L-thyroxine therapy in subclinical hypothyroidism – effect on cardiovascular risk factors, endothelial function and patient-reported outcomes.

Thesis submitted for the degree of Doctorate of Medicine

Salman Razvi

University of Newcastle upon Tyne

July 2006

This work is dedicated to my wife Zarine and daughter Dania

Contents

Abstract

Context: It is controversial whether the treatment of subclinical hypothyroidism (SCH) with L-thyroxine improves cardiovascular (CV) risk factors and quality of life (QoL).

Objective: To determine whether CV risk factors, endothelial function and patient-reported outcomes improve in people with SCH with L-thyroxine treatment.

Design: Randomised double blind, cross-over study.

Setting: Patients from primary care practices identified from laboratory database.

Patients: One hundred patients (81 females) with mild SCH, and no existing thyroid or vascular disease, mean (SD) age 53.8 (12) years, thyrotropin (TSH) of 6.6 (1.3) mIU/L. One patient withdrew due to perceived side-effects.

Intervention: Oral 100 mcg of L-thyroxine or matching placebo daily for twelve weeks each.

Main outcome measures: Powered to detect significant improvements in two primary parameters: total cholesterol (TC) levels and endothelial function (brachial artery flow mediated dilatation-FMD), the earliest marker of atherosclerosis.

Results: L-thyroxine treatment reduced (mean difference, 95% CI) TSH (5.64 mIU/L, 4.11 to 7.17), increased FT4 and FT3 levels (6.98 pmol/L, 5.97 to 7.98 and 0.6 pmol/L, 0.37 to 0.82, respectively), FMD improved (1.65%, 1.2 to 2.1) and TC levels reduced (-0.35 mmol/L, -0.52 to –0.16). Increase in FT4 levels was the only significant determinant of the improvement in TC and FMD. Sex-life and overall QoL were less negatively impacted by SCH during L-thyroxine treatment. Symptom bother scores did not benefit by L-thyroxine but there was a significant improvement in the frequency of tiredness - from 89% to 78%, $p<0.05$. Health status and treatment satisfaction did not show any significant change.

Conclusion: SCH treated by L-thyroxine leads to a significant improvement in CV risk factors and some patient-reported outcomes. The benefit of CV risk reduction is related to the increased level of achieved FT4 concentration.

List of figures and tables:

Figures

Tables

Abbreviations

SCH – Subclinical hypothyroidism.

CV – Cardiovascular.

QoL – Quality of life.

RCT – Randomised controlled trial.

TSH – Thyrotropin, Thyroid stimulating hormone.

IHD – Ischemic heart disease.

T4 – Thyroxine.

Anti-TPO – Anti thyroid peroxidase antibody.

LDLc – Low density lipoprotein cholesterol.

HDLc – High density lipoprotein cholesterol.

FMD – Brachial artery flow mediated dilatation.

BMI – Body mass index.

CRP – C reactive protein.

IMT – Intima media thickness.

PAI 1 – Plasminogen activator inhibitor 1.

tPA – Tissue plasminogen activator.

OR – Odds ratio.

CARDIOVASCULAR DISEASE AND ITS RISK FACTORS IN SCH

INTRODUCTION (A)

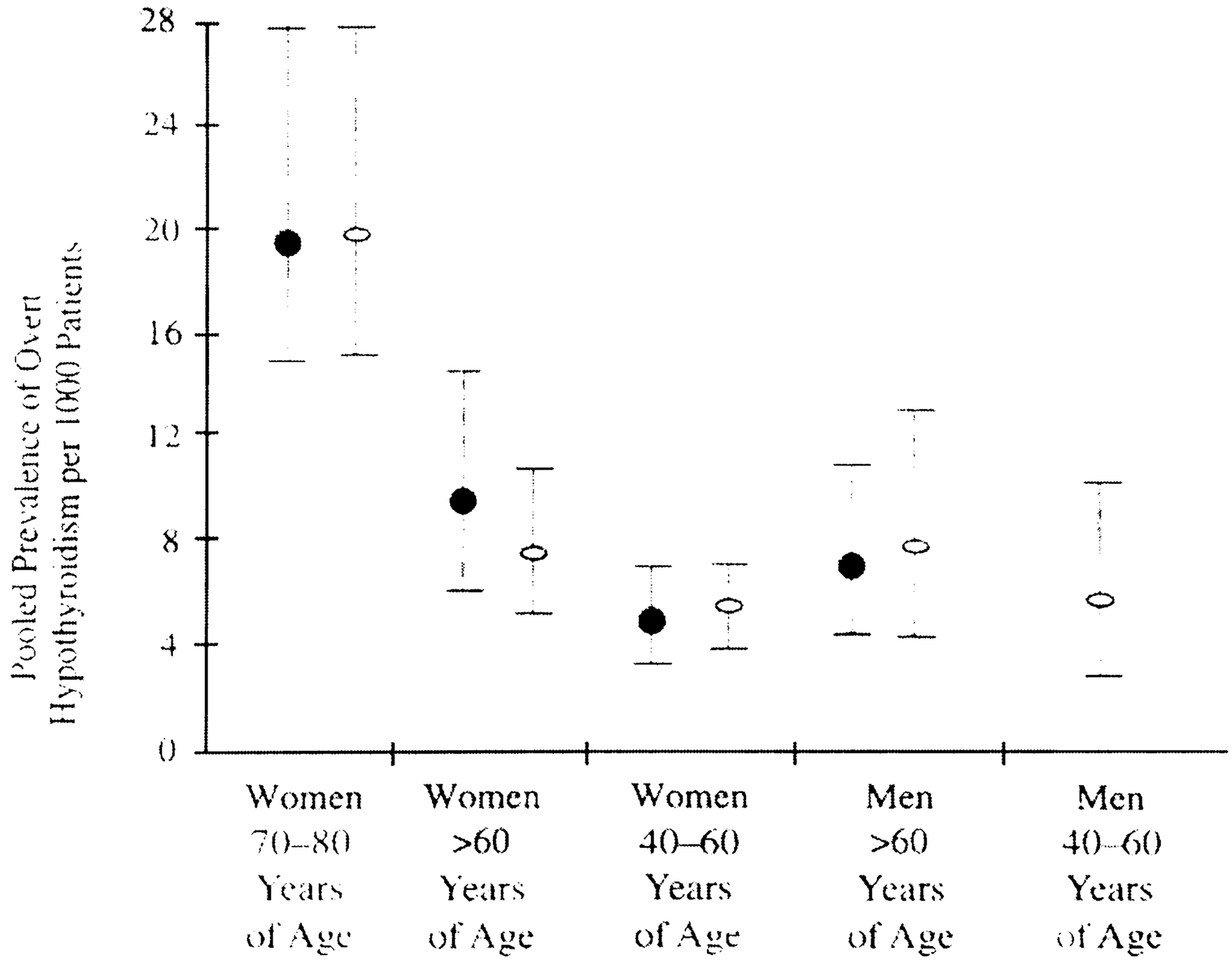
Background.

Thyroid dysfunction is the second commonest endocrine abnormality after diabetes mellitus. Typical clinical features, a raised serum thyrotropin (TSH) and reduced serum thyroid hormone levels characterize hypothyroidism.

Prevalence and incidence of hypothyroidism:

The Whickham survey, conducted in the north of England, revealed a prevalence of hypothyroidism of at least 7.5% in females and 2.8% in males in the UK (Tunbridge, *et al* 1977b). A pooled prevalence from different studies is shown in figure 1 across various age groups for each gender. A 20-year follow-up study of the population of Whickham reported a mean incidence of 4.1/1000 per year for hypothyroidism in women, the incidence in men being 0.6/1000 per year respectively (Vanderpump, *et al* 1995).

Figure 1.
Pooled prevalence of overt hypothyroidism per 1000 patients (Closed circles represent population-based studies; open ovals represent office-based studies)



From: Helfand, M. et. al. Ann Intern Med 1998;129:144-158.

Overt hypothyroidism could lead to typical symptoms and signs as well as cardiovascular effects, all of which can impact on morbidity and mortality.

Cardiovascular disease:

Overt hypothyroidism is associated with an increased risk of cardiovascular (CV) disease, although the evidence for a true association is confined to older literature investigating relatively fewer numbers of patients (Klein and Ojamaa 2000, Steinberg 1968, Vanhaelst, *et al* 1967). An association between the two is likely given that diastolic hypertension, higher serum cholesterol levels and low cardiac output is common (Klein 1990). The diastolic hypertension and increased vascular resistance contribute to increased cardiac afterload and cardiac work (Bengel, *et al* 2000). However, not all patients have hypertension or abnormal lipid profile (Streeten, *et al* 1988), suggesting that there are other mechanisms at work in the development of atherosclerosis. These may be collagen induced platelet aggregation, impaired vascular smooth muscle relaxation, or impaired fibrinolytic activity or thrombosis (Erem, *et al* 2003, Ishikawa, *et al* 1989, Mamiya, *et al* 1989). Plasma homocysteine levels are also elevated in this condition (Nedrebo, *et al* 1998) and this is now known to be an independent risk factor for cardiovascular disease (Boushey, *et al* 1995, Clarke, *et al* 1991). It has also been suggested that hypothyroid patients are at an increased risk for atherosclerosis based on animal studies that showed that development of atherosclerosis in cholesterol fed animals is enhanced by the presence of hypothyroidism and reduced when thyroxine is administered (Steinberg 1968). The other possible mechanism of development of atherosclerosis in people with hypothyroidism may be due to endothelial dysfunction (Lekakis, *et al* 1997). Hypothyroidism is associated with blunted endothelium-dependent vasorelaxation (Delp, *et al* 1995, Moreno, *et al* 2003, Vargas, *et al* 1995) and reduced aortic nitric oxide (NO) synthase activity in rats (Quesada, *et al* 2002). Hypothyroidism, even in the subclinical stage, is associated with changes in arterial stiffness which may have detrimental effects on left ventricular function and coronary perfusion in hypothyroid subjects (Dagre, *et al* 2005). Hypothyroid patients have increased peripheral arterial resistance (Graettinger, *et al* 1958) (Klein 1989). Elevated diastolic blood pressure is commonly found in hypothyroid patients that is reversible with L-

thyroxine replacement therapy (Fuller, *et al* 1966). Twenty percent of patients with hypothyroidism have diastolic hypertension and systemic arterial hypertension increases by up to 30% (Klein and Ojamaa 2001).

Thyroxine therapy reverses all the CV and endothelial changes associated with hypothyroidism (Klein 1990, Wieshammer, *et al* 1989) (Crowley, *et al* 1977) (Papaioannou, *et al* 2004) (Fuller, *et al* 1966). In a large study of patients with hypothyroidism who were evaluated for clinical evidence of ischemic heart disease after the initiation of thyroid hormone therapy, new or worsening angina or acute myocardial infarction was rare, and more patients had improvement in anginal symptoms (Keating, *et al* 1961). These findings reinforce the important and potentially beneficial effects of thyroid hormone in improving the efficiency of myocardial oxygen consumption (Bengel, *et al* 2000) and simultaneously lowering systemic vascular resistance (Ojamaa, *et al* 1996)

Subclinical hypothyroidism (SCH)

Definition: The terms subclinical hypothyroidism and mild thyroid failure refer to patients who have an elevated TSH level and a free T4 level within the laboratory reference range (Ross 2001). In these patients, the serum thyroxine level is reduced from the physiologically normal level for that patient but does not fall below the lower limit of the laboratory's reference range for the thyroxine assay. Symptoms of hypothyroidism are not necessary for this condition to be diagnosed since, it has been argued, most patients on close questioning disclose mild, non-specific symptoms (Ayala, *et al* 2000).

Since serum TSH levels tend to have a skewed distribution with a "tail" towards higher concentrations in a healthy population (that is, not normally distributed), it is likely that some people with subclinical disease are included in the upper limit of the reference range (Surks, *et al* 2004). The NHANES III survey in the United States measured TSH levels in a subset (n=13344) aged 12 years or more and without any confounding factors (pregnancy, medications known to affect thyroid hormone metabolism or positive anti-TPO antibodies). In this population, the reference range of TSH concentration (5^{th} –95^{th} percentile) was 0.4 to 4.0 mIU/L, with a geometric mean value of 1.4 mIU/L (Hollowell, *et al* 2002).

There has been a debate whether upper limit of the reference range for serum TSH should be reduced. Over the last two decades, the upper reference limit for TSH has steadily declined from about 10 mIU/L to approximately 4.0 - 4.5 mIU/L. This decrease reflects a number of factors including the improved sensitivity and specificity of current monoclonal antibody based immunometric assays, the recognition that normal TSH values are log-distributed and importantly, improvements in the sensitivity and specificity of the thyroid antibody tests that are used to pre-screen subjects. The follow-up study of the Whickham cohort has found that individuals with a serum TSH >2.0 mIU/L at their primary evaluation had an increased odds ratio of developing hypothyroidism over the next 20 years, especially if thyroid antibodies were elevated (Vanderpump, *et al* 1995). An increased odds-ratio for hypothyroidism was even seen in antibody-negative subjects. It is likely that such subjects had low levels of thyroid antibodies that could not be detected by the insensitive

microsomal antibody agglutination tests used in the initial study (Tunbridge, *et al* 1977b). Even the current sensitive anti-thyroperoxidase antibody (anti TPO) immunoassays may not identify all individuals with occult thyroid insufficiency. In the future, it is possible that the upper limit of the serum TSH euthyroid reference range may be reduced to 2.5 mIU/L because >95% of rigorously screened normal euthyroid volunteers have serum TSH values between 0.4 and 2.5 mIU/L (Baloch, *et al* 2003). There is data indicating that African-Americans with very low incidence of Hashimoto thyroiditis have a mean TSH level of 1.18 mIU/L, which strongly suggests that this value is the true normal mean for a normal population (Wartofsky and Dickey 2005). On the other hand, it has been argued that there is no evidence for associated adverse outcomes in people with TSH values between 2.5 - 4.0 mIU/L and that some of these TSH levels may be due to technical reasons with the TSH assay (abnormal isomers and heterophile antibodies) (Surks, *et al* 2004).

Current diagnostic methods are capable of measuring TSH at the lower end and now cite lower normal limits between 0.2 and 0.4 mIU/L (Spencer, *et al* 1996). As the sensitivity of the methods has improved, there has been an increased interest in defining the true lower limit of normal to better determine the presence of mild (subclinical) hyperthyroidism. Current studies suggest that TSH values in the 0.1 to 0.4 mIU/L range may represent thyroid hormone excess and in elderly patients might be associated with an increased risk of atrial fibrillation, and cardiovascular mortality (Sawin, *et al* 1991) (Sawin, *et al* 1994) (Parle, *et al* 2001).

Prevalence and incidence:

Subclinical hypothyroidism is quite common. Biochemical assessment of thyroid function in a large cohort of 25,863 subjects attending a State-wide health fair in Colorado revealed a prevalence of elevated TSH of 9.5%, with most subjects being diagnosed due to the blood test (Canaris, *et al* 2000). In agreement with previous studies, the prevalence of subclinical hypothyroidism was found to be greater in women and increased with age, reaching nearly 21% in women aged 74 years and 16% in men of similar age. A survey of 1210 patients, aged 60 or more from one general practice, indicated rates of subclinical hypothyroidism of 11.6% in females and 2.9% in males (Parle, *et al*

1991). In an analysis of the Third National Health and Nutrition Examination Survey (NHANES III), a population-based survey of 17,353 people at least 12 years of age representing the U.S. population, the prevalence of subclinical hypothyroidism was 5.8% among white, non-Hispanic women; 1.2% among black, non-Hispanic women; and 5.3% among Mexican-American women. The prevalence of subclinical hypothyroidism was 3.4% among white men, 1.8% among black men, and 2.4% among Mexican-American men (Hollowell, *et al* 2002). In the Whickham survey, a large, population-based cohort study, prevalence was 4% to 5% among women age 18 to 44 years, 8% to 10% among women age 45 to 74 years, and 17.4% among women older than age 75 years. The prevalence was 1% to 3% among men age 18 to 65 years and 6.2% among men older than age 65 years. Goitre is twice as prevalent among patients with this condition as in the general population. Up to 75% of patients with SCH have only mildly elevated serum TSH values (5-10 mIU/L), and 50-80% of patients have positive thyroid autoantibody tests, depending on the age, sex, and serum TSH levels (Tunbridge, *et al* 1977b). However, the prevalence of SCH has been found to be lower in more older women; being 6.2% in those over 80 (Parle, *et al* 1991). It is not clear whether this reduced prevalence is due to a self-selection bias, in that more people with SCH may have died before they reach 80 years.

These data indicate that the prevalence of SCH is much greater than overt untreated and unrecognised hypothyroidism and that the prevalence seems to increase when other autoimmune conditions are present (Gray, *et al* 1980) (Kahaly, *et al* 1995).

Causes and differential diagnoses:

Patients with treated hyperthyroidism, a history of neck irradiation, postpartum thyroiditis, and certain autoimmune diseases, especially type 1 diabetes mellitus, are at increased risk for SCH. It may also develop in patients who are being treated with the iodine containing antiarrythmic agent amiodarone, lithium, or immune response modulators, such as interferon alpha, but most patients have no obvious risk factors. The differential diagnoses of elevated serum TSH and normal levels of serum free thyroxine include intermittent non-compliance with

L-thyroxine therapy, recovery from non-thyroidal illness, chronic renal failure, primary adrenal failure, artifactual high TSH due to circulating heterophilic antibodies against TSH, and mutations causing inactivation of the TSH receptor. SCH is usually detected when patients with a history of thyroid disease are followed up or as a result of biochemical screening for non-specific symptoms (Surks, *et al* 1990).

Due to the minor alterations in thyroid hormone levels and the wide levels at which homeostatic mechanisms may occur, it is predictable that metabolic and organ function indexes will deviate only slightly from the normal. Nevertheless, such modifications may be clinically relevant, because they affect organ function over the course of many years. SCH is also likely to progress to overt hypothyroidism in a large number of patients, especially if it is caused by an autoimmune process (Parle, *et al* 1991).

Screening:

Since the majority of patients with this condition are asymptomatic or have very few or mild symptoms, some authors recommend routine screening (Danese, *et al* 1996). Using a decision and cost effectiveness model, it was calculated that screening women older than 35 years old every five years would cost about $9200 per quality adjusted year of life. Half of this benefit would accrue due to prevention of progress to overt hypothyroidism with its attendant morbidity, 30% from improved symptoms and a smaller benefit from a decrease in heart disease due to a reduction in serum cholesterol levels. The costs of screening were mostly due to the TSH assay whereas the potential savings were due to decrease in costs of evaluating and treating non specific symptoms, as well as possible savings on lipid lowering therapy. In interpreting these conclusions, it is important to note that Danese and colleagues assumed that early treatment improved health outcomes and then proceeded to examine the likely consequences and costs of a screening program. Other researchers (Wiersinga 1995) (1990) (Glenn 1996) (Franklyn 1995) have questioned these assumptions, citing flaws in the literature on which they are based. The Royal College of Physicians states that screening the healthy adult population is not justified since

the benefits of subsequent therapy are not proven by large prospective clinical trials (Vanderpump, *et al* 1996a).

Implications of SCH

The potential complications of subclinical hypothyroidism are progression to overt hypothyroidism, presence of symptoms and hyperlipidemia and CV disease. The potential of SCH to lead to overt hypothyroidism is discussed next whereas the implications of SCH on CV disease and its risk factors as well as symptoms and quality of life are discussed in subsequent chapters.

Progression to overt hypothyroidism:

Over time, asymptomatic patients with subclinical hypothyroidism may progress to overt hypothyroidism at a rate of 2-5% per year. Progression is diagnosed when a patient with subclinical hypothyroidism develops a low free thyroxine level. The presence of thyroid autoantibodies in serum is a strong risk factor for progression. Older age and a higher TSH level also increase the chance that a patient with subclinical hypothyroidism will progress. The Whickham survey provides the best data on the chance that a person with subclinical hypothyroidism found by screening will develop overt hypothyroidism. The Whickham investigators defined a TSH level of 6 mIU/L or more as elevated. Two thirds of women with an elevated TSH level had antithyroid antibodies in serum. During 20 years of follow-up, 55% of women with a TSH level of 6 mIU/L or more and a positive antibody test result developed overt hypothyroidism. About 25% of these women had an initial TSH level of 10 mIU/L or more; for these women, the risk for overt hypothyroidism over 20 years was close to 90%, or about 0.11 per year. Younger women and women with a mildly elevated TSH level (6 to 9 mIU/L) had a lower risk for progression (Vanderpump, *et al* 1995). A logistic regression equation developed by the Whickham investigators can be used to estimate risk in these groups. For a 50-year-old woman with a positive test result for thyroid antibodies, the 20-year risk for developing overt hypothyroidism was 0.57 (57%) if the TSH level was 6 mIU/L and 0.72 (72%) if the TSH level was 9 mIU/L. For a 35-year-old woman with a positive antibody test result, the 20-year risk for developing overt hypothyroidism was 0.47 (47%) if the TSH level was 6 mIU/L and 0.67 (67%) if the TSH level was 9 mIU/L. The risk for progression was not evenly distributed

throughout the follow-up period. By 5 years, 8% of patients with an elevated TSH level developed overt hypothyroidism and 92% remained well. Almost all patients who progressed within 5 years had a TSH level of 10 mIU/L and high titres of circulating antibodies. Of 57 women who had an initial TSH level between 6 and 10 mIU/L, none progressed within 2 years and 3 (5.2%) progressed within 5 years. In patients with a mildly elevated TSH level, the risk for progression after 5 years was not distinguishable from that of euthyroid patients.

In individuals with SCH, not on L-thyroxine replacement therapy, serum TSH levels return to within the normal reference range after 1 year of follow-up in approximately 5% (Parle, *et al* 1991), whilst the rest remained in SCH state. Another prospective study of 82 women with SCH, with a mean follow-up period of 9.2 years, showed that 28% progressed to overt disease, 68% remained subclinically hypothyroid, whilst the remaining 4% returned to normal (Huber, *et al* 2002). When patients in this study were stratified according to their initial TSH levels, it was found that none of the patients with mild SCH (TSH <6 mIU/L) progressed to overt hypothyroidism, whereas the corresponding figures for moderate (TSH >6 and <12 mIU/L) and severe (>12 mIU/L) SCH were 43 and 77% respectively. The results of this study cannot be applied to the primary SCH patients since 61% of these patients had SCH as a result of treatment (radioiodine or thyroid surgery) for hyperthyroidism in the past.

Prevention of progression to overt hypothyroidism:

As stated before, the 20-year follow-up of the Whickham survey cohort has provided the best estimates of risk of developing overt hypothyroidism in women with positive thyroid autoantibodies or SCH- 4.3% / year or 38 times that of people without antibodies or normal TSH (Vanderpump, *et al* 1995). The number of patients needed to treat (NNT) to prevent one case of overt hypothyroidism ranges from 4.3 to 14.3, depending on age and TSH level at baseline (Helfand and Redfern 1998). This is in a similar range as that of other commonly practiced strategies, for example, statin treatment for hypercholesterolemia (Kumana, *et al* 1999).

Cardiovascular disease and its risk factors.

The CV system (myocytes and vascular smooth muscle) has receptors for thyroid hormones and is a sensitive marker of peripheral thyroid hormone action (Klein and Ojamaa 2001). Type II 5' monodeiodinase (which converts thyroxine to triiodothyronine) is found on non-muscle heart cells and vascular smooth muscle cells of the aorta and coronary arteries (Mizuma, *et al* 2001). This suggests that the CV system may respond to fluctuations in serum thyroid hormone levels (Biondi and Klein 2004). Effects of hypothyroidism on exchange of plasma proteins between the intravascular and interstitial fluid spaces, and on lipid metabolism and atherogenesis add further dimensions to the CV implication of SCH.

The long-term effects of deficiency of thyroid hormones on the CV system can be assessed by CV events (by means of cross-sectional and longitudinal case-control and cohort studies) as well as by its influence on established CV risk factors.

The concept of risk assessment was first introduced by the Framingham Heart Study, and has been expanded upon in the decades since (Kannel, *et al* 1976). Traditional risk factors routinely used in risk profiles or algorithms include age, blood pressure, serum cholesterol (high-density lipoprotein and low-density lipoprotein), diabetes, and cigarette smoking. About 300 such CV risk factors have been reported in the literature. Those described below are a combination of traditional and emerging risk factors that address the diverse pathogenic mechanisms. These biomarkers may better predict clinical events either alone or in combination with other CV risk factors. However, the independent relation of the new risk factors with atherosclerotic disease has not yet been conclusively proven.

Blood pressure

Hypertension is a strong independent risk factor for heart disease and stroke and a predictor of premature death and disability from CV complications (Chobanian, *et al* 2003). The association between blood pressure (BP) and major CV events including stroke, myocardial infarction, organ damage, and mortality are well documented in both normotensive and hypertensive individuals, and

this association is greatly influenced by age. Numerous observational epidemiological studies and clinical trials, including the Framingham Heart Study, have shown a strong positive and continuous association between brachial artery systolic and pulse pressures and adverse CV events, especially in people older than 50 years of age (Domanski, *et al* 2001). The long-term beneficial effects of lowering arterial BP on CV events (e.g., myocardial infarction, stroke, and mortality) have been well documented in large clinical trials in both hypertensive and normotensive patients (Davis, *et al* 2002) (Dahlof, *et al* 2002).

Lipids

Results of observational studies in different populations indicate a continuous positive relationship between CV disease risk and blood cholesterol concentrations that extends well below the range seen in many developed populations, without any definite threshold below which a lower cholesterol concentration is not associated with lower risk (Stamler, *et al* 1993). Several large studies of interventions designed to reduce cholesterol levels have shown a reduction in CV mortality and morbidity (The 4S Study 1994) (Shepherd, *et al* 1995).

Body weight and distribution

The importance of obesity as a risk factor for several diseases including type 2 diabetes, CV disease, hypertension, gallstone disease, and certain cancers, is well documented (Eckel 2003). Abdominal obesity is the body fat parameter that is closely associated with the metabolic syndrome (and hence CV disease). Any effective weight reduction reduces the CV risk (Eckel, *et al* 2005).

.

Inflammatory markers

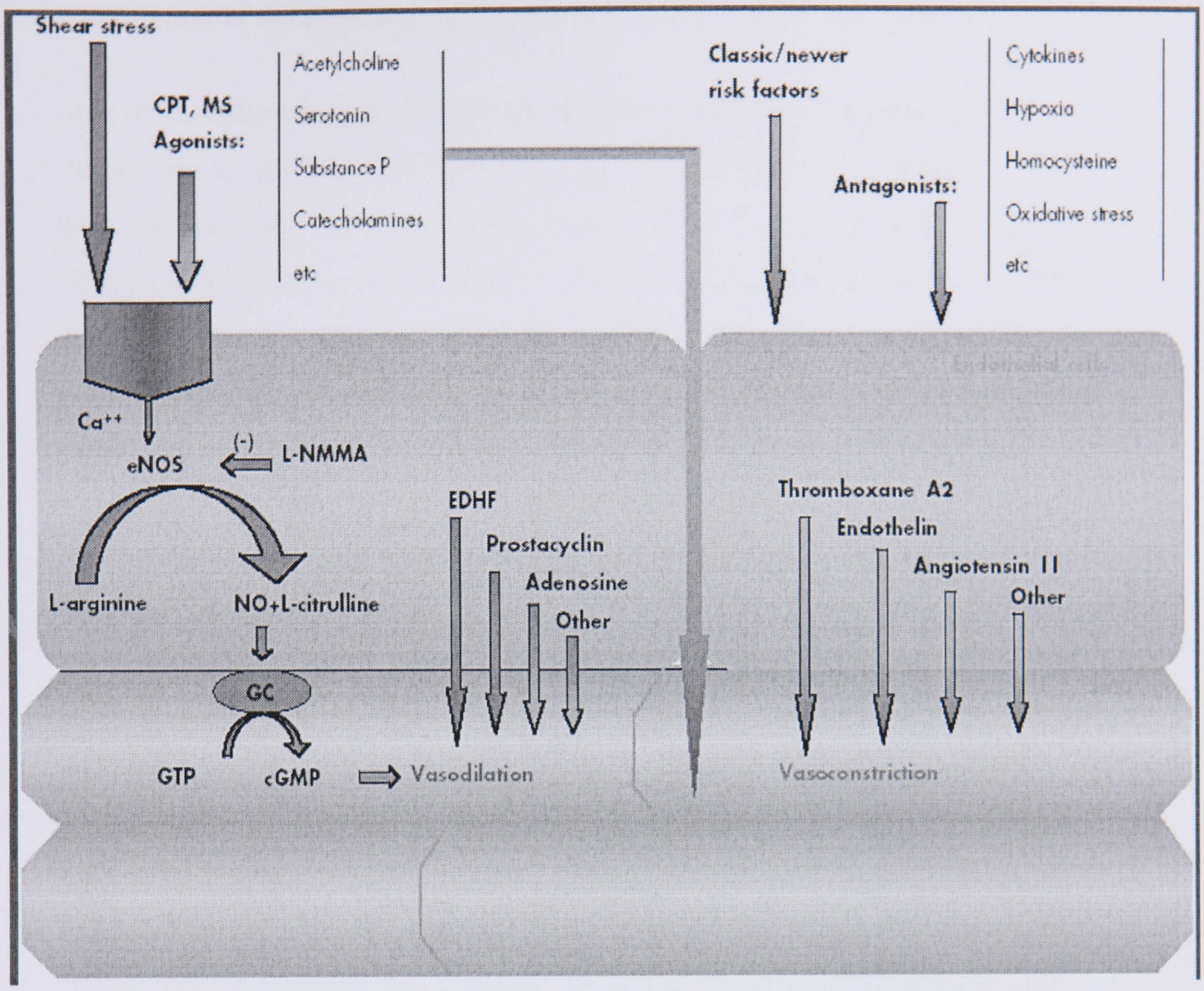
Inflammation may be both important in the pathogenesis of athero-thrombosis and a distal marker of an advancing disease process. Increases in the serum C-reactive protein (CRP) prospectively predict coronary events (Ridker, *et al* 1997) (Thompson, *et al* 1995) (Liuzzo, *et al* 1994). However, the results of a recent report from the Reykjavik prospective study indicated that elevated CRP levels

were only a moderate predictor of risk compared with established risk factors such as total cholesterol levels and cigarette smoking (Danesh, *et al* 2004).

Endothelial function

The endothelium regulates vascular homeostasis by secreting a variety of autocrine and paracrine substances that act locally in the vessel and lumen (Gokse, *et al* 1998). It is of primary importance due to its strategic location between the blood and underlying smooth muscle. Under normal circumstances, the secreted endothelial factors maintain normal vascular tone, blood fluidity, and limit vascular inflammation and smooth muscle proliferation (see figure I). One of these factors is endothelium-derived nitric oxide (NO), which modulates the tone of the underlying vascular smooth muscle and also inhibits pro-atherogenic processes, including monocyte and platelet adhesion, oxidation of low density lipoproteins, synthesis of inflammatory cytokines, smooth muscle proliferation and migration, and platelet aggregation. However, in the presence of coronary risk factors, the endothelium adopts a state that facilitates inflammation, thrombosis, vasoconstriction, and atherosclerotic plaque formation (Levine, *et al* 1995). In humans, endothelium dysfunction manifests prior to the development of frank atherosclerosis and is associated with traditional risk factors like hypercholesterolemia, hypertension, and diabetes mellitus and with newer risk factors like hyperhomocystinaemia, obesity, and systemic inflammation (Gokse, *et al* 1998). Endothelial dysfunction is an early physiological event in atherogenesis (Healy 1990). In vitro studies have shown that this dysfunction is present in the earliest stages, before plaques exist and well before clinical manifestation of the disease (Ross 1986). Thus assessment of endothelial function by several different methods has emerged as a tool for detection of evidence of pre-clinical CV disease (Anderson 1999). Additionally, there is also evidence that endothelial dysfunction also contributes to the later stages of the disease when patients develop clinical symptoms. Cross-sectional studies have demonstrated the most severe endothelial dysfunction in arteries containing a culprit lesion that precipitates unstable angina or myocardial infarction (Okumura, *et al* 1992) (Bogaty, *et al* 1994). The pathophysiological role of endothelial dysfunction is evident by interventional studies, which show an improvement in endothelial function by diverse interventions proven to reduce cardiovascular risk (Vita and Keaney 2000). For example, lipid lowering

Figure I. Function of the endothelial cell



From: Tousoulis et al, Heart 2005;91:353-358

therapy, ACE-inhibitors, smoking cessation, and physical exercise have been to shown to reduce cardiovascular risk and to improve endothelial dependent vasodilation in the coronary and peripheral circulations (Gokse, *et al* 1998).

Loss of vascular integrity can expose sub-endothelium and cause the efflux of fluids from the intravascular space. Upregulation of leucocyte adhesion molecules such as E-selectin, ICAM-1, and VCAM-1 allows leucocytes to adhere to endothelium and then move into the tissues (Adams and Shaw 1994). The pro-thrombotic effects of endothelial cell activation include loss of the surface anticoagulant molecules thrombomodulin and heparan sulphate; reduced fibrinolytic potential due to enhanced plasminogen activator inhibitor type 1 release; loss of the platelet anti-aggregatory effects of ecto-ADPases and prostacyclin; and production of platelet activating factor, nitric oxide, and expression of tissue factor.

There is also evidence from outcome studies linking endothelial dysfunction with future events. Suwaidi et al examined 157 patients with mild coronary disease and demonstrated a greater incidence of CV events during 2.3 year follow-up in patients with impaired endothelium dependent vasodilatation of coronary resistance and conduit arteries (Suwaidi, *et al* 2000). This study is limited by the relatively small number of clinical events and the inclusion of coronary revascularisation procedures as events but, it provides the first evidence that endothelial dysfunction has prognostic value. Halcox et al studied 308 patients undergoing cardiac catheterisation and examined coronary blood flow and epicardial coronary diameter responses to endothelium dependent and independent vasodilators (Halcox, *et al* 2002). All patients had an average 46-month follow-up and they observed a total of 35 ischemic events, including sudden cardiac death, acute myocardial infarction, unstable angina, and stroke. These events were independently associated with impaired endothelium dependent dilatation, even after controlling for other clinical variables. In contrast vasodilator responses to endothelium independent vasodilators did not predict events, proving specific relationship with endothelial dysfunction. Patients with impaired endothelium dependent vasodilatation predicted CV events even in patients with angiographically normal coronary arteries.

Several studies have reported that the risk of ischemic CV events is increased in patients with impaired fibrinolytic function (Pahor, *et al* 1999) (Salomaa, *et al* 1995b) (Thompson, *et al* 1995). Fibrinolytic activity is primarily determined by the balance between the levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 (PAI-1). The endothelial cells are responsible for the production and blood release of tPA and of PAI-1 to some extent. Multiple factors, such as lipoproteins, cytokines, and inflammatory markers, modulate endothelial cells to produce tPA and PAI-1 (Pearson 1993). There are several arguments to suggest that hypofibrinolysis could be considered to be a surrogate marker of endothelial cell dysfunction (Tomiyama, *et al* 1998) (Poredos 2002). In prospective studies PAI-1 and tPA independently predicted CV events or mortality (Held, *et al* 1997) (Ridker, *et al* 1994) (Ridker, *et al* 1993). While some studies (Ridker, *et al* 1994) (Ridker, *et al* 1993) found that the significant associations of tPA with CV disease were independent of other risk factors, others (Juhan-Vague, *et al* 1996) (van der Bom, *et al* 1997) have found that fibrinolytic markers were correlated with obesity, and serum lipids such as total cholesterol and Lp(a), suggesting that the prothrombotic effect of altered lipids and insulin resistance are mediated by an impairment of fibrinolysis.

Increased levels of biochemical markers of endothelial function and cell adhesion—P-selectin, E-selectin, soluble intercellular adhesion molecule 1 (sICAM 1), vascular cell adhesion molecule 1 (VCAM 1), and thrombomodulin—have been found in patients with atherosclerosis and dyslipidaemia (Belch, *et al* 1997) (Blann, *et al* 1997b) (Blann, *et al* 1997a) (Morisaki, *et al* 1997). In the Atherosclerosis Risk in Communities Study, increased plasma levels of sICAM 1 and E-selectin prospectively predicted coronary events (Hwang, *et al* 1997). In the Physician's Health Study, sICAM 1 was significantly and independently associated with incident myocardial infarction (Ridker, *et al* 1998).

Assessment of endothelial function

Endothelial function has been assessed with a variety of invasive and noninvasive surrogate assays (see table 1). Elevation of serum markers (e.g., adhesion molecules, selectins, C-reactive protein) has been associated with endothelial dysfunction and its risk factors, but distinguishing between endothelial stimulation and endothelial damage is difficult (Raitakari and Celermajer 2000). In addition, assays measuring NO activity in plasma and urine exist, but are heavily affected by dietary habits (Wang, *et al* 1997). As a result, a direct measure of endothelial function, with a variety of techniques, is frequently used. Although direct visualization of the coronary artery dilator response to acetylcholine challenge with angiography and endothelial function in the forearm circulation using plethysmography after brachial artery infusion of a variety of dilatory triggers have been studied and validated, their widespread clinical use is limited because of their invasive nature.

Recently, non-invasive measures of endothelial function have become available. Reduced coronary flow reserve, as measured with positron emission tomography (PET) before and after provocation with adenosine or dipyridamole, has been shown to occur in patients with risk factors for vascular disease and improve with statin therapy (Huggins, *et al* 1998). However, this technique is expensive and involves radiation exposure. Forearm plethysmography and brachial artery ultrasound scanning may be used to assess increased flow in response to NO stimuli, and both are well tolerated and reproducible. However, data suggest that forearm hyperaemia is less dependent on NO release than is flow in larger circulatory beds (Honing, *et al* 2000). Moreover, there is concern that forearm plethysmographic measurements exhibit considerable day-to-day variability, potentially limiting their use in long-term studies (Anderson 1999).

Accordingly, the most widely used technique for assessing endothelial function is brachial artery ultrasound scanning for flow-mediated dilatation (FMD).

Brachial artery flow mediated dilatation (FMD):

Coronary endothelial dysfunction has been shown in response to various pharmacological and physiological stimuli, in patients with symptoms of established coronary atherosclerosis (Ludmer, *et al* 1986). The technique of assessing coronary endothelial function is useful for coronary artery events, but this method is limited by the risk of and expense of coronary angiography and

selective intra-coronary agonist infusion. Therefore, there has been considerable interest in the study of endothelial vasomotor function in more accessible vascular beds, such as the brachial circulation. Venous occlusion plethysmography has been used to examine vasomotor responses of forearm resistance vessels during brachial artery infusion of endothelium dependent vasodilators like acetylcholine (Creager, *et al* 1990). This approach has several advantages including the ability to examine dose-response relations and use specific agonists and antagonists. However, these studies are limited by the requirement for arterial catheterisation that renders them less well suited for large scale and intervention studies. An alternative approach uses vascular ultrasound to examine endothelium dependent flow mediated dilatation of the brachial artery (Corretti, *et al* 2002). This was first developed by Celermajer et al, who followed changes in vessel diameter, in response to increased flow and to glyceryl trinitrate (GTN) (Celermajer, *et al* 1992). In arteries lined by healthy endothelium, increased flow causes vessel dilatation, via release of NO. This mechanism fails in endothelial dysfunction. In contrast, GTN causes vasodilatation by direct action on the smooth muscle; its effect is therefore independent of the endothelium. Since then, this non-invasive technique has gained popularity as an assessment of endothelial function that can safely be applied to large and varied group of patients that may involve repeated measurement of vascular function over time. As with the coronary circulation, endothelial function in the brachial artery is impaired in individuals with risk factors and responds to interventions known to reduce CV disease risk (Gokse, *et al* 1998).

The systemic nature of many risk factors makes it reasonable to assume that they affect central and peripheral arteries in a parallel manner. In fact, there have been studies to suggest that endothelial dysfunction detected non-invasively in the arm correlates well with coronary artery endothelial dysfunction (Anderson, *et al* 1995). Some more recent studies have shown that impaired ultrasound detected flow mediated dilatation predicts future CV events. Neunteufl and colleagues observed a relation between endothelial dysfunction and need for revascularisation procedure, although their study had a relatively small group of subjects and the relation between endothelial dysfunction and events was lost after controlling for extent of coronary artery disease (Neunteufl, *et al* 2000).

Another prospective study by Gokce et al showed that impaired brachial artery flow mediated dilatation is an independent predictor of short-term events in high-risk patients undergoing surgery for vascular disease (Gokce, *et al* 2002). Thus, endothelial function represents a very good and accessible tool to measure underlying vascular health.

Blood flow through the brachial artery is increased in response to transient hyperaemia, which is provoked by inducing post-ischemic dilation of distal vascular beds. Ischemia is induced by the inflation of an arterial occlusion cuff, positioned on the proximal or mid-forearm. After cuff deflation, brachial artery flow increases because of downstream vessel dilation, and this augmented flow increases brachial artery shear stress, resulting in vasodilatation. The precise mechanism of FMD is not completely understood, but it is generally believed to be mediated by NO produced by the endothelial cells, perhaps via shear-stress-induced phosphorylation of endothelial nitric oxide synthase (eNOS) (Dimmeler, *et al* 1999). NO is of particular interest to researchers as it is an anti-atherogenic molecule, and a reduction in its bioavailability may play a role in the pathogenesis of vascular disease (Cooke and Dzau 1997).

Biochemical endothelial markers:

These are either secreted by the endothelium or shed from its surface in disease states, can be used to measure endothelial activity. Some of these markers are von Willebrand factor, thrombomodulin, E-selectin, P-selectin, sICAM 1, VCAM 1 and vascular endothelial growth factor. Adhesion molecules (sICAM 1 and E-selectin, etc) are shed into the circulation. These can be measured and provide a biochemical means for assessing endothelial function (Abdu, *et al* 2001). The clotting cascade is activated by the endothelial products tissue plasminogen activator (tPA), thrombomodulin and plasminogen activator inhibitor-1 (PAI-1), which contribute to thrombosis formation on atheromatous plaques. Von Willebrand factor (vWF) generated by endothelial cells also favours thrombosis.

sICAM 1: This is one of the cell adhesion molecules (CAMs) expressed in response to vascular endothelial activation via the stimulus of cytokines, tumour necrosis factor alpha and interleukin-1. sICAM 1 is a marker of white blood cell (WBC) interaction with the vascular endothelium, and it facilitates the trans-endothelial migration of WBCs into the sub-endothelial space (Smith, *et al*

1989).

VCAM-1: Supports the adhesion of lymphocytes, monocytes, natural killer cells, eosinophils and basophils to the endothelium. It is not constitutively expressed on endothelium, but can be upregulated invitro in response to several cytokines (Blann and Lip 1998).

E-selectin: is one of the CAMs shed from the endothelium into the plasma and shown to be a specific marker of endothelial dysfunction as it is exclusively expressed by the activated vascular endothelium (Bevilacqua, *et al* 1989). It mediates the initial interaction of leukocytes and platelets with endothelial cells.

Table 1. Surrogate indices of endothelial function

Serum markers

Endothelin-1 (ET-1)

Von Willebrand factor (vWF)

Tissue-type plasminogen activator (t-PA)

Plasminogen activator inhibitor-1 (PAI-1)

Intercellular adhesion molecules (ICAMs)

Vascular cell adhesion molecules (VCAMs)

E-selectin, P-selectin

Asymmetric dimethylarginine (ADMA)

Nitric oxide production assays

Urine nitrate (NO^{3-})

Urine cyclic GMP functional tests

Invasive provocative testing

1. With forearm plethysmography

2. With coronary angiography

Positron emission tomography

Flow mediated dilation

1. With forearm plethysmography

2. With brachial artery ultrasonography

Detection of subclinical atherosclerosis with carotid intima-media thickness:

Measurement of arterial wall intima-media thickness (IMT) made with high-resolution B-mode ultrasound imaging was first presented as a means of assessing atherosclerotic changes in the aorta in 1986, when studies of excised aorta showed close correlation between ultrasonically measured IMT and the same thickness measured by light microscopy (Pignoli, *et al* 1986). Because of its ease of study, the carotid artery quickly became the vessel of choice for ultrasonic examination of IMT. Multiple studies have shown that the carotid artery IMT, as measured non-invasively by ultrasonography, is directly associated with an increased risk of CV disease (O'Leary, *et al* 1996) (Kuller, *et al* 1995) (Bots, *et al* 1997) (O'Leary, *et al* 1999). Because it has been shown to be an independent predictor of CV disease after adjustment for traditional risk factors, it is the only non-invasive imaging test currently recommended by the American Heart Association for inclusion in the evaluation of risk (Smith, *et al* 2000). However, it remains unclear how much additional information beyond that afforded by traditional risk factors is gained by inclusion of IMT in risk profiles (del Sol, *et al* 2001). Change in IMT is increasingly being used as the end point in interventional trials. Meaningful differences in progression rates have been shown in progression rates in trials of either lipid-lowering drugs or beta-blockers involving several hundred subjects over a period of several years (Furberg, *et al* 1994) (Smilde, *et al* 2001). Acceptance of a standardized protocol for measuring IMT change would facilitate comparison of results from the many trials using this technique. However, uncertainty about which measure of IMT offers the best end point has inhibited methodological standardisation.

Arterial stiffness as a marker of atherosclerosis:

Results from several studies have suggested that subjects with CV disease have increased arterial stiffness compared with subjects without (Hirai, *et al* 1989) (Dart, *et al* 1991). Arterial stiffness may be an important, independent predictor of CV risk. The association between arterial stiffness and CV disease may be explained by an increase in pulse pressure following increased arterial stiffness or through an association between arterial stiffness and atherosclerosis. Studies

examining the association between arterial stiffness and atherosclerosis have reported conflicting results (Maarek, *et al* 1987) (Wada, *et al* 1994) (Riley, *et al* 1997) (Megnien, *et al* 1998). Traditionally, structural components within the arterial wall, together with mean arterial pressure, were thought to be the major determinants of vessel stiffness. However, arterial stiffness is a dynamic parameter, which can be modulated by changes in smooth muscle tone, and it is now recognized that the vascular endothelium plays an important role in the functional regulation of arterial stiffness. Importantly, direct pharmacological manipulation of arterial stiffness is possible and therapeutic strategies that specifically target the large arteries to reduce stiffness may be helpful, particularly in those individuals with increased or premature arterial stiffening. Nitric oxide donor drugs are one such strategy and may be particularly useful in this regard. However, therapies that target changes arterial structure provide an interesting alternative. Further studies are required to determine the most effective therapies with which to reduce large artery stiffness and, thus, potentially, CV risk.

Cardiovascular disease in SCH

The association of SCH with CV disease has been quite controversial. One of the earliest case-control studies showed a strong association between SCH (as defined by exaggerated response to thyrotropin releasing hormone) and angiographically demonstrated coronary artery disease (Dean and Fowler 1985). Since then, there have been several community-based cross-sectional (Hak, *et al* 2000) (Tunbridge, *et al* 1977a) (Imaizumi, *et al* 2004) (Lindeman, *et al* 2003) (Rodondi, *et al* 2005) (Walsh, *et al* 2005) (Cappola, *et al* 2006) as well as longitudinal studies (Hak, *et al* 2000) (Imaizumi, *et al* 2004) (Vanderpump, *et al* 1996b) (Parle, *et al* 2001) (Gussekloo, *et al* 2004) (Rodondi, *et al* 2005) (Walsh, *et al* 2005) (Cappola, *et al* 2006) that have assessed this relationship. There has been no large scale randomised controlled trial of treatment of SCH in assessing CV disease.

The cross-sectional component of the Rotterdam study concluded that SCH was a risk factor for aortic atherosclerosis and myocardial infarction in women aged 55 years or more with a risk comparable to that associated with diabetes mellitus, smoking and hypercholesterolemia (Hak, *et al* 2000). However, the longitudinal component of this study (4.6 year follow-up period), did not demonstrate this association, but total CV events were quite low.

The cross-sectional Whickham study showed a weak association between minor ECG changes and SCH in women, independent of other variables. The authors stated that this finding was of questionable importance since detection of ECG changes was observer dependent (Tunbridge, *et al* 1977a). A 20-year follow-up study of the cohort did not reveal an association between autoimmune thyroid disease and CV disease (Vanderpump, *et al* 1996b). But many patients with SCH in the original survey received L-thyroxine replacement therapy and the analysis did not differentiate between treated and not treated patients. The study also did not differentiate between SCH and euthyroid people with positive antibodies.

A Japanese study showed that SCH was associated with CV disease independent of all other variables in men but not in women in the cross-sectional analysis. There was no association with cerebrovascular disease. The longitudinal arm of

the same study (10-year follow-up period) showed increased all-cause mortality in men with SCH (the exact nature of death was not investigated) (Imaizumi, *et al* 2004).

A longitudinal case-control study, in Birmingham, UK, of 1191 people aged more than 60 years followed-up for 10-years, showed no increased risk of CV disease in the group with SCH, although it did not differentiate between treated and untreated patients (Parle, *et al* 2001).

Similarly, the prevalence of CV disease was not increased in SCH patients in a cross-sectional survey of 3410 elderly people in Maryland, USA (Cappola, *et al* 2006).

However, a cross-sectional study in New Mexico, USA, of a randomly selected sample of 112 people aged 65 years or more, found that there was an increased prevalence of CV disease in participants whose TSH >10mIU/L (Lindeman, *et al* 2003).

A recent study with both cross-sectional and longitudinal arms of people aged between 70-79 years reported no association between SCH and CV disease at baseline but there was an increased incidence of congestive heart failure after 4 years of follow-up only in the moderate and severe SCH groups (TSH 7-9.9 and >10 mIU/L, respectively) but not the mild SCH group (Rodondi, *et al* 2005).

Another recent study that had cross-sectional and longitudinal arms (follow-up of 20-years) found a significant association of CV disease at baseline as well at follow-up (Walsh, *et al* 2005).

On the other hand, the Leiden study of people aged 85 years or more showed that an elevated TSH was associated with a decreased risk of death from CV disease during 4 years of follow-up (Gussekloo, *et al* 2004). However, 62% of the participants with SCH had reverted to being euthyroid at the time of follow-up, suggesting that a high proportion of people with SCH at the outset may have had non-thyroidal illness or their SCH was not stable.

Details of these studies ate given in Tables 4 and 5. As can be seen from these tables, there have been a number of cross-sectional as well as longitudinal studies that have assessed the risk of ischemic heart disease (IHD) in people with SCH, with varying results. The differences in results are quite likely to be due to the different population samples studied (inclusion or exclusion of subjects with history of thyroid disease, previous CV event, current L-thyroxine

therapy) as well as variations in definitions of IHD, length of follow-up and varying limits of TSH cut off values that defined SCH. Therefore, a systematic review and meta-analysis of these studies that have assessed IHD and its risk factors was performed. The methods of the meta-analysis are outlined below.

Methods:

Inclusion criteria:

Cross-sectional and longitudinal studies assessing IHD risk, mortality, and cross-sectional studies assessing lipids and body mass index (BMI):

1. Population-based cross-sectional or longitudinal study of unselected community living adults.
2. Should have reported validated IHD events (myocardial infarctions, angina, coronary artery interventions like angioplasty or surgery), mortality, lipids and BMI in both SCH and euthyroid groups, and stated variance, if applicable.
3. Should have measured thyroid hormone (thyroxine) as well as TSH levels as a prerequisite to diagnose SCH.
4. Should have included patients with TSH levels < 10 mIU/L in the study.

Literature search criteria:

A comprehensive search of PubMed, Embase and the Cochrane database of systematic reviews was conducted between February 2004 and June 2006, for all relevant articles published between 1976, when a reliable TSH assay became available, and 2006, using the Mesh terms "thyroid", "cardiovascular", "ischemic heart disease", "lipids" and "cholesterol". The references of these articles were then studied to compile any missed articles. Authors of studies where data was incomplete were contacted for additional information.

Data abstraction:

IHD events or mortality were abstracted from included studies along with number of participants in each arm. Where data was presented for IHD events, strokes and peripheral vascular disease, then only IHD data was included. If data

was reported as CV disease events, then all data was included for both groups. For those studies that reported results that were stratified according to baseline TSH levels, data was abstracted for TSH levels < 10 mIU/L. When studies reported data for different subgroups (for example by age or by gender), the average across all subgroups was calculated for both euthyroid and SCH groups. For those studies where variance of difference of means was not available, variance was calculated (for trials that reported difference from baseline) or imputed (for trials that reported final values). All analyses were by intention to treat.

Statistical analyses

The results are calculated using both fixed and random effect models. IHD events (both prevalence and incidence) and mortality was expressed as odds ratio (OR). Continuous data is expressed as weighted mean difference. Heterogeneity was tested by the χ^2 test and I^2 test, $p < 0.1$ and a value greater than 50% is indicative of substantial heterogeneity, respectively. Odds ratio and the mean difference is expressed in a fixed manner for analyses that are statistically homogenous and in a random manner for those that are heterogeneous. The statistical package Revman 4.2 was used for analyses and for generating figures.

Results

The studies that assessed IHD prevalence, incidence and mortality are shown in tables 2 – 3, and meta-analysis of the data shown in figures 2 – 4.

Prevalence of IHD in SCH (table 2 and figure 2): It is significantly increased with an odds ratio (OR) of 1.27 (95% CI 1.03 – 1.58), p=0.03. Tests for heterogeneity reveal that the studies are significantly different (Chi^2 18.36, df =9, p=0.03), hence the random effects model was used. Subgroup analysis shows that the prevalent IHD association with SCH is due to trials that have studied individuals less than 65 years of age, OR 1.55 (1.10 – 2.19), p=0.01. Studies of populations aged more than 65 years failed to show this association, OR 1.04 (0.88 – 1.22), p=0.64.

Table 2.

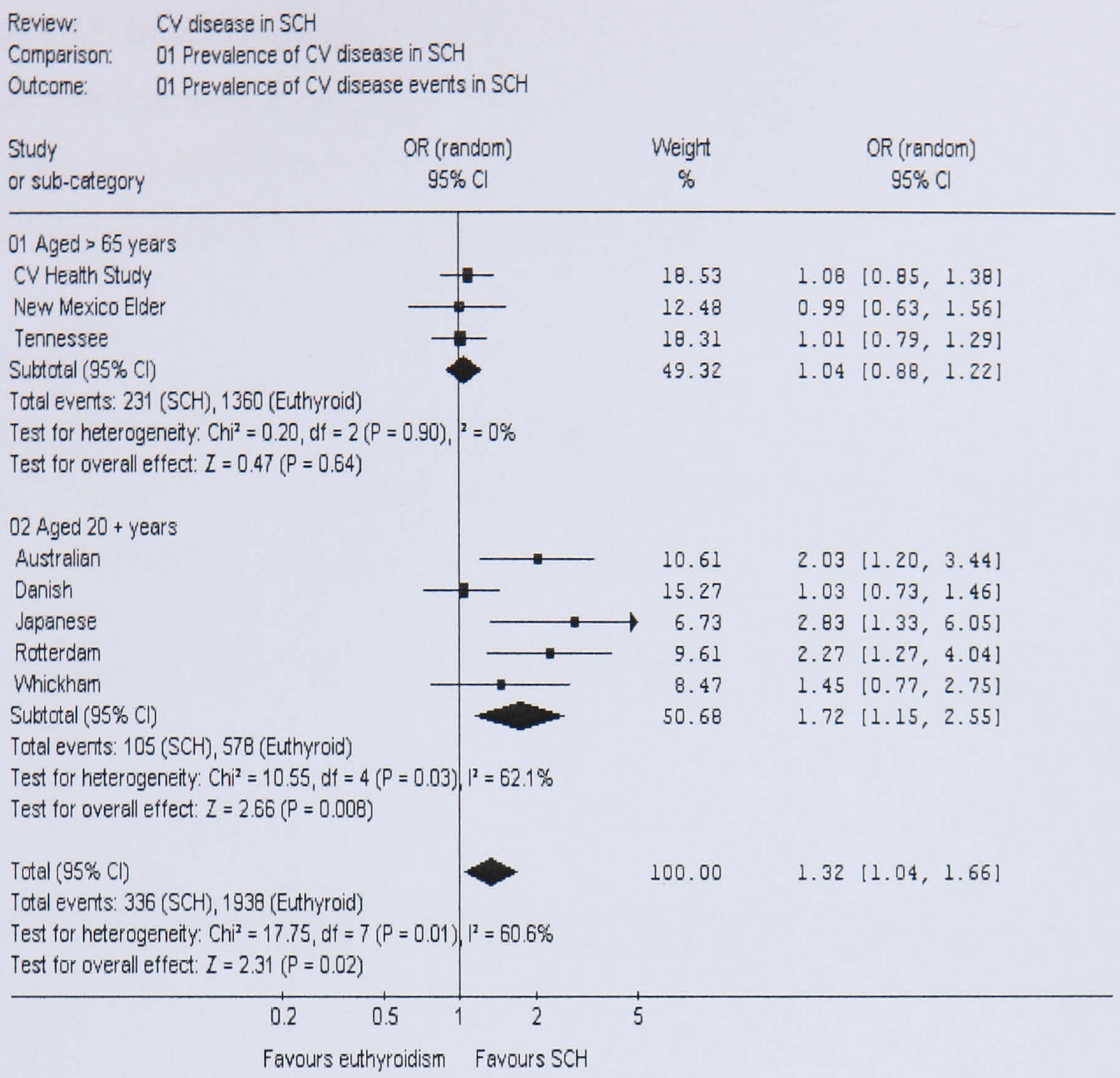
Cross-sectional studies of cardiovascular disease in SCH

Study	No. of participant Eu	SCH	Recruitment	CVD in Eu n (%)	CVD in SCH n (%)	Significance
Whickham	2460	132	Population	145 (5.9)	11 (8.3)	NS
Rotterdam	867	116	Population	61 (7)	17 (14.6)	S
CV Health	2639	496	> 65 years	489 (18.5)	98 (19.7)	Ns
Japanese	2293	257	Atomic bomb survivors	29 (1.3)	9 (3.5)	S
New Mexico	643	112	>65 years	181 (28.1)	32 (28.6)	Ns
Australian	1906	119	Population	154 (8.1)	18 (15.1)	S
Tennessee	2392	338	70-79 years	710 (29.7)	101 (29.9)	Ns
Denmark	963	249	1 PHC	189 (19.6)	50 (20.1)	S (men)
German	1745	29	Population	96 (5.5)	2 (6.9)	NS
NHANES	1551	57	Population	218 (12)	7 (13)	NS

Eu – Euthyroid, SCH – Subclinical hypothyroidism, CVD – Cardiovascular disease, Ns – Not significant, S – Significant, PHC – Primary Health Centre.

Figure 2.

Forrest plot of CV disease in cross-sectional studies of SCH



Incidence of IHD in SCH (table 3 and figure 3): Incidence of IHD is not increased in the total cohort of SCH patients, random OR 1.25 (0.70 – 2.24), p=0.45. In subgroup analysis by age, trials that studied subjects with SCH below 65 years showed a significant association with incident IHD, OR 3.04 (1.97 – 4.69), p<0.00001. In contrast, trials with subjects aged 65 years or more failed to show any association, OR 0.87 (0.68 – 1.12), p=0.28.

Table 3.

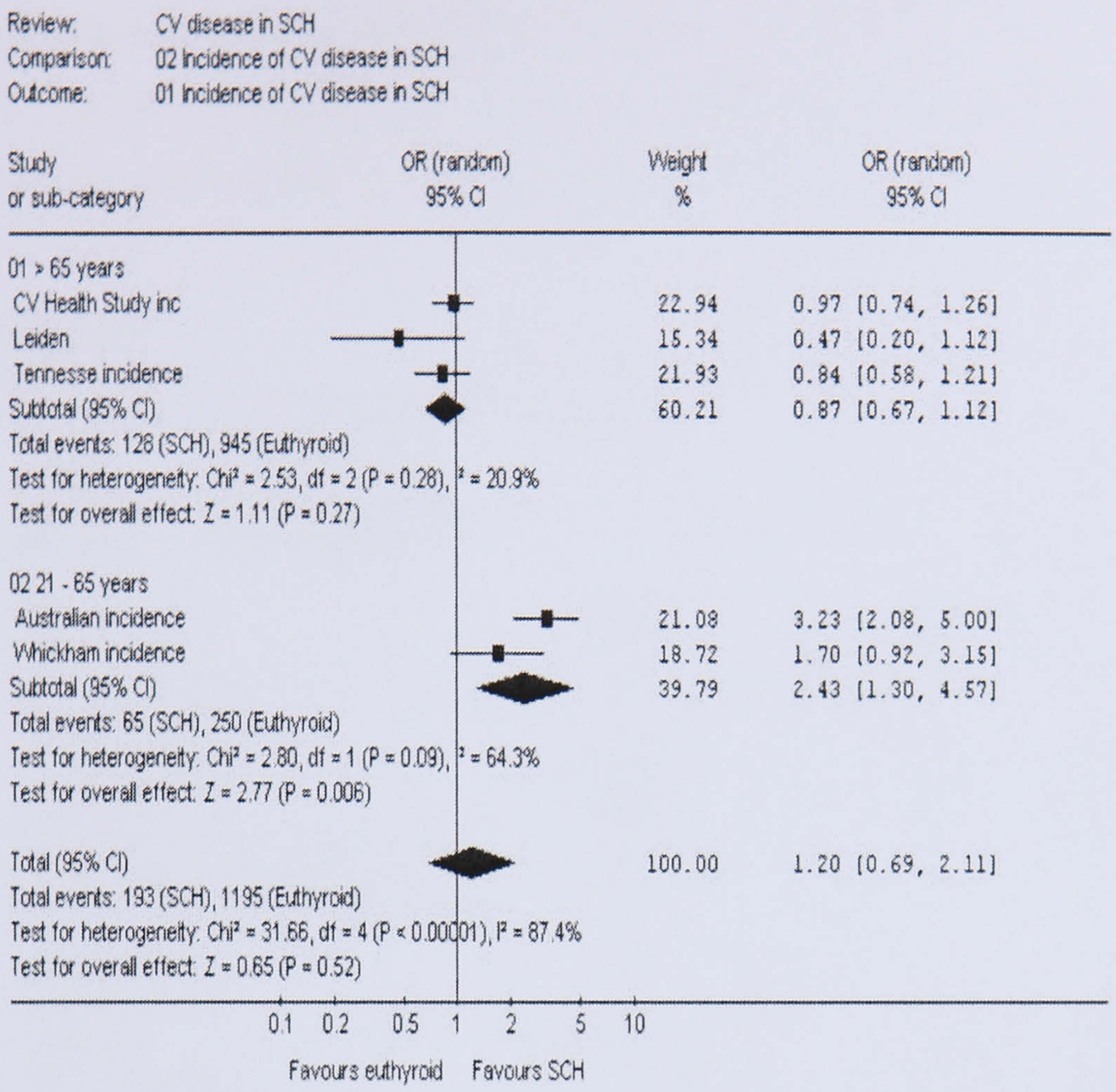
Longitudinal studies of CVD in SCH.

Study	No. of participants Eu	SCH	F/U in years	Age	CVD in EU N (%)	CVD in SCH N (%)	Sig	Remarks
Whickham	126	126	20	20 +	21 (16.7)	32 (25.4)	NS	SCH - +ve antibodies & normal TSH
Birmingham	1026	76	8.2	20 +	180 (17.5)	11 (14.5)	NS	30 pts in SCH on LT4
Australian	1752	101	20	58	229 (13.1)	33 (32.7)	S	Excluded patients on LT4
Tennessee	2392	338	4	70 - 79	298 (12.4)	36 (10.6)	NS	51 pts in SCH on LT4
Leiden	472	30	4	> 85 years	185 (39.2)	7 (23.3)	NS	62% were eu at f/u
CV Health Study	1838	347	12.5	> 65 years	462 (25.1)	85 (24.5)	NS	142 pts in SCH on LT4

Eu – Euthyroid, SCH – Subclinical hypothyroid, CVD – Cardiovascular disease, Ns – Not significant, S – Significant, ATD – autoimmune thyroid disease.

Figure 3.

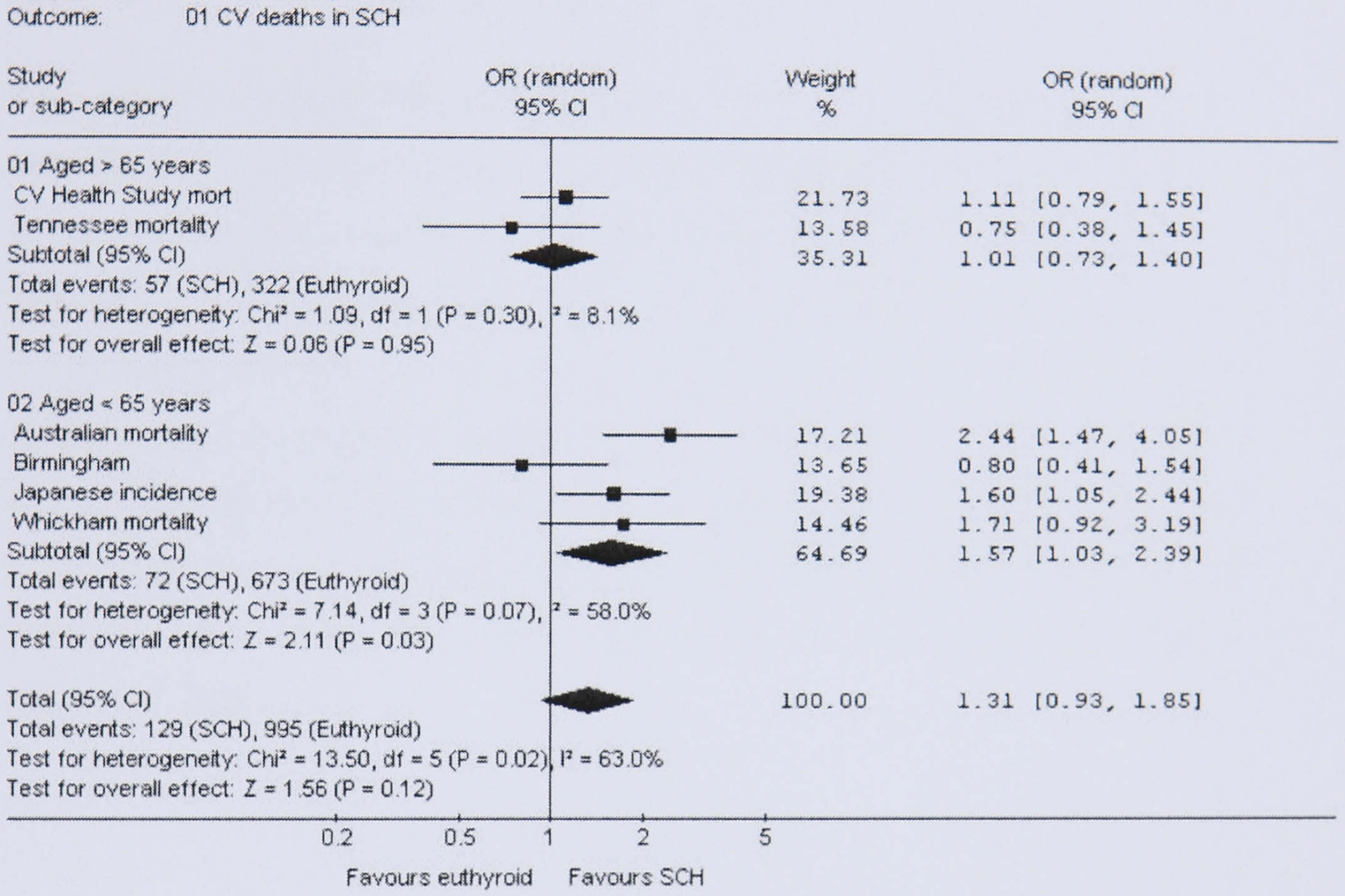
Forrest plot of CV disease in longitudinal studies of SCH



Mortality (due to IHD) (figure 4): Mortality due to IHD is not increased, random OR 1.31 (0.93 – 1.85), p=0.12. In subgroup analyses by age, studies of people with SCH aged less than 65 years showed a significant association, OR 1.57 (1.03 - 2.39), p=0.03. People with SCH aged 65 years or more did not show this association with mortality, OR 1.01 (0.73 – 1.40), p=0.95.

Figure 4.

Forrest plot of CV mortality in SCH.



It is not clear why SCH may have a protective CV influence in older people (> 65 years). Many negative longitudinal studies of CV endpoints have included patients on L-thyroxine therapy, which could have a normalising influence on important parameters like endothelial function and lipids (table 3).

The impact of SCH on the CV system has been evaluated by investigating cardiac function and anatomy, as well as vascular resistance and endothelial function. Diastolic and systolic function, both on effort as well at rest have been shown to be impaired in patients with SCH (Monzani, *et al* 2001) (Vitale, *et al* 2002) (Biondi, *et al* 1999) (Bell, *et al* 1985) (Forfar, *et al* 1985). Another study

has shown impaired cardiopulmonary exercise testing (Kahaly 2000). Another study, using ultrasonic myocardial textural analysis has found an altered myocardial composition which may represent early structural changes (Di Bello, *et al* 2000). Studies have shown that systemic vascular resistance has a significant inverse correlation with FT3 and a direct relationship with TSH in people with SCH (Faber, *et al* 2002). There have been 2 studies that have shown impaired endothelial function in people with SCH, suggesting that nitric oxide availability is reduced in this condition (Lekakis, *et al* 1997) (Taddei, *et al* 2003).

Thyroid autoimmunity and CV disease: The association between thyroid autoimmunity and cardiovascular risk is also similarly controversial. Autopsy studies (Gaspar 1968) and hospital inpatient studies (Bastenie, *et al* 1967) (Bastenie, *et al* 1971) (Tieche, *et al* 1981) suggested a link between asymptomatic autoimmune thyroiditis and coronary artery disease. But these findings were not confirmed by other studies (Heinonen, *et al* 1972) (Tunbridge, *et al* 1977a) (Miura, *et al* 1996) (Wells and Hueston 2005). The Rotterdam study found a significantly higher association of a history of myocardial infarction and atherosclerosis in women who were positive to thyroid peroxidase antibodies (Hak, *et al* 2000).

CV risk factors in SCH

The relationship between SCH and serum lipids is unclear (Tanis, *et al* 1996) (Helfand and Redfern 1998) (Toft 1994). This is partly because of the range of populations studied and different designs addressing the issue. The list of different population based cross-sectional studies is given below (table 4). All the twenty studies are cohort studies apart from the one reported by Parle and colleagues, which is a case-control study where patients with SCH were identified from one primary health care centre in Birmingham and matched to euthyroid controls. Figure 5 shows the difference in meta-analysis between SCH and euthyroid individuals in terms of total cholesterol levels.

Total cholesterol (figure 5): Total cholesterol is higher in patients with SCH as compared to euthyroid individuals, weighted mean difference (95% CI) of 0.2 mmol/L (0.1 – 0.3), $p<0.0001$. The studies were sufficiently heterogeneous ($Chi^2 = 157.5$, df=19, $p<0.00001$), therefore a random effects model was used for analysis.

Other lipid parameters: LDL cholesterol is higher in individuals with SCH than euthyroid people by random weighted difference of 0.20 mmol/L (0.08 – 0.33), $p<0.002$. The studies were positive for heterogeneity ($Chi^2 = 161$, df=11,$p<0.00001$). HDL cholesterol showed no difference at all in SCH versus euthyroid individuals, random weighted difference of 0.0 mmol/L (-0.07 – 0.06), p=0.90. Test for heterogeneity was positive ($Chi^2 = 135.6$, df=11, $p<0.00001$). Triglyceride levels are higher in SCH patients as compared to euthyroid counterparts by 0.28 mmol/L (0.12 – 0.44), $p<0.0008$. The tests for heterogeneity were positive, necessitating the use of a random effects model ($Chi^2 = 76$, df=10, $p<0.00001$).

BMI: There is no difference in the BMI of people with SCH as compared to euthyroid individuals, weighted mean difference of 0.16 kg/m^2 (-0.1 – 0.43), p=0.22. The studies were significantly heterogeneous to warrant analysis by the random effects model, $Chi^2 = 15.27$, df=9, p=0.08.

Blood pressure: There was no difference in systolic blood pressure in either group (SCH versus euthyroid), random weighted mean difference of 1.00 (-1.30 – 3.31), p=0.39. Diastolic blood pressure tended to be higher in SCH group but

failed to reach statistical significance, fixed weighted mean difference of 0.57 (-0.26 – 1.40), p=0.18.

Table 4.

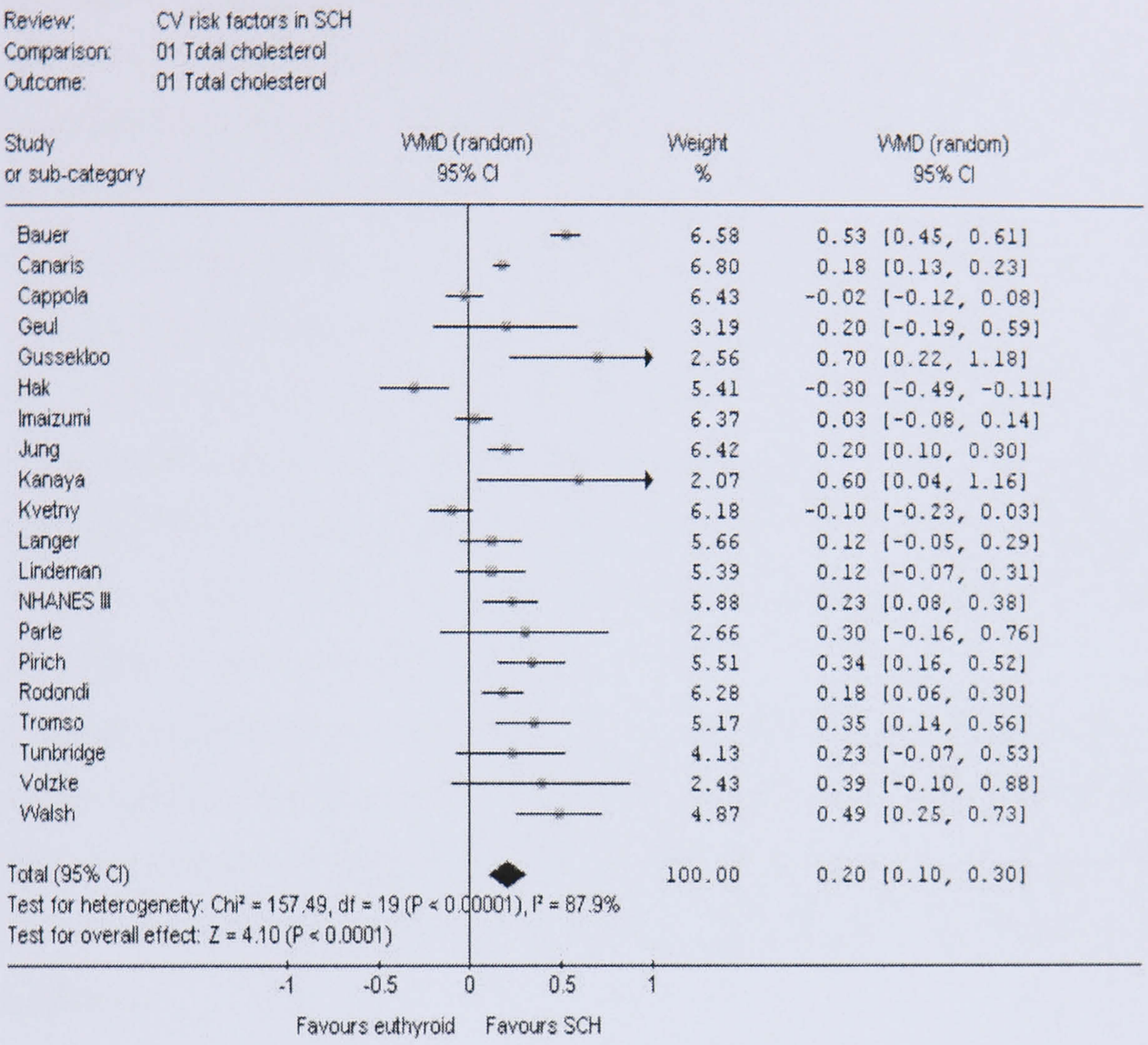
Cross-sectional population based unselected studies of lipids in SCH patients versus euthyroid controls.

Study	Patients		TC		Triglycerides		LDL c		HDL c	
	SCH	Eu	SCH	Eu	SCH	Eu	SCH	Eu	SCH	Eu
Australian	119	1906	6.3	5.8	1.7	1.4	4.1	3.5	1.5	1.5
NHANES III	215	8013	5.8	5.6	2	1.8	3.6	3.5	1.3	1.3
Danish	249	963	5.2	5.3	1.4	1.3	2.8	2.9	1.5	1.5
Slovakian	169	1797	5.7	5.4	2.2	1.8	-		-	
Korean	375	65017	5.2	5.0	-		3.2	3.1	-	
Kanaya(America)	62	1858	5.9	5.3	-		-		-	
New Mexico	112	643	5.4	5.3	-		3.5	3.3	1.3	1.2
Birmingham	57	?57	6.6	6.3	-		4.4	4.2	1.4	1.4
SOF study	19	250	6.7	6.2	2.1	1.9	4.4	4.0	1.2	1.4
Whickham 1977	132	2460	6.2	6.0	1.4	1.3	-		-	
CV Health Study	496	2639	5.5	5.5						
Colarado	2336	22842	5.7	5.5	-		-		-	
German study	29	1745	6.5	6.1	-		4.1	3.9	1.6	1.4
Tennessee	338	2392	5.4	5.2	-		-		-	
Rotterdam	116	867	6.7	7.0	-		-		1.4	1.5
Japanese	257	2293	5.0	5.0	-		-		-	
Geul study	31	1167	7.2	7.4	-		-		-	
Leiden	30	472	6.4	5.7	1.9	1.5	-		-	
Pirich	22	1885	5.9	5.6	2.8	1.4	3.8	3.7	1.2	1.3
Tromso	127	4894	6.6	6.2	1.6	1.5	4.4	4.0	1.6	1.5

SCH – subclinical hypothyroidism, Eu – euthyroid, TC – Total cholesterol, LDL c – Low density lipoprotein cholesterol, HDL c – High density lipoprotein cholesterol. Cholesterol and triglyceride levels are in mmol/L.

Figure 5.

Forrest plot of difference in total cholesterol levels in SCH versus euthyroid people in population-based unselected studies.



There have also been other cross-sectional studies of people with hypercholesterolemia that have reported increased prevalence of SCH compared to normocholesteroleamic control groups (Oettgen, *et al* 1994) (Ball, *et al* 1991) (Pallas, *et al* 1991) (Series, *et al* 1988). Since SCH may be present for many years before overt hypothyroidism develops, it may be worthwhile to know whether there is any potential to improve lipid profiles in this group.

Conclusion: The meta-analysis shows that SCH is associated with increased prevalence and incidence of IHD as well as increased CV mortality in people less than 65 years of age. There is an also increased total cholesterol level of 0.20 mmol/L in people with SCH as compared to euthyroid individuals. It is unclear why there seems to be a difference in outcomes in people with SCH

according to age. It may be that there is a self-selection bias in these trials in that some people with SCH may not reach an age greater than 65 and beyond, and those that do have an inherently strong and healthy constitution that overrides the negative impact of SCH. The other possibility is SCH has a protective influence in elderly people, by some unknown mechanism. There is also a slight but significant increase in BMI in people with SCH although blood pressure is not significantly different. One of the explanations, which is not accounted for by the meta-analysis is that there might be other differences in people with SCH that could explain some of these differences, compared to euthyroid individuals. It is well known that SCH is more prevalent in older individuals and a difference in age could explain all of these differences, especially in differences in lipids and BMI. The mean ages of people with SCH in all the different studies in tables 4-7 were no different compared to the euthyroid group, random weighted mean difference 0.98 years (-0.53 – 2.50), p=0.20.

It therefore seems quite likely that SCH is associated with a significantly worse CV risk factor profile in people with SCH compared to euthyroid individuals. The next chapter examines whether treatment of SCH with L-thyroxine has shown any significant improvement in these risk factors in the published literature.

Effect of L-thyroxine treatment on cardiovascular risk factors.

The potential benefits and risks of treating SCH have been debated for a few decades. The possible advantages are prevention of progression to overt hypothyroidism, reversal of symptoms of hypothyroidism and improvement of QoL, and potentially decrease CV events and mortality.

There has been no randomised controlled trial (RCT) that has investigated the effect of L-thyroxine on CV disease incidence. There have been a number of studies that have looked at various CV risk factors. RCTs of L-thyroxine in SCH are shown below (table 5).

Table 5.

RCTs assessing effect of L-thyroxine therapy on lipid profile in SCH.

Study	TC			LDLc			HDLc			Triglycerides		
	Before	Change	Sig	Before	Change	Sig	Before	Change	Sig	Before	Change	Sig
Cooper	6.5	-0.33	NS	-			-			1.4	-0.12	NS
Nystrom	6.8	-0.2	NS	-			-			-		
Jaeschke	5.7	0.3	NS	3.6	0.18	NS	1.4	0.04	NS	1.5	0.07	NS
Meier	6.3	-0.1	S	4.1	-0.2	S	1.7	0	NS	1.3	0	NS
Caraccio	5.5	-0.5	S	3.6	-0.6	S	1.5	-0.1	NS	1.3	0	NS
Monzani	5.5	-0.8	S	3.5	-0.6	S	1.5	0	NS	1.0	-0.15	NS
Kong	5.5	0.2	NS	3.3	0.1	NS	1.0	0.02	NS	1.8	-0.1	NS
Iqbal	5.9	-0.2	NS	3.7	-0.1	NS	1.5	0	NS	1.5	0	NS

SCH – subclinical hypothyroidism, TC – total cholesterol, LDL c – Low density lipoprotein cholesterol, HDL c – High density lipoprotein cholesterol.

These studies show that the effect of L-thyroxine on serum lipids is variable.

The variability arises due to the differing nature and number of patients recruited, study design and dose of L-thyroxine therapy. Previous meta-analysis has shown that reduction in total cholesterol ranges from 0.2 to 0.4 mmol/L and LDL cholesterol by 0.26 mmol/L (Tanis, *et al* 1996) (Danese, *et al* 2000). There has been no reported beneficial effect on HDL cholesterol or triglycerides.

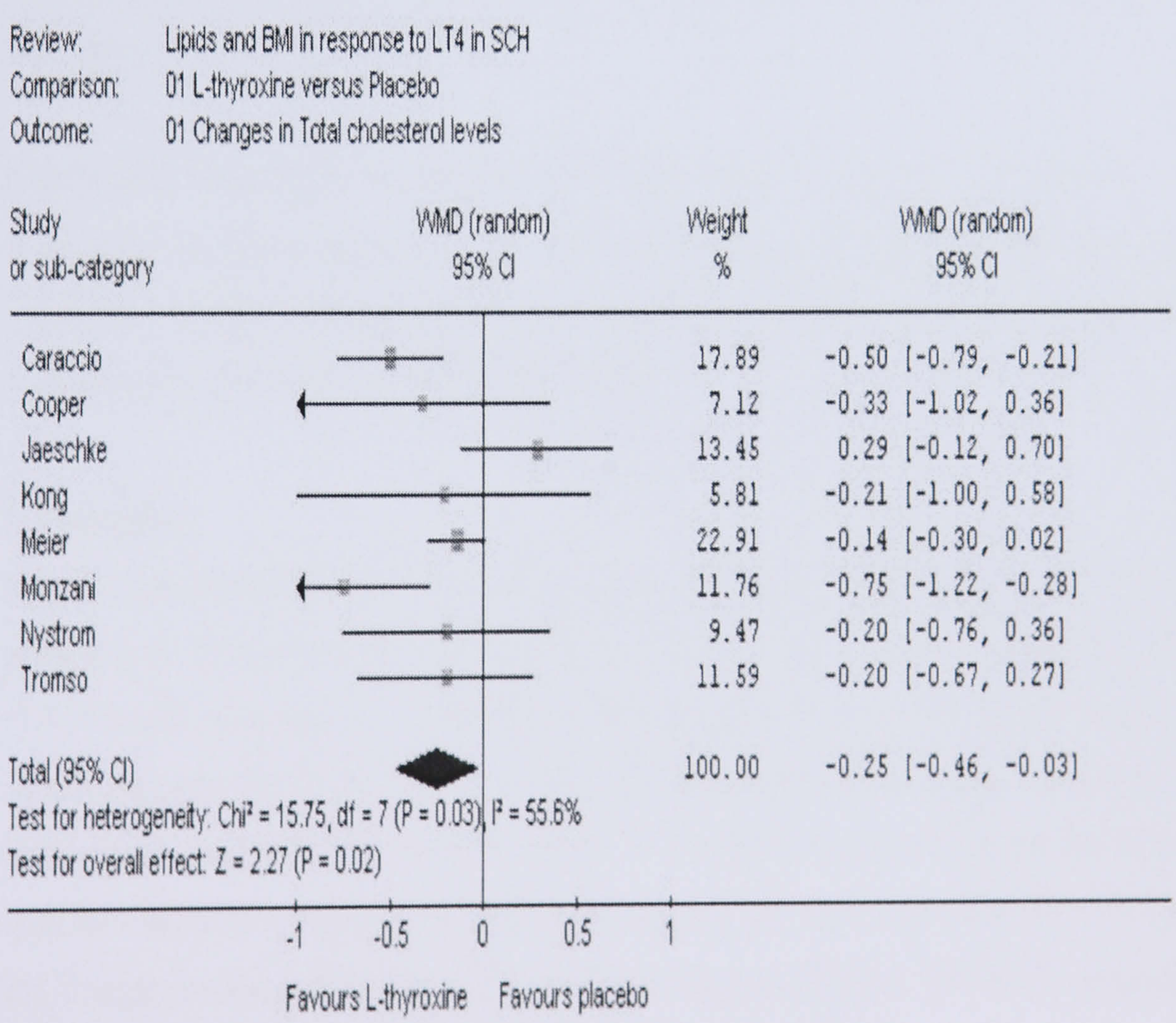
There has also been studies investigating the effect of L-thyroxine on cardiac function that have shown a beneficial effect (Ridgway, *et al* 1981) (Cooper, *et al* 1984) (Nystrom, *et al* 1988) (Bell, *et al* 1985) (Forfar, *et al* 1985) (Foldes, *et al* 1987) (Kahaly 2000) (Arem, *et al* 1996) (Monzani, *et al* 2001) (Biondi, *et al* 1999) (Yazici, *et al* 2004). One study that looked at endothelial dysfunction by intra-arterial infusion of acetyl-choleine found that L-thyroxine had a beneficial effect (Taddei, *et al* 2003).

Results of meta-analysis on CV risk factors in SCH

Effect of L-thyroxine on total cholesterol levels: The meta-analysis done here reveals that the mean reduction in total cholesterol is 0.25 mmol/L (0.03 – 0.46), p=0.02, as seen in figure 6. Tests for heterogeneity show that there was significant diversity in all the trials included, and therefore a random effect model was chosen (Chi^2 15.75, df=7, p=0.03).

Figure 6.

Forrest plot of effect of L-thyroxine treatment on total cholesterol levels in randomised controlled trials of SCH.



This is very similar to the results of the previous meta-analyses, although the previous studies had included many before-after studies and only three RCTs and therefore had potential for bias. Furthermore, there have been five more RCTs that have published their results since the last meta-analysis.

Effect of L-thyroxine on other lipid parameters: L-thyroxine reduces LDLc by 0.24 mmol/L (0.02 – 0.46), p=0.04. This was analysed by a fixed effect model since test for heterogeneity was negative (Chi^2 =6.76, df=5, p=0.24). There was no significant effect of L-thyroxine on HDLc or serum triglyceride levels noted in the meta-analysis of the RCTs that have assessed them. Serum apolipoprotein B was measured in only two trials and showed a significant reduction in both, whereas there was no effect on apolipoprotein A1.

Effect of L-thyroxine on BMI: L-thyroxine reduces BMI by 0.38 kg/m^2 (0.15 – 0.60), p=0.001. Tests for heterogeneity were negative (Chi^2 =8.34, df=6, p=0.21), therefore a fixed effects model was used. This has not been shown in any of the individual trials that have assessed this parameter, and confirms that none of them were designed to detect body weight response to L-thyroxine therapy.

Effect of L-thyroxine on blood pressure: There have been eight RCTs assessing the effects of L-thyroxine on various parameters but only one has reported changes in blood pressure, and that showed no significant difference as compared to placebo (Monzani, *et al* 2001).

Conclusion

It can be seen that the CV risk factor profile in SCH is an unclear area. This absence of clarity is even more present in people with milder forms of SCH (TSH levels between 4 – 10 mIU/L). The reason for this uncertainty is lack of well-designed RCTs that have sample sizes calculated to detect a significant difference. Furthermore, there is no RCT that has assessed endothelial function and its response to treatment with L-thyroxine in patients with SCH. Therefore a RCT was conducted to assess CV risk factors, endothelial function and patient-reported outcomes in a large group of patients with SCH.

Aims of the study

It can be seen that the area of SCH has remained controversial and unclear despite much research having been conducted. Although there is some evidence, by no means unchallenged, that there is increased risk of CV disease in people with SCH, it is unclear whether traditional CV risk factors account for this increased risk or whether it could be attributed to by other "newer" risk factors like endothelial dysfunction and vascular inflammation. There has been no RCT measuring endothelial function, which is the earliest marker of atherosclerosis in SCH patients. One of the major reasons for this lack of clarity has been the absence of proper design in terms of power calculations in all the previous studies.

The area of QoL has remained untested in people with hypothyroidism and there has been no systematically designed and validated instrument to measure this important aspect of patient reported outcome. Also, other instrument to measure satisfaction with treatment and symptom bother scores have also not been designed or validated in this area.

This study was therefore designed with the following aims in mind:

1.To perform a double-blind placebo-controlled trial of L-thyroxine treatment in patients with SCH. The aim was to recruit a large sample, reinforced by power calculations, to be able to detect very subtle improvement as well as side-effects, due to the mild area of the disease spectrum being studied.

2.To recruit at least 75% of patients with TSH levels between 4.0 – 10.0 mIU/L, since this is the degree of SCH with the greatest degree of confusion.

3.To set up and validate the technique of non-invasively measuring endothelial function via the technique of FMD and to assess it in people with SCH, before and after treatment with L-thyroxine in a double-blind controlled manner.

4.To design and validate instruments to measure disease-specific QoL, treatment satisfaction and frequency of symptoms and their bother-scores and to utilise these instruments in assessing these parameters in people with SCH.

METHODS (A)

Hypothesis and endpoints

Hypothesis: Treatment of SCH with L-thyroxine improves CV risk factors and patient-reported outcomes.

Primary endpoints:

1. Improvement in brachial artery flow mediated dilatation (FMD) as a marker of vascular endothelial function

2. Reduction in total cholesterol (TC) levels, after 12 weeks of L-thyroxine treatment.

The 2 primary endpoints were chosen because:

Reduction in total cholesterol, especially LDL cholesterol is probably the most widely used and recognised CV risk factor ((Expert Panel on Detection 2001). There is some controversy whether L-thyroxine therapy reduces TC levels and if so, by how much ((Cooper 1998).

Endothelial function is a novel and increasingly recognised method of assessing CV risk status and an excellent barometer of vascular health ((Vita and Keaney 2002); and FMD is the most reproducible way of measuring this. It also has the advantage of being most influenced by nitric oxide activity. There has been no RCT assessing the effect of L-thyroxine on endothelial function.

Secondary endpoints: Changes in:

Weight and its distribution (assessed by weight, waist-hip ratio and waist circumference).

Triglyceride (TG).

HDL cholesterol (HDLc).

LDL cholesterol (LDLc).

Apolipoprotein A1 (apoA1).

Apolipoprotein B (apoB).

Patient-reported outcomes, (assessed by questionnaire):

Perceived health status.

Hypothyroidism-specific quality of life (QoL).

Hypothyroid symptoms.

Hypothyroid-specific satisfaction with treatment.

Vascular studies: validation and measurement

Technique of FMD.

The capacity of blood vessels to respond to physical and chemical stimuli in the lumen confers the ability to self-regulate tone and to adjust blood flow and distribution in response to changes in the local environment. The phenomenon of blood vessels dilating in response to an increase in flow (shear stress) is called flow-mediated dilatation or FMD. A principal mediator of FMD is endothelium derived Nitric Oxide (NO).

Numerous factors affect flow-mediated vascular reactivity, including temperature, food, drugs and sympathetic stimuli, among others (Corretti, *et al* 2002). Therefore subjects were prepared as follows:

1. Fast for at least 12 hours before.
2. Studied in a quiet, temperature controlled room.
3. All vasoactive medications withheld for at least 4 half-lives, if possible.
4. No exercise, caffeine, high fat foods, vitamin C or tobacco for at least 4-6 hours before.
5. The phase of the subject's menstrual cycle should be taken into account. All pre-menopausal women were scanned in follicular phase.

Brachial arteries were imaged with a standard HDI 5000 ultrasound system (ATL, Bothell, Washington, USA) with a 5–12 MHz linear transducer (figure 7A). The ultrasound system was connected to a personal computer equipped with a frame grabber and artificial neural network wall detection software [vessel image analysis (VIA)]. The VIA software automatically detects and tracks the anterior and posterior walls within a user defined region of interest (figure 7B). The vessel diameter is determined by averaging a large number of local vessel diameters. The software can also accommodate angulation of the artery (up to 20°) relative to the perpendicular. The B mode images are processed at 25 frames/s and the vessel diameter, including diameter changes over the cardiac cycle, is displayed in real time (figure 8). This allows ultrasound-imaging parameters to be optimised at the start of the scan and the transducer position to be adjusted immediately for optimum tracking

performance during the entire test. The brachial artery was scanned longitudinally 2–10 cm above the elbow until the clearest possible image of the anterior and posterior wall media was obtained. Depth and gain settings were kept constant during the rest of the study. A stereotactic clamp was used to hold the transducer and a screw gauge was used to make small compensatory movements of the transducer to accommodate subject movement during the test. The distance of the transducer from the antecubital fossa was noted and a two dimensional image of the brachial artery was saved on the computer's hard drive for reference in repeat studies.

Brachial artery FMD was determined according to a conventional protocol (Corretti, *et al* 2002). The right brachial artery was scanned continually throughout the test. Pulsed Doppler was used to assess arterial flow at rest and immediately after tourniquet deflation. Firstly, a baseline scan was performed for 2 minutes. Then a tourniquet located at the right proximal forearm was inflated to a pressure of 250 mm Hg for 5 minutes. Brachial artery dilatation following reactive hyperaemia was recorded for 5 minutes after tourniquet release. After at least ten minutes, to allow for baseline conditions to be re-established, sublingual glyceryl trinitrate (400 μg) was then administered and imaging performed for another 5 minutes to determine endothelium independent vasodilatation. At the end of the study a graph of diameter against time was immediately displayed. The FMD (defined by the percentage increase in mean diameter over a 10 second period, 55 seconds after tourniquet deflation) was automatically calculated by VIA from diastolic vessel diameters (figure 9). The endothelium independent dilatation was calculated similarly to the percentage increase in mean diameter 5 minutes after glyceryl trinitrate administration.

Figure 7.

(A) The brachial artery is imaged such that the media–lumen interface is clearly seen.

(B) The arterial media–lumen interface is automatically located and tracked within the region of interest.

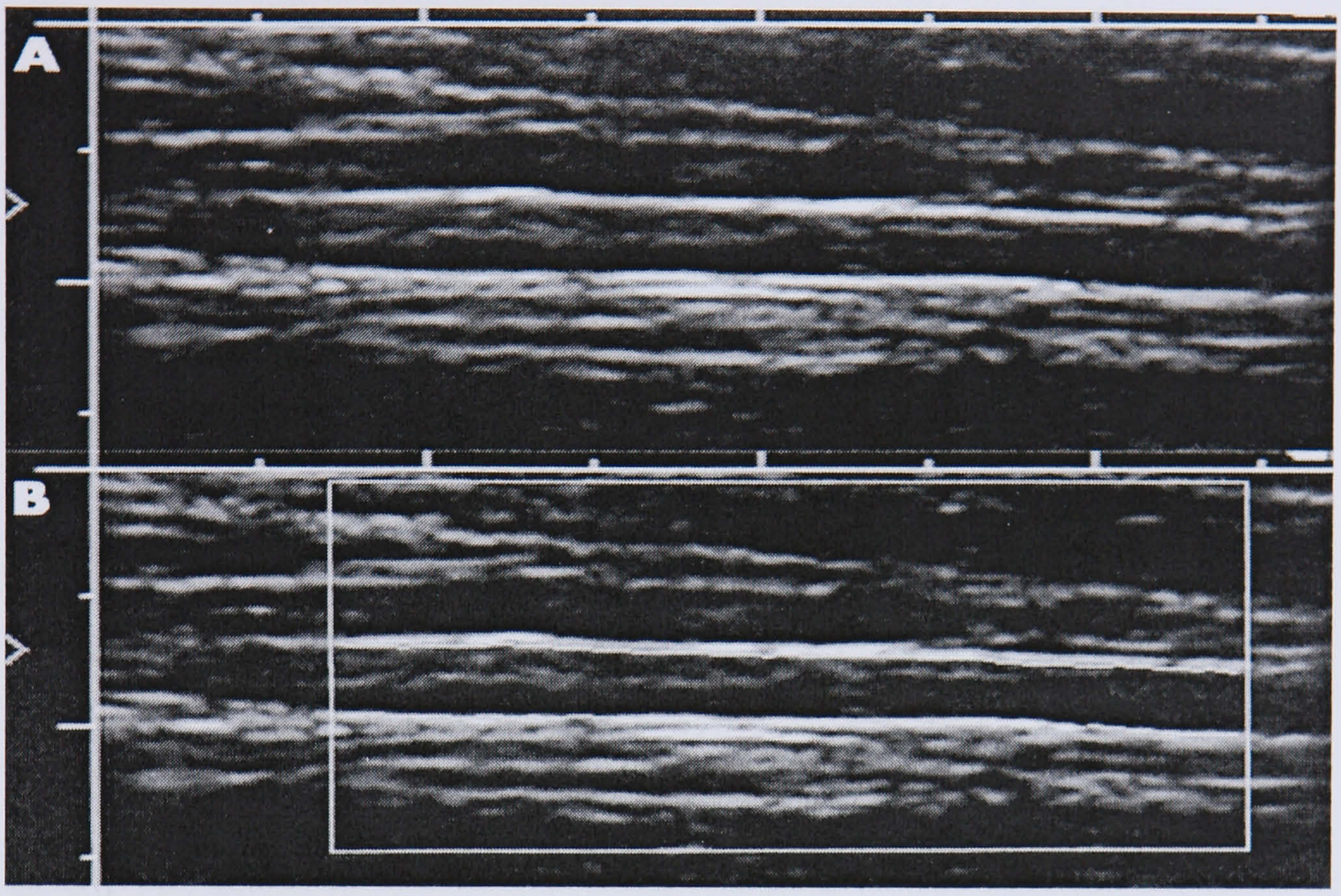


Figure 8.

The mean vessel diameter within the region of interest displayed in real time at 25 frames/s. This allows the operator to optimise image quality continually.

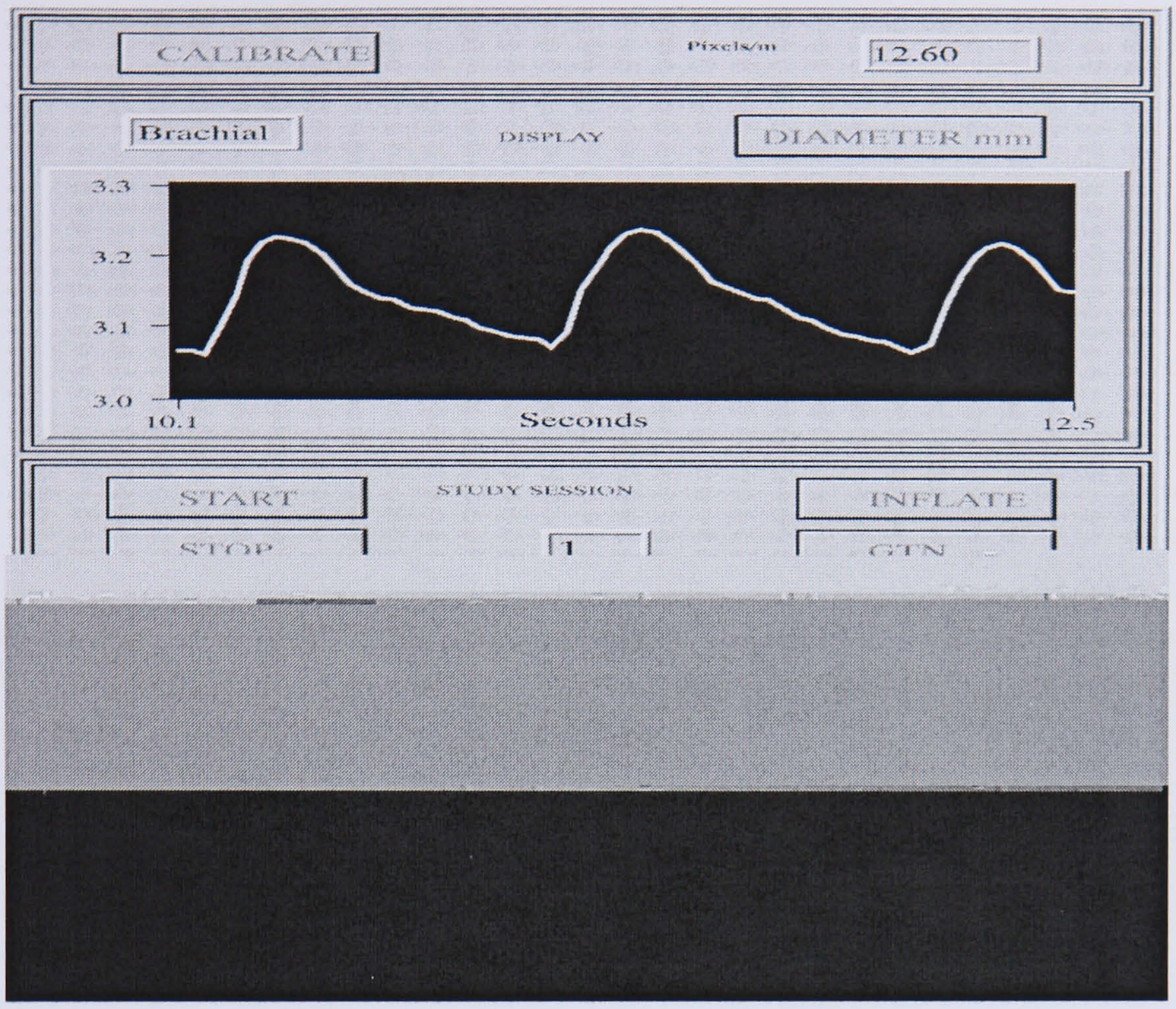
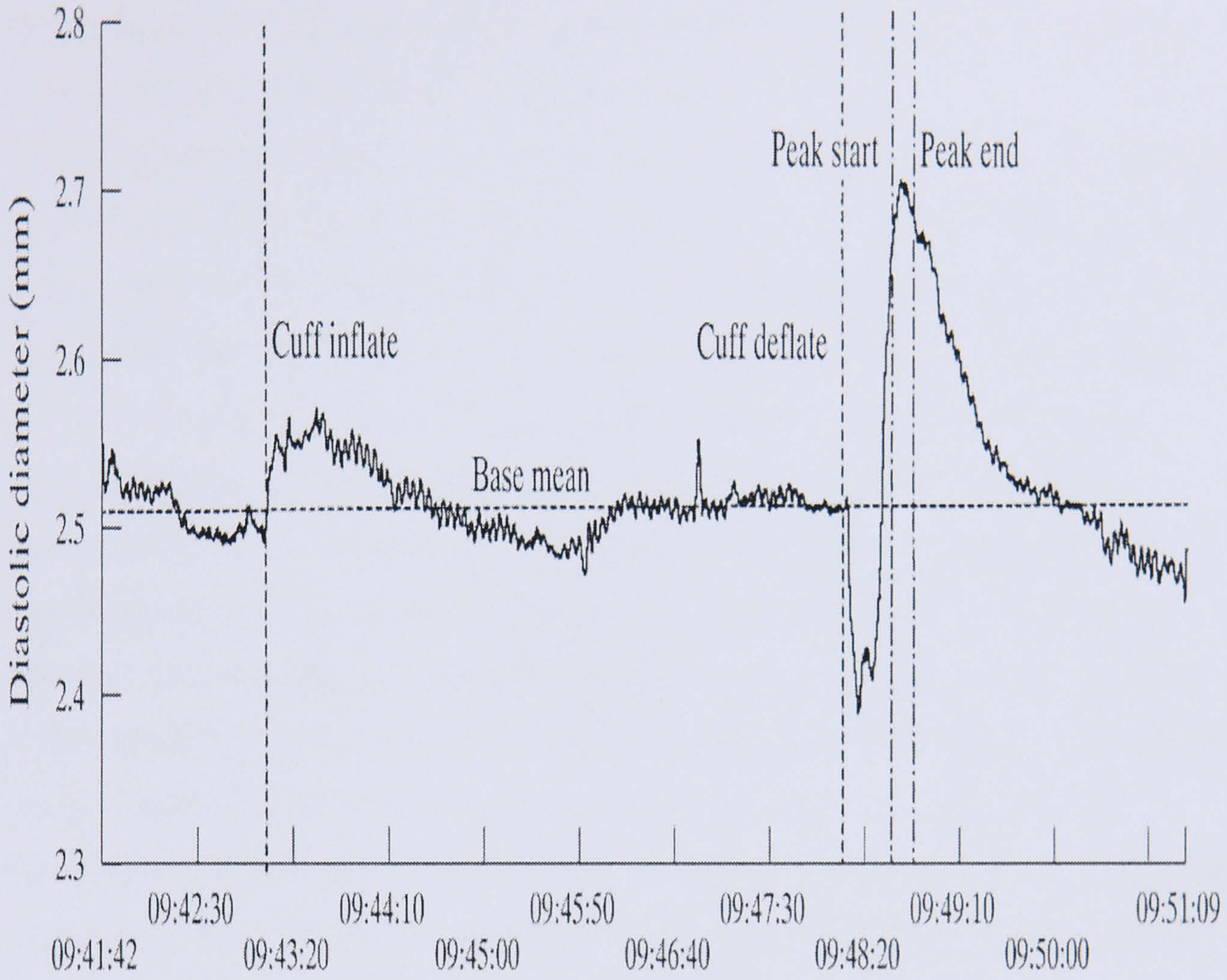


Figure 9.

Graph of brachial artery diameter versus time in a normal subject. Flow mediated dilatation for this subject was 7.3% when comparing mean diastolic diameter before cuff inflation and between the "peak start" and "peak end" cursors.



VIA Software:

Each conventional FMD study (with manual diameter calculation) typically lasts for 10 to 15 minutes and images are usually updated at diastole and recorded. Artery diameter is calculated by detecting the vessel walls within a user-defined image region, using an automated computer algorithm. However, retrospective analysis can give rise to several problems. At commencement of the study, adjusting the scanner controls to suit the visual preferences of the operator optimises the images. This may adversely influence performance of the wall detection algorithm, but the effect will not be apparent until the study is completed. Additional operator effort and time is required for analysis. VCR recording involves some loss of image quality during record and playback, and

computer storage may require a low acquisition rate or short acquisition period to avoid unwieldy archives. For example, storing a reduced image section of 256 × 256 pixels at 25 images s−1 requires almost 1 Gbyte of disk space for a 10-min study. It is not possible to recover the artery diameter changes as a function of the cardiac cycle if the image acquisition rate is low. Recovery of these changes allows diastole to be established without the need for image synchronisation and is potentially useful in elasticity studies. These problems can be resolved if the data are analysed online.

Several groups have reported retrospective methods of automatically identifying vessel walls. However, the reported techniques do not lend themselves easily to online analysis. For example, dynamic programming (Wendelhag, *et al* 1997) requires the images to be intensity-normalised, based on the average intensity over all images, and smoothed horizontally to remove vessel wall dropouts. Smoothing may compromise accuracy due to blurring on all but straight horizontal vessel walls, and some rotational normalisation is, therefore, desirable. To recover diameter changes over the cardiac cycle, it is necessary to measure vessel diameter at twice the Nyquist frequency of the cardiac cycle to avoid aliasing. Output from most scanners is limited to 25 images s−1, giving 40 ms per image for all processing. The graph-search dynamic programming method of Liang and colleagues (Liang, *et al* 2000) is computationally intensive, requiring 1 s per image for processing. Some current retrospective systems also require significant manual intervention in setting up and/or in monitoring performance.

Therefore a PC-based system that automatically locates the correct vessel walls in a user-defined region-of-interest (ROI) and measures vessel diameter online throughout a FMD study was used (Newey and Nassiri 2002). The system was designed to minimise operator workload; the only user input normally required is to drag an orthogonal ROI over the required vessel section and to press a start button. This technique has several advantages over established practice. FMD results are available immediately. Data for the complete study are available, rather than just a few salient events, and changes in vessel diameter over the cardiac cycle are recovered. Vessel wall tracking quality can be optimised by adjustment of the scanner controls before the study proper. This largely normalises the intensity range of the images to the range presented to the neural

networks in the training regimen, thereby optimising the images to suit the networks. With retrospective analysis, however, images are subjectively optimised for visual, rather than wall detection properties and the detection algorithm must, therefore, handle a wider range of image quality. Online analysis provides continuous graphical presentations of vessel diameter, detected walls and wall probability levels as tracking quality indicators. These features, some of which are only available retrospectively with off-line techniques, make minor changes in image and tracking quality and vessel alignment readily apparent at a time when they can be rectified. The method also avoids the image quality loss associated with VCR recording, and no processing of the image is necessary. Retrospective systems, however, often require processing steps, such as intensity or rotational normalisation or smoothing which, although improving the tracking qualities may cause some spatial degradation of the image. There is no unwieldy image archive; file size for a complete study is typically approximately 0.3 Mb and the study is completed much faster than retrospective methods, contributing to lower study costs. Although conferring more robust tracking, these points correspond to the media interface. The intima interface was ignored and the technique, therefore, overestimates vessel diameter because the intima-media distance represents the wall thickness. However, these error sources should not be significant in FMD studies, where relative rather than absolute change in diameter is of importance. As with all FMD studies, good image quality is mandatory for both accurate measurements and optimum wall tracking. The technique can also be used to detect non-horizontal vessel interfaces by searching the ROI sequentially with network input line sections at more than one orientation (i.e., vertical and horizontal) and combining the outputs to obtain the probability matrix.

The simulated cardiac sequence required 7 to 8 min of data to recover diameter changes over the cardiac cycle with reasonable quality. In clinical practice, however, the cardiac cycle is generally recovered with good quality from 1 to 3 min of data. Recovery of diameter changes over the cardiac cycle may be useful in other studies, such as investigation of the elastic properties of the vessel wall, where wall displacement combined with blood pressure can be used to calculate elasticity indices.

Validation of FMD technique

The ultrasonographic assessment of brachial artery FMD is technically challenging and has a significant learning curve. FMD guidelines suggest that initial training is most efficiently gained by visiting experienced laboratories and hands-on training by an experienced individual (Corretti, *et al* 2002). Both these criteria were met by obtaining the initial training from Coronary Artery Disease Research Unit, St George's Hospital Medical School, London with Professor Juan Kaski (learning and orientation on 6 healthy volunteers) and by further training with Dr Crispian Oates, Head of Vascular Ultrasound, Newcastle General Hospital, Newcastle upon Tyne (further practice and training on 24 healthy volunteers at least on 100 occasions). After 6 months of learning and practicing, normal healthy volunteers were scanned on 2 separate days under similar conditions to assess intra-observer variability.

The baseline demographic, clinical examination and biochemical parameters are outlined in table 6. The characteristics of the vascular ultrasound results are shown in table 7.

Table 6.

Clinical examination and biochemical characteristics of healthy volunteers for FMD studies (n=29).

Characteristics	Results Mean (SD)
Age (years)	34.9 (7.2)
Male/Female	13/16
Systolic/diastolic blood pressure (mm Hg)	123 (6.4) / 75 (5.7)
BMI (kg/m^2)	23.1 (2.3)
Waist circumference (cm)	79.2 (8.9)
Waist hip ratio	0.8 (0.1)
Total cholesterol (mmol/L)	4.7 (0.7)
HDL cholesterol (mmol/L)	1.5 (0.5)
LDL cholesterol (mmol/L)	2.6 (0.5)
Triglycerides (mmol/L)	1.1 (0.4)
Glucose (mmol/L)	4.9 (0.4)
TSH (mIU/L)	1.8 (0.9)

Table 7.

Brachial artery FMD characteristics on healthy volunteers on 2 separate occasions (n=29).

Characteristic	Value (95%CI)	Pearson's correlation coefficient
Baseline diameter (mm)		
1st measurement	3.7 (3.4 – 3.9)	0.98 (p<0.001)
2nd measurement	3.6 (3.3 – 3.9)	
FMD (%)		
1st measurement	6.4 (5.1 – 7.6)	0.71 (p<0.01)
2nd measurement	6.4 (5.2 – 7.6)	
Absolute change in diameter (mm)		
1st measurement	0.2 (0.2 – 0.3)	0.73 (p<0.01)
2nd measurement	0.2 (0.2 – 0.3)	

The mean of the differences (SD) in FMD for the healthy volunteers on 2 occasions was 0.1% (2.1), suggesting that the mean difference in result for the group as a whole was minimal but there was a higher intra-individual variation (Sidhu, *et al* 2002).

Carotid intima-media thickness

Common carotid artery (CCA) imaging was performed with an ATL HDI 5000 ultrasound system by use of a 5- to 12-MHz linear transducer. All examinations were performed on images frozen on the ultrasound screen. Settings for depth-gain compensation, pre-processing, persistence, and post-processing were held constant. Images were analyzed with the researcher and patient in a state of being blinded to the treatment group. Mean CCA intima-media thickness (IMT) was measured in the far wall over the distal 2-cm segment of the right common carotid artery, defined by the carotid bulb. Far wall measurements were chosen in accordance with methodological recommendations because the far wall is more easily and consistently visualized than the near wall ((Kanters, *et al* 1997). Mean IMT was measured from the lumen-intima interface to the media-adventitia interface, taking care to avoid areas of arterial plaque formation. Single IMT values were obtained from measurements on neighbouring lines perpendicular to the vertical line and then averaged and expressed as the mean IMT for that patient. The outcome measure was the difference in mean CCA IMT at the end of the study as compared to baseline.

Reproducibility: Eight subjects had scans performed by the same researcher separated by 1 to 2 weeks. The mean of the absolute difference (SD) between the paired mean CCA IMT measurements was 0.05 (0.03) mm, and Pearson's correlation coefficient was 0.81, which compares satisfactorily with that reported in previous studies.

Carotid distensibility and stiffness.

Distensibility is the ability of the artery to expand as a response to pulse pressure, that is, the change in arterial diameter during the cardiac cycle. Distensibility is the inverse phenomenon of stiffness, that is, if distensibility is decreased then that reflects increased arterial stiffness. Distensibility decreases with age. Cross-sectional studies showed associations between decreased distensibility and cardiovascular risk factors, i.e., hypertension, diabetes mellitus, hypercholesterolemia, and myocardial infarction ((Arnett, *et al* 1994) (Safar, *et al* 1987) (Salomaa, *et al* 1995a) (Riley, *et al* 1986).

All measurements were performed with patient lying supine on the right common carotid artery, 2 cm proximal to the carotid bulb. The ultrasound scanner was connected to a vessel wall tracking system for elasticity measurements (Newey and Nassiri 2002). The same researcher who was blinded to the patients treatment group performed all scans. Blood pressure was recorded at baseline prior to each study using an automated blood pressure recorder. Arterial distensibility is calculated by the formula: $(dA/A_d)/dP$

Where dA = systolic – diastolic arterial cross-sectional area change.

A_d = diastolic arterial cross-sectional area.

dP = systolic – diastolic pressure change.

The CCA was scanned continuously for at least two minutes and measurements noted.

Reproducibility: Scans were performed on 8 healthy volunteers 1 – 2 weeks apart, showed that the mean of the paired differences (SD) of distensibility was 0.5 (0.9) $mmHg^{-1} \times 10^{-3}$.

Biochemical investigations

Blood samples were drawn in the morning after at least 12 hours of fasting and immediately centrifuged. Samples were then stored at -40°C until analysis. Samples belonging to the same participants were analysed as one batch, in duplicate. Serum free thyroxine (FT4) free tri-iodothyronine (FT3) and TSH concentrations were measured by an electro-chemiluminescence immunoassay (Roche Diagnostics, UK). Thyroid autoimmunity was assessed by the quantitative measurement of anti-thyroid peroxidase autoantibodies (anti-TPO) by ELISA (Orgentec Diagnostika GmbH, Mainz, Germany). Serum TC, HDLc and TG were assayed using automated enzymatic methods (Roche Diagnostics, UK). LDLc was calculated as per Friedewald's formula. Serum apoA1, apoB and hsCRP were determined by immunoturbidimetric methods (Roche Diagnostics, UK). Serum sICAM-1, e-selectin (R&D Systems, UK), and PAI-1and tPA (Diagnostica Stago, France) were measured by sandwich immunoassay technique. Normal ranges in our laboratory are as follows: FT4 = 9 – 25 pmol/L, FT3 = 5 – 8.5 pmol/L, TSH = 0.4 – 4 mIU/L, and anti-TPO antibody less than 50 IU/mL. Co-efficients of variation were below 5% for all tests except FT3, which was 5.5%.

Study design

Randomised controlled trials are generally and rightfully regarded as the best forms of evidence to evaluate the effectiveness of any intervention. Since clinicians, decision makers, scientists and increasingly patients turn to medical literature, it is imperative that all trials are conducted and reported in a rigorous and transparent manner (Moher, *et al* 2001a) (Moher, *et al* 2001b).

Design

Crossover trial: In an AB/BA crossover trial, patients are randomly assigned to receive either treatment A in the first period followed by treatment B in the second period or treatment B in the first period followed by treatment A in the second period. The crossover trial allows for a within-patient comparison between treatments and comparison between treatments, and can provide unbiased estimates for the differences between treatments in the two periods. The advantages of using a crossover design are:

1. Removes inter-patient variability since each patient act as their own control.
2. Smaller sample sizes are required to achieve a specific power.
3. More statistical power due to paired comparisons.
4. Sometimes, patients might agree to take part if they are assured that they would get to experience one of the drugs at least once.

The disadvantages and pitfalls that can occur and need to be kept in mind are:

1. Period effect: Differences in the effectiveness of interventions that occurred between the treatment periods due to the passage of time are called period effects. This can occur when a patients' condition changes between the two observations. Example: drug tolerance or resistance. Period effects increase within-patient variability and therefore reduce the overall power of the study. Period effects that affect both treatment conditions equally have a neutral effect on results.
2. Sequence effect: Difference in effectiveness that results due to the order in which the drugs were administered.

3. Carryover effect: This is the effect of the first treatment period that persists into the second period. Unlike sequence effects, carryover effects only affect the response in the second period. The effects of carryover can be reduced by a washout period in-between the two treatment periods.
4. Double the time: Since each patient takes part in both interventions, the time period required to be available for the study is twice as long. This may lead to higher dropout rates.

Sample size calculation

Sample size calculation: The sample size needed to show an intended treatment benefit was based on the primary outcomes (FMD and TC), α =0.05 and β=0.20. For FMD: to detect a minimal improvement of 1%, standard deviation of 2.1, the required sample size was 81. The obtained sample size of 100 would give the study a power of 0.99 to detect the above difference. For TC: to detect a difference of 0.2 mmol/L, standard deviation of 0.5, sample size was calculated as 101 patients.

Patient recruitment

Patient recruitment to a clinical trial is recognised as a very difficult task (Lovato, *et al* 1997). Patients (n= 864), from General Practices in Gateshead, were identified from the laboratory database after they had a raised index TSH in the presence of normal FT4 level, in the period starting January 2003 and up to March 2003. General Practitioners had been informed via a letter, outlining the aims, objectives and details of the study, and their consent obtained to recruit their patients for this study. Inclusion and exclusion criteria were applied (those that could be determined from laboratory data like age, L-thyroxine treatment, diabetes mellitus, ischeamic heart disease, previous treatment for thyroid disease, concomitant medications, renal impairment, psychiatric disease and current pregnancy) and potential participants short-listed (n=322). In this group, thyroid function tests (TFTs) had been undertaken due to symptoms that could be attributed to hypothyroidism (n= 179), coincidental finding (n= 103), or due to family history of thyroid disease (n= 24). No reason for undertaking TFTs could be ascertained in 16 people. Those people who fitted the criteria, or the

criteria were not clear or who had had only one blood test for thyroid function tests (TFTs) at least 3 months prior were invited to come to the Hospital Diabetes Research Centre for a screening visit in a fasting state. This was done either via telephone or by sending a letter in the post. Of the 322 people so identified, 196 people were excluded after telephonic contact:

1. Already on L-thyroxine (n=75).
2. Previous thyroid disease or its treatment (n=59).
3. Refused (n=36).
4. Could not be contacted (n=26).

Of the 126 people who attended for a screening visit, the following were excluded (n=26):

1. Normal TFTs (n=23).
2. Abnormal electrocardiogram (n=1).
3. Raised fasting plasma glucose (n=2)

Inclusion criteria:

1. Persons aged between 18-80 years.
2. Stable SCH (TSH > 4 mIU/L and FT4 levels in the normal reference range, on at least two occasions, at least three months apart)

Exclusion criteria:

1. Previous thyroid disease and its treatment.
2. Medications that could cause thyroid hormone dysfunction (interferon, lithium, amiodarone, corticosteroids and dopamine.
3. Diabetes mellitus (by history and a fasting plasma glucose test).
4. Renal impairment (serum creatinine > 120 umol/L).
5. Vascular disease (history and ECG) for ischeamic heart disease, strokes and peripheral vascular disease.
6. Psychiatric conditions or their treatment (by history).
7. Current or previous pregnancy in the last 2 years.

Therefore, the sample size of 100 participants was obtained. In all participants, TFTs were performed at least 3 months apart (median 5 months, range 3 to 41 months).

Ethical approval and registration

The local (Gateshead) research ethics committee and the Gateshead NHS Trust Research validation committee approved the study. In keeping with recent guidelines from the International Committee of Medical Journal Editors (De Angelis, *et al* 2005), this trial was registered on a database, the ISRCTN with number ISRCTN35570362.

Intervention

One hundred mcg of L-thyroxine or matching placebo capsules (Royal Hallamshire Hospital Pharmacy, Sheffield, UK) were obtained. Approval from the Medicinal and Healthcare Regulatory Authority (MHRA) was obtained prior to manufacture of the capsules. The participants were asked to swallow the treatment capsules whole with water early in the morning, half an hour before food. Compliance was assessed at the next visit by counting the number of capsules left over in the container, and was judged to be good (median 94%, range 83-100%).

Previously it has been suggested that the dose of L-thyroxine required to treat SCH is between 50 – 75 mcg per day(Cooper 2001). This is based on three studies that used mean doses ranging from 68 to 150 mcg per day and the treated group's TSH values ranged from 1.9 to 4.6 mIU/L(Cooper, *et al* 1984, Jaeschke, *et al* 1996, Nystrom, *et al* 1988). However, another study that used 100 mcg per day in biochemically-euthyroid patients with hypothyroid symptoms found that mean TSH levels did not drop below the reference range(Pollock, *et al* 2001). Thus, the dose of 100 mcg per day was deemed adequate to treat patients in our study. Also, the aim was to increase the free thyroid hormone levels significantly and a treatment dose of 1.6 mcg/kg/day would be required – for persons weighing between 60 and 70 kg, a dose of 96 to 112 mcg/day would be sufficient. Therefore, 100 mcg capsules were deemed adequate for the trial. It was expected that there would be certain patients in whom the dose would be excessive or inadequate, but the large study numbers would compensate for this eventuality.

The treatment period of twelve weeks duration was deemed adequate for the present study since it takes about 4-6 weeks of full replacement therapy with L-thyroxine to correct the dyslipidaemia of overt hypothyroidism(Kuusi, *et al*

1988). However, it may be insufficient time for some benefits (such as perceptible reduction in some symptoms and psychological factors) to become apparent to patients.

Randomisation

Sequence generation: Independent external pharmacists (Royal Hallamshire Hospital Pharmacy, Sheffield, UK) drew up a computer generated randomisation list and the treatment was then distributed in sequentially numbered identical containers. The investigators having no knowledge of treatment allocated the next available number on entry to the trial.

Allocation concealment: A generated allocation schedule should ideally be implemented by using allocation concealment, a process that prevents foreknowledge of treatment assignment and prevents enrollers of study participants from being influenced by this knowledge. This is not to be confused with blinding, a process that tries to prevent performance and ascertainment bias. Since a third party assignment is desirable, the pharmacy department of Royal Hallamshire Hospital, Sheffield, UK, the producers of the interventional capsules generated, assigned and distributed the sequenced containers.

Implementation: Failure to separate the creation of allocation sequence from study group assignment can introduce bias in a clinical trial. Therefore, these processes were independent of each other and the two did not have any knowledge of the other.

Blinding

Blinding refers to keeping participants, study investigators and also those who collect and analyse data unaware of the assigned intervention since this may be a major source of bias at several stages in a trial. In this trial, all study investigators and participants remained blinded to the treatment assignment for the duration of the study and the analysis. Even the analysis was done as treatment "A" versus "B" rather than L-thyroxine and placebo, respectively. The study code was only broken after all analysis had been completed. The blinded

nature of participants was assessed at the end of the two treatment periods by asking them to identify the L-thyroxine phase. 44% of patients correctly identified the active treatment period, 32% did not while 24% were unsure (p=0.12).

Statistics

Data analyses were performed by one investigator (SR) and then confirmed by another (JUW). All analyses were performed as per pre-established plan and with an intention to treat. The data were analysed in accordance with previous guidance on the analyses of crossover trials (Hills and Armitage 1979). This method (difference of differences) takes into account period and subject effects and also checks for any carry-over effect. Suppose participants allocated to L-thyroxine first and then placebo are termed Group A and those to placebo and then L-thyroxine as Group B; and the results of variables assessed in each period are termed y1 and y2, then:

Group A

Study No.	Period on L-thyroxine	Period on placebo	Difference (dA)	Sum (sA)
1	y1(1)	y2(1)	y2(1)-y1(1)	y2(1)+y1(1)
3	y1(3)	y2(3)	y2(3)-y1(3)	y2(3)+y1(3)

and so on….

Group B

Study No.	Period on placebo	Period on L-thyroxine	Difference (dB)	Sum (sB)
2	y1(2)	y2(2)	y2(2)-y1(2)	y2(2)+y1(2)
4	y1(4)	y2(4)	y2(4)-y1(4)	y2(4)+y1(4)

and so on……

Comparing half of the mean of the differences between dA and dB by unpaired Student's t-test can assess whether variable "y" is significantly different between L-thyroxine and placebo. The treatment effect is measured by subtracting dB from dA. This method takes into account period and sequence effect.

If instead of difference, the variable y in period 1 and 2 are added up separately for the two groups (sA and sB), and are compared by unpaired Student's t-test, then this assesses for carry-over effect.

To test for proportions, it is possible that there may be a time trend in response and it is sensible to carry out a test that takes order of treatment into account.

	Group A	Group B
Prefers period 1	nA(1)	nB(1)
Prefers period 2	nA(2)	nB(2)
Total	nA(1+2)	nB(1+2)

To test whether the difference between nA(1)/nA(1+2) and nB(1)/nB(1+2) is significant, Chi-squared test on 1 degree of freedom was used. This can be done since the sample size was relatively large.

Since intention to treat analyses does not always reflect clinical practice, we also analysed the data after excluding patients with discordant TFT results (TSH and FT4 levels outside the expected values during the course of the study).

Normally distributed data were analysed using student's t-test and Pearson's r correlation coefficient. Non-normally distributed data were analysed using Wilcoxon's rank sum test and Spearman's rho correlation coefficient. Treatment effects are reported as the mean difference between the two treatment periods, with both 95% confidence intervals and p value. Since the order of administration of L-thyroxine or placebo did not alter the results, the results for each were combined. Two-sided significance tests were used throughout. Multivariate analyses were conducted by general linear model with backward selection, after assessment for collinearity and interactions. The two primary outcomes (TC and FMD) were the dependent variables and correlated factors as independent variables. The binomial sign test was used to estimate if there were significant differences between the two treatment periods in a consistent direction within a questionnaire, even if the magnitude of the difference were small. The statistical software SPSS 11.0 for Windows was used to perform analyses (SPSS, Chic, Ill).

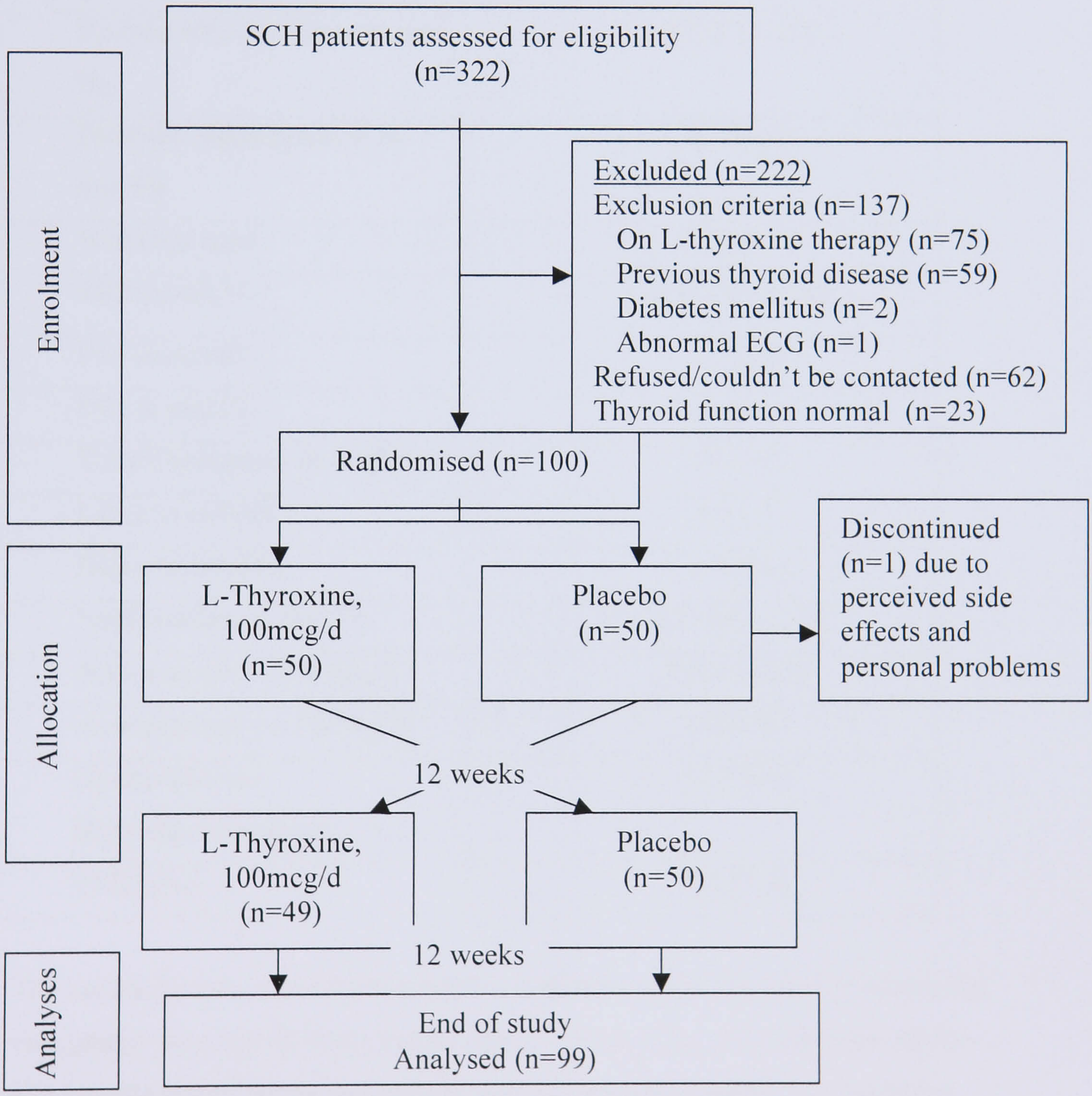
Adjustments for multiple comparisons: In a clinical trial, if a large number of variables are tested, then there is a possibility that one or more of these will be found to be significantly different (Bland and Altman 1995). In general, if we have a number (kappa) of independent significance tests at the significance level alpha (usually 0.05), all of whose null hypothesis are true, then the probability of getting no significant difference is $(1\text{-}0.05)^{kappa}$. Even if the tests are dependent on each other, the problem remains the same. For example, if a clinical trial analyses and reports 20 different variables, then the required p value to detect a true significance will be 0.05/20=0.0025. Since many variables will not be independent of each other, the required correction by the Bonferroni method is too stringent. Some others have called for other corrective tests to be used (Bender and Lange 1999). In fact, other statisticians have questioned the need to correct raw p values (Rothman 1990) (Perneger 1998) (Perneger 1999). They have argued that Bonferroni correction leads to type 2 error (finding no significant difference where one exists), which leads to truly important significant differences being discarded as non-significant. They cite the analogy with real-life clinical situation where results of tests are interpreted in their clinical context rather than being based on what other tests have been asked for. They advocate that simply describing what tests of significance have been used, and why, are all that is necessary. In this study, therefore, we report the raw p values and also state what results would remain significant if the Bonferroni correction is applied.

RESULTS (A)

Baseline results

The study protocol is outlined in figure 10. Participants attended for randomisation (baseline visit), 12 weeks for cross over, and at 24 weeks. Outcome measures were obtained at each visit. Ninety-nine participants completed the study. One person dropped out of the study, after reporting side effects following 12 days of placebo treatment; therefore baseline results were carried forward in the final data analyses. There was no significant carry-over effect in any of the outcomes reported, endorsing the decision to not have a washout period between the two treatment periods.

Figure 10.
Flow of patients through each stage of the study.



The baseline clinical and biochemical characteristics are outlined in table 8.

Table 8.

Baseline clinical and biochemical parameters of entire group (n=100).

	Mean (SD) or median (range)
Age in years	53.8 (12.6)
Male (n)	18
Weight in kg	76.5 (16.4)
Smokers (n)	25
Medications (n) Antihypertensive Statins	 18 6
Systolic blood pressure in mm Hg	132.5 (21.5)
Diastolic blood pressure in mm Hg	79.9 (9.2)
Waist hip ratio	0.83 (0.1)
TSH in mIU/L	5.3 (3.7 - 15.8)
FT4 in pmol/L	13.6 (2)
FT3 in pmol/L	4.7 (0.6)
Total Cholesterol in mmol/L	6.0 (1.2)
LDLc in mmol/L	3.6 (1)
HDLc in mmol/L	1.7 (0.5)
Triglycerides in mmol/L	1.2 (0.5 – 3.7)
Apolipoprotein B in mg/dl	104.4 (33.8)
Apolipoprotein A1 in mg/dl	152 (30)
Apolipoprotein B/Apolipoprotein A1	0.7 (0.3)
FMD (%)	4.8 (3.2)

The randomisation of the participants was effective as seen by table 9, where the two groups were not different in any aspect. This is not a very important aspect in a crossover trial where each patient acts as their own control, but highlights the fact that randomisation was efficient and successful.

Table 9.

Various clinical and biochemical parameters of the two groups at randomisation (baseline).

Mean (SD) or Median (range)	**Randomised to L-thyroxine (n=50)**	**Randomised to placebo (n=50)**
Age in years	53.5 (13.3)	54.2 (12.1)
Males (n)	10	8
Weight in kg	75.9 (15.9)	77(16.9)
Smokers (n)	14	11
Medications (n)		
Antihypertensives	10	8
Statins	3	3
Systolic blood pressure in mm Hg	135.7 (22.6)	129.4 (20.1)
Diastolic blood pressure in mm Hg	80.8 (8.3)	79.1 (10)
Waist hip ratio	0.84 (0.1)	0.83 (0.1)
TSH in mIU/L	5.4 (3.8 – 15.8)	5.3 (3.7-13.9)
Free T4 in pmol/L	13.5 (2.1)	13.7 (2)
Free T3 in pmol/L	4.7 (0.7)	4.7 (0.6)
Total Cholesterol in mmol/L	6.1 (0.9)	6.0 (1.4)
LDL Cholesterol in mmol/L	3.6 (0.8)	3.6 (1.2)
HDL Cholesterol in mmol/L	1.7 (0.5)	1.6 (0.4)
Triglyceride in mmol/L	1.2 (0.7 – 3.7)	1.2 (0.5 – 3.1)
Apolipoprotein B in mg/dl	104.7 (34)	104.1 (33.6)
Apolipoprotein A1 in mg/dl	157.2 (31.3)	147 (28)
Apolipoprotein B/A1	0.7 (0.3)	0.7 (0.3)
FMD in %	5.1 (3.3)	4.6 (3)

Other baseline anthropometric and biochemical parameters are outlined next. Table 10 shows the body composition of participants at baseline as measured by bio-impedance method.

Table 10.

Baseline body composition parameters (n=100).

	Mean (SD)
Fat (%)	37.2 (8.3)
Fat mass (kg)	28.8 (10.5)
Lean mass (kg)	47.7 (10.6)
Water (%)	48.1 (6.4)
Basal metabolic rate (kcal/kg)	1499.8 (249.5)

Table 11 outlines the biochemical markers of endothelial function (pro and anti-thrombotic) as well as a marker of vascular inflammation at baseline.

Table 11.

Baseline biochemical parameters of thrombosis and inflammation (n=100).

	Mean (SD) or median (range)
PAI-1	338.7 (487.7)
sICAM 1	257.4 (60.6)
e-selectin	42.3 (21.4)
tPA	51.0 (30.4)
hsCRP	2 (0-40)

The effect of thyroid autoantibodies on various baseline parameters

Thyroid auto-antibodies were measured to elucidate the nature of the SCH. Forty nine patients had positive anti-TPO antibody levels (titre >50) whereas the rest were negative. There have been concerns in the past as well as more recently that people with positive thyroid antibodies are at an increased risk of vascular disease (Bastenie 1967; Bastenie 1971; Hak et al 2000). This association between thyroid autoimmunity and CV disease has not been shown in some other studies (Tunbridge et al 1977) (Hueston et al).

The results were therefore compared in all 100 patients at baseline with regards to positive versus negative antibody status (table 12). This shows that anti-TPO antibody positive individuals were younger, had a higher proportion of men, have a higher serum TSH level and lower serum free T3 level. The rest of the CV risk factor profile was similar in both groups. This suggests that auto-immune SCH is more likely to affect people at a younger age, likely to involve a higher proportion of men, and have a more advanced disease in terms of higher serum TSH and lower free T3 levels.

Table 12.

Various clinical and biochemical parameters at baseline in positive versus negative anti-TPO antibody individuals.

Mean (SD) or median (range)	**Anti-TPO positive (n=49)**	**Anti-TPO negative (n=51)**	**P value**
Age (years)	51.0 (12.2)	56.6 (12.6)	0.02
Gender (n) (Male/Female)	11/38	7/44	0.01
Body mass index (kg/m^2)	27.7 (4.5)	29.3 (5.7)	0.13
Waist circumference (cm)	89.2 (14.2)	92.3 (15.1)	0.30
FMD (%)	5.3 (3.4)	5.3 (3.4)	0.95
TSH (mIU/L)	5.8 (2.9 – 15.4)	5.0 (2.7 – 15.8)	0.02
Free T4 (pmol/L)	13.3 (1.8)	13.9 (2.1)	0.13
Free T3 (pmol/L)	4.8 (0.6)	4.6 (0.6)	0.04
Total Cholesterol (mmol/L)	5.8 (1.2)	6.2 (1.2)	0.17
LDL cholesterol (mmol/L)	3.5 (1.1)	3.8 (1)	0.10
HDL cholesterol (mmol/L)	1.7 (0.5)	1.6 (0.5)	0.30
Triglycerides (mmol/L)	1.2 (0.5 – 3.7)	1.3 (0.5 – 3.7)	0.24
Apolipoprotein B (mg/dl)	99.2 (31.2)	109.3 (35.5)	0.14
Apolipoprotein A1 (mg/dl)	153.3 (29.8)	150.8 (30.5)	0.68
hs CRP (mg/dl)	2 (0 – 13)	2 (0 – 40)	0.65

Effect of TSH levels on baseline parameters.

It is possible that SCH may have a graded effect depending on the degree of thyroid failure. The best way to gauge whether patients with lesser degree of SCH have different levels of various parameters was to evaluate results at baseline based on serum TSH levels. Therefore, baseline results were compared between two groups of SCH patients, based on their mean TSH level (6.1 mIU/L). These results are shown in table 13. These do not show any significant differences between the two groups for any parameter.

Table 13.

Various clinical and biochemical baseline results based on serum TSH levels at baseline.

Mean (SD) or median (range)	TSH ≤ 6.1 mIU/L (n=61)	TSH > 6.1 mIU/L (n=39)	P value
Age (years)	54 (13.6)	53.6 (11.2)	0.89
Gender (n) (Male/Female)	10/51	8/31	0.31
Body mass index (kg/m^2)	29.3 (5.3)	27.2 (4.9)	0.06
Waist circumference (cm)	92.5 (15)	88.1 (13.8)	0.14
FMD (%)	5.0 (3.2)	4.6 (3.2)	0.54
TSH (mIU/L)	4.7 (3.7 – 5.9)	7.9 (6 – 15.9)	<0.001
Free T4 (pmol/L)	13.9 (2)	13.3 (2)	0.14
Free T3 (pmol/L)	4.8 (0.7)	4.6 (0.6)	0.28
Total Cholesterol (mmol/L)	6.0 (1.2)	5.9 (1.1)	0.67
LDL cholesterol (mmol/L)	3.7 (1.1)	3.6 (1)	0.67
HDL cholesterol (mmol/L)	1.7 (0.5)	1.7 (0.4)	0.70
Triglycerides (mmol/L)	1.2 (0.5 – 3.7)	1.3 (0.5 – 3.1)	0.46
Apolipoprotein B (mg/dl)	105.6 (33.2)	102.5 (34.7)	0.66
Apolipoprotein A1 (mg/dl)	148.9 (30.1)	156.9 (29.6)	0.19
Hs CRP (mg/dl)	2 (0 – 27)	2 (0 – 40)	0.91
Body fat (%)	38.2 (8.1)	35.7 (8.4)	0.15
Body fat (kg)	30.3 (10.7)	26.6 (9.9)	0.08
Lean mass (kg)	48.1 (10.4)	47.0 (10.9)	0.63
Basal metabolic rate (kcal/kg)	1509.9 (245.8)	1483.9 (257.7)	0.61

Baseline correlations

Variables that were not normally distributed were transformed and then correlations calculated. High sensitive CRP could not be transformed into normality, therefore non-parametric tests were utilised for analysis. Figure 11, and tables 14 and 15 show the correlations between serum TSH and free T4 and various clinical and biochemical parameters, respectively.

Table 14.

Correlations between inverse serum tan TSH levels and various clinical and biochemical parameters at baseline (n=100).

Parameters	**Pearson's correlation co-efficient (r) or Spearman's rho**	**P value**
Age in years	-0.13	0.21
Systolic blood pressure (mm Hg)	0.03	0.76
Diastolic blood pressure (mm Hg)	-0.05	0.64
Weight (kg)	-0.17	0.09
Waist (cm)	-0.18	0.07
Waist hip ratio	-0.13	0.20
Square root FMD (%)	-0.03	0.74
Fat mass (kg)	-0.16	0.12
Total cholesterol (mmol/L)	-0.18	0.06
Log Triglycerides (mmol/L)	-0.10	0.32
Log HDL cholesterol (mmol/L)	0.10	0.38
Log free T4 (pmol/L)	-0.18	0.08
hs CRP (mg/dl)	-0.07 (rho)	0.31

Figure 11.

Correlation between baseline serum TSH levels and baseline total cholesterol levels.

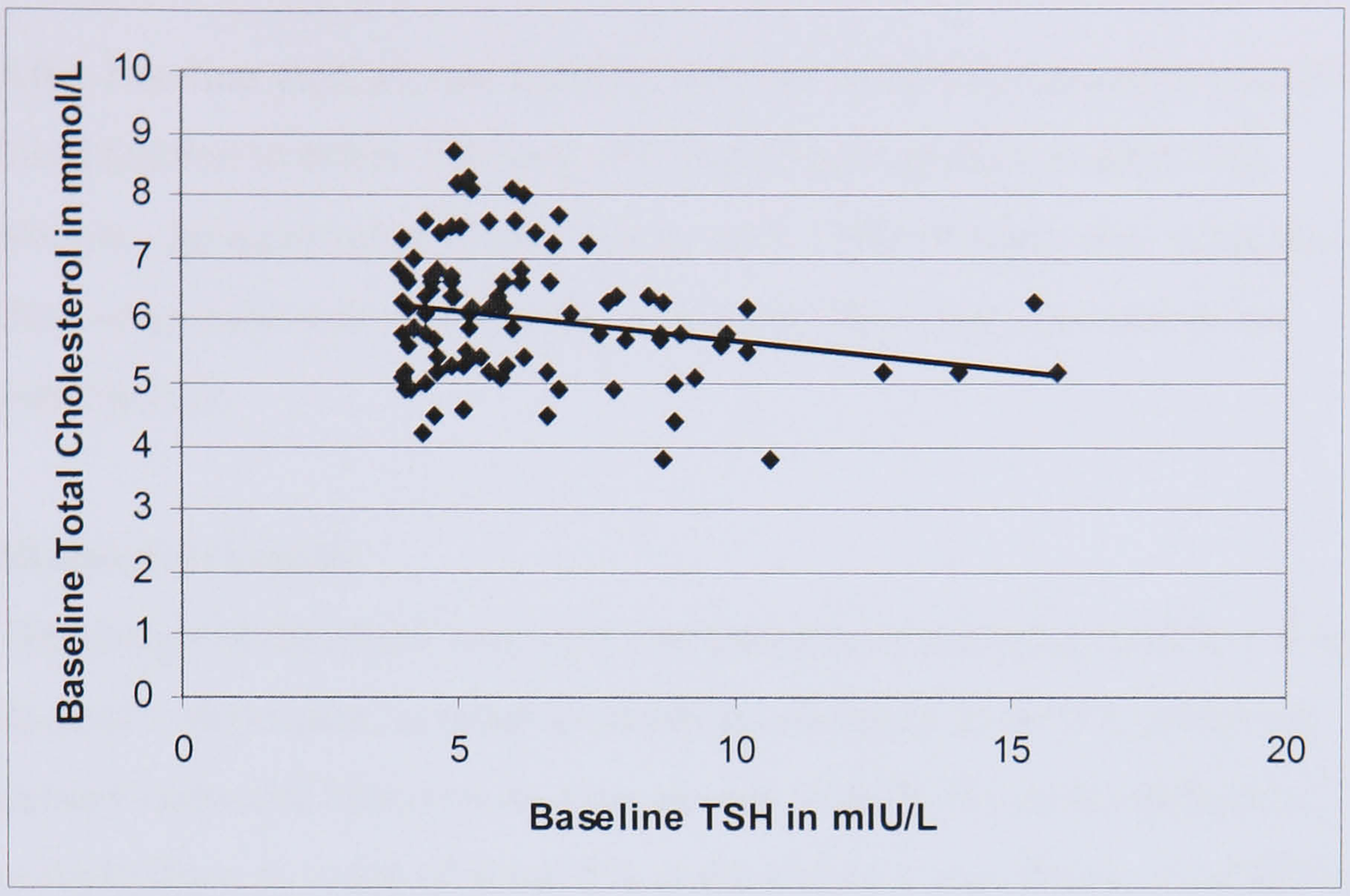


Table 15.

Correlations between log serum free T4 levels and various clinical and biochemical parameters at baseline (n=100).

Parameters	**Pearson's correlation co-efficient (r) or Spearman's rho**	**P value**
Age in years	0.09	0.37
Systolic blood pressure in mm Hg	0.14	0.17
Diastolic blood pressure in mm Hg	0.16	0.10
Weight in kg	0.08	0.45
Waist in cm	0.12	0.25
Waist hip ratio	0.16	0.11
Square root FMD	-0.05	0.64
Fat mass in kg	0.05	0.60
Total cholesterol in mmol/L	0.02	0.87
Log Triglycerides in mmol/L	0.11	0.28
Log HDL cholesterol in mmol/L	-0.01	0.92
hs CRP	-0.02 (rho)	0.87

Effects of intervention with L-thyroxine versus placebo in people with SCH

After baseline visit, all one hundred patients were randomised in a double blind fashion to either 100 mcg of L-thyroxine capsules or matching placebo, for a period of twelve weeks each. Fifty patients were allocated to the L-thyroxine arm whereas the remaining fifty were allocated to the placebo arm.

Discordant results

The design of the study was such that patients were randomised to a fixed dose of L-thyroxine, in order to increase efficiency as well as minimise patient visits and blood tests. Also, people with SCH can revert back to euthyroidism at a rate of about 5% at the end of a year (Parle, *et al* 1991). Intermittent compliance or even missing some capsules for a few days and then taking them all together may also account for some of these results. During the course of the study, there were four groups of patients whose TFTs were outside the expected range. This was seen at the end of the study at the time of analyses of data. The details of discordant groups have never been previously described in detail by the authors of other RCTs in SCH. These groups were:

1. Normal TSH at baseline (n=8): Despite having had abnormal TSH levels with normal free T4 concentrations on at least three occasions, each at least three months apart, eight patients had reverted back to normal TSH levels at randomisation. This is difficult to explain and the normal result may represent an anomaly; for example, this may be a manifestation of non-thyroidal illness at randomisation.
2. TSH levels below 0.4 mIU/L on L-thyroxine therapy (=10): The fixed dose of 100 mcg/day was slightly excessive for some patients. Of these, 2 people had suppressed TSH levels whereas 8 had levels between 0.01 and 0.4 mIU/L. The two patients with undetectable TSH levels also had mildly elevated free T4 levels (26 and 27 pmol/L) whereas none had free T3 levels outside the reference range.

3. TSH levels above 4.0 mIU/L on L-thyroxine therapy (n=2): This may be due to either non-compliance or inadequate dose of L-thyroxine therapy.
4. Normal TSH on placebo therapy (n=14): Three patients had normalised their TSH levels during placebo therapy when they were randomised to it during the first period treatment, and 11 patients had normal TSH levels during placebo phase of treatment after they had completed the L-thyroxine phase. This may be due to non thyroidal illness, spontaneous normalisation or a carryover effect of L-thyroxine.
5. TSH levels above 15 mIU/L on placebo therapy (n=2): This could represent progression of hypothyroidism.

Altogether there were 36 instances of discordant results but 7 patients had these on more than one occasion, therefore 29 patients' endpoint data were excluded and results analysed separately to see if there was any difference in results for each parameter.

Effect of L-thyroxine on thyroid function tests (TFTs)

The aim of utilising a 100 mcg of L-thyroxine replacement therapy was to normalise serum TSH concentration and to increase serum free T4 and free T3 levels. The result of intervention with L-thyroxine on TFTs can be seen in tables 16 and 17.

Table 16.

Effect of L-thyroxine on serum thyroid function tests (n=100).

Mean (SD) or median (range)	**L-thyroxine**	**Placebo**	**Adjusted difference (95% CI)** †	**P value**
TSH (mIU/L)	0.53 (0.01 – 12.1)	5.25 (0.9 – 63.4)	- 5.64 (-7.17 to –4.11)	<0.001
Free T4(pmol/L)	20.5 (4.8)	13.5 (2.3)	6.98 (5.97 to 7.98)	<0.001
Free T3 (pmol/L)	5.3 (1)	4.7 (0.7)	0.6 (0.37 to 0.82)	<0.001

† Adjusted for subject and period effects.

Table 17.

Effect of L-thyroxine on serum thyroid function tests with discordant TFTs excluded (n=71).

Mean (SD) or median (range)	**L-thyroxine**	**Placebo**	**Adjusted difference (95% CI) †**	**P value**
TSH (mIU/L)	0.8 (0.4 – 3.9)	5.2 (4.1 – 12.1)	-4.7 (-5.1 to –4.3)	<0.001
Free T4 (pmol/L)	20.2 (4.2)	13.8 (2.2)	6.4 (5.7 to 7.1)	<0.001
Free T3 (pmol/L)	5.2 (0.8)	4.7 (0.6)	0.4 (0.3 to 0.5)	<0.001

† Adjusted for subject and period effects.

These results show that the intervention with L-thyroxine was effective in normalising serum TSH levels and also increasing free T4 and free T3 levels significantly. Table 16 shows that the dose of 100 mcg daily of L-thyroxine suppressed TSH levels in some individuals and also increased free T 4 levels but serum free T3 levels were never outside the reference range at any point during the study. This table also shows that in some individuals, serum TSH remained above the desired reference range whilst on L-thyroxine (this may represent non-compliance), and in certain others serum TSH normalised on the placebo. There has been a recent trial that utilised a dose-titration approach to the dose of L-thyroxine in SCH that found that some individuals still do not achieve the desired TFT levels (Iqbal, *et al* 2006). It is seen in table 17, after exclusion of individuals of discordant results, that 71 participants achieved the desired TFT criteria. All results were therefore analysed for all 100 participants and also for these 71 individuals, to see if there was any significant difference for all parameters.

Effect of L-thyroxine on vascular function.

Flow mediated dilation:

L-thyroxine had a positive influence on endothelial function as measured by FMD. This was not associated with any change in baseline diameter or baseline blood flow or peak flow after reactive hyperaemia. This improvement was independent of smooth muscle function since there was no change in response to GTN (table 18).

Table 18.

Effect of L-thyroxine on brachial artery measurements (n=100).

Mean (SD)	L-thyroxine	Placebo	Adjusted difference (95% CI) †	P value
Baseline diameter (mm)	3.44 (0.6)	3.47 (0.6)	0.02 (-0.005 to 0.05)	0.11
Baseline flow (ml/minute)	58.5 (43.8)	55.1 (42.4)	3.4 (-4.9 to 11.7)	0.42
Peak flow (ml/minute)	147.3 (59.2)	142.7 (56.5)	4.6 (-8.1 to 17.3)	0.48
Absolute change in diameter (mm)	0.2 (0.09)	0.14 (0.1)	0.06 (0.02 to 0.08)	<0.001
FMD (%)	5.9 (3.1)	4.2 (3.0)	1.65 (1.19 to 2.1)	<0.001
GTN (%)	21.3 (6.3)	20.6 (7.1)	0.7 (-0.26 to 1.65)	0.15

† Adjusted for subject and period effects.

FMD measurement enables us to potentially identify patients at risk for atherosclerotic complications. Hypothyroidism can also lead to smooth muscle dysfunction (Ojamaa, *et al* 1996). The lack of change in GTN mediated dilatation along with the improvement in FMD confirms that this is due to increased NO availability rather than due to changes in blood flow.

vessel diameter or smooth muscle function. The increase in absolute terms confirms that the change in diameter is not due to change in baseline diameter since any increase in percentage terms is higher if baseline diameter is smaller (Corretti, *et al* 2002)

Table 19.

Effect of L-thyroxine on brachial artery measurements with discordant patients excluded (n=71).

Mean (SD)	**L-Thyroxine**	**Placebo**	**Adjusted difference (95% CI)†**	**P value**
Baseline diameter (mm)	3.5 (0.6)	3.5 (0.6)	-0.0 (-0.0 to 0.1)	0.06
Baseline flow (ml/minute)	60.5 (46.4)	59.3 (45.2)	1.9 (-6 to 9.7)	0.69
Peak flow (ml/minute)	147.2 (56.1)	150.3 (61.4)	-2.4 (-13.9 to 9.1)	0.76
FMD (%)	5.8 (3.1)	4.2 (3.2)	1.6 (1.2 to 2.0)	<0.001
Absolute change in diameter (mm)	0.2 (0.1)	0.15 (0.1)	0.06 (0.04 to 0.07)	<0.001
GTN (%)	21.1 (6.1)	20.2 (6.6)	0.7 (-0.2 to 1.5)	0.23

† Adjusted for subject and period effects.

Tables 18 and 19 show that there was no significant difference in any of the parameters when comparing all 100 patients to the ones without discordant TFTs. This confirms that people with TSH levels in the desired range of 0.4 to 4.0 mIU/L after treatment, still have a similar improvement in FMD response without any significant changes to baseline diameter, blood flow or response to GTN.

Carotid intima-media thickness (CIMT) and distensibility:

This was measured in some individuals (n=39). The reason that this was not measured in all was because this was an add-on to the study protocol after the initiation of the study. Furthermore, some individuals declined to take part in this part of the study due to the greater time commitment required. A preliminary study of healthy volunteers (n=8), examined on 2 separate occasions, showed that the mean difference (SD) in CIMT was 0.01 mm (0.03). The characteristics of these 39 individuals were no different to those of the larger group. The results of the effects of L-thyroxine compared to placebo on CIMT and carotid artery elastic properties are outlined in table 20.

Table 20.

Effect of L-thyroxine on carotid artery measurements (n=39)

Mean (SD)	**L-thyroxine Mean (SD)**	**Placebo Mean (SD)**	**Adjusted difference (95% CI)** †	**P value**
CIMT (mm)	0.1 (0.0)	0.1 (0.0)	0 (-0.0 to 0.0)	0.50
Carotid elasticity	12.3 (5.5)	11.0 (4.4)	1.2 (-0.2 to 2.6)	0.11
Carotid stiffness	12.0 (5.0)	10.5 (3.8)	1.2 (-0.0 to 2.4)	0.07
Carotid distensibility	2.3×10^{-3} (0.0)	2.2×10^{-3} (0.0)	0 (-0.0 to 0.0)	0.64

† Adjusted for subject and period effects. CIMT= Carotid intima-media thickness, Elasticity= dP/[(Ds-Dd)/Dd x100], Stiffness= Ln (Ps/Pd)/[(Ds-Dd)/Dd], Distensibility= (dA/Ad)/dP. *d*A=systolic-diastolic artery cross-sectional area change; Ad=diastolic artery cross-sectional area; *d*P=systolic-diastolic pressure change; *Ln*=logarithm base n; Ps=systolic blood pressure; Pd=diastolic blood pressure; Ds=artery diameter at systole and Dd=artery diameter at diastole.

There was no significant change observed in any carotid artery parameter in people with SCH after treatment with L-thyroxine when compared to placebo. This could be because the treatment period of 12 weeks may not be sufficient to observe any significant changes. One RCT in the past has shown the beneficial effect of L-thyroxine in improving carotid IMT but the treatment period was much longer at six months (Monzani, *et al* 2004).

Effect of L-thyroxine on anthropometric and clinical parameters.

Blood pressure:

There is a tendency to increased diastolic hypertension in patients with SCH, which extends even into the euthyroid range (Biondi and Klein 2004) (Gumieniak, *et al* 2004). There was no effect of L-thyroxine on either systolic or diastolic blood pressure as seen in tables 21 and 22.

Weight and waist/hip measurements:

There is some evidence that body weight may be influenced by thyroid function status, although it is not consistent (Manji, *et al* 2006) (Nyrnes, *et al* 2006).

Table 21.

Effect of L-thyroxine on blood pressure, weight and waist/hip measurements(n=100)

Mean (SD)	**L-thyroxine**	**Placebo**	**Adjusted difference (95% CI) †**	**P value**
Systolic blood pressure (mmHg)	132.8 (22.8)	134.6 (22.9)	- 1.8 (-4.6 to 1.0)	0.21
Diastolic blood pressure (mm Hg)	78.8 (10.3)	79.9 (9.6)	- 1.1 (-2.8 to 0.5)	0.16
Pulse rate per minute	68.4 (10.9)	67.9 (11.4)	0.47 (-0.7 to 1.6)	0.57
Weight (kg)	75.8 (16.5)	76.5 (16.7)	- 0.6 (-1.1 to –0.1)	0.02
BMI (kg/m^2)	28.3 (5.2)	28.5 (5.3)	- 0.2 (-0.37 to – 0.03)	<0.02
Waist circumference (cm)	89.1 (14.1)	90.3 (14.2)	-1.13 (-2 to –0.23)	0.01
Waist hip ratio	0.81 (0.1)	0.83 (0.1)	- 0.01 (-0.02 to – 0.01)	0.001

† Adjusted for subject and period effects

There was no significant reduction in either systolic or diastolic blood pressure. This could be because the study was not powered to detect a significant change in mild hypothyroidism. There was a significant reduction in weight and waist circumference as well as waist hip ratio by L-thyroxine. This is a novel result that has not been shown before in any RCT. This may be because:

1. A relatively higher dose of L-thyroxine was used than most other studies.
2. A higher number of patients were studied as compared to any other RCT.

The concern that the reduction in weight could be due to significant over-treatment (low TSH levels with or without high free T4 levels) was addressed by analysing the data with patients with discordant TFTs excluded (table 22).

Table 22.

Effect of L-thyroxine on blood pressure, weight and waist/hip measurements with discordant patients excluded (n=71).

Mean (SD)	**L-thyroxine**	**Placebo**	**Adjusted difference (95% CI)** †	**P value**
Systolic blood pressure (mmHg)	134.5 (22.7)	136.2 (22.8)	-1.9 (-4.4 to 0.6)	0.28
Diastolic blood pressure (mm Hg)	79.4 (10.4)	80.6 (9.9)	-1.4 (-2.9 to 0.04)	0.16
Pulse rate per minute	66.7 (11.4)	67.2 (10.9)	-0.61 (-2.0 to 0.8)	0.52
Weight (kg)	77.9 (17.5)	78.4 (17.9)	-0.5 (-0.85 to –0.15	0.04
BMI (kg/m^2)	28.6 (5.3)	28.8 (5.5)	-0.17 (-0.3 to –0.05)	0.04
Waist circumference (cm)	90.2 (14.1)	91.1 (14.5)	-0.87 (-1.5 to –0.3)	0.05
Waist hip ratio	0.82 (0.1)	0.83 (0.1)	-0.01 (-0.01 to –0.004)	0.009

† Adjusted for subject and period effects.

Body composition:

The effect of L-thyroxine on body composition in patients with SCH was assessed by electrical bio-impedance. The results are outlined in tables 23 and 24.

This method has been shown to be a valid tool to measure body fluid distributions in SCH (De Lorenzo, *et al* 2000) (Seppel, *et al* 1997) and has been used in assessing response to thyroid function changes (Hsieh, *et al* 2002) (Pinkney, *et al* 2000).

Table 23.

Effect of L-thyroxine on body composition measurements (n=100).

Mean (SD)	L-thyroxine	Placebo	Adjusted difference (95% CI) †	P value
Fat (%)	36.9 (7.8)	37.4 (7.7)	-0.44 (-1.26 to 0.38)	0.14
Fat (kg)	28.3 (10.0)	28.9 (10.2)	-0.57 (-0.93 to – 0.21)	0.03
Lean mass (kg)	47.5 (10.8)	47.6 (10.9)	-0.1 (-0.64 to 0.52)	0.79
Water (%)	48.6 (5.8)	48.2 (5.7)	-0.35 (-1.10 to 0.40)	0.21
Basal metabolic rate (kcal/kg)	1495.9 (254.8)	1493.9 (259.1)	2.19 (-9.8 to 14.2)	0.65

† Adjusted for subject and period effects.

Table 24.

Effect of L-thyroxine on body composition measurements with discordant TFTs excluded (n=71).

Mean (SD)	L-thyroxine	Placebo	Adjusted difference (95% CI) †	P value
Fat (%)	37.0 (8.1)	37.1 (8.4)	-0.2 (-1.3 to 1.5)	0.92
Fat (kg)	29.1 (10.5)	29.4 (11.2)	-0.4 (-0.9 to 0.1)	0.33
Lean mass (kg)	48.8 (11.7)	49.0 (11.9)	0.1 (-0.4 to 0.5)	0.47
Water (%)	48.3 (5.8)	48.3 (6.0)	0.1 (-1.2 to 1.4)	0.96
Basal metabolic rate (kcal/kg)	1524.9 (278.5)	1524.6 (284.8)	0.1 (-8.7 to 8.9)	0.96

† Adjusted for subject and period effects.

This is the first time that body composition has been studied in a randomised controlled fashion and shows that body fat in terms of kilograms is reduced by L-thyroxine in people with SCH. The reduction is not by a large amount but may account for some reduction in body weight. The reduction was no longer significant when people with discordant results were excluded. This could be due to loss of power since less number of patients were analysed or could be because that people who had discordant results were the driving force of the significant results in all 100 patients. It should also be kept in mind that the magnitude of weight reduction may change in the longer term. This can be assessed in a study of a longer duration.

Effect of L-thyroxine on lipids in patients with SCH.

There have been a number of studies that have looked at the effect of L-thyroxine in patients with SCH, but the results have been inconsistent. This study showed a significant reduction in total and LDL cholesterol in response to treatment with L-thyroxine and this result remained significant when patients with discordant TFTs were excluded (tables 25 and 26).

Table 25. Effect of L-thyroxine on serum lipids and apolipoproteins in patients with SCH (n=100).

Mean (SD)	L-thyroxine	Placebo	Adjusted difference (95% CI) †	P value
Total cholesterol (mmol/L)	5.7 (1)	6.0 (1)	- 0.35 (-0.5 to - 0.2)	<0.001
LDL cholesterol (mmol/L)	3.4 (0.8)	3.7 (0.9)	- 0.2 (-0.4 to - 0.1)	0.01
HDL cholesterol (mmol/L)	1.6 (0.5)	1.7 (0.5)	- 0.06 (-0.1 to - 0.01)	0.02
Triglycerides (mmol/L)	1.3 (0.5 – 4.1)	1.3 (0.4 – 5.1)	- 0.06 (-0.2 to 0.1)	0.26
Apolipoprotein B (mg/dL)	101.6 (34)	108.8 (38)	- 7.2 (-12.7 to - 1.7)	0.01
Apolipoprotein A1 (mg/dL)	152.1 (30.6)	156.8 (34.4)	- 4.8 (-8.9 to – 0.6)	0.02
ApoB/ApoA1	0.69 (0.2)	0.72 (0.3)	- 0.04 (-0.1 to – 0.01)	0.04

† Adjusted for subject and period effects

Table 26.

Effect of L-thyroxine on serum lipids and apolipoproteins in patients with SCH with discordant TFTs excluded (n=71).

Mean (SD)	L-thyroxine	Placebo	Adjusted difference (95% CI) †	P value
Total cholesterol (mmol/L)	5.7 (1.1)	6.0 (1)	-0.28 (-0.4 to -0.1)	0.008
LDL cholesterol (mmol/L)	3.4 (0.9)	3.7 (0.9)	-0.2 (-0.3 to –0.1)	0.02
HDL cholesterol (mmol/L)	1.7 (0.5)	1.7 (0.5)	-0.01 (-0.04 to 0.02)	0.98
Triglycerides (mmol/L)	1.3 (0.5 – 4.1)	1.4 (0.5 – 4.3)	-0.1 (-0.2 to 0)	0.09
Apolipoprotein B (mg/dL)	102.2 (33.9)	106.5 (35.7)	-6.4 (-12.5 to -0.3)	0.04
Apolipoprotein A1 (mg/dL)	152.1 (32.1)	153.8 (34.3)	-2.1 (-5.7 to 1.4)	0.41
ApoB/ApoA1	0.70 (0.3)	0.72 (0.3)	-0.04 (-0.09 to 0.01)	0.05

† Adjusted for subject and period effects.

Table 25 shows that there was not only a significant reduction in serum total cholesterol but also LDL cholesterol. In addition, serum apolipoproteins B and A1 reduced significantly, but the atherogenic apoB reduced more than the protective A1, as seen by the ratio of the two. Similarly, there was a statistically

significant reduction in HDL cholesterol, although the clinical relevance of a reduction of 0.06 mmol/L is questionable.

Table 26 is of considerable interest since it shows that the reduction on HDL cholesterol as well as apolipoprotein A1 was primarily due to inclusion of individuals who had discordant TFTs, since this was no longer significant. This may be due to inclusion of people with suppressed TSH levels and high free T4 levels. It is also interesting to note that the apoB/A1 ratio loses its significance in this group. This may be due to reduction in numbers.

It can be estimated that the reduction in LDL cholesterol alone could amount to a 10-year CV mortality reduction by 10% (Anderson, *et al* 1991). There may be further benefits of improvement in endothelial function and central reduction in adiposity that cannot be quantified.

Effect of L-thyroxine on biochemical endothelial markers and inflammatory protein.

The influence of L-thyroxine on these parameters is outlined in tables 27 and 28. This shows that there was no effect of L-thyroxine on any biochemical endothelial markers, apart from tPA.

Table 27.

Effect of L-thyroxine on thrombotic, endothelial and inflammatory biochemical markers in patients with SCH (n=100).

Median (range)	**L-thyroxine**	**Placebo**	**Adjusted difference (95% CI)** †	**P value**
hsCRP mg/L	2 (0 – 17)	2 (0 – 25)	- 0.4 (-0.86 to 1.2)	0.29
e-selectin	37.2 (11.5 – 103)	37.85 (9.7 – 118.4)	- 0.4 (-1 to 1.3)	0.52
sICAM ng/ml	251.4 (165.8 – 602.4)	247.1 (165.1 – 603.8)	2.2 (-4.2 to 8.6)	0.51
PAI-1	194.7 (49.9 – 726.9)	177.6 (50.1 – 815.9)	10.5 (-14.5 to 35.5)	0.4
tPA	50.9 (21.4 – 322)	46.1 (22.1 – 321.4)	1.6 (-1.2 to 4.4)	0.01*

† Adjusted for subject and period effects.

hsCRP=high sensitive CRP, PAI-1=plasminogen activator 1, tPA=tissue plasminogen activator.

* p as calculated by Wilcoxon's rank sum test. But there was a significant carry-over effect of L-thyroxine into the placebo period making analyses by the adjusted method meaningless.

Since there was a significant carry over effect for tPA, this was analysed as a parallel group trial as well and this showed no significant difference, p 0.23.

Table 28.

Effect of L-thyroxine on thrombotic, endothelial and inflammatory biochemical markers with discordant TFTs excluded (n=71).

Median (range)	**L-thyroxine**	**Placebo**	**Adjusted difference (95% CI)** †	**P value**
hsCRP mg/L	2 (0 – 17)	2 (0 – 25)	-0.5 (-1.3 to 0.2)	0.16
e-selectin	40.1 (11.5 – 103)	39.2 (9.7 – 118.4)	0.5 (-1.6 to 2.1)	0.58
sICAM ng/ml	243.8 (165.8 – 388.8)	246.4 (165.1 – 465.4)	-3.6 (-8.9 to 1.7)	0.86
PAI-1	199.3 (49.9 – 682.9)	191.5 (68.8 – 748.9)	8.4 (-10.8 to 27.6)	0.56
tPA	51.2 (21.4 – 122.6)	47.7 (22.2 – 129.9)	1.9 (- 0.9 to 4.7)	0.09*

† Adjusted for subject and period effects.

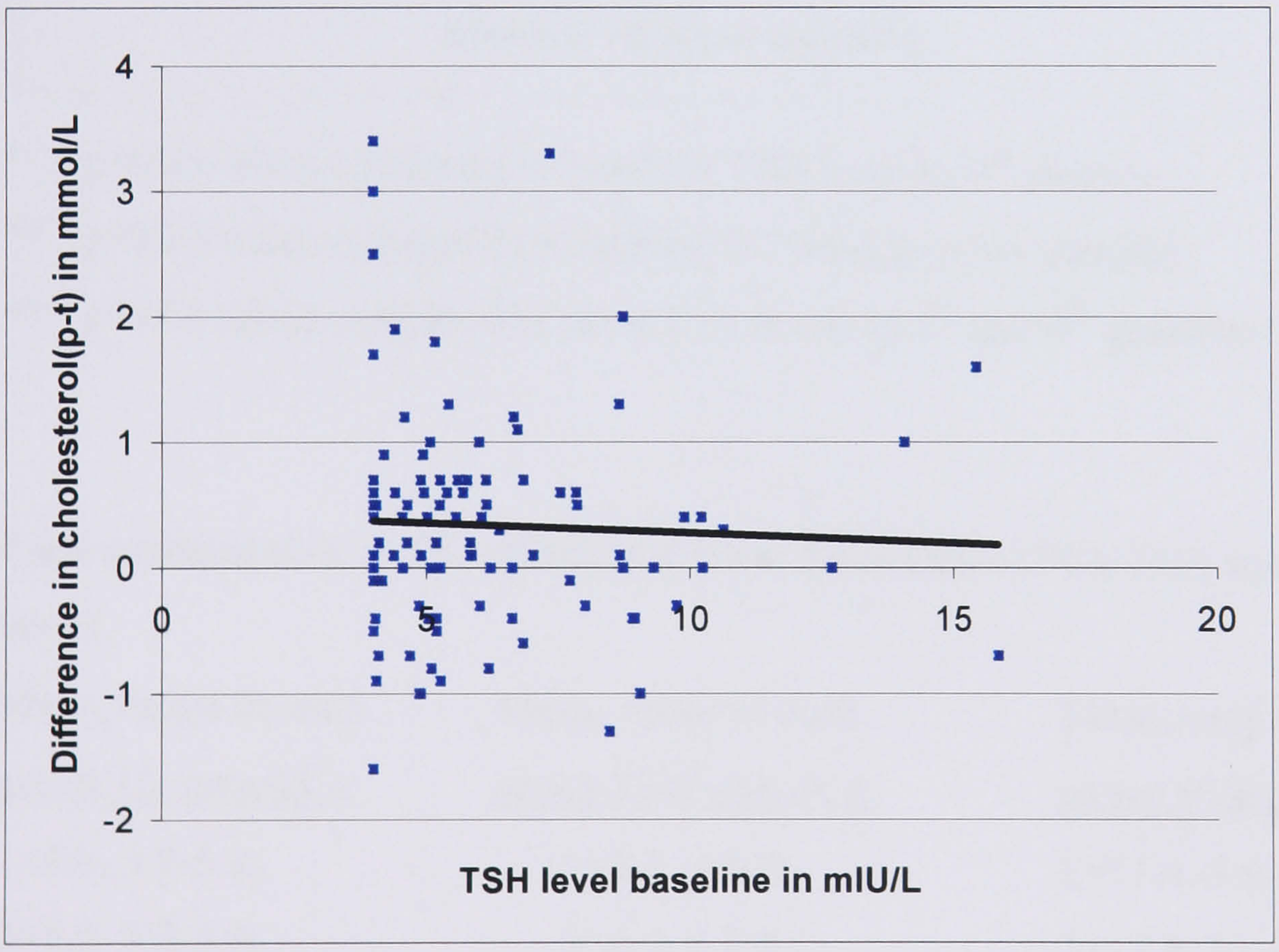
Association between serum TFTs and cardiovascular risk factors after treatment.

There were significant improvements in the two primary outcomes of this trial, namely improvement in total cholesterol levels as well as improvement in endothelial function as measured by FMD, after L-thyroxine therapy. Further tests were then performed to try and observe how these improvements related to thyroid function tests.

There was no correlation between baseline serum TSH levels and change in total cholesterol levels (figure 12). This suggests that, at least in participants in this study, that there was no cut off TSH level at which therapy is beneficial. This shows that all participants had a similar degree of benefit.

Figure 12.

Correlation between TSH level at baseline and change in total cholesterol level.

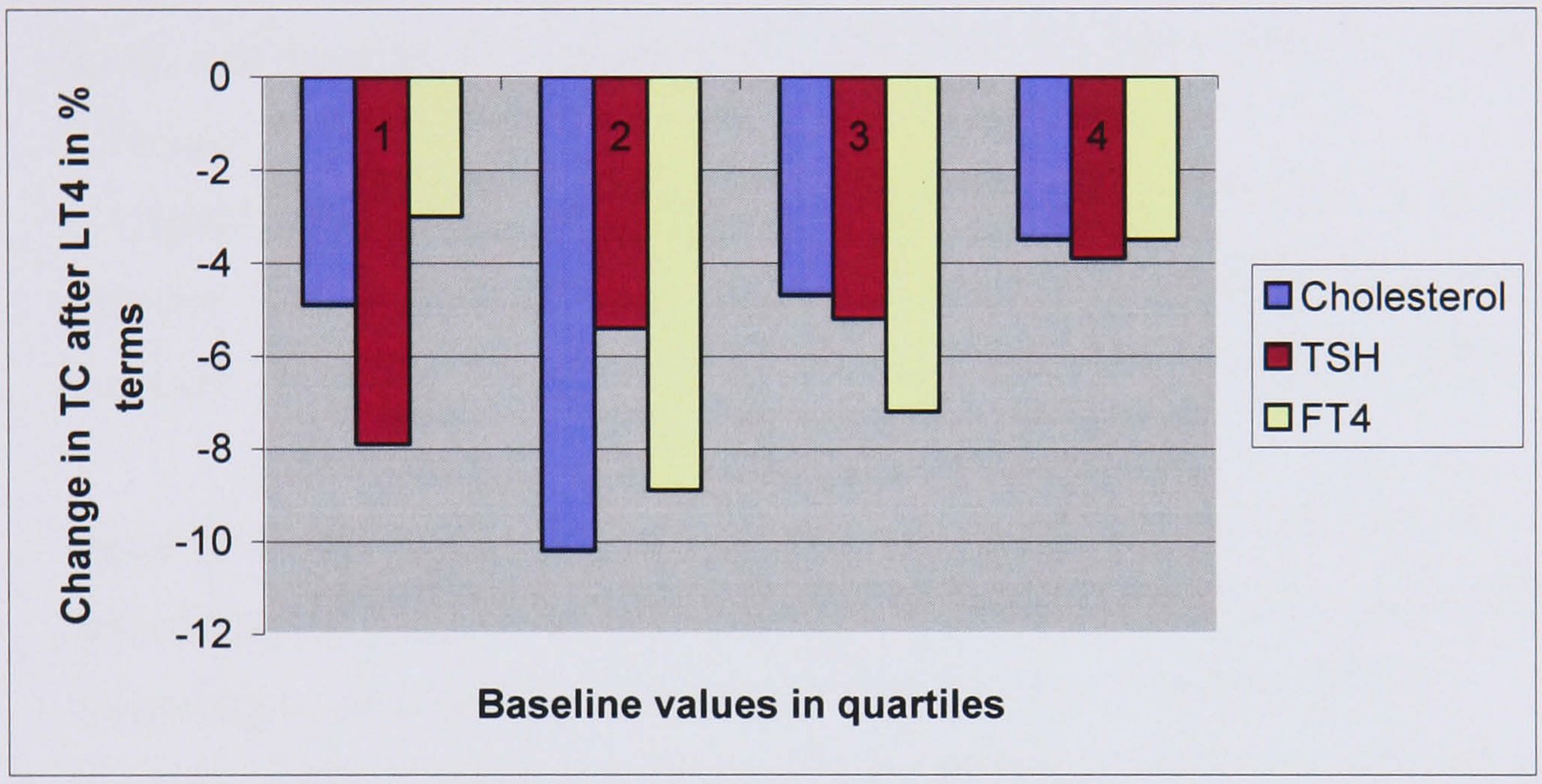


To investigate if there were any differences between various baseline parameters that affected the change in total cholesterol levels, baseline serum TSH levels, baseline serum free T4 levels and baseline serum total cholesterol levels were divided into quartiles and this was analysed in relation to change in

total cholesterol levels after treatment (figure 13). This shows that the people who derive the most benefit with L-thyroxine therapy are those whose serum total cholesterol levels are between 5.3 and 5.9 mmol/L, whose free T4 levels are between 12.4 and 14.4 pmol/L and whose serum TSH is between 4.0 and 4.6 mIU/L.

Figure 13.

Relation between baseline serum TSH, free T4 and total cholesterol levels and change in total cholesterol after treatment with L-thyroxine.



* $p<0.05$ when compared to baseline TSH level in 4th quartile.

** $p<0.05$ when compared to baseline TC level in other quartiles.

*** $p<0.05$ when compared to other FT4 levels in 1st and 4th quartiles.

Each quartiles (1-4, n=25) of baseline Total Cholesterol (TC), TSH and FT4 levels.

Mean, range in each group TC mmol/L):	Mean, range in each group TSH (mIU/L):	Mean, range in each group FT4(pmol/L):
1=4.8, 3.8-5.2;	1=4.3, 4-4.6;	1=11.4, 9.6-12.3;
2=5.6, 5.3-5.9;	2=4.9, 4.7-5.2;	2=12.9, 12.4-13.4;
3=6.3, 6-6.6;	3=6, 5.3-6.8;	3=13.9, 13.5-14.4;
4=7.4, 6.7-8.7.	4=9.6, 7-15.8.	4=16.2, 14.5-22.6.

The possible reasons for these results are:

1. Highest reduction in total cholesterol in patients with baseline TSH between 4.0 and 4.6 mIU/L: This is likely to be due to the fact that a fixed dose of 100 mcg of L-thyroxine was used in the entire group, thus the group with the mildest increase in TSH levels had the greatest reduction.
2. Highest reduction in total cholesterol in patients with baseline total cholesterol between 5.3 and 5.9 mmol/L: This could be due to the fact that individuals with total cholesterol at the lowest and highest end of the spectrum (3.8 to 5.2 and 6.7 to 8.7 mmol/L) are genetically programmed to have those levels, and therefore the least likely for SCH and L-thyroxine to have any major influence.
3. Highest reduction in total cholesterol inpatients with baseline free T4 levels between 12.4 and 14.4 pmol/L: This result is unexpected and there is no direct explanation for this. This would need to be confirmed in a prospective study.

Since there was no association between baseline total cholesterol levels and baseline serum TSH levels and reduction in total cholesterol levels, associations were sought between other parameters. There was no correlation between increase in free T3 levels and change in total cholesterol ($r=-0.13$, $p=0.34$). There was a significant negative correlation between increase in free T4 levels and reduction in total cholesterol levels ($r= -0.43$, $p < 0.01$) (figure 14). There was also a significant positive correlation between change in free T4 levels and increase in FMD ($r=0.3$, $p < 0.0.5$) (figure 15).

Figure 14.

Relationship between change in total cholesterol levels with change in serum free T4 levels (significant outliers not excluded).

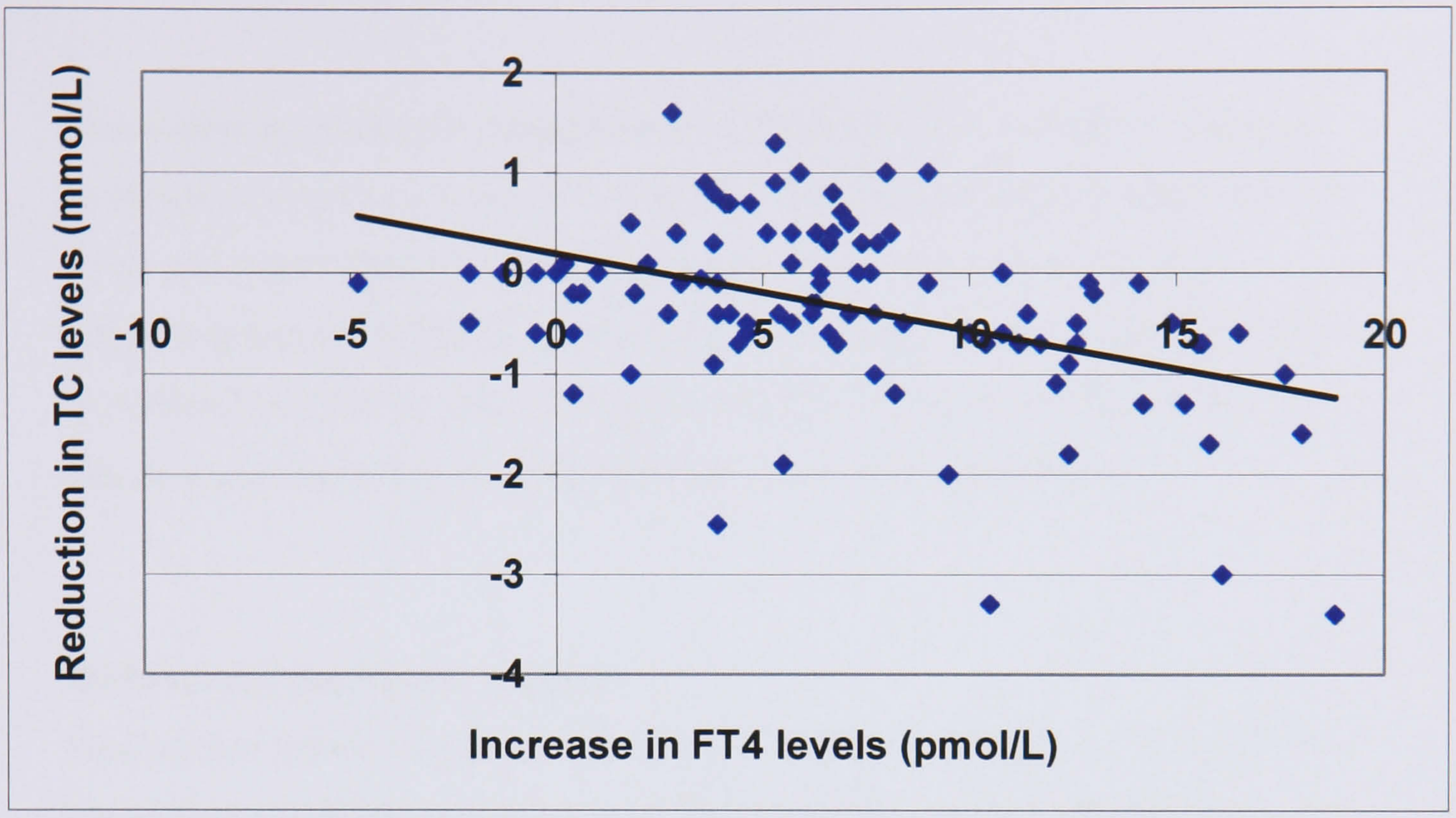
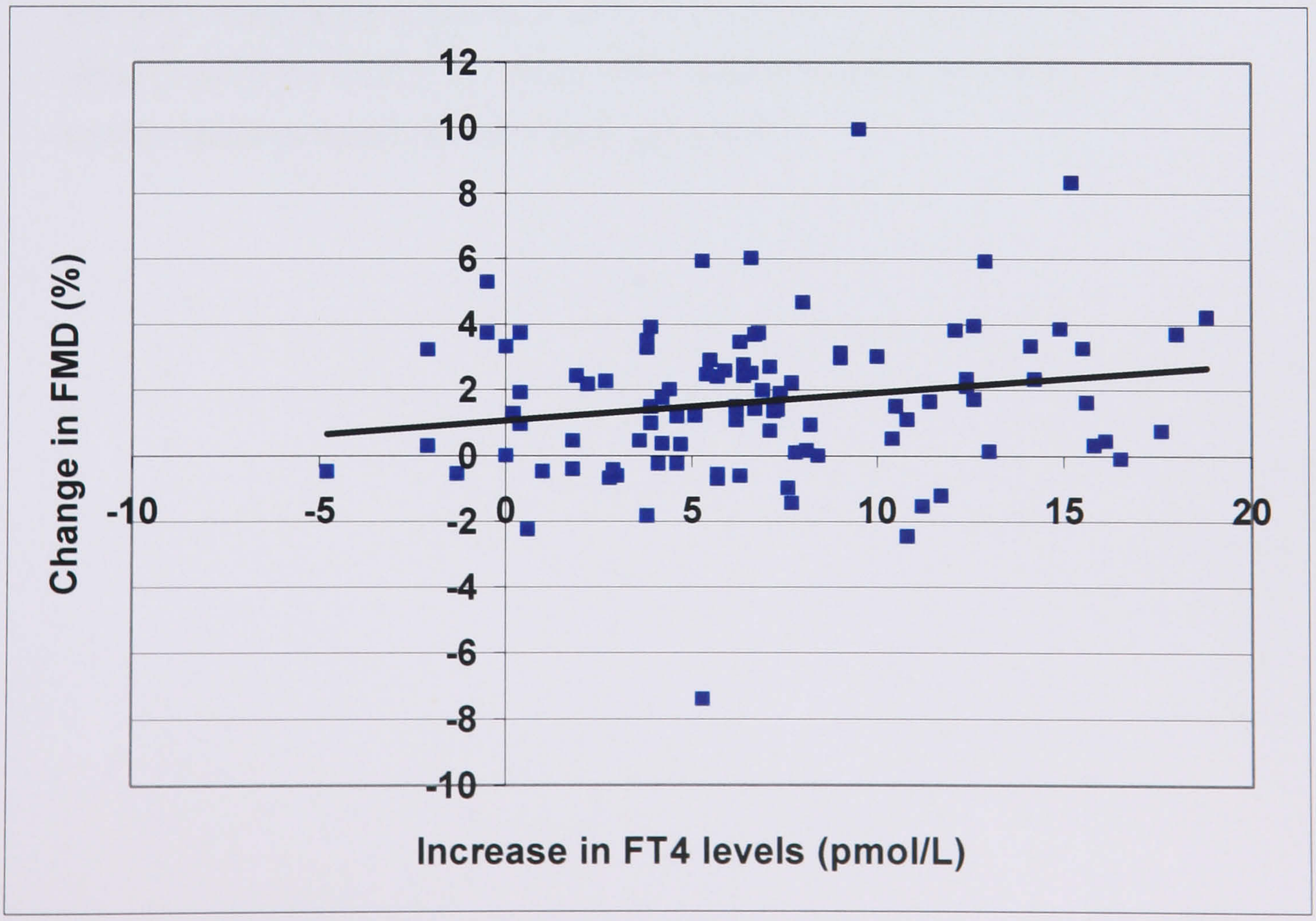


Figure 15.

Relationship between changes in FMD with change in serum free T4 levels (significant outliers not excluded).



There were no significant correlations between change in FT4 levels and reduction in weight (r= -0.05, p=0.76), and reduction in waist-hip ratio (r= -0.04, p=0.52).

Correction for multiple comparisons: If the Bonferroni correction is applied (6 variables: required p value is <0.008), the primary endpoints (reduction in TC levels and improvement in FMD) remain significant, as well as the most frequent symptom of SCH (improvement in tiredness). The six variables are the two primary endpoints, total cholesterol and FMD, weight, and the patient reported outcomes of QoL, symptoms and perceived health status.

Multivariate regression analyses:

Multivariate forward stepwise regression analyses, for changes in TC and FMD (dependent variables) and gender, smoking, waist hip ratio, TSH and FT4, (independent variables), showed that the change in FT4 concentrations was the only variable which predicted these two outcomes [change in TC: adjusted r^2=0.28 for whole model with change in FT4 (F=9.2, df=2, p<0.005) and change in FMD: adjusted r^2=0.31 for whole model and change in FT4 (F= 13.8, df=3, p<0.001), respectively)] (tables 29 and 30). Addition of change in diastolic blood pressure (less likely to change with changes in arterial compliance than systolic blood pressure) did not change the results.

Table 29.

Model of forward stepwise regression analysis for change in total cholesterol levels in people with SCH treated by L-thyroxine (n=100).

Variables	Adjusted R^2	F change	df	p value
Gender	-0.02	0.18	2	0.84
Gender + Smoking	-0.01	0.70	2	0.50
Gender + Smoking + Δ WHR	0.04	0.44	2	0.66
Gender + Smoking + Δ WHR + Δ TSH	0.06	1.12	3	0.18
Gender + Smoking + Δ WHR + Δ TSH + Δ Free T4	0.28	9.2	2	<0.005

Δ = Difference between treatment and baseline levels.

Table 30.

Model of forward stepwise regression analysis for change in FMD in people with SCH treated by L-thyroxine (n=100).

Variables	Adjusted R^2	F change	df	p value
Gender	-0.005	0.48	1	0.48
Gender + Smoking	-0.01	0.20	1	0.65
Gender + Smoking + Δ WHR	-0.23	0.16	1	0.69
Gender + Smoking + Δ WHR + Δ TSH	-0.16	1.64	2	0.20
Gender + Smoking + Δ WHR + Δ TSH + Δ Free T4	0.31	13.8	3	<0.001

Δ = Difference between treatment and baseline levels.

The effect of thyroid antibodies and serum TSH levels at baseline on various parameters after treatment

Forty-nine patients had positive anti-TPO antibodies (titre > 50). The results were then compared in all 100 patients with regards to positive versus negative antibody status. This showed no significant changes between individuals who were anti-TPO positive compared to anti-TPO negative with regards to any parameter.

Participants were then compared with regards to their baseline TSH levels. Sixty-two individuals had TSH < 6.1 mIU/L (the mean TSH of the group) and the remaining 38 had TSH > or = 6.1 mIU/L. There was no significant difference in change of any parameter measured in any individual apart from change in fat measured in kilograms as calculated by bio impedance. The change in fat mass in individuals with initial TSH < 6.1 mIU/L averaged 0.3 kg (1%) whereas the change averaged 1 kg (3.8%) in those with TSH > 6.1 mIU/L, p< 0.03.

DISCUSSION (A)

Synopsis of study findings

This randomised controlled study shows that treatment of SCH with L-thyroxine provides significant improvement across a wide spectrum of cardiovascular risk factors. The reduction in total cholesterol was consistent with reductions seen in previous studies. The improvement in endothelial function is a new finding that had never been assessed by a RCT before. There was no improvement in other CV risk factors like biochemical markers of endothelial function or markers of vascular inflammation. There was no improvement in carotid intima-media thickness in this 12-week study.

Possible mechanisms and explanations of findings

Elevated total and LDL cholesterol levels are a well documented feature of overt hypothyroidism (Staub, *et al* 1992), and treatment with L-thyroxine is standard practice. The association between increased total, LDL cholesterol levels and SCH has been inconsistent. There is evidence that SCH is associated with increased CV risk (Hak, *et al* 2000) (Imaizumi, *et al* 2004) (Walsh, *et al* 2005), although it is not supported by all (Tunbridge, *et al* 1977a) (Parle, *et al* 1991) (Rodondi, *et al* 2005) (Cappola, *et al* 2006). This increased risk may be as a direct result of higher concentrations of LDL cholesterol and its constituent apolipoprotein B in these patients. This study, which is the largest to date, shows that there is a significant reduction in LDL cholesterol by 0.2 mmol/L. It can be estimated that the possible relative reduction in 10-year CV mortality, due to reduction in LDL cholesterol alone, at about 10% (Anderson, *et al* 1991). The effect of L-thyroxine on LDL cholesterol may be due its action of reducing LDL cholesterol synthesis and increasing degradation (Friis and Pedersen 1987) (Walton, *et al* 1965). Data from cultured human skin fibroblast cells suggest that the increased LDL cholesterol degradation is mediated by triiodothyronine (T3) induced increase in LDL receptor number and not due to changes in the receptor's affinity to LDL cholesterol (Chait, *et al* 1979). Functional elements for thyroid hormones have been observed in the promoter region of the LDL receptor gene (Bakker, *et al* 1998). Previously it has been shown that doses of L-thyroxine that suppress TSH below the normal level have a more powerful LDL cholesterol reducing effect than doses that normalise TSH (Diekman, *et al* 2000). The present study confirms that finding.

It is well known that HDL cholesterol and its constituent apolipoprotein A1 are protective against atherosclerosis. Most studies have observed that SCH does not seem to have any effect on serum HDL cholesterol levels (Walsh, *et al* 2005) (Hueston and Pearson 2004) (Kvetny, *et al* 2004) (Canaris, *et al* 2000), with the exception of a few (Althaus, *et al* 1988) (Caron, *et al* 1990). RCTs that have examined the effect of L-thyroxine on HDL cholesterol have not found any benefit (Meier, *et al* 2001) (Kong, *et al* 2002) (Iqbal, *et al* 2006). There was a trend towards reduction in two other studies although it did not reach statistical significance (Caraccio, *et al* 2002) (Monzani, *et al* 2004). The present study did show a statistical reduction in HDL cholesterol and apolipoprotein A1 levels, although its clinical significance is questionable (0.06 mmol/L and 4.8 mg/dl, respectively). L-thyroxine therapy, at TSH suppressive doses, leads to a significant reduction in HDL cholesterol levels due to increased activation of hepatic lipase (Barth, *et al* 1987). This finding was confirmed in the present study when the reduction in HDL cholesterol levels became statistically non-significant when patients with biochemical evidence of over-replacement (TSH < 0.4 mIU/L) were excluded from the analyses.

It has been argued recently that apolipoprotein B and A1 are better predictors of CV risk than conventional cholesterol levels (Walldius, *et al* 2001). It has also been shown that the ratio of apolipoprotein B to A1 (apoB/apoA1) is linked to the highest risk of developing a cardiac event (Yusuf, *et al* 2004). The present study found a reduction in apoB/apoA1.

Vascular inflammation has been shown to predict CV disease and its effect is seen above and beyond traditional risk factors like cholesterol and blood pressure (Ridker, *et al* 1997). There is conflicting evidence that CRP is increased in people with SCH. Three large population-based studies found no difference in CRP levels between euthyroid controls and SCH patients (Hueston, *et al* 2005) (Kvetny, *et al* 2004) (Cappola, *et al* 2006), whereas a case-control study has shown a higher level in the SCH group (Christ-Crain, *et al* 2003). The intervention arm of the latter study found no reduction, following L-thyroxine therapy, in CRP levels. This was confirmed in the present study, where no improvement in hsCRP levels was noticed.

The present study has found a significant reduction in body weight, especially central adiposity as measured by waist circumference and waist-hip ratio. This

has never been shown before in a RCT. Body fat analysis by bio-impedance showed that the reduction in weight was correlated to a reduction in body fat mass. The mechanism of this action is unclear. It may be related to increase in resting energy expenditure, although this was not tested. It is also possible that body weight may be modulated by thyroid hormones due to effects on adipokines (Yu, *et al* 2006), although these were not measured in this study. There is no evidence that people with SCH have increased body weight. Most population-based studies that have identified SCH by screening have reported a small but non-significant increase in body weight (Imaizumi, *et al* 2004) (Iqbal, *et al* 2006) (Gussekloo, *et al* 2004) (Cappola, *et al* 2006) (Tunbridge, *et al* 1977a) (Pirich, *et al* 2000) (Volzke, *et al* 2004), whereas some have reported lower or no different values (Rodondi, *et al* 2005) (Kvetny, *et al* 2004) (Walsh, *et al* 2005). This study has shown a significant effect of L-thyroxine on reducing BMI, especially central adiposity as measured by waist circumference, which is an independent risk factor for CV disease (Hirsch, *et al* 2001).

The positive effect of L-thyroxine on endothelial function may be due to its action in increasing insulin-like growth factor-1 and vascular endothelial growth factor, both of which can improve endothelial nitric oxide synthase activity (Schmid, *et al* 2004). An improvement in FMD response may suggest better nitric oxide bioavailability and an associated improvement in vasoprotection in clinically relevant areas of the vasculature, such as coronary and carotid circulation (Pyke and Tschakovsky 2005). This improvement in endothelial function could translate into reduction in CV morbidity and mortality (Bonetti, *et al* 2003).

This study failed to find any reduction in carotid-intima media thickness in a subgroup of patients. This is dissimilar to the findings of a RCT that investigated this CV disease marker (Monzani, *et al* 2004). This could be because the duration of treatment with L-thyroxine was only 12 weeks in this study whereas the Monzani study had a treatment period of 6 months. Also patient numbers were low in this study. Similarly, there was no improvement in carotid elasticity and stiffness markers in this study, although it has never been investigated in a randomised fashion before.

Comparison with relevant findings from other published studies

Previous RCTs studying the effect of L-thyroxine on LDL cholesterol have shown conflicting results. Some RCTs (number of patients ranging from 45 to 63) (Meier, *et al* 2001) (Caraccio, *et al* 2002) (Monzani, *et al* 2004) showing an improvement in the atherogenic lipid profile whereas other RCTs (number of patients ranging from 17 to 84) (Cooper, *et al* 1984) (Nystrom, *et al* 1988) (Jaeschke, *et al* 1996) (Kong, *et al* 2002) (Iqbal, *et al* 2006) showing no difference. The variation in results may be due to small numbers, inappropriate selection of patients and study design (Ineck and Ng 2003). A systematic review of the effect of L-thyroxine on lipids in SCH suggested that the approximate mean reductions in TC is -0.24 mmol/L (95% CI, -0.06 to –0.42) and LDLc is -0.3 mmol/L (95% CI, -0.01 to –0.54) with no significant change in HDLc (Danese, *et al* 2000). The same review concluded that serum apoB decreased by 8.5mg/dl (95% CI, -4.2 to –13) whereas apoA1 did not change significantly. Another systematic review concluded that the reduction in total cholesterol due to L-thyroxine in patients with SCH was 0.4 mmol/L (Tanis, *et al* 1996). The present study confirms these findings.

The reduction in body weight, especially central adiposity as measured by waist circumference has not been shown by any previous randomised controlled trial. This could be due to the fact that in comparison to others we studied more patients and used 100 mcg of L-thyroxine per day. Previous studies used doses less than 100 mcg, with one exception (Nystrom, *et al* 1988). The reduction in BMI and waist circumference was obtained in this study even when patients with evidence of over-replacement (TSH < 0.4 mIU/L) were excluded.

This study has shown that a significant increase in FT4, although within the normal reference range, may be a better marker for risk factors for CV disease in monitoring response to treatment in SCH than TSH level alone. This is in agreement with previous research that has shown that changes in serum lipoproteins, in both hypothyroid and hyperthyroid patients, are correlated with changes in FT4 levels (Wiseman, *et al* 1993).

Brachial artery FMD is emerging as an independent predictor of future cardiac events (Gokce, *et al* 2002). FMD in brachial artery correlates very well with FMD in a major coronary artery (Takase, *et al* 1998). The present study has confirmed the beneficial effect of treatment with L-thyroxine on brachial artery

endothelial function in people with SCH, as found in a previous study (Taddei, *et al* 2003). However the latter was not a randomised controlled trial and studied only six patients whose TSH was below 10 mIU/L.

Limitations of the study

The limitations of the present study are that patients were not identified from a population sample, the length of treatment was only twelve weeks, and the dose of L-thyroxine was a fixed 100 mcg per patient. The patient sample was obtained primarily from people presenting to general practice and excluded those with other chronic (and high CV risk) diseases, the results cannot therefore be extrapolated to these patient groups. The patient sample was primarily selected to reflect mild SCH, as this is the commonest and most controversial area of clinical practice (Tunbridge, *et al* 1981). The treatment period of twelve weeks duration was deemed adequate for the present study since it takes about 4-6 weeks of full replacement therapy with L-thyroxine to correct the dyslipidaemia of overt hypothyroidism (Kuusi, *et al* 1988). However, it may be insufficient time for some benefits (such as perceptible reduction in some symptoms and psychological factors) to become apparent to patients. The fixed dose of 100 mcg per day was deemed adequate, as a previous study that had used it in biochemically euthyroid patients with hypothyroid symptoms had shown that TSH did not drop below the reference range (Pollock, *et al* 2001). This may have led to a few patients (10%) being over-treated, but the subgroup analysis of patients who had achieved desired TSH and free T4 levels confirmed all of the major findings of the study (apart from the reduction in HDL cholesterol and apolipoprotein A1, which become non-significant and the QoL domain of motivation which became significant). Another recent RCT that titrated the dose of L-thyroxine based on patient's TSH levels utilised a mean dose of 97.5 mcg/day (Iqbal, *et al* 2006), further justifying the decision to employ the standard dose of 100 mcg/day.

Summary

In conclusion, people with SCH can obtain significant improvement in their CV risk factor profile (weight loss with reduction in central adiposity, a favourable shift in lipoprotein pattern and improvement in endothelial function), and reduced perceived negative impact of hypothyroidism on QoL, after treatment with 100 mcg of L-thyroxine. These results suggest that serum FT4 levels should also be taken into account when monitoring treatment. Long-term studies are required to confirm whether this translates into reduction in CV mortality and morbidity.

REFERENCES (A)

(1990) Periodic health examination, 1990 update: 1. Early detection of hyperthyroidism and hypothyroidism in adults and screening of newborns for congenital hypothyroidism. Canadian Task Force on the Periodic Health Examination. *Cmaj,* **142,** 955-961.

(1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet,* **344,** 1383-1389.

Abdu, T.A., Elhadd, T., Pfeifer, M. & Clayton, R.N. (2001) Endothelial dysfunction in endocrine disease. *Trends Endocrinol Metab,* **12,** 257-265.

Adams, D.H. & Shaw, S. (1994) Leucocyte-endothelial interactions and regulation of leucocyte migration. *Lancet,* **343,** 831-836.

Althaus, B.U., Staub, J.J., Ryff-De Leche, A., Oberhansli, A. & Stahelin, H.B. (1988) LDL/HDL-changes in subclinical hypothyroidism: possible risk factors for coronary heart disease. *Clin Endocrinol (Oxf),* **28,** 157-163.

Anderson, K.M., Odell, P.M., Wilson, P.W. & Kannel, W.B. (1991) Cardiovascular disease risk profiles. *Am Heart J,* **121,** 293-298.

Anderson, T.J. (1999) Assessment and treatment of endothelial dysfunction in humans. *J Am Coll Cardiol,* **34,** 631-638.

Anderson, T.J., Uehata, A., Gerhard, M.D., Meredith, I.T., Knab, S., Delagrange, D., Lieberman, E.H., Ganz, P., Creager, M.A., Yeung, A.C. & et al. (1995) Close relation of endothelial function in the human coronary and peripheral circulations. *J Am Coll Cardiol,* **26,** 1235-1241.

Arem, R., Rokey, R., Kiefe, C., Escalante, D.A. & Rodriguez, A. (1996) Cardiac systolic and diastolic function at rest and exercise in subclinical hypothyroidism: effect of thyroid hormone therapy. *Thyroid,* **6,** 397-402.

Arnett, D.K., Evans, G.W. & Riley, W.A. (1994) Arterial stiffness: a new cardiovascular risk factor? *Am J Epidemiol,* **140,** 669-682.

Ayala, A.R., Danese, M.D. & Ladenson, P.W. (2000) When to treat mild hypothyroidism. *Endocrinol Metab Clin North Am,* **29,** 399-415.

Bakker, O., Hudig, F., Meijssen, S. & Wiersinga, W.M. (1998) Effects of triiodothyronine and amiodarone on the promoter of the human LDL receptor gene. *Biochem Biophys Res Commun,* **249,** 517-521.

Ball, M.J., Griffiths, D. & Thorogood, M. (1991) Asymptomatic hypothyroidism and hypercholesterolaemia. *J R Soc Med,* **84,** 527-529.

Baloch, Z., Carayon, P., Conte-Devolx, B., Demers, L.M., Feldt-Rasmussen, U., Henry, J.F., LiVosli, V.A., Niccoli-Sire, P., John, R., Ruf, J., Smyth, P.P., Spencer, C.A. & Stockigt, J.R. (2003) Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid,* **13,** 3-126.

Barth, J.D., Jansen, H., Kromhout, D., Reiber, J.H., Birkenhager, J.C. & Arntzenius, A.C. (1987) Progression and regression of human coronary atherosclerosis. The role of lipoproteins, lipases and thyroid hormones in coronary lesion growth. *Atherosclerosis,* **68,** 51-58.

Bastenie, P.A., Vanhaelst, L., Bonnyns, M., Neve, P. & Staquet, M. (1971) Preclinical hypothyroidism: a risk factor for coronary heart-disease. *Lancet,* **1,** 203-204.

Bastenie, P.A., Vanhaelst, L. & Neve, P. (1967) Coronary-artery disease in hypothyroidism. *Lancet,* **2,** 1221-1222.

Belch, J.J., Shaw, J.W., Kirk, G., McLaren, M., Robb, R., Maple, C. & Morse, P. (1997) The white blood cell adhesion molecule E-selectin predicts restenosis in patients with intermittent claudication undergoing percutaneous transluminal angioplasty. *Circulation,* **95,** 2027-2031.

Bell, G.M., Todd, W.T., Forfar, J.C., Martyn, C., Wathen, C.G., Gow, S., Riemersma, R. & Toft, A.D. (1985) End-organ responses to thyroxine therapy in subclinical hypothyroidism. *Clin Endocrinol (Oxf),* **22,** 83-89.

Bender, R. & Lange, S. (1999) Multiple test procedures other than Bonferroni's deserve wider use. *Bmj,* **318,** 600-601.

Bengel, F.M., Nekolla, S.G., Ibrahim, T., Weniger, C., Ziegler, S.I. & Schwaiger, M. (2000) Effect of thyroid hormones on cardiac function, geometry, and oxidative metabolism assessed noninvasively by positron emission tomography and magnetic resonance imaging. *J Clin Endocrinol Metab,* **85,** 1822-1827.

Bevilacqua, M.P., Stengelin, S., Gimbrone, M.A., Jr. & Seed, B. (1989) Endothelial leukocyte adhesion molecule 1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. *Science,* **243,** 1160-1165.

Biondi, B., Fazio, S., Palmieri, E.A., Carella, C., Panza, N., Cittadini, A., Bone, F., Lombardi, G. & Sacca, L. (1999) Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab,* **84,** 2064-2067.

Biondi, B. & Klein, I. (2004) Hypothyroidism as a risk factor for cardiovascular disease. *Endocrine,* **24,** 1-13.

Bland, J.M. & Altman, D.G. (1995) Multiple significance tests: the Bonferroni method. *Bmj,* **310,** 170.

Blann, A.D., Amiral, J. & McCollum, C.N. (1997a) Prognostic value of increased soluble thrombomodulin and increased soluble E-selectin in ischaemic heart disease. *Eur J Haematol,* **59,** 115-120.

Blann, A.D. & Lip, G.Y. (1998) Raised levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in the plasma of patients with ischaemic heart disease and hyperlipidaemia. *Atherosclerosis,* **141,** 177-178.

Blann, A.D., Lip, G.Y., Beevers, D.G. & McCollum, C.N. (1997b) Soluble P-selectin in atherosclerosis: a comparison with endothelial cell and platelet markers. *Thromb Haemost,* **77,** 1077-1080.

Bogaty, P., Hackett, D., Davies, G. & Maseri, A. (1994) Vasoreactivity of the culprit lesion in unstable angina. *Circulation,* **90,** 5-11.

Bonetti, P.O., Lerman, L.O. & Lerman, A. (2003) Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol,* **23,** 168-175.

Bots, M.L., Hoes, A.W., Koudstaal, P.J., Hofman, A. & Grobbee, D.E. (1997) Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation,* **96,** 1432-1437.

Boushey, C.J., Beresford, S.A., Omenn, G.S. & Motulsky, A.G. (1995) A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. *Jama,* **274,** 1049-1057.

Canaris, G.J., Manowitz, N.R., Mayor, G. & Ridgway, E.C. (2000) The Colorado thyroid disease prevalence study. *Arch Intern Med,* **160,** 526-534.

Cappola, A.R., Fried, L.P., Arnold, A.M., Danese, M.D., Kuller, L.H., Burke, G.L., Tracy, R.P. & Ladenson, P.W. (2006) Thyroid status, cardiovascular risk, and mortality in older adults. *Jama,* **295,** 1033-1041.

Caraccio, N., Ferrannini, E. & Monzani, F. (2002) Lipoprotein profile in subclinical hypothyroidism: response to levothyroxine replacement, a randomized placebo-controlled study. *J Clin Endocrinol Metab,* **87,** 1533-1538.

Caron, P., Calazel, C., Parra, H.J., Hoff, M. & Louvet, J.P. (1990) Decreased HDL cholesterol in subclinical hypothyroidism: the effect of L-thyroxine therapy. *Clin Endocrinol (Oxf),* **33,** 519-523.

Celermajer, D.S., Sorensen, K.E., Gooch, V.M., Spiegelhalter, D.J., Miller, O.I., Sullivan, I.D., Lloyd, J.K. & Deanfield, J.E. (1992) Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet,* **340,** 1111-1115.

Chait, A., Bierman, E.L. & Albers, J.J. (1979) Regulatory role of triiodothyronine in the degradation of low density lipoprotein by cultured human skin fibroblasts. *J Clin Endocrinol Metab,* **48,** 887-889.

Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Jr., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., Jr. & Roccella, E.J. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *Jama,* **289,** 2560-2572.

Christ-Crain, M., Meier, C., Guglielmetti, M., Huber, P.R., Riesen, W., Staub, J.J. & Muller, B. (2003) Elevated C-reactive protein and homocysteine values: cardiovascular risk factors in hypothyroidism? A cross-sectional and a double-blind, placebo-controlled trial. *Atherosclerosis,* **166,** 379-386.

Clarke, R., Daly, L., Robinson, K., Naughten, E., Cahalane, S., Fowler, B. & Graham, I. (1991) Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med,* **324,** 1149-1155.

Cooke, J.P. & Dzau, V.J. (1997) Nitric oxide synthase: role in the genesis of vascular disease. *Annu Rev Med,* **48,** 489-509.

Cooper, D.S. (1998) Subclinical Thyroid Disease: A Clinician's Perspective. *Ann Intern Med,* **129,** 135-138.

Cooper, D.S. (2001) Clinical practice. Subclinical hypothyroidism. *N Engl J Med,* **345,** 260-265.

Cooper, D.S., Halpern, R., Wood, L.C., Levin, A.A. & Ridgway, E.C. (1984) L-Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Ann Intern Med,* **101,** 18-24.

Corretti, M.C., Anderson, T.J., Benjamin, E.J., Celermajer, D., Charbonneau, F., Creager, M.A., Deanfield, J., Drexler, H., Gerhard-Herman, M., Herrington, D., Vallance, P., Vita, J. & Vogel, R. (2002) Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol,* **39,** 257-265.

Creager, M.A., Cooke, J.P., Mendelsohn, M.E., Gallagher, S.J., Coleman, S.M., Loscalzo, J. & Dzau, V.J. (1990) Impaired vasodilation of forearm resistance vessels in hypercholesterolemic humans. *J Clin Invest,* **86,** 228-234.

Crowley, W.F., Jr., Ridgway, E.C., Bough, E.W., Francis, G.S., Daniels, G.H., Kourides, I.A., Myers, G.S. & Maloof, F. (1977) Noninvasive evaluation of cardiac function in hypothyroidism. Response to gradual thyroxine replacement. *N Engl J Med,* **296,** 1-6.

Dagre, A.G., Lekakis, J.P., Papaioannou, T.G., Papamichael, C.M., Koutras, D.A., Stamatelopoulos, S.F. & Alevizaki, M. (2005) Arterial stiffness is increased in subjects with hypothyroidism. *Int J Cardiol,* **103,** 1-6.

Dahlof, B., Devereux, R.B., Kjeldsen, S.E., Julius, S., Beevers, G., de Faire, U., Fyhrquist, F., Ibsen, H., Kristiansson, K., Lederballe-Pedersen, O., Lindholm, L.H., Nieminen, M.S., Omvik, P., Oparil, S. & Wedel, H. (2002) Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet,* **359,** 995-1003.

Danese, M.D., Ladenson, P.W., Meinert, C.L. & Powe, N.R. (2000) Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab,* **85,** 2993-3001.

Danese, M.D., Powe, N.R., Sawin, C.T. & Ladenson, P.W. (1996) Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. *Jama,* **276,** 285-292.

Danesh, J., Wheeler, J.G., Hirschfield, G.M., Eda, S., Eiriksdottir, G., Rumley, A., Lowe, G.D., Pepys, M.B. & Gudnason, V. (2004) C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med,* **350,** 1387-1397.

Dart, A.M., Lacombe, F., Yeoh, J.K., Cameron, J.D., Jennings, G.L., Laufer, E. & Esmore, D.S. (1991) Aortic distensibility in patients with isolated hypercholesterolaemia, coronary artery disease, or cardiac transplant. *Lancet,* **338,** 270-273.

Davis, B.R., Cutler, J.A., Furberg, C.D., Wright, J.T., Farber, M.A., Felicetta, J.V. & Stokes, J.D. (2002) Relationship of antihypertensive treatment regimens and change in blood pressure to risk for heart failure in hypertensive patients randomly assigned to doxazosin or chlorthalidone: further analyses from the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial. *Ann Intern Med,* **137,** 313-320.

De Angelis, C.D., Drazen, J.M., Frizelle, F.A., Haug, C., Hoey, J., Horton, R., Kotzin, S., Laine, C., Marusic, A., Overbeke, A.J., Schroeder, T.V., Sox, H.C. & Van Der Weyden, M.B. (2005) Is this clinical trial fully registered?--A statement from the International Committee of Medical Journal Editors. *N Engl J Med,* **352,** 2436-2438.

De Lorenzo, A., Andreoli, A., Fusco, A., Magnani, A., D'Orazio, N. & Bertoli, A. (2000) Effect of subclinical hypothyroidism on body fluid compartments. *Horm Metab Res,* **32,** 359-363.

Dean, J.W. & Fowler, P.B. (1985) Exaggerated responsiveness to thyrotrophin releasing hormone: a risk factor in women with coronary artery disease. *Br Med J (Clin Res Ed),* **290,** 1555-1561.

del Sol, A.I., Moons, K.G., Hollander, M., Hofman, A., Koudstaal, P.J., Grobbee, D.E., Breteler, M.M., Witteman, J.C. & Bots, M.L. (2001) Is carotid intima-media thickness useful in cardiovascular disease risk assessment? The Rotterdam Study. *Stroke,* **32,** 1532-1538.

Delp, M.D., McAllister, R.M. & Laughlin, M.H. (1995) Exercise training alters aortic vascular reactivity in hypothyroid rats. *Am J Physiol,* **268,** H1428-1435.

Di Bello, V., Monzani, F., Giorgi, D., Bertini, A., Caraccio, N., Valenti, G., Talini, E., Paterni, M., Ferrannini, E. & Giusti, C. (2000) Ultrasonic myocardial textural analysis in subclinical hypothyroidism. *J Am Soc Echocardiogr,* **13,** 832-840.

Diekman, M.J., Anghelescu, N., Endert, E., Bakker, O. & Wiersinga, W.M. (2000) Changes in plasma low-density lipoprotein (LDL)- and high-density lipoprotein cholesterol in hypo- and hyperthyroid patients are related to changes in free thyroxine, not to polymorphisms in LDL receptor or cholesterol ester transfer protein genes. *J Clin Endocrinol Metab,* **85,** 1857-1862.

Dimmeler, S., Fleming, I., Fisslthaler, B., Hermann, C., Busse, R. & Zeiher, A.M. (1999) Activation of nitric oxide synthase in endothelial cells by Akt-dependent phosphorylation. *Nature,* **399,** 601-605.

Domanski, M., Norman, J., Wolz, M., Mitchell, G. & Pfeffer, M. (2001) Cardiovascular risk assessment using pulse pressure in the first national health and nutrition examination survey (NHANES I). *Hypertension,* **38,** 793-797.

Eckel, R.H. (2003) *Obesity: mechanisms and clinical management.* Lippincott Williams & Wilkins., Philadelphia.

Eckel, R.H., Grundy, S.M. & Zimmet, P.Z. (2005) The metabolic syndrome. *Lancet,* **365,** 1415-1428.

Erem, C., Kavgaci, H., Ersoz, H.O., Hacihasanoglu, A., Ukinc, K., Karti, S.S., Deger, O. & Telatari, M. (2003) Blood coagulation and fibrinolytic activity in hypothyroidism. *Int J Clin Pract,* **57,** 78-81.

Expert Panel on Detection, E., and Treatment of High Blood Cholesterol in Adults, (2001) Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA,* **285,** 2486-2497.

Faber, J., Petersen, L., Wiinberg, N., Schifter, S. & Mehlsen, J. (2002) Hemodynamic changes after levothyroxine treatment in subclinical hypothyroidism. *Thyroid,* **12,** 319-324.

Foldes, J., Istvanfy, M., Halmagyi, M., Varadi, A., Gara, A. & Partos, O. (1987) Hypothyroidism and the heart. Examination of left ventricular function in subclinical hypothyroidism. *Acta Med Hung,* **44,** 337-347.

Forfar, J.C., Wathen, C.G., Todd, W.T., Bell, G.M., Hannan, W.J., Muir, A.L. & Toft, A.D. (1985) Left ventricular performance in subclinical hypothyroidism. *Q J Med,* **57,** 857-865.

Franklyn, J. (1995) 'Subclinical hypothyroidism': to treat or not to treat, that is the question. *Clin Endocrinol (Oxf),* **43,** 443-444.

Friis, T. & Pedersen, L.R. (1987) Serum lipids in hyper- and hypothyroidism before and after treatment. *Clin Chim Acta,* **162,** 155-163.

Fuller, H., Jr., Spittell, J.A., Jr., McConahey, W.M. & Schirger, A. (1966) Myxedema and hypertension. *Postgrad Med,* **40,** 425-428.

Furberg, C.D., Adams, H.P., Jr., Applegate, W.B., Byington, R.P., Espeland, M.A., Hartwell, T., Hunninghake, D.B., Lefkowitz, D.S., Probstfield, J., Riley, W.A. (1994) Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. *Circulation,* **90,** 1679-1687.

Gaspar, I.A. (1968) Postmortem observations on the thyroid in atherosclerosis. *J Am Geriatr Soc,* **16,** 686-695.

Glenn, G.C. (1996) Practice parameter on laboratory panel testing for screening and case finding in asymptomatic adults. Laboratory Testing Strategy Task Force of the College of American Pathologists. *Arch Pathol Lab Med,* **120,** 929-943.

Gokce, N., Keaney, J.F., Jr., Hunter, L.M., Watkins, M.T., Menzoian, J.O. & Vita, J.A. (2002) Risk stratification for postoperative cardiovascular events via noninvasive assessment of endothelial function: a prospective study. *Circulation,* **105,** 1567-1572.

Gokse, N., Keaney, J.F., Jr. & Vita, J.A. (1998) Endotheliopathies:clinical manifestation of endothelial dysfunction. In: *Thrombosis and hemorrhage.* (ed. by J. Loscalzo & A.I. Shafer), pp. 901-924. Williams and Wilkins, Baltimore.

Graettinger, J.S., Muenster, J.J., Checchia, C.S., Grissom, R.L. & Campbell, J.A. (1958) A correlation of clinical and hemodynamic studies in patients with hypothyroidism. *J Clin Invest,* **37,** 502-510.

Gray, R.S., Borsey, D.Q., Seth, J., Herd, R., Brown, N.S. & Clarke, B.F. (1980) Prevalence of subclinical thyroid failure in insulin-dependent diabetes. *J Clin Endocrinol Metab,* **50,** 1034-1037.

Gumieniak, O., Perlstein, T.S., Hopkins, P.N., Brown, N.J., Murphey, L.J., Jeunemaitre, X., Hollenberg, N.K. & Williams, G.H. (2004) Thyroid function and blood pressure homeostasis in euthyroid subjects. *J Clin Endocrinol Metab,* **89,** 3455-3461.

Gussekloo, J., van Exel, E., de Craen, A.J., Meinders, A.E., Frolich, M. & Westendorp, R.G. (2004) Thyroid status, disability and cognitive function, and survival in old age. *Jama,* **292,** 2591-2599.

Hak, A.E., Pols, H.A., Visser, T.J., Drexhage, H.A., Hofman, A. & Witteman, J.C. (2000) Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med,* **132,** 270-278.

Halcox, J.P., Schenke, W.H., Zalos, G., Mincemoyer, R., Prasad, A., Waclawiw, M.A., Nour, K.R. & Quyyumi, A.A. (2002) Prognostic value of coronary vascular endothelial dysfunction. *Circulation,* **106,** 653-658.

Healy, B. (1990) Endothelial cell dysfunction: an emerging endocrinopathy linked to coronary disease. *J Am Coll Cardiol,* **16,** 357-358.

Heinonen, O.P., Gordin, A., Aho, K., Punsar, S., Pyorala, K. & Puro, K. (1972) Symptomless autoimmune thyroiditis in coronary heart-disease. *Lancet,* **1,** 785-786.

Held, C., Hjemdahl, P., Rehnqvist, N., Wallen, N.H., Bjorkander, I., Eriksson, S.V., Forslund, L. & Wiman, B. (1997) Fibrinolytic variables and cardiovascular prognosis in patients with stable angina pectoris treated with verapamil or metoprolol. Results from the Angina Prognosis study in Stockholm. *Circulation,* **95,** 2380-2386.

Helfand, M. & Redfern, C.C. (1998) Clinical guideline, part 2. Screening for thyroid disease: an update. American College of Physicians. *Ann Intern Med,* **129,** 144-158.

Hills, M. & Armitage, P. (1979) The two-period cross-over clinical trial. *Br J Clin Pharmacol,* **8,** 7-20.

Hirai, T., Sasayama, S., Kawasaki, T. & Yagi, S. (1989) Stiffness of systemic arteries in patients with myocardial infarction. A noninvasive method to predict severity of coronary atherosclerosis. *Circulation,* **80,** 78-86.

Hirsch, J., Salans, L.B. & Aronne, L.J. (2001) Obesity. In: *Principles and practice of endocrinology and metabolism* (ed. by K.L. Becker), pp. 1239-1246. Lippincott, Williams and Wilkins., Philadelphia.

Hollowell, J.G., Staehling, N.W., Flanders, W.D., Hannon, W.H., Gunter, E.W., Spencer, C.A. & Braverman, L.E. (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab,* **87,** 489-499.

Honing, M.L., Smits, P., Morrison, P.J. & Rabelink, T.J. (2000) Bradykinin-induced vasodilation of human forearm resistance vessels is primarily mediated by endothelium-dependent hyperpolarization. *Hypertension,* **35,** 1314-1318.

Hsieh, C.J., Wang, P.W., Wang, S.T., Liu, R.T., Tung, S.C., Chien, W.Y., Lu, Y.C., Chen, J.F., Chen, C.H. & Kuo, M.C. (2002) Serum leptin concentrations of patients with sequential thyroid function changes. *Clin Endocrinol (Oxf),* **57,** 29-34.

Huber, G., Staub, J.J., Meier, C., Mitrache, C., Guglielmetti, M., Huber, P. & Braverman, L.E. (2002) Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab,* **87,** 3221-3226.

Hueston, W.J., King, D.E. & Geesey, M.E. (2005) Serum biomarkers for cardiovascular inflammation in subclinical hypothyroidism. *Clin Endocrinol (Oxf),* **63,** 582-587.

Hueston, W.J. & Pearson, W.S. (2004) Subclinical hypothyroidism and the risk of hypercholesterolemia. *Ann Fam Med,* **2,** 351-355.

Huggins, G.S., Pasternak, R.C., Alpert, N.M., Fischman, A.J. & Gewirtz, H. (1998) Effects of short-term treatment of hyperlipidemia on coronary vasodilator function and myocardial perfusion in regions having substantial impairment of baseline dilator reverse. *Circulation,* **98,** 1291-1296.

Hwang, S.J., Ballantyne, C.M., Sharrett, A.R., Smith, L.C., Davis, C.E., Gotto, A.M., Jr. & Boerwinkle, E. (1997) Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. *Circulation,* **96,** 4219-4225.

Imaizumi, M., Akahoshi, M., Ichimaru, S., Nakashima, E., Hida, A., Soda, M., Usa, T., Ashizawa, K., Yokoyama, N., Maeda, R., Nagataki, S. & Eguchi, K. (2004) Risk for ischemic heart disease and all-cause mortality in subclinical hypothyroidism. *J Clin Endocrinol Metab,* **89,** 3365-3370.

Ineck, B.A. & Ng, T.M. (2003) Effects of subclinical hypothyroidism and its treatment on serum lipids. *Ann Pharmacother,* **37,** 725-730.

Iqbal, A., Jorde, R. & Figenschau, Y. (2006) 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. *J Intern Med,* **260,** 53-61.

Ishikawa, T., Chijiwa, T., Hagiwara, M., Mamiya, S. & Hidaka, H. (1989) Thyroid hormones directly interact with vascular smooth muscle strips. *Mol Pharmacol,* **35,** 760-765.

Jaeschke, R., Guyatt, G., Gerstein, H., Patterson, C., Molloy, W., Cook, D., Harper, S., Griffith, L. & Carbotte, R. (1996) Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med,* **11,** 744-749.

Juhan-Vague, I., Pyke, S.D., Alessi, M.C., Jespersen, J., Haverkate, F. & Thompson, S.G. (1996) Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. ECAT Study Group. European Concerted Action on Thrombosis and Disabilities. *Circulation,* **94,** 2057-2063.

Kahaly, G., Mohr-Kahaly, S., Beyer, J. & Meyer, J. (1995) Prevalence of myxomatous mitral valve prolapse in patients with lymphocytic thyroiditis. *Am J Cardiol,* **76,** 1309-1310.

Kahaly, G.J. (2000) Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid,* **10,** 665-679.

Kannel, W.B., McGee, D. & Gordon, T. (1976) A general cardiovascular risk profile: the Framingham Study. *Am J Cardiol,* **38,** 46-51.

Kanters, S.D., Algra, A., van Leeuwen, M.S. & Banga, J.D. (1997) Reproducibility of in vivo carotid intima-media thickness measurements: a review. *Stroke,* **28,** 665-671.

Keating, F.R., Jr., Parkin, T.W., Selby, J.B. & Dickinson, L.S. (1961) Treatment of heart disease associated with myxedema. *Prog Cardiovasc Dis,* **3,** 364-381.

Klein, I. (1989) In: *Endocrine mechanisms in hypertension* (ed. by J.H. Laragh, B.M. Brenner & N.M. Kaplan), Vol. 2. Raven Press, New York.

Klein, I. (1990) Thyroid hormone and the cardiovascular system. *Am J Med,* **88,** 631-637.

Klein, I. & Ojamaa, K. (eds.) (2000) *The cardiovascular system in hypothyroidism.* Lippincott Wiliam & Wilkins, Philadelphia.

Klein, I. & Ojamaa, K. (2001) Thyroid hormone and the cardiovascular system. *N Engl J Med,* **344,** 501-509.

Kong, W.M., Sheikh, M.H., Lumb, P.J., Naoumova, R.P., Freedman, D.B., Crook, M., Dore, C.J. & Finer, N. (2002) A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med,* **112,** 348-354.

Kuller, L.H., Shemanski, L., Psaty, B.M., Borhani, N.O., Gardin, J., Haan, M.N., O'Leary, D.H., Savage, P.J., Tell, G.S. & Tracy, R. (1995) Subclinical disease as an independent risk factor for cardiovascular disease. *Circulation,* **92,** 720-726.

Kumana, C.R., Cheung, B.M. & Lauder, I.J. (1999) Gauging the impact of statins using number needed to treat. *Jama,* **282,** 1899-1901.

Kuusi, T., Taskinen, M.R. & Nikkila, E.A. (1988) Lipoproteins, lipolytic enzymes, and hormonal status in hypothyroid women at different levels of substitution. *J Clin Endocrinol Metab,* **66,** 51-56.

Kvetny, J., Heldgaard, P.E., Bladbjerg, E.M. & Gram, J. (2004) Subclinical hypothyroidism is associated with a low-grade inflammation, increased triglyceride levels and predicts cardiovascular disease in males below 50 years. *Clin Endocrinol (Oxf),* **61,** 232-238.

Lekakis, J., Papamichael, C., Alevizaki, M., Piperingos, G., Marafelia, P., Mantzos, J., Stamatelopoulos, S. & Koutras, D.A. (1997) Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values. *Thyroid,* **7,** 411-414.

Levine, G.N., Keaney, J.F., Jr. & Vita, J.A. (1995) Cholesterol reduction in cardiovascular disease. Clinical benefits and possible mechanisms. *N Engl J Med,* **332,** 512-521.

Liang, Q., Wendelhag, I., Wikstrand, J. & Gustavsson, T. (2000) A multiscale dynamic programming procedure for boundary detection in ultrasonic artery images. *IEEE Trans Med Imaging,* **19,** 127-142.

Lindeman, R.D., Romero, L.J., Schade, D.S., Wayne, S., Baumgartner, R.N. & Garry, P.J. (2003) Impact of subclinical hypothyroidism on serum total homocysteine concentrations, the prevalence of coronary heart disease (CHD), and CHD risk factors in the New Mexico Elder Health Survey. *Thyroid,* **13,** 595-600.

Liuzzo, G., Biasucci, L.M., Gallimore, J.R., Grillo, R.L., Rebuzzi, A.G., Pepys, M.B. & Maseri, A. (1994) The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N Engl J Med,* **331,** 417-424.

Lovato, L.C., Hill, K., Hertert, S., Hunninghake, D.B. & Probstfield, J.L. (1997) Recruitment for controlled clinical trials: literature summary and annotated bibliography. *Control Clin Trials,* **18,** 328-352.

Ludmer, P.L., Selwyn, A.P., Shook, T.L., Wayne, R.R., Mudge, G.H., Alexander, R.W. & Ganz, P. (1986) Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med,* **315,** 1046-1051.

Maarek, B., Simon, A.C., Levenson, J., Pithois-Merli, I. & Bouthier, J. (1987) Heterogeneity of the atherosclerotic process in systemic hypertension poorly controlled by drug treatment. *Am J Cardiol,* **59,** 414-417.

Mamiya, S., Hagiwara, M., Inoue, S. & Hidaka, H. (1989) Thyroid hormones inhibit platelet function and myosin light chain kinase. *J Biol Chem,* **264,** 8575-8579.

Manji, N., Boelaert, K., Sheppard, M.C., Holder, R.L., Gough, S.C. & Franklyn, J.A. (2006) Lack of association between serum TSH or free T4 and body mass index in euthyroid subjects. *Clin Endocrinol (Oxf),* **64,** 125-128.

Megnien, J.L., Simon, A., Denarie, N., Del-Pino, M., Gariepy, J., Segond, P. & Levenson, J. (1998) Aortic stiffening does not predict coronary and extracoronary atherosclerosis in asymptomatic men at risk for cardiovascular disease. *Am J Hypertens,* **11,** 293-301.

Meier, C., Staub, J.J., Roth, C.B., Guglielmetti, M., Kunz, M., Miserez, A.R., Drewe, J., Huber, P., Herzog, R. & Muller, B. (2001) TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). *J Clin Endocrinol Metab,* **86,** 4860-4866.

Miura, S., Iitaka, M., Suzuki, S., Fukasawa, N., Kitahama, S., Kawakami, Y., Sakatsume, Y., Yamanaka, K., Kawasaki, S., Kinoshita, S., Katayama, S., Shibosawa, T. & Ishii, J. (1996) Decrease in serum levels of thyroid hormone in patients with coronary heart disease. *Endocr J,* **43,** 657-663.

Mizuma, H., Murakami, M. & Mori, M. (2001) Thyroid hormone activation in human vascular smooth muscle cells: expression of type II iodothyronine deiodinase. *Circ Res,* **88,** 313-318.

Moher, D., Schulz, K.F. & Altman, D. (2001a) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Jama,* **285,** 1987-1991.

Moher, D., Schulz, K.F. & Altman, D.G. (2001b) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet,* **357,** 1191-1194.

Monzani, F., Caraccio, N., Kozakowa, M., Dardano, A., Vittone, F., Virdis, A., Taddei, S., Palombo, C. & Ferrannini, E. (2004) Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo- controlled study. *J Clin Endocrinol Metab,* **89,** 2099-2106.

Monzani, F., Di Bello, V., Caraccio, N., Bertini, A., Giorgi, D., Giusti, C. & Ferrannini, E. (2001) Effect of levothyroxine on cardiac function and structure in subclinical hypothyroidism: a double blind, placebo-controlled study. *J Clin Endocrinol Metab,* **86,** 1110-1115.

Moreno, J.M., Wangensteen, R., Sainz, J., Rodriguez-Gomez, I., Chamorro, V., Osuna, A. & Vargas, F. (2003) Role of endothelium-derived relaxing factors in the renal response to vasoactive agents in hypothyroid rats. *Am J Physiol Endocrinol Metab,* **285,** E182-188.

Morisaki, N., Saito, I., Tamura, K., Tashiro, J., Masuda, M., Kanzaki, T., Watanabe, S., Masuda, Y. & Saito, Y. (1997) New indices of ischemic heart disease and aging: studies on the serum levels of soluble intercellular adhesion molecule-1 (ICAM-1) and soluble vascular cell adhesion molecule-1 (VCAM-1) in patients with hypercholesterolemia and ischemic heart disease. *Atherosclerosis,* **131,** 43-48.

Nedrebo, B.G., Ericsson, U.B., Nygard, O., Refsum, H., Ueland, P.M., Aakvaag, A., Aanderud, S. & Lien, E.A. (1998) Plasma total homocysteine levels in hyperthyroid and hypothyroid patients. *Metabolism,* **47,** 89-93.

Neunteufl, T., Heher, S., Katzenschlager, R., Wolfl, G., Kostner, K., Maurer, G. & Weidinger, F. (2000) Late prognostic value of flow-mediated dilation in the brachial artery of patients with chest pain. *Am J Cardiol,* **86,** 207-210.

Newey, V.R. & Nassiri, D.K. (2002) Online artery diameter measurement in ultrasound images using artificial neural networks. *Ultrasound Med Biol,* **28,** 209-216.

Nyrnes, A., Jorde, R. & Sundsfjord, J. (2006) Serum TSH is positively associated with BMI. *Int J Obes (Lond),* **30,** 100-105.

Nystrom, E., Caidahl, K., Fager, G., Wikkelso, C., Lundberg, P.A. & Lindstedt, G. (1988) A double-blind cross-over 12-month study of L-thyroxine treatment of women with 'subclinical' hypothyroidism. *Clin Endocrinol (Oxf),* **29,** 63-75.

Oettgen, P., Ginsburg, G.S., Horowitz, G.L. & Pasternak, R.C. (1994) Frequency of hypothyroidism in adults with serum total cholesterol levels > 200 mg/dl. *Am J Cardiol,* **73,** 955-957.

Ojamaa, K., Klemperer, J.D. & Klein, I. (1996) Acute effects of thyroid hormone on vascular smooth muscle. *Thyroid,* **6,** 505-512.

Okumura, K., Yasue, H., Matsuyama, K., Ogawa, H., Morikami, Y., Obata, K. & Sakaino, N. (1992) Effect of acetylcholine on the highly stenotic coronary artery: difference between the constrictor response of the infarct-related coronary artery and that of the noninfarct-related artery. *J Am Coll Cardiol,* **19,** 752-758.

O'Leary, D.H., Polak, J.F., Kronmal, R.A., Manolio, T.A., Burke, G.L. & Wolfson, S.K., Jr. (1999) Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med,* **340,** 14-22.

O'Leary, D.H., Polak, J.F., Kronmal, R.A., Savage, P.J., Borhani, N.O., Kittner, S.J., Tracy, R., Gardin, J.M., Price, T.R. & Furberg, C.D. (1996) Thickening of the carotid wall. A marker for atherosclerosis in the elderly? Cardiovascular Health Study Collaborative Research Group. *Stroke,* **27,** 224-231.

Pahor, M., Elam, M.B., Garrison, R.J., Kritchevsky, S.B. & Applegate, W.B. (1999) Emerging noninvasive biochemical measures to predict cardiovascular risk. *Arch Intern Med,* **159,** 237-245.

Pallas, D., Koutras, D.A., Adamopoulos, P., Marafelia, P., Souvatzoglou, A., Piperingos, G. & Moulopoulos, S.D. (1991) Increased mean serum thyrotropin in apparently euthyroid hypercholesterolemic patients: does it mean occult hypothyroidism? *J Endocrinol Invest,* **14,** 743-746.

Papaioannou, G.I., Lagasse, M., Mather, J.F. & Thompson, P.D. (2004) Treating hypothyroidism improves endothelial function. *Metabolism,* **53,** 278-279.

Parle, J.V., Franklyn, J.A., Cross, K.W., Jones, S.C. & Sheppard, M.C. (1991) Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf),* **34,** 77-83.

Parle, J.V., Maisonneuve, P., Sheppard, M.C., Boyle, P. & Franklyn, J.A. (2001) Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet,* **358,** 861-865.

Pearson, J.D. (1993) The control of production and release of haemostatic factors in the endothelial cell. *Baillieres Clin Haematol,* **6,** 629-651.

Perneger, T.V. (1998) What's wrong with Bonferroni adjustments. *Bmj,* **316,** 1236-1238.

Perneger, T.V. (1999) Adjusting for multiple testing in studies is less important than other concerns. *Bmj,* **318,** 1288.

Pignoli, P., Tremoli, E., Poli, A., Oreste, P. & Paoletti, R. (1986) Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. *Circulation,* **74,** 1399-1406.

Pinkney, J.H., Goodrick, S.J., Katz, J.R., Johnson, A.B., Lightman, S.L., Coppack, S.W., Medbak, S. & Mohamed-Ali, V. (2000) Thyroid and sympathetic influences on plasma leptin in hypothyroidism and hyperthyroidism. *Int J Obes Relat Metab Disord,* **24 Suppl 2,** S165-166.

Pirich, C., Mullner, M. & Sinzinger, H. (2000) Prevalence and relevance of thyroid dysfunction in 1922 cholesterol screening participants. *J Clin Epidemiol,* **53,** 623-629.

Pollock, M.A., Sturrock, A., Marshall, K., Davidson, K.M., Kelly, C.J., McMahon, A.D. & McLaren, E.H. (2001) Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. *Bmj,* **323,** 891-895.

Poredos, P. (2002) Endothelial dysfunction in the pathogenesis of atherosclerosis. *Int Angiol,* **21,** 109-116.

Pyke, K.E. & Tschakovsky, M.E. (2005) The relationship between shear stress and flow-mediated dilatation: implications for the assessment of endothelial function. *J Physiol,* **568,** 357-369.

Quesada, A., Sainz, J., Wangensteen, R., Rodriguez-Gomez, I., Vargas, F. & Osuna, A. (2002) Nitric oxide synthase activity in hyperthyroid and hypothyroid rats. *Eur J Endocrinol,* **147,** 117-122.

Raitakari, O.T. & Celermajer, D.S. (2000) Testing for endothelial dysfunction. *Ann Med,* **32,** 293-304.

Ridgway, E.C., Cooper, D.S., Walker, H., Rodbard, D. & Maloof, F. (1981) Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab,* **53,** 1238-1242.

Ridker, P.M., Cushman, M., Stampfer, M.J., Tracy, R.P. & Hennekens, C.H. (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med,* **336,** 973-979.

Ridker, P.M., Hennekens, C.H., Roitman-Johnson, B., Stampfer, M.J. & Allen, J. (1998) Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet,* **351,** 88-92.

Ridker, P.M., Hennekens, C.H., Stampfer, M.J., Manson, J.E. & Vaughan, D.E. (1994) Prospective study of endogenous tissue plasminogen activator and risk of stroke. *Lancet,* **343,** 940-943.

Ridker, P.M., Vaughan, D.E., Stampfer, M.J., Manson, J.E. & Hennekens, C.H. (1993) Endogenous tissue-type plasminogen activator and risk of myocardial infarction. *Lancet,* **341,** 1165-1168.

Riley, W.A., Evans, G.W., Sharrett, A.R., Burke, G.L. & Barnes, R.W. (1997) Variation of common carotid artery elasticity with intimal-medial thickness: the ARIC Study. Atherosclerosis Risk in Communities. *Ultrasound Med Biol,* **23,** 157-164.

Riley, W.A., Freedman, D.S., Higgs, N.A., Barnes, R.W., Zinkgraf, S.A. & Berenson, G.S. (1986) Decreased arterial elasticity associated with cardiovascular disease risk factors in the young. Bogalusa Heart Study. *Arteriosclerosis,* **6,** 378-386.

Rodondi, N., Newman, A.B., Vittinghoff, E., de Rekeneire, N., Satterfield, S., Harris, T.B. & Bauer, D.C. (2005) Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med,* **165,** 2460-2466.

Ross, D.S. (2001) Serum thyroid-stimulating hormone measurement for assessment of thyroid function and disease. *Endocrinol Metab Clin North Am,* **30,** 245-264, vii.

Ross, R. (1986) The pathogenesis of atherosclerosis--an update. *N Engl J Med,* **314,** 488-500.

Rothman, K.J. (1990) No adjustments are needed for multiple comparisons. *Epidemiology,* **1,** 43-46.

Safar, M.E., Laurent, S., Pannier, B.M. & London, G.M. (1987) Structural and functional modifications of peripheral large arteries in hypertensive patients. *J Clin Hypertens,* **3,** 360-367.

Salomaa, V., Riley, W., Kark, J.D., Nardo, C. & Folsom, A.R. (1995a) Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation,* **91,** 1432-1443.

Salomaa, V., Stinson, V., Kark, J.D., Folsom, A.R., Davis, C.E. & Wu, K.K. (1995b) Association of fibrinolytic parameters with early atherosclerosis. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation,* **91,** 284-290.

Sawin, C.T., Geller, A., Kaplan, M.M., Bacharach, P., Wilson, P.W. & Hershman, J.M. (1991) Low serum thyrotropin (thyroid-stimulating hormone) in older persons without hyperthyroidism. *Arch Intern Med,* **151,** 165-168.

Sawin, C.T., Geller, A., Wolf, P.A., Belanger, A.J., Baker, E., Bacharach, P., Wilson, P.W., Benjamin, E.J. & D'Agostino, R.B. (1994) Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med,* **331,** 1249-1252.

Schmid, C., Brandle, M., Zwimpfer, C., Zapf, J. & Wiesli, P. (2004) Effect of thyroxine replacement on creatinine, insulin-like growth factor 1, acid-labile subunit, and vascular endothelial growth factor. *Clin Chem,* **50,** 228-231.

Seppel, T., Kosel, A. & Schlaghecke, R. (1997) Bioelectrical impedance assessment of body composition in thyroid disease. *Eur J Endocrinol,* **136,** 493-498.

Series, J.J., Biggart, E.M., O'Reilly, D.S., Packard, C.J. & Shepherd, J. (1988) Thyroid dysfunction and hypercholesterolaemia in the general population of Glasgow, Scotland. *Clin Chim Acta,* **172,** 217-221.

Shepherd, J., Cobbe, S.M., Ford, I., Isles, C.G., Lorimer, A.R., MacFarlane, P.W., McKillop, J.H. & Packard, C.J. (1995) Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med,* **333,** 1301-1307.

Sidhu, J.S., Newey, V.R., Nassiri, D.K. & Kaski, J.C. (2002) A rapid and reproducible on line automated technique to determine endothelial function. *Heart,* **88,** 289-292.

Smilde, T.J., van Wissen, S., Wollersheim, H., Trip, M.D., Kastelein, J.J. & Stalenhoef, A.F. (2001) Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet,* **357,** 577-581.

Smith, C.W., Marlin, S.D., Rothlein, R., Toman, C. & Anderson, D.C. (1989) Cooperative interactions of LFA-1 and Mac-1 with intercellular adhesion molecule-1 in facilitating adherence and transendothelial migration of human neutrophils in vitro. *J Clin Invest,* **83,** 2008-2017.

Smith, S.C., Jr., Greenland, P. & Grundy, S.M. (2000) AHA Conference Proceedings. Prevention conference V: Beyond secondary prevention: Identifying the high-risk patient for primary prevention: executive summary. American Heart Association. *Circulation,* **101,** 111-116.

Spencer, C.A., Takeuchi, M. & Kazarosyan, M. (1996) Current status and performance goals for serum thyrotropin (TSH) assays. *Clin Chem,* **42,** 140-145.

Stamler, J., Vaccaro, O., Neaton, J.D. & Wentworth, D. (1993) Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care,* **16,** 434-444.

Staub, J.J., Althaus, B.U., Engler, H., Ryff, A.S., Trabucco, P., Marquardt, K., Burckhardt, D., Girard, J. & Weintraub, B.D. (1992) Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. *Am J Med,* **92,** 631-642.

Steinberg, A.D. (1968) Myxedema and coronary artery disease--a comparative autopsy study. *Ann Intern Med,* **68,** 338-344.

Streeten, D.H., Anderson, G.H., Jr., Howland, T., Chiang, R. & Smulyan, H. (1988) Effects of thyroid function on blood pressure. Recognition of hypothyroid hypertension. *Hypertension,* **11,** 78-83.

Surks, M.I., Chopra, I.J., Mariash, C.N., Nicoloff, J.T. & Solomon, D.H. (1990) American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. *Jama,* **263,** 1529-1532.

Surks, M.I., Ortiz, E., Daniels, G.H., Sawin, C.T., Col, N.F., Cobin, R.H., Franklyn, J.A., Hershman, J.M., Burman, K.D., Denke, M.A., Gorman, C., Cooper, R.S. & Weissman, N.J. (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *Jama,* **291,** 228-238.

Suwaidi, J.A., Hamasaki, S., Higano, S.T., Nishimura, R.A., Holmes, D.R., Jr. & Lerman, A. (2000) Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. *Circulation,* **101,** 948-954.

Taddei, S., Caraccio, N., Virdis, A., Dardano, A., Versari, D., Ghiadoni, L., Salvetti, A., Ferrannini, E. & Monzani, F. (2003) Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab,* **88,** 3731-3737.

Takase, B., Uehata, A., Akima, T., Nagai, T., Nishioka, T., Hamabe, A., Satomura, K., Ohsuzu, F. & Kurita, A. (1998) Endothelium-dependent flow-mediated vasodilation in coronary and brachial arteries in suspected coronary artery disease. *Am J Cardiol,* **82,** 1535-1539, A1537-1538.

Tanis, B.C., Westendorp, G.J. & Smelt, H.M. (1996) Effect of thyroid substitution on hypercholesterolaemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. *Clin Endocrinol (Oxf),* **44,** 643-649.

Thompson, S.G., Kienast, J., Pyke, S.D., Haverkate, F. & van de Loo, J.C. (1995) Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. *N Engl J Med,* **332,** 635-641.

Tieche, M., Lupi, G.A., Gutzwiller, F., Grob, P.J., Studer, H. & Burgi, H. (1981) Borderline low thyroid function and thyroid autoimmunity. Risk factors for coronary heart disease? *Br Heart J,* **46,** 202-206.

Toft, A.D. (1994) Thyroxine therapy. *N Engl J Med,* **331,** 174-180.

Tomiyama, H., Kimura, Y., Mitsuhashi, H., Kinouchi, T., Yoshida, H., Kushiro, T. & Doba, N. (1998) Relationship between endothelial function and fibrinolysis in early hypertension. *Hypertension,* **31,** 321-327.

Tunbridge, W.M., Brewis, M., French, J.M., Appleton, D., Bird, T., Clark, F., Evered, D.C., Evans, J.G., Hall, R., Smith, P., Stephenson, J. & Young, E. (1981) Natural history of autoimmune thyroiditis. *Br Med J (Clin Res Ed),* **282,** 258-262.

Tunbridge, W.M., Evered, D.C., Hall, R., Appleton, D., Brewis, M., Clark, F., Evans, J.G., Young, E., Bird, T. & Smith, P.A. (1977a) Lipid profiles and cardiovascular disease in the Whickham area with particular reference to thyroid failure. *Clin Endocrinol (Oxf),* **7,** 495-508.

Tunbridge, W.M., Evered, D.C., Hall, R., Appleton, D., Brewis, M., Clark, F., Evans, J.G., Young, E., Bird, T. & Smith, P.A. (1977b) The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol (Oxf),* **7,** 481-493.

van der Bom, J.G., de Knijff, P., Haverkate, F., Bots, M.L., Meijer, P., de Jong, P.T., Hofman, A., Kluft, C. & Grobbee, D.E. (1997) Tissue plasminogen activator and risk of myocardial infarction. The Rotterdam Study. *Circulation,* **95,** 2623-2627.

Vanderpump, M.P., Ahlquist, J.A., Franklyn, J.A. & Clayton, R.N. (1996a) Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. The Research Unit of the Royal College of Physicians of London, the Endocrinology and Diabetes Committee of the Royal College of Physicians of London, and the Society for Endocrinology. *Bmj,* **313,** 539-544.

Vanderpump, M.P., Tunbridge, W.M., French, J.M., Appleton, D., Bates, D., Clark, F., Grimley Evans, J., Hasan, D.M., Rodgers, H., Tunbridge, F. & et al. (1995) The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf),* **43,** 55-68.

Vanderpump, M.P., Tunbridge, W.M., French, J.M., Appleton, D., Bates, D., Clark, F., Grimley Evans, J., Rodgers, H., Tunbridge, F. & Young, E.T. (1996b) The development of ischemic heart disease in relation to autoimmune thyroid disease in a 20-year follow-up study of an English community. *Thyroid,* **6,** 155-160.

Vanhaelst, L., Neve, P., Chailly, P. & Bastenie, P.A. (1967) Coronary-artery disease in hypothyroidism. Observations in clinical myxoedema. *Lancet,* **2,** 800-802.

Vargas, F., Fernandez-Rivas, A., Garcia Estan, J. & Garcia del Rio, C. (1995) Endothelium-dependent and endothelium-independent vasodilation in hyperthyroid and hypothyroid rats. *Pharmacology,* **51,** 308-314.

Vita, J.A. & Keaney, J.F., Jr (2002) Endothelial Function: A Barometer for Cardiovascular Risk? *Circulation,* **106,** 640-642.

Vita, J.A. & Keaney, J.F., Jr. (2000) Exercise--toning up the endothelium? *N Engl J Med,* **342,** 503-505.

Vitale, G., Galderisi, M., Lupoli, G.A., Celentano, A., Pietropaolo, I., Parenti, N., De Divitiis, O. & Lupoli, G. (2002) Left ventricular myocardial impairment in subclinical hypothyroidism assessed by a new ultrasound tool: pulsed tissue Doppler. *J Clin Endocrinol Metab,* **87,** 4350-4355.

Volzke, H., Robinson, D.M., Schminke, U., Ludemann, J., Rettig, R., Felix, S.B., Kessler, C., John, U. & Meng, W. (2004) Thyroid function and carotid wall thickness. *J Clin Endocrinol Metab,* **89,** 2145-2149.

Wada, T., Kodaira, K., Fujishiro, K., Maie, K., Tsukiyama, E., Fukumoto, T., Uchida, T. & Yamazaki, S. (1994) Correlation of ultrasound-measured common carotid artery stiffness with pathological findings. *Arterioscler Thromb,* **14,** 479-482.

Walldius, G., Jungner, I., Holme, I., Aastveit, A.H., Kolar, W. & Steiner, E. (2001) High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet,* **358,** 2026-2033.

Walsh, J.P., Bremner, A.P., Bulsara, M.K., O'Leary, P., Leedman, P.J., Feddema, P. & Michelangeli, V. (2005) Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med,* **165,** 2467-2472.

Walton, K.W., Scott, P.J., Dykes, P.W. & Davies, J.W. (1965) The significance of alterations in serum lipids in thyroid dysfunction. II. Alterations of the metabolism and turnover of 131-I-low-density lipoproteins in hypothyroidism and thyrotoxicosis. *Clin Sci,* **29,** 217-238.

Wang, J., Brown, M.A., Tam, S.H., Chan, M.C. & Whitworth, J.A. (1997) Effects of diet on measurement of nitric oxide metabolites. *Clin Exp Pharmacol Physiol,* **24,** 418-420.

Wartofsky, L. & Dickey, R.A. (2005) The evidence for a narrower thyrotropin reference range is compelling. *J Clin Endocrinol Metab,* **90,** 5483-5488.

Wells, B.J. & Hueston, W.J. (2005) Are thyroid peroxidase antibodies associated with cardiovascular disease risk in patients with subclinical hypothyroidism? *Clin Endocrinol (Oxf),* **62,** 580-584.

Wendelhag, I., Liang, Q., Gustavsson, T. & Wikstrand, J. (1997) A new automated computerized analyzing system simplifies readings and reduces the variability in ultrasound measurement of intima-media thickness. *Stroke,* **28,** 2195-2200.

Wiersinga, W.M. (1995) Subclinical hypothyroidism and hyperthyroidism. I. Prevalence and clinical relevance. *Neth J Med,* **46,** 197-204.

Wieshammer, S., Keck, F.S., Waitzinger, J., Henze, E., Loos, U., Hombach, V. & Pfeiffer, E.F. (1989) Acute hypothyroidism slows the rate of left ventricular diastolic relaxation. *Can J Physiol Pharmacol,* **67,** 1007-1010.

Wiseman, S.A., Powell, J.T., Humphries, S.E. & Press, M. (1993) The magnitude of the hypercholesterolemia of hypothyroidism is associated with variation in the low density lipoprotein receptor gene. *J Clin Endocrinol Metab,* **77,** 108-112.

Yazici, M., Gorgulu, S., Sertbas, Y., Erbilen, E., Albayrak, S., Yildiz, O. & Uyan, C. (2004) Effects of thyroxin therapy on cardiac function in patients with subclinical hypothyroidism: index of myocardial performance in the evaluation of left ventricular function. *Int J Cardiol,* **95,** 135-143.

Yu, H.Y., Yang, Y., Zhang, M.X., Lu, H.L., Zhang, J.H., Wang, H.W. & Cianflone, K. (2006) Thyroid status influence on adiponectin, acylation stimulating protein and complement C3 in hyperthyroid and hypothyroid subjects. *Nutr Metab (Lond),* **3,** 13.

Yusuf, S., Hawken, S., Ounpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J. & Lisheng, L. (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet,* **364,** 937-952.

PATIENT-REPORTED OUTCOMES IN SCH

INTRODUCTION (B)

Overt hypothyroidism

Symptoms and Quality of life (QoL):

Hypothyroidism often remains undetected because of the difficulty with ascribing symptoms to disease. The pathophysiologic changes generally require months or years to manifest as clinical signs and symptoms (Larsen and Ingbar 1992). Furthermore, the onset of hypothyroidism is so insidious that even classic symptomatology may go unnoticed or undiagnosed (Gavin 1988). Although most hypothyroid patients do have some signs and symptoms indicative of disease (Tachman and Guthrie 1984), it may be difficult to identify a "classic" clinical picture because symptoms may be nonspecific and thus confused with other health problems (Schectman, *et al* 1989).

The relation between symptoms and physiologic disease is so complex that clinicians turn to biochemical measures of thyroid dysfunction for diagnosis. However, it is unclear who should be tested. Many investigators (Bahemuka and Hodkinson 1975) (Sawin, *et al* 1979) (Eggertsen, *et al* 1988) (Danese, *et al* 1996) (Helfand and Crapo 1990) and several organizations, such as the American Thyroid Association and the American Association of Clinical Endocrinologists recommend testing persons who have a greater likelihood of being hypothyroid (Singer, *et al* 1995) (2002). The U.S. Preventive Services Task Force does not recommend for or against screening in high-risk patients, such as older women. However, it does alert clinicians to maintain a low threshold for diagnostic evaluation of thyroid function when subtle or nonspecific symptoms of thyroid dysfunction occur in such patients (Helfand 2004). In the UK, the Working Group of the Royal College of Physicians and Society for Endocrinology, in a consensus statement for good practice in thyroid diseases, did not focus on presenting symptoms or signs since they were detailed in the report by the American Thyroid Association (Vanderpump, *et al* 1996). Evidence is lacking as to which symptom or symptoms increase the likelihood of confirming biochemical hypothyroidism. However, patients who report more symptoms, and more recently developed symptoms, are more likely to have hypothyroidism. This being the case, patients who report more symptoms, particularly recent symptoms, should be tested with serum thyroid function tests. See tables 31 – 33 [from: (Canaris, *et al* 1997)]. These highlight the prevalence

of common symptoms usually attributed to hypothyroidism, subsequently confirmed via biochemical means, by hypothyroid patients, and compared to euthyroid controls and also test the likelihood of predicting the disease (table 31). Table 32 shows the prevalence of recently acquired symptoms amongst hypothyroid and euthyroid individuals, permitting evaluation of onset of symptoms in portrayal of the disease. This showed that change in symptoms is more powerful in predicting the disease than current symptoms. Table 33 shows that higher number of symptoms reported (current as well as changed), the more the likelihood of predicting hypothyroidism. For example, an individual reporting 11 or more recently acquired symptoms of hypothyroidism has a 13.5 times chance of having the disease compared to euthyroid controls.

Table 31.

Current symptoms of Hypothyroidism (from Canaris et al, 1997)

Symptom	Hypothyroid with Symptoms, %	Euthyroid with Symptoms, %	Likelihood Ratio (95% Confidence Interval)	*p* Value
Hoarse voice*	17	4	4.2 (1.7, 10.6)	.001
Deep voice	16	8	2.1 (1.0, 4.6)	.05
Dry skin*	71	54	1.3 (1.1, 1.6)	.02
Coarse hair	9	14	0.7 (0.3, 1.5)	.32
Cold sensitive	51	40	1.3 (0.9, 1.7)	.12
Tired	40	30	1.4 (0.9, 2.0)	.12
Puffy eyes	27	17	1.6 (1.0, 2.7)	.08
Muscle cramps*	34	15	2.2 (1.4, 3.7)	.001
Weak muscles	21	21	1.0 (0.6, 1.7)	.96
Constipated	17	10	1.6 (0.8, 3.3)	.15
Depressed	16	12	1.4 (0.7, 2.7)	.37
Slow thinking	18	10	1.8 (0.9, 3.5)	.08
Poor memory	18	16	1.1 (0.6, 2.0)	.71
Math difficulty	15	11	1.4 (0.7, 2.8)	.41
Irregular menses	30	29	1.0 (0.5, 2.0)	.90
Heavy menses	36	29	1.2 (0.7, 2.3)	.48

**Indicates statistical significance.*

Table 32.

Changed symptoms of Hypothyroidism (from Canaris et al 1997).

Symptom	Hypothyroid with Symptoms, %	Euthyroid with Symptoms, %	Likelihood Ratio (95% Confidence Interval)	p Value
Hoarser voice*	21	4	5.2 (2.1, 12.6)	<.0001
Deeper voice*	14	2	7.1 (2.0, 24.7)	.0006
Drier skin*	48	24	2.0 (1.4, 2.9)	.0003
Coarser hair	7	2	3.2 (0.8, 13.1)	.12
Colder*	39	11	3.5 (2.0, 6.0)	<.0001
More tired*	54	26	2.1 (1.5, 3.0)	<.0001
Eyes more puffy*	36	9	4.0 (2.2, 7.3)	<.0001
Sleep more	42	31	1.4 (0.9, 1.9)	.11
Muscles cramp more*	39	16	2.4 (1.5, 3.8)	.0001
Weaker muscles*	41	18	2.2 (1.4, 3.4)	.0003
Constipated more often*	20	6	3.6 (1.6, 8.1)	.001
More depressed*	38	18	2.2 (1.4, 3.4)	.0008
Slower thinking*	36	14	2.5 (1.5, 4.2)	.0002
Poorer memory*	39	15	2.6 (1.6, 4.2)	<.0001
Math more difficult*	22	4	5.4 (2.2, 13.1)	<.0001
Menses more irregular	44	27	1.6 (0.9, 2.9)	.10
Heavier menses	38	26	1.5 (0.8, 2.8)	.24

* *Indicates statistical significance.*

Table 33.

Number of symptoms reported by hypothyroid patients and controls (from Canaris et al, 1997).

Symptoms Reported, *n*	Cases, *n* (%)	Controls, *n* (%)	Likelihood Ratio (95% CI)
"Current" symptoms			
0 (of 3)*	15 (19.7)	58 (39.4)	0.5 (0.3, 0.8)
1	35 (46.1)	72 (49.0)	0.9 (0.7, 1.3)
2*	22 (28.9)	15 (10.2)	2.8 (1.6, 5.1)
3	4 (5.3)	2 (1.4)	3.9 (0.7, 20.6)
"Changed" symptoms			
0 (of 13)*	13 (17.1)	54 (36.7)	0.5 (0.3, 0.8)
1–2*	19 (25.0)	63 (42.9)	0.6 (0.4, 0.9)
3–4	10 (13.2)	13 (8.8)	1.5 (0.7, 3.2)
5–6	7 (9.2)	11 (7.5)	1.2 (0.5, 3.0)
7–8*	14 (18.4)	3 (2.0)	9.0 (2.7, 30.4)
9–10*	6 (7.9)	2 (1.4)	5.8 (1.2, 28.1)
≥11*	7 (9.2)	1 (0.7)	13.5 (1.7, 108.0)

* *Indicates statistical significance.*

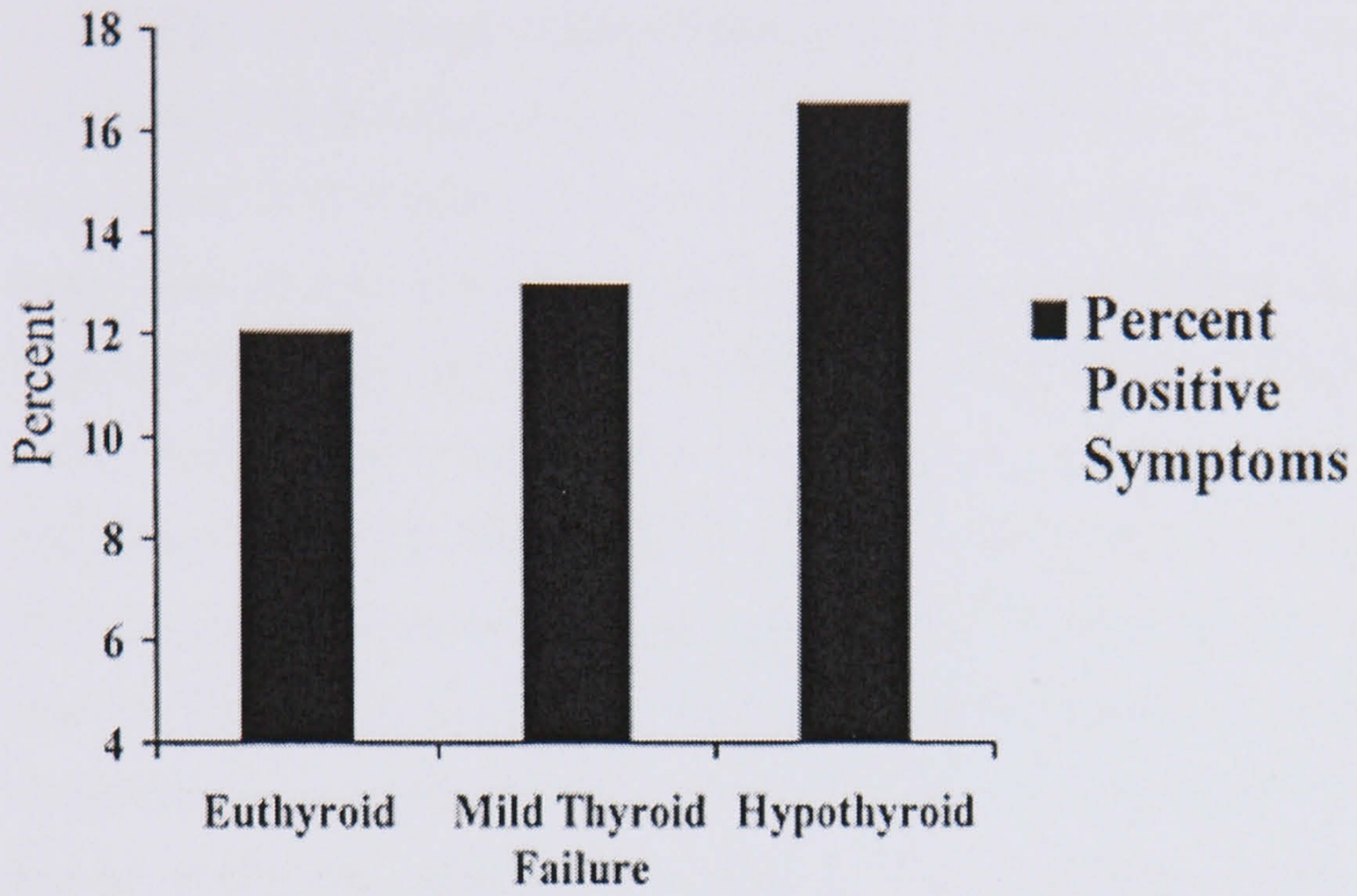
Thus, overt hypothyroidism is a common condition that may be difficult to diagnose on clinical grounds alone and requires a high degree of clinical suspicion as well as confirmation with biochemical testing for serum TSH and thyroid hormone levels. Untreated, it may cause CV disease and may have the potential to be fatal, although this has never been tested in a controlled fashion. Overt hypothyroidism should be suspected in any person who complains of typical symptoms and the chances of diagnosing the disease are directly proportional to the number of symptoms. Reliance on blood testing to diagnose an easily treatable condition has led to a spectrum of results, one of which is the state of a raised TSH with free thyroid hormone levels, called subclinical hypothyroidism.

Symptoms and Quality of life in SCH.

Most patients found by screening to have subclinical hypothyroidism have at least one symptom that could be related to this diagnosis (Parle, *et al* 1991). Symptoms include muscle cramps, dry skin, intolerance to cold, constipation, poor energy levels, fatigue, and mental slowness. Baseline data from a study by Cooper et al showed an increased prevalence of hypothyroid symptoms (Cooper, *et al* 1984). The Colorado cross-sectional study of 25,862 participants reported increased prevalence of hypothyroid symptoms in response to a validated survey. The 2,336 subjects who were identified as having SCH, more often reported having dry skin (28%; $P < 0.001$), poor memory (24%; $P < 0.001$), slow thinking (22%; $P < 0.001$), muscle weakness (22%; $P < 0.001$), fatigue (18%; $P < 0.01$), muscle cramps (17%; $P < 0.001$), cold intolerance (15%; $P < 0.001$), puffy eyes (12%; $P < 0.05$), constipation (8%; $P < 0.05$), and voice hoarseness (7%; $P < 0.05$) than did euthyroid subjects (Canaris, *et al* 2000). It is important to note that, whereas euthyroid subjects experienced a mean of 12.1% of all listed symptoms, overtly hypothyroid subjects had 16.6% of these symptoms ($P < 0.05$ *vs.* euthyroid group), and subjects with mild thyroid failure reported an intermediate 13.7% of the symptoms ($P < 0.05$ *vs.* euthyroid group) (figure 16). This suggests a "dosage effect" between the degree of thyroid failure and symptoms. Consistent with these findings, a Swiss study involving 332 women with hypothyroidism reported that 24% of the 93 subjects with mild thyroid failure exhibited typical symptoms of hypothyroidism (Zulewski, *et al* 1997).

Figure 16.

The Colorado Thyroid Disease Prevalence Study-symptom frequency stratified according to thyroid status (from McDermott & Ridgway, JCEM 2001)



Other cross-sectional studies have demonstrated evidence of specific neurobehavioral and neuromuscular dysfunction in SCH patients. Depression (Monzani, *et al* 1993) (Tappy, *et al* 1987) (Joffe and Levitt 1992) (Haggerty, *et al* 1993) (Manciet, *et al* 1995), memory loss (Canaris, *et al* 2000) (Monzani, *et al* 1993) (Baldini, *et al* 1997), cognitive impairment (Ganguli, *et al* 1996), and a range of neuromuscular complaints (Monzani, *et al* 1997) have been reported to occur more frequently in patients with this condition. Objective peripheral nerve dysfunction, manifested by decreased conduction amplitude in peripheral nerves (Misiunas, *et al* 1995), and an abnormal stapedial reflex (Goulis, *et al* 1998) have been demonstrated in these patients. Skeletal muscle abnormalities, including elevated serum creatinine phosphokinase levels (Beyer, *et al* 1998), increased circulating lactate levels during exercise (Monzani, *et al* 1997), and repetitive discharges on surface electromyography (Monzani, *et al* 1999) have also been reported. Finally, there is compelling evidence that mild thyroid failure in pregnant women may result in reduced intellectual development of their euthyroid offspring (Haddow, *et al* 1999).

Reacting to some of this, some experts have argued that the Colorado study was not a population-based study and it also included people with under-treated hypothyroidism (Surks, *et al* 2004). The only cross-sectional study that stratified individuals by TSH levels noted significantly altered ankle reflex times and myoglobin levels only in those patients with TSH higher than 12 mIU/L (Staub, *et al* 1992). The biological significance of the impairment of the stapedial reflex in patients with SCH has also been questioned (Chu and Crapo 2001). The association of SCH with psychiatric disorders has also not been consistent. Many such reports are hindered by not controlling for the effects of age, gender, inpatient hospitalisation, and use of lithium on the prevalence of elevated TSH levels (Griffin 1990). Additionally, the mere association between SCH and psychiatric disorders should not lead to the conclusion that SCH brings about these associated disorders (Haggerty, *et al* 1993). The four large epidemiological studies that examined cognitive and affective scores in SCH subjects found few (Lindeman, *et al* 1999) (Manciet, *et al* 1995) or no (Luboshitzky, *et al* 1996) (Jorde, *et al* 2006) significant differences overall, and none in those with TSH between 5 and 10 mIU/L.

There has been no large-scale population-based study to investigate QoL in people with SCH. Sonino and Fava have pointed out the need for multidimensional assessments of the effects of treatment in thyroid disorders. These should also include psychosocial aspects, as there is "a new interest for a global approach to the endocrine patient" (Sonino and Fava 1998). The symptoms of hypothyroidism, if present, are likely to have a considerable impact on QoL, yet there is no known measure of QoL in hypothyroidism in use, nor any measure of satisfaction with thyroid hormone treatment. Searches of websites including QOLID (Quality of Life Instruments Database) and ISOQoL (International Society for Quality of Life) did not indicate any hypothyroid QoL instruments available. Searches of Web of Science, PubMed and PsychLit found a Canadian disease-specific health-related QoL instrument, the Chronic Thyroid questionnaire, with questions relating to symptoms of hypothyroidism (Jaeschke, *et al* 1994). This is not, however, a measure of QoL or of the impact of thyroid conditions on QoL, but rather, more specifically, a measure of symptoms. The term 'health-related quality of life' is often misleadingly used to refer to measures of health status and symptoms when it

blurs the boundaries between quality of *health* and quality of *life*. Health-related QoL emphasises *quantity* of life, physical function and symptoms; whilst often including aspects of psychological well being there is less emphasis on the individual patient's perceptions of their *quality* of life. Even if people feel that their health is poor, they may or may not also feel that their QoL is impaired, and vice versa (Bradley 2001) (Razvi, *et al* 2005).

No search found any measures of treatment satisfaction relating to hypothyroidism. The Chronic Thyroid questionnaire is not suitable to measure patients' perceptions of their QoL for reasons discussed above. The research required developing questionnaires to measure the impact of hypothyroidism on QoL or treatment satisfaction in this disorder has not been conducted before. Measures of individualised condition-specific QoL and of treatment satisfaction in hypothyroidism were not available for use in clinical trials. Therefore a disease specific QoL and treatment satisfaction questionnaire would be a useful tool in assessing patients who require treatment as well as their satisfaction with subsequent treatment

Effect of L-thyroxine therapy on patient-reported outcomes in SCH.

There have been 6 randomised, prospective, placebo-controlled trials of L-thyroxine therapy in SCH published so far, that have assessed symptoms of hypothyroidism or health status (Cooper, *et al* 1984) (Nystrom, *et al* 1988) (Jaeschke, *et al* 1996) (Kong, *et al* 2002) (Meier, *et al* 2001) (Jorde, *et al* 2006). Cooper et al and Nystrom et al reported significant improvements in symptoms of hypothyroidism. Jaeshke and colleagues did not find any improvement in health status (general or disease-specific) in their patients with SCH, apart from some improvement in a composite psychometric memory score. This study has been criticised because of insufficient treatment of the SCH patients – the treated patients' mean TSH levels were 4.61 mIU/L. Meier and colleagues concluded that physiological L-thyroxine replacement therapy in people with SCH (the mean TSH at baseline in this group was 12.1 mIU/L at baseline) improves clinical symptoms of hypothyroidism (as assessed by Billewicz index and Zulewski's scores). On the other hand, Kong et al did not find any significant improvement in their patients with mild SCH, in terms of symptom scores as measured by modified Billewicz and Zulewski's scores. In fact, there was a significant worsening in anxiety scores on L-thyroxine therapy. The patients in this study were not recruited by population screening and did not have stable SCH, and had a rigid dosing regimen (50 or 100 mcg/day) leading to a treated TSH level of 3.4mIU/L (towards upper limit of normal range) (Biondi, *et al* 2003). The most recent study by Jorde and colleagues did not find any significant improvement in symptoms or other psychological parameters after L-thyroxine therapy. All RCTs assessing symptoms in response to L-thyroxine are summarised in table 34.

Table 34.

RCTs assessing effect of L-thyroxine therapy on hypothyroid symptoms in SCH.

Study	No. of patients	Mean TSH levels mIU/L		Dose of LT4 mcg	Duration of treatment (months)	Significant improvement?
		Initial	Final			
Cooper	33	10.8	2.6	71.2	12	Yes
Nystrom	17	7.7	1.9	150	6	Yes (analysed as before-after)
Jaeschke	31	12.1	4.6	68	6-10	No
Meier	63	12.8	3.1	85.5	11	Yes
Kong	35	8	3.4	77.5	6	No
Jorde	36	5.6	1.5	110	12	No

RCT – Randomised controlled trial, SCH – subclinical hypothyroidism, LT4 – levothyroxine.

The effect of L-thyroxine on cognitive function and memory are not clear. Some studies have shown a beneficial effect whereas others have not (Nystrom, *et al* 1988) (Jaeschke, *et al* 1996) (Monzani, *et al* 1993) (Baldini, *et al* 1997) (Jorde, *et al* 2006).

One of the most important reasons for the conflicting results in all the trials listed above could be the small sample size. As seen above from the Colorado study, people with mild TSH elevations are likely to have fewer symptoms unlike those with higher TSH levels. This would mean a higher sample size would be required to show a significant improvement after intervention. In other words, it would be easier to detect a significant difference in a smaller sample if the degree of thyroid failure was higher as compared to when the failure was relatively mild and subtler. For example, in the trial by Meier and colleagues, subgroup analysis failed to show significant improvement in symptoms in people with TSH less than 10 mIU/L.

Instruments available to assess patient-reported outcomes in hypothyroidism

Symptoms of hypothyroidism can be varied and are frequently found in the general population (Ladenson, *et al* 2000). This makes it impossible for clinicians to diagnose the condition solely on clinical grounds and they therefore have to rely on biochemical measurement of thyroid hormones and TSH in confirming the diagnosis (Spencer, *et al* 1996). On the other hand, the wide use of these biochemical measurements has led to a spectrum of abnormalities being detected, ranging from subclinical to overt disease (Cooper 2001).

Patients with both overt and SCH may have symptoms, which could lead to impairment in health status and QoL (Jaeschke, *et al* 1994). There is evidence that not everyone is satisfied with treatment due to persisting symptoms (Kaplan, *et al* 2003) (Saravanan, *et al* 2002). It is therefore important to assess QoL and symptoms in patients with hypothyroidism to help in assessing its appropriate management.

In achieving efficiency and high level of quality of care, health providers need to estimate as best they can the relationship between medical interventions and health outcomes (Guyatt, *et al* 1997). Measuring health status is imperative when the goal of treatment is to improve how people are feeling and physiological parameters of patients' experience are lacking. QoL is the sense of well-being that addresses multiple dimensions of life. It has been defined by the World Health Organisation as 'an individual's perception of their position in life in the context of the culture and value system in which they live, and in relation to their goals, expectations, standards and concerns'(1995). Patients are the best judges of their own perceived QoL and tools should be designed keeping their perspective in mind (Guyatt, *et al* 1997). There is evidence that although it is feasible to measure QoL accurately in randomised trials, it is still not widely done (Guyatt, *et al* 1989).

It is therefore very useful for clinicians to monitor the patient's perspective in addition to disease progress. Below is a discussion and review of various instruments currently available and used in adult hypothyroidism.

Method of acquiring evidence: All published literature was obtained from MEDLINE until March 2005 using the search terms "hypothyroidism", "symptoms", "quality of life" and "health status". Only articles reporting controlled trials or reporting the design of instruments to be used in hypothyroidism, and written in English, were included in the review, and were analysed to ascertain which instruments were used in relation to the stated objective (see table 35).

Instruments to measure QoL and Health Status: Measurement of QoL is becoming a key component in the evaluation of controlled clinical trials and interventions, being an important outcome of interest in evaluating treatment effect (Guyatt, *et al* 1997). Patients are sometimes more concerned about their present QoL than longevity (McNeil, *et al* 1981). Many studies have erroneously measured presence or absence of symptoms when assessing QoL. Health status has often been described as QoL (Smith, *et al* 1999) (Bradley 2001) due to lack of clear understanding of the term. QoL and health status are distinct and separate entities, as people may not necessarily feel that their QoL is impaired if their health is poor, and vice versa, and instruments for one should not be used for measuring the other since the results could be misleading. Psychological well-being is another patient-reported outcome frequently described as QoL.

Tools measuring patient-reported outcomes can be broadly divided into two categories; generic and disease-specific.

Generic tools

Generic instruments are designed to measure very broad aspects of health and are therefore potentially suitable for a wide range of patient groups and the general population. The main advantage of generic instruments is that they are suitable for use across an extensive range of health problems. They can be used for comparisons between treatments for different patient groups to assess comparative effectiveness. They can also be used with healthy populations to generate normative data to compare different patient groups. Their broad scope means that they have potential to capture the influence of co-morbidity on health, as well as unexpected positive or negative effects of an intervention. This makes them useful for assessing the impact of new health care technologies

when the therapeutic effects are uncertain. Their disadvantage is that wide applicability means that some level of detail has to be sacrificed which may limit the relevance of generic instruments when applied to a specific patient population. Generic instruments are less responsive to clinically important changes in health.

Two instruments in use to measure perceived health status are the Short Form-36 (SF-36) (Ware, *et al* 2000a) and the Nottingham Health Profile (NHP) (Hunt, *et al* 1985). The General Health Questionnaire (GHQ) (Goldberg and Williams 1988) and the Hospital Anxiety and Depression Scale (HADS) (Herrmann 1997) measure psychological well-being/mental health, and are, therefore, more dimension specific. These are briefly described below and their use in hypothyroidism discussed.

SF-36: The SF-36 has been used in evaluating a wide variety of medical interventions (Garratt, *et al* 1993), yet its layout and wording of some items have been criticised. Therefore a newer modified version has been produced with improved wording and instructions- the SF-36 version 2. This has better internal consistency reliability and reduced floor and ceiling effects than the earlier version – and this increases its precision (ability to differentiate between groups) and its sensitivity to change (Jenkinson, *et al* 1999). Despite this, suitability of the SF-36 in older people is uncertain (Hayes, *et al* 1995).

The SF-36 has been used widely in studies involving thyroid diseases. Bianchi and colleagues assessed health status in people with various thyroid disorders including euthyroid goitre (Bianchi, *et al* 2004). Pollock et al found no difference in health status in treating euthyroid individuals presenting with hypothyroid symptoms with L-thyroxine (Pollock, *et al* 2001). Health status has also been assessed using the SF-36 in patients with thyroid cancer (Botella-Carretero, *et al* 2003) (Golger, *et al* 2003) (Crevenna, *et al* 2003) and in studies of L-thyroxine versus L-thyroxine/liothyronine combination therapy in hypothyroidism (Walsh, *et al* 2003) (Sawka, *et al* 2003) (Escobar-Morreale, *et al* 2005), and erroneously as a QoL measure in assessing subtle changes in doses of L-thyroxine (Walsh, *et al* 2006).

NHP: This generic instrument assessing perceived health status has been widely used in a variety of chronic diseases (O'Brien, *et al* 1988) (Jenkinson, *et al* 1988). It is acceptable to the general population and takes little time to complete

(Wiklund, *et al* 1988). It has been criticised for tapping the extreme end of ill-health and therefore being unsuitable to detect improvements in health in a general population, or those with less severe disease, since it produces highly skewed distributions (Kind and Carr-Hill 1987). The SF-36 may be better in picking up minor derangements in health status in the community or in general practice (Brazier, *et al* 1992) where the majority of patients with hypothyroidism are seen. Nevertheless, the NHP has been used in hypothyroidism in a few studies (Bianchi, *et al* 2004) (Botella-Carretero, *et al* 2003) (Escobar-Morreale, *et al* 2005). Expectedly, in one of these studies (Bianchi, *et al* 2004), the NHP was found to be less sensitive than the SF-36 in people with hypothyroidism. In another study (Botella-Carretero, *et al* 2003), both the SF-36 and the NHP have been incorrectly reported as measures assessing QoL.

GHQ: The GHQ is a measure of current mental health. Originally developed as a 60-item instrument (Goldberg, *et al* 1976), a range of shortened versions of the questionnaire including the GHQ-30, the GHQ-28, the GHQ-20, and the GHQ-12 are now available. The questionnaire asks whether the respondent has experienced a particular symptom or behaviour recently. Each item is rated on a four-point scale (less than usual, no more than usual, rather more than usual, or much more than usual); but scores may vary depending on the selected scoring method, for example the GHQ-12 has a total score of either 36 or 12 (Goldberg and Williams 1988). The GHQ has been used in assessing psychiatric symptoms in different thyroid function states as well as response to treatment (Saravanan, *et al* 2002) (Walsh, *et al* 2003) (Kent, *et al* 1999) (Larisch, *et al* 2004) (Saravanan, *et al* 2005). It has been erroneously described as measuring health-related QoL in a study of treatment of SCH (Kong, *et al* 2002), and also as a measure of generic QoL in a study assessing symptoms and well-being in response to small L-thyroxine dose changes (Walsh, *et al* 2006) .

Hospital Anxiety and Depression Scale: A questionnaire that can be used to establish the presence and severity of both anxiety and depression simultaneously, and separate scores for each can be calculated (Herrmann 1997). This scale has been used to study the effects of combined L-thyroxine/liothyronine therapy (Saravanan, *et al* 2005) as well as the effects of L-thyroxine therapy in SCH (Kong, *et al* 2002).

Both the GHQ and HADS were developed with the primary measurement objective to screen for psychological disorders; hence before being used in evaluative applications, their appropriateness as an outcome measure should be examined carefully.

Life Satisfaction Questionnaire: Petersen and colleagues designed and used this tool to measure satisfaction with different aspects of life in patients receiving L-thyroxine therapy and compared it to euthyroid controls (Petersen, *et al* 1990), although it is not a disease-specific measure. There are 19 randomly selected questions about aspects of life, such as home, family, work, leisure time, hearing, physical fitness, etc. This questionnaire is a life satisfaction and sensory function assessment since it asks respondents to indicate their perceived position in various aspects of life as well as health. It is not clear how the items were generated and whether the instrument had been validated previously.

Disease-specific questionnaires

These instruments measure the patient's perceptions of a specific disease or health problem. The targeted focus of disease-specific instruments makes them clinically relevant. An instrument developed to address a particular disease should be responsive to clinically important changes in health that result from interventions. Disease-specific instruments should not contain any items or health dimensions that are not pertinent to the disease. Furthermore, if the instrument has clear applicability to patients with the presenting problem, acceptability is likely to be high.

The disadvantage of these instruments is that it is not generally possible to administer disease-specific instruments to samples that do not have the relevant health problem. This means that health status scores cannot be compared with those for the general population, which is a common approach for assessing the impact of a particular disease on health status. It follows that it is not possible to make comparisons across treatments for different diseases, which limits the application of disease-specific instruments in economic evaluation. Finally, the restricted focus of disease-specific instruments may prevent them from detecting side effects or unforeseen effects of treatment.

Most disease-specific instruments in use assess symptoms and/or signs in hypothyroidism. However, we first describe a disease–specific measure of quality of life and health status, noting that, there is no hypothyroid-specific

measure of QoL, although there is one available for patients with Grave's ophthalmopathy - the GO-QoL (Terwee, *et al* 1998).

The Chronic Thyroid Questionnaire (CTQ): This instrument measuring health status in hypothyroidism was developed after a literature review, and discussion with specialists and hypothyroid patients (Jaeschke, *et al* 1994). It has 104 items grouped into four domains: physical complaints, energy and general well-being, and mood/emotions and cognitive functioning, and requires an interviewer's help to complete. An impact score is calculated as the product of the item score and the importance attributed to it by a respondent. The items were included after asking patients to focus on problems that improved after treatment with L-thyroxine. The CTQ was piloted by distribution to 220 hypothyroid patients of whom 70 completed the questionnaire (response rate of 31.6%). The characteristics of the non-responders are not known, as the authors themselves acknowledge. It is possible that patients with severe symptoms or those who were highly motivated (45 of the 70 responders were members of the Thyroid Foundation of Canada) completed the pilot questionnaire thus incorporating a certain amount of bias in the items. This questionnaire has been validated in patients with SCH (Jaeschke, *et al* 1996). The authors found that the symptoms in SCH patients were similar to those with overt hypothyroidism although not as frequent. A modified version of this instrument has since been used in a study of combined L-thyroxine and liothyronine therapy in primary hypothyroidism (Clyde, *et al* 2003).

Questionnaires assessing symptoms and signs

There have been a number of questionnaires developed over the years to aid in assessing symptoms and diagnosing hypothyroidism. Physical examination on its own does not always help in diagnosing hypothyroidism (Indra, *et al* 2004). Tools to quantify symptoms and signs are useful in situations where a biochemical diagnosis of SCH has been made incidentally or in a clinical trial to assess response to treatment. Some of these questionnaires are briefly discussed below.

Billewicz index: Billewicz and colleagues designed this as a diagnostic index for hypothyroidism (Billewicz, *et al* 1969). Twenty-one symptoms and signs of hypothyroidism were evaluated in 152 patients with suspected hypothyroidism. The final diagnosis of hypothyroidism (in an era before ultra sensitive TSH

assays were available) was based upon 48-hour radioactive iodine uptake, serum protein bound iodine, thyroid autoantibodies, electrocardiogram, serum cholesterol and therapeutic response to L-thyroxine replacement therapy. A higher positive score indicates a greater degree of clinical hypothyroidism. The same results were obtained in a further 110 patients assessed by colleagues at three other hospitals, although no further details have been provided. A large British follow-up study of 1017 patients given radioactive iodine therapy confirmed the usefulness of this score in the absence of ultra-sensitive TSH assays (Philp, *et al* 1968). A double blind cross-over study of twenty women with SCH by Nystrom and colleagues used a modification of this index in detecting the usefulness of L-thyroxine in treatment (Nystrom, *et al* 1988). Cooper et al used a modified version in their study of SCH, in which patients were also asked about any change in symptoms on subsequent visit (Cooper, *et al* 1984).

The Billewicz index is therefore useful in detecting symptoms and signs of hypothyroidism but is not useful anymore in diagnosis since the advent of biochemical thyroid hormone measurements.

Zulewski index: Zulewski and colleagues designed a symptom rating score based on the Billewicz index to evaluate symptoms and signs in the new thyroid function-testing era (Zulewski, *et al* 1997). Fourteen symptoms and signs of hypothyroidism, similar to the ones described by Billewicz and colleagues were evaluated in 332 subjects (50 with overt hypothyroidism, 93 with sub clinical hypothyroidism and 189 euthyroid controls based on TSH assays). Using this score, 62% of overtly hypothyroid patients were correctly diagnosed as compared to 42% with the Billewicz index. Similarly, 24% of sub clinically hypothyroid patients were classed as overtly hypothyroid (Billewicz index - 6%). This score showed correlation with free thyroid hormone levels but not with TSH in overtly hypothyroid patients. In sub clinically hypothyroid patients, there was positive correlation with free thyroxine and TSH levels. This score is currently useful in helping to evaluate overt hypothyroidism clinically but is less helpful in the context of SCH. It also carries the inconvenience of a trained clinician asking patients about 12 symptoms and examining them for 5 signs. It has nevertheless been used, sometimes with the original Billewicz index, in

some clinical trials (Escobar-Morreale, *et al* 2005) (Saravanan, *et al* 2005) (Meier, *et al* 2001) (Meier, *et al* 2003).

The Thyroid Symptom Questionnaire (TSQ): Designed by Saravanan et al, the TSQ assesses persisting symptoms in people with hypothyroidism on treatment with L-thyroxine (Saravanan, *et al* 2002). The TSQ has 12 questions based on the same format as the General Health Questionnaire (GHQ-12), and derived from the response to a British Thyroid Foundation newsletter (Roberts 1996). This study showed that hypothyroid patients, even with adequate L-thyroxine replacement therapy, have significant psychological impairment and hypothyroid symptoms when compared to euthyroid controls.

The 12 symptoms seem to have been rather arbitrarily chosen, as the questionnaire has no questions about skin, hair and depression, which are quite common and important for patients with hypothyroidism (Jaeschke, *et al* 1994). It had not previously been validated and is not clear whether a pilot study was conducted before being used in the community study. The TSQ has since been used thrice in studying the effects of combined L-thyroxine /liothyronine versus L-thyroxine alone in the treatment of hypothyroidism (Walsh, *et al* 2003) (Saravanan, *et al* 2005) or effect of small changes in L-thyroxine dose (Walsh, *et al* 2006).

Colorado Health Fair Thyroid Disease Symptom Survey: This study was undertaken to determine the prevalence of abnormal thyroid function as well as to determine symptoms (Canaris, *et al* 2000). Participants were recruited from a state wide health fair (n=25,862) and their total thyroxine and TSH levels measured. A questionnaire for hypothyroid symptoms (14 items) was also administered to all participants. The items selected were based on a previous study in which 76 newly diagnosed patients with overt hypothyroidism were compared for traditional symptoms of hypothyroidism with 147-matched euthyroid controls (Canaris, *et al* 1997). The questionnaire is divided into two parts based on whether the symptom was present at the time of completion (current symptom - three items) or whether the symptom was a new occurrence compared to the previous year (changed symptom - 11 items). This study found that people with overt hypothyroidism were more likely to have symptoms than euthyroid participants (16.6% vs 12.1%, $p<0.05$) and that people with SCH were between the two other groups in terms of total symptom score (13.7%, $p<0.05$ in

comparison to the euthyroid group). This symptom score has high specificity (74.7% - 95%) but low sensitivity (2.9% - 28.3%) and low positive predictive value suggesting that the absence of a symptom does not rule out hypothyroidism.

Hypothyroid clinical scoring system: Seshadri and colleagues designed a score using symptoms of hypothyroidism and compared it to biochemical testing for TSH and thyroxine levels (Seshadri, *et al* 1989). This score had a false positive result in 45% of euthyroid individuals and the authors concluded that this score should only be used as a screening tool where resources are limited and biochemical testing difficult.

Other symptom scores: Barker et al (Barker and Bishop 1969) and Harrison et al (Harrison, *et al* 1977) designed tools to detect patients with hypothyroidism secondary to treatment for thyrotoxicosis based on computer screening and postal questionnaire system respectively, based on symptoms. The utility of these early measures in the era of cheap and reliable biochemical hormone measurement is redundant.

Discussion

A number of instruments have been used to assess symptoms, health status and QoL, to aid diagnosis and monitor treatment in hypothyroidism. This review of published literature has found that some of the instruments used for these purposes have either not been designed scientifically (lack of validation and/or psychometric analyses), or that they have been incorrectly used in measuring the stated outcome of the study. This does raise questions about the validity of the results found and has implications about the soundness of published literature in this area, on which we base our clinical practice.

The relationship between physiologic and clinical measures and patient-reported outcomes are modest and quite variable. Wilson and Cleary have proposed a model of different measures of health outcome: biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life (Wilson and Cleary 1995). They have proposed that all these different measures have a causal relationship between them and that each one is a measure of different physiological parameters, extending from the cell to the individual and that person's interaction with society as a whole. There is some evidence that this concept works in the hypothyroid setting, where the number

of hypothyroid symptoms has been directly related to TSH level (Canaris, *et al* 1997). Trying to measure all these outcomes using a single instrument is not only difficult but also implies a lack of understanding of the concept. For example, the outcome scores of a generic instrument depend not only on the disease but also on the other health conditions affecting the individuals in the population being studied (Woodcock, *et al* 2001). Also, generic instruments on their own may lack responsiveness and not be as sensitive to change after intervention as a disease-specific one, primarily because such instruments cover each area superficially (Jaeschke, *et al* 1992). On the other hand, disease-specific measures, although sampling most aspects of health status or QoL relevant to a specific illness, are unlikely to deal with effects due to other co-existing conditions. Therefore, when measuring patient-reported outcomes, namely symptoms, health status and QoL, different instruments should be used for each (Guyatt and Jaeschke 1997).

The order and method (face-to-face, postal, telephonic, etc) of administration is important and needs to be taken into consideration (Cook, *et al* 1993). The generic instrument should precede the specific one because this minimises bias from order effects -generic health scores are more likely to be favourable if disease-specific questions are asked first since the disease items have already been responded to and therefore excluded in replies to the generic ones (Bowling, *et al* 1999). The source of patient recruitment should also be borne in mind when analyzing scoring systems. For example, patients who self-select for thyroid testing may have an underlying psychological illness and any comparison with healthy controls is likely to be flawed.

The limitation of this review is that it has only looked at instruments used in controlled trials or those that measure symptoms, health status or QoL. It has not reviewed visual analogue scores or instruments to measure cognitive functioning.

In conclusion, hypothyroidism is a common yet complex condition with a wide spectrum of presentation and symptoms. Assessing symptoms, health status and quality of life is essential in managing and monitoring the condition and to aid diagnosis. In this review we have set out the various instruments currently available as well as some under development and recommend that clinicians and researchers take due care and consideration when selecting appropriate

measures. This could go a long way towards being more patient-centred in our approach.

Table 35.
Qualities of different instruments used in assessing patient-reported outcomes in hypothyroidism.

Instrument	No. of items	Patient (P) or clinician (C) completed	How developed	Validated
Health status and well-being				
SF –36	36	P	Patient interviews	Yes
NHP	45 (in 2 parts)	P	Patient interviews	Yes
GHQ	60,30,28,20,12	P	Patient assessment*	Yes
QoL				
CTQ	104	Both	Patient responses	Yes#
Symptoms				
Billewicz index	14	C	Patient exam	Yes
Zulewski score	12	C	Patient exam	Yes
TSQ	12	P	Patient responses	No
Colarado Symptom	14	P	Patient responses	Yes

* In primary care setting, # Only in SCH.
SF-36 – Short Form 36, NHP –Nottingham Health Profile, GHQ – General Health Questionnaire, CTQ – Chronic Thyroid Questionnaire, TSQ – Thyroid Symptom Questionnaire.

METHODS (B)

Hypothesis and endpoints

Hypothesis: Treatment of SCH with L-thyroxine improves CV risk factors and patient-reported outcomes.

The primary endpoints were improvement in endothelial function and total cholesterol levels but changes in patient-reported outcomes were amongst the secondary endpoints.

Patient-reported outcomes, (assessed by questionnaire):

Perceived health status.

Hypothyroidism-specific quality of life (QoL).

Hypothyroid symptoms.

Hypothyroid-specific satisfaction with treatment.

There were no disease-specific (hypothyroid) instruments available to assess QoL, symptom bother scores and satisfaction with treatment. Therefore, collaboration with health psychologists with immense experience in questionnaire design and validation was initiated.

The SF-36v2 was utilised for the assessment of perceived health status.

Designing the questionnaires

Introduction

Although there has been much interest in clinical aspects of hypothyroidism and its treatment over the past 20 years, psychosocial aspects have received less attention. Sonino and Fava have pointed out the need for multidimensional assessments of the effects of treatment in thyroid disorders, including psychosocial aspects (Sonino and Fava 1998). However, there is no published self-completion measure of QoL in hypothyroidism. A literature search found two measures, neither of which fulfils the requirements for a condition-specific measure of QOL: the Canadian disease-specific Chronic Thyroid questionnaire, comprising questions relating to symptoms of hypothyroidism (Jaeschke, *et al* 1996), is for completion by health professionals during interviews with patients; the QOL-Thyroid Scale evaluates the impact of thyroid hormone withdrawal on aspects of QoL of patients with thyroid cancer undergoing scanning procedures (Dow, *et al* 1997), and is not suitable for the majority of people with hypothyroidism. The simple tablet treatment regimen for hypothyroidism is unlikely to be a major cause of dissatisfaction to patients compared to, for example, injecting growth hormone to treat growth hormone deficiency. However, some patients with hypothyroidism may not be satisfied with L-thyroxine treatment because they do not feel as well as they did before the onset of the thyroid disorder. Many patients complain of persistent symptoms while taking L-thyroxine (Kaplan, *et al* 2003). Patients on L-thyroxine replacement can have significant impairment in psychological well being compared to controls of similar age and sex (and who had not had thyroid disease), even though their TSH levels are within the normal laboratory reference range (Saravanan, *et al* 2002). Such patients are likely to be dissatisfied with their current treatment. There is some evidence of poor adherence to treatment by patients, perhaps signifying some dissatisfaction with treatment. Ladenson quoted unpublished data from one American clinical laboratory that indicated the possibility that patients do not fully adhere to two thirds of thyroxine prescriptions dispensed (Ladenson 2002). Toft and Beckett (Toft and Beckett 2003) reported, "Some patients achieve a sense of well-being only if free T4 is slightly elevated and TSH low or undetectable." There is also research and

increasing discussion in the literature about the benefits of combined treatment with L-thyroxine and triiodothyronine (Bunevicius, *et al* 1999) (Sawka, *et al* 2003) (Walsh, *et al* 2003) (Saravanan, *et al* 2005). A sensitive measure of treatment satisfaction is needed for clinical trials of any new treatments or treatment combinations in the future. No such measures of treatment satisfaction are known to exist at present.

There are instruments in place for the diagnosis of hypothyroidism on the basis of symptoms (Billewicz, *et al* 1969) (Zulewski, *et al* 1997) but they are for completion by health professionals. Other symptom measures exist, usually designed specifically for a clinical trial (Jaeschke, *et al* 1994) (Canaris, *et al* 1997) (Saravanan, *et al* 2002) (Cooper, *et al* 1984), but which do not appear to have been validated psychometrically, or designed on the basis of interviews with patients. Although patients were involved in the identification of important symptoms in the development of the Chronic Thyroid Questionnaire, the measure itself is completed by 3 clinicians (Jaeschke, *et al* 1994). Measures of symptom frequency or relative change (Canaris, *et al* 1997) (Saravanan, *et al* 2002) (Cooper, *et al* 1984) are not eliciting how much 'bothered' a patient is by a symptom: a symptom might occur frequently, but not trouble the patient unduly and vice versa. There is a need for a short, validated self-completion measure of the most common hypothyroid symptoms that has been developed through interviews with patients.

This study aimed to design three new condition-specific questionnaires based on the views and experiences of people with hypothyroidism, which were: the Underactive Thyroid-Dependent Quality of Life Questionnaire (ThyDQoL), the Underactive Thyroid Treatment Satisfaction Questionnaire (ThyTSQ) and Underactive Thyroid Symptom Checklist (ThySC).

Materials and Methods

Patient recruitment criteria

Patients were recruited at three U.K. centers: Queen Elizabeth Hospital, Gateshead, Royal Surrey County Hospital, Guildford, and St. Thomas' Hospital, London, with some patients also being identified and recruited at primary care clinics local to the Gateshead and London hospitals. Recruitment took place by

telephone or in person during clinics. The patients were representative of the age range and typical female: male ratio found in hypothyroidism (approximately 6:1), and of a wide sociodemographic and ethnic mix, noting that there is higher prevalence of thyroid disease in white compared to black people (Hollowell, *et al* 2002). The age range was 18+ years (no upper limit). There was to be a broad spectrum of hypothyroidism, ranging from subclinical to overt, and including those with postpartum hypothyroidism, or those rendered hypothyroid after surgery or radioiodine therapy. The proportion of people with subclinical hypothyroidism was limited to a maximum of 10% of the total. The great majority of patients would be treated with L-thyroxine. Exclusion criteria were: pregnancy, current or previous thyroid cancer, and non-English–speakers. Patients with other chronic conditions such as diabetes or heart disease were not excluded, nor were patients with central hypothyroidism, even though the latter might have particular difficulty differentiating the symptoms of hypothyroidism from those of other pituitary-hypothalamic hormone deficiencies.

Interviews

Psychologists experienced in questionnaire design conducted semistructured interviews with 38 patients. Each interview lasted approximately 75 minutes and was tape-recorded. An iterative approach was used to determine item selection for the new questionnaires. Twenty-five of the 38 interviews started with open questions about the effects of hypothyroidism on QoL, and experiences of treatment. These 25 patients were asked: "If you woke up tomorrow to find that you no longer had underactive thyroid, and you were producing normal amounts of thyroid hormone, how would that affect your quality of life?" Life domains and aspects of treatment mentioned spontaneously by patients and before they were presented with draft questionnaires were noted down. Interviewees then completed and commented on the draft questionnaires, and possible changes to the questionnaires were discussed and new or modified items piloted with subsequent patients. To check that questionnaires could be completed easily, without the priming effects of previous open questions, 13 of the later interviews were reversed (i.e., the nearly finalized draft questionnaires were presented first before any open questions about QoL and treatment satisfaction were asked). These 13 patients were not asked the above question imagining life without

underactive thyroid. Few "spontaneous" mentions were therefore possible in reversed interviews, although some patients started to talk freely as soon as the interview started, and any spontaneous mentions were noted and included in summaries of spontaneous mentions. Interview data were analysed for content. The following research ethics committees (REC) gave approval for the interview study: Gateshead Local REC, South West Surrey Local REC, and Lewisham REC.

Patient recruitment

Gateshead recruited 18 patients, and 1 additional volunteer was interviewed (a sibling who accompanied her sister to interview but who did not complete the questionnaires); Guildford recruited 9 patients and London 10 patients. All but 1 of the 38 interviewees were being treated with L-thyroxine. Primary care practitioners or hospital clinicians diagnosed all participants after a minimum of two thyroid function tests at least three months apart. Table 36 provides details of patient characteristics, and shows that patients with a broad spectrum of hypothyroidism were recruited.

Table 36.

Patient characteristics and centre recruitment details.

		n
Source of recruitment	Hospital clinic	26
	Primary care	11
	Self-referral	1
Mean age (range)	51.9 (29-79)	38
Ratio women: men		30:8
Diagnosis of hypothyroidism	Primary autoimmune	27
	Primary (secondary to thyroidectomy or radioiodine)	9
	Secondary	2
Treated with L-thyroxine		37
Other conditions	Osteoarthritis	6
	Asthma	4
	Type 2 Diabetes Mellitus	3
	Pernicious anaemia	3
	Lupus	1
	Rheumatoid arthritis	1
	Polycystic ovarian syndrome	1
Ethnicity	White Caucasian	35
	African or Afro-Caribbean	3

ThyDQoL questionnaire

The first draft of the ThyDQoL for use in early interviews was informed by a review of the literature on hypothyroidism and discussions with clinicians. Design of the ThyDQoL was based on the Audit of Diabetes-Dependent Quality of Life (ADDQoL) (Bradley, *et al* 1999), which in turn was influenced by the generic interview method known as the SEIQoL (Schedule for the Evaluation of Individual Quality of Life (McGee, *et al* 1991). Adaptations of the ADDQoL for people with renal disease [RDQoL (Bradley 1997)], macular disease [MacDQoL

(Mitchell and Bradley 2004)], diabetic retinopathy [RetDQoL (Woodcock, *et al* 2004)] and growth hormone deficiency [HDQoL (McMillan, *et al* 2003)] were also considered when designing the ThyDQoL, and relevant items adapted for inclusion. All these questionnaires define QoL as "how good or bad you feel your life to be," on the basis that QoL is "what the patient says it is" (Joyce 1994). Twenty-six of 34 interviewees did not understand the term "hypothyroidism." An additional 5 patients were confused by the distinction between hypothyroidism and hyperthyroidism. On the other hand, the term "underactive thyroid" was used spontaneously by 21 patients, and understood by 15 more patients. One patient did not understand the term, and one patient was unsure of the difference between underactive and overactive thyroid. Because a great majority of patients understood the term underactive thyroid, it was used to refer to the hypothyroid condition throughout, after the first few interviews had been conducted.

Overview items: The first section of the ThyDQoL has two items providing an overview of the respondent's QoL. Question I (QI-present QoL) asks people to rate their present QoL on a 7-point scale from *excellent* to *extremely bad* (scored +3 to -3). Question II (QII-impact on QoL) asks people to rate what their QoL would be if they did not have underactive thyroid, on a 5-point scale from *very much better* to *worse* (scored -3 to +1), providing a global measure of perceived impact of underactive thyroid on QoL. Responses to the two overview items (QI and QII) showed that present QoL was between good and excellent for the great majority (81%), and from bad to extremely bad for only two patients (6%). Despite this, 62% perceived the overall impact of hypothyroidism on QoL as negative (i.e., that their QoL would be better if they did not have underactive thyroid). However, 38% reported that the disorder had no impact on their QoL.

Life domains: The first draft of the ThyDQoL then had 40 life domain items that cover relationships, work and leisure, physical aspects including symptoms, cognitive aspects including memory, psychological aspects including depression, and managing everyday activities. Many of these items are derived from the ADDