment for thyroid antibodies, region, socio-economic status, and urban versus rural residence, the TSH levels in Whites remained higher than Blacks detecting no other association other than ethnicity [39]. Similar findings were found in a study in Brazil, where Blacks had the lowest prevalence of hypothyroidism (6.9%) compared with Mulatto (8.0%) and White (16.7%) [218]. After adjustment for age, income, smoking and the presence of anti-TPO, Black and Mulatto people still had a lower prevalence of hypothyroidism. Differences in thyroid antibody levels by ethnicity are not known in New Zealand.

Urinary iodine levels were similar between ethnicities in the NHANES III study [39]. This indicates that significant dietary differences between ethnicities in this study were less likely. Studies of twins in the United Kingdom and Denmark which have evaluated the role of genetics in thyroid function variability show that genetic and hereditary factors influence thyroid hormone, TSH values and the hypothalamic-pituitary-axis set-point [219, 220]. The relationship between ethnicity and hypothalamic-pituitary-axis set-points is yet to be determined.

ENVIRONMENT

While factors such as family history, autoimmune disease, age, gender and ethnicity have been cited as contributing factors in developing hypothyroidism, environmental factors such as diet and smoking and seasonal variation have been studied for their impact on thyroid dysfunction epidemiology. Effects of radiation and the role of medication will also be discussed.

Diet has been discussed previously in this chapter with relation to iodine consumption. Goitrogens will be discussed briefly here but effects on thyroid function are rare in New Zealand and not commonly associated with hypothyroidism. Goitrogens act by inhibiting thyroid hormone synthesis similar to thiourea medications such as propylthiouracil or carbimazole [3]. Goitrogens have been found in drinking supplies, the milk of cows who have eaten a certain green fodder, and in brassica vegetables in developing countries [5]. Effects of goitrogens have not often been seen in New Zealand except for the infrequent import of tainted soy milk [221].

The role of selenium has been studied in relation to thyroid function [222-224]. Selenium is required in the peripheral conversion of thyroxine (T_4) to the active form 3,3',5-triiodothyronine (T_3). The relationship between selenium and iodine in New Zealand have been studied especially as this country's population have relatively low intakes of both trace elements [222]. Changes in dietary patterns and in selenium concentrations in some foods have led to the blood selenium of New Zealanders to be increased in recent years [180]. Even with increasing dietary selenium intake, evidence suggests that selenium intake is insufficient for maximal activity of selenoproteins [222]. The evidence for the influence of selenium on thyroid function is not as strong as that for iodine, although there are indications that severe deficiency may affect thyroid function [225].

Adverse consequences of selenium deficiency have been explained more fully since the recognition of the important role of selenoproteins in metabolism [224]. Two recognised human selenium-deficiency diseases, Keshan disease and Kashin-Beck disease, are found mainly in China, where selenium intake is less than 20 mcg/day resulting in these conditions. Physiological requirements for optimal deiodinase activity requires 30-40 mcg/day and for enzyme activity (glutathione peroxidase) 50-60 mcg/day is needed [222]. While no established cut-off value exists for plasma selenium levels to identify 'deficiency', an arbitrary cut-off value based on a level for maximal selenoprotein activities has been used in the past [222, 226, 227]; however, this level varies with different selenoproteins and other factors.

A double-blind placebo controlled study in the United Kingdom, set up as a pilot to a larger study 'Prevention of Cancer by Intervention with Selenium (PRECISE)', examined whether low selenium intake contributed to the development of marginal hypothyroidism in elderly subjects [228]. A total of 501 euthyroid subjects aged 60-74 years of age were recruited and randomly given 100, 200 or 300 mcg Se/day. Euthyroid subjects were deemed to reduce 'noise' and give a better chance of evaluating modification in T_3: T_4 as a result of supplementation. This study reported no difference between populations with marginal hypothyroidism when compared with controls [228]. Having excluded patients with TSH levels outside the reference intervals, this study was unable to establish whether selenium would have a clinical benefit on individuals with subclinical hypothyroidism as has been reported in other studies [227, 229]. In addition, the study population in the United Kingdom study, despite being larger than other selenium studies and having a longer follow-up period, had a higher

selenium level (91 mcg/L) than the general population for that age group in the United Kingdom (79 mcg/L) [228].

Recent population-based studies carried out in New Zealand have shown no clear direction in TSH levels following selenium supplementation as the number of participants with subclinical hypothyroidism was small [230]. More powered studies in SCH subjects with low selenium intakes will have the potential to identify whether increasing dietary selenium will have a positive impact on mild thyroid failure. As yet, the role of selenium supplementation in thyroid function has not been determined.

SMOKING

Several studies have highlighted the role of cigarette smoking in relation to thyroid physiology [51, 52, 54, 201, 231-235]. A low prevalence of hypothyroidism and lower levels of TSH has been reported in smokers compared with non-smokers [201, 232, 234]. Additionally, there are studies to indicate that smokers have reduced levels of thyroid autoantibodies [51, 52].

A study in a random sample of 1154 middle-aged and elderly residents in Gothenburg, Sweden aimed to define reference intervals for thyroid function tests for the purposes of an integrated care programme for long-term thyroid follow-up [201]. Data were analysed in relation to age and smoking status. TSH levels were significantly lower in smokers than non-smokers in subjects less than 60 years of age. These findings were replicated in the NHANES III study which showed that for every 10 ng/mL of serum cotinine, a biomarker for exposure to tobacco smoke, the odds of having elevated TSH levels were reduced by 1.4% [39, 51].

Serum was obtained from 237 healthy, non-pregnant women between aged 18-44 years in a United States study [235]. Nearly 60% of participants were White and 56% had a college or professional school qualification. Eighty-three percent were within normal BMI limits. Subjects were classified as active smokers, passive smokers or non-smokers. While no difference was detected in TSH levels, significant differences were found in thyroid hormone levels by smoking classification although all remained within the reference intervals [235]. In the Gothenburg study, as described above, thyroid hormones were no different between smokers versus non-smokers or by age groups in a study of older women [201].

Smoking has also been associated with lower levels of thyroid autoantibodies in smokers compared with non-smokers in several studies [51, 52, 232]. A study of 521 euthyroid women

without detectable thyroid antibodies and who had a first degree relative with autoimmune thyroid disease were recruited to evaluate environmental factors contributing to the occurrence of thyroid antibodies [232]. The 5-year probability of converting to anti-TPO and/or anti-Tg was 20.1% although only TSH contributed to the risk of seroconversion. In a 13-yr longitudinal study, smoking was not associated with a reduction in risk of hypothyroidism [183].

Cigarette smoking may alter thyroid autoimmunity which in turn may affect iodide transportation and organification causing an inhibitory effect on the thyroid [235]. Additionally, women may have smoke-induced decreases in serum oestrogens which effect levels of TBG and FT_4. The effect of a decrease in TBG would decrease T_4 binding and increase the amount of FT_4, thus resulting in a small but statistically significant reduction in TSH [235].

The associations between smoking, thyroid autoantibodies and hypothyroidism are unclear. Some studies have demonstrated a relationship between smoking and reduced antibodies, while other studies have indicated an association between smoking and reduced TSH. However, anti-TPO antibody is a marker for hypothyroidism and not a cause of hypothyroidism. It is a leap of faith to imply that smoking reduces thyroid antibodies as well as TSH and therefore reduces hypothyroidism. These relationships may be biased by the survivor effect in longitudinal studies. Long-term effects of smoking on thyroid function are outweighed by the effects of smoking on the circulatory system. Tobacco smoking is estimated to kill between 4300 and 4700 New Zealanders each year [236]. A report on mortality from smoking in developed countries found that half of these deaths are in 35-69 year olds [237]. There is good evidence for the impact on smoking on cardiovascular health [20].

SEASONALITY

Seasonal variation in morbidity and mortality relating to thyroid dysfunction have been investigated [238]. There is evidence for increased thyroid hormone requirements in winter. Although no seasonal variation has been reported to affect TSH, thyroid volume could be demonstrated to increase with 23% higher volume in the winter than in the summer [48]. Thyroid hormone levels have been studied in two cohorts who spent summer (n=100) and/or winter (n=85) at McMurdo in Antarctica [239]. This found that higher thyroid hormone levels were present in colder temperatures and/or higher altitude. This suggests lower thyroid hormone levels in summer months; however, the lack of seasonal variation of TSH may indicate another mechanism by which the hypothalamic-pituitary-axis may adapt to the

changing circumstances. A study on Siberian hamsters showed that the availability of thyroid hormone within the hypothalamus was a key factor of seasonal changes [62].

Several studies have reported seasonal variation in cholesterol levels [240]. A study of 517 healthy volunteers was commenced for a 12-month period [240]. Results showed a peak in cholesterol levels in winter and a trough in summer. The authors report that seasonal changes in plasma volume were found to explain a sizeable proportion of the observed variation in cholesterol levels. This variation was greatest in women and in individuals with existing hypercholesterolaemia, which were linked with increases in body temperature and physical activity. In addition, a study assessing high associations between cardiovascular disease and certain cancers with winter months reported correlations with seasonal changes in diet [241].

The clinical picture for general practitioners does not appear to change in relation to the management of individuals as a result of seasonal variation in thyroid hormones. This is mostly due to existing internal compensatory mechanisms as identified in the Antarctic study [239]. Other environmental stimuli, such as exercise, have been shown to have a positive effect on the prevention of coronary health disease [20, 242] as well as improving endothelial-dependent arterial dilation in patients with subclinical thyroid disease [243]. Seasonality, therefore, although an environmental factor in thyroid physiology, does not play a major role in the diagnosis or management of hypothyroidism.

OTHER FACTORS ASSOCIATED WITH HYPOTHYROIDISM

EXPOSURE TO RADIATION

Radiation to the neck area is considered a known risk factor for the development of thyroid dysfunction. Excessive doses of radiation such as those from Chernobyl and Mururoa have contributed to long-term consequences of thyroid cancer which are well documented. [244, 245]. Radioactive iodine, in the form of sodium iodide (I^{131}), is usually administered to treat hyperthyroidism and thyroid malignancy. Iatrogenic hypothyroidism is an inevitable consequence of radioactive iodine therapy. Hypothyroidism occurs in approximately 80% of patients who have been adequately treated for thyrotoxicosis within 6-12 months from treatment [117]. It has been reported that physicians in North America recommend a dose of I^{131} that will render the patient hypothyroid, so that the need for thyroid replacement therapy is predictable [7, 246].

MEDICINES

Drugs that can cause hypothyroidism do so by decreasing the secretion of thyroid hormone or by decreasing TSH secretion. Medication such as carbimazole and propylthiouracil are prescribed for the purpose of inhibiting thyroid hormone production in patients with hyperthyroidism. Other commonly used drugs are lithium carbonate and iodine-containing medications such as amiodarone.

Long-term treatment with lithium inhibits thyroid hormone secretion resulting in TSH stimulation of the thyroid [7, 247]. The prevalence of goitre has been reported in up to 60% of long-term lithium users and of these as many as 23% will develop hypothyroidism [248 247]. Lithium users with thyroid antibodies are reported to have an increased susceptibility to hypothyroidism, which are said to increase the sensitivity of the thyroid gland to the thyroid actions of lithium [248].

Amiodarone is used for prophylaxis and treatment of many cardiac rhythm disturbances [249]. It is similar in structure to thyroid hormones and contains 39% iodine by weight: a 100 mg tablet contains 250 times the recommended daily requirement of iodine [250]. Long-term treatment with amiodarone increases plasma and urinary iodide levels 40-fold [251]. Amiodarone can cause either amiodarone-induced thyrotoxicosis or more-commonly amiodarone-induced hypothyroidism [250, 252, 253]. Risk factors for the development of amiodarone-induced hypothyroidism include iodine intake, Hashimoto's thyroiditis, an elevated baseline TSH, and dose and duration of amiodarone treatment [250]. In a study of patients in an area of moderately low iodine intake, 6% developed amiodarone-induced hypothyroidism compared with an area of sufficient iodine intake in which 22% developed amiodarone-induced hypothyroidism [253, 254].

Cytokines such as interferon-alpha and interleukin-2 cause hypothyroidism as a side effect. Risk factors include being female, long duration of treatment, older age and pre-existing thyroid antibodies [7]. Some hypothyroidism is transient during the administration of the cytokine medication although pooled data indicates that 30-44% may develop persistent hypothyroidism [255].

MEASURING THYROID ACTION

TESTS TO DETERMINE THYROID DYSFUNCTION AND CAUSE

Whilst the classical signs and symptoms of both hyperthyroidism and hypothyroidism are well known, the features of early hypothyroidism are subtle and reliance on signs and symptoms will mean many cases are missed [256]. Consequently general practitioners have a low threshold for ordering thyroid function tests in adult patients. It is important that thyroid function is measured correctly and appropriately.

The advance in diagnostic procedures has led to greater specificity and sensitivity of tests which enhances the likelihood of early detection of thyroid dysfunction; however, this may lead to results obscured by coincidental non-thyroidal illness [69]. Therefore, it is imperative that the rationale for testing is clear. In the absence of hypothalamic pituitary disease, illness, drugs, given that pituitary and hypothalamic causes of thyroid dysfunction are rare in comparison to primary hypothyroidism, and that TSH has a high negative predictive value, TSH is a reliable indicator of thyroid function, a first-line approach for measuring TSH alone is acceptable [30, 69].

Reducing levels of thyroid hormone results in increased synthesis of TSH by the pituitary gland [114]. While a decrease in FT_4 may remain within the normal reference intervals, a concurrent increase in TSH, due to the highly sensitive pituitary thyrotroph for monitoring circulating thyroid hormone, raises TSH above normal reference intervals [21]. The log-linear relationship between TSH and T_4 is such that a 2-fold change in FT_4 represents a 100-fold change in TSH [69]. Thyroid hormone levels are required to confirm a diagnosis of thyroid dysfunction and to rule out secondary causes of thyroid dysfunction caused by pituitary or hypothalamic abnormalities [10].

With malfunction of the hypothalamic-pituitary axis, the pituitary may continue to produce TSH which may have reduced bioactivity but which retains immunoactivity [114]. TRH is able to modify the sialic acid, sulfate, and carbohydrate components of TSH; the clinical observation in some patients with central hypothyroidism is of a slightly elevated basal serum TSH level from a pituitary gland that secretes TSH with reduced biological activity [257]. This is of greatest importance in conditions affecting the pituitary gland, such as hypopituitarism and central hypothyroidism, where measuring TSH alone may give an erroneous impression of normal thyroid function. In primary care, it is essential, in the presence or suspicion of a

pituitary or hypothalamic condition, that TSH is not used as the sole measure of thyroid function [69].

Understanding thyroid hormone transport and metabolism is important in order to appreciate changes, which may occur when measuring thyroid function, brought about by illness or certain medications [38]. About 75% of total circulating T_4 is carried on thyroid binding globulin (TBG), a carrier protein [38]. A further 10-15% is attached to transthyretin (formerly known as prealbumin) and 10-15% is bound to albumin. The lipoproteins transport a minor fraction of T_4 and T_3 [37, 38]. Approximately 0.02% to 0.03% of T_4 are unbound (FT_4). Total hormone concentrations (bound + FT_4) can vary due to causes independent of thyroid status [38].

Concentrations of thyroid hormone bound to carrier proteins maintain a regulatory influence on tissue function by adjusting to maintain pre-existing concentrations of free hormone set by the feedback relationship with TSH [3, 38, 114]. Only the unbound hormone is biologically available to tissues and therefore homeostatic mechanisms that regulate the hypothalamic-pituitary-axis are directed towards maintenance of normal concentrations of unbound thyroid hormones [114]. Total thyroid hormone concentrations (bound + free hormone levels) are not a reliable measure of thyroid function as alterations to the amount bound to carrier proteins may lead to errors in diagnosis and management [2].

Carrier protein abnormalities affect the total thyroid hormone concentrations [114]. Certain drugs can compete with iodothyronine for binding to thyroid binding proteins thus changing the fraction of unbound thyroxine (free T_4) in serum. In addition, certain drugs can displace T_4 from carrier protein binding (Table 4).

TABLE 4: DRUGS THAT HAVE EFFECTS ON CARRIER PROTEINS IN HUMANS [38]

Increases TBG	Decreases TBG	Displaces T_4 from TBG
Oestrogens, Tamoxifen, Heroin, Methadone, 5-Fluoruracil, Perphenazine, Clofibrate, Mitotane	Thyroid hormones, Androgens, anabolic steroids, Glucocorticoids, L-Asparaginase, Interleukin-6	Salicylates, Frusemide, Fenclofenac, Mefenamic acid, Flufenamic acid, Diclofenac, Diflunisal, Phenytoin, Carbamazepine
Increases transthyretin	**Decreases transthyretin**	
Androgens, Glucocorticoids	Oestrogens	

In response to these changes, the hypothalamic-pituitary axis re-adjusts to regulate iodothyronine levels in serum resulting in lower levels of total iodothyronine [3]. This compensatory adjustment can also occur in starvation or disease states allowing maintenance of adequate free T_4 concentrations at the euthyroid level [3]. Direct measurement of free hormones circumvents the effects of concentration or binding affinity to the carrier proteins and is preferred as it corresponds to the biologically available hormone pool [3, 114].

It is necessary that FT_4 levels are obtained to confirm thyroid dysfunction in persons with raised TSH. On occasion, both FT_4 and FT_3 are obtained; however, FT_3 measurements are not considered a reliable indicator of hypothyroidism [3], due to circulating FT_3 levels which have been found to be normal in 25% of patients with hypothyroidism, reflecting an adaptive response [114]. FT_4 and FT_3 assays are often used in commercial practice; however, do not always reflect the actual level of FT_4 or FT_3 measured by equilibrium dialysis or other more precise methodology [258].

TSH REFERENCE RANGE

The establishment of a reference range for TSH is essential in enabling useful understanding of normal thyroid function and suggestive absence of disease, as well as for monitoring thyroid hormone therapy [259]. The measurement of TSH is the most sensitive test of thyroid function [260]. The second- and third-generation tests of TSH measurement have seen the identification of pre-clinical disease such as subclinical hypothyroidism (SCH), also called biochemical hypothyroidism and mild thyroid failure, due to signs of failing thyroid function being identified before symptoms are apparent [38].

Dramatic improvements have been made in assays for TSH over the last four decades [69, 261]. Initial radioimmunoassay methods were unable to determine lower reference limits and therefore could not detect differences between normal and reduced values of TSH [261]. In addition, tests were unable to determine upper reference intervals - these were set at 10 mIU/L - due to the inability to always detect TSH in some euthyroid individuals; the clinical utility of the test was in diagnosing primary hypothyroidism [69].

The development of immunoradiometric assays methods enabled tighter refinement of reference intervals. The upper reference interval has reduced from 10 mIU/L to 4.5 mIU/L since around 1980. In the past decade automated systems have been launched to maximise sensitivity [262].

Currently there is no one universal reference interval for TSH assays. Laboratory TSH assays vary widely due to the use of monoclonal antibodies that differ in specificity and may measure different TSH isoforms [64 263]. This makes the establishment of a universal reference range for TSH difficult and therefore TSH is mostly referenced according to the manufacturer's clinical assay [64, 264]. In addition, the suitability and recruitment of a high number of recruits to match selection and clinical characterisation can be time-consuming, and expensive [264].

The inter-assay coefficient of variance is calculated to yield concentrations close to the lowest reference limit. The detection limit is defined as the concentration 2 standard deviations above the dose response at zero dosage (zero concentration of analyte) [262, 265]. This establishes a precise measure to discriminate between the lower limit of the reference range i.e. improved sensitivity of the assay.

TSH reference intervals are derived from log-transformed arithmetic values taken from a large cohort of individuals. The raw TSH result does not reflect a Gaussian distribution, therefore log-transformation allows derivations to a normal distribution curve (mean value ±2 standard deviations) [259]. The National Academy of Clinical Biochemistry (NACB) guidelines for establishing TSH reference intervals [264, 266] stipulate that serum be obtained from euthyroid (normal functioning thyroid) individuals to establish the 95% confidence limits from log-transformed values of at least 120 individuals who meet the following criteria:

- No detectable thyroid auto antibodies, anti-TPO or anti-Tg (measured by sensitive immunoassay)
- No personal or family history of thyroid dysfunction
- No visible or palpable goitre
- No medications (except oestrogen).

In order to select individuals for a reference population, the key criterion is to ensure an unbiased healthy population [267]. A homogenous reference group in a well-defined state of health aims to reduce the inter-individual variability. In addition, the NACB guidelines establish interdependency between TSH concentrations and thyroid antibody levels [46].

The Busselton study established reference intervals for TSH, FT_4, anti-TPO and anti-Tg by examining the blood results of 2026 ambulatory adults residing in the Busselton community in Western Australia who had previously participated in a cross-sectional health survey in

1981 [46]. The reference interval for TSH was found to be 0.4 – 4.0 mIU/L in the euthyroid population. The study was further examined on standardised statistical approaches and guidelines recommended by NACB as described above. Using these methods, a total of 166 men aged less than 30 fitted the criteria. Euthyroid men must have serum TSH concentrations between 0.5 – 2 mIU/L and be under 30 years of age to meet the criteria to establish reference intervals for thyroid antibodies. In addition, participants are required to have no family history of thyroid or non-thyroid autoimmune disease [264]. The use of such complex selection criteria may not be necessary to establish reference intervals for TSH just as the need for thyroid ultrasonography to exclude thyroid nodules and enlargement may not be required in reference studies for thyroid hormones. The TSH reference interval derived from the Busselton participants who fitted the NACB criteria gave a TSH range of 0.6 – 3.4 mIU/L. Data were not verified for self-reported family history of thyroid disease or for the presence of goitre in individuals [46]. However, a 20-year follow-up of the Whickham study found that the presence of goitre or a positive family history of any form of thyroid disease was not associated with an increased risk of developing hypothyroidism [79], suggesting that these characteristics will not affect the true population reference range.

In the NHANES III study, 13,344 people made up a purposively-selected reference population [39]. The reference population came from within a pre-defined disease-free population who were not pregnant, taking oestrogen or androgen, no detectable thyroid antibodies, and without laboratory evidence of hypothyroidism or hyperthyroidism. The findings demonstrated a TSH reference interval of 0.45 to 4.12 mIU/L. Despite differences in statistical approaches between the Busselton [46] and NHANES III [39] studies, results were similar to those found using NACB guidelines.

A population of 1488 individuals was selected from a previously iodine-deficient area to take part in a study to establish reference intervals for thyroid function tests [268]. Participants were aged 20-79 and excluded subjects with known thyroid disease and as yet unknown thyroid disorders, such as goitre, thyroid nodules, hypoechogenicity and anti-TPO seropositivity. Reference intervals for TSH were found not to be comparable to results established elsewhere, that is, from the NHANES III survey [39] and suggest this is due to prior iodine sufficiency in other countries [268].

Despite the issues around transferability further considerations must be discussed in relation to statistical and epidemiological differences relating to TSH assays, for instance, will

lowering the upper TSH reference interval make a difference to treatment or outcome [66, 269]. There remains confusion around nomenclature pertaining to the terms 'reference intervals' and 'reference ranges' in relation to TSH [259]. As described above, reference intervals are statistical concepts derived from 95% limits of log-transformed arithmetic TSH values to produce a Gaussian distribution of test results from a supposed large cohort of individuals without known disease. The distribution curve may be skewed dependent on various factors such as age of individuals, unrecognised underlying thyroid disease in the reference population and the unknown quantity of individual thyroid hormone set points within populations [13, 270]. In addition, the use of different isoforms and the presence of TSH fragments and heterophilic antibodies may have small effects on overall findings [64, 270]. These differences make it difficult to establish a universal reference range. As a result, reference intervals are broad to encompass individual variation [259]. The reference range, however, is not based on statistical considerations but on the cut-off at which the TSH value is not associated with adverse outcomes. These decisions impact on the management of hypothyroidism, especially for patients with thyroid function tests within the subclinical range.

It has been reported that there is a positive relationship between thyroid antibodies and TSH. The exclusion of thyroid antibody positivity within reference samples has allowed a universal reference interval for men and women [271]. To enable utilisation of TSH results independent of thyroid antibody status, a study of 1007 Japanese individuals was carried out to evaluate reference intervals using different outlier tests [272]. The study found that the conventional outliner rejection test, which rejected values ±3 standard deviations, gave results nearly identical to testing all subjects irrespective of antibody status. Utilising the conventional outlier rejection test was found to be convenient and appropriate in providing reference intervals for TSH and FT_4 without regard to thyroid antibodies using large samples [272]. The statistical method for establishing thyroid function test results has been questioned for being two-dimensional and failing to recognise that the bivariate distributions of TSH and FT_4 are mutually interdependent [273]. The argument centres around 95% of the population distributed within each of the reference intervals. The use of both TSH and FT_4, it is interpreted, gives 95% of 95% i.e. 90.25% of all data points, therefore leaving 9.95% of the population outside the normal thyroid function reference intervals. Using this rationale of over-estimation, suggests that 4.75% of the population would be classified as subclinically hyper- or hypothyroid. In reality, the prevalence of subclinical thyroid disease is much higher. The Colorado study found a total of 9.4% of the population not on thyroid medication to be within

these subclinical categories, while the Whickham study found 7.5% of women and 2.8% of men with subclinical hypothyroidism [40, 43].

Established manufacturers may have their own systematic biases in establishing reference intervals, for example, Roche E170 used serum specimens from 870 blood donors between 18-60 years of age to inform adult reference intervals [274]. Blood donors tend to be employed and self-selected, thus a systematic bias is introduced through the healthy worker effect; however, this is in keeping with the NACB guidelines which encourage the use of only healthy individuals as described above. There needs to be an awareness that reference intervals for TSH are based on young, healthy populations; it is likely that the application of reference intervals from an unmatched population is a contributing factor in the increase in the prevalence of thyroid dysfunction with age and to the 2.5% with raised TSH who may be euthyroid outliers [87]. The transferability of reference intervals that have been derived from specific reference groups is explored further to identify variability in TSH and thyroid hormone findings within and between individuals in relation to age, gender and ethnicity.

BIOLOGIC VARIATION

For the majority of the population (95%) with 'normal' thyroid function, TSH is expected to fall between the upper and lower limits of the defined reference interval. Minimally abnormal values may represent a normal variant for an individual [2]. Many hormones are released in a periodic or cyclic fashion with levels varying through the day [2]. TSH serves as a useful physiological marker of thyroid hormone action [114].

TSH is released in a pulsatile manner and exhibits diurnal variation [114]. The nocturnal surge of TSH persists in patients with subclinical hypothyroidism but is not present in central hypothyroidism caused by hypothalamic or pituitary disease or in those who have non-thyroidal illness [69]. TSH has a relatively long plasma half-life of about 50mins; consequently, single measurements of TSH are adequate for assessing its circulating level [114].

It is difficult to correlate possible adverse effects at the tissue level based on TSH cut-off values due to individual set-points of the hypothalamic-pituitary axis [50]. The hypothalamic-pituitary axis is established by TSH following thyroid hormone feedback which negatively inhibits TRH and TSH production [114]. Inter-individual variation in the hypothalamic-pituitary axis set-points may be genetically determined, which might explain different symptoms, signs, and peripheral iodothyronine effects with the same hormonal pattern [64]. This suggests

that a test result may be abnormal for an individual while still falling within the laboratory-specified reference interval [13].

As described above, statistical reference intervals which are usually two standard deviations either side of the mean in disease-free individuals derive population reference intervals. There is some discussion in literature regarding the clinical relevance of statistically derived reference intervals in favour of epidemiological reference ranges. This refers to the level at which abnormal values are associated with adverse outcomes. Data are not often available for the epidemiological approach and therefore statistical approaches are more commonly used [13].

Arguments arise over the importance of individual variation in relation to aspect of age (young versus old age), weight (normal versus obese), smoking (non versus current), sample time (time of test), gender (male versus female; menopausal versus non-menopausal), and antibodies (present or absent) and this has previously been discussed. These all contribute to variations within and between individuals which have an effect on statistically-derived reference ranges as well as a theoretical effect on 5% of the population whose individual levels may fall outside of what is deemed 'normal'. In addition, the use of TSH in combination with FT_4 when assessing thyroid function has been deemed to increase the population with 'abnormal' results to 9.75% as a result of using 95% of 95% of the population when combining two tests with individual means and standard deviations [273].

Thyroid function tests taken repeatedly on the same people show a narrow range in which result vary, confirming that these variables regulate in humans around slightly different set-points [13, 275]. The variation in set-points of hypothalamic-pituitary axis may be tightened using stratification by age and sex, however this will not change reference intervals to any great extent [41]. However, no amount of statistical manipulation will overcome the issue of the impracticality of obtaining a large number of tests that are required to determine an individual set-point [50].

CALLS TO LOWER THE UPPER REFERENCE INTERVAL

Over the last two decade, the upper reference range for TSH has reduced from approximately 10 mIU/L to around 4-4.5 mIU/L. This reflects improvements in sensitivity and specificity of TSH assays, recognition that TSH values are log-distributed, and improvements in

autoantibody tests to pre-screen individuals for inclusion [64, 69]. The NACB has recommended reducing the upper reference range from 5.5 mIU/L to 4.1 mIU/L [266].

There has been considerable debate over whether the upper reference range for TSH should be lowered further. The Whickham study found that the potential future risk of hypothyroidism was greater in individuals with a TSH >2 mIU/L [79]. In addition, a TSH >4 mIU/L has been reported to increase the risk of cardiac disease [16].

There is a higher rate of thyroid antibodies in individuals with a TSH level between 3-4.5 mIU/L [64]. In a subsequent Busselton study report, which was a 13-year community longitudinal study with 1184 study subjects, the risk of subclinical hypothyroidism for women with positive thyroid antibodies was approximately 1% per year with a 0.2% per year risk of overt hypothyroidism when TSH was less than 2.5 mIU/L compared with a risk of 4% and 1% respectively when TSH was 2.5 - 4.0 mIU/L [183]. Further rationale for lowering the upper reference range of TSH is the greater risk of progression to hypothyroidism in ambulatory patients with a TSH ≥2.5 mIU/L [11, 79].

Many endocrinologists have rejected the call to reduce the upper reference limit for TSH. A critical analysis of reference group data from NHANES III showed that half of those who would fit into the NACB category of having a TSH between 2.5-4.0 mIU/L have thyroid disease by means of being thyroid autoantibody positive. However, most with thyroid disease in the form of anti-TPO have TSH levels < 2.5 mIU/L [276].

There has been a lack of a defined reference population for determining TSH reference intervals [277], as well as confusion between the upper limit of the reference range, the cut-off for subclinical hypothyroidism [65], and difference between normal ranges and reference intervals [259]. This confusion centres on the point at which statistical and epidemiological cut-offs differ and at which point TSH levels have a clinical impact on morbidity and mortality. Guidelines produced by The National Academy of Clinical Biochemistry [United States] [266]; The Associations for Clinical Biochemistry [United Kingdom], and British Thyroid Association [United Kingdom] [68]; The American Association of Clinical Endocrinologists [United States] [14, 31]; the American Thyroid Association [United States] [33] and The Endocrine Society [United States] all vary on a number of key points in relation to the reference groups, reference intervals, screening populations, and targets for case-finding.

The validity of reference intervals has been questioned suggesting inaccuracies in the sensitivity and specificity of the laboratory tests [264]. A study which assessed confounding factors that alter the limits of TSH reference intervals recruited 870 apparently healthy individuals found that just over one-half (52%) remained after excluding family history of thyroid disease, pathological thyroid ultrasonography results, and increased anti-TPO or anti-Tg [264]. Furthermore, the high prevalence of raised TSH in the general population suggests that the current upper limit of the population reference range may be skewed by the inclusion of persons with occult thyroid dysfunction and that tests to detect autoimmune thyroid antibodies are not yet sensitive enough [39].

The main impetus for lowering the upper reference range is based on epidemiological evidence that identifies a higher rate of disease in persons with TSH levels >2.5 mIU/L [39, 40, 79]. However, evidence of any clinical difference when comparing people with TSH levels between 2.5 and 4.5 mIU/L with a lower range TSH level of 0.4 – 2.5 mIU/L are likely to be marginal [12]. It can be argued that there is currently no clear evidence, in the form of randomised controlled trials, to support the lowering of the upper reference interval for short- or long-term benefit in patients [13, 46].

SYMPTOMS

The symptoms and signs of hypothyroidism are often non-specific leading to a reliance on thyroid function testing [278]. In addition, the onset of disease can be so subtle that common symptoms of hypothyroidism may go unnoticed [138]. In one study in general practice, 55% of thyroid function tests were initiated to investigate reported symptoms [279].

A cross-sectional study of seventy-six newly diagnosed subjects with overt hypothyroidism and 147 controls were recruited to determine the relationship between symptoms and biochemical disease [138]. Symptoms were assessed concurrently with thyroid function test using a 20-item questionnaire. Three symptoms were found in univariate analysis to differ significantly between cases and control subjects: hoarse voice, dry skin and muscle cramps. In multivariate analysis, hoarse voice and muscle cramps remained significant as well as puffier eyes and being constipated more often. Using likelihood ratios to evaluate the number of symptoms, patients with seven or more symptoms that had changed in the past year were more likely to have hypothyroidism. A positive correlation was found between the number of symptoms of hypothyroidism and the TSH concentration.

A symptom such as tiredness is often the rationale for testing for more serious underlying physical disease. However, one report ranks tiredness at 48 out of 119 in a list of most common problems managed in general practice [280]. Weight gain is another symptom linked to hypothyroidism. In the past, levo-thyroxine was given to increase metabolism to combat weight gain in euthyroid individuals [81, 281].

A randomised controlled trial was carried out in 25 patients with symptoms of hypothyroidism but with biochemically normal thyroid function to assess whether thyroxine made a difference to psychological and physical wellbeing [278]. This double-blind cross-over study found no benefit from thyroxine although more symptomatic patients gained benefit from placebo than did the controls.

A study of the effects of thyroxine on patients with subclinical hypothyroidism found that fewer patients reported tiredness, however, patients scores for symptom severity did not improve [279]. One suggested explanation of this was that the patients had adapted to their symptoms. The yield of hypothyroid patients from symptom-based testing in general practice has been reported to be low [282].

THE ROLE OF GENERAL PRACTITIONERS IN HYPOTHYROIDISM

Thyroid dysfunction is one of the more common endocrine conditions found in general practice [283].The vast majority of thyroid function tests are initiated by general practitioners [10]. A 2001 survey of general practitioners in New Zealand estimated that thyroid function tests were requested in 4.1% of patient visits [284]. It is evident from epidemiological studies that the burden of hypothyroidism is in the ageing population and is more prevalent in women than in men.

In general practice, women are seen on average at a rate of 1.3 times more than men [284]. In addition, the rate of general practice visits increases steadily from 45 years of age for men and women, with rate differences peaking in 55-64 year old women. Women are more likely to be offered thyroid function tests of which approximately 6-10% will be found to be abnormal [39, 43]. In 1999, nearly 900,000 TSH tests were performed in Scottish laboratories [285]. There is agreement that TSH is likely to be have been tested indiscriminately in patients with and without vague symptoms [286].

While there are 'how to' articles for diagnosing and managing hypothyroidism in general practice [287-289], and on interpreting laboratory tests [290-292] there are few articles that establish current practice. In particular, literature on the rationale for decision-making around testing and for managing abnormal results is scarce. One study in Italy sent questionnaires to 620 general practitioners to assess their attitudes to and knowledge of thyroid disease [293]. Despite a poor response rate (19.7%), 72% reported initiating thyroid function tests if they had clinical suspicion, followed by utilising them as part of a routine check (16%). The study found general practitioners knowledge of the therapeutic regime for thyroxine replacement therapy was incorrect with 35% believing that thyroxine replacement therapy should be taken at least 15 minutes after breakfast (the correct response cited is that it should be taken after fasting) [293]. Over half (54%) believed FT_4 to be more valuable than TSH when assessing thyroid function.

Education strategies for physicians have in the past met with mixed success [294, 295]. A study in Auckland to explore general practitioners ability to assess their own level of knowledge in specific areas, one of which was thyroid disease, reported that general practitioners could not accurately do so [75]. Further, results indicated a divergence between how well general practitioners believed they knew a topic compared with how they scored in disease-specific knowledge questionnaires. Not realising the need for further education may hamper efforts to improve general practitioner knowledge on thyroid disease.

The goal of treatment for hypothyroidism is to restore thyroid function to normal by replenishing thyroxine levels [296]. A study in West Midland, England, reported on 146 patients who were prescribed thyroxine [81]. Ninety-seven patients were recruited to have their TSH levels examined. There was a clear relationship between thyroxine dosage and median TSH level, with patients who were prescribed less than 100 mcg per day of thyroxine having higher TSH levels. Conversely low levels were found in those patients prescribed over 100 mcg per day. In total, 48% of treated patients with hypothyroidism had abnormal TSH levels. Other studies have reported similarly abnormal results in treated hypothyroid patients [43, 297]. In addition, as many as 92% of patients in one study had reported to have seen a general practitioner in the previous 12 months [43]. The use of thyroxine for non-thyroid indications has also been reported. A study of thyroxine prescribing in one community in the United States reported many patients prescribed thyroxine for non-thyroid indications such as obesity and fatigue [298]. This may add to the failure of general practitioners to respond to changes in TSH.

In 2001, a New Zealand general practice study (NatMedCa) reported thyroxine to be the third most common endocrine treatment prescribed after corticosteroids and oestrogen and progestin hormone replacement therapy (HRT) preparations [284]. This prescribing pattern is likely to have changed since a 2002 report demonstrated that overall health risks exceeded benefits when using HRT consisting of oestrogen plus progestin in healthy post-menopausal women [299]. There are no recent general practice surveys in New Zealand that examining recent prescribing patterns of endocrine preparations.

The Best Practice Advocacy Centre (BPACnz) is an independent organisation in New Zealand which identifies healthcare interventions that meet patients' needs [300]. As part of their function, they develop best practice guidelines based on evidence and cost-effectiveness that are suitable for the New Zealand context. In October 2005, BPACnz published best practice guidelines for investigating thyroid function [30]. This promoted TSH as a first-line strategy, stating that improvements in the past 10-15 years have meant TSH is now the preferred test over FT_4.

Despite the availability of guidelines, a New Zealand study determining general practitioners use and perceived usefulness of clinical guidelines found that their use was dependent on the interest of the general practitioner [301]. They found lipid guidelines were scored as most used and useful by a high proportion of clinicians, while dysmenorrhoea guidelines scored better with female general practitioners. Additionally, they support the growing evidence that the publication of guidelines does not necessarily promote change.

The New Zealand BPACnz guidelines for investigating thyroid function are inadequately substantiation, with 12 references and no reported grading of evidence [30]. There is a heavy reliance on the few studies cited. Substantive work has been done in the United States where there are several contributions to thyroid guidelines [14, 32-34, 266, 302, 303]. All the guidelines vary to some degree but a joint consensus statement to address these issues found that conclusive evidence was lacking in three areas: evidence for screening of SCH, routine screening for SCH in women who are pregnant or planning pregnancy, and the treatment of patients with SCH whose TSH levels are between 5-10 mIU/L [31]. The latter is of concern to general practitioners who are often faced with this scenario. One study to determine practice compliance with guidelines found that general practitioners often fail to adequately monitor patients with SCH and many were inappropriately prescribing life-long thyroxine therapy [304]. Another study suggests laboratory-generated cascade testing for anti-TPO as an integral part

of the investigation of SCH, complete with appropriate intervention and advice [305]. The authors report that offering appropriate advice leads to better compliance with guidelines.

DISCUSSION

This chapter begins by giving a brief introduction into the complexities that impact on the diagnosis and management of hypothyroidism. The anatomy and physiology of the thyroid gland is described as well as the metabolism of the thyroid hormones. Hypothyroidism relates to having a TSH result above the reference interval for normal and having a low free T_4 result. Individuals with SCH also have a raised TSH result but free T_4 is within the normal reference interval. A number of international studies describe the prevalence of hypothyroidism as between 1% to 10.3%. The wide range of disease depends on the definition; some data includes individuals with subclinical disease.

TSH investigations are commonly initiated with many tests requested from general practitioners. The rationale and debate of a first-line TSH strategy has been discussed. Arguments centre on the theoretical statistical nuances of reference intervals and cut-offs. The Whickham study cites potential future risk of hypothyroidism is greater in individuals with a TSH >2 mIU/L [79]; well within the reference interval for TSH. As a result, there are calls to lower the upper reference interval of TSH; however, there are many detractors who do not believe this to be necessary. Debate on upper reference interval is premature in light of a lack of evidence on how to manage subclinical hypothyroidism.

Apart from iatrogenic causes of primary hypothyroidism and rare disease, the aetiology of hypothyroidism is most often through lymphocytic infiltration of the thyroid gland; however how this is acquired is yet to be determined. Thyroid autoantibodies act as a marker for thyroid disease but these are not believed to be causative [184]. The role of autoantibodies, particularly anti-TPO, in predicting hypothyroidism is still under investigation.

The burden of hypothyroidism lies mostly with women and in the ageing population; yet, numerous other individual and environmental factors also impact on thyroid function, theoretically making population reference intervals less meaningful. Considerations for individual variation make the task of diagnosing hypothyroidism more difficult. Additionally, an ageing population with a higher prevalence of hypothyroidism will increase the workload on general practitioners.

STRUCTURE OF THIS THESIS AND AUTHOR'S CONTRIBUTION

Chapter 1 is a literature review outlining concepts around thyroid function and dysfunction including current controversies. This chapter includes the epidemiology of hypothyroidism, thyroid function testing, and the anatomy and physiology of the thyroid gland and system.

Chapter 2 illustrates the studies undertaken locally which establish the epidemiology of thyroid dysfunction in Hamilton, New Zealand, reviews the use of thyroid function tests by general practitioners in Hamilton, explores the decision-making around requests for thyroid function tests with general practitioners in Waikato and reviews the management of raised TSH from a laboratory data set. Each study is described individually, including design, methodology and results. A discussion bringing together the findings of all these studies concludes this chapter.

Chapters 3, 4 and 5 developed from gaps in evidence identified from work carried out in Chapter 2 examines the journey of patients in diagnosing and testing for central hypothyroidism, cardiovascular event survival in patients with hypothyroidism over a period of time, and the benefit of thyroxine in patients with subclinical hypothyroidism (identified within a defined TSH range of 5-10 mIU/L). Having this knowledge would impart substantial evidence for general practitioners to make enhanced informed choices.

Chapter 6 concludes the thesis by summarising the overall findings with recommendations for general practice.

AUTHOR'S CONTRIBUTION

The author of this thesis was involved with the following aspects of this study:

- Writing of research proposal and ethics application for all study projects
- Involvement and input into study design and methodology for all projects
- Data analyses: collection of data, coding, analysing and reporting for all projects.
- Drafting of all peer-reviewed publications [306-309] and abstracts [310-315].
- Writing all chapters of this thesis.

- Statistics for survival analysis paper: design, methodology, data analysis, interpretation, and write up. Data cleaning was performed by Dr Grace Joshy, biostatistician.

PUBLICATIONS

Gibbons, V, Conaglen JV, Lawrenson R (2010) A raised thyroid stimulating hormone result – a 12-month follow-up study in General Practice. Journal of Primary Health Care. 2 (1): 29-34.

Gibbons V. (2009) Should we treat patients with subclinical hypothyroidism? Journal of Primary Health Care; 1(3): 237.

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Gibbons V, Conaglen JV, Lillis S, Naras V, Lawrenson R (2008). Epidemiology of thyroid disease in Hamilton (New Zealand) general practice. Australian and New Zealand Journal of Public Health 32 (5) 421-423

Lim S, Gibbons V, Conaglen JV (2007). Assessment and management of thyroid nodules in general practice. NZFP 34 (4) 274-277 August

PAPERS IN THE PIPELINE

Gibbons V, Sleigh P, Yarndley T, Lawrenson R, Conaglen JV. (in draft) A journey through central hypothyroidism: completing the fuzzy picture.

Gibbons V, Conaglen JV, Lawrenson R (in draft) The effectiveness of thyroxine in preventing cardiovascular disease in patients with subclinical hypothyroidism: A systematic review.

Gibbons V, Conaglen JV, Lawrenson R (in draft) Long-term outcomes of patients with raised thyroid stimulating hormone results: an analysis of cardiovascular morbidity and mortality over a decade (1997 – 2006).

CHAPTER 2 - THE EPIDEMIOLOGY AND MANAGEMENT OF THYROID DISEASE IN HAMILTON, NEW ZEALAND GENERAL PRACTICE

There is a lack of recent studies in New Zealand establishing the prevalence of hypothyroidism and it is unknown whether the results vary from studies carried out in other countries. The last published study focussing on thyroid disease in Waikato, New Zealand, the area in which the studies in this thesis take place, was from six decades ago (between 1944 – 1953) in which diagnosis was confirmed through pathological classifications following surgery for medical management [316]. At this time, the clinical picture differed; with goitre from iodine deficiency being common in New Zealand, and surgical intervention being prioritized over anti-thyroid medication. Other thyroid studies from New Zealand have focused on the epidemiology of hyperthyroidism [317] and thyroid function test abnormalities in patients with atrial fibrillation and flutter [318]. The New Zealand Ministry of Health survey on the health of the population identifies 3.6% of the adult population with a self-reported thyroid conditions [209].

Factors that impact on the relationship between thyroid dysfunction epidemiology and the burden on general practice include the levels of testing (numbers of laboratory requests) [8], improvements in laboratory assays which refine classifications of thyroid disease [319] and best practice guidelines recommending the use of thyroid stimulating hormone (TSH) assays as the first-line request for investigating thyroid dysfunction [30]. One feature of increased testing for investigating overt hypothyroidism is that it identifies a group of patients with subclinical hypothyroidism.

Overt thyroid dysfunction is reported to be common within the community[46], with a wide variation in the reported incidence and prevalence [43, 151]. Prevalence estimates of hypothyroidism range from 1% to 10.3%[6, 41, 43, 46, 47, 151, 152] and hyperthyroidism from 0.5% to 2.5%[6, 40, 41, 43, 46, 47, 79]. Prevalence of thyroid disease is strongly influenced by dietary iodine.

Iodine deficiency affects over one billion people worldwide,[155] and was common in New Zealand in the late nineteenth and early twentieth century. However, since the introduction of iodised table salt and the use of iodophor detergents in the dairy industry,[163] adequate levels of iodine intake have been reported [142]. Recent reports indicate that the current iodine status of New Zealanders is declining [164, 167, 172, 179, 180, 320]. Concern has been raised that without intervention, iodine deficiency will again cause significant morbidity [163, 164, 167, 172].

It is unclear whether prevalence data from the international literature can be generalised to the New Zealand population, due to differences in dietary iodine intake, population structure, ethnic variations, general practitioners' testing habits and variation in laboratory indices for interpreting thyroid function. The declining iodine status of New Zealanders, and tighter recommendations for testing [30], will need baseline data if changes in either disease incidence or outcomes of any public health strategies to curb declining iodine intake are to be measured.

Due to limited data on the prevalence and nature of thyroid dysfunction in the New Zealand community we sought to establish the current burden of thyroid dysfunction on general practice. Burden is defined in terms of the burden of responsibility - the burden of not having clear evidence of the epidemiology and management of hypothyroidism in New Zealand to make informed decisions and for patients to make informed choices. A cross-sectional study was commenced using a representative population from two large general practices in Hamilton City, New Zealand. This enabled comparisons between New Zealand and international data on the epidemiology of hypothyroidism.

The cross-sectional study was followed by a succession of related studies to further establish the burden of hypothyroidism in general practice. First, a retrospective study using laboratory data of thyroid function requests examined the numbers of tests and rate of testing by general practitioners. TSH is one of the more common biochemistry tests requested by general practitioners, with over 850,000 assays being ordered in New Zealand each year [8]. Initiatives had been developed in order that general practitioners be accountable for their use of thyroid function tests as part of the New Zealand Ministry of Health Primary Health Organisation Performance Management Programme [163]. This identified eight clinical indicators, of which the investigation of thyroid dysfunction (by laboratory tests) was included as a Phase 1 indicator of this programme. This proposed that the ratio of TSH tests to free thyroxine (FT_4) tests be used as an indicator of general practice quality in primary care. In the United Kingdom, a similar programme to address the use of thyroid function tests in primary care was commenced, focussing on the percentage of patients with hypothyroidism that have had thyroid function tests recorded [321].

In an earlier move to limit thyroid function testing, countries such as Australia restricted the number of thyroid function tests by only funding Medicare payments for both TSH and FT_4 within tight clinically defined circumstances [322], a position later reinforced with economic

data seven years on [323]. Other countries, including New Zealand, have sought to limit testing through a first-line TSH strategy [30, 297]. This stance has not been universally accepted, especially by senior endocrinologists and biochemical pathologists [10, 324 9]. We investigated the number of tests being performed in Waikato as well as the rate of testing to ascertain a picture of burden within general practice. This indicated how general practitioners were using the tests and also defined a population at risk of thyroid dysfunction.

Second, focus groups explored the views of general practitioners in their use of thyroid function testing and the role of testing in the decision-making processes for managing hypothyroidism, with particular emphasis on subclinical hypothyroidism. General practitioners are often faced with the scenario of a patient with a mildly raised TSH whose presenting symptoms are non-specific [319]. Routine analysis of thyroid function tests from laboratory data alone cannot discriminate between those which have been ordered by the general practitioner for the purpose of monitoring known thyroid dysfunction cases from situations where tests are ordered as a diagnostic aid [279].

The relative information derived from thyroid function tests aid general practitioners in decision-making on further management of patients [325]. Recommendations for the treatment of subclinical hypothyroidism (SCH) are contentious; with protagonists disagreeing over the rationale for medical intervention [87, 89]. Justifications for treatment with thyroxine include reducing the risks of cardiovascular disease (e.g. by altering lipid levels), preventing progression to overt hypothyroidism, or reducing adverse effects on quality of life and cognitive function [107, 122, 199, 326-328]. However, other investigators have not been able to replicate these findings [109, 147, 208, 329-331]. The conflicting evidence regarding the benefit of treating SCH greatly increases the uncertainty amongst general practitioners as to how to manage this condition. Focus groups with general practitioners were held to discuss their use of thyroid function tests and to explore their rationale for testing. Issues around managing discordant results and considerations for treatment were also examined.

Finally, a retrospective study reviewed the general practice laboratory data of thyroid function requests as well as computerised patient records to examine the management of patients with raised TSH against New Zealand best practice guidelines. SCH is diagnosed by demonstrating elevated levels of TSH with levels of FT_4 within the normal reference range [140]. It is recognised that SCH may have subtle symptoms, yet the definition is purely a biochemical one [64]. In some studies, SCH has been based on TSH levels alone [41, 127, 332].

The literature is unclear over the inclusion or exclusion of symptoms in the definition [14, 47, 140, 142]. If symptoms are considered part of the presentation of SCH they are invariably vague and are a poor indicator of abnormal thyroid function tests [143]. International literature estimates the prevalence of SCH at 6.4-10%[39, 43, 46, 113]. Current TSH assays have high sensitivity as they are able to detect very low levels of TSH, and are recommended as a first-line strategy for identifying changes in thyroid function[30, 263, 297, 325, 333, 334]. The rationale for this is the log-linear relationship between TSH and FT_4, which shows that a 2-fold change in FT_4 represents a 100-fold change in TSH [69]. Therefore, TSH has greater sensitivity in detecting changes in thyroid hormone levels well before these changes will show on testing [287].

Whilst widespread testing will identify patients with overt hypothyroidism in which treatment options are well recognised, a larger number of patients will be identified with SCH. There is a lack of consensus amongst 'expert groups' on the management of SCH[14, 30-32, 34, 87, 335, 336]. Best Practice Advocacy Centre New Zealand (BPACnz) guidelines recommend that initial testing for thyroid dysfunction be based on clinical suspicion and that TSH be used as the sole test in most situations [30]. Furthermore, the use of FT_4 is indicated where TSH levels are abnormal.

We followed a cohort of adults in general practice with laboratory results suggestive of SCH to ascertain their management in the subsequent 12-months and compared this to current New Zealand guidelines on investigating thyroid function [30].

STUDY POPULATION

The Waikato District Health Board (DHB) is one of 20 DHBs in New Zealand. The Waikato DHB region includes ten distinct areas (Territorial Local Authorities or TLAs): Thames Coromandel, Hauraki, Hamilton City, Waikato, Waipa, Matamata-Piako, South Waikato, Otorohanga, Waitomo and part of Ruapehu area. The region covers 21,220 km^2 and comprises 7.9% of New Zealand's land area (Figure 3). The population comprises 353, 460 people which represent 8.36% of the New Zealand population [337]. Of the population of Waikato, approximately 94% are enrolled with a primary health organisation who deliver primary health care services [338].

Hamilton City is the only city within Waikato DHB and is New Zealand's fourth-largest city with a population of 129,249 people [337]. From the Hamilton population, the study population

were adults over the age of 18 who were registered with the participating general practices. This excluded temporary residents and those who had died.

There are approximately 250 general practitioners currently practicing in the Waikato DHB region of whom 105 work in Hamilton City [339]. The study population was recruited from two general practices within Hamilton City with a combined total of approximately 32,000 patients. This represented 25% of the Hamilton City population.

FIGURE 3: WAIKATO DHB AREA MAP

DATABASES

To help inform our studies, we utilised three main sources of data – laboratory data of thyroid function tests, disease coding from general practice computerised records and prescribing history from general practice computerised records - which were linked via a national health index (NHI) number. The NHI number is a unique identifier assigned to every individual who uses a health or disability service [340]. It is managed by the New Zealand Health Information service (NZHIS). Alongside the collection of health services utilisation, the NHI number also holds demographic information and flags medical warnings and donor information.

Within New Zealand general practice, there are various practice management systems for computerised patient medical records. MedTech32 is one such system with core modules that include demographics, accounts, appointments, clinical notes, recalls, prescribing and screening [341]. This is purported to be the most commonly used practice management system by 70% of New Zealand general practitioners [341]. The system uses Read Classification (Read version 3) for disease coding [342].

The Read Classification system was developed and named by Dr James Read, a general practitioner from Loughborough, England, as a thesaurus of medical terms to be used as a computerised medical language. The hierarchical nature allows cross-referencing to standard classifications such as the International Classification of Diseases (ICD) [343] and are used to systematically record the presence of disease in a patient [344]. Read codes are made up of five alphanumeric characters. At each level the code may be either lower or upper case letters or a number. There is an upper limit of 58 available characters at each level and a theoretical maximum of 656,356,768 available codes; providing considerable flexibility and space to develop further codes and additional hierarchies [343]. The two general practices involved in this study collected data using MedTech32.

DISEASE CODING

There are 40 Read codes relating to different aspects of thyroid dysfunction (Table 5). Using the MedTech32 search function (query builder), codes can be linked with patient data.

TABLE 5: READ CODES RELATING TO THYROID DYSFUNCTION

Read Code	Diagnosis
C0.00	Disorders of the thyroid gland
C00.00	Simple and unspecified goitre
C000.00	Simple goitre
C000.13	Thyroid nodule
C000.14	Colloid goitre
C00z.11	Thyroid enlargement
C01.00	Nontoxic nodular goitre
C011.00	Nontoxic multinodular goitre
C01z.00	Nontoxic nodular goitre NOS
C02.00	Thyrotoxicosis
C02.11	Hyperthyroidism
C02.12	Toxic goitre
C020.00	Toxic diffuse goitre
C020.12	Grave's disease
C0200.00	Toxic diffuse goitre-no crisis
C020z.00	Toxic diffuse goitre NOS
C022.00	Toxic multinodular goitre
C0230.00	Toxic nodular goitre unspecified with no crisis
C023z.00	Toxic nodular goitre
C02z.00	Thyrotoxicosis unspecified
C02zz.00	Thyrotoxicosis NOS
C03.00	Congenital hypothyroidism
C04.00	Acquired hypothyroidism
C04.11	Myxoedema
C04.13	Hypothyroidism
C040.00	Post surgical hypothyroidism
C041z.00	Post ablative hypothyroidism NOS
C042.00	Iodine hypothyroidism
C043z.00	Iatrogenic hypothyroidism NOS
C04y.00	Other acquired hypothyroidism
C04z.00	Hypothyroidism NOS
C04z.13	Hypothyroid goitre, unspecified
C05.00	Thyroiditis
C051.00	Subacute thyroiditis
C052.00	Chronic lymphocytic thyroiditis
C052.12	Hashimoto's disease
C05z.00	Thyroiditis NOS
C062.00	Thyroid cyst
C06yz.00	Other specified thyroid disorder NOS

PRESCRIBING DATA

Patient prescription data are stored within the MedTech32 PMS system. Patients' prescription histories are accessed via query builder searches using generic or trade names which are entered into the search function. Prescriptions are classed as either short-term medications or long-term medications. Assigning an individual to either classification has no bearing on the relationship of that medication with the patient. Anecdotally, long-term medications are classified as such for administrative reasons or are related to the doctors' preferences and familiarity with the software. Using the query builder on MedTech32, we were able to build a list of patients who were prescribed drugs to treat thyroid dysfunction, which included thyroxine, carbimazole and propylthiouracil. Both thyroxine and carbimazole are available to be freely prescribed by general practitioners. Propylthiouracil requires a special authority form and is able to be prescribed by a general practitioner once it has been approved through the Endocrinology Outpatient Clinic. We expected most patients who had been prescribed these medications; apart from new cases seen in the endocrinology outpatient clinics, to have a documented history in general practice records.

LABORATORY DATA

Laboratory data were obtained from both community laboratories within Waikato (Waikato Pathlab and Medlab Hamilton) that held contracts to deliver services to primary care. Requests for thyroid function tests included TSH, FT_4 and FT_3. Each test has its own reference range and these are most often based on manufacturer's recommendations as described in Chapter 1. The two laboratories had different reference ranges and results were coded against the supplied laboratory reference ranges (Table 6) and categorised in their respective thyroid status (Table 7).

TABLE 6: KEY TO LABORATORY REFERENCE VALUE (CUT-OFFS) FOR THYROID FUNCTION TEST SERUM ASSAYS FROM LABORATORIES AS AT NOVEMBER 2006

WAIKATO PATHLAB	CODE	MEDLAB HAMILTON
TSH (mIU/L)		
<0.1	0	<0.1
0.1 - 0.3	1	0.1 - 0.3
0.3 - 3.1	2	0.3 - 5
3.2 - 9.9	3	5.1 - 9.9
≥10	4	≥10
FT4 (pmol/L)		
<9	1	<10
9-19	2	10-25
≥20	3	≥26

TABLE 7: CATEGORISATION OF THYROID STATUS

Thyroid status* was defined as follows:

Euthyroid (TSH within the normal range, TSH = 2)

Hypothyroid (TSH = 4, or TSH=3 & FT_4=1)

Subclinical hypothyroid (TSH = 3 & FT_4 = 2)

Hyperthyroid (TSH = 0, or TSH = 1 & FT_4 = 3)

Subclinical hyperthyroid (TSH = 1 & FT_4 = 2)

*These categories do not take into account central hypothyroidism or T3 thyrotoxicosis. A TSH of 10 mIU/ml has been used as a cut-off in New Zealand for recommending treatment for subclinical hypothyroidism regardless of FT_4 level and this has been used as the upper limit [14]. The results of thyroid antibodies to aid definition were not available here.

EPIDEMIOLOGY OF THYROID DISEASE IN HAMILTON GENERAL PRACTICE

The aim of this study was to establish the prevalence of diagnosed thyroid dysfunction in adults enrolled in general practice, through linking three data sources to estimate the prevalence of diagnosed thyroid dysfunction from health records in two general practices in Hamilton, New Zealand.

RESEARCH DESIGN AND METHODS

A cross-sectional study was commenced in the summer of 2006/7 following ethics approval from the Northern Y Regional Ethics Committee (NTY/06/07/059). Cross-sectional studies, also termed prevalence studies, enable a snapshot of the burden of disease, can be used to assess the need for health services, are useful for comparing the prevalence of disease with different populations and can be used to compare changes over time within the same population.

We first identified patients who were aged 18 years and over, registered in general practice (as of 1/12/06) by age, gender and ethnicity. Data were collected from three sources: disease coding of thyroid dysfunction, general practitioner prescribing of drugs to treat thyroid dysfunction, and laboratory requests for thyroid function tests. Information from disease coding and prescribing was obtained from the computerised patient records in the practice management system – MedTech32. Additional permission had been sought from all general practitioners in both practices for direct access to thyroid function tests data directly from the laboratory. This included tests on patients requested by locum general practitioners and former general practitioners attached to these practices.

Using MedTech32 query builder, we sought patients with a Read Code relating to the diagnosis of thyroid dysfunction (Table 5). Read codes were used to systematically record the presence of disease in a patient [344]. These were imported into a Microsoft Excel spreadsheet. Patients with any history of prescriptions for drugs to treat thyroid dysfunction, which include thyroxine, carbimazole and propylthiouracil, were identified using the search function on MedTech32. These data were imported onto a Microsoft Excel spreadsheet.

Records of TSH and FT_4 results were obtained from both private laboratories which operate in the local area and who hold contracts for primary care services. Requests for thyroid function tests generated by the two general practices between 1/12/05 - 30/11/06 were used to

identify additional cases. Laboratory results were reviewed and categorised based on their set reference ranges in order to identify additional cases. These data were coded (Table 6) and categorised (Table 7) (page 69). These were imported to a Microsoft Excel spreadsheet.

We used NHI numbers to merge the lists together to provide one list of potential cases of thyroid dysfunction. The NHI number is a unique patient identifier that is assigned to every individual who uses a health or disability service. Each source of identification was noted and duplicates were discarded. All cases were confirmed by manually reviewing the computerised and written records of patients relating to thyroid dysfunction. Individuals were assigned to a category (hyperthyroid, hypothyroid or other) based on their status at 30/11/06.

Patients with a history of carcinoma of the thyroid, primary pituitary disease (including panhypopituitarism and central hypothyroidism) or those using thyroxine for non-endocrine indications were excluded. Non-endocrine indications included treatments used in psychiatry [345].

STATISTICAL ANALYSIS

Prevalence of diagnosed thyroid dysfunction was described by age, gender and ethnicity. Numerical data and categorical data are expressed as percentages. Excel (Microsoft 2003) was used to examine laboratory data. Data were analysed using Stata 8 (Stata Corporation, 2003) to assess differences amongst groups.

RESULTS

All patients aged 18 years and over registered with these practices as of 1/12/2006 were included in this study. Both practices managed their patient records through MedTech32. Using the search function we found that the combined total adult practice population was determined to be 21,290. When compared with the population of Hamilton City (www.stats.govt.nz/census), the study population were similar in age and gender distribution; however, there were differences in ethnicity where Māori representation was less than expected (7.2% c.f. 14.0%).

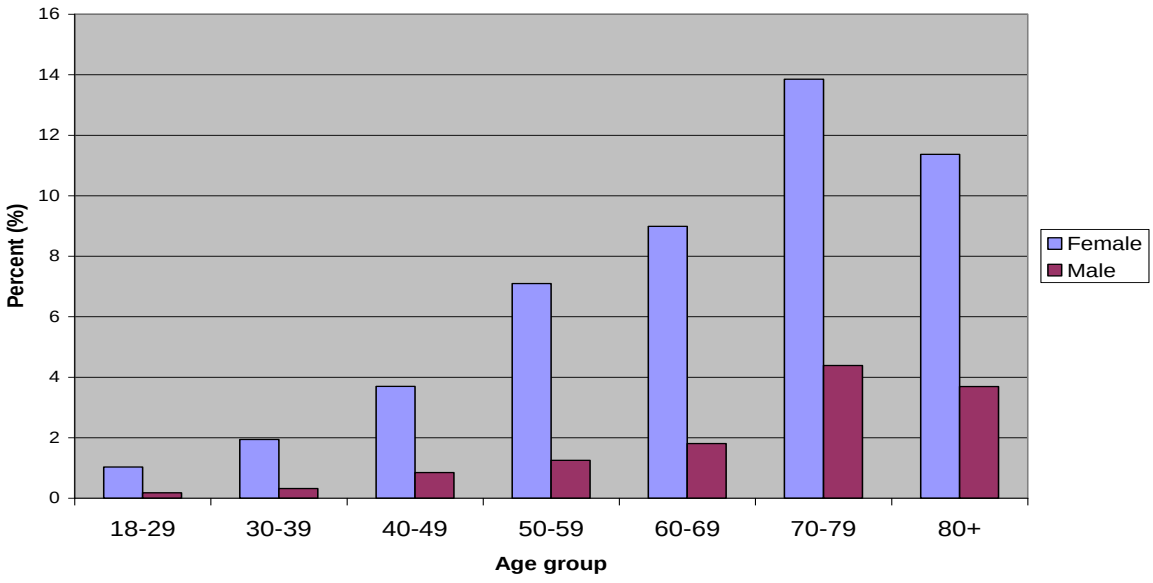
Six hundred and seventy-two patients registered with the general practices were identified as having thyroid dysfunction from Read Code or from prescriptions. Of these, 644 were confirmed from computerised and written records. Of those excluded: six patients' paper records could not be found and information relating to thyroid dysfunction could not be

ascertained from the computerised records; 10 patients were euthyroid following prior surgery or pharmacotherapy; 3 were commenced on thyroxine for psychiatric reasons with no record of thyroid dysfunction; 4 had sub-acute thyroiditis in the past, which had now resolved; 5 were coded incorrectly and related to another family member.

Analysis of laboratory data revealed a further 36 patients with results suggestive of thyroid dysfunction. On further examination, 18 patients fitted the criteria for inclusion in the study. Of the 18 patients excluded: 4 had died and 14 were either: inactive (not currently enrolled); had transferred to another practice; or, were not registered at the practice.

Thyroid dysfunction was identified in 662 patients (3.1%, 95% CI 2.9-3.3) registered in general practice. The prevalence by age and gender is shown in Figure 4. There is an increase in thyroid dysfunction with age for both male and female.

FIGURE 4: PERCENT OF THYROID DYSFUNCTION BY AGE GROUP AND GENDER



Overall prevalence in women was 4.8% (95% CI 2.1-7.5) and in men was 1.1% (95% CI -1.5-3.7). Women were nearly 4.5 times more likely to have thyroid dysfunction than men (RR=4.5, 95% CI 3.7-5.5, p=0.0001).

The prevalence by ethnicity was greatest in the New Zealand European population at 3.5% (582/17165) when compared with Māori 2.1% (31/1527), Pacific 1.8% (6/345), Asian 1.8% (22/1224) and "Other" ethnic categories 2.0% (21/1029). Patients of Maori ethnicity were less likely to have thyroid dysfunction compared with New Zealand European (RR 0.6, 95%

CI 0.4-0.9). After adjustment for age and gender, there was no statistical difference between Māori and New Zealand European (OR 0.8, 95% CI 0.6 - 1.2).

Of those with thyroid dysfunction, hypothyroidism was diagnosed in 2.5% of the study population and hyperthyroidism in 0.2% of the population. Other conditions such as goitres, nodules and sub-acute thyroiditis were diagnosed in 0.4% of the populations. Hypothyroidism accounted for 78.9% of diagnosed thyroid disorders in general practice (one-fifth resulting from surgery or radio-active iodine), hyperthyroidism accounted for 7.2% of cases and other thyroid disorders accounted for 13.9% of cases.

A comparison by age and gender in a subset of the Framingham study showed that in the 60-89 year age group 7% of women and 3% of men had thyroid dysfunction compared with our findings of 11% of women and 3% of men in this age group [151].

For the 12 months between 1/12/05 and 31/11/06, 42 new cases (N=20,670) of thyroid dysfunction occurred, an overall incidence of 2.0 per 1000 per annum. Incidence by gender was 2.8/1000 in women and 1.1/1000 in men. The age range was 27-90 years (median 55). Most were European (88.1%).

The incidence of hyperthyroidism was 0.63/1000 (13/20670), including 4 patients diagnosed with Graves' disease and 1 patient with amiodarone-induced hyperthyroidism. Of the study population, 1.02/1000 (21/20670) were diagnosed with hypothyroidism including 1 patient with amiodarone-induced hypothyroidism.

Thyroxine was prescribed in 93.1% (491/527) of patients with hypothyroidism. Carbimazole was prescribed in 41% (19/46) and PTU in 2.2% (1/46) of hyperthyroid patients.

DISCUSSION

This research was prompted by potential changes in thyroid dysfunction epidemiology and the resultant burden on primary care as a result of changing iodine status amongst the population.

The prevalence and incidence findings of the Whickham studies in the United Kingdom [40 79] have been corroborated by smaller studies from Europe [45, 143]. In addition, Australian epidemiological studies found similar results to the Whickham study [46] . This suggests that the Whickham results are generalisable to countries where there are no obvious

environmental influences that may cause thyroid disease [203]. We therefore fully expected our study to find similar incidence and prevalence rates as previously reported in European and Australian studies.

The prevalence of overt thyroid dysfunction in our population-based study from general practice is 3.1% based on note review of cases found on disease coding, prescriptions for thyroid specific pharmaceuticals and laboratory data. This is similar to the findings contained in the New Zealand health survey of self-reported thyroid dysfunction carried out around the same time [209]. In addition, our gender differences were nearly identical.

Prevalence studies are difficult to compare due to differences in sampling frame, age groups, gender and iodine intake. Results from large community screening surveys have previously been published [40, 43] whereas our study was based on computerised records in a general practice setting and relies heavily on patients reporting symptoms, accurate, timely reporting and coding by general practitioner as well as decision-making for ordering tests. This can be exemplified by one example, of an over 60 year population in a Madrid (Spain) study[44], which found a prevalence of 8.5% (2% hypothyroid, 6.5% hyperthyroid) compared with our finding of 7.3% (6.4% hypothyroid, 0.4% hyperthyroid) in the same age group. Closer inspection reveals that the Madrid study is a community prevalence study based on blood results from a population sample without known thyroid dysfunction. Of the high number of undiagnosed hyperthyroid subjects, only one individual had manifest symptoms of hyperthyroidism. Therefore, in comparison to our study, many of those without symptoms may not have attended a general practitioner for testing and therefore not have been identified. We calculated the incidence rate of hypothyroidism in women aged 70-79 years to enable comparison with international findings; our rate of 2.8/1000 per annum (2/722) in this age group falls within the 2.4 - 3.5 range obtained in overseas studies [79, 346].

This study reported on the prevalence and incidence of thyroid dysfunction in a population-based sample of adults (derived from general practice). Our study had good power owing to the large sample size (one-quarter of the Hamilton City population). The use of general practice databases has been used more widely in research, in particular the General Practice Research Database (GPRD) in the United Kingdom. Most general practices in New Zealand are recording data electronically and this provides an important source of data for researchers [347]. Data on occurrence of symptoms, disease, treatment and care was able to be obtained alongside demographic data.

We relied heavily on disease coding data being accurate. With 40 Read Codes for thyroid dysfunction and the ability to develop new codes, we felt we were able to capture all patients through our search methods which have been validated against international findings in similar settings. By matching lab results, we were able to identify patients with abnormal test results. Relying solely on test data for thyroid prevalence is likely to both underestimate and overestimate thyroid dysfunction with conditions such as goitre, which may be present in euthyroid individuals not being counted and non-thyroidal illness, which may alter thyroid physiology, being counted. Patients with thyroid antibodies and multinodular goitres are poorly recorded in these two practices.

Our study is generalisable to the European population of New Zealand. The proportion of Māori in our study population was half that of the Hamilton City and New Zealand populations (7% vs. 14%). Further research study will need to be undertaken to ascertain whether the prevalence of thyroid dysfunction in indeed less in Māori and what may be the cause of any difference. It is possible that dietary factors may contribute to differences in thyroid dysfunction between Maori and European populations in New Zealand due to Maori traditionally having a higher intake of fish and shell food (higher iodine source) than European diets. We do not believe that biological determinism is the reason behind differences which may be found. There may also be evidence of variation in rates of diagnosis and testing between populations. The population of Pacific and Asian peoples in Hamilton and in the Waikato region as a whole is less than the New Zealand average and therefore our study may not be generalisable to these ethnic groups.

CONCLUSION

This study confirms that the epidemiology of thyroid dysfunction corresponds with prevalence from abroad in iodine replete areas. The population-based research was undertaken prior to quality initiatives to reduce and restrict the use of thyroid function tests. Our study indicates a prevalence of thyroid dysfunction of 3.1% in adults. Our data are similar to national and international literature with the burden of thyroid dysfunction being greater in women and in the ageing population.

THE UTILITY OF THYROID FUNCTION TESTS IN HAMILTON GENERAL PRACTICE

The presenting features of early thyroid disease can be subtle and non-specific; consequently, general practitioners have a low threshold for ordering thyroid function tests. This study examined the use and results of thyroid function tests by general practitioners in a 1-year period in a population-based sample of adults without known thyroid disease enrolled in general practice.

RESEARCH DESIGN AND METHODS

We examined the use of thyroid function tests through analysis of laboratory requests from two Hamilton general practices over a one year period following ethics approval from the Northern Y Regional Ethics Committee (NTY/06/07/059). The two laboratories each held contracts to provide laboratory services to general practice in the Waikato DHB region. Data were supplied in Microsoft Excel format providing information on laboratory identification number, national health index (NHI) number, date of birth, gender, description of test, test code, reference interval and requesting doctor. Data were linked with General Practice computerised records via NHI to establish prior thyroid disease and ethnicity.

Laboratory data were used to identify patterns of request by age and gender as well as by numbers of tests. The number of tests, rate of testing and population at risk are described in the results section. The two laboratories had different TSH assay analysers (Abbott Architect I2000 & Roche E170) and therefore standardisation of results was problematic. Results were based on each laboratory's given reference intervals. All TSH levels were categorised 1-4 and FT_4 was categorised 1-3. We used the first TSH (and FT_4 test where available) for each individual test during the data collection period. These are described in more detail in Table 6 on page 69.

RESULTS

The laboratory data identified 5169 TSH tests and 1977 FT_4 tests had been reported in the 12-month period in a population of 21,290 patients. Excluding 662 patients identified with thyroid disease (3.1%) left a total of 20,628 patients without known thyroid disease in the study population. Of 662 excluded patients, 18.0% of TSH tests (931/5169) were conducted

on 476 of 662 excluded individuals and 30.5% of FT_4 tests (603/1977) were conducted on 303 patients. Thus, 4,238 TSH tests were examined on 20,628 individuals.

To ascertain a fuller picture of the burden of thyroid dysfunction in general practice in relation to the volume of thyroid function testing that is requested, the laboratory data from Medlab Hamilton alone, which accounted for 80% of the thyroid function data, was further analysed for the 12-month period (1/12/2005 – 30/11/2006). In this laboratory data set, from our study population, general practitioners ordered 4184 TSH tests on 3459 individuals - an average of 1.2 TSH tests per person-tested per year, and 1374 FT_4 tests on 1010 individuals - an average of 1.4 FT_4 tests per person-tested per year. This represented TSH testing in 16.8% (3459/20628) of the 'at risk' population. The number of TSH tests by individual ranged from 1-11, with 79.0% having a single test (2734/3459) and 1.0% (34/3459) having more than three TSH tests.

The age of the study population ranged from 18-99 yrs (median 52yrs, inter-quartile range 39-65yrs). Of those having TSH testing, 2381/3459 (68.8%) were women. The number of TSH tests per patient increased with increasing age. The rate of testing was greater in women than men although the relative proportion decreased in older patients (Table 8).

TABLE 8: RATE OF TSH TESTING PER 1000 BY AGE AND GENDER

Age Group and Gender (denominator)	Female (11029)	Male (9599)	By study population (20,628)	Ratio of testing (Female/Male)
18-29yrs	126.5	43.5	87.4	2.9
30-39yrs	163.0	55.6	115.4	2.9
40-49yrs	207.4	93.8	154.0	2.2
50-59yrs	258.9	156.8	210.4	1.7
60-69yrs	285.1	205.7	245.4	1.4
70-79yrs	332.8	240.1	288.0	1.4
80+yrs	532.6	325.1	460.9	1.6
Grand total	215.9	112.3	167.7	1.9

According to the laboratory reference intervals identified in Table 6 (page 69) for Medlab Hamilton and in the thyroid categorisations in Table 7 , 8.0% of the study population had results indicating abnormal thyroid function (Table 4). There were 242 patients (7.0%) with an elevated TSH concentration; most of whom were subclinically hypothyroid (235/241). There were 35 patients (1.0%) with a low TSH concentration; most of whom were subclinically hyperthyroid (29/35). The remaining 3182 patients (92.0%) had serum TSH concentrations within the reference interval as shown below in Table 9.

TABLE 9: PERCENTAGE OF THYROID DYSFUNCTION FROM FIRST TSH TEST (AND FT4 WHERE AVAILABLE)

Thyroid Status	No. Of subjects (%)
Results	N=3459
Euthyroid	3182 (92.0)
Hypothyroid	7 (0.2)
Subclinical hypothyroid	235 (6.8)
Hyperthyroid	6 (0.2)
Subclinical hyperthyroid	29 (0.8)

The percentage of tests which fell within the reference interval decreased as age increased. This was similar for women and men (Table 10).

TABLE 10: PERCENT OF TSH TESTS THAT WERE WITHIN THE REFERENCE INTERVAL BY AGE GROUP AND GENDER

Age Group (years)	Female	Male	By study population
18-29	96.2	93.8	95.7
30-39	95.4	98.1	96.3
40-49	94.2	94.1	94.2
50-59	93.3	93.5	93.4
60-69	86.1	93.7	89.3
70-79	84.5	87.9	85.9
80+	84.9	82.3	84.3
Grand total	91.7	92.6	92.0

DISCUSSION

The diagnosis of subclinical thyroid disease can be difficult due to conflicting data on the relevance of the diagnosis and inconsistencies with laboratory parameters. We found that this disease was not usually coded. Anecdotally, practitioners had differing views on their definition, investigation and treatment of patients who fell within this category. The absence of clear guidelines for the management of subclinical thyroid disease indicates the need for further work in this area.

We identified that in the two practices 1 in 6 adult patients without known thyroid disease who visit their general practitioner in a 12-month period will have a TSH test. It is likely that this testing profile would be common amongst the wider general practice community. This level of testing is akin to an opportunistic screening programme rather than targeted use of a test in a specific group of patients with signs and symptoms of disease. The results confirm that thyroid function testing is used often in primary care. In the study group, 8.0%

(277/3459) of the population without identified thyroid disease had abnormal thyroid function results, with the majority (84.8%) having subclinical hypothyroidism.

If patients tested were considered as having a high likelihood of disease, based on clinical presentation, one would expect a high rate of abnormality. However, similar to population-based screening programmes such as the Colorado study, we find that when allowing for our smaller sample size the percent of individuals with previously unidentified thyroid dysfunction is similar to that found in a population-based screen (Table 11) [43].

TABLE 11: COMPARISON OF OUR STUDY AGAINST COLORADO STUDY DATA

Thyroid status	Our study (N=3459)	Colorado study (N=24337)	Difference in proportions p>|z|
Euthyroid	92.0	90.1	0.0007
Hypothyroid	0.2	0.4	0.9344
Subclinical hypothyroid	6.8	8.5	0.371
Hyperthyroid	0.2	0.1	0.9470
Subclinical hyperthyroid	0.8	0.9	0.9577

The relative incident cases of hypothyroidism identified in our study appeared low at 0.2% (or 2 per 1000 per year) compared to the overall prevalence of hypothyroidism of 2.5% identified in an earlier study [306]. This rate is not dissimilar to that of the Colorado study when testing proportions (p=0.9344). The low number of incident cases may be a combination of hypothyroidism being a slowly progressing condition, in which the prevalent cases have had hypothyroidism for a number of years, or to the age structure in which diagnosis later in life will not impact on prevalence due to the force of mortality (death is 100% and the likelihood increases with advancing age). When those identified with hypothyroidism and hyperthyroidism are combined to account for iatrogenic hypothyroidism the incidence rate becomes 3.75 per 1000; this is similar to the rate from the follow-up Whickham study of 4.1 per 1000 (95% CI 3.3 – 5.0) [79].

Clinical presentation has been reported as the main reason for requesting a thyroid function test [293]. However, symptoms of thyroid dysfunction are ‘soft’ and mimic those of other

pathologies. Symptoms alone have been found not to differentiate the majority of patients with elevated thyroid stimulating hormone values from those with normal values [143]. This study supports the hypothesis that signs and symptoms of thyroid dysfunction have poor prognostic value in a general practice setting [143]. Other than using age and gender to inform the decision to test thyroid function (older patients and female patients are more likely to be tested), case identification of patients at risk is no better than a population based screen. Although screening remains controversial, it appears that de facto, general practitioners are using opportunistic screening with TSH to identify new cases.

Arguments arise over the use of TSH alone as a first-line strategy based on the risk of not detecting thyroid dysfunction arising from hypothalamic-pituitary dysfunction [10, 73, 291]. In this 12-month period under study, the cost to the practice laboratory budget for thyroid function tests were in the region of NZ$40,600 in 3459 individuals without known thyroid dysfunction. We identified 13 patients (9 women and 4 men) with a median age of 66yrs with overt thyroid dysfunction; a cost per case of NZ$3123. In patients over 40 years of age the cost per case reduces to NZ$2190 (NZ$1780 in women, NZ$4040 in men), reducing to NZ$1800 in patients over 50 years of age (NZ$1467 in women, NZ$3170 in men). The cost of including FT_4 alongside TSH for all testing to prevent missed cases of central hypothyroidism has not been evaluated. The incidence of central hypothyroidism is 42 per million and the cost per test is approximately NZ$7.31c, giving a cost per case identified of NZ$347,619 [9, 348-351]. A more thorough decision and cost-effectiveness analysis has found costs associated with screening for thyroid dysfunction comparable to other currently funded preventative medical strategies [352]. As in our study, the cost-effectiveness of screening improves with increasing age and is more favourable in older women [352, 353].

For the 7.6% of patients labelled as having subclinical thyroid disease there is evidence to support treatment in subclinical hyperthyroidism to improve quality of life, cardiovascular risk factors, bone mineral density and possible progression to overt disease but evidence is not so clear cut with subclinical hypothyroidism [64, 151, 331]. However, there are some data suggesting treatment in this group may be worthwhile, although opinions differ on the management of mild disease [87, 89]. Until further data are forthcoming, clinical judgement and patients' preferences currently remain the recommended manner to decide whether treatment should be started [24].

This study is a population-based sample where we were able to link laboratory and patient data through the use of the unique NHI number. Primary Health Organisation enrolment within Waikato DHB is reported at 94% overall [338]. Owing to high enrolment numbers, using general practice registration is considered adequate to examine prevalence in a population.

We were able to focus on patients without previous evidence of thyroid dysfunction and examine the use of thyroid function tests and subsequent results. The study is based on laboratory results from one laboratory service of persons presenting to their general practitioner and is limited to those who access these services. In New Zealand there is a cost associated with visiting a general practitioner. These costs represent a barrier for some who require a consultation [354-356]. Furthermore, phlebotomy is not routinely performed within general practice (as they are elsewhere, for example, in the United Kingdom) and requires the patient to travel to a private laboratory for blood tests thus adding to issues of access and cost. Fortunately these two general practices under study had laboratory services in the immediate vicinity of the practice. It is therefore unlikely that barriers relating to cost and access for having a blood test were an issue. The proportion of the practice populations who have been tested will also be biased - assuming patients identified by 'clinical suspicion' as having a higher risk of underlying disease will be tested. There is also a bias in that women are more likely to attend a general practitioner than men and so presumably are more likely to be screened [357]. Despite these problems what we have presented are the actual outcomes of the use of thyroid function tests in a reasonably sized population.

The rate of TSH testing in our population who were aged 20 years and over in a 12-month period including repeated measures was 237/1000, which is similar to the Waikato DHB rate of 260/1000 for the same population age group [358]. These figures include all patients regardless of thyroid disease status. Clearly there is variation in TSH testing within and between general practices and this variation may be due to demographics of the patient population as well as that of the requesting general practitioner, which is beyond the scope of this research.

While screening for hypothyroidism is currently not recommended by the British Thyroid Association [68], recent noted increases in the prevalence of hypothyroidism in the United Kingdom may be attributed to the incentives provided to general practitioners, better biochemical assays, or a true increase [359]. Other guidelines have recommended case-finding

for hypothyroidism in patients presenting in general practice particularly in women over 40 who attend for an unrelated reason appears reasonable [348].

CONCLUSION

This study suggests that TSH alone as a case-finding tool in the undifferentiated general practice population appears to be a strategy used by general practitioners. The development of New Zealand evidence-based guidelines in the management of subclinical hypothyroidism, evidence for benefits for screening and treatment of subclinical thyroid disease, and decision support on the cost-effectiveness of screening for central hypothyroidism is lacking.

INSIGHTS INTO THE MANAGEMENT OF SUBCLINICAL HYPOTHYROIDISM IN GENERAL PRACTICE

How general practitioners manage patients with elevated thyroid TSH and normal FT_4/FT_3 results is unknown. The aim of this study was to explore how general practitioners think about diagnosing and managing SCH.

RESEARCH DESIGN AND METHODS

Focus groups were conducted in the Waikato region to gain more in-depth knowledge of the use of thyroid function tests by general practitioners and to explore their rationale for testing following approval from the Northern X Regional Ethics Committee (NTX/07/07/068). In particular, we wished to investigate their management of a raised TSH. Focus groups are a way of extracting information from people on a given topic and allow a safe space for sharing one's life experiences [360]. The purpose of the focus group was to encourage participants to share their perceptions and points of view without feeling the need to be part of a consensus [361]. It was hoped that participants would respond to ideas that were discussed and to make comments; to be able to further elaborate conversations that developed within the group.

A request to hold a focus group meeting with the general practitioners of five general practices was sent through their practice manager. Each practice had to have three or more general practitioners working in them and was chosen for the variable size of practice populations and geographical location. Three practices approached agreed to participate in the study, one was urban, one semi-rural and one rural. These were completed between December 2007 and July 2008. Each focus group contained at least four general practitioners.

It is recommended that teams of two conduct focus groups, one person to concentrate on facilitating the group and the other to take detailed notes, deal with mechanics such as tape recorders and other matters that may arise [361]. For each focus group, we had two people, as recommended. We used an external facilitator as they were experienced in conducting interviews in a focus group situation and were less likely to introduce bias when interviewing [362]. Our focus group facilitator, who was also a general practitioner, utilised a semi-structured approach with guided discussion around set themes - defining subclinical hypothyroidism, decision-making around testing, leading to and confirming diagnosis, managing diagnosis and support. Furthermore, our facilitator was known to the participants as a colleague and an academic, however, this topic was not one which was associated with the facilitator's research and experience.

Each focus group lasted about 40 minutes. Meetings were held at the recruited general practices. Interviews were recorded and transcribed. Transcripts were reviewed by two researchers and a coding list developed. Transcripts were then coded line by line using NVivo software (QSR, 1999 version 2). A general inductive approach was taken using open coding. Each new code prompted a re-read of the previous transcripts to ensure there was consistency between coding methods. Coding underwent a series of iterations leading to key themes being identified and a model of SCH in general practice developed.

RESULTS

Three focus groups were held within the Waikato DHB area in general practices that had consented to take part. 10 male and 3 female general practitioners participated and were employed by the practice in which the focus group took place. 6 participants had completed their medical training in New Zealand and 7 participants completed their medical training overseas - mostly in the United Kingdom. The New Zealand trained doctors on average had completed their training earlier (1980 vs. 1984). By location average year of registration for participants were urban 1980, semi-rural 1983 and rural 1982.

Transcripts were coded according to thematic analysis in a series of iterations, resulting in five key themes. These were: why test, what tests, defining SCH, managing and medicating for SCH.

WHY TEST?

The rationale for testing can be separated between predominantly disease-focused testing, patient focused imperatives and doctor centred activities.

Predominantly disease focused testing for thyroid disease was undertaken when the general practitioner felt there was an increased risk of thyroid disease. General practitioners referred to the symptom of tiredness as a common complaint …*tiredness is such a general symptom that it usually doesn't have clinical causes* (GP10), …*you know just "tired all the time", one in four consultations "tired all the time"* (GP3) and …*commonest time to tick [TSH] is when someone says they are tired* (GP2). Other symptoms included weight gain and fatigue, a common picture being of …*a lot of these women that are overweight and lethargic and around menopause* (GP10). Apart from symptoms of thyroid dysfunction, there are also a range of clinical situations where testing was thought important: a family history of thyroid dysfunction, prescribed medication such as lithium or amiodarone, having goitre, other endocrine or other autoimmune conditions.

Patient focused imperatives encompassed situations where the general practitioner felt there was a low likelihood of the test being positive but tested anyway as part of patient management. In some cases general practitioners did not believe that the patient had any thyroid abnormality prior to testing but undertook a patient-centred approach …*to show that there is not something nasty going on … just to prove that to people…you're not particularly looking for thyroid disease but you're actually reassuring people there is nothing sinister or seriously wrong … part of the process is talking through the things that it could be, the exclusion of things even* (GP3), and …*patient's are looking for why they are not feeling well…it shows that you're taking them seriously and listening* (GP2). A blood test was sometimes seen as an important as part of the management of a clinical situation: …*I find myself, when someone comes in and says "Doc, I must have something wrong with me" and you think "yeah, yeah, yeah, you just need a break, you're just a bit stressed or whatever", but you find yourself ticking boxes just for something to do for them. It's the management. It's not that you're looking for disease; it's the management* (GP13).

Symptoms were not always behind the decision to request a thyroid function test: …*some colleagues may do the general tick the box* (GP11) or …*if the patient stated they wanted a check up, so you tick TSH* (GP4). In this sense, the general practitioner was effectively screening for thyroid disease at the patients request. Most general practitioners were clear that TSH was not being used as a screening test. However, screening was associated with a cost

…I could think of a lot of other things that we could put money into screening before that (GP11) but it was believed that this was not screening *…we're not thinking subclinical hypothyroidism; we're just thinking "Is their thyroid working?"* (GP3).

Doctor centred reasons for testing included medico-legal issues as well as safeguarding the doctor/patient relationship. Risk of complaint would seem to be one driver for testing: *…You think that if you don't do [thyroid function testing] and they go somewhere else where they may have a TSH and it is abnormal, you then get into trouble. So you just tick it to make sure that everything is alright* (GP12). The implications of not testing on reputation was that *…you look a bit of a dunce if you've been telling someone they've been stressed all the time and they end up with a hypothyroidism* (GP3). Changing expectations regarding expediency of diagnosis also influenced the decision to test: *…you know, medicine these days, we rely on a lot to make diagnoses reasonably early…we rely on laboratories* (GP9). Requesting a TSH test supported the discussion they had with their patient where they felt that the problem was not organic*…most of the time you are reinforcing the words you have spoken with hard evidence to back up what you think the problem is…it's not positively looking for something, it's almost negatively looking…as a reassurance factor that a) they do need to take a break and b) this is life catching up with them not some dreaded disease* (GP11). The perception of thoroughness and professional responsibility was considered important: *…if you'd done a TSH then and it was normal, and then it was abnormal two years later, then you'd say well that wasn't my fault. You were just tired then but now you're hypothyroid* (GP3). In this situation, TSH is requested to enable a paper trail of what has taken place at that time to guard against litigation in the event of future changes in health status.

WHAT TO TEST?

TSH was most commonly used as a first-line test but there was particular reference to current policy recommendations concerning this *…We used to always do TSH and T_4 and T_3 and now we don't* (GP3). However, where this was not always done *…I checked T_4 and T_3, which you aren't allowed to do nowadays but I did* (GP3), it mostly related to the perceived risk of thyroid disease being the cause of symptoms *…If I think it's a very long shot [of having thyroid dysfunction] I will just order TSH* (GP10) or *…If I think there may be a basis for a thyroid problem going on then I order all three* (GP1). General practitioners were mindful of recommendations but used clinical judgement to guide their practice although some may continued to request more than TSH alone regardless of guidelines *…I do TSH and T_4 but the authorities recommend you do TSH first* (GP12).

Many quoted advice from the local consultant endocrinologist as a guide to decision-making for which test to perform, *…[He] said at a meeting, if they come in with a symptom then they are not asymptomatic - then you shouldn't just do a TSH* (several GPs). Another reason for requesting more than TSH alone was *…to exclude if there are any pituitary/hypothalamic axis problems* (GP12).

DEFINING SCH

There was both variation and lack of clarity regarding the term "subclinical hypothyroidism". Some referred to 'subclinical' in the literal sense of having no clinical findings *…that there are no symptoms*…(GP9), or indicated uncertainty regarding the term *…I'm confused…we're giving you all the clinical things that you would find in hypothyroidism so therefore it is not subclinical* (GP10). Some defined subclinical hypothyroidism as *…having a mildly elevated TSH without any symptoms* (GPs 1,4,8) while another stated that they just *…[didn't] know what the criteria are* (GP7). Subclinical hypothyroidism was also described in terms of *…an incidental laboratory finding* (GP10), and without need of clinical intervention. Others queried *…is it actually a disease?* (GP7) or stated that they had *…never even thought of that term before* (GP3).

There was uncertainty about the risks posed by having subclinical hypothyroidism - whether that be *…excess morbidity or mortality* (GP11) *…quality of life* (GP10) or *…anaesthetic risks* (GP9). There was reference to the existing evidence base regarding SCH: …we *don't believe at the moment there is any harm in [not treating]* (GP3), a suggestion that *…there's been no good research suggesting that there's any morbidity associated with this phenomenon* (GP7). Lack of evidence would seem to influence how general practitioners perceive and manage SCH *…If it is proven…then we might change our ways* (GP3).

MANAGING SCH

There was considerable variability in how general practitioners managed SCH and this was based on how they defined SCH. Some general practitioners adhered to rule-based management *…My teaching for TSH has been about 10, then you probably should do something about it* (GP10), with variable thresholds *…8? I'd start thinking about it around there* (GP13), *…I'd go for 9. I think there was some paper that came out and said that this type of subclinical thyroid wasn't that dangerous* (GP7) *…I'd say above 7 I would want to see them back* (GP4). The interval to further tests was also variable, ranging from one month to one year, some acknowledging the advice of the consultant endocrinologist *…[he] says it*

takes about 3 months for the TSH to change (GP9) and …*I remember him saying there is no point doing it under 3 months* (GP10). This situation was further complicated by laboratories having different reference ranges. …*What about the lab changing, getting a new reference range and decide now that you don't have the disease?* (GP3). Patients may be told …*they've got a 'lazy thyroid' and we'd just keep an eye on it and see how things go* (GP12) or … *their TSH is slightly up. It may or may not be part of the spectrum of what's causing their tiredness but it's certainly not THE cause* (GP9) or … *their thyroid is a 'bit lazy' or 'under-active' or it's a bit 'sluggish' and people are quite happy to accept that…generally speaking* (GP11).

MEDICATING FOR SCH

In some instances a raised TSH leads to consideration about thyroxine medication. For both patient and doctor, there may be a choice: …*Well, if someone's trucking along quite happily and incidentally you find this slight lab abnormality and say to them look your TSH is up a bit, this could indicate that you're somewhere along the line of [your thyroid] being under-active, just tell them that if this progresses then….do you want to consider treatment?* (GP9). The choice of treatment may depend on how the patient is feeling …*a lot of patient's are quite delighted that you find something is abnormal, you know, starting them on treatment…found something wrong…"I'm not going nuts", you know what I mean?* (GP3) or …*if they're symptomatic I treat them, even if their [TSH levels are] 6, 7, 8…* (GP8). Many general practitioners considered low doses of thyroxine as a trial …*they're getting more and more tired, and you keep putting them off and [their TSH level] gets to 7, 8…you would certainly tend to start them as a trial…on a small dose of thyroxine and give it a go* (GP9). The informal rules tended to be …*50 mcg thyroxine once a day* (GP5) and …*start low, go slow* (GP11). The aim of treatment, if instituted, was to improve symptoms …*After three months of treatment… the TSH is then normal and they still have their symptoms, then you have to think of other things* (GP8). Once treatment was started one of the aims was to bring TSH into the normal range …*if their TSH is still the same as subclinical TSH…why worry about it now? I guess I'm a bit obsessive and it has to fit in a range* (GP10).

DISCUSSION

For general practitioners, SCH represents a poorly defined condition that exists in a wide variety of contextual circumstances and where the value of intervention is questionable. From the focus group study, exploring the use of thyroid function tests by general practitioners and their rationale for testing, in particular their management of a raised TSH, it is clear that

general practitioners experience uncertainty both in interpreting tests suggestive of SCH, and in the management of SCH. This uncertainty amongst general practitioners reflects the conflicting literature regarding the diagnosis, prognosis and treatment of SCH [64].

The variation in the ways general practitioners define SCH indicate that at one extreme SCH does not represent a disease but simply an abnormal laboratory result with no relationship to symptoms or prognosis. The other view is that SCH is a disorder with justification for treatment or monitoring. Complicating this picture is the patient-centred focus that is characteristic of general practice and was widely prevalent in the participant general practitioners; laboratory tests and presenting symptoms need to be contextualised on an individual basis. A diagnosis of a disease may be a relief to some patients and a challenge to others even if the symptoms and tests are identical. General practitioners were aware of the tensions between the imperatives of population-based principles and the needs of individual patients.

Three quite different yet complementary reasons for ordering thyroid function tests have been identified, namely, the search for disease, the desire to meet patient expectations and the needs of the general practitioner to secure against breakdown in the doctor/patient relationship. It would appear that the predominant reason for ordering a TSH assay is for the investigation of vague symptoms. Ill-defined symptoms are common in general practice. The management of a patient with such symptoms can be complex as the cause can range from the life-threatening to the self-limiting. The discovery of SCH when testing for more serious thyroid disease can be seen as an inadvertent and awkward result where the meaning attached to the label is dependent on patient-focused contextual circumstances.

TSH testing was regarded by some general practitioners as a defence in a potential medico-legal dispute. A TSH assay was viewed as documentation supporting discussion which has taken place within a consultation. Testing also serves to reinforce to a patient that they are being listened to, their symptoms are taken seriously and that the doctor is being thorough. Historically, these qualities were recognised as desirable for general practitioners if they wished to survive in private practice [363].

Patient expectations also contribute to the demand for general practitioners to identify ‘disease’ early. The status of general practitioners has altered, which in part can be attributed to the empowerment of patients as consumers of health [364]. Having deficient clinical

knowledge in the eyes of the patient may threaten the position of privilege in which doctors have historically been placed [365].

While the use of TSH is not considered screening by the general practitioners, a described population - particularly those who are female, overweight and post-menopausal would seem to be targeted opportunistically. There is evidence to support that older populations and women have more thyroid disease then the younger population and men [40, 43].

Expert advice by the local consultant endocrinologist was influential for some general practitioners when interpreting laboratory tests and in the timing of follow-up tests. Underlying this are patients presenting with symptoms, most commonly tiredness, who feel that something is wrong. When diagnosing possible thyroid dysfunction, symptoms are taken into account. Often these are the sole rationale for requesting thyroid function tests. In many instances, general practitioners appear to intuitively manage their patients - where TSH levels form part of a total picture, rather than as the whole clinical picture. TSH levels of 6, 7 or 8 mIU/ml described as a threshold for treatment shows that arbitrary cut-offs are decided by general practitioners in providing patient-centred care. The approach depends on whether general practitioners manage results in terms of 'mild thyroid failure' with the likelihood of thyroid function remaining constant (to treat patients based on symptoms) or as part of a disease process that could progress (to treat patients based on laboratory results). In addition, there was no consensus for when a patient should return for follow-up blood tests.

The decision to treat subclinical hypothyroidism would seem to incorporate a patient-centred approach that is based on symptoms (or lack of symptoms), negotiation and request. Once treatment was commenced general practitioners commonly tended to continue this approach, where the aim of treatment was to improve a set of vague and non-specific symptoms. Alternatively, some general practitioners chose to treat a raised TSH level by returning it to within the normal reference range irrespective of quality of life.

One aspect in decisions to test and treat is costs to the health system and to the patient. Costs and benefits of a screening approach to SCH were discussed but other costs and benefits to the health system had very limited acknowledgement by the participants. General practitioners appear to take a strongly patient-centred and not population-centred approach to their clinical role. The cost-effectiveness of treatment, although outside the realms of this paper, needs to be considered with emphasis on the intended outcomes for management and treatment. While the risk of progression of disease was mentioned, the potential for

cardiovascular risks, effects on cognitive function or on mental health were not stated even with current literature identifying these as possible effects [99, 105, 149, 366, 367].

The demography of practices and of general practice profiles reflects the range of general practitioners working in New Zealand, in particular over 34% who have come from overseas and over 50% who work within general practice [368]. It is doubtful that doctors from overseas have had more experience or training in managing SCH considering the lack of international guidelines on this topic and the improvement in TSH assay testing in the past two decades.

We held three separate focus groups using topic ideas to prompt discussion. Qualitative methodologies such as focus groups enable the exploration of topics in more depth than afforded by semi-structured questionnaires. The recommended size for dealing with complex topics is 6-8 participants [361]. Our groups had an average of four participants. These are termed mini-focus groups which have 4-6 participants and are suggested to be limited by the total range of experiences [361]. Our study involved general practitioners with vast experience which averaged 25 years since medical training. In addition, mini-focus groups were valid for this topic of study in view of the fact that participants would have had a great deal to share about the topic and would have intense or lengthy experiences with the topic of discussion [361]. The small participant numbers in these mini-focus groups enabled general practitioners to be able to participate more readily and, as a benefit to researchers, were easier to recruit and host.

CONCLUSION

The exploration of the rationale for testing and decision-making processes by general practitioners through focus groups highlights the need for clearer guidance when managing raised TSH. Subclinical hypothyroidism remains a complex entity because of ambiguity regarding symptoms, uncertainty regarding prognosis and variation in advice regarding treatment. This complexity is reflected in the quite disparate responses of general practitioners to the diagnosis and management of SCH. Further complicating the picture is the patient-centred nature of general practice where imperatives of population-focused medicine and disease-focused secondary care represent only part of an intricate decision-making process. In such circumstances, it is understandable that general practitioners take an eclectic approach to both diagnosis and management of SCH. Indeed, it could be said that this is a pragmatic response to an otherwise unsolvable dilemma. Guidelines that would

provide principles and decision support for the management of SCH would be of considerable advantage to general practitioners.

A RAISED THYROID STIMULATING HORMONE RESULT - A 12-MONTH FOLLOW-UP STUDY IN GENERAL PRACTICE

We reviewed the medical notes of a cohort of adults identified by thyroid function tests suggestive of SCH to ascertain their management in the subsequent 12-months and compared their management to current guidelines from the New Zealand Best Practice Advocacy Centre (BPACnz) on investigating thyroid function.

RESEARCH DESIGN AND METHODS

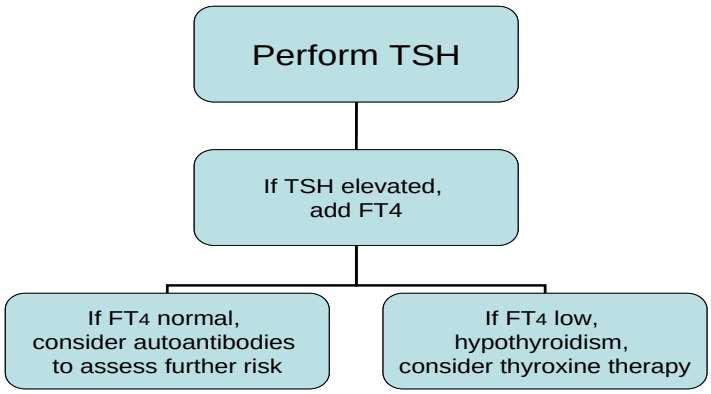
We analysed TSH data for the 12-month period (1/12/2005 – 30/11/2006) to identify adult patients (20 years and over) with results suggestive of SCH from a cohort without known thyroid dysfunction following approval from the Northern X Regional Ethics Committee (NTX/07/07/068). The laboratory data set contained reports from Medlab Waikato and were coded as shown in Table 6 and categorised according to Table 7 (page 69) as previously outlined. The starting point for SCH was based on raised TSH results alone as recommended for initial investigation of thyroid function by BPACnz.

We employed two practice nurses to review notes from general practice computerised records to identify aspects of the management of SCH in the subsequent 12 months from each patient's initial SCH result. Data were collected on symptoms leading to first test; use of thyroid antibodies; further relevant investigations since first test, symptoms noted since first test; use of thyroid medication; use of Read codes for thyroid disease; family history of thyroid disease, and history of diabetes, heart failure or depression. Data were analysed using Stata 8 (Stata Corporation, 2003) and Microsoft Excel (Microsoft Corporation, 2003).

Symptoms relating to hypothyroidism included: tiredness/lethargy, weight gain, cold intolerance, constipation, dry skin, hair loss, sluggish thinking, general slowing, deepening voice, shortness of breath on exertion, menorrhagia, and ataxia [1].

We used the BPACnz best practice guidelines for investigating thyroid function to compare the management of SCH from retrospective note review. The order of tests recommended by BPACnz are shown in Figure 5.

FIGURE 5: BEST PRACTICE GUIDELINES IN NEW ZEALAND (BPACNZ) FOR INVESTIGATING THYROID FUNCTION



In addition, BPACnz recommend that the decision to initiate thyroid replacement therapy for patients with SCH:

"should be based on the presence of symptoms; patients with TSH between 5-6 mIU/L usually have no symptoms, while as the TSH approaches 10 mIU/L more symptoms are probable. In the remainder of patients thyroxine should be considered for those with a TSH persistently >10 mIU/L. Patients not treated with thyroxine should be monitored using TSH every 6-12 months" *(BPACnz, Investigating Thyroid Function, p 7)* [30].

STATISTICAL ANALYSIS

Retrospective note review and laboratory data set review of the management of SCH used descriptive statistics. Chi-squared tests were used to calculate statistical significant between age groups (test for trend), gender (2x2 contingency) and ethnicity groups (2x2 contingency). In addition, we examined whether there was an association between having a 2nd TSH test and age, gender or ethnicity.

RESULTS

Thyroid function testing data were obtained on 3459 patients during the study period. Of these, 270 individuals fitted the inclusion criteria with laboratory results suggestive of SCH. Five patients were excluded following note review - one recently diagnosed with hypothyroidism, one with an alternative NHI number which revealed a previous history of hypothyroidism, and three patients with histories of thyroid operations which were not noted on the general practice computerised records until 2007 (after our larger study). This left 265 individuals in the study with a raised TSH result - a total of 6.4% of tested individuals.

The patients were aged between 19 - 93yrs (median age 61yrs, SD 17.4yrs). 82 males (31.0%) and 183 females (69.0%) were identified. From initial thyroid function tests, women had nearly twice the rate of SCH than men (16.6 vs. 8.5 per 1000 population) but this was not statistically significant when compared with the number of thyroid function tests performed by gender (2830 vs. 1308, p=0.81). 225 (84.9%) of patients with SCH were of European descent, 10 (3.8%) were Māori, 15 (5.6%) were Asian, 6 (2.3%) were Pacific and 9 (3.4%) were of other ethnicities. The number of follow-up tests in individuals ranged from 0 - 5 tests in the 12 month period.

FOLLOW-UP TESTING

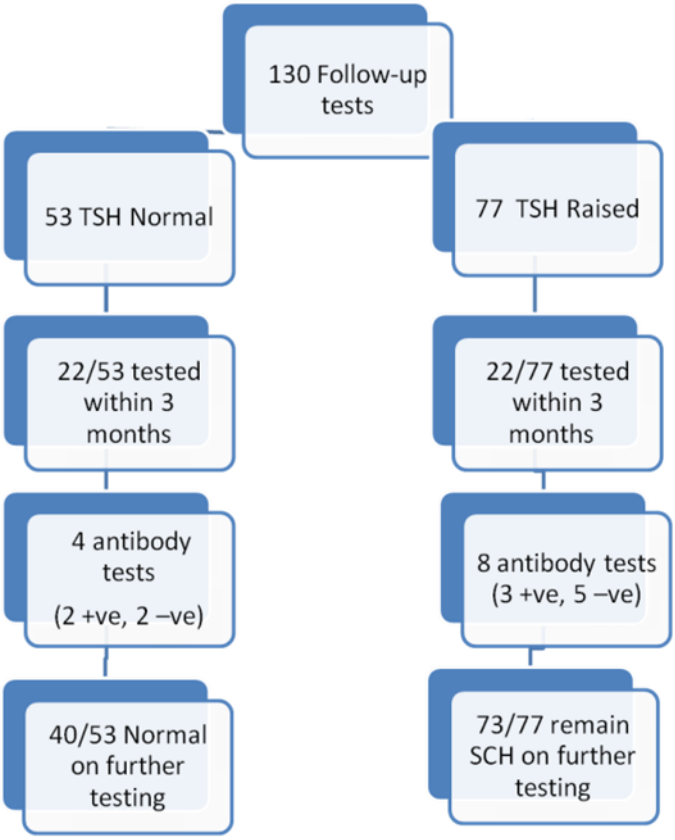
Fifty-one percent (135/265) of patients had no follow-up TSH testing including 7 patients who had transferred out of the practice and 4 patients who had died. Two patients were prescribed thyroxine replacement medication; one of them coded for hypothyroidism. No further investigations of any kind had been recorded in this group of patients. Another three patients had thyroid hormone testing only (FT_4 and/or FT_3) and four patients had thyroid antibody testing only (anti-thyroid peroxidise (anti-TPO) and anti-thyroglobulin (anti-Tg)); one patient had a positive anti-TPO result. No further investigations were recorded in this group during the 12-month follow-up. Of the three patients with negative thyroid antibodies, one had been placed on thyroxine replacement therapy.

Overall, a second TSH test was performed on 49.1% (130/265) of patients. There was no difference in second testing by age group (p=0.9357), gender (p=0.0631) or ethnicity (p=0.9869) compared with no follow-up TSH testing. The time difference between first and second TSH tests ranged between 5-362 days (mean 149 days, median 109 days).

Forty-one percent (53/130) of second TSH results fell within the reference intervals and 59.2% (77/130) remained above the reference interval. No 2nd TSH levels were over 10 mIU/L. Tests within three months are likely to capture the recovery of TSH from illness, if that has occurred at the time of the first test; a gap in testing is recommended. 44/130 (33.8%) of repeat tests were within this three month window. There were 12 individuals who had antibody testing - 5 positive results and 7 negative results. No results showed anti-Tg in isolation. On examination of subsequent tests, 40/53 (75.5%) of patients whose second TSH result were within the reference interval remained within the reference interval, while 73/77 (94.8%) of patients whose second TSH result was raised remained above the upper limit on

subsequent tests. Fourteen patients had no further tests after the follow-up test including one patient who was placed on thyroxine.

FIGURE 6: TESTING FOLLOWING A FIRST RAISED TSH RESULT



FT_4 was tested at least once in 55.1% (146/265) of patients during the 12-month follow-up period. 41/146 (28.1%) patients had one or more repeat FT_4 tests. There was no difference in FT_4 testing by age group (p=0.2512), gender (p=0.1420) or ethnicity (p=0.5197). The time difference between TSH and first FT_4 test ranged between 0-304 days (mean 26 days, median 0 days).

Of the patients who had a FT_4 test, as previously mentioned, 74.0% (108/146) had it taken concurrently with their first TSH test. A further 5.5% (8/146) were tested within 2 weeks, 7.5% (11/146) by 3 months, 9.6% (14/146) at 6 months and 3.4% (5/146) between 6 and 12 months. All FT_4 results were within the reference interval except two individual results who had slightly low results (FT_4=8 p/mol/L). Neither of these individuals were prescribed medication, coded for hypothyroidism, had a family history of thyroid disease or had antibody testing.

Overall, 6.0% (16/265) of patients had thyroid antibody testing results; four patients had no further TSH tests (one with positive anti-TPO), four patients had second TSH results within the reference intervals (two with positive antibodies), and 8 patients had raised second TSH results (three with positive antibodies). Overall, thirty percent (6/20) of patients having thyroid antibody testing had positive results - two patients positive for anti-TPO and four patients positive for both anti-TPO and anti-Tg. One patient with positive antibodies and persistent raised TSH levels was referred to endocrinology.

Of the 4.9% (13/265) of patients placed on thyroxine replacement medication, no patient had a TSH result greater than 10 mIU/ml. Two patients had no follow-up investigations (one was subsequently coded for hypothyroidism) and one had no TSH follow-up and negative auto-antibodies. Four patients had one or more follow-up TSH results all within the reference interval; possibly the result of thyroxine replacement. Six patients on medication had results indicating SCH, two were coded for hypothyroidism and one had their second test within the three month window and therefore could not be confirmed. No other blood tests or investigations were carried out in this group.

Symptoms leading to first thyroid function tests were reported in 29.1% (77/265) of patients with the general practice recording from 1-3 symptoms. The most common symptoms reported were tiredness/lethargy in 32.5% (25/77) of patients, weight gain (14.3%) and sluggish thinking (14.3%). Cold intolerance, constipation, dry skin, hair loss, general slowing, heart failure, deepening voice, shortness of breath on exertion, menorrhagia and ataxia were also recorded.

In the 12-months following first test 25.7% (68/265) of patients had symptoms recorded. Tiredness/lethargy remained the most commonly reported symptom in 47.1% (32/68) of patients, followed by weight gain (20.1%). Of the 88 patients with both height and weight measures, BMI ranged from 19 - 44 (average and median = 29).

Recorded co-morbidities included depression in 15.8% (42/265) of patients, followed by diabetes in nearly 9.8% (26/265) and heart failure in 5.3% (14/265) of patients. Of other possible investigations, one patient had a thyroid ultrasound with no abnormality detected and one patient had an inpatient Technetium scan performed. One patient had been referred to Waikato Health Endocrinology (SCH with positive antibodies).

Less than 2% (5/265) of patients with raised TSH had a subsequent (not concurrent) FT_4, and where this was normal had antibody testing. However, three out of the five patients had FT_4 and antibodies taken concurrently. Therefore, less than two percent of patients in this follow-up study appeared to be managed according to BPACnz guidelines.

DISCUSSION

To clarify the focus group discussions around the management of SCH, we followed a retrospective cohort of patients with no prior thyroid dysfunction and laboratory results suggestive of SCH. The use of tests and management of SCH were compared to current guidelines from the New Zealand Best Practice Advocacy Centre (BPACnz) on investigating thyroid function as outlined on page 93 [30]. We also examined computerised patient records for symptoms which had been recorded around the time of the first TSH test and for the subsequent 12 months.

What we found was a lack of consistency with the guidelines following on from a raised TSH result. Of the 265 individuals with results indicating SCH, 51% had no follow-up TSH investigations. Of those with further tests nearly 45% of patients had no FT_4 test. Guidelines suggest 'reflex testing', which relates to further testing from retained blood samples at the laboratory and indicated by the TSH result [30]. This gives the opportunity for general practitioners to directly request an FT_4 test using the original blood sample without the need to recall the patient. Three percent of FT_4 tests were taken within two weeks of the initial TSH test with forty percent of FT_4 tests taken concurrently with TSH. The number of follow-up TSH tests returning to within the reference interval (40.8%) was similar to international literature which ranges from 37.5% in the first 12 months to 50% over 5 years [109, 110].

Ninety-four percent of patients had no thyroid antibody tests despite guidelines to do so where FT_4 remains within the reference interval. Autoimmune thyroid disease is the most common cause of primary hypothyroidism in the western world and has been associated with an increased likelihood of progression from SCH to overt hypothyroidism [66]. General practitioners who use thyroid antibody assays to guide decision-making are found to be more likely to adhere to guidelines for managing thyroid dysfunction [305].

The use of symptoms in the clinical picture is less clear in the literature. New Zealand guidelines advise that the decision to initiate treatment should be based on evidence of symptoms. In our study, the most commonly recorded symptoms were tiredness/lethargy and

weight gain. Symptoms were recorded in 29.1% of patients; however, this does not necessarily indicate that those without recorded symptoms had no symptoms. Reviewing symptomatology using clinical notes may be problematic if, for example, basic clinical information such as weight is inconsistently recorded. This implies, as with hand-held records, that computerised records are only as good as the information inputted into them. Of 265 patients in our cohort, 23% (61/265) of patients had no weight recorded. Furthermore, symptoms are often non-specific and are not considered a good predictor of hypothyroidism [280].

Data from practice management systems were consistent with findings from recent focus groups [309]. General practitioners identified a range of responses to retesting which corresponded with our findings of 0-5 further tests in a 12 month period. Symptoms identified in focus groups such as tiredness/lethargy and weight gain were also the most prominent symptoms of any that were recorded [309].

For the forty-eight percent of patients with no further investigations, thyroid function tests examined in isolation may not give a full clinical picture. In the context of co-existing acute illness the TSH levels may give results that are potentially misleading as they may echo non-thyroidal illness. Guidelines advise against testing thyroid function at such times as TSH is altered independent of thyroid status [30].

For patients with untreated SCH, TSH monitoring is recommended every 6-12 months. Our study may underestimate re-testing due to the exact 12-month cut-off that we used. Due to a lack of FT_4 tests, SCH was confirmed by two raised TSH results no less than three months apart, which may not provide a true picture of aetiology of thyroid function or confirmation of SCH.

We found inconsistencies in the management of SCH that were unrelated to patient characteristics such as age, gender or ethnicity. No clear pattern emerged in the timing of FT_4 tests, repeat TSH testing, antibody testing, prescribing or recording of symptoms and this is reflected in the number of patients whose management did not follow the guidelines. A departure from guideline recommendations may be due to the general practitioners wish to maintain a good relationship with their patient through responding to patient requests, to back up their advice or to provide safe-guard against the possibility of future litigation [309 369]. In addition, general practitioners may lack recognition of their need for further training, specifically in topics such as thyroid disease [75]. Unwittingly, general practitioners may be less

able to make informed decisions about their patient care: for instance, when abnormal TSH results present [80]. Guidelines are not always accepted by or acceptable to general practitioners [301, 370].

The lack of consistency in providing a standardised approach in view of current guidelines needs to be addressed in a way which recognises the experience of the general practitioner and the rights of the patient in following a pathway of care. Current guidelines in the assessment and management of SCH provide a theoretical basis which is controversial [66, 67].

CONCLUSION

Despite a lack of alignment to current guidelines as shown in our retrospective follow-up of SCH patients in general practice, there remain unanswered questions in relation to SCH. A recent Cochrane Review regarding the use of thyroxine for subclinical hypothyroidism lacks decisive answers for general practitioners, concluding the need for practitioners to use clinical judgement [24]. With the current available evidence regarding the clinical significance of subclinical hypothyroidism, general practitioners remain disempowered to adequately manage their patients who present with inadvertent raised TSH, with or without symptoms, suggestive of subclinical hypothyroidism. Further studies are recommended which demonstrate the impact of using TSH as a first-line strategy, whether SCH is associated with increased morbidity, and whether there is benefit in treating SCH patients with thyroxine.

OVERALL SUMMARY OF STUDIES

We established the prevalence of hypothyroidism in our population to be similar to that of international literature, therefore, suggesting that currently New Zealand has a pattern of disease that has no major environmental influence. We estimated the prevalence of hypothyroidism to be 2.5% in the adult population, occurring mainly in women and in older adults.

We found that 1 in 6 adults without known thyroid dysfunction will be offered a thyroid function test by their general practitioners over a 12-month period. The rate of testing increases with advancing age and is higher in women than men. A high proportion of adults had normal thyroid function (92%) but this differed by age, with 96% in 20-29 year age group decreasing to 84% in the 80+ age groups.

General practitioners had several reasons for requesting a thyroid function test which did not always relate to the belief that a thyroid condition existed. Generally, patients with symptoms suggestive of thyroid dysfunction were offered TSH, FT_4 and FT_3, while patients with vague symptoms had TSH alone. General practitioners were aware of policy guidelines regarding investigating thyroid function, however, they utilised clinical judgement when requesting tests. There was concern regarding central hypothyroidism, a rare condition, which may be missed if a TSH alone strategy was adhered to. In some situations TSH was requested to reinforce the discussion between the general practitioner and patient where it was most likely that there was nothing wrong but showed that the general practitioner was taking note and shown to be taking the patient's concerns seriously. General practitioners also felt that this gave added protection in case of future changes to the patient's thyroid function in light of increased litigation around medical practice. Having concrete evidence of a test result was valuable in this situation. In addition, an abnormal TSH was increasingly common, which may be due to an increase in testing, and there were differing views on what to do about this. Future management tended to favour further interaction with the patient to guide decision making where TSH was within the subclinical hypothyroidism range. The views on whether to treat with thyroxine varied as did the point at which treatment should be considered.

When retrospectively following a cohort of patients with laboratory results indicative of SCH, we found a lack of consistency with national guidelines. However, it can be argued that the guidelines remain vague in terms of outcomes for patients with SCH. Despite national guidelines, where results were in the subclinical range, general practitioners maintained overall clinical judgement to decide further management which was made in conjunction with patient's preferences. Until evidence showed an increased risk in not treating patients with SCH, the choice for thyroxine in this patient group did not prevail.

RECOMMENDATIONS FOR FURTHER STUDY

Three aims have been identified which will provide evidence to support decision-making by general practitioners. These are:

- To investigating the pathways in primary practice leading to the diagnosis of central hypothyroidism prior to the establishment of TSH as a first-line test for testing thyroid dysfunction;

- To analyse long-term outcomes of patients with hypothyroidism (subclinical and overt) in relation to cardiovascular events; and,

- To establish the effectiveness of thyroxine in preventing cardiovascular morbidity in patients with subclinical hypothyroidism.

CHAPTER 3 - INVESTIGATING THE PATHWAYS IN PRIMARY PRACTICE LEADING TO THE DIAGNOSIS OF CENTRAL HYPOTHYROIDISM

General practitioners request the majority of thyroid function tests [350]. Since October 2005, recommendations have been made which limited thyroid function testing to using thyroid stimulating hormone (TSH) as a first-line strategy for investigating thyroid function [30]. This has been developed as a response to economic pressures to reduce the overwhelming number of requests for tests [9, 10, 309]. Additionally, the majority of thyroid function testing in adults are within the normal range [308]; which supports the view that thyroid tests are requested in the absence of strong clinical suspicion of disease [73]. Recommendations, therefore, would appear appropriate. However, endocrinologists and biochemical pathologists have suggested that a TSH first-line strategy will lead to avoidable delays in diagnosis and treatment for patients with central hypothyroidism [9, 10, 73]. Central hypothyroidism is rare and is associated with a varied and prolonged course prior to diagnosis which can make the diagnosis difficult for general practitioners.

Central hypothyroidism, formerly known as secondary hypothyroidism (see page 16), relates to anatomical or functional conditions of the pituitary or hypothalamus, or both [371]. The term conveys quantitative and qualitative abnormalities of TSH secretion, irrespective of whether it is of hypothalamic or pituitary origin [371]. Central hypothyroidism is rarely an isolated defect, usually part of a more complex condition, hypopituitarism, which also affects other pituitary hormone secretions such as growth hormone, gonadotropin, prolactin and adrenocorticotropin hormone [371]. Current literature suggests that the incidence of hypopituitarism, which includes central hypothyroidism, is around 4-5 per 100,000 population per year [9, 351, 371]. It is distributed equally between sexes and peaks between 30 and 60 years of age [371].

As described in Chapter 1, the pituitary gland secretes trophic hormones that control the production of certain hormones by the pituitary's target organs. In the case of the thyroid gland, the pituitary secretes TSH which acts as a trophic hormone controlling the secretion of thyroid hormones by the thyroid. Under normal circumstances the production of TSH is regulated by the level of thyroid hormones, such that when the thyroid is overproducing thyroid hormones, the TSH level is suppressed and the converse occurs in primary hypothyroidism [1, 120].

In primary hypothyroidism the thyroid gland is not able to secrete sufficient thyroxine (T_4) and triiodothyronine (T_3) and the levels of TSH rise to stimulate the thyroid gland to secrete

more thyroid hormone. This results in the patient having a low free or total T_4 and an increased level of TSH. In central hypothyroidism there is diminished secretion of TSH as the primary defect resulting in low or 'normal' levels of TSH and a low T_4 [371, 372]. This may be caused by the partial or complete lack of pituitary hormone secretion [373]. Paradoxically, on rare occasions, TSH secretion can be impaired qualitatively, demonstrating a raised TSH level due to secretion of TSH that is immunoreactive but biologically inactive [374-376]. In some patients with hypopituitarism free T_4 (FT_4) or total T_4 can be low yet the TSH level is normal or even slightly raised [68].

A Spanish study identified 79% of hypopituitarism patients with more than one pituitary hormone deficiency and of the types of hormonal deficiencies, 64% of patients had TSH involvement; the second most common hormonal deficiency after luteinising hormone/follicle stimulating hormone [351]. Where hypopituitarism was of tumoral origin, growth hormone deficiency was more frequent than in cases of non-tumoral origin. In another study, 56,000 tests were prospectively audited from a population of 471,000 in Liverpool [9]. A series of tests including TSH and total T_4 were followed up with FT_4, total T_3 and other pituitary hormone tests. As a result of this strategy, a total of 17 patients with results suggestive of central hypothyroidism were found. TSH results were within the normal range; however, total T_4 and FT_4 were low, as were a number of other hormones, indicating panhypopituitarism (affecting all of the pituitary hormones) in nine of the seventeen cases.

These findings estimated an incidence of 5.5 cases per 100,000 per year, with as many as 3.2 cases per 100,000 per year going undiagnosed if a first-line TSH strategy is used [9]. A Glasgow study with an outpatient population of approximately 200,000, used strict criteria for using reflective testing to examine raised TSH (up to 10 mIU/L) and low FT_4 (<9 pmol/L). They added a repeat FT_4 along with measurements of gonadotropin, cortisol, prolactin, total T_3 and testosterone (in males) using the same blood sample. With this strategy they found 10 new cases of hypopituitarism (4 cases/100,000/year); incidence figures similar to the Liverpool study [350].

The causes of central hypothyroidism vary, with the most common cause being pituitary adenomas which account for over 50% of cases (Table 12) [371].

TABLE 12: CAUSES OF ACQUIRED CENTRAL HYPOTHYROIDISM

Cause
Classical causes
Space-occupying lesions (pituitary adenoma, craniopharygioma, etc)
Radiation
Vascular disease (Sheehan syndrome, etc)
Non-classical causes
Traumatic brain injury or subarachnoid haemorrhage
Drug-induced e.g. carbemaxepine (Tegretol®)
Growth hormone therapy
Infection
Inflammation (lymphocytic hypophysitis)
Idiopathic

Modified from Yamada, 2008 [372]

The clinical presentation of central hypothyroidism can often be similar to that of primary thyroid disease [349, 371, 377]. The investigations into the diagnosis of central hypothyroidism are hampered by the use of TSH alone as a first-line thyroid test [373]. It is likely that the true incidence of central hypothyroidism will be missed as TSH may remain within the reference interval despite T_4 and T_3 being low [9, 350 372 10, 73].

Current recommendations for investigating thyroid function are believed to be a barrier for general practitioners in diagnosing central hypothyroidism and may lead to under- or delayed diagnosis and treatment [10]; further potentially increasing morbidity and reducing the quality of life for these patients [73 9]. Best Practice Advocacy Centre (BPACnz) guidelines suggest a first-line TSH policy based on symptomatic presentation showing that, unless the patient has a goitre or delayed reflexes in which hypothyroidism is suspected, the likelihood of thyroid dysfunction is low (below 3%)[378]. Therefore TSH would be adequate with additional testing of FT_4 and thyroid autoantibodies as appropriate based on this rationale [30]. Extrapolating to New Zealand guidelines, the decision to test TSH alone adequately fits 99.6% of testing strategies and it is acknowledged that there are limitations in using this when investigating central hypothyroidism [30].

Achieving an accurate and timely diagnosis is relevant because central hypothyroidism is a readily treatable disease [9]. Clinical diagnosis is not always obvious: patients may live for

years with symptoms [379]. The clinical picture varies widely and is dependent on the severity of thyroid failure, the age of the patient at time of onset, other associated hormone deficiencies and the nature of the underlying lesion [380]. In addition, the majority of thyroid function tests are requested by primary care doctors who may have very little experience with pituitary disease and may not consider that a TSH value within the normal range does not rule out central hypothyroidism [10, 73, 350].

In order to improve timely diagnosis and thus decrease morbidity from a treatable disease, this study aimed to investigate the diagnostic journey of patients with central hypothyroidism in the Waikato region.

RESEARCH DESIGN AND METHODS

We used note review and semi-structured questionnaires to retrospectively review patients with a diagnosis of central hypothyroidism following ethics approval from the Northern Y Regional Ethics Committee (NTY/08/09/091). We sought a convenience sample of 20 patients from the 100 patients with a diagnosis of hypopituitarism (including those with panhypopituitarism and central hypothyroidism) whose details were held on the Waikato Hospital endocrine database. Notes were reviewed to confirm that patients had central hypothyroidism as evidenced by patterns of thyroid function testing and consultant diagnosis. In addition to searching the database, patients with a diagnosis of central hypothyroidism who presented to the endocrinology department for a routine visit while the study was being carried out were invited to participate. Patients who were diagnosed with central hypothyroidism before 1990 were excluded to reduce recall bias. We also excluded patients whose diagnosis was as a result of pituitary surgery or radiotherapy to the pituitary or hypothalamus. The pathway for surgical patients is through secondary care and is outside the aims of this study.

A timeline of the diagnostic process was constructed for each patient as accurately as possible from the hospital files. Further information was supplemented through patient interviews. The semi-structure questionnaires were conducted either face-to-face at the patient's home or over the telephone depending on the patient's place of residence (e.g. if >1 hour's drive from Waikato Hospital). General questions for every participant included information about the symptoms leading to general practitioner visits and to their first endocrinology visit leading to diagnosis. These were supplemented with specific questions about the experience leading

up to their diagnosis to attain a full picture of the process. With the patients' permission, their general practitioner and specialists who were involved with their care around the time of diagnosis, including those from outside of Waikato, were contacted for further information if needed.

We aimed to include twenty participants for detailed assessment, a number considered large enough yet manageable within the time constraints of the study.

RESULTS

Of the 20 people selected, 16 agreed to take part in the study. 8 were male and 8 were female, ages ranged from 39 - 83 years (mean age 65, median age 67.5). The age range at diagnosis was 35-80 years (mean age 58, median age 57.5). Our sample included one Māori and 15 New Zealand European participants.

TESTING THYROID FUNCTION

Both TSH and T_4 tests were taken in 81% (13/16) participants prior to their first endocrine assessment, with 75% (12/16) having results suggesting either pituitary disease or that further investigation would be required. Of the 13 participants with prior testing, general practitioners requested 69% (9/13) of these.

In 38% (6/16) of participants diagnosis was made by the general practitioner. For two participants, their diagnosis was made when, independently of each other, they had moved to register with the same general practitioner. Another two participants had their diagnosis immediately identified by their general practitioner and in the remainder, a further two participants, central hypothyroidism was identified by their general practitioner after a period of more than six months.

For five participants (31%) a diagnosis of overt hypothyroidism had been made by the general practitioner prior to their correct central hypothyroidism diagnosis.

LENGTH OF DIAGNOSTIC PROCESS

Time to diagnosis ranged from 3 months to over 25 years. Table 13 summarises the length of the diagnostic process. (Some rows do not add up to 16 participants as certain data were not able to be obtained for some participants.)

TABLE 13: LENGTH OF THE DIAGNOSTIC PROCESS

Months /General practitioner visits	<3	3 to 6	6 to 12	>12
Number of participants with symptoms by **months** prior to a first general practitioner visit	5	1	1	7
Number of participants by number of **general practitioner visits** prior to diagnosis	2	7	5	0
Number of participants by **months** to diagnosis	5	2	3	6
Number of participants by overall number of **months** with symptoms prior to central hypothyroidism diagnosis	3	2	1	10

Five participants had symptoms for less than three months, while seven participants had symptoms for greater than a year before seeing a general practitioner. Seven participants identified having 3 - 6 visits to their general practitioner and five participants made 6 to 12 visits to their general practitioner prior to diagnosis. The time between the first general practice visit to being diagnosed varied with five participants being diagnosed in less than three months and six patients being diagnosed over 1 year later. Overall, 69% (11/16) of participants were diagnosed after 6 months. Thirty-eight percent (6/16) of participants lived with symptoms for more than 2 years (not shown).

SYMPTOMS

One or more of the following symptoms were reported by the participants: headaches, lethargy, visual disturbances, weight change, joint or muscle pain, change in skin texture, change in body hair distribution or texture, mood changes, irritability, menstruation irregularities in women, loss of facial hair in men, erectile dysfunction and loss of sexual drive.

Lethargy was the most common symptom in 94% (15/16) of participants. This was followed by changes in skin texture and body hair distribution and texture in 75% (12/16) of participants and headaches in 63% (10/16) of participants.

The subsequent expressions listed in Table 14 are examples of sentiments from interviews showing the effect that undiagnosed and untreated central hypothyroidism had on the participants.

TABLE 14: RELATING TO SYMPTOMS - FROM INTERVIEWS WITH PARTICIPANTS

Retired early due to fatigue.
Marriage strained due to mood changes (reported in three participants).
Felt like she "*couldn't go on*".
Lack of libido for years affected marriage (reported in two participants).
Felt that *no one was listening*, that she (wife) *was going mad*.
Knew that something was not right but frustrated because no one knew what was going on (reported in 5 participants).

Interviews with participants highlighted frustration of the impact pituitary disease had on their day to day lives. Many felt extremely discouraged that they knew "*something was really wrong*" but no one seemed to know what or why. An example of this was revealed in one participant's statement, her general practitioner "*didn't recognise the symptoms*" and was unable to pinpoint the problem. This created a sense of isolation for participants and their families. As one individual stated, his wife "*felt like she was going mad, and no one was listening (to her)*".

Extreme lethargy resulted in one man retiring earlier than he would have liked, mothers and fathers were unable to take part in child rearing, and attending work became increasingly difficult. Examples of the severity of the symptoms included being "*unable to get out of a chair for 5 months*", "*inability to get out of the bath*" and "*falling asleep for days at a time*".

Erectile dysfunction in men and lack of sexual desire created discord amongst couples, and mood changes and irritability generally disrupted family dynamics. One participant described his lack of sexual desire as "*not wanting it at all*" for more than 4 years. The effects on family life were further evident. One participant stated that she, "*was surprised the family was still together*" due to her irritability. Another participant remembers her daughter describing her as having been bad tempered and apologetic. Headaches were described as debilitating,

severe and continuous, "*for 4 months*" in one participant and "*painful enough to prevent sleep*" in another.

DISCUSSION

Central hypothyroidism is rare: the incidence of central hypothyroidism is approximately 0.005% in the general population [371]. The rarity of central hypothyroidism means the likelihood of having this condition is small, however, there is a suggestion that it may be more common than already reported [9]. Symptoms are vague and there is low clinical suspicion for this condition [350].

Thyroid function tests are the most commonly requested endocrine investigation [308, 350]. Patterns of central hypothyroidism are recognised by endocrinologists and likely to be acted upon [350]. General practitioners, who request the majority of tests, are more likely to miss cases [350 10]. Acknowledging that clinical suspicion should override any misleading biochemical findings places undue weight on the clinical skills of general practitioner who appear to rely more heavily on investigations [10]. Because central hypothyroidism is rare, we identified known cases in order to examine the journey of the participants to diagnosis.

Three methods of information gathering were used to ensure accuracy of information; using each source to confirm or correct another. It was also necessary to garner a full picture of the process for each patient. We sought one-to-one interviews with patients in order to gain insight into their quality of life prior to diagnosis.

The limitations of this study included the time taken in identifying the primary diagnosis of central hypothyroid patients from the endocrine database. Due to the time taken to confirm the diagnosis all possible files could not be identified. A convenience sample was undertaken based on the first 20 people who met the criteria from the order in which they appeared in the database (by NHI number) or referred by the endocrinology team. While we set a minimum diagnosis date after 1990, those with an NHI number (a 3-letter, 4-number health identifier) who are early in the numbering sequence, e.g. closer to AAA1111, are likely to be older. Due to participants' age or the length of time since diagnosis, this study is likely to suffer from recall bias. However the three methods used - hospital records, patient interview and general practice records - were able to clarify where there may have been gaps.

The small number of participants interviewed is a limitation of this study, although it can be argued that the message they gave about their symptoms was consistent. The majority of participants who had thyroid function tests with results suggestive of pituitary or hypothalamic involvement, lived with symptoms for over 12 months prior to diagnosis. Furthermore, symptoms reached a point where immediate life-saving action was taken leading to their diagnosis. Of the 16 participants, 9 were diagnosed upon acute admission to Waikato Hospital with symptoms severe enough to cause in-patient admission.

The lengthy diagnostic process is likely due to a lack of recognition and a low clinical suspicion when faced with abnormal thyroid function test results [9, 333, 350]. Thyroid function test results are often used by general practitioners as a diagnostic tool [308]. Eighty-one percent (13/16) of participants had at least one abnormal thyroid function test result prior to being seen by an endocrine specialist. The majority of participants in this study were diagnosed prior to October 2005 when current BPACnz guidelines for investigating thyroid function were released. The utility of TSH, FT_4 and FT_3 by general practitioners were not limited at this time.

Of participants who received thyroid function tests prior to their first endocrine specialist appointment, 12 had results that warranted further investigation. This appears to have delayed diagnosis with the majority of participants waiting more than 6 months to be diagnosed and 10 out of 16 living with symptoms for more than 12 months. Furthermore, six of these 10 lived with symptoms for over 2 years. Contrary to what is currently implied in the literature, that a first-line TSH policy will delay diagnosis [9, 10], even with the full range of thyroid function tests, general practitioners were failing to investigate abnormal results. This situation may be more evident in future with current recommendations of testing TSH alone.

With the majority of participants having at least three related visits to a general practitioner and 12 months of symptoms before diagnosis, it is evident that the clinical suspicion of central hypothyroidism needs to be raised. Earlier identification of central hypothyroidism would avoid patients reaching a point where immediate action is required. The low incidence of central hypothyroidism means a GP may see a case every 14-28 years. Therefore, better awareness of indicators of central hypothyroid to include the identification of patterns of disease based on thyroid function tests as well as investigating specific symptoms could be achieved. Furthermore, greater provision for reflective testing which implies additional testing at the discretion of the reporting biochemical pathologist given relevant clinical and

biochemical information, would provide timely input into the diagnostic process [350]. This is in contrast to reflex testing, where additional tests are added automatically [30, 350].

Headaches and visual disturbances may present before symptoms of pituitary failure. In addition, a clear history of a change in sexual desire, sexual function and menstruation is likely to antedate clinical evidence of central hypothyroidism [379]. However, irregularities in these areas may not readily be conveyed to a general practitioner because of the intimate nature of symptoms involving sexual function. During patient interviews, information about sexual desire and function may have been under-reported due to participants feeling uncomfortable disclosing this information with the researcher who they did not know. Furthermore, a natural reluctance of health professionals to inquire into a patient's sex life has also been described previously, although it has been noted in a 1954 study that female patients suffering from hypopituitarism lose their 'bashfulness' [379]. Suspicion of central hypothyroidism should actively follow these lines of questioning even if they are not readily offered by the patient.

The patient interviews in particular allowed an insight into quality of life prior to diagnosis that is often difficult to obtain from written medical notes. This showed the impact of central hypothyroidism on participants' ability to function in several areas of their life. Participants described experiencing "extreme lethargy": the inability to get out of the bath; go to work; get out of bed for an entire weekend; statements that quantified the seriousness of this disease when left untreated. The repetition of statements regarding the impact on family life and the degree of frustration that was felt showed that central hypothyroidism had a consistent impact not only on an individual's physical health but also on their mental health.

Several prevalent symptoms of central hypothyroidism are like those of primary hypothyroidism [371 350]; causing difficulties in diagnosis. Thirty-one percent of participants (5/16) were misdiagnosed with primary hypothyroidism. Central hypothyroidism is treated with levo-thyroxine similar to primary hypothyroidism. As thyroid hormones are known to increase cortisol clearance [373], there is a danger when adrenocorticotropin, and as a result cortisol secretion, is inadequate thus precipitating an adrenal crisis. . Where adrenocorticotropin production is deficient, adrenal steroid replacement must be initiated prior to levo-thyroxine treatment.

When presented with vague symptoms of thyroid dysfunction, investigating central hypothyroid-specific symptoms may quickly distinguish between the two. Several

differentiating features relating to hyposecretion of other pituitary hormones help this. Changes in skin texture and body hair distribution may be evident - the skin is pale and cool in central hypothyroidism compared with coarse and dry from primary hypothyroidism; loss of body hair and thinning of lateral eyebrows are usually more pronounced in central hypothyroidism. Body weight is likely to be reduced rather than increased in central hypothyroidism [371]. In addition, periorbital and peripheral oedema and hoarseness of the voice are uncommon in central hypothyroidism.

CONCLUSION

A first-line TSH strategy works only if the hypothalamic-pituitary-axis is normal [372]. This strategy may also work as long as limitations are appreciated [291]. While it can be argued that symptoms such as tiredness and lethargy are common in the general population, these findings are also common in patients with a diagnosis of central hypothyroidism. We found that the diagnosis of central hypothyroidism in the Waikato area was delayed for the majority of participants until they had received specialist involvement due to a lack of recognition by general practitioners [9, 350, 374, 379]. Due to the time-frame in which participants were diagnosed, we did not find that a delay in diagnosis was due to an absence of FT_4 requests which a first-line TSH strategy would imply. Rather it appeared to be due to a lack of appropriate response from general practitioners to central hypothyroidism indicators (low TSH, low T_4 and presenting symptoms). This has been borne out in the literature.

Suggestions for improving diagnosis involve raising awareness of the signs and symptoms of central hypothyroidism, along with the inclusion of free thyroxine (FT_4) testing as appropriate. Greater input from endocrinologists and from biochemical pathologists when faced with abnormal thyroid function tests would create a better opportunity for diagnosis [350].

Raising awareness with general practitioners of these indicators is warranted because of the physiological, social and psychological impacts of central hypothyroidism. Central hypothyroidism is rare, but if general practitioners suspect abnormalities in thyroid function, it is essential that they accurately interpret thyroid function tests, seek advice from endocrinologists and biochemical pathologists, recognise that TSH may be unreliable, and thoroughly pursue relevant symptoms.

CHAPTER 4 – LONG-TERM OUTCOMES OF PATIENTS WITH HYPOTHYROIDISM: AN ANALYSIS OF CARDIOVASCULAR MORBIDITY AND MORTALITY OVER A DECADE (1997-2006).

BACKGROUND

General practitioners have unanswered concerns regarding the treatment of subclinical hypothyroidism [309] and believe there is no evidence of harm by not treating. An association between hypothyroidism and cardiovascular disease has been established. A major concern highlighted by recent observational studies is the increased risk of cardiovascular morbidity and mortality in subjects with subclinical hypothyroidism [17, 22, 27, 381]. Large randomised controlled trials investigating the benefits of treatment in patients with subclinical hypothyroidism have not as yet been conducted [24]; nevertheless, a 20-year cohort study indicates that treatment for these patients appears to attenuate ischaemic heart disease-related mortality and morbidity [17].

Cardiovascular disease remains a leading cause of morbidity and mortality in New Zealand [382]. The effects of thyroid hormones on the cardiovascular system are well documented [14, 122]. The pathophysiological effects of thyroid function on the cardiovascular system are directly related to the consequences of thyroid hormone on the heart and vascular system [122, 123]. Changes in cardiovascular function in patients with hypothyroidism include: an increased systemic vascular resistance; decreased heart rate; slight reduction in cardiac output; an increase in isovolumic relaxation time; and, decreased percentage of blood volume [122]. However, due to internal compensatory mechanisms these cardiovascular manifestations may not produce overt clinical symptoms in patients with raised TSH. Treatment with thyroxine replacement therapy (TRT) is standard for overt hypothyroidism.

There are difficulties in interpreting whether an individual with subclinical hypothyroidism, characterised by a raised thyroid-stimulating hormone (TSH) result, requires chemoprophylaxis, especially where TSH remains below the recommended level for commencing TRT (10 mIU/L) and the FT_4 is within normal reference intervals [30]. Further evidence is required regarding the management of subclinical hypothyroidism, in particular, the potential benefits and harms for instigating treatment, where the outcomes are presently uncertain.

This study aimed to examine survival in individuals $\geq$ 20 years of age with varying degrees of hypothyroidism, namely subclinical and overt hypothyroidism, in relation to cardiovascular morbidity and mortality over a decade (1997-2006) by age, gender, ethnicity and deprivation score and comparing them with euthyroid individuals (with normal thyroid function).

RESEARCH DESIGN AND METHODS

This cohort study utilises laboratory data of thyroid function tests to establish links with cardiovascular outcomes from the National Minimum Data Set (NMDS) for hospital events and national Mortality Collection (MORT). Data are assessed by the following potential confounders: age, gender, ethnicity and deprivation index.

A unique patient identifier, the national health index (NHI) number, is assigned to every individual using a health or disability service and this was used to link data. The NHI data set holds information such as names and addresses, ethnicity, gender and date of birth.

Ethical approval for this study was granted by the Northern Y Regional Ethics Committee (Reference NTY/06/11/124).

STUDY POPULATION

The study population includes all individuals over 20 years of age with a valid NHI number who had a thyroid function test (thyroid stimulating hormone (TSH), free thyroxine (FT_4) with or without a free triiodothyronine (FT_3)) through Medlab Hamilton within a 14-year period from 1993 – 2006.

All thyroid function tests performed within the territory of Medlab Hamilton (from Turangi to Te Kauwhata and from Kawhia to Whitianga) between 1/1/1993-31/03/2007 were captured in this data set.

DATASETS

LABORATORY DATA SET

The laboratory data set contained 1,322643 observations and was used to define the study population. Data included the national health index (NHI), test code, test name, laboratory reference interval, date sample collected, date reported, requesting doctor, demographic data including gender and date of birth, laboratory identifying number and result for each observation.

NATIONAL MINIMUM DATA SET (NMDS) FOR HOSPITAL EVENTS

The NMDS is a national collection of hospital discharge information from public and private hospitals [340]. Clinical information is coded using the International Classification of Diseases (ICD). The original NMDS was introduced in 1993 and back loaded to 1988. The current NMDS was introduced in 1999. At this time, some of the data subsets, such as the Cancer Registry and the Mortality Collection, were removed and are held separately.

Publicly funded hospitals have been submitting electronic data in an agreed format since 1993. They are required to load events into the NMDS within 21 days of a patient being discharged from hospital. Private hospital discharge information for publicly funded events has been collected since 1997. Data provided from larger private hospitals, maternity and geriatric events and some surgical events are up-to-date.

Clinical coding within NMDS is through a clinical coding system ID, which identifies the clinical diagnoses and procedures based on ICD coding. Previously known as the 'Diagnosis coding system code', data that has earlier entered ICD codes are mapped to new ICD codes as they are updated. ICD-9-CM was used between 1988 and 1995 and was mapped to ICD-9-CM-A when this was later introduced. Subsequently, data that were submitted in either ICD-9-CM-A or ICD-10-AM 1st edition when that was introduced was mapped so that it was held in both systems from July 1999. Data originally coded from ICD-9-CM is now no longer used [340].

Mapping of previous editions of ICD-10 continues to be mapped to earlier classifications where mappings exist as shown in Table 15.

TABLE 15: THE RELATIONAL AND REPRESENTATIONAL ATTRIBUTES OF THE CLINICAL CODING SYSTEM

1988 – 30/6/1995	ICD-9-CM
1/7/1995 – 30/6/1999	ICD-9-CM mapped to ICD-9-CM-A and ICD-10-AM-v1
1/7/1999 – 30/6/2001	ICD-9-CM-A and ICD-10-AM-v1 mapped to be held on both systems
1/7/2001 – 30/6/2004	ICD-10-AM-v2 mapped to earlier classifications
1/7/2004 – 30/6/2008	ICD-10-AM-v6 mapped to ICD-10-AM-v3

Access to NMDS is controlled by the Ministry of Health and the release of information recognises any legislation related to the privacy of health information Acts: in particular, the Official Information Act 1982, the Privacy Act 1993 and the Health Information Privacy

Code 1994. Identifiable data required for this study were obtained through the New Zealand Health Information Service (NZHIS) with approval from the Northern Y Regional Ethics Committee (NTY/06/11/124).

The NMDS data set was provided from NZHIS based on the study population of 160,222 individual NHI numbers from the laboratory data set. For each NHI number provided, where a hospital event had occurred, data were provided for up to 20 ICD codes per date of event. We sought the first date of cardiovascular disease entry by ICD code for all entries; thereby capturing individuals who have ever had a cardiovascular event. The NMDS data set also includes information such as date of birth, date of event, gender, ethnicity, and New Zealand Deprivation Index (NZDep) at the time of the event.

MORTALITY COLLECTION (MORT)

The Mortality Collection (MORT) classifies the underlying cause of death for all deaths that have been registered in New Zealand [383]. This includes registrable stillbirths (foetal deaths). MORT was established to provide data for public health research, policy formulation, development and monitoring, and for cancer survival statistics. This information is provided yearly to the World Health Organization to be used for international comparison of mortality statistics.

All deaths registered in New Zealand since 2000 are coded using the ICD-10AM 2nd Edition and adhere to the World Health Organization Rules and Guidelines for Mortality Coding. Prior to this deaths since 1988 held in MORT were coded to ICD-9-CM-A and are not mapped forward to ICD-10-AM.

Information to be held within MORT is routinely sent to NZHIS from Births, Deaths, and Marriages on a monthly basis. The data from Births, Deaths, and Marriages is collated from Medical Certificates of Causes of Death (BDM 50) and the Medical Certificate of Causes of Fetal and Neonatal Death (BDM 167), and from Coroners' reports. Additional information on the underlying cause of death is obtained from: the NMDS and private hospital discharge returns; the New Zealand Cancer Registry; the Department for Courts; the Police; the Land Transport Safety Authority; Water Safety New Zealand; Media Search; and from writing letters to certifying doctors, coroners, and medical records officers in public hospitals.

As with the NMDS, the Ministry of Health is required to ensure that the release of information recognises any legislation related to the privacy of health information (the Official Information Act 1982, the Privacy Act 1993 and the Health Information Privacy Code 1994). An amendment to the ethics approval was obtained from Northern Y Regional Ethics Committee (NTY/06/11/124) to enable provision of mortality data relating to NHI numbers from the laboratory data set.

The MORT data set was provided from NZHIS based on the study population of 160,222 individual NHI numbers from the laboratory data set. Data included NHI, date of birth, ethnicity, gender, date of death, cause of death (ICD coding up to 10 codes), and New Zealand Deprivation Index (NZDep).

DEMOGRAPHIC DATA SET

A demographic data set was provided which matched supplied NHI numbers (from the laboratory data set) with primary NHI numbers (as at July 2010). Data included supplied NHI, primary NHI, gender, ethnicity, date of birth, and NZDep. This enabled linking of demographic data to individuals who have not died or attended hospital during the study period (1/1/1997 – 31/12/2006) and therefore would not be on either the NMDS or MORT data sets.

ETHNICITY CODING

There is a known association between ethnicity and cardiovascular events in New Zealand [384, 385]; therefore, ethnicity was included as a variable in the data to test for possible confounding. There are differences in relation to thyroid dysfunction and ethnicity when comparing Blacks with Whites in the NHANES III study [39]. Any relationship between thyroid dysfunction and Maori ethnicity has not as yet been established.

Ethnicity data in this data set has been provided by NZHIS. Ethnicity data is obtained during a health related episode and linked with NHI numbers. The concept of ethnicity in New Zealand is described as a social construct of group affiliation and identity rather than biological basis [386]; allowing people to change ethnicity and to relate to more than one ethnic group. Ethnicity data are standardised according to protocols from the Ministry of Health for collation, recording and output for the New Zealand health and disability sector [387].

Ethnicity coding is based on the Statistics New Zealand Census ethnicity question which at 2001 was, "What ethnic group do you belong to?", which provides the opportunity for individuals to identify with one or more ethnic groups [387]. From the basic ethnicity coding structure, prioritisation ethnicity coding has been developed by Statistics New Zealand and used by NZHIS. Prioritisation ethnicity coding aims to ensure that where some need exists to assign people to a single ethnic group, ethnic groups of policy importance, or of small size, are not swamped by the New Zealand European ethnic group [387]. The prioritised coding list is found in Appendix 1.

NZDep provides a numerical rating of socioeconomic position based on a neighbourhood (a 'meshblock' containing on average 90 residences within a defined geographical area). These ratings are derived from nine variables from the Census (Table 16). Data provided by NZHIS was collated from Census 2006 data (NZDep06).

TABLE 16: CENSUS VARIABLES INCLUDED IN NZDEP

Deprivation indicators	Variable description
Income	People aged 18-64 years receiving a means tested benefit
Income	People living in households with income below an income threshold*
Owned home	People not living in own home
Support	People aged <65 years living in a single parent family
Employment	People aged 18-64 years without employment
Qualifications	People aged 18-64 years without any qualifications
Living space	People living in households below a bedroom occupancy threshold*
Communication	People with no access to a telephone
Transport	People with no access to a car

*Statistical methods are applied to control for household composition

There is a known relationship between deprivation and risk of cardiovascular disease [20]; therefore, deprivation was included as a potential confounder. A relationship between thyroid category and deprivation is not known.

The NZDep index is grouped into deciles scoring from 1 (least deprived) to 10 (most deprived). By definition, each decile would account for 10% of the population. For New Zealand as a whole the deprivation indexes are fairly evenly distributed at approximately 10% for each decile (Appendix 2). Although 20% of the New Zealand population may live in areas with the most deprivation (Deciles 9 & 10), this differs by area with 24% of the

Waikato population living in these deciles [388]. It is important to note that decile scores are used as a proxy for deprivation and relate to an area rather than an individual. This indicates that not everyone in an area will necessarily be in the same socioeconomic position.

ICD CODING AS USED IN NMDS AND MORT DATA SETS

The International Classification of Diseases and Related Health Problems (abridged as ICD) is an international standard diagnostic classification. They are used for the compilation of national mortality and morbidity statistics by World Health Organization Member States of which New Zealand is a member. The first edition of the ICD was adopted in 1900 with revisions taking place 10-yearly [389]. In 1948, World Health Organization took charge of the 6th edition as well as responsibility for subsequent revisions. The 10th revision (ICD-10) is currently in use and, since 1996, goes through annual updates rather than complete revisions [389].

This study uses both the 9th and 10th revisions as these cross through the study period 1993-2007. The 9th revision (ICD-9), which was developed in 1975, retained the basic structure of previous editions although included much additional detail at the level of four-digit subcategories and some optional five-digit subdivisions [390]. ICD-10 is organised into 22 disease categories, utilising three-character codes of one letter followed by two numbers. For this study, we utilise various subheadings within two categories: relating to circulatory diseases; and endocrine, nutritional and metabolic diseases.

VALIDITY OF ICD CODING

A potential weakness of outcome classification is the reliance of ICD coding in ascertaining the cause of hospitalisation or death. A review of the validity of ICD-based diagnoses relating to circulatory diseases [391] identified that the last New Zealand validation study on hospital reporting indicated ICD-9 :410 (acute myocardial infarction) having a sensitivity of 86% and the broader range of ICD-9: 410-414 (all coronary heart disease) had a sensitivity of 95% [392]. Furthermore, the review highlighted a 1988 audit of coronary heart disease death certificates which indicated that the broad official statistics for the category coronary heart disease mortality (codes 410-414) are accurate to within approximately 10% in New Zealand and that the narrower sub-codes within this have lower sensitivity [391, 393].

A large United States study indicated good agreement between sources of diagnosis and endpoints as validated by two different levels of physician review of medical records for myocardial infarction (MI), cerebrovascular accident (CVA), pulmonary embolism (PE) and venous thrombosis (kappa=0.64-0.84) but considerable misclassification for angina, congestive heart failure (CHF) and peripheral vascular disease (PVD), indicating that these endpoints remain difficult to classify reliably [394]. To enhance the endpoint of MI, physicians review of CHF and angina was recommended as an important source of validated events.

Age is suggested as a factor in biasing assignment of ICD codes for circulatory diseases. General atherosclerosis, unspecified heart disease and cardiac arrest are more commonly used in younger age groups than in older age groups, while the coding of heart failure is more often indicated as a cause of death with increasing age [395]. These four diagnoses have been termed 'ill-defined', suggesting coronary heart disease as their underlying pathology [395]. In addition, racial and gender effects on coronary heart disease assignment may reflect disparities in access to care and quality of care [395].

The Global Burden of Disease Study, which investigated the variation in the level of ill-defined cardiovascular deaths across countries, showed New Zealand has the lowest inter-country variation in coronary heart disease mortality (at 7%) and the highest proportion of non-stroke cardiovascular deaths coded to coronary heart disease (75-80%) [396]. This was further confirmed in the World Health Organization MONICA project, which monitored trends and determinants of cardiovascular disease where enormous variation was identified across countries with respect to coding practices for ill-defined cardiovascular codes; however, New Zealand was identified as a low ill-defined coding country [397]. A New Zealand study examining the possibility of a new epidemic in coronary heart disease following an increase in absolute numbers of hospitalisations for acute MI [398] found that, after examining 324,663 electronic records of New Zealand public coronary heart disease hospitalisations between 1993 and 2005, factors such as inter-hospital transfers and re-admissions accounted for a large proportion of coronary heart disease hospitalisations. Furthermore, there were reciprocal trends in acute MI and angina hospitalisations, indicating changes in diagnostic criteria [398].

To ensure that cardiovascular outcomes were correctly accounted for in our study, two recent reports were identified which also used cardiovascular disease as outcomes [391, 399]. ICD-10-AM codes relating to ischaemic cardiovascular events were used in a cohort study testing the

use of a computerised decision support tool (PREDICT) [391]. In addition, a report in one New Zealand DHB examining health care costs relating to cardiovascular disease and diabetes used ICD-9, ICD-10 version 2 and ICD-10 version 3 or 6 [399]. The coding identified in the latter report was utilised in this study to ensure we captured all possible outcomes for cardiovascular disease in light of the age bias and ill-defined coding as described above. Specifically, we identified hospital admissions and deaths due to cardiovascular disease as recorded in the NMDS and MORT data sets.

CODING OF DATA FOR CARDIOVASCULAR EVENTS

The period of time covered by the NMDS and MORT data sets (1997-2006) uses ICD code 9 & 10 codes. Codes related to ischaemic cerebrovascular disease, coronary heart disease, cardiac arrest or sudden cardiac death, peripheral vascular disease, and heart failure are listed in Appendix 3. In addition, individuals were identified who had codes relating to thyroid dysfunction to validate our thyroid categorical data (Appendix 4).

DATA CLEANING

All data were cleaned to enable linkage with mortality and morbidity data provided by NZHIS up to 31st December, 2006. Only entries with a valid NHI were included. Furthermore, we wished to make inferences relating to age and gender; therefore, requested demographic data to be provided on all 170,104 individuals with a NHI number. Where a change in gender may have occurred since 1997, such as in the event of gender reassignment, the gender provided by NZHIS was taken as the gender for the duration of the study period. In addition, laboratory data does not provide ethnicity data. Data provided by NZHIS enabled the analysis of ethnicity data linked by NHI number.

Data were excluded that prevented data set linkage or had missing information that was essential for analysis. The following were excluded:

- Entries without a valid NHI
- Date reported is missing
- Date reported >2006
- Gender is undefined
- Date of birth is missing
- Reference interval is undefined
- Age <20 years
- Data were duplicated (matched by test code, NHI and date reported on same day)
- NHI number not recognised by NZHIS.

While NHI numbers are unique to an individual, in some cases individuals have more than one NHI number. This is most likely due to a new assignment of an NHI number at the time of an event where an individual's true NHI number is not known. The NZHIS actively addresses duplicates by providing both supplied NHI numbers and primary NHI numbers (prim_hcu) with their data extraction service. The laboratory data set included 4800 entries where the supplied NHI did not match the prim_hcu number. These were linked and prim-hcu numbers were used as the primary NHI number (now using NHI) to avoid double-counting of the same individual in the final data set.

ESTABLISHING A REFERENCE INTERVALS FOR TSH

Reference intervals used to categorise individuals by thyroid function were established by analysing mean TSH for each calendar year reflecting the possibility that difference analysers may have been utilised during the 14-year data collection period and that each reference interval reflected the analyser and population referenced at that time. Anecdotally the upper reference intervals for TSH was altered at the laboratory after input from the consultant endocrinologist, which sought to restrict referrals for specialist opinion where specialist input was deemed unnecessary [400]. Due to changes to the TSH reference intervals over time, the given reference intervals in the laboratory data set were assessed by gender, age group and year of testing to establish whether changes may have occurred due to a change in immunoassay analyser, in population or due to specialist input.

Overall crude results for TSH showed the mean TSH result was 2.54 mIU/L. Mean result by age increased with advancing years: 20-44 years = 2.14 mIU/L; 45-64 years = 2.57 mIU/L; >65 years = 2.85 mIU/L. Mean result by gender was similar: Female = 2.56 mIU/L and Male = 2.5 mIU/L. Mean result by year of request varied during difference time periods: 1993-1996 = 1.94 mIU/L; 1997-2001 = 2.79 mIU/L; and, 2002-2006 = 2.54 mIU/L. Within these time periods reference intervals change markedly within the first time period of 1993-1996 from 0.3-3.0 mIU/L to 0.3-5.5 mIU/L compared with the remaining two time periods at 0.3 – 5.0 or 0.3-5.5 mIU/L. We wished to standardise the reference intervals in conjunction with these findings and those provided in literature. The reference intervals proposed by current assay manufacturers are: TSH (Elecsys): 0.27-4.20 mIU/L and TSH (IRMA): 0.38-4.84 mIU/L [262]. The upper reference interval used in literature ranges from 4-6 mIU/L [17, 41, 43, 46, 79]. The lower mean TSH encountered during 1993-1996 corresponded with the reference intervals of 0.3-3.0 mIU/L used during this time, therefore, this was taken as the reference

interval for those results where it was indicated in the laboratory data set (approx. years 1993-mid 1995). All other results were analysed using a reference interval of 0.3-5.0 mIU/L. Reference intervals for FT_4 and FT_3 remained unchanged over time. Most importantly, a raised TSH was taken as being over 5.0 mIU/L.

CATEGORISING THYROID DYSFUNCTION

Results for TSH were categorised into high, sub-hypo, normal, sub-hyper, and low (Table 17). Thyroid hormone tests (FT_4 and FT_3) were categorised as high (above the reference interval), normal (within the reference interval) or low (below the reference interval).

TABLE 17: KEY TO LABORATORY REFERENCE VALUES FOR TSH SERUM ASSAYS

TSH status* is defined as follows:

- normal = TSH within the reference interval
- high = TSH ≥10 mIU/L
- sub-hypo = TSH above the upper reference interval but below 10 mIU/L
- low = TSH ≤0.1 mIU/L
- sub-hyper = TSH below the lower reference interval but above 0.1 mIU/L

*These categories do not take into account central hypothyroidism or T_3-thyrotoxicosis.

Once test results were categorised, data were linked by NHI to match TSH & FT_4 tests carried out on individuals within a two week interval. FT_3 tests which were high were linked to couplings where TSH was low and FT_4 was normal to identify T_3-thyrotoxicosis. No other use of FT_3 assays were made due to its lack of reliability as an indicator for hypothyroidism. These groups of tests were identified as one event. These events were then categorised into overt hyperthyroidism (OHe), subclinical hyperthyroidism (SCHe), normal, subclinical hypothyroidism (SCH), overt hypothyroidism (OH), pituitary (Pit) or T_3-thyrotoxicosis (T_3-OHe) (Table 18). Approximate percentages of individuals in each category are given. This is prior to linking establishing thyroid status and described on the next page.

TABLE 18: TABLE OF EVENTS

TSH result	FT4 result	Event Category	Description	Approx. percent of results by description
normal	normal	normal	normal	87.8%
high	normal	OH	overt hypothyroidism	
high	low	OH	overt hypothyroidism	3.3%
sub-hypo	low	OH	overt hypothyroidism	
sub-hypo	normal	SCH	subclinical hypothyroidism	5.2%
normal	low	SCH	subclinical hypothyroidism	
sub-hypo	high	Pit	pituitary	
high	high	Pit	pituitary	0.2%
sub-hyper	low	Pit	pituitary	
low	low	Pit	pituitary	
low	normal	SCHe*	subclinical hyperthyroidism	
normal	high	SCHe	subclinical hyperthyroidism	2.3%
sub-hyper	normal	SCHe	subclinical hyperthyroidism	
sub-hyper	high	OHe	overt hyperthyroidism	
low	high	OHe	overt hyperthyroidism	1.2%

*Where TSH is low and FT_4 is normal, if FT_3 is elevated, this is categorised as T_3-thyrotoxicosis (T_3-OHe).

In many instances, full thyroid function could not be ascertained due to a lack of FT_4 result. This is likely to be due to strategies to utilise TSH as a first-line test. Where no FT_4 result was available, events were based on TSH alone as outlined in Table 17, where normal = Normal, high = OH, sub-hypo = SCH, low = OHe and sub-hyper = SCHe.

To establish confirmed SCH and SCHe, two separate events were required. Data were linked by NHI to establish results that had occurred between 6 – 52 weeks after the first test. The date of entry for SCH and SCHe respectively was taken as the first test date. Where only one raised test was present these were coded as Normal.

An individual remained in the category from the time they entered until Exit. Individuals who entered as Normal and remained Normal at Exit were classified as Normal. An individual NHI number could only occur once in the analysis; therefore, where an individual was in

three categories (OH, SCH and Normal), OH took precedence, followed by SCH and then normal. This ensured priority was given to increasing thyroid dysfunction. The date of entry into the cohort was taken from the date of the test according to the prioritisation i.e. the first time they appeared in this category.

Date of Exit was at the first cardiovascular event (including death from a cardiovascular event) or at 31st December 2006, whichever occurred first. Individuals who died during the study from a non-cardiovascular event were censored at the date of death. Time was taken as person-years from date of entry to date of exit (cardiovascular event). Where the cardiovascular event occurred prior to the date of the thyroid function grouping (i.e. date of entry), these were classed as 'Previous cardiovascular disease' and did not form part of the analysis. Only individuals whose date of entry preceded the date of exit were included in the analysis.

CATEGORISING CARDIOVASCULAR EVENTS

All cardiovascular events were coded according to ICD 9 & 10 coding as described above. Codes related to ischaemic cerebrovascular disease, coronary heart disease, cardiac arrest or sudden cardiac death, peripheral vascular disease, and heart failure were further categorised to represent two distinct groups, coronary heart disease and other cardiovascular diseases. Where an individual had been coded with more than one cardiovascular event on one occasion, coronary heart disease was prioritised. This fitted with validity data which showed that there was age-bias and ill-defined coding relating to cardiovascular events, most of which would have coronary heart disease as their underlying aetiology [397].

STATISTICAL ANALYSIS

All individuals diagnosed with OHe, SCHe, Pit, SCH, OH or T3-OHe (i.e. not Normal) in the first four years of data (1993-1996) were 'censored'. By using four-year censoring, entries which are considered to have had prior thyroid dysfunction, including possible iatrogenic cases, were removed. Data were also validated against the NMDS data set using ICD9 & 10 codes for thyroid dysfunction (Appendix 2).

Date of entry (index date) into the study was the date of first thyroid function event after 1/1/1997 based on priority categorisation of thyroid dysfunction. All entries before this were excluded. Data were characterised by age, gender, ethnicity and deprivation index in relation

to pre and post cardiovascular disease status, as described above. Patients were followed from index date until the date of exit (cardiovascular event by morbidity or mortality, by censoring or at the end of the study period, whichever came first).

Using the Kaplan-Meier estimator to determine survival rates, data were plotted by cardiovascular event over the 10 year period, overall and stratified by age, gender, ethnicity and deprivation index. The covariates eligible for inclusion in this model as potential confounders were gender, age as a binary variable, ethnicity grouping and deprivation index quintiles. Kaplan-Meier survival curves using 1-survival method from time from categorisation to event are presented [401].

Using the Cox proportional hazards regression model, the hazards ratios were calculated with 95% confidence intervals comparing cardiovascular event rates by thyroid category within gender, age, ethnicity and deprivation index. For each group, the category with the lowest characterisation coding was set as the reference i.e. female gender, age 20-64 years, European ethnicity and deprivation quintile 1 (deprivation index 1&2). To examine any interaction between covariates, stratified analysis was performed on all four covariates. In the overall analysis we adjusted for the remaining covariates. The proportional hazards requirement means the hazard ratio is constant over the time of follow-up [402]. Factors which warranted further investigation were analysed *post hoc* and, due to their potential for bias, findings were described and discussed.

Data cleaning was performed by Dr Grace Joshy, University of Auckland biostatistician, using SAS 9.1 (SAS Foundation, 2007), with data from file formats in Microsoft Excel (Microsoft Corporation, 2007) and Microsoft Access (Microsoft Corporation, 2008). Statistical analysis was performed using Stata 11 (Stata Corporation, 2010). Significance was set at *P*_0.05.

POPULATION DEMOGRAPHICS

There were 1,322,643 observations on the laboratory data set relating to 171,158 individuals who had one or more thyroid function tests from Medlab Hamilton. We excluded 1054 individuals without a NHI number leaving 170,104 individuals. Data were cleaned further according to our exclusion criteria, including removing duplicate results, to reveal a population of 82,357. Population characteristics compared with Waikato and New Zealand Census adult populations for 2001 are shown in Table 19. Deprivation quintiles from the

study population were compared against Waikato and New Zealand Census adult populations for 2006.

When compared with the general adult population (≥20 years) of Waikato and of New Zealand, the study population was older, had more women, had less Pacific and Asian peoples represented, and had more people with lower socioeconomic positions (quintile 3-5) as shown in Table 19. All strata showed significant differences between populations except for individuals aged between 40-49 years for both Waikato and New Zealand (p=0.106 and p=0.246 respectively). There were similarities between Pacific and Asian populations when compared to the Waikato population only.

TABLE 19: STUDY POPULATION CHARACTERISTICS COMPARED TO WAIKATO AND NEW ZEALAND POPULATION

	Proportion of subjects		
Characteristics	Study population (N=82,357)	Waikato Population (N=247,866)	NZ Population* (N=2,637,876)
Age distribution			
20-29 years	11,931 (15.6)	48,258 (19.5)	513480 (19.5)
30-39 years	13,505 (17.6)	54,348 (21.9)	588,498 (22.3)
40-49 years	25,406 (20.1)	51,165 (20.6)	538,278 (20.4)
50-59 years	13,506 (17.6)	39,000 (15.7)	411,834 (15.6)
60-69 years	10,852 (14.1)	26,952 (10.9)	275,493 (10.4)
70-79 years	7,797 (10.2)	19,044 (7.7)	205,512 (7.8)
80+ years	3,722 (4.9)	9,099 (3.7)	205,512 (4.0)
Age, y (median)	49	37	42
Sex			
Female	47,181 (61.5)	129123 (52.1)	1,384,389 (52.5)
Male	29,541 (38.5)	188743 (47.9)	1,253,487 (47.5)
Ethnicity			
European	56,939 (74.2)	196380 (79.2)	2,067,636 (78.4)
Maori	8,860 (11.6)	38301 (15.5)	280,272 (10.6)
Pacific	858 (1.1)	4974 (2.0)	120,165 (4.6)
Asian	1,770 (2.3)	7329 (3.0)	154,800 (5.9)
Other	8,295 (10.8)	876 (0.4)	150,00 (0.6)

NZDep06 Quintiles**			
1	9,069 (11.8)	35,365 (15.0)	586,335 (20.5)
2	10,181 (13.3)	42,438 (18.0)	577,754 (20.2)
3	16,618 (21.7)	47,153 (20.0)	566,314 (19.8)
4	23,546 (30.7)	54,226 (23.0)	563,453 (19.7)
5	17,301 (22.6)	56,583 (24.0)	566,314 (19.8)

* New Zealand Population taken from Census 2001; ** Waikato (N=235,764) and New Zealand Population (N=2,860,170) taken from variables of New Zealand Census 2006.

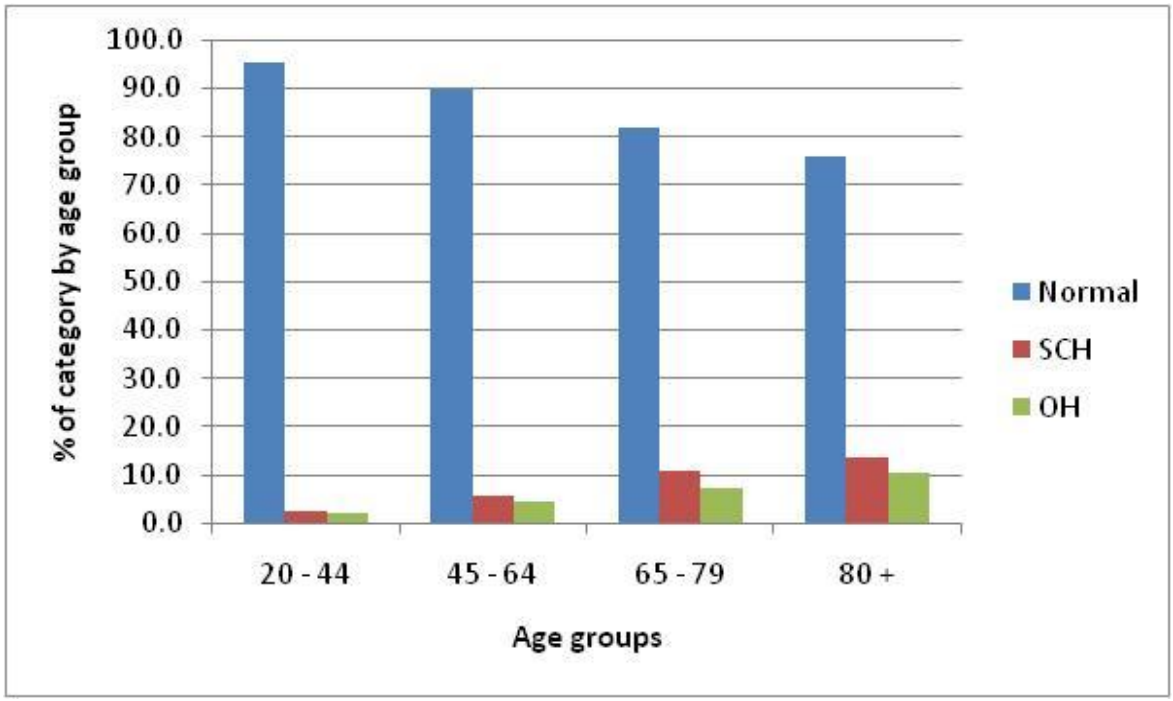
Over 10% of the study population were identified in the 'Other' ethnic category. This was significantly higher than Waikato and New Zealand populations, therefore this category was removed as it is believed that ethnicity may have an association with thyroid dysfunction, as has been found in studies elsewhere [39] and not knowing the ethnicity of this 'Other' group means that inferences cannot be made upon it relating to ethnicity. In addition, there were small numbers of Pacific and Asian peoples representing less than 3% of the study population. These were removed to concentrate on differences between European and Maori peoples; therefore only data for these two ethnic groups will be presented. A further 143 individuals were excluded who were missing data on deprivation index. Results were based on the remaining 70, 490 individuals.

RESULTS

DISTRIBUTION OF THYROID DYSFUNCTION IN STUDY POPULATION

At entry into the study, based on thyroid category, the majority of individuals had normal thyroid function (90.0%) but this decreased with age (Figure 7). The correspondent increase in thyroid dysfunction was greater in the SCH group.

FIGURE 7: PERCENT WITHIN EACH THYROID CATEGORY BY AGE GROUPS



Prevalence of hypothyroidism was 10% (4.2% OH and 5.8% SCH). Table 20 shows the study population characteristics by thyroid category. Those with normal thyroid function were on average age 12 years younger than individuals with either SCH or OH. Prevalence of thyroid dysfunction increased with advancing age with euthyroidism declining from 95.3% in the 20-44yr age group to 76% in the 80+ age group. Women were twice as likely as men to have OH (5.1% vs. 2.6% respectively). Thyroid dysfunction appeared to increase with decreasing socioeconomic position with the prevalence of OH being 3.6% in Deprivation Quintile 1 increasing to 4.8% in Quintile 5.

Associations with thyroid category were tested using chi-squared statistic for binary variables and by chi-squared test for trend for ordered categorical variables. Unadjusted associations between thyroid category and gender and ethnicity were statistically significant (both <0.0001). There was a statistically significant trend of increasing thyroid dysfunction with increasing age and social deprivation index (both <0.0001) (Table 20).

TABLE 20: STUDY POPULATION CHARACTERISTICS BY THYROID CATEGORY

	Normal	SCH	OH	p-value†
Total sample	n=63,462 (90.0)	n=4,048 (5.8)	n=2,970 (4.2)	
Mean age at entry, years	48.5 (17.6)	60.7 (16.9)	60.4 (16.9)	
Age				
20-44y	28,333 (95.3)	759 (2.6)	568 (1.9)	
45-64y	22,033 (89.7)	1,436 (5.8)	1,101 (4.5)	
65-79y	10,109 (82.0)	1,334 (10.8)	886 (7.2)	
80+	2,987 (76.0)	529 (7.2)	415 (10.6)	<0.0001
Gender				
Female, No (%)	39,996 (88.6)	2,832 (6.3)	2,308 (5.1)	
Male, No (%)	23,466 (92.6)	1,226 (4.8)	662 (2.6)	<0.0001
Ethnicity				
European, No (%)	54,623 (89.6)	3,701 (6.1)	2,632 (4.3)	
Māori, No (%)	8,839 (92.3)	357 (3.7)	338 (3.5)	<0.0001
Deprivation quintile				
1	7,382 (91.2)	428 (5.3)	288 (3.6)	
2	8.387 (90.6)	522 (5.6)	345 (3.7)	
3	13,660 (90.7)	815 (5.4)	585 (3.9)	
4	19,601 (89.5)	1,321 (6.0)	974 (4.5)	
5	14,432 (89.2)	972 (6.0)	778 (4.8)	<0.0001

Data are n=sample number, % = percent of total, Age in Mean (SD); † z-test for trend or chi2 for binary variables

ESTABLISHING CARDIOVASCULAR EVENTS

A total of 66,632 individuals were included in the survival analysis after excluding 3,858 individuals who were identified with cardiovascular events (failure) prior to index date. 6,318 individuals with a cardiovascular event following index date contributed a total of 19,846 out of 333,582 person-years at risk during the period 1997-2006. Follow-up ranged from 0 to 9.99 years. This estimated an overall unadjusted cardiovascular event rate of 18.9 per 1000 person-years (95% CI = 18.5 – 19.4 per 1000 person-years).

The mean of the first index date for individuals within each thyroid category was examined to assess for selection bias due to censoring. The mean date for all categories fell within 2001 – normal 22/8/2001, SCH 21/9/2001 and OH 27/4/2001.

Crude rates of failure appeared to increase with increasing thyroid dysfunction. These are shown in Table 21.

TABLE 21: NUMBER AND CRUDE RATES OF CARDIOVASCULAR EVENTS PER 1000 PERSON-YEARS BY THYROID CATEGORY

Thyroid category	Sample size	No. Of cardio-vascular events	Person-time (1000 yrs)	Cardio-vascular events per (1000)/p-y	Lower CI*	Upper CI*
Normal	60,451	5,245	304.29	17.24	16.78	17.71
SCH	3,587	569	16.78	33.91	31.23	36.81
OH	2,594	504	12.51	40.29	36.92	43.97

*CI = confidence intervals

CARDIOVASCULAR EVENTS

There were 6,318 individuals with a cardiovascular event. A total of 2,656 individuals were coded with coronary heart disease (CHD), the largest individually coded group, followed by peripheral vascular disease (PVD) (1540 individuals), cerebrovascular accident (CVA) (1198 individuals) and heart failure (HF) (924 individuals). (Table 22)

TABLE 22: PREVALENCE OF CARDIOVASCULAR DISEASE BY THYROID STATUS

Prevalent Cardiovascular diseases	Total (n=6,318) (%)	Euthyroidism (n=5,245) (%)	Subclinical Hypothyroidism (n=569) (%)	Overt Hypothyroidism (n=504) (%)
CHD	2,656 (42.0)	2,172 (41.4)	251 (44.1)	233 (46.2)
CVA	1,198 (19.0)	1,011 (19.3)	108 (19.0)	79 (15.7)
PVD	1,540 (24.4)	1,332 (25.4)	114 (20.0)	94 (18.7)
HF	924 (14.6)	730 (13.9)	96 (16.9)	98 (19.4)

Categories were dichotomised into: any coronary heart disease (2,656 individuals) and Other cardiovascular disease (3,662 individuals). There was an increasing trend between thyroid status and cardiovascular event (X^2 test for trend p<0.0001). This association remained when age was dichotomised into below 65 yrs of age and 65+ groupings.

Overall, the prevalence of coronary heart disease was 3.6% with normal thyroid function, 7% with SCH and 9% with OH. Other cardiovascular events were 5.1%, 8.9% and 10.5% respectively.

CARDIOVASCULAR EVENTS AND THYROID OUTCOMES IN RELATION TO COVARIATES

The incident rate ratio when comparing having a cardiovascular event with being euthyroid ('Normal') or having thyroid dysfunction ('SCH' and 'OH' combined) was 2.1 (95% confidence intervals (CI) 2.0, 2.3). A weighted summary, Mantel-Haenzel, was used to test whether there were differences between strata and to assess the changes made after each variable was controlled for. There was evidence of association for all variables when tabulated using the chi-squared statistic. The crude rate ratios were compared against adjusted rate ratios using stratified analysis.

When adjusted by age groups (20-44 yrs, 45-64 yrs, 65-79 yrs, 80+ yrs) the incident rate ratio reduced to 1.2 (95% CI 1.8, 1.3) indicating that age had an influence on the outcome. The stratum specific rate in aged 20-44 yrs (2.0) was much higher than for other groups (1.3, 1.2, and 1.3 respectively). The test for heterogeneity was statistically significant (Pr=0.0390) indicating that age strata should not be combined as age has a modifying effect on cardiovascular events and on thyroid dysfunction.

Gender confounds the association between thyroid dysfunction and cardiovascular event. This is shown by the Mantel-Haentzel (M-H) incident rate ratio (2.4) being further from the crude rate (2.1) after controlling for gender. The stratum-specific rate in women is much higher (2.6) than the rates for men (2.0). The test for heterogeneity rejects the null hypothesis that the strata are the same (Pr=0.0003). Gender modifies the effect of cardiovascular events on thyroid dysfunction. Therefore, analysis of gender should be by strata and not be grouped together.

Ethnicity does not appear to have an effect on the relationship between thyroid dysfunction and cardiovascular events. The adjusted incident rate (2.1) is similar to the crude rate and the

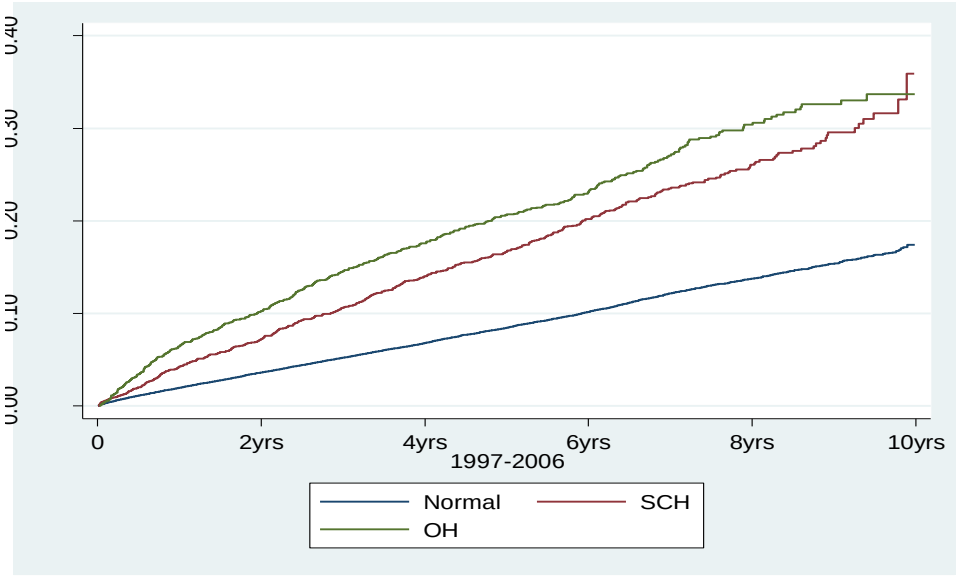
test for heterogeneity indicates that ethnicity does not modify the effect between exposure (thyroid dysfunction) and outcome (cardiovascular event) by strata (Pr=0.9321). Ethnicity will be grouped in further analysis.

Adjusting for deprivation had a small positive effect on the crude ratio but this was not statistically significant. The test for interaction showed weak evidence of an effect of deprivation on the association between thyroid dysfunction and cardiovascular event (Pr=0.0731). In addition, there is a known relationship between ethnicity and deprivation; Maori are more likely to be in deprivation quintile 5 (poorest group) than non-Maori [385]. Ethnicity data will be grouped but the interaction between ethnicity and deprivation will be tested using the likelihood ratio test.

CUMULATIVE FAILURE

All categories of thyroid dysfunction were plotted against failure over time. A straight line represents a constant rate over time, and the rate is equal to the slope of the line. The x-axis represents the 10 years of the study and the y-axis represents the proportion of failures at each failure point. As revealed the crude rate of cardiovascular events (failure) was greater in SCH and OH when compared with Normal thyroid function (Figure 8).

FIGURE 8: CUMULATIVE HAZARDS PLOT OF FIRST CARDIOVASCULAR EVENT BY THYROID CATEGORY



To study the effects of age on the risk of failure, data were analysed using life tables to visualise rates of cardiovascular events by thyroid category against age groups. Differences

between thyroid dysfunction and cardiovascular events were greatest in the 20-44 year age group where there was a statistical difference between having normal thyroid function and having thyroid dysfunction; confidence intervals did not cross.

Rates of failure for 45-64 year olds increased in each thyroid category (range 16.5 – 22.3 per 1000), these were not statistically significant. Likewise, rates increased with thyroid category in individuals aged 65-79 years (range 52-73 per 1000) but were not statistically significant. The greatest rates were in the 80+ age group (range 88-125 per 1000) and were also not statistically significant.

The categories appeared heterogeneous demonstrating no overlap in rates and confidence intervals between ages 20-44yrs and 45-64yrs. There was also no overlap between the lowest two age groups and the upper two age groups. When combined into binary age groups 20 – 64 and 65+, there remained no overlap between groups with rates in 20-64 yrs from 8.7 per 1000 euthyroid, 14.0 per 1000 SCH, and 16.3 per 1000 OH compared with 65+ age group rates of 59.2, 67.5 and 86.3 respectively (Figure 9 & Figure 10).

FIGURE 9: CUMULATIVE HAZARDS PLOT BY THYROID CATEGORY IN <65 YEAR AGE GROUP

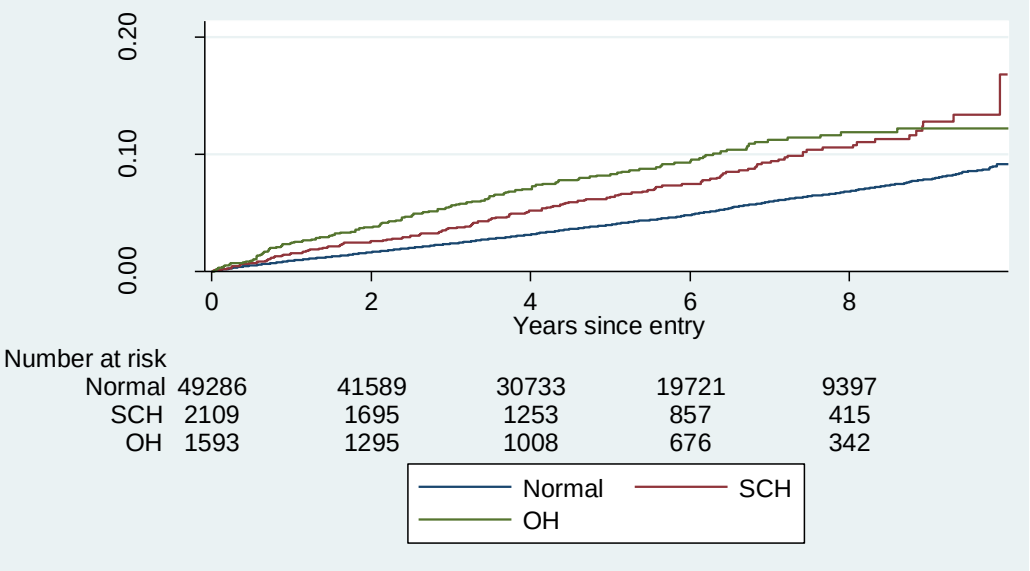
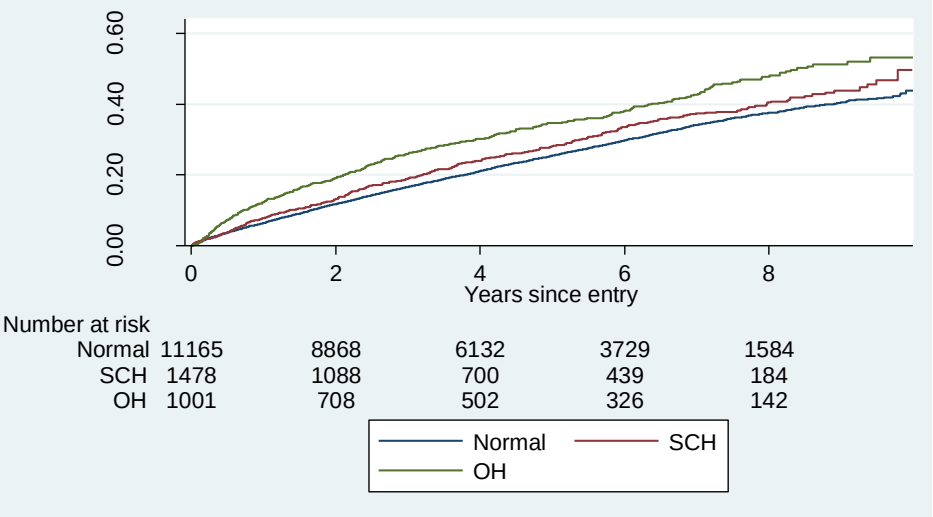


FIGURE 10: CUMULATIVE HAZARDS PLOT BY THYROID CATEGORY IN 65+ AGE GROUP



The graph shows differences in risk of failure between normal, SCH and OH. The risk of failure with SCH appears greater in subjects <65 years of age and closely follows the OH data with increasing time (between 6 & 8 years), while in the 65+ age group, the risk of failure in the SCH category appears closer to normal.

SURVIVAL ANALYSIS

Survival analysis is used where the key variable is the time to an event and where censored data can still be used to estimate the proportion of survivors until the end of follow-up [403].

The survival distribution function at a given time represents the proportion of patients who have had a cardiovascular event at that time. At four years after entry, there was a 5.5% difference in survival between those with normal thyroid dysfunction and individuals with SCH. The difference between normal and OH at four years was nearly 10%. By 8 years, there was a 12% difference between normal thyroid dysfunction and SCH and a 15% difference between normal and OH (Table 23).

TABLE 23: LIFE TABLE OF FAILURE (CARDIOVASCULAR EVENT) AND SURVIVAL BY THYROID CATEGORY

Interval		Beg. Total	Failure	Survival	Std. Error	[95% Conf.	Interval]
Normal							
0	2	60451	2035	0.9640	0.0008	0.9625	0.9656
2	4	50723	1391	0.9340	0.0011	0.9318	0.9361
4	6	37167	1019	0.9033	0.0014	0.9004	0.906
6	8	23734	614	0.8721	0.0018	0.8684	0.8757
8	.	11216	186	0.8436	0.0027	0.8382	0.8489
SCH							
0	2	3587	233	0.9296	0.0044	0.9204	0.9378
2	4	2800	161	0.8690	0.0062	0.8563	0.8807
4	6	1980	98	0.8187	0.0077	0.8032	0.8332
6	8	1308	56	0.7725	0.0094	0.7534	0.7903
8	.	619	21	0.7218	0.0138	0.6936	0.7479
OH							
0	2	2594	237	0.9021	0.006	0.8896	0.9133
2	4	2013	131	0.8377	0.0078	0.8217	0.8523
4	6	1522	70	0.7927	0.009	0.7743	0.8098
6	8	1017	55	0.7373	0.0111	0.7148	0.7583
8	.	500	11	0.7055	0.0141	0.6768	0.7322

Note: survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

There was strong evidence that age was an effect modifier. Age is sometimes set along the time axis to reflect the different ages in which individuals enter and exit the study; however, controlling for age at the outset prevents comparisons between age groups. Study time was taken as the time since recruitment into the study as this varied according to the date of thyroid categorisation (exposure) within a 10-year time frame (1/1/1997-31/12/2006). Age was included as an exposure variable in Cox regression to address implications of age the relationship between thyroid dysfunction and cardiovascular event.

COX REGRESSION

Cox proportional hazards regression make no assumptions about the effects of time on outcomes and allows estimates to be made comparing different exposure groups using hazard ratios [404]. This assumes that the hazards in the two groups remain constant over time i.e. the proportional hazards assumption. To test that our data meet the requirements for using this test, the Schoenfeld test was used to examine that proportional hazards assumptions were met. The Schoenfeld test showed a linear trend with time; evidence of proportionality meaning that the Cox regression model could be used with this data.

Covariates such as age, gender, ethnicity and deprivation were considered confounders and age and gender were effect modifiers between thyroid categories and cardiovascular event. In addition, within the covariates are interactions between ethnicity and deprivation which makes intuitive sense. In New Zealand, Maori are overrepresented in both the poorest socioeconomic position and in cardiovascular outcomes [20 385]. A model was fitted which controlled for the effects of these covariates as shown in Equation 1.

EQUATION 1: COX REGRESSION MODEL FOR CARDIOVASCULAR EVENT BY THYROID CATEGORY

Hazards ratio for **failure (cardiovascular event)** = **thyroid category** by stratum x **age group** by stratum x **gender** by stratum x (**ethnicity** interacting with **deprivation quintile**)

This model was not developed along the lines of forward or backward fitting models as the identified covariates are potential confounders. There is no method for test for confounding but the use of Chi-squared testing to test for an association between exposure and outcome and Mantel-Haentzel analysis to assess for interaction informed whether covariates were analysed using stratum-specific estimates or grouped variables. In addition, the relationship between deprivation and ethnicity was tested using the likelihood ratio test to assess whether there is interaction between these two variables. Evidence for interaction was supported by the likelihood ratio test which rejected the null hypothesis of no interaction (X^2=0.0049).

Hazards ratios for each covariate (left hand column) are shown within strata as unadjusted rates (middle column) and after inputting all covariates into the model are controlled for by each of the stratified variables shown as adjusted rates in Table 24.

TABLE 24: CARDIOVASCULAR EVENT HAZARD RATIOS WITHIN AND ADJUSTED FOR THYROID CATEGORY, GENDER, ETHNICITY AND DEPRIVATION QUINTILE

	Hazard ratios (95% CIs)	
	Unadjusted	**Adjusted**
Thyroid category		
Normal	1.00 (reference)	1.00 (reference)
SCH	1.96 (1.80 - 2.14)	1.22 (1.12-1.33)
OH	2.33 (2.13-2.56)	1.58 (1.44-1.73)
Age group		
20-44 years	1.00 (reference)	1.00 (reference)
45-64 years	5.67 (5.13-6.30)	5.32 (4.80-5.90)
65-79 years	18.40 (16.6-20.34)	16.55 (14.95-18.33)
80+ years	31.69 (28.39-35.38)	30.03 (26.84-33.60)
Gender		
Female	1.00 (reference)	1.00 (reference)
Male	2.07 (1.97-2.18)	1.67 (1.58-1.75)
Ethnicity		
European	1.00 (reference)	1.00 (reference)
Maori	0.86 (0.80–0.93)	1.32 (0.88-2.00)
Deprivation quintile		
1	0.64 (0.58-0.71)	0.89 (0.57-1.40)
2	0.78 (0.71-0.86)	0.74 (0.71-0.86)
3	1.00 (reference)	1.00 (reference)
4	1.05 (0.98-1.13)	0.87 (0.81-0.93)
5	1.24 (1.16-1.34)	1.09 (1.01-1.18)

NB: each covariate is controlled for by the other covariates in the adjusted analysis.

The influence of age was further analysed, examining the cohort that is <65 years of age and 65+ years separately. In the <65 years age group, there were 52,988 subjects with 2,472 failures. This contributed a risk time of 271,451 person-years at risk and an incidence rate of

9.1 per 1000 person-years, which is just less than one person out of 100 people per year. In contrast, in the 65+ years age group, there were 13,644 subjects with 3,846 failures. This contributed a risk time of 62,130 person-years and an incidence rate of 61.9 per 1000 person-years: 6 times as many as the <65 year age group per year. Further analysis by gender found that men <65 years of age had a higher rate of cardiovascular events (16.1 per 1000 person-years) compared with women <65 years of age (5.9 per 1000). Likewise, men aged 65+ had a higher rate of cardiovascular events (69.9 per 1000) than women of the same age group (55.9 per 1000).

When each cohort was adjusted for gender, ethnicity and deprivation quintile using Cox Regression analysis, the Hazards ratio of cardiovascular events by thyroid group was similar at 1.26 (95% CI 1.07, 1.49) for SCH and 1.59 (1.33, 1.90) for OH in the <65 year group. In the 65+ group, after adjustment, the rate of cardiovascular events reduced to 1.14 (1.03, 1.27) for SCH and 1.46 (1.31, 1.63).

DISCUSSION

In this laboratory-defined cohort, age, gender, ethnicity and deprivation were important predictors of a cardiovascular event for individuals with thyroid dysfunction.

When the relationship between thyroid category and cardiovascular events were crudely analysed, the rate of cardiovascular event was nearly twice in individuals with SCH than for those with Normal thyroid function. In individuals with OH, cardiovascular events were 2.3 times greater compared with Normal thyroid function. The rate of cardiovascular event was 2.1 times greater in men compared with women and there was a lower rate in Maori. In addition, the rate of cardiovascular event increased with age and deprivation quintile.

When controlling for age, gender, ethnicity and deprivation quintile, cardiovascular events were 22% higher in individuals with SCH and 58% higher in individuals with OH. When age was controlled for by thyroid category, gender, ethnicity and deprivation quintile, the rate of cardiovascular events increased with increasing age and were similar to unadjusted rates. The rate of cardiovascular events in Maori was 32% greater when controlling for other covariates although this was not statistically significant and had wide confidence intervals. This may reflect that the majority of the population were European (86%).

Unadjusted deprivation quintiles showed a trend with increasing deprivation; however, when adjusted for other covariates, there was no difference between strata. The middle stratum was used as the reference category to reflect the study population mean falling within category 3.

ALL-CAUSE MORTALITY

A total of 66,632 individuals contributed a total time at risk of 333,582.04 person-time during the period 1997-2006. Of these, 4462 individuals (6.7%) contributed 21,011.7 person-time before they had died. The mortality rate was 13.4 per 1000 (95% CI 12.99-13.77) All-cause mortality was assessed in relation to thyroid status.

TABLE 25: NUMBER AND CRUDE RATES OF MORTALITY PER 1000 PERSON-YEARS BY THYROID CATEGORY

All-cause mortality:		N	No. Of deaths	Person-time (1000 yrs)	Rates per (1000)/ p-y	Lower CI*	Upper CI*
Thyroid category	Normal	60,451	3,618	304.29	11.89	11.51	12.28
	SCH	3,587	463	16.78	27.59	25.19	30.22
	OH	2,594	381	12.51	30.46	27.55	33.68

*CI = Confidence Intervals. NB: unadjusted for age

Mortality rates appeared to increase with increasing thyroid dysfunction (Table 25). Data for SCH and OH appears to overlap. Using a test for trend to assess the ordinal categories of thyroid dysfunction there appears to be a trend in mortality across the ordered levels of thyroid categories ($p<0.0001$). Thyroid dysfunction also increases with age.

The association between all-cause mortality and thyroid categories was heterogeneous ($p<0.0001$) indicating a difference between strata. Overall, the combined Mantel-Haentzel mortality rate ratio was 2.42 (95% CI 2.25,2.61). Unadjusted for confounding variables, the rate of death in individuals with thyroid dysfunction was 2.42 times greater than in individuals with normal thyroid function.

ALL-CAUSE MORTALITY AND THYROID CATEGORY IN RELATION TO COVARIATES

Age, gender, ethnicity and deprivation index were tabulated against exposure and outcome to assess for association. There was evidence of an association between all-cause mortality for all variables except ethnicity when tabulated using a chi-squared statistic. When tested for heterogeneity, there was weak evidence (X^2 p=0.0657) of a difference between strata. Individuals in the 20-44yr age group had an incident rate ratio of 2.27, with wide confidence intervals (1.36-3.61) compared to the overall Mantel-Haentzel adjusted incidence rate of 1.26. The age groups above 45 years of age fell within the adjusted ratio with overlapping confidence intervals.

There was no heterogeneity by gender (X^2 p=0.2620); gender did not statistically affect the relationship between death and thyroid category. When deprivation quintiles were assessed, the confidence intervals for the adjusted Mantel-Haentzel incidence ratio assessing the relationship between mortality and thyroid category overlapped with the crude incident ratio indicating no difference between adjusted and unadjusted index. However, the test for heterogeneity indicated that there were differences between strata. This indicated that deprivation affects the relationship between thyroid dysfunction and death. The deprivation data were assessed by strata.

SURVIVAL ANALYSIS

The life-table shows unadjusted differences in all-cause mortality by thyroid category (Table 26). Four years into the study, there was nearly 97% survival in individuals with normal thyroid function compared with 92% with SCH and 89% with OH. By 8 years, there was 90% survival in individuals with normal thyroid function compared with 80% with SCH and 79% with OH. All cause-mortality appeared to be greatest in individuals with SCH and OH compared with normal thyroid function.

TABLE 26: LIFE TABLE SHOWING AGE-ADJUSTED DIFFERENCES BY THYROID CATEGORY IN ALL-CAUSE MORTALITY

Interval			Beg. Total	Deaths	Survival	Std. Error	[95% Conf.	Int.]
Normal								
0		2	60451	781	0.9860	0.0005	0.985	0.987
2		4	50457	736	0.9695	0.0008	0.968	0.971
4		6	36865	712	0.9469	0.0011	0.9446	0.9491
6		8	23450	723	0.9080	0.0018	0.9044	0.9114
8	.		10981	666	0.8041	0.0041	0.7959	0.812
SCH								
0		2	3587	129	0.9603	0.0034	0.953	0.9665
2		4	2783	103	0.9194	0.0051	0.9088	0.9289
4		6	1953	74	0.8785	0.0068	0.8645	0.8911
6		8	1296	85	0.8030	0.01	0.7827	0.8218
8	.		599	72	0.6307	0.0196	0.5909	0.6678
OH								
0		2	2594	139	0.9413	0.0048	0.9311	0.9501
2		4	2003	83	0.8978	0.0066	0.8842	0.91
4		6	1510	53	0.8607	0.008	0.8442	0.8757
6		8	1002	59	0.7950	0.0111	0.7723	0.8157
8	.		484	47	0.6543	0.0207	0.6119	0.6932

Note: survivor function is calculated over full data and evaluated at indicated times; it is not calculated from aggregates shown at left.

All-cause mortality was assessed by age. Visually it appeared that at 4 years individuals with SCH were twice more likely to die than individuals with normal thyroid function. Individuals with OH appeared four times as likely in the <65 year age group. At 6 years, SCH was similar to OH in this age group. In the 65+ year age group, at 4 years, individuals with OH appeared twice as likely to die as those in the SCH and Normal groups. SCH and Normal groups were closer together than in the <65 year age group (Figure 11).

FIGURE 11: KAPLAN-MEIER ALL-CAUSE MORTALITY BY THYROID CATEGORY IN <65 YEAR AGE GROUP

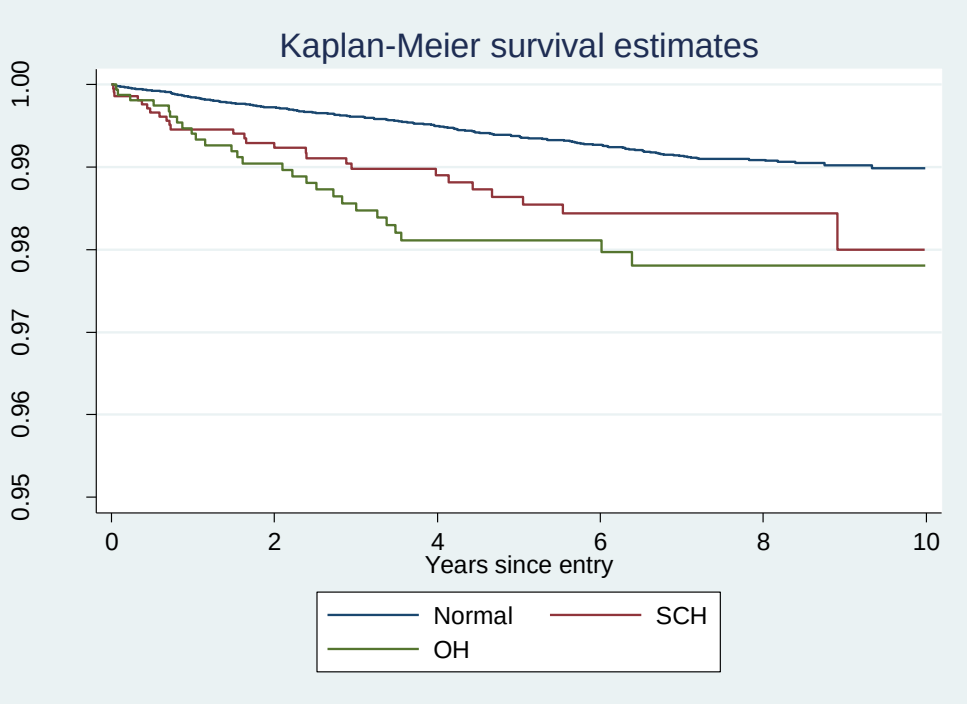
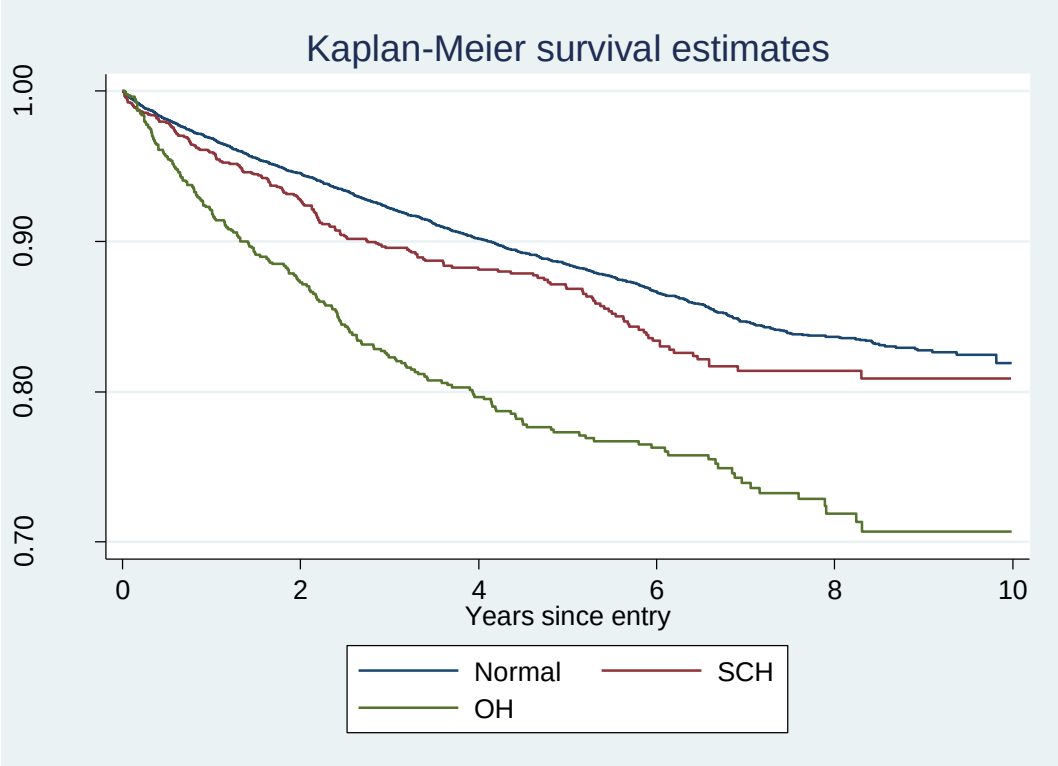


FIGURE 12: KAPLAN-MEIER ALL-CAUSE MORTALITY BY THYROID CATEGORY IN 65+ YEAR AGE GROUP



The relationship of all-cause mortality and thyroid category was assessed using Cox regression. There appeared to be an association between all-cause mortality and increasing thyroid dysfunction (not shown). A difference in survival appears evident; poorest survival was seen in individuals with OH.

Unadjusted hazard ratios showed mortality rates to be twice as high in individuals with thyroid dysfunction compared with those with normal thyroid function. A Cox regression model was developed using age, gender, ethnicity and deprivation. Although ethnicity does not appear to have an association when assessed using the chi-squared test, Maori have a shorter life expectancy than non-Maori, therefore a relationship between Maori and mortality needs further examination. In addition, the relationship between ethnicity and deprivation is likely to modify the effect of any outcome due to the Maori being over-represented in the lowest socioeconomic position when compared with non-Maori [385].

The model, based on possible confounders and effect modifiers is shown in Equation 2.

EQUATION 2: COX REGRESSION MODEL TO ASSESS THE RELATIONSHIP BETWEEN ALL-CAUSE MORTALITY AND THYROID CATEGORY

Hazards ratio for **failure (all-cause mortality)** = **thyroid category** by stratum x **age group** by stratum x **gender** x (**ethnicity** interacting with **deprivation quintile** by stratum)

TABLE 27: CRUDE AND ADJUSTED HAZARD RATIOS FOR ALL-CAUSE MORTALITY

	Hazard ratios (95% CIs)	
	Unadjusted	**Adjusted**
Thyroid category		
Normal	1.00 (reference)	1.00 (reference)
SCH	2.48 (2.23-2.76)	1.29 (1.17-1.42)
OH	2.31 (2.09-2.54)	1.45 (1.31-1.62)
Age group		
20-44 years	1.00 (reference)	1.00 (reference)
45-64 years	5.71 (4.92-6.63)	5.52 (4.75-6.41)
65-79 years	29.07 (25.20-33.53)	27.82 (24.07-32.15)
80+ years	95.76 (82.78-110.77)	97.89 (84.38-113.57)
Gender		
Female	1.00 (reference)	1.00 (reference)
Male	2.00 (1.88-2.12)	1.61 (1.51-1.71)
Ethnicity		
European	1.00 (reference)	1.00 (reference)
Maori	1.01 (0.93-1.10)	2.31 (1.83-2.89)
Deprivation quintile		
1	0.61 (0.53-0.69)	0.75 (0.65-0.86)
2	0.97 (0.87-1.42)	0.95 (0.85-1.07)
3	1.00 (reference)	1.00 (reference)
4	1.31 (1.20-1.42)	0.99 (0.91-1.08)
5	1.44 (1.32-1.57)	1.15 (1.04-1.26)

NB: Adjusted rates are adjusted for all covariates in the model.

When controlled for other covariates, the adjusted mortality rate remained higher in individuals with thyroid dysfunction compared with normal thyroid function but was not as marked. Nevertheless, the all-cause mortality rate was 29% higher in SCH and 45% higher in OH when adjusted for age, gender, ethnicity and deprivation. Ethnicity which appeared not to be associated with mortality rates in crude analysis has 2.3 times the mortality rate of non-Maori after adjusting for other covariates. Age remained the highest indicator of mortality.

The influence of age was further analysed using all-cause mortality data, examining the cohort that were <65 years of age and 65+ years separately. In the <65 years age group, there were 52,988 subjects with 1157 deaths. This contributed a risk time of 271,451 person-years at risk and a death rate of 4.3 per 1000 person-years i.e. approximately 1 person out of 250 people per year. In contrast, in the 65+ years age group, there were 13,644 subjects with 3,305 deaths. This contributed a risk time of 62,130 person-years and a death rate of 53.2 per 1000 person-years: 12 times as many as the <65 year age group per year. Further analysis by gender found that men <65 years of age had a higher mortality rate (7.03 per 1000 person-years) compared with women <65 years of age (3.0 per 1000). Likewise, men aged 65+ had a higher mortality rate (60.0 per 1000) than women of the same age group (48.1 per 1000).

When adjusted for gender, ethnicity and deprivation quintile, the mortality rate by thyroid group increased to 2.11 (95% CI 1.68, 2.64) for SCH and 1.88 (1.42, 2.47) for OH in the <65 year group. In the 65+ group, after adjustment, the mortality rate reduced in SCH to 1.28 (1.14, 1.42) and increased in OH to 1.58 (1.41, 1.78).

DISCUSSION

The prevalence of hypothyroidism was 10% in our study with 5.8% of individuals categorised with SCH and 4.2% with OH. The rate of hypothyroidism increased with advancing age and is consistent with prevalence reports from Colorado and Whickham studies [43, 79]. This study examined survival in individuals ≥ 20 years of age with varying degrees of hypothyroidism, namely subclinical and overt hypothyroidism, in relation to cardiovascular morbidity and mortality over a decade (1997-2006). These data were adjusted by age, gender, ethnicity and deprivation index and compared with euthyroid individuals (with normal thyroid function). Our results show an increase in cardiovascular events and in all-cause mortality in individuals with hypothyroidism which persisted after further distinguishing data into two age cohorts and controlling for gender, ethnicity and deprivation.

Cardiovascular disease accounts for over 40% of deaths in New Zealand [382]. Overt hypothyroidism is known to exert adverse effects on the cardiovascular system as a result of reduced thyroid hormone levels [123]. It is a national priority for health professionals to identify ways to reduce morbidity and mortality relating to cardiovascular events [20, 405]. Despite the number of thyroid function tests requested in primary care, questions remained regarding the long-term outcomes of having a SCH. This study addresses this question.

Cardiovascular event rates remained higher, after adjustment for age, gender, ethnicity and deprivation, in individuals with hypothyroidism (22% SCH and 58% OH) than with normal thyroid function. All-cause mortality rates were also higher after adjustments for age, gender, ethnicity and deprivation in individuals with hypothyroidism being 29% SCH and 45% OH greater than individuals with normal thyroid function. Age confounded the relationship between hypothyroidism and both cardiovascular event and all-cause mortality. Cardiovascular event rates were similar in the <65 year age group to overall adjusted rates and were reduced in individuals 65+ years. In all-cause mortality, the rate of death was highest for individuals with SCH who were <65 years of age.

The usual treatment for OH is thyroid replacement therapy (TRT). TRT mimics the natural role of thyroxine in the body. We present these findings independent of current or present thyroid treatment. It would be assumed that individuals with OH are receiving TRT together with adequate treatment and monitoring. Therefore, it is expected that their survival would be similar to those with normal thyroid function. However, this is not the case. Many studies have shown that as many as 50% of patients on TRT were inadequately treated – either over prescribed or under-prescribed [81 80]. A Hamilton study demonstrated that raised TSH results are not well managed in two general practices [307]. It is also possible that TRT is unable to affect changes on cardiovascular risk parameters or that the cohort needs to be followed for a longer time period. In negotiation with patients, some general practitioners are known to treat patients with TRT at TSH levels between 5-10 mIU/L, while some do not, citing the lack of evidence to support treatment in this patient group [309] . Medication may modify thyroid function but it may not bring it back to within the normal reference interval.

Our data lacked information about thyroid autoantibodies, thyroid history, medication history, smoking, weight and diet. In particular, smoking, obesity and poor diet are independent risk factors for cardiovascular disease [20]. This information may have altered our findings in relation to cardiovascular events and all-cause mortality.

In this laboratory defined cohort, age and gender were important predictors of a cardiovascular event for individuals with thyroid dysfunction. In particular, thyroid dysfunction impacted on cardiovascular event rates at a younger age and failure rates were higher in men compared with women of the same age range. This chapter identified the cardiovascular event rate for morbidity and all-cause mortality outcomes in relation to thyroid dysfunction. We found that the risk of having a cardiovascular event was higher in individuals with SCH and OH. Studies have shown that TRTs may not be monitored adequately in patients with OH. More evidence is required to assess the benefits of TRT in reducing cardiovascular risk parameters especially for individuals characterised by SCH. The next chapter will address this issue in the form of a systematic review.

CHAPTER 5 - SYSTEMATIC REVIEW: WHAT IS THE EFFECTIVENESS OF THYROXINE IN REDUCING CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM (SCH)?

BACKGROUND

Population studies have identified a positive correlation between subclinical hypothyroidism (SCH) and levels of total cholesterol and low-density lipoprotein (LDL) compared with those subjects whose TSH levels are within the normal reference interval [93-95]. Almost all cases of suspected hypothyroidism will present to the general practitioner in the first instance. Whilst the classical signs and symptoms of both hyperthyroidism and hypothyroidism are well known the features of early thyroid dysfunction are subtle [256]. SCH is a common laboratory finding in general practice affecting up to one-fifth of women over 60 years of age [43]; consequently, general practitioners have a low threshold for ordering thyroid function tests in adult patients [306]. It remains contentious whether the discovery of a raised TSH level in general practice, with or without symptoms, is significant [66, 67, 86-92]. This review aims to establish whether the null hypothesis is true: that there is no positive cardiovascular benefit in prescribing LT_4 to patients with SCH.

EPIDEMIOLOGY

International estimates report the prevalence of SCH between 4-8% [39, 43, 46, 113]. Studies have shown that prevalence varies with age; gender; genetic factors, such as the presence of thyroid autoimmunity; iodine intake; and tobacco smoking [40, 43, 47, 83, 406, 407]. Women are nearly 5 times more likely than men to develop thyroid dysfunction[79]. Progression from SCH to overt hypothyroidism occurs at a rate of 4.3% a year in women with elevated TSH and anti-thyroid antibodies [39, 79].

DESCRIPTION OF THE CONDITION

Subclinical hypothyroidism (SCH) is biochemically identified as a raised thyroid stimulating hormone (TSH) result with thyroid hormone levels within normal limits [140]. Due to improved sensitivity in the determination of TSH concentrations there has been an increase in the number of newly diagnosed cases of subclinical hypothyroidism [76]. However, not all are related to thyroid dysfunction and may be due to non-thyroidal illness. The progression of hypothyroidism may be slow, showing changes in TSH well before thyroid hormone levels decrease [185]. Factors such as autoimmune antibodies have been associated with greater progression to overt disease [39, 79, 107]. In addition, subclinical hypothyroidism has been associated with reduced cognitive function [103, 147, 408], a reduction in measurable quality of

life [409, 410], and an increased risk of atherosclerosis and cardiovascular disease [96, 112, 366, 381, 411, 412]. SCH has been suggested to be a normal part of the ageing process; a reduced heart rate is beneficial in older people with coronary artery disease [22]. However, if coronary artery disease is due to earlier untreated SCH then it is imperative to determine the effects of SCH on cardiovascular health and to identify where preventative measures should be actively considered.

DESCRIPTION OF THE INTERVENTION

Levo-thyroxine (LT_4) medication is a synthetic form of thyroxine most commonly used in the treatment of hypothyroidism [5]. Treatment of hypothyroidism with levo-thyroxine is usually life-long as the thyroid gland is unable to manufacture thyroxine to meet the requirements of the body. LT_4 mimics the actions of T_4. The dose of LT_4 is 1.6 micrograms (mcg)/kilogram (kg) per day in adults. The dose is started at 50 mcg/day increasing to a dose which normalises TSH. In older adults or adults with pre-existing cardiac disease, the dose is 1 mcg/kg per day with a starting dose of 25 mcg/day. This lower dose per kilogram is suggested as the starting dose for subclinical hypothyroidism .

HOW THE INTERVENTION MIGHT WORK

Observational studies have suggested that treatment with levo-thyroxine appears to attenuate ischaemic heart disease-related morbidity and mortality in individuals with SCH [16, 17, 78, 96-99]. In addition, benefits of treatment on cardiovascular outcomes may be age-related[22]. Conversely, inherent risks in overprescribing include a reduction in bone mineral density [83] and the precipitation or exacerbation of existing acute coronary syndromes in older individuals [84, 85] are described. On the contrary, a slightly raised TSH has been found to be beneficial in older patients with severe coronary artery disease since a lowered basal metabolic rate is cardioprotective [22].

CONSENSUS FOR TREATMENT

There remains a lack of consensus amongst expert groups on the management of SCH [14, 30-32, 34, 87, 335, 336]. Despite evidence from observational studies, debate concerning the benefits of treating with thyroxine replacement therapy continues [88, 92, 306, 335, 413, 414]. General practitioners need definitive guidelines for the treatment of patients with SCH within a

narrow range of TSH (5-10 mIU/L) and to know that the benefit of any treatment would outweigh the risks.

WHY IT IS IMPORTANT TO DO THIS REVIEW

A recent Cochrane Review of thyroid hormone replacement for subclinical hypothyroidism failed to demonstrate improved survival or reduced cardiovascular morbidity following LT_4 therapy for asymptomatic subclinical hypothyroidism; however, it did indicate improvements in some parameters of lipid profiles and left ventricular function [24]. With an ageing population, in which SCH is most prevalent, this is likely to be an important future public health issue [22, 39]. Furthermore, in New Zealand and in many other countries, a TSH consistently over 10 mIU/L signals impending thyroid failure, regardless of thyroid hormone status, increasing the consideration for levo-thyroxine [31, 34, 415, 416]. For general practitioners, a question mark remains over whether there is significant justification in treating patients with raised TSH who remain under this threshold, i.e. 5-10 mIU/L. Our systematic review incorporates studies with mean TSH values up to 12 mIU/L to accommodate studies where a good proportion of participants will have TSH levels <10 mIU/L.

The aim of this systematic review is to examine the relationship between levo-thyroxine treatment and cardiovascular risk factors in individuals with SCH within the TSH range of 5-10 mIU/L. Secondly we assessed this association in relation to gender, age, antibody status (where known), quality of studies and type of study.

OBJECTIVES

To assess the efficacy and safety of levo-thyroxine (LT4) in primary prevention of cardiovascular morbidity in adults with SCH.

The following hypotheses will be tested:

1. Thyroid hormone replacement (LT_4) is more effective than placebo or no intervention in reducing cardiovascular risk factors in adults with subclinical hypothyroidism within a defined range of 5-10 mIU/L
2. Thyroid hormone replacement (LT_4) is safe to use in reducing cardiovascular risk factors in adults with subclinical hypothyroidism within a defined range of 5-10 mIU/L

METHODS

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

TYPES OF STUDIES

Only randomised controlled trials were included. Studies were restricted from 1998 to the present. This ensured available articles were more likely to conform to the CONSORT Statement, first published in August 1996, for improving the quality of the reporting of randomised controlled trials [417].

TYPES OF PARTICIPANTS

Studies were included if: they assessed the efficacy of thyroxine versus placebo or no treatment; participants were adults (>18 years) with SCH; SCH was defined; thyroxine treatment was given for a minimum of one month; the mean thyroid stimulating hormone (TSH) range was between 5 - 12 mIU/L; there was no documented prior history of thyroid dysfunction including thyroid surgery, head or neck radiation (including radioactive iodine treatment); and there was a cardiovascular risk factor measured.

For this review, subclinical hypothyroidism was defined within a raised mean TSH level of 5 – 12 mIU/L and normal values of total thyroxine (T_4) or free T_4 (FT_4), with or without total triiodothyronine (T_3) or free T_3 (FT_3).

Participants were from outpatients or community settings with no severe illness reported. Children and adolescents were excluded.

TYPES OF INTERVENTIONS

Treatment with levo-thyroxine (LT_4) compared with placebo or no treatment. The length of treatment had to be at least one month in duration and a minimum length of follow-up of two months.

TYPES OF OUTCOME MEASURES

PRIMARY OUTCOMES

Cardiovascular morbidity - cardiovascular risk factors include: lipid levels (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density (HDL) cholesterol, triglycerides, lipoprotein (a)), systolic and diastolic heart functions, risk factors for atherosclerosis (e.g. BMD), Doppler echocardiography and ECG changes.

Cardiovascular mortality

SECONDARY OUTCOMES

All-cause mortality;

Adverse effects of treatment.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

ELECTRONIC SEARCHES

Published studies were identified through online searches of two databases: MEDLINE (until September 2010) and EMBASE (until September 2010). MEDLINE and EMBASE database searches were used to identify studies specific to subclinical hypothyroidism and thyroxine replacement therapy.

The following search strategy for MEDLINE was used and adapted for use with EMBASE:

1. (l-thyroxine or levo-thyroxine or eltroxin or levo-thyroxine sodium).mp.
2. (L-T4 or l-T4).mp.
3. Thyroxine/
4. Hormone Replacement Therapy/ or thyroid replacement.mp.
5. #1 OR #2 OR #3 OR #4
6. (suspected or asymptomatic or subclinical biochemical).mp.
7. Hypothyroidism/
8. #6 AND #7
9. (low thyroid reserve or mild thyroid failure).mp.
10. #8 OR #9
11. (pregnan* or trimester or congenital).mp.

12. #5 AND #10
13. #12 NOT #11
14. Limit #13 to yr="1998-Current"

Search terms ending with a "/" were Medical Subject Heading [MeSH] terms, ".mp." identifies keywords in the title, subject heading word, abstract, and instrumentation. "#" is to indicate a number and was not required for searching.

SEARCHING OTHER RESOURCES

We reviewed the citation lists from identified studies and reviews, and from systematic reviews identified.

We used key words of relevance during additional electronic searches and modified the search strategies to incorporate these. No new studies were found when adding further search terms or when narrowing by outcome (e.g. cardiovascular outcomes, such as atherosclerosis, ischaemic heart disease).

DATA COLLECTION AND ANALYSIS

SELECTION OF STUDIES

Studies were assessed by titles and abstracts identified by the electronic search. Full text hard copies were obtained for studies that appeared to meet the requirements of the selection criteria and for studies were there may have been doubt. Five questions were compulsory for inclusion and are listed in bold in Table 28.

TABLE 28: STUDY REVIEW QUESTIONS

Questions:
Is this a Randomised Controlled Trial?
Is thyroxine compared with placebo (or no treatment)?
Are participants with previous thyroid dysfunction/treatment excluded?
Is the endpoint related to cardiovascular risk or physiology?
Do patients fit with the study definition of SCH?

For the purpose of the analysis, previous thyroid dysfunction includes thyroid conditions that have required a surgical or therapeutic intervention, e.g. radioactive iodine (radioiodine) therapy, including surgery for multi-nodular goitre; and thyroid or anti-thyroid medication.

DATA EXTRACTION AND MANAGEMENT

Data were extracted using a standard data extraction form developed for the review. The authors or results of the study were not masked. The following key data were collected:

Methods: aim, description of randomisation process, allocation concealment, length of follow-up period, baseline assessment of primary outcomes, setting, representativeness, power calculations.

Participants: inclusion and exclusion criteria, cause of disease, gender, presence of thyroid antibodies, previous treatment or thyroid treatment, mean age, mean TSH, description of withdrawals, side effects

Interventions: Use of levo-thyroxine, starting dose, procedure for follow-up, increasing doses, duration of treatment, mean dose of treated group

Outcomes: Primary and secondary outcomes as described above.

Results: Converted to standard international units (SI - Système International d'unités) where comparable, any intention to treat analysis described.

Key data were collected and critically appraised using the GATE frame, a modified version of the EBM working group approach using a Graphic Appraisal Tool for Epidemiology (GATE) [418]. The GATE method uses a PECOT framework described below and illustrated in Figure 13:

Populations/Participants (P)

Exposure of interest/intervention (E)

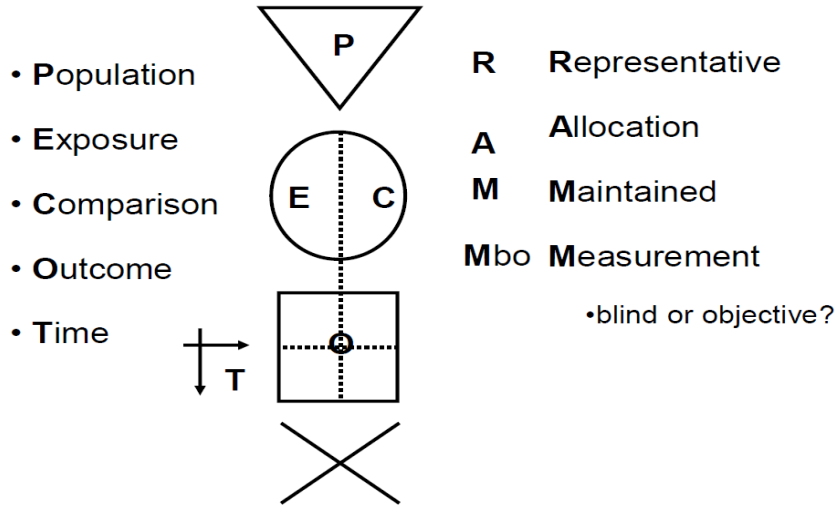
Comparison (alternative intervention/ routine care) (C)

Outcomes assessed (O)

Time period of the study or treatment (T)

The PECOT method was modified from an existing tool for students at the University of Auckland to facilitate the assessment of overall study quality [418]. In addition, quality of studies was assessed using the GATE evaluation criteria, RAMMbo, which is described in more detail below.

FIGURE 13: GATE FRAMEWORK FOR STUDY DESIGN AND EVALUATION CRITERIA [418]



ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Consideration was given to the inclusion of non-randomised trials. There are considerable biases inherent in non-randomised trials, such as selection bias and risk of confounding. Specific tools to address the quality of non-randomised studies are less developed than RCTs [419]. Many current tools for nonrandomised trials are based on those used for RCTs [420]. Literature around the use of non-randomised intervention studies in systematic reviews differ –suggesting that these should be used where RCTs are infeasible or unethical [419, 421]. Another suggestion encourages reviewers to investigate the degree and circumstances to which bias may be present in individual studies rather than using a generic scale to evaluate methodological quality in non-randomised trials [420]. In any event, a great deal of judgement is said to be necessary when critically appraising observational studies as well as a thorough understanding of the problem that the review focuses on and the methodological considerations inherent [422]. For this study, only RCTs were used. We assessed bias through the use of the Jadad scale [423] which grades methodological quality using the following scoring criteria:

1. Was the trial described as randomised (this includes the use of words such as random, randomly and randomisation)? (1 point).

2. Is the method of randomisation appropriate (1 point is added if the methods to generate the sequence of randomisation is described) and it is appropriate (for example, table of random numbers, computer generated). (0 points if the method of randomisation is not described).

3. Was the study described as double-blind? (1 point for yes, 0 points for no).

4. Is the method of blinding used appropriately? One point is added if the method of masking is described and appropriate (for example, identical placebo) (1 point is deducted if the method of masking is inappropriate (comparison of tablet versus injection with no double dummy), 0 points if the method of masking is not described.

5. Is there a description of withdrawals and dropouts? (1 point is given if the numbers and reasons for withdrawal in each group are stated. If there are no withdrawals, the report must say so. If there is no statement of withdrawals, this item is given no points).

The scale awards one to five points to randomised controlled trials (RCTs). RCTs with one and two points are considered low quality and RCTs with three to five points are considered high quality.

All studies were individually assessed using RAMMbo – **R**epresent, **A**llocation (or **A**djustment for non-randomised trials), well **M**aintained, **M**easured accurately, **B**lind or **O**bjective [418]. Grades are '+' (Good: low risk of bias or measurement error), 'x' (Poor: flawed and unreliable) and '?' (unclear, not well reported, unable to assess). This tool for appraising studies and assigning a grade for study quality has been developed by the University of Auckland (EPIQ – Effective Practice, Informatics & Quality improvement www.epiq.co.nz).

The criteria specified by RAMMbo summarises the following questions:

- Can the applicability of the results (i.e. external validity) be determined? (**R**epresented)
    - Study setting well described
    - Eligible population well described and appropriate
    - Participants represent eligible population
    - Relevant personal characteristics of participants reported
    - Interventions can be applied in usual practice
    - Follow-up was meaningful

- Are the study results internally valid (i.e. unbiased)? (**A**llocated well, well **M**aintained, **M**easured **B**lind or Objective)
    - Exposure and comparison of interventions well described and valid
    - Allocation to exposure and comparison groups: random or by measurement
    - Outcome of randomisation tamper resistant (allocation concealment)
    - If by measurement, these are accurate, blind to outcomes, objective
    - Participants and/or staff blind to exposure and outcome
    - Compliance with exposure and comparison adequate
    - Contamination acceptably low
    - Co-interventions are similar between groups
    - All participants accounted for at study conclusion
    - Outcome measures well described and valid
    - Blinded outcome measurement
    - All important outcomes assessed
    - Similar follow-up time in exposure and comparison groups
    - Exposure and comparison groups are similar at baseline or were adjusted
    - Intention to treat analysis

- Are results precise enough to be meaningful? If not, was power sufficient?
    - Estimates of intervention effects given or calculable
    - Precision of intervention effects given or calculable
    - Analytical methods appropriate.

Assessing heterogeneity is addressed below and in the section on subgroup analysis. Briefly where there was no heterogeneity between comparator groups, for example, non-RCTs and RCTs, these were pooled.

ASSESSMENT OF HETEROGENEITY

To assess for heterogeneity studies were entered into Review Manager 5.0.24 [424]. Due to the likelihood of clinical, methodological or statistical heterogeneity, study results used the random effects model. This assumes that all studies are heterogeneous; therefore, providing a more conservative estimate. Clinical and methodological diversity is nearly always inevitable [425]. Heterogeneity was identified by visual inspection of the forest plots, by using a standard X^2 test and a significance level of $\alpha=0.05$. Where $P<0.05$ this was indicative of the studies being heterogeneous. In addition, Review Manager quantifies the heterogeneity by including a test for inconsistency in the forest plots, which examines the magnitude of heterogeneity. Values greater than 50% represents substantial heterogeneity. When heterogeneity was found, an attempt to determine potential reasons for this were examined using individual study characteristics and subgroups of the main body of evidence as described below.

ASSESSMENT OF REPORTING BIASES

A funnel plot, in which the odds ratios are plotted on a logarithmic scale, was used to assess for reporting bias in published data. This was performed within RevMan 5.0.24 [424].

DATA SYNTHESIS

Data were summarised statistically if they were available, of sufficient quality and sufficiently similar. Dichotomous data were expressed as odds ratios. Continuous data were expressed as mean differences and an overall mean difference was calculated. Possible sources of heterogeneity were assessed by *a priori* subgroup and sensitivity analysis as described below.

SUBGROUP ANALYSIS AND INVESTIGATION OF HETEROGENEITY

If results for primary outcomes had significant heterogeneity or visual inspection of forest plots questioned the outcome, subgroup analyses were planned in order to explore effect size differences according to:

Age: 18-64 years; 65 years or older;

Anti-thyroid antibodies: present in all; present in some or none;

TSH difference: Mean TSH <8 mIU/L; Mean TSH ≥8 mIU/L

Gender: All female; mixed

SENSITIVITY ANALYSIS

Comparing RCTs of those scoring low on the Jadad scale (score 1-3) compared to those who scored 4-5.

STUDIES IDENTIFIED

The literature searches identified a total of 1506 studies. 1081 studies were reviewed by title and abstract for relevance according to the study review questions after excluding: letters (27 studies), comments (12), editorials (11), historical articles (1), evaluation studies (3), case reports (59), short surveys (16), notes (11), conference abstracts (48), conference papers (22) and reviews (215). Seventy-nine potential studies were retrieved for further scrutiny. Ten studies met the inclusion criteria and 69 studies were excluded. These are described in Figure 14 and Table 29.

FIGURE 14: FLOW CHART OF SEARCH CRITERIA AND STUDY SELECTION

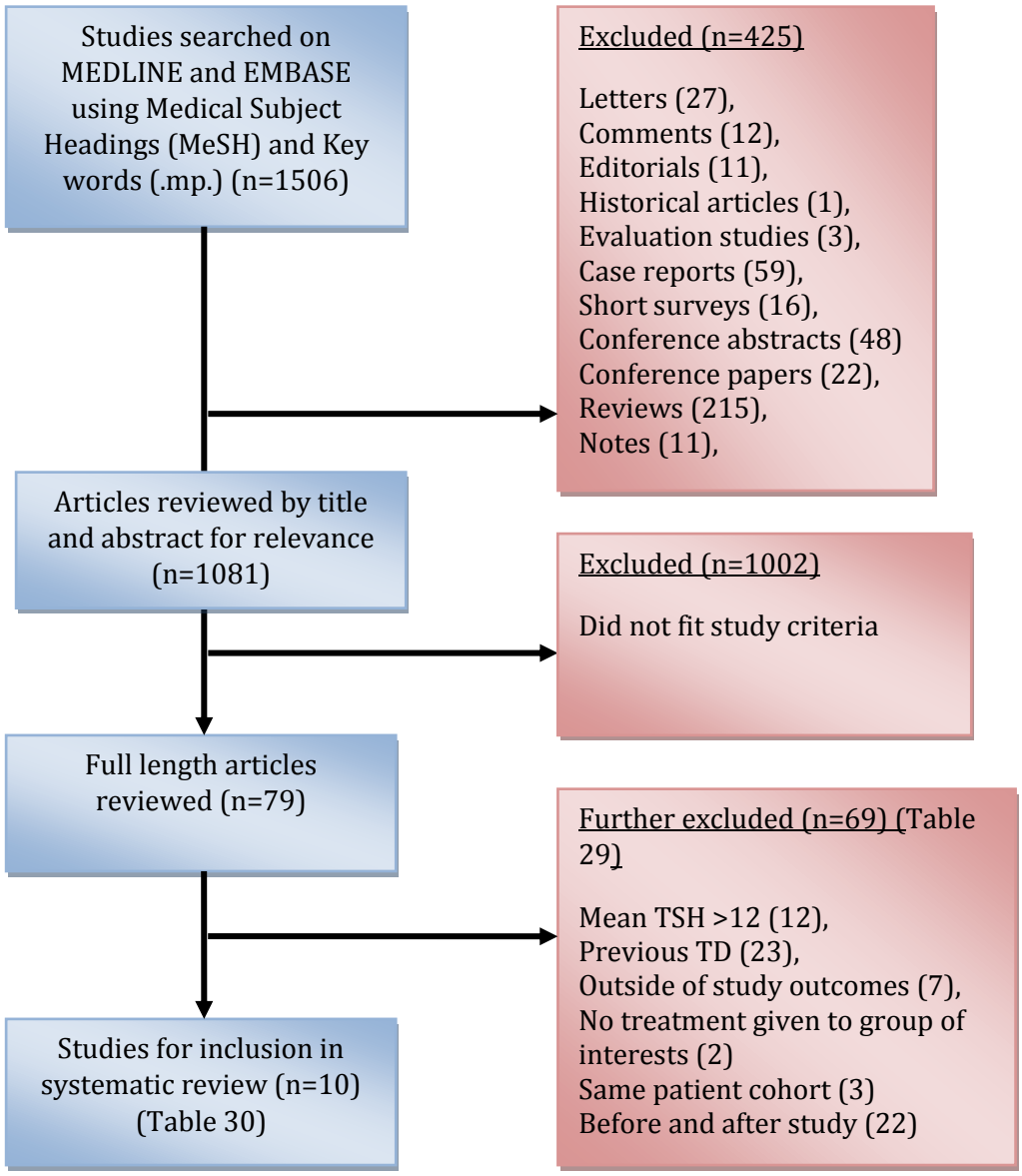


TABLE 29: EXCLUDED STUDIES

Author (alphabetical)	Year	Reason for exclusion
Abdul Shakoor [426]	2010	Before and after study
Adrees [427]	2009	Mean TSH above range
Akinci [428]	2007	Mean TSH above range
Akinci [429]	2007	Mean TSH above range
Arinzon [18]	2007	Previous thyroid dysfunction
Bakiner [430]	2008	No treatment in group of interest
Baldini [431]	2009	Before and after study
Beyhan [432]	2006	Previous thyroid dysfunction
Brenta [433]	2007	Previous thyroid dysfunction
Brenta [434]	2003	Previous thyroid dysfunction
Cakal [435]	2007	Mean TSH above range
Canturk [436]	2003	Before and after study
Canturk [437]	2003	Previous thyroid dysfunction
Caraccio [438]	2005	Outside of study outcomes
Caraccio [439]	2002	Previous thyroid dysfunction
Christ-Crain [440]	2003	Previous thyroid dysfunction
Christ-Crain [441]	2005	Previous thyroid dysfunction
Cinemre [442]	2009	Outside of study outcomes
Deicher [443]	2002	Before and after study
Duman [444]	2007	Same patient cohort as earlier study [445]
Duntas [446]	2002	Outside of study outcomes
Efstathhiadou [447]	2001	Before and after study
Erdal [448]	2008	Before and after study
Faber [132]	2002	Mean TSH above range
Fadeyev [84]	2006	Outside of study outcomes
Galetta [449]	2006	Before and after study
Ganotakis [450]	2003	Before and after study
Gullu [451]	2005	Before and after study
Hamano [452]	2005	Mean TSH above range
Ito [453]	2007	Previous thyroid dysfunction
Ito [454]	2004	Previous thyroid dysfunction
Kebapcilar [455]	2007	Mean TSH above range
Kebapcilar [456]	2010	Previous thyroid dysfunction
Kim [457]	2009	Previous thyroid dysfunction
Koren Peleg [458]	2008	Before and after study
Mariotti [459]	2008	Before and after study
Meek [437]	2003	Outside of study outcomes
Merchante-Alfaro [460]	2006	Before and after study
Meier [327]	2001	Previous thyroid dysfunction
Milionis [461]	2003	Same patient cohort [447]
Milionis [462]	2005	Same patient cohort [447]

Mishra [463]	2005	Before and after study
Monzani [328]	1999	Previous thyroid dysfunction
Monzani [98]	2004	Previous thyroid dysfunction
Nagasaki [135]	2007	Before and after study
Oflaz [464]	2007	Before and after study
Oge [465]	2004	Mean TSH above range
Owen [466]	2006	Before and after study
Ozcan [467]	2005	Previous thyroid dysfunction
Perez [468]	2004	Previous thyroid dysfunction
Paoli [469]	1998	Before and after study
Prats Julia [470]	2009	Mean TSH above range
Rezzonico [471]	1999	Outside of study outcomes
Riis [472]	2005	Outside of study outcomes
Roos [473]	2005	Mean TSH above range
Schultz [474]	2004	Mean TSH above range
Sengul [475]	2004	Previous thyroid dysfunction
Serter [476]	2004	Before and after study
Taddei [124]	2003	Previous thyroid dyfunction
Tagami [477]	2010	Previous thyroid dysfunction
Teixeira [478]	2008	Previous thyroid dysfunction
Teixeira [53]	2008	Previous thyroid dysfunction
Turhan [479]	2006	Before and after study
Tzotzas [480]	2000	Before and after study
Unal [481]	2007	Before and after study
Velija-Asimi [482]	2007	Before and after study
Vilcheza [483]	1998	Mean TSH above range
Xiang [243]	2009	No treatment in group of interest
Yazici [484]	2004	Previous thyroid dysfunction

STUDY DESIGN

A total of 10 RCTs met the inclusion criteria for our systematic review (Table 30). All studies refer to being randomised although only three studies describe the method of randomisation[279, 485, 486] and one partially describes it [487]. Allocation concealment was described in four studies [99, 279, 485, 488]. One study was a cross-over design [279]. Blinding occurred in five studies – two studies identified blinding of echocardiographers to the patients' grouping [19, 99], two described both patients and investigators were blinded [279, 485] and one had patients blinded to their allocation [488]. Placebo was given in 6 studies [94, 99, 279, 485, 486, 488], although there was no description of the placebo regime in two of these studies [94, 486]. Three studies described the placebo intervention as being similar to the LT_4 tablets in every respect to maintain blinding [99, 485, 488].

TABLE 30: INCLUDED STUDIES

Author (alphabetical)	Year	Country of study
Biondi [19]	1999	Italy
Duman [445]	2007	Turkey
Franzoni [489]	2006	Italy
Iqbal [94]	2006	Norway
Kong [485]	2002	England
Mainenti [487]	2009	Brazil
Mikhail [486]	2008	Kuwait
Monzani [99]	2001	Italy
Nagasaki [488]	2009	Japan
Razvi [279]	2007	England

INTERVENTION

All studies compared LT_4 with either placebo or no treatment. One study additionally studied the effects of simvastatin on patients with SCH to compare with a euthyroid control group [445]. Doses of LT_4 were titrated until euthyroidism was restored in eight studies [19, 94, 99, 445, 485-488]. One study gave no description of intervention dosages or regimes [489] and another gave a fixed dose of 100 mcg/day [279]. Restoration of euthyroidism is described in 5 studies, with mean doses of LT_4 equal to 25.8 mcg/day [488], 42.25 mcg/day [487], 65 mcg/day [99], 68 mcg/day [19] and 72 mcg/day [486].

PARTICIPANTS

A total of 669 SCH patients were involved in the 10 studies. The majority of participants were female (74.9%). In four studies, all participants were female [445, 485, 487, 488]. Three studies had provided LT_4 intervention to a subgroup with SCH, the gender of the subgroups was not detailed [19, 94, 489].

The mean ages of study participants ranged from 32.1 ± 10.1 – 64.4 ± 2.59 years of age. Studies in which the demographics of the subgroups were not identified, the mean age from the SCH group was used. The mean ages for all studies fell within the 20-64 year category.

Four studies identified all SCH participants as being anti-thyroid antibody positive (Hashimoto's thyroiditis, or chronic autoimmune thyroiditis) [99, 445, 488, 489]. In addition, two studies identified greater than 50% of participants as being anti-thyroid antibody positive [279,

[486]. Studies that described all SCH participants as having anti-thyroid antibodies were compared against those that did not describe all SCH participants as having anti-thyroid antibodies in subgroup analysis.

The mean TSH of studies ranged from 5.3 – 10.9 mIU/L. To direct the focus on results in participants with a TSH level between 5-10 mIU/L, two groups were identified for subgroup analysis: 1) mean TSH <8 mIU/L [94, 99, 279, 486-488], and 2) mean TSH ≥8 mIU/L [19, 445, 485, 489].

SCH was defined as being above the upper TSH limit of normal with normal thyroid hormones. The upper TSH reference interval ranged from >3.0 mIU/L to >5.0 mIU/L. Two studies stipulated an upper cut-off level for SCH recruitment of 10 mIU/L [94, 485]. Seven studies identified participants to have had stable SCH prior to enrolment by, two tests within 4 weeks [486, 487], two tests within 3 months [279, 489], two tests within six months [19, 488], and stable for a year [99]. Three studies used one measure of TSH and FT_4 [94, 445, 485]. In addition, one study also measured thyroid replacement hormone (TRH) to confirm subclinical status [19].

DURATION OF STUDIES

Study duration ranged from three months to 12 months. The majority of studies were for 6 months.

OUTCOMES

Six studies analysed outcomes related to lipids [94, 279, 445, 485, 486, 488]; three studies analysed apo A and apo B [94, 279, 485]; Doppler echocardiography was investigated in two studies [19, 99]; three studied blood pressure [99, 279, 487]; pulsed tissue Doppler imaging (TDI) [489], brachial artery pulsed-wave velocity (baPWV) [488] and oxygen update (VO_2) [487] were each studied once.

METHODOLOGICAL QUALITY

RANDOMISATION METHOD

All studies were randomised controlled trials. Methods of randomisation were described in three studies [279, 485, 486] and partly described in one study [487]. Allocation concealment was described in four studies [99, 279, 485, 488]. Four studies did not mention methods of randomisation or allocation concealment [19, 94, 445, 489].

BLINDING METHODS

Double-blinding was mentioned in titles or abstracts for six studies [94, 99, 279, 485, 486, 488]. Double-blinding was fully described in three of these studies [99, 279, 485]. One study provided partial details of blinding [488] and two provided no details [94, 486]. These two latter studies were based on laboratory results, and are less likely to be biased than investigator initiated tests such as echocardiography or blood pressure measurements.

ATTRITION RATES

Four studies described attrition rates [279, 445, 485, 488]. There were no withdrawals in one study [488], one withdrawal in one study [279], two withdrawals in another study [445] and five withdrawals in the other study [485]. Two studies had withdrawals from the placebo group for perceived side effects [279, 485] and two had withdrawals due to poor compliance [445, 485]. Side effects (unwell, increased fatigue) were noted in one study [485]; however, apart from reasons for withdrawals, side effects were not noted separately in any studies.

ADDITIONAL CONSIDERATIONS

The quality of studies was assessed using both the Jadad scale [423] and GATE methods [418] as described earlier. The Jaded scale was used to grade studies from 1-5. The median mark allocated was 2/5. Three studies graded >3/5 [279, 485, 488]. A subgroup analysis will be done between the studies scoring >3/5 and those that scored ≤3/5. The Jadad grades and GATE methods for each of these studies can be found in Appendix 5.

RESULTS

PRIMARY OUTCOMES

Cardiovascular risk factors that were investigated included: lipid levels (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density (HDL) cholesterol, triglycerides), systolic and diastolic blood pressure, and Doppler echocardiography. These were able to be compared between studies.

One study used pulsed tissue Doppler imaging [489], one studied brachial artery pulse wave velocity [488], while another measured submaximal cardiopulmonary parameters – oxygen

uptake, minute ventilation, carbon dioxide production [487]. These studies were not able to be compared to any other studies.

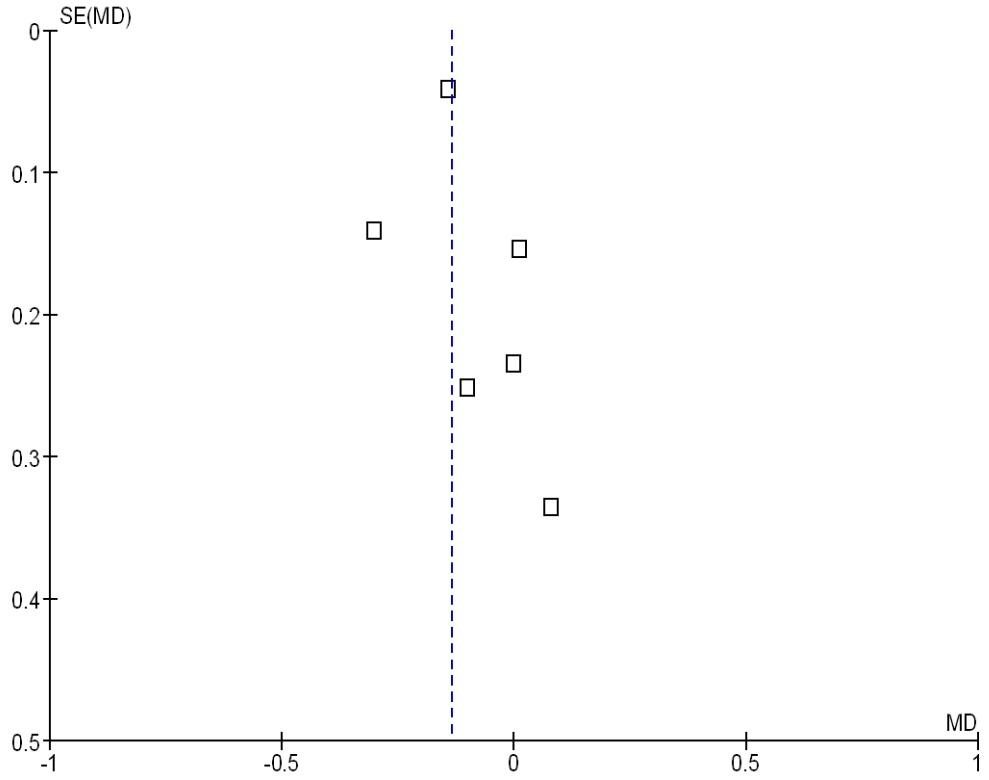
Cardiovascular mortality was not investigated in any of the included studies.

LIPID STUDIES

Six studies reported outcomes on 545 subclinical hypothyroid (SCH) participants, 276 who had a trial of levo-thyroxine (LT_4) [94, 279, 445, 485, 486, 488]. Trials ranged from 3 months to 12 months, averaging 7 months.

A funnel plot shows the comparison of studies (Figure 15). There appears to be some publication bias indicated by a lack of studies in the left quadrant. This was reduced as much as possible by using a random effects model when analysing the studies.

FIGURE 15: FUNNEL PLOT OF COMPARISON OF STUDIES FOR TOTAL CHOLESTEROL IMPROVEMENT



To allow comparison between studies, where the unit of measure was milligrams per decilitre (mg/dL) this was converted to millimoles per litre (mmol/L) by multiplying total cholesterol (TC), Low-density lipoprotein (LDL) and High-density lipoprotein (HDL) by a factor of 0.0259. Triglycerides were multiplied by 0.0113 to convert mg/dL to mmol/L. Total

cholesterol (TC) levels (Figure 16) and LDL (Figure 17) appear to reduce as a result of LT_4. TC differed by 0.13 mmol/L and LDL differed by 0.22 mmol/L. Both of these were statistically significant (p=0.0003 and <0.0001, respectively). HDL (Figure 18) and triglycerides (Figure 19) showed no difference between intervention and placebo groups and these were not statistically significant.

Lipid measurements tested underwent subgroup analysis. The difference between groups remained the same for total cholesterol when studies only had female participants [445, 485, 488] (p=0.001) compared with studies of mixed gender (p=0.16). Studies examining LDL remained unchanged with subgrouping and all were statistically significant with no heterogeneity. TC and LDL remained unchanged when studies had a mean TSH <8 mIU/L [94, 279, 486, 488] compared to studies ≥8 mIU/L. When comparing studies with and without antibodies, the effect of LT_4 on TC remained unchanged but was not statistically significant when studies in which all participants had antibodies were removed. The difference between groups did not change with LDL. Subgroup analysis did not change the result of HDL and triglycerides and continued to favour no treatment.

In sensitivity analysis, the effect of LT_4 on TC and LDL strengthened statistically when studies with a Jadad score ranging from 1-3 were removed [94, 445, 486].

When assessing the change in LDL from baseline in the treated groups, there was a 0.27 mean reduction (95% CI 0.09-0.44). There appeared to be some heterogeneity (p=0.07) with grouping all these studies. After subgroup analysis, the heterogeneity was removed when studies where all participants were antibody positive where removed, when only female participants were included and when studies with a mean TSH of <8 mIU/L were included. Sensitivity analysis revealed that the improvement in LDL strengthened (0.3 mmol/L mean reduction, 95% CI 0.05-0.55) when studies with a Jadad score ranging from 1-3 were removed.

No significant effects between intervention and control groups were found in apoprotein A (Figure 20) and apoprotein B results (Figure 21).

BODY MASS INDEX (BMI)

Five studies consisting of 245 participants reported the effects of treatment on BMI [94, 99, 445, 485, 488]. The intervention was administered in 126 participants. The effect of LT_4 favoured

treatment (p=0.003) (Figure 22) with a reduced BMI of 0.3 between treated and untreated groups. There were no significantly enhanced effects when subgrouped.

BLOOD PRESSURE

Blood pressure was reported in four studies with a total of 338 participants [99, 279, 487, 488]. Mean diastolic blood pressure reduced in two studies [279, 488] and increased in two studies [99, 487] after intervention. Overall, the effect of LT_4 on diastolic blood pressure was not statistically significant (p=0.59), tending towards no treatment (Figure 23). In sensitivity analysis, the overall effect of LT_4 on diastolic blood pressure was a difference of 0.19 mm Hg, when studies with a Jadad score ranging from 1-3 were removed [99, 487]; however, the difference between treatment and control groups was not statistically significant (p=0.65)

There was a statistically significant effect of LT_4 on systolic blood pressure, reducing systolic blood pressure by >3mm Hg (95% CI 1.89-4.75) (p=<0.0001) (Figure 24). Subgroup analysis revealed that the statistically significant effect remained with studies where all patients were antibody positive [99, 488] or where all were female [487, 488]. All studies had a mean TSH <8 mIU/L.

The overall effect of LT_4 on systolic blood pressure was increased by 0.2mm Hg when studies with a Jadad score ranging from 1-3 were removed [99, 487] and this was statistically significant (p<0.0001) .

SYSTEMIC RESISTANCE

Two studies involving 239 participants reported outcomes in brachial artery diameter and brachial artery flow [279, 445]. The effect of LT_4 on brachial artery diameter was a mean difference between groups of 0.09mm; however, this was not statistically significant (p=0.19) (Figure 25). Subgroup analysis and sensitivity analysis showed no change. Likewise, the difference between the treatment and control groups was an increase in brachial artery flow of 2.2 ml/sec; however, this was not statistically significant (p=0.67) (Figure 26) and did not change as a result of subgroup or sensitivity analysis.

CARDIAC FUNCTION

Two studies with a total of 56 participants examined outcomes on systolic (fractional shortening and systemic vascular resistance) (Figure 27 and Figure 28) and diastolic function

(early and late transmitral flow velocity, and transmitral valve ratio) (Figure 29) using Doppler echocardiography [19, 99]. Both studies had groups with mixed gender and had the same Jadad score. Twenty participants received LT_4 treatment. The duration of the studies was 6 months.

The effect of LT_4 on fractional shortening showed weak evidence for favouring treatment (p=0.09). All results were in the normal range for this measure (30-42%) however, the untreated group had results 2% lower than the treated group in these studies. There remained no difference between groups when subgrouped antibody status or mean TSH.

Systemic vascular resistance was less in treated patients than in the control group. This favoured the treated group; however was not statistically significant (p=0.45). Subgroup analysis showed no differences between groups, as expected.

The early-to-late transmitral flow velocity ratio (E/A) favoured treatment and was statistically significant (p=0.01). The control groups had lower E/A than the treatment group in both studies. The E/A is reduced in diastolic dysfunction.

FIGURE 16: FOREST PLOT OF COMPARISON: CHOLESTEROL (MMOL/L) IMPROVEMENT.

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [mmol/L]	SD [mmol/L]	Total	Mean [mmol/L]	SD [mmol/L]	Total	Weight	IV, Random, 95% CI [mmol/L]	IV, Random, 95% CI [mmol/L]
Duman 2007	5.2318	0.73	20	5.2318	0.73	19	2.6%	0.00 [-0.46, 0.46]	
Iqbal 2006	5.7	1.1	32	5.8	0.9	32	2.2%	-0.10 [-0.59, 0.39]	
Kong 2002	5.7	1.01	16	5.62	0.73	11	1.3%	0.08 [-0.58, 0.74]	
Mikhail 2008	5.05	0.98	60	5.04	0.67	60	6.0%	0.01 [-0.29, 0.31]	
Nagasaki 2009	5.19	0.16	48	5.33	0.24	47	80.7%	-0.14 [-0.22, -0.06]	
Razvi 2007	5.7	1	100	6	1	100	7.1%	-0.30 [-0.58, -0.02]	
Total (95% CI)			**276**			**269**	**100.0%**	**-0.13 [-0.21, -0.06]**	

Heterogeneity: Tau² = 0.00; Chi² = 3.04, df = 5 (P = 0.69); I² = 0%

Test for overall effect: Z = 3.58 (P = 0.0003)

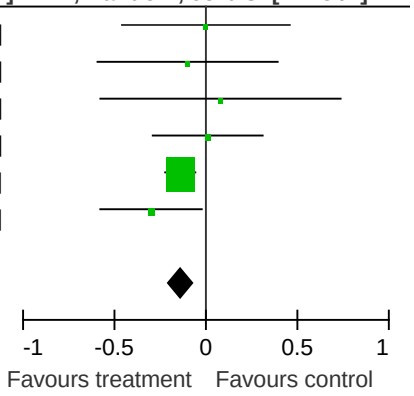


FIGURE 17: FOREST PLOT OF COMPARISON: LDL IMPROVEMENT [MMOL/L].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [mmol/L]	SD [mmol/L]	Total	Mean [mmol/L]	SD [mmol/L]	Total	Weight	IV, Random, 95% CI [mmol/L]	IV, Random, 95% CI [mmol/L]
Duman 2007	3.367	0.83	20	3.3152	0.83	19	2.5%	0.05 [-0.47, 0.57]	
Iqbal 2006	3.6	0.9	32	3.6	1	32	3.1%	0.00 [-0.47, 0.47]	
Kong 2002	3.4965	1.5022	16	3.6001	1.6058	11	0.5%	-0.10 [-1.30, 1.10]	
Mikhail 2008	2.89	0.59	60	3.11	0.77	60	11.3%	-0.22 [-0.47, 0.03]	
Nagasaki 2009	3.14	0.29	48	3.36	0.19	47	70.4%	-0.22 [-0.32, -0.12]	
Razvi 2007	3.4	0.8	100	3.7	0.9	100	12.2%	-0.30 [-0.54, -0.06]	
Total (95% CI)			**276**			**269**	**100.0%**	**-0.22 [-0.30, -0.13]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.37, df = 5 (P = 0.80); I² = 0%

Test for overall effect: Z = 5.12 (P < 0.00001)

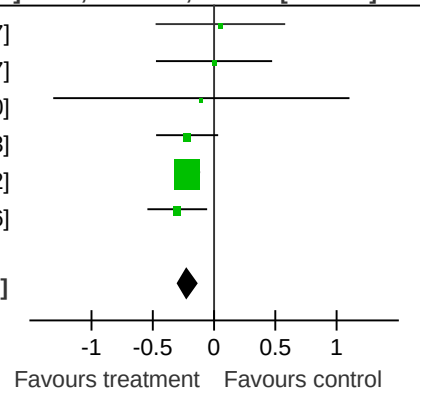


FIGURE 18: FOREST PLOT OF COMPARISON: HDL IMPROVEMENT [MMOL/L].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean [mmol/L]**	**SD [mmol/L]**	**Total**	**Mean [mmol/L]**	**SD [mmol/L]**	**Total**	**Weight**	**IV, Random, 95% CI [mmol/L]**	**IV, Random, 95% CI [mmol/L]**
Duman 2007	1.3727	0.4144	20	1.374772	0.22274	19	9.2%	-0.00 [-0.21, 0.21]	
Iqbal 2006	1.5	0.4	32	1.5	0.5	32	8.2%	0.00 [-0.22, 0.22]	
Kong 2002	1.036	0.518	16	1.4763	0.5957	11	2.5%	-0.44 [-0.87, -0.01]	
Mikhail 2008	1.19	0.32	60	1.1	0.25	60	22.8%	0.09 [-0.01, 0.19]	
Nagasaki 2009	1.41	0.08	48	1.39	0.06	47	41.0%	0.02 [-0.01, 0.05]	
Razvi 2007	1.6	0.5	100	1.7	0.5	100	16.3%	-0.10 [-0.24, 0.04]	
Total (95% CI)			**276**			**269**	**100.0%**	**0.00 [-0.07, 0.07]**	

Heterogeneity: Tau² = 0.00; Chi² = 9.04, df = 5 (P = 0.11); I² = 45%

Test for overall effect: Z = 0.03 (P = 0.97)

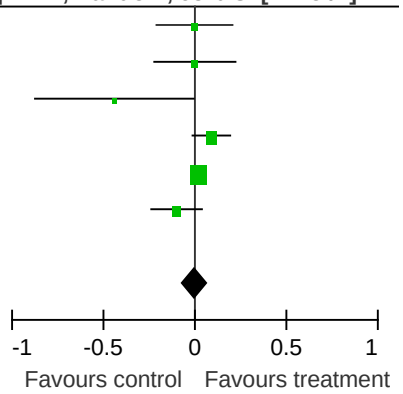


FIGURE 19: FOREST PLOT OF COMPARISON: TRIGLYCERIDE IMPROVEMENT [MMOL/L].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	**Mean [mmol/L]**	**SD [mmol/L]**	**Total**	**Mean [mmol/L]**	**SD [mmol/L]**	**Total**	**Weight**	**IV, Random, 95% CI [mmol/L]**	**IV, Random, 95% CI [mmol/L]**
Duman 2007	1.0509	0.4181	20	1.4464	0.6554	19	18.9%	-0.40 [-0.74, -0.05]	
Iqbal 2006	1.5	1	32	1.6	0.7	32	15.4%	-0.10 [-0.52, 0.32]	
Kong 2002	1.8984	2.0905	16	1.2995	0.6893	11	3.6%	0.60 [-0.50, 1.70]	
Mikhail 2008	0.95	0.53	60	1.06	0.59	60	27.5%	-0.11 [-0.31, 0.09]	
Nagasaki 2009	1.5	0.16	48	1.38	0.14	47	34.6%	0.12 [0.06, 0.18]	
Total (95% CI)			**176**			**169**	**100.0%**	**-0.06 [-0.28, 0.16]**	

Heterogeneity: Tau² = 0.04; Chi² = 13.85, df = 4 (P = 0.008); I² = 71%

Test for overall effect: Z = 0.51 (P = 0.61)

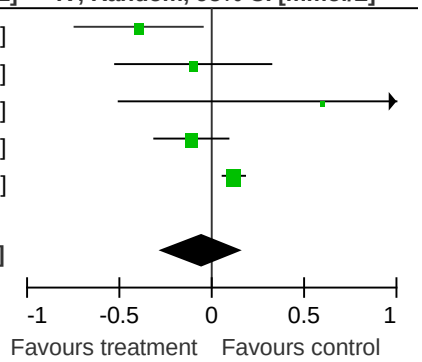


FIGURE 20: FOREST PLOT OF COMPARISON: APOPROTEIN A IMPROVEMENT [G/L].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [g/L]	SD [g/L]	Total	Mean [g/L]	SD [g/L]	Total	Weight	IV, Random, 95% CI [g/L]	IV, Random, 95% CI [g/L]
Iqbal 2006	1.4	0.2	32	1.5	0.3	32	30.8%	-0.10 [-0.22, 0.02]	
Kong 2002	1.7	0.7	16	1.7	0.6	11	2.0%	0.00 [-0.49, 0.49]	
Razvi 2007	1.52	0.31	100	1.52	0.3	100	67.2%	0.00 [-0.08, 0.08]	
Total (95% CI)			**148**			**143**	**100.0%**	**-0.03 [-0.10, 0.04]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 2 (P = 0.43); I² = 0%

Test for overall effect: Z = 0.87 (P = 0.38)

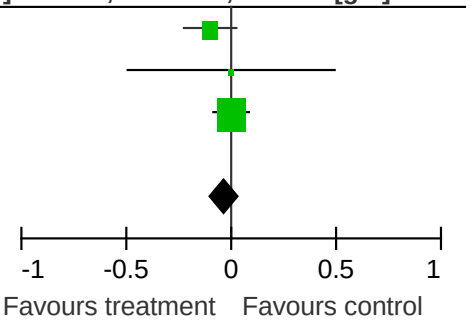


FIGURE 21: FOREST PLOT OF COMPARISON: APOPROTEIN B IMPROVEMENT [G/L].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Iqbal 2006	1.2	0.3	32	1.2	0.3	32	30.4%	0.00 [-0.15, 0.15]	
Kong 2002	1.4	0.7	16	1.3	0.4	11	3.8%	0.10 [-0.32, 0.52]	
Razvi 2007	1.02	0.34	100	1.09	0.38	100	65.8%	-0.07 [-0.17, 0.03]	
Total (95% CI)			**148**			**143**	**100.0%**	**-0.04 [-0.12, 0.04]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 2 (P = 0.59); I² = 0%

Test for overall effect: Z = 1.02 (P = 0.31)

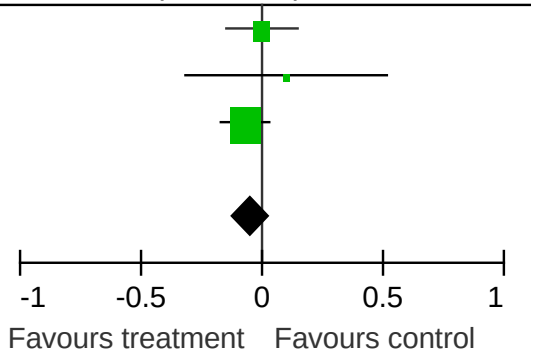


FIGURE 22: FOREST PLOT OF COMPARISON: BMI IMPROVEMENT.

Study or Subgroup	Treatment Mean	Treatment SD	Treatment Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Duman 2007	24.8	3.2	20	25.5	3.8	19	0.8%	-0.70 [-2.91, 1.51]
Iqbal 2006	28.4	5.8	32	27	4.1	32	0.6%	1.40 [-1.06, 3.86]
Kong 2002	25.4	4.1	16	27.4	5.7	11	0.2%	-2.00 [-5.92, 1.92]
Monzani 2001	23.1	4.7	10	23.1	2.2	10	0.4%	0.00 [-3.22, 3.22]
Nagasaki 2009	21.8	0.48	48	22.1	0.5	47	98.0%	-0.30 [-0.50, -0.10]
Total (95% CI)			**126**			**119**	**100.0%**	**-0.30 [-0.49, -0.10]**

Heterogeneity: Tau² = 0.00; Chi² = 2.71, df = 4 (P = 0.61); I² = 0%

Test for overall effect: Z = 2.97 (P = 0.003)

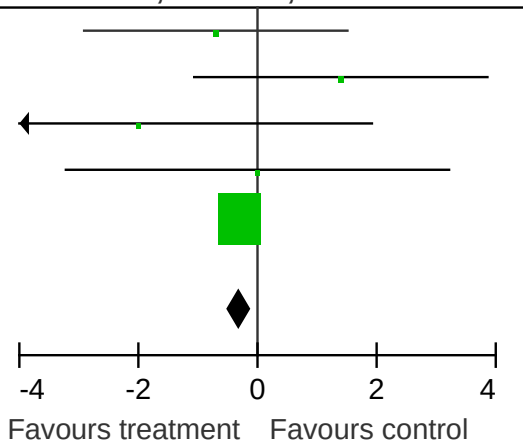


FIGURE 23: FOREST PLOT OF COMPARISON: DIASTOLIC BLOOD PRESSURE IMPROVEMENT (MM HG)

Study or Subgroup	Treatment Mean [mm Hg]	Treatment SD [mm Hg]	Treatment Total	Control Mean [mm Hg]	Control SD [mm Hg]	Control Total	Weight	Mean Difference IV, Random, 95% CI [mm Hg]
Mainenti 2009	88.6	7.5	12	83.2	6.4	11	10.7%	5.40 [-0.28, 11.08]
Monzani 2001	74.8	7.2	10	71	7	10	9.2%	3.80 [-2.42, 10.02]
Nagasaki 2009	72.7	2.2	48	72.8	2	47	51.9%	-0.10 [-0.95, 0.75]
Razvi 2007	78.8	10.3	100	79.9	9.6	100	28.2%	-1.10 [-3.86, 1.66]
Total (95% CI)			**170**			**168**	**100.0%**	**0.57 [-1.50, 2.63]**

Heterogeneity: Tau² = 1.95; Chi² = 5.56, df = 3 (P = 0.13); I² = 46%

Test for overall effect: Z = 0.54 (P = 0.59)

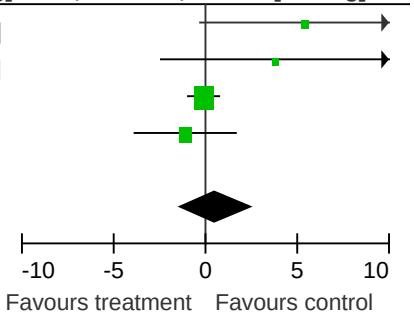


FIGURE 24: FOREST PLOT OF COMPARISON: SYSTOLIC BLOOD PRESSURE [MM HG] IMPROVEMENT.

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [mm Hg]	SD [mm Hg]	Total	Mean [mm Hg]	SD [mm Hg]	Total	Weight	IV, Fixed, 95% CI [mm Hg]	IV, Fixed, 95% CI [mm Hg]
Mainenti 2009	154.6	23.9	12	142.3	18.2	11	0.7%	12.30 [-4.98, 29.58]	
Monzani 2001	117.3	6.8	10	116.8	9.6	10	3.7%	0.50 [-6.79, 7.79]	
Nagasaki 2009	128.8	3.8	48	132.2	3.5	47	90.8%	-3.40 [-4.87, -1.93]	
Razvi 2007	132.8	22.8	100	134.6	22.9	100	4.9%	-1.80 [-8.13, 4.53]	
Total (95% CI)			**170**			**168**	**100.0%**	**-3.08 [-4.47, -1.68]**	

Heterogeneity: Chi² = 4.31, df = 3 (P = 0.23); I² = 30%

Test for overall effect: Z = 4.31 (P < 0.0001)

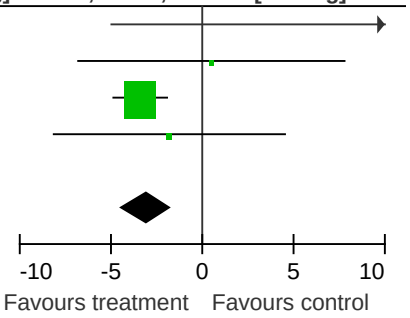


FIGURE 25: FOREST PLOT OF COMPARISON: BRACHIAL ARTERY DIAMETER [MM] IMPROVEMENT.

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [mm]	SD [mm]	Total	Mean [mm]	SD [mm]	Total	Weight	IV, Random, 95% CI [mm]	IV, Random, 95% CI [mm]
Duman 2007	3.46	0.46	20	3.54	0.44	19	25.7%	-0.08 [-0.36, 0.20]	
Razvi 2007	3.4	0.6	100	3.5	0.6	100	74.3%	-0.10 [-0.27, 0.07]	
Total (95% CI)			**120**			**119**	**100.0%**	**-0.09 [-0.24, 0.05]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%

Test for overall effect: Z = 1.30 (P = 0.19)

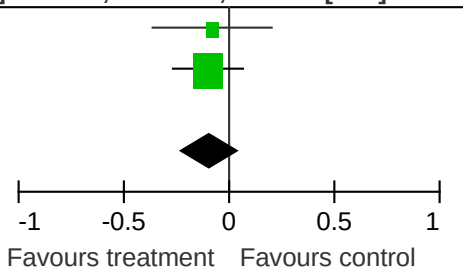


FIGURE 26; FOREST PLOT OF COMPARISON: BRACHIAL ARTERY FLOW IMPROVEMENT [ML/MIN].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [ml/min]	SD [ml/min]	Total	Mean [ml/min]	SD [ml/min]	Total	Weight	IV, Random, 95% CI [ml/min]	IV, Random, 95% CI [ml/min]
Duman 2007	68.6	33.6	20	69.2	24	19	30.0%	-0.60 [-18.86, 17.66]	
Razvi 2007	58.5	43.8	100	55.1	42.4	100	70.0%	3.40 [-8.55, 15.35]	
Total (95% CI)			**120**			**119**	**100.0%**	**2.20 [-7.80, 12.20]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%

Test for overall effect: Z = 0.43 (P = 0.67)

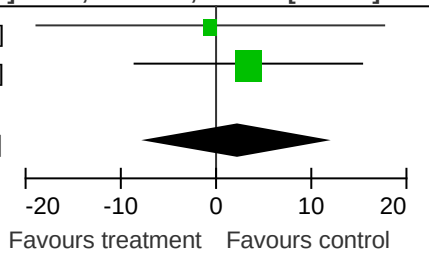


FIGURE 27: FOREST PLOT OF COMPARISON: SYSTOLIC FUNCTION: FRACTIONAL SHORTENING [%].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total	Weight	IV, Random, 95% CI [%]	IV, Random, 95% CI [%]
Biondi 1999	39	7	10	36	4.5	26	34.5%	3.00 [-1.67, 7.67]	
Monzani 2001	41	4.2	10	39	3.5	10	65.5%	2.00 [-1.39, 5.39]	
Total (95% CI)			**20**			**36**	**100.0%**	**2.34 [-0.40, 5.09]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%

Test for overall effect: Z = 1.68 (P = 0.09)

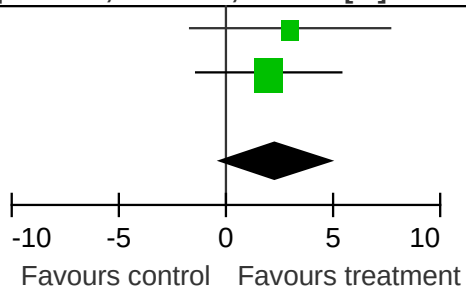


FIGURE 28: FOREST PLOT OF COMPARISON: SYSTOLIC FUNCTION: SYSTEMIC VASCULAR REISTANCE [DYNE/SEC.CM-5].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [dyn/s.cm-5]	SD [dyn/s.cm-5]	Total	Mean [dyn/s.cm-5]	SD [dyn/s.cm-5]	Total	Weight	IV, Fixed, 95% CI [dyn/s.cm-5]	IV, Fixed, 95% CI [dyn/s.cm-5]
Biondi 1999	1,361	383	10	1,470	372	26	45.8%	-109.00 [-386.12, 168.12]	
Monzani 2001	1,366	337	10	1,406	235	10	54.2%	-40.00 [-294.64, 214.64]	
Total (95% CI)			**20**			**36**	**100.0%**	**-71.59 [-259.09, 115.91]**	

Heterogeneity: Chi² = 0.13, df = 1 (P = 0.72); I² = 0%

Test for overall effect: Z = 0.75 (P = 0.45)

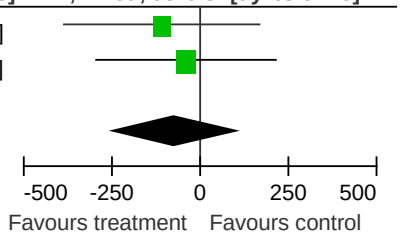
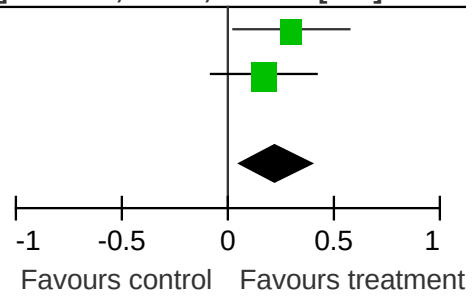


FIGURE 29: FOREST PLOT OF COMPARISON: DIASTOLIC FUNCTION: TRANSMITRAL FLOW VELOCITY RATIO [E/A].

	Treatment			Control				Mean Difference	Mean Difference
Study or Subgroup	Mean [E/A]	SD [E/A]	Total	Mean [E/A]	SD [E/A]	Total	Weight	IV, Fixed, 95% CI [E/A]	IV, Fixed, 95% CI [E/A]
Biondi 1999	1.7	0.4	10	1.4	0.3	26	45.4%	0.30 [0.03, 0.57]	
Monzani 2001	1.5	0.4	10	1.33	0.04	10	54.6%	0.17 [-0.08, 0.42]	
Total (95% CI)			**20**			**36**	**100.0%**	**0.23 [0.04, 0.41]**	

Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%

Test for overall effect: Z = 2.44 (P = 0.01)



SECONDARY OUTCOMES

All-cause mortality was not investigated in any of the studies.

Adverse effects were studied in one study using an anxiety score, a depression score and a general health questionnaire [485], and in another study using a thyroid specific quality of life measure [279].

ADVERSE EFFECTS

Separate anxiety, depression and general health questionnaires were administered to 34 participants in one study – 20 treated with LT_4 and 14 on placebo (12 on placebo for general health questionnaire). Anxiety scores improved in 50% of patients in both the intervention and placebo groups; however, anxiety scores worsened in a greater number of patients receiving the intervention (40% vs. 7%) [485]. Depression scores improved in around 65% in both groups and worsened less in the intervention group (10% vs. 29%). Scores in the General Health Questionnaire improved in 60% of the treated group compared with 92% in the placebo group, with 30% in the treated group having worse scores after 6 months compared with 8% in the placebo group. Overall, none of these differences were statistically significant.

Participants were blinded to which treatment they were on; there is evidence that 80% of the 20 participants on LT_4 answering questionnaires thought they were on placebo and 47% on placebo thought they were on LT_4 [485].

Thyroid specific patient-reported outcomes showed improvements in tiredness and in sex life after thyroxine therapy although after statistical analysis using Bonferroni correction these no longer remained significant [279]. Other domains of the quality of life measure showed improvements in hypothyroid symptoms; however, none reached statistical significance.

DISCUSSION

Many interventional studies have examined the role of thyroxine in patients with SCH: as far as we are aware this is the first systematic review and meta-analysis to scrutinize RCTs on the effects of LT_4 on mild SCH (TSH 5-10 mIU/L). The particular focus of this review is to provide evidence for primary care physicians with regard to the effect of LT_4 on

cardiovascular morbidity when faced with the decision to provide treatment. The findings of this study support the role of LT_4 in the management of patient with SCH in the community.

A total of 10 RCTs were identified with 669 participants randomised into intervention and placebo groups [19, 94, 99, 279, 445, 485-489]. The number of participants is larger than in any previous reviews around this topic [24, 146, 490]. The studies in this review concentrated on the lipid profile, vascular changes and cardiac function. These findings have been investigated in large population studies with mixed results [39, 79, 98, 279, 327, 485]. These prior studies have differences in the aetiology of SCH, sex, age of patients and TSH level. In addition, the previous reviews of LT_4 on SCH did not stratify for the effects on patients with subclinical SCH [24, 146, 490].

Associations between lipids and cardiovascular diseases are well established. Prospective studies have identified a linear relationship between cardiovascular risk and total cholesterol [20]; nevertheless, the effect of SCH on lipids remains unresolved [94, 95, 124, 127, 436, 450, 465, 491]. The seminal Whickham study, a population-based study, found SCH was not related to hyperlipidaemia [40]. This is in contradiction to the Colorado study, another large population-based thyroid study, which found that there was an inverse relationship between thyroid function and lipids; as thyroid function declined, lipid levels increased [43].

Our studies showed that intervention with LT_4 had a statistically significant effect on TC, LDL, BMI, systolic blood pressure and early-to-late transmitral flow velocity ratio (E/A). All findings were stratified further by subgroup and sensitivity analysis to confirm the results. In addition, adverse effects of LT_4 were not statistically different between intervention and placebo groups.

Six studies were able to be utilised to assess serum lipids with 545 participants. Our finding of a reduction in TC of 0.13 mmol/L is less than the mean taken from a previous review, however that review found the magnitude of reduction to be greater in patients on treatment for overt hypothyroidism who were undertreated [146]. Our review endeavoured to exclude studies where participants had prior thyroid dysfunction. A reduction in TC of 10% may reduce cardiovascular mortality by 20% [492].

The lowering of LDL as a result of LT4 treatment is an important finding. While modest, the reduction is significant in terms of a reduction in incidence of coronary artery disease [486]. A reduction of 1.0 mmol/L equates to a 30-35% reduction in coronary heart disease [20]. Our

finding of 0.29 mmol/L when utilising studies of high quality (Jadad 4-5) equates to a 10-12% reduction in coronary heart disease.

The risk of cardiovascular morbidity and mortality is increased in individuals with a BMI >25 [493]. Our study found a small but significant reduction in BMI of 0.3 from 245 participants in 5 studies. It has been suggested that people with a history of weight gain are more likely to have their thyroid function tests measured resulting in a bias association with SCH and weight gain [485].

Systolic blood pressure was reduced by >3mm Hg from four studies with 348 participants. These effects increased when studies of lower quality were removed. A 5% reduction in cardiovascular death over 10 years would result from a 3 mmHg reduction [15].

Studies have shown impairment in both left ventricular diastolic and systolic function which are reversible with LT_4 [485], however, our study did not show statistically significant changes as a result of treatment. The short time periods of the studies may contribute to the lack of reversibility in left ventricular diastolic function although this is reported to be the most consistent finding of SCH [64]. We were able to show that the early-to-late transmitral flow velocity ratio (E/A) was altered following LT_4 treatment. Impaired diastolic dysfunction may suggest that SCH is a condition of minimal tissue hypothyroidism rather than a compensated state [19].

Studies reporting adverse effects of LT_4 were lacking. The two studies differed in their use of scales, one using generalised measurement scales [485], while the other using a thyroid-specific quality of life scale [279]. Quality of life does not always equate to assessing the side effects of drugs. Withdrawals were not mentioned in many studies. Of those that were noted the majority were due to a lack of compliance. This is likely to bias results if an intention to treat analysis is not performed. One study identified an intention to treat analysis but this was not done [485]. Adverse effects such as worsening angina, new-onset atrial fibrillation and palpitations, which have been described in other studies [326, 494, 495] are likely to be related to the age of participants. All the studies in this review had a mean age of <65 years of age which may limit the reporting of adverse events.

Using a random effects model allowed changes to vary within and between different studies and this was reflected in weighting of the standard errors. We were able to stratify our results according to pre-defined subgroups of mean age, gender, antibody status and mean TSH. We

also graded studies using the Jadad scale [423] to evaluate the quality which was used for sensitivity analysis.

We endeavoured to use studies with individuals without prior thyroid disease. In some studies, having prior thyroid disease was explicitly excluded, while in others information regarding prior disease was unclear. We used GATE and RAMMbo methods [418] to further appraise the quality of studies. This review was strengthened by the use of individuals with stable SCH, i.e. either two tests taken within 4 weeks and 6 months. All studies reported that participants had no prior disease or that they were stable with SCH.

This review adds to the evidence around the use of LT_4 in patients with SCH. The findings are likely to reduce uncertainty around prescribing in general practice particularly for younger patients. Cardiovascular risk factors can be treated in several ways, including weight loss, reduction in smoking, exercise and healthy eating. There is a valid argument in treating the cause rather than the symptoms.

Our findings are generalisable to the <65 year population but due to the lack of studies in the 65+ age group are not able to be extrapolated further. The finding of SCH in young adults should instigate proactive treatment with thyroid replacement therapy to addresses the underlying issue of hypothyroidism rather than a wait and see approach currently favoured.

CHAPTER 6 - CONCLUSION

KEY FINDINGS FROM THE RESEARCH

Hypothyroidism is a common disease in general practice. It is the clinical manifestation of a biochemical disease in which the number of symptoms increases as TSH levels increase and thyroid hormone levels decrease. Subclinical hypothyroidism is less obvious, as symptoms by the very nature of the nomenclature are not always present – the slow progression of disease enables the person to adapt. The lack of symptoms may underestimate the long-term impact of subclinical hypothyroidism on morbidity and mortality. On the contrary, symptoms may be vague and non-specific alerting the general practitioner to initiate testing.

Advances in TSH assays have led to recommendations for first-line TSH testing when investigating thyroid function. This has caused concern amongst general practitioners who rely on biochemical results to aid diagnosis. In addition, there is disquiet amongst biochemical pathologists and endocrinologists who consider central hypothyroidism will be missed. This thesis has explored several of these components and suggests the need for further research. Data were gathered on current guidelines, current practice and current evidence to inform debate. This new knowledge will provide general practitioners with evidence to enhance clinical practice.

Table 31 (over the page) summarises the key findings from each chapter.

TABLE 31: SUMMARY OF KEY FINDINGS

1 - The epidemiology and management of hypothyroidism in general practice
• Hypothyroidism is common in general practice • Thyroid function tests can provide essential information to aid clinicians in their management of hypothyroidism • The epidemiology of hypothyroidism in New Zealand is unknown • Thyroid physiology is complex and requires the health professional to understand the feedback loops to interpret thyroid function tests • There is insufficient highly graded evidence to inform GPs on the management of subclinical hypothyroidism • Arguments for lowering the upper reference range of TSH are premature when the management of patients with TSH between 5-10 mIU/L continues to be debated
2 – The epidemiology and management of thyroid disease in Hamilton, New Zealand general practice
• The prevalence of hypothyroidism in Hamilton general practice is 2.5% based on note review of case found by disease coding, prescriptions for thyroid-specific pharmaceuticals and laboratory data • Prevalence of subclinical hypothyroidism is 6.8% based on laboratory results • The cost-effectiveness of screening improves with age and is favourable in women • One in six adult patients will have a TSH test in a 12-month period • General practitioners are not necessarily looking for disease when requesting a TSH test. They use thyroid function tests opportunistically as part of a general health check • At one end of the scale, general practitioners believe subclinical hypothyroidism is a biochemical disease. At the other it is a disorder with justification for treatment and monitoring • Decision-making within general practice is performed in negotiation with patient preferences • Three reasons for ordering thyroid function tests include: searching for a disease, a desire to meet the expectations of the patient and to secure against a breakdown in the general practitioner/patient relationship • There is a lack of consistency with New Zealand recommendations following a raised

TSH result • 94% of patients with a raised TSH had no antibody testing despite recommendations to do so. General practitioners may not find thyroid antibody testing worthwhile. • Variations in the management of subclinical hypothyroidism are unrelated to age, gender or ethnicity • Two percent of patients with a raised thyroid function test result were managed according to BPACnz guidelines.
3 – Investigating the pathways in primary practice leading to the diagnosis of central hypothyroidism
• The majority of participants lived with symptoms for over 12 months prior to diagnosis • Lethargy was the most common symptom in 94% of participants, followed by changes in skin texture and body hair distribution • The delay in diagnosis of central hypothyroidism is due to the lack of recognition by the general practitioners • Improving diagnosis involves better awareness of the signs and symptoms of central hypothyroidism • Greater input from endocrinologists and from chemical pathologists when a person has abnormal TFTs would improve diagnosis and management
4 – Long-term outcomes of patients with hypothyroidism: an analysis of cardiovascular morbidity and mortality over a decade (1997-2006)
• This is a large study investigating the outcomes of hypothyroidism - using a data set with 1.3 million entries over 14 years • Individuals with hypothyroidism were identified to examine whether there is an association between thyroid status and cardiovascular events and all-cause mortality • Data were linked to a second test to increase the finding of individuals with stable thyroid status • When adjusted for age, gender, ethnicity and social deprivation index, there remained an increased rate of cardiovascular events (failure) in patients with subclinical and overt hypothyroidism • Age is a strong confounder. When examined by age (<65 years and 65+ years), the

cardiovascular event rate for individuals categorised with SCH who were <65 years increased at a rate similar to OH, while individuals with SCH in the 65+ age group had a cardiovascular event rate similar to those in the normal group • The findings for all-cause mortality were similar to cardiovascular event rates
5 – Systematic review: What is the effectiveness of thyroxine in reducing cardiovascular risk factors in patients with subclinical hypothyroidism (SCH)?
• This review defined SCH as being between 5-10 mIU/L and excluded patients with a past history of thyroid dysfunction • All studies included were randomised controlled trials • Our studies showed that intervention with LT4 had a statistically significant effect on TC, LDL, BMI, systolic blood pressure and early-to-late transmitral flow velocity ratio (E/A) • We found a reduction in TC of 0.13 mmol/L. A reduction in TC of 10% may reduce cardiovascular mortality by 20% [492] • We demonstrated a reduction in LDL of 0.29 mmol/L. A 1.0 mmol/L equates to a 30-35% reduction in coronary heart disease [20]. Our finding of 0.29 mmol/L when utilising studies of high quality (Jadad 4-5) equates to a 10-12% reduction in coronary heart disease • Systolic blood pressure was reduced by >3mm Hg from four studies with 348 participants. A 5% reduction in cardiovascular death over 10 years would result from a 3 mmHg reduction • The study was generalisable to adults <65 years of age but could not be extrapolated to 65+ age groups

We conducted several studies to establish the epidemiology and management of hypothyroidism in general practice. Each study follows a sequence of events similar to snowballing techniques used in social science and led to hypothesis generating. The epidemiology of thyroid dysfunction in Hamilton, New Zealand, was established using patient data from two large general practices with a population representing a quarter of the Hamilton City adult population. Our study indicates a prevalence of hypothyroidism of 2.5% in adults. The prevalence and incidence findings of the Whickham studies in the United Kingdom [40] [79] have been corroborated by smaller studies from Europe and Australia [45, 143]. This suggests our findings are similar to the Whickham study which is generalisable to countries where there are no obvious environmental influences that may cause thyroid disease [203]. The rate of hypothyroidism found in our study population corresponds with the prevalence from abroad in iodine-sufficient areas. The burden of hypothyroidism is greater in women and in the ageing population.

We then investigated how thyroid function tests were being utilised. Using a general practice population without known thyroid dysfunction, we linked laboratory and patient data through the use of the unique NHI number. We were able to focus on patients without previous evidence of thyroid dysfunction and examine the use of thyroid function tests and subsequent results. We identified that in the two Hamilton City general practices, 1 in 6 adult patients without known thyroid disease who visit their general practitioner in a 12-month period will have a TSH test. It is likely that this testing profile would be common amongst the wider general practice community. This level of testing is akin to an opportunistic screening programme rather than targeted use of a test in a specific group of patients with signs and symptoms of disease. The results confirm that thyroid function testing is used often in primary care. In the study group, 8.0% (277/3459) of the population without identified thyroid disease had abnormal thyroid function results, with the 6.8% of the population having subclinical hypothyroidism.

Following on from this, we sought to explore the views of general practitioners. Focus groups were conducted in the Waikato region to gain more in-depth knowledge of the use of thyroid function tests by general practitioners and to explore their rationale for testing. We found that, for general practitioners, subclinical hypothyroidism represents a poorly defined condition that exists in a wide variety of contextual circumstances and where the value of

intervention is questionable. General practitioners define subclinical hypothyroidism along a spectrum ranging from: a) abnormal laboratory results with no relationship to symptoms or prognosis, to: b) a disorder with justification for treatment or monitoring. It is clear that general practitioners experience uncertainty both in interpreting tests suggestive of subclinical hypothyroidism, and in the management of subclinical hypothyroidism. This uncertainty amongst general practitioners reflects the conflicting literature regarding the diagnosis, prognosis and treatment of this condition [64].

A characteristic of the work of general practitioners is the patient-centred way in which they work. Different general practitioners described TSH levels of 6, 7 or 8 mIU/ml as their threshold for treatment which shows that arbitrary cut-offs are used in providing patient-centred care. Other general practitioners firmly believed that the lack of proof of adverse outcomes of subclinical hypothyroidism meant that giving thyroxine treatment may be of more harm than benefit. Until further evidence was established there was no reason to change current prescribing behaviour.

General practitioners are aware of the tensions between the imperatives of population-based principles and the needs of individual patients. A diagnosis of a subclinical hypothyroidism may be a relief to some patients and a challenge to others even if the symptoms and tests are identical. Three quite different yet complementary reasons for ordering thyroid function tests in general practice have been identified: the search for disease; the desire to meet patient expectations; and, the needs of the general practitioner to secure against breakdown in the doctor/patient relationship. Ill-defined symptoms are common in general practice. General practitioners may not be investigating failing thyroid function when requesting a TSH test. On the contrary, many general practitioners in our study use TSH as part of a ‘wellness check’. They are implying to the patient that ‘it may be something’, ‘it may be nothing’ and that ‘I am listening’. In doing so, general practitioners are partly relying on biochemical results to guard against their future.

To clarify the focus group discussions around the management of subclinical hypothyroidism, we followed a retrospective cohort of patients with no prior thyroid dysfunction and with laboratory results suggestive of subclinical hypothyroidism. We found was a lack of consistency with the BPACnz guidelines, in line with the views expressed by the general practitioners in the focus groups. Of the 265 individuals with results indicating subclinical hypothyroidism, 51% had no follow-up TSH investigations. Of those with further tests nearly

45% of patients had no FT_4 test within the 12 month period. However, the number of follow-up TSH tests returning to within the reference interval (40.8%) was similar to international literature which was 37.5% in the first 12 months [109, 110].

The use of symptoms in the clinical picture is less clear in the literature. BPACnz guidelines advise that the decision to initiate treatment should be based on evidence of symptoms. Symptoms were recorded in 29% of patients; however, this does not necessarily indicate that those without recorded symptoms had no symptoms. Data from practice management systems were consistent with findings from recent focus groups [309]. Symptoms identified in focus groups such as tiredness/lethargy and weight gain were the most prominent symptoms of any that were recorded [309]. In addition, as with focus group findings, five percent of patients, none of whom had a thyroid stimulating hormone result greater than 10 mIU/L, were placed on thyroxine replacement medication in the 12 months following their raised TSH result.

Autoimmune thyroid disease is the most common cause of primary hypothyroidism in the western world and has been associated with an increased likelihood of progression from SCH to overt hypothyroidism [66]. Ninety-four percent of patients had no thyroid antibody tests despite guidelines to do so where FT_4 remains within the reference interval. Guidelines are not always accepted by or acceptable to general practitioners [301, 370].General practitioners who use thyroid antibody assays to guide decision-making are found to be more likely to adhere to guidelines for managing thyroid dysfunction [305]. In our study investigating the management of patients with a raised TSH, less than two percent of patients appeared to be managed according to BPACnz guidelines.

Currently available evidence, both in New Zealand and internationally, lack detailed evidence and are based on expert opinion [31]. A recent Cochrane Review regarding the use of thyroxine for subclinical hypothyroidism lacks decisive answers for general practitioners, concluding the need for practitioners to use clinical judgement and patient preference [24]. This is criticised for including patients with overt hypothyroidism, defined as a TSH result over 10 mIU/L, and including patients with prior thyroid disease. We concur with these findings from our focus group interviews that general practitioners do use clinical judgement and concordance in managing patients who present with inadvertently raised TSH.

THE JOURNEY OF PATIENTS WITH CENTRAL HYPOTHYROIDISM WAS NOT HAMPERED BY A FIRST-LINE TSH STRATEGY FOR INVESTIGATING THYROID FUNCTION

In focus groups, general practitioners expressed consternation in being limited by BPACnz recommendations to a first-line TSH strategy. General practitioners felt this would hamper their ability to diagnose pituitary and hypothalamic causes of raised thyroid function. Central hypothyroidism is rare with a theoretical possibility of a general practitioner diagnosing one patient in a twenty year period in New Zealand. Central hypothyroidism is associated with a varied and prolonged course prior to diagnosis which can make the diagnosis difficult for general practitioners. In order to improve timely diagnosis and thus decrease morbidity from a treatable disease, this study aimed to investigate the diagnostic journey of patients with central hypothyroidism in the Waikato region. In addition, we wished to investigate whether the recommendations for a first-line TSH strategy would limit general practitioners in diagnosing central hypothyroidism.

Three methods of information gathering were used to ensure accuracy of information; using each source to confirm or correct another. It was also necessary to garner a full picture of the process for each patient. We sought one-to-one interviews with patients in order to gain insight into their quality of life prior to diagnosis.

The majority of participants in our study who had thyroid function tests with results suggestive of pituitary or hypothalamic involvement, lived with symptoms for over 12 months prior to diagnosis. Nine participants had been diagnosed upon acute admission to Waikato Hospital with symptoms severe enough to cause in-patient admission. The lengthy diagnostic process is likely due to a lack of recognition and a low clinical suspicion when faced with abnormal thyroid function test results [9, 333, 350].

Lethargy was the most common symptom reported in 94% of participants. Participants described experiencing “extreme lethargy”: the inability to get out of the bath; go to work; get out of bed for an entire weekend; statements that quantified the seriousness of this disease when left untreated. Other common symptoms were changes in skin texture and body hair distribution and texture in 75% of participants and headaches in 63% of participants. The repetition of statements regarding the impact on family life and the degree of frustration that was felt showed that central hypothyroidism had a consistent impact not only on an individual’s physical health but also on their mental health.

The majority of participants in this study were diagnosed prior to October 2005 when current BPACnz guidelines for investigating thyroid function were released. The utility of TSH, FT_4 and FT_3 by general practitioners were not limited at this time. Contrary to what is currently implied in the literature, that a first-line TSH policy will delay diagnosis [9, 10], even with the full range of thyroid function tests, general practitioners were failing to investigate abnormal results. This situation may be more evident in future with current recommendations for investigating thyroid function.

Central hypothyroidism is rare, but if general practitioners suspect abnormalities in thyroid function, it is essential that they accurately interpret thyroid function tests, seek advice from endocrinologists and biochemical pathologists, recognise that TSH may be unreliable, and thoroughly pursue relevant symptoms.

INDIVIDUALS WHO HAVE A RAISED TSH RESULT HAVE AN INCREASED RATE OF CARDIOVASCULAR EVENTS AND ALL-CAUSE MORTALITY COMPARED WITH INDIVIDUALS WITH NORMAL THYROID FUNCTION

Cardiovascular disease remains a leading cause of morbidity and mortality in New Zealand [382]. The effects of thyroid hormones on the cardiovascular system are well documented [14, 122]. The pathophysiological effects of thyroid function on the cardiovascular system are directly related to the consequences of thyroid hormone on the heart and vascular system [122, 123].

Changes in cardiovascular function in patients with hypothyroidism include: an increased systemic vascular resistance; decreased heart rate; slight reduction in cardiac output; an increase in isovolumic relaxation time; and, decreased percentage of blood volume [122]. Due to internal compensatory mechanisms these cardiovascular manifestations may not produce overt clinical symptoms in patients with raised TSH. Treatment with thyroxine replacement therapy is standard for overt hypothyroidism where TSH is over 10 mIU/L. However, for patients with results between 5-10 mIU/L, general practitioners have unanswered concerns regarding the treatment of subclinical hypothyroidism [309]. Large randomised controlled trials investigating the benefits of treatment in patients with subclinical hypothyroidism have not as yet been conducted [24]. Further evidence is required regarding the management of subclinical hypothyroidism, in particular, the potential benefits and harms for instigating treatment, where the outcomes are presently uncertain.

This study aimed to examine survival in individuals ≥ 20 years of age with varying degrees of hypothyroidism, namely subclinical and overt hypothyroidism, in relation to cardiovascular morbidity and mortality over a decade (1997-2006) by age, gender, ethnicity and deprivation score and comparing them with euthyroid individuals (with normal thyroid function). As far as we are aware, this is the largest study to investigate the association between thyroid function and cardiovascular morbidity using laboratory data. Despite different methodologies, the next largest study included 3,233 individuals, of which 496 had subclinical hypothyroidism [496].

Laboratory data were analysed and individuals were categorised by thyroid function based on results from TSH and FT_4 tests. Key findings are that subclinical hypothyroidism in patients under 65 years of age is a marker for worse outcomes with double the mortality and a 26% increased rate of cardiovascular events compared with euthyroid individuals.

In the 65 year plus age group, although absolute risk is higher, the excess risk of death is only 1.28 and for cardiovascular events is 1.14. This suggests that the expected benefit of treatment is likely to be greatest in those under 65 years.

THYROXINE IS EFFECTIVE IN REDUCING CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM

Almost all cases of suspected hypothyroidism will present to the general practitioner in the first instance. It remains contentious whether the discovery of a raised TSH level in general practice, with or without symptoms, is significant [66, 67, 86-92]. The aim of the systematic review is to examine the relationship between levo-thyroxine treatment and cardiovascular risk factors in individuals with subclinical hypothyroidism within the TSH range of 5-10 mIU/L. Secondly we assessed this association in relation to gender, age, antibody status (where known), quality of studies and type of study.

Many interventional studies have examined the role of thyroxine in patients with subclinical hypothyroidism. Prospective studies have identified a linear relationship between cardiovascular risk and total cholesterol [20]; nevertheless, the effect of subclinical hypothyroidism on lipids remains unresolved [94, 95, 124, 127, 436, 450, 465, 491]. The studies in this review concentrated on the lipid profile, vascular changes and cardiac function. These findings have been investigated in large population studies with mixed results [39, 79, 98, 279, 327, 485]. These prior studies have differences in the aetiology of subclinical hypothyroidism, sex,

age of patients and TSH level. In addition, the previous reviews of LT_4 on subclinical hypothyroidism did not stratify for the effects on patients with subclinical hypothyroidism [24, 146, 490].

As far as we are aware this is the first systematic review and meta-analysis to scrutinize RCTs on the effects of levo-thyroxine treatment on mild subclinical hypothyroidism (TSH 5-10 mIU/L). Patients with a known history of thyroid dysfunction were excluded. The particular focus of this review is to provide evidence for primary care physicians with regard to the effect of levo-thyroxine treatment on cardiovascular morbidity when faced with the decision to provide treatment.

A total of 10 RCTs were identified with 669 participants randomised into intervention and placebo groups [19, 94, 99, 279, 445, 485-489]. Our studies showed that intervention with levo-thyroxine had a statistically significant effect on total cholesterol, low-density lipoprotein cholesterol, Body Mass Index, systolic blood pressure and early-to-late transmitral flow velocity ratio. All findings were stratified further by subgroup and sensitivity analysis to confirm the results. In addition, adverse effects of LT_4 were not statistically different between intervention and placebo groups.

We found a reduction in total cholesterol of 0.13 mmol/L. A reduction in total cholesterol of 10% may reduce cardiovascular mortality by 20% [492]. There was a modest reduction in low-density lipoprotein of 0.29 mmol/L when utilising studies of high quality (Jadad 4-5), which equates to a 10-12% reduction in coronary heart disease [20]. Systolic blood pressure was reduced by >3mm Hg. A 5% reduction in cardiovascular death over 10 years would result from a 3 mmHg reduction [15].We were able to show that the early-to-late transmitral flow velocity ratio (E/A) was altered following levo-thyroxine treatment. Impaired diastolic dysfunction may suggest that subclinical hypothyroidism is a condition of minimal tissue hypothyroidism rather than a compensated state [19].

Studies reporting adverse effects of levo-thyroxine were lacking. Adverse effects such as worsening angina, new-onset atrial fibrillation and palpitations, which have been described in other studies [326, 494, 495] are likely to be related to the age of participants. All the studies in this review had a mean age of less than 65 years of age which may contribute to lack of adverse events reported. In line with the previous study, it would be hard to show benefit in the 65 year plus age group when excess risk is small, therefore, the likelihood of benefit from treatment in the under 65 year group is more clear.

This review adds to the evidence around the use of levo-thyroxine treatment in patients with subclinical hypothyroidism. The findings are likely to reduce uncertainty around prescribing in general practice particularly for younger patients. Cardiovascular risk factors can be treated in several ways, including weight loss, reduction in smoking, exercise and healthy eating; however, there is a valid argument in treating the cause rather than the symptoms.

RECOMMENDATIONS FOR GENERAL PRACTICE

This research adds clinical evidence to demonstrate that a raised TSH has adverse outcomes on cardiovascular event rates and all-cause mortality. To prevent this, evidence is presented that supports the prescribing of levo-thyroxine treatment to individuals less than 65 years of age who have a diagnosis of subclinical hypothyroidism.

There are other alternatives to reducing cardiovascular risk such as stopping smoking, reducing Body Mass Index to between 20-25, making healthy eating choices and increasing physical activity. These contribute to improving lipids, blood pressure, Body Mass Index and echocardiography changes. However, treating patients with subclinical hypothyroidism addresses one of the causes of abnormality and is likely to benefit cardiovascular risk.

Ensuring patients are managed well in terms of follow-up will reduce adverse affects associated with treatment. Levo-thyroxine has a half-life of seven days allowing greater options in terms of titration to optimal levels. There are cautions for treating older patients with levo-thyroxine where existing coronary artery disease may be exacerbated. In patients less than 65 years of age, the risks as a result of treatment reduces, however, contraindications remain valid.

STRENGTHS AND WEAKNESSES

Strengths

Our initial studies in general practice were based on two practices which have a good-sized population base representing 25% of the Hamilton City adult population. In addition, Primary Health Organisation enrolment within Waikato District Health Board is reported at 94% overall [338]. Owing to high enrolment numbers, using general practice registration is considered adequate to examine prevalence in a population. Our data were further validated against national and international data. This thesis was focussed on building evidence for general practice.

We benefited from the use of fourteen years of laboratory data. We had a large cohort of 1.3 million tests available from one community laboratory that held contracts with primary care in the Waikato District Health Board region. Data with a valid NHI number were able to link two tests to reduce the number of transient raised thyroid stimulating hormone results. We were also able to link NHI numbers with National Minimum Data Set and Mortality Data available from the New Zealand Health Information Service. The linking of data via NHI enabled analysis by ethnicity, which is not collected through laboratories.

Weaknesses

Many of the studies were undertaken in the Waikato District Health Board area. Again, this may not be valid in other areas within New Zealand; however, we were able to validate our data with national and international data and found our results to be similar. We believe these results are generalisable for New Zealand.

Our focus group interviews were small but were able to provide rich data. This may not be representative of all general practices. We validated our findings by investigating the management patterns in patients with subclinical hypothyroidism. These data may very well be typical of general practice in New Zealand and elsewhere.

Laboratory data were not able to be scrutinised according to reason for why the test was initiated which may have been as a result of symptoms, as part of a wellness check or coincidental findings related to a non-thyroidal illness. In addition, data were not adjusted for body mass index, smoking, lipids, or medication.

FUTURE DIRECTIONS

The role of general practitioners in the management of hypothyroidism is important. Thyroid stimulating hormone tests are critical in the initial investigation thyroid function. Clear guidelines are required to address raised thyroid stimulating hormone results. When thyroid stimulating hormone assays are used to investigate hypothyroidism, lines of questioning will need to be established to critically examine the symptomatology related to hypothyroidism. In particular, this would help distinguish between primary and central hypothyroidism.

A raised thyroid stimulating hormone must be repeated to confirm a diagnosis. BPACnz guidelines state that these tests should not be taken when there is concurrent illness. This is more likely in older patients and in patients where medication is likely to affect thyroid function, for example, lithium and amiodarone. A confirmed diagnosis of subclinical hypothyroidism must be established prior to consideration of levo-thyroxine treatment. The development of guidelines for subclinical hypothyroidism would require grades of evidence. This allows general practitioners to assess where the basis for recommendations have been made.

There is a role for biochemical pathologists in the management of abnormal assays. Reflex testing as suggested in BPACnz guidelines should be automatic, for instance, where a second raised thyroid stimulating assay results within a certain timeframe, for example, 6-12 months later, is automatically re-tested to establish the free thyroxine index.

At present, thyroid autoantibodies are not often tested in general practice. General practitioners may not feel antibody testing is worthwhile. This may relate to the natural history of subclinical hypothyroidism, which is reported to be a slow progression to hypothyroidism [79]. Thyroid autoantibodies are a marker for disease and knowing an individual's antibody status, given that 18% of the euthyroid population have positive thyroid autoantibodies, are unlikely to have much effect on the management of hypothyroidism if the aim is to reduce the cardiovascular risk.

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APPENDIX 1 – 4: ICD 9 & 10 CODING FOR SURVIVAL ANALYSIS.

APPENDIX 1: PRIORITISATION FOR LEVEL 2 (L2) ETHNICITY CODING

Priority order	Ethnic group code (L2)	Ethnic group code description
1	21	Maori
2	35	Tokelauan
3	36	Fijian
4	34	Niuean
5	33	Tongan
6	32	Cook Island Maori
7	31	Samoan
8	37	Other Pacific Island
9	30	Pacific Island Not Further Defined
10	41	South East Asian
11	43	Indian
12	42	Chinese
13	44	Other Asian
14	40	Asian NFD
15	52	Latin American / Hispanic
16	53	African
17	51	Middle Eastern
18	54	Other
19	12	Other European
20	10	European Not Further Defined
21	11	NZ European

From Statistics New Zealand

APPENDIX 2: NEW ZEALAND DEPRIVATION INDEX DISTRIBUTION ACROSS NEW ZEALAND

NZdep06 deciles	Population count	Percent of population
1	415,155	10.3
2	410,361	10.2
3	409,266	10.2
4	401,736	10.0
5	397,242	9.9
6	399,828	9.9
7	397,074	9.9
8	394,425	9.8
9	401,916	10.0
10	396,219	9.8
Unspecified	4,923	0.1
Total	4,028,145	100

From Statistics New Zealand

APPENDIX 3: ICD 9 & 10 CODES OF INTEREST RELATING TO CARDIOVASCULAR DISEASE

Diagnosis Code	Diagnosis Description
ISCHAEMIC CEREBROVASCULAR DISEASE	
430	Htlv-111 causing lymphadenopat
431	Htlv-111 causing disease c.n.s
432	Htlv-111 disorder immune mech
433	Htlv-111 causing oth spec cond
434	Occlusion of cerebral arteries
435	Transient cerebral ischemia
436	Ac/ill-def cerebrovascular dis
437	Oth & ill-def cerebrovascular dis
438	Late effect cerebrovascular dis
G450	Vertebro-basilar artery syndrome
G451	Carotid artery syndrome (hemispheric)
G452	Multiple and bilateral precerebral artery syndromes
G453	Amaurosis fugax
G454	Transient global amnesia
G458	Other transient cerebral ischaemic attacks and related syndromes
G459	Transient cerebral ischaemic attack, unspecified
G460	Middle cerebral artery syndrome (I660+)
G461	Anterior cerebral artery syndrome (I661+)
G462	Posterior cerebral artery syndrome (I662+)
G463	Brain stem stroke syndrome (I60-I67+)
G464	Cerebellar stroke syndrome (I60-I67+)
G465	Pure motor lacunar syndrome (I60-I67+)
G466	Pure sensory lacunar syndrome (I60-I67+)
G467	Other lacunar syndromes (I60-I67+)

G468	Other vascular syndromes of brain in cerebrovascular diseases (I60-I67+)
I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
I601	Subarachnoid haemorrhage from middle cerebral artery
I602	Subarachnoid haemorrhage from anterior communicating artery
I603	Subarachnoid haemorrhage from posterior communicating artery
I604	Subarachnoid haemorrhage from basilar artery
I605	Subarachnoid haemorrhage from vertebral artery
I606	Subarachnoid haemorrhage from other intracranial arteries
I607	Subarachnoid haemorrhage from intracranial artery, unspecified
I608	Other subarachnoid haemorrhage
I609	Subarachnoid haemorrhage, unspecified
I610	Intracerebral haemorrhage in hemisphere, subcortical
I611	Intracerebral haemorrhage in hemisphere, cortical
I612	Intracerebral haemorrhage in hemisphere, unspecified
I613	Intracerebral haemorrhage in brain stem
I614	Intracerebral haemorrhage in cerebellum
I615	Intracerebral haemorrhage, intraventricular
I616	Intracerebral haemorrhage, multiple localised
I618	Other intracerebral haemorrhage
I619	Intracerebral haemorrhage, unspecified
I620	Subdural haemorrhage (acute)(nontraumatic)
I621	Nontraumatic extradural haemorrhage
I629	Intracranial haemorrhage (nontraumatic), unspecified
I630	Cerebral infarction due to thrombosis of precerebral arteries
I631	Cerebral infarction due to embolism of precerebral arteries
I632	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
I633	Cerebral infarction due to thrombosis of cerebral arteries
I634	Cerebral infarction due to embolism of cerebral arteries

I635	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I636	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I638	Other cerebral infarction
I639	Cerebral infarction, unspecified
I64	Stroke, not specified as haemorrhage or infarction
I650	Occlusion and stenosis of vertebral artery
I651	Occlusion and stenosis of basilar artery
I652	Occlusion and stenosis of carotid artery
I653	Occlusion and stenosis of multiple and bilateral precerebral arteries
I658	Occlusion and stenosis of other precerebral artery
I659	Occlusion and stenosis of unspecified precerebral artery
I660	Occlusion and stenosis of middle cerebral artery
I661	Occlusion and stenosis of anterior cerebral artery
I662	Occlusion and stenosis of posterior cerebral artery
I663	Occlusion and stenosis of cerebellar arteries
I664	Occlusion and stenosis of multiple and bilateral cerebral arteries
I668	Occlusion and stenosis of other cerebral artery
I669	Occlusion and stenosis of unspecified cerebral artery
I670	Dissection of cerebral arteries, nonruptured
I671	Cerebral aneurysm, nonruptured
I672	Cerebral atherosclerosis
I673	Progressive vascular leukoencephalopathy
I674	Hypertensive encephalopathy
I675	Moyamoya disease
I676	Nonpyogenic thrombosis of intracranial venous system
I677	Cerebral arteritis, not elsewhere classified
I678	Other specified cerebrovascular diseases
I679	Cerebrovascular disease, unspecified

I680	Cerebral amyloid angiopathy (E85-+)
I681	Cerebral arteritis in infectious and parasitic diseases classified elsewhere
I682	Cerebral arteritis in other diseases classified elsewhere
I688	Other cerebrovascular disorders in diseases classified elsewhere
I690	Sequelae of subarachnoid haemorrhage
I691	Sequelae of intracerebral haemorrhage
I692	Sequelae of other nontraumatic intracranial haemorrhage
I693	Sequelae of cerebral infarction
I694	Sequelae of stroke, not specified as haemorrhage or infarction
I698	Sequelae of other and unspecified cerebrovascular diseases

CIRCULATORY DISEASES

CORONARY HEART DISEASE

4100	Myocardial inf anterolateral wl
4101	Myocardial inf oth anterior wal
4102	Myocardial inf inferolateral wl
4103	Myocardial inf inferopostr wall
4104	Myocardial inf oth inferior wal
4105	Myocardial inf oth lateral wall
4106	True posterior wall infarction
4107	Subendocardial infarction
4108	Myocardial inf other spec sites
4109	Myocardial infarction unsp site
41091	Acute MI initial episode
4110	Postmyocardial infarc synd
4111	Intermediate coronary synd
4129	Old myocardial infarction
4130	Angina decubitus
4131	Prinzmetal angina

4139	Oth & unspec angina pectoris
4140	Coronary atherosclerosis
41401	Coronary atherosclerosis coronary artery
41402	Coronary atherosclerosis autologous vein graft
4141	Aneurysm of heart
41410	Aneurysm of heart/wall
41411	Aneurysm coronary vessels
41419	Aneurysm of heart/other
4148	Oth sp chr ischemic heart dis
4149	Chr ischemic heart dis, unsp
E1053	Type 1 diabetes mellitus with diabetic cardiomyopathy
E1153	Type 2 diabetes mellitus with diabetic cardiomyopathy
E1453	Unspecified diabetes mellitus with diabetic cardiomyopathy
E1059	Type 1 diabetes mellitus with other specified circulatory complication
E1159	Type 2 diabetes mellitus with other specified circulatory complication
E1459	Unspecified diabetes mellitus with other specified circulatory complication
I200	Unstable angina
I201	Angina pectoris with documented spasm
I208	Other forms of angina pectoris
I209	Angina pectoris, unspecified
I210	Acute transmural myocardial infarction of anterior wall
I211	Acute transmural myocardial infarction of inferior wall
I212	Acute transmural myocardial infarction of other sites
I213	Acute transmural myocardial infarction of unspecified site
I214	Acute subendocardial myocardial infarction
I219	Acute myocardial infarction, unspecified
I220	Subsequent myocardial infarction of anterior wall
I221	Subsequent myocardial infarction of inferior wall

I228	Subsequent myocardial infarction of other sites
I229	Subsequent myocardial infarction of unspecified site
I230	Haemopericardium as current complication following acute myocardial infarction
I231	Atrial septal defect as current complication following acute myocardial infarction
I232	Ventricular septal defect as current complication following acute myocardial infarction
I233	Rupture of cardiac wall without haemopericardium as current complication following acute MI
I234	Rupture of chordae tendineae as current complication following acute myocardial infarction
I235	Rupture of papillary muscle as current complication following acute myocardial infarction
I236	Thrombosis of atrium auricular appendage & ventricle as current complications following acute MI
I238	Other current complications following acute myocardial infarction
I240	Coronary thrombosis not resulting in myocardial infarction
I241	Dressler's syndrome
I248	Other forms of acute ischaemic heart disease
I249	Acute ischaemic heart disease, unspecified
I250	Atherosclerotic cardiovascular disease, so described
I2510	Atherosclerotic heart disease, of unspecified vessel
I2511	Atherosclerotic heart disease, of native coronary artery
I2512	Atherosclerotic heart disease, of autologous bypass graft
I2513	Atherosclerotic heart disease, of nonautologous bypass graft
I252	Old myocardial infarction
I253	Aneurysm of heart
I254	Coronary artery aneurysm
I255	Ischaemic cardiomyopathy
I256	Silent myocardial ischaemia
I258	Other forms of chronic ischaemic heart disease

I259	Chronic ischaemic heart disease, unspecified

CARDIAC ARREST OR SUDDEN CARDIAC DEATH

I461	Sudden cardiac death, so described
I469	Cardiac arrest, unspecified
R960	Instantaneous death
R98	Unattended death

PERIPHERAL VASCULAR DISEASE

4400	Atherosclerosis aorta
4401	Atherosclerosis of renal artery
4402	Atherosclerosis artery extremit
4408	Atherosclerosis oth sp artery
4409	Gen/unspec atherosclerosis
4410	Dissecting aneurysm (any part)
4411	Thoracic aneurysm, ruptured
4412	Thoracic aneurysm no rupture
4413	Abdominal aneurysm, ruptured
4414	Abdominal aneurysm no rupture
4415	Aortic aneurysm unsp site rupt
4419	Aort aneurysm unsp site no rupt
4420	Aneurysm artery upr extremity
4421	Aneurysm of renal artery
4422	Aneurysm of iliac artery
4423	Aneurysm artery lwr extremity
4428	Aneurysm other spec artery
4429	Aneurysm of unspec site
4430	Raynaud's syndrome
4431	Thromboangiitis obliterans
4438	Oth sp peripheral vascular dis

4439	Peripheral vascular dis unsp
4440	Embolism/thromb abdominal aorta
4441	Embolism/thromb thoracic aorta
4442	Embolism/thromb extremity arty
4448	Embolism/thromb oth sp artery
4449	Embolism/thromb unspec artery
4460	Polyarteritis nodosa
4461	Ac feb mucocutaneous l/n synd
4462	Hypersensitivity angiitis
4463	Lethal midline granuloma
4464	Wegener's granulomatosis
4465	Giant cell arteritis
4466	Thrombotic microangiopathy
4467	Takayasu's disease
4470	Arteriovenous fistula, acquired
4471	Stricture of artery
4472	Rupture of artery
4473	Hyperplasia of renal artery
4474	Celiac artery compression synd
4475	Necrosis of artery
4476	Arteritis, unspec
4478	Oth sp disorder artery/arteriol
4479	Unsp disorder artery/arterioles
4480	Hereditary haem telangiectasia
4481	Nevus, non-neoplastic
4489	Oth & unsp capillary disease@
E1050	Type 1 diabetes mellitus with circulatory complication unspecified
E1051	Type 1 diabetes mellitus with peripheral angiopathy, without gangrene
E1052	Type 1 diabetes mellitus with peripheral angiopathy, with gangrene

E1150	Type 2 diabetes mellitus with circulatory complication unspecified
E1151	Type 2 diabetes mellitus with peripheral angiopathy, without gangrene
E1152	Type 2 diabetes mellitus with peripheral angiopathy, with gangrene
E1450	Unspecified diabetes mellitus with circulatory complication unspecified
E1451	Unspecified diabetes mellitus with peripheral angiopathy, without gangrene
E1452	Unspecified diabetes mellitus with peripheral angiopathy, with gangrene
I700	Atherosclerosis of aorta
I701	Atherosclerosis of renal artery
I7020	Atherosclerosis of arteries of extremities, unspecified
I7021	Atherosclerosis of arteries of extremities with intermittent claudication
I7022	Atherosclerosis of arteries of extremities with rest pain
I7023	Atherosclerosis of arteries of extremities with ulceration
I7024	Atherosclerosis of arteries of extremities with gangrene
I708	Atherosclerosis of other arteries
I709	Generalised and unspecified atherosclerosis
I7100	Dissection of aorta, unspecified site
I7101	Dissection of thoracic aorta
I7102	Dissection of abdominal aorta
I7103	Dissection of thoracoabdominal aorta
I711	Thoracic aortic aneurysm, ruptured
I712	Thoracic aortic aneurysm, without mention of rupture
I713	Abdominal aortic aneurysm, ruptured
I714	Abdominal aortic aneurysm, without mention of rupture
I715	Thoracoabdominal aortic aneurysm, ruptured
I716	Thoracoabdominal aortic aneurysm, without mention of rupture
I718	Aortic aneurysm of unspecified site, ruptured
I719	Aortic aneurysm of unspecified site, without mention of rupture
I720	Aneurysm of carotid artery

I721	Aneurysm of artery of upper extremity
I722	Aneurysm of renal artery
I723	Aneurysm of iliac artery
I724	Aneurysm of artery of lower extremity
I728	Aneurysm of other specified arteries
I729	Aneurysm of unspecified site
I730	Raynaud's syndrome
I731	Thromboangiitis obliterans [Buerger]
I738	Other specified peripheral vascular diseases
I739	Peripheral vascular disease, unspecified
I740	Embolism and thrombosis of abdominal aorta
I741	Embolism and thrombosis of other and unspecified parts of aorta
I742	Embolism and thrombosis of arteries of upper extremities
I743	Embolism and thrombosis of arteries of lower extremities
I744	Embolism and thrombosis of arteries of extremities, unspecified
I745	Embolism and thrombosis of iliac artery
I748	Embolism and thrombosis of other arteries
I749	Embolism and thrombosis of unspecified artery
I770	Arteriovenous fistula, acquired
I771	Stricture of artery
I772	Rupture of artery
I773	Arterial fibromuscular dysplasia
I774	Coeliac artery compression syndrome
I775	Necrosis of artery
I776	Arteritis, unspecified
I778	Other specified disorders of arteries and arterioles
I779	Disorder of arteries and arterioles, unspecified
I780	Hereditary haemorrhagic telangiectasia
I781	Naevus, non-neoplastic

I788	Other diseases of capillaries
I789	Disease of capillaries, unspecified
I790	Aneurysm of aorta in diseases classified elsewhere
I791	Aortitis in diseases classified elsewhere
I792	Peripheral angiopathy in diseases classified elsewhere
I798	Other disorders of arteries, arterioles and capillaries in diseases classified elsewhere

HEART FAILURE

40201	Mal hypertensv heart dis/chf
40211	Ben hypertensv heart dis/chf
40291	Unsp hypertensive heart d/chf
40493	Hypertensive renal disease w renal failure & CCF
I500	Congestive heart failure
I501	Left ventricular failure
I509	Heart failure, unspecified
I110	Hypertensive heart disease with (congestive) heart failure
I130	Hypertensive heart and kidney disease with (congestive) heart failure
I132	Hypertensive heart and kidney disease with both (congestive) heart failure and kidney failure

APPENDIX 4: ICD 9 & 10 CODES OF INTEREST RELATING TO THYROID DISEASE

Diagnosis Code	Diagnosis Description
Hypothyroidism	
2442	Iodine hypothyroidism
2443	Oth iatrogenic hypothyroidism
2448	Oth sp acquired hypothyroidism
2449	Unsp hypothyroidism
E035	Myxoedema coma
E038	Other specified hypothyroidism
E039	Hypothyroidism, unspecified
2452	Chr lymphocytic thyroiditis
2453	Chr fibrous thyroiditis
2454	Iatrogenic throiditis
2458	Oth & unsp chr thyroiditis
E062	Chronic thyroiditis with transient thyrotoxicosis
E063	Autoimmune thyroiditis
E065	Other chronic thyroiditis
Hyperthyroidism	
2420	Toxic diffuse goiter
2421	Toxic uninodular goiter
2422	Toxic multinodular goiter
2423	Toxic nodular goiter unsp type
2424	Thyrotoxicosis/ectopic thy nod
2428	Th'toxicosis oth sp origin
2429	Thyrotoxicosis nos
E050	Thyrotoxicosis with diffuse goitre
E051	Thyrotoxicosis with toxic single thyroid nodule
E052	Thyrotoxicosis with toxic multinodular goitre

E053	Thyrotoxicosis from ectopic thyroid tissue
E054	Thyrotoxicosis factitia
E055	Thyroid crisis or storm
E058	Other thyrotoxicosis
E059	Thyrotoxicosis, unspecified

Secondary hypothyroidism

2532	Panhypopituitarism
E230	Hypopituitarism

OTHER ENDOCRINE DISORDERS

2450	Acute thyroiditis
2451	Subacute thyroiditis
2459	Thyroiditis unspec
E060	Acute thyroiditis
E061	Subacute thyroiditis
E064	Drug-induced thyroiditis
E069	Thyroiditis, unspecified

APPENDIX 5: EVIDENCE TABLES FOR SYSTEMATIC REVIEW

Study author and reference: Biondi, B, et al. *Left Ventricular Diastolic Dysfunction in Patients with Subclinical Hypothyroidism.* Journal of Clinical Endocrinology & Metabolism, 1999. **84**(6): p. 2064-2067.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Biondi, 1999	A before and after study with RCT substudy Setting: not described. Study from Naples, Italy.	10 participants with SCH from a total of 26. SCH associated with a supranormal response to TRH (DTSH above 30 mIU/L). Pts had stable TSH and thyroid hormone levels for at least 6 months before the enrolment, all had positive antibodies. TSH and thyroid hormone levels were considered stable if their variations were lower than 20% in three consecutive evaluations performed in the 6 months before study. Mean age 36 ±12, Mean TSH 8.6±4.8 Exclusions: excluding patients with confounding factors particularly affecting the cardiovascular system (not described)	A subgroup of 10 patients, randomly selected, were re-evaluated after 6 months of LT4 therapy, at substitutive doses ranging from 50–100 mg daily, with a mean dose of 68 mg.	Doppler echo Time: 6 months of LT4	Represent: randomly selected subgroup but not stated how this was done. Study group were comparable to control group at baseline but no indication of subgroup characteristics. Adjusted, well maintained: No adjustments made. No withdrawals or side effects discussed. Measured accurately: The investigator reading the echo was blinded to patient's status.

Notes: Both subclinical hyperthyroidism and hypothyroidism patients show similar diastolic abnormalities despite opposite hormonal patterns. SCH may impair directly diastolic function by reducing sarcoplasmatic calcium ATPase activity, with consequent impairment of ventricular diastolic function.

Aim: To assess cardiac morphology and function, using non-invasive methods, in patients with SCH before and after LT4.

Results: The results of the present study demonstrate that abnormal LV diastolic filling (suggestive of impaired LV relaxation) is a common finding in patients with SCH and that this abnormality may be reversed by a short-term substitutive LT4 therapy.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	1
Method for randomisation appropriate?	0	Withdrawals mentioned and described?	0
Blinding and or masking?	1	TOTAL	3

Study author and reference: Duman, D, et al. *Simvastatin improves endothelial function in patients with subclinical hypothyroidism.* Heart & Vessels, 2007. **22**(2): p. 88-93.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Duman, 2007	RCT(?) Patients with SCH randomised to three groups to receive no tx, simvastatin or LT4. Setting not described. Study from Turkey	63 women with newly diagnosed SCH, all Hashimotos with antibodies. All premenopausal – 22 patients into the LT4 group. Mean age 36 ± 11, mean TSH 10.5 ± 6.6 Exclusions: smokers, obese, DM, hypertension, CAD, renal or hepatic failure and familial hypercholesterolaemia.	25 mcg LT4 gradually increased until euthyroid state was restored. Final dosage 100 mcg/day.	Brachial artery reactivity, pulsed Doppler, lipid profile Time: 8 month study	Represent: ANOVA - no statistical difference between groups. Randomisation mentioned but not described. Unsure of setting or eligibility. Allocated and well Maintained: No mention of allocation concealment. SCH randomised to LT4 group, 20 of 22 completed tx – poor compliance (10% dropout). Not ITT analysis and only remaining participant results presented. Measured accurately: Unblinded study. This would not affect laboratory measures for lipids but may affect Doppler studies.

Notes: 10% withdrawal.

Aim: To compare the effects of simvastatin versus LT4 therapy on endothelial function and lipid profile in patients with SCH

Results: No significant change in lipids was observed in the LT4 group before and after the study period. All TSH levels decreased and returned to the normal range in patients on LT4. Brachial artery diameters did not change after tx.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	0
Method for randomisation appropriate?	0	Withdrawals mentioned and described?	1
Blinding and or masking?	0	TOTAL	2

Study author and reference: Franzoni, F, et al. *Effect of l-thyroxine treatment on left ventricular function in subclinical hypothyroidism.* Biomedicine & Pharmacotherapy, 2006. **60**(8): p. 431-436.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Franzoni, 2006	RCT Setting: not described but likely to be the outpatients department of Internal medicine where controls were from, Pisa, Italy.	16 patients with SCH caused by Hashimoto's thyroiditis. Subjects had a BMI <30 kg/m2, BP less than 140/90. Age 52.2 ±15.1, TSH 8.8 ± 1.7 Exclusions: abnormal physical exam, smoking habits, diabetes, or received any drug treatment in the previous 3 months.	16 pts from 32 were randomly assigned to receive LT4. No description provided of dosages or protocol.	Doppler studies Time: 6 months	Represent: No idea. No description of SCH treated subgroup, no comparison between this group and untx SCH group. Adjustment, well maintained: no adjustments made, no mention of withdrawals or side effects. Measured accurately: No blinding. Inter and intra operator variability was less than 5%.

Notes: Description of participants does not match the study tables but participant numbers do match another study with a different first author. Unable to perform ITT analysis with information available.

Aim: to investigate the effects of LT4 on myocardial regional left ventricular (LV) systolic and diastolic function in patients with SCH by tissue Doppler imaging (TDI).

Results: Our data suggest that SCH is associated with a subtle, reversible impairment of myocardial function. TDI analysis detects and extends these functional defects by displaying alterations in regional myocardial function. L-T4 replacement therapy should be advised for these patients with the aim to correct preclinical cardiac dysfunction and prevent the development of clinically significant myocardial dysfunction.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	0
Method for randomisation appropriate?	0	Withdrawals mentioned and described?	0
Blinding and or masking?	0	TOTAL	1

Study author and reference: Iqbal, A, R. Jorde, and Y. Figenschau, *Serum lipid levels in relation to serum thyroid-stimulating hormone and the effect of thyroxine treatment on serum lipid levels in subjects with subclinical hypothyroidism: the Tromso Study.* Journal of Internal Medicine, 2006. **260**(1): p. 53-61.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Iqbal, 2006	RCT (We are focussing on) placebo controlled double-blind intervention study. Clinical research unit at the University Hospital of Tromso, Norway	32 subjects (16F/16M) with TSH between 3.5 and 10 mIU/L on two separate occasions – mean TSH 5.8±1.8, mean age 62.0±11.9 Exclusions: hx of coronary infarction, angina pectoris, stroke, over age of 80, serious diseases identified from hospital records. In addition, subjects using lipid lowering medication were excluded.	Treatment group given 50 mcg LT4 for 6 weeks then 100 mcg for next 6 weeks, thereafter TSH taken every third month and thyroxine dose adjusted accordingly. Mean thyroxine dose 97.1±20.1, mean compliance was 91%.	Lipids including Apo A Time: study length 12 months	Represent: No statistical difference between groups. Eligibility described well. Allocated and well Maintained: Randomised to LT4 or placebo group but not described. No description of any allocation concealment. TSH measured every 6 weeks then 3 monthly to adjust LT4 dose. Two subjects had iatrogenic hyperthyroidism, seven had subclinical hyperthyroidism on follow-up. No withdrawals or side effects described. Measured accurately: Patients not aware of thyroid function level. No description of whether investigation team were blinded. This would not affect laboratory measures from blood tests.

Notes: Not ITT analysis but provided all the information.

Aim: To evaluate the relationship between serum TSH and lipids

Results: Significant reduction in Apo B. Serum TC and LDL significantly reduced in those with TSH between 0.2-2mIU/L.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	0
Method for randomisation appropriate?	0	Withdrawals mentioned and described?	0
Blinding and or masking?	0	TOTAL	1

Study author and reference: Kong, W.M, et al, *A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism.* American Journal of Medicine, 2002. **112**(5): p. 348-354.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Kong, 2002	RCT – randomised, double-blind, placebo-controlled trial, recruited consecutively, referred by general practitioners Setting: Department of Metabolic Medicine, Hammersmith Hospital, London, UK	40 women with SCH (TSH 5-10 mIU/L and normal FT_4) assigned to LT4 or placebo (23 in tx group). Mean age - 53±3, mean TSH 8.0±1.5 Exclusion: hx of previous TD, psychiatric disorder, or anticipated pregnancy.	50 mcg/day thyroxine increased to 100 mcg/day as required to restore euthyroidism	QoL, Symptom scores, anthropometry and metabolic measurements, thyroid hormones and antibodies, fasting lipid profile. Time: 6 months.	Represent: 52 met inclusion criteria and 45 agreed to participate. Age difference between Tx and placebo group (53±3 c.f. 45±4 respectively). Allocation and well Maintained: Randomisation by computer generated methods, blinding of participants and of physician who read thyroid function tests. Five participants who were assigned dropped out prior to baseline measurements. Withdrawals and side effects described. Measured accurately: ITT described but not demonstrated.

Notes: Data from tx group not available for all parameters - 16 participants with lipid data, 15 with metabolic data, 20 with QoL data.

Aim: To evaluate the short-term effects of LT4 on QoL, symptoms, body weight, energy expenditure and lipid profiles in women with mild SCH (TSH 5-10 mIU/L) and no previous history of thyroid disease.

Results: No significant differences in the baseline to 6 month changes for any metabolic, anthropometric or lipid measurements between the two groups.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	1
Method for randomisation appropriate?	1	Withdrawals mentioned and described?	1
Blinding and or masking?	1	TOTAL	5

Study author and reference: Mainenti MRM, Vigario PS, Teixeira PFS, Maia MDL, Oliveira FP, Vaisman M. Effect of levo-thyroxine replacement on exercise performance in subclinical hypothyroidism. J Endocrinol Invest. 2009;32(5):470-3.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Mainenti, 2009	RCT Setting: outpatients Endocrine clinic	23 untreated women aged 30 – 60 years of age with spontaneous SCH in two samples at least 4 weeks apart. Exclusions: thyroid drugs, HR or BP drugs, diagnosed cardiac diseases or systemic arterial hypertension, pain or physical symptoms that would interfere with walking.	Levo-thyroxine at an initial dose of 0.75 mcg/kg day according to pts weight, progressively titrated to achieve euthyroidism. Mean dose 42.25±22.24 mcg.	V02, HR, SBP, DBP Time: 6 months	Represent: recruited from prevalent cases. No allocation concealment. Adjusted: similar baseline characteristics. No blinding of outcomes. No withdrawals noted. Small sample size.

Notes: No medication or intervention given to untreated group (i.e. no allocation concealment).

Aim: To verify possible cardiopulmonary changes during exercise in patients with subclinical hypothyroidism on LT4 replacement six months after normalisation of TSH.

Results: Oxygen uptake decreased significantly after hormone replacement (24.1+/-6.3 vs. 17.1+/-4.2 ml x kg x min(-1); p=0.03).Minute ventilation also showed an enhanced performance in treated patients (28.0+/-8.1 vs. 23.5+/-5.6 l x min(-1); p=0.03), as did the heart rate (128+/-17 vs. 121+/-17 bpm; p=0.03). There were no changes in the untreated group. The results demonstrate that submaximal cardiopulmonary exercise performance improved after six months of TSH normalization and this improvement can help enhance the ability to carry out daily life activities in patients with subclinical hypothyroidism.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	0
Method for randomisation appropriate?	½	Withdrawals mentioned and described?	0
Blinding and or masking?	0	TOTAL	1 ½

Study author and reference: Mikhail, G.S, et al. *Increased atherogenic low-density lipoprotein cholesterol in untreated subclinical hypothyroidism.* Endocrine Practice, 2008. **14**(5): p. 570-5.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Mikhail, 2008	Prospective double-blind, placebo-controlled trial of pts with SCH from outpatients between January 2005-November 2006. Setting: Jahra Hospital, Kuwait	60 of 120 pts with SCH confirmed on 2 occasions 4 weeks apart. Mean age 32.13 ± 10.2, mean TSH 6.4 ± 1.41. Exclusions: prev. TD, radioiodine therapy or any thyroid medication, known dyslipidaemia or lipid lowering agents, CAD, diabetes, renal or hepatic failure or other systemic diseases or smoking.	25 mcg/day LT4 with dose adjustments every 6 weeks until attainment of a euthyroid state. Mean dosage 72 ± 3.8 daily.	Lipids Time: study duration was 52 weeks.	Represent: predefined randomisation list, Allocation and well Maintained: No mention of allocation concealment or description of placebo. No mention of withdrawals or side effects. Measured accurately: No blinding although this will not affect laboratory measures of lipids.

Notes: Assumption is that there were no dropouts.

Aim: to evaluate the therapeutic effect of physiologic doses of LT4 on lipoprotein profile in pts with confirmed SCH.

Results: TC decreased by 0.31 mmol/L or 6.1% ($p<0.0001$), LDL decreased by 0.41mmol/L or 12% ($p<0.1$) and TG level decreased significantly ($p<0.02$). No significant changes to HDL.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	0
Method for randomisation appropriate?	1	Withdrawals mentioned and described?	0
Blinding and or masking?	0	TOTAL	2

Study author and reference: Monzani F, Di Bello V, Caraccio N, Bertini A, Giorgi D, Giusti C, et al. Effect of levo-thyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. J Clin Endocrinol Metab. 2001 Mar;86(3):1110-5

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Monzani, 2006	RCT Setting: Outpatients clinic	20 patients (18 women and 2 men) mean age 32.6±12.1, mean TSH >3.6 (range 3.8-12 mIU/L) 5.44. All have Hashimoto's. Stable SCH for at least 1yr. Half randomised to intervention. 10 non-SCH also examined. Exclusions: Cardiovascular and respiratory diseases, no drugs.	LT4 50 mcg daily or two identical placebo tabs in a blinded manner. Follow-up: 6m after normalisation or final dose of meds for placebo group.	Echo Doppler Time: 6 months	Represent: Not told how they were chosen. Allocation concealment: Yes. Intra- and Inter observer coefficients of variation averaged 7.5% and 10%, respectively. Echo blinded. No withdrawals or side effects reported. Small sample size.

Notes: SCH affects both myocardial structure and contractility.

Aim: to investigate whether SCH induces cardiovascular alterations.

Results: Patients had significantly higher isovolumic relaxation times and pre-ejection/ejection time and a lower CVI than controls. CVI was inversely related to TSH level. LT4 tx pts showed a sig reduction of the PEP/ET ratio, peak A and isovolumic relaxation time along with a normalisation of CVI.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	1
Method for randomisation appropriate?	0	Withdrawals mentioned and described?	0
Blinding and or masking?	1	TOTAL	3

Study author and reference: Nagasaki, T, et al. *Decrease of brachial-ankle pulse wave velocity in female subclinical hypothyroid patients during normalization of thyroid function: a double-blind, placebo-controlled study.* European Journal of Endocrinology, 2009. **160**(3): p. 409-15.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Nagasaki, 2009	Randomised placebo-controlled study. Consecutive patients with newly detected were enrolled during a 24-month period (June 2005 to May 2007). Setting was not described: part of studies at Osaka City University Hospital.	48 female subjects with SCH were randomised to LT4 group. SCH established on 2 occasions within 6 months. All subjects had antibodies. Exclusion: factors known to affect atherosclerosis, patients suffering from major diseases such as hypertension, hyperlipidaemia, diabetes mellitus or patients receiving other hormone replacement therapy or taking any drugs that affect the lipid profile and atherosclerosis such as antihypertensive agents, lipid-lowering drugs, anti-platelet drugs, and bisphosphonates including etidronate.	SCH group initially treated with LT4 at 12.5 mcg, checked every 4 weeks and increased serially to 18.75 mcg/day, 25 mcg/day and maximally to 37 mcg/day. Mean dose was 25.8 mcg/day)	baPWV, lipids, BP, BMI Time: monitored for an average of 4.8 ± 0.24 months.	Represent: No statistical differences between groups. Allocation and well Maintained: allocation concealment, blinding of patients described, no side effects or withdrawals noted. Measured well: automated measures, no blinding described. Unlikely to cause contamination.

Notes: Brachial-ankle pulse wave velocity (baPWV) is a measure of arterial stiffening and an independent predictor for cardiovascular events.

Aim: To assess the changed in baPWV in female SCH patients with Hashimoto's after restoration of normal thyroid function.

Results: baPWV higher in SCH subjects than in normal subjects. Significant decrease in baPWV in pts tx with LT4 but these were not correlated with TSH. Multiple regression failed to reveal an association between parameters.

Jadad scoring:

Randomised?	1	Methods for blinding or masking appropriate?	1
Method for randomisation appropriate?	0	Withdrawals mentioned and described?	1
Blinding and or masking?	1	TOTAL	4

Study author and reference: Razvi, S, et al. *The Beneficial Effect of L-Thyroxine on Cardiovascular Risk Factors, Endothelial Function, and Quality of Life in Subclinical Hypothyroidism: Randomized, Crossover Trial.* Journal of Clinical Endocrinology & Metabolism, 2007. **92**(5): p. 1715-1723.

Study	Methods and setting	Participants	Intervention	Outcomes and Time	Notes (RAMMBO)
Razvi, 2007	Randomised (computer-generated) cross-over trial. Patients identified from the laboratory database recruited from 27 general practices in an urban UK population. Setting: general practice, Gateshead, UK.	100 pts (82F/18M) with SCH after two measures at least 3 months apart and initial screening. Mean age 53.8 ± 12.6, mean TSH 5.3 (3.7 – 15.8).	One hundred participants were randomised to receive either 100 mcg l-thyroxine or matching for 12 wk before being crossed over to the other treatment.	Primary end points included: improvement in brachial artery flow mediated dilatation (FMD) as a marker of vascular endothelial function and total cholesterol (TC) levels after 12 wk of l-thyroxine treatment. Secondary end points. These included changes in weight and its distribution (assessed by body mass index and waist to hip ratio) and patient reported outcomes (assessed by questionnaires), such as perceived health status, hypothyroidism-specific quality of life (QoL), and hypothyroid symptoms. Time: 3m each	Represent: Pts were identified, screened and included (or excluded) in a systematic manner. Allocated, well Maintained: Allocation concealment and follow-up well described. Measured accurately: one investigator for FMD assessment – intraoperator variability good, all investigators blinded. Pts blinded.

Notes: Ad hoc showed no difference between positive and negative TPO-antibodies to any measured outcome. No difference between patients with TSH above or below 6.1 mIU/L when compared.

Aim: to assess CV risk factors and patient-reported outcomes after treatment.

Results: The present study has shown that treatment of SCH with l-thyroxine is associated with significant, although modest, improvement across a wide spectrum of CV risk factors. If the reduction in LDL alone were sustained long term in SCH patients taking T4, we estimate this would result in a relative reduction in 10-yr CV mortality of about 10%.

Jadad scoring

Randomised?	1	Methods for blinding or masking appropriate?	1
Method for randomisation appropriate?	1	Withdrawals mentioned and described?	1
Blinding and or masking?	1	TOTAL	5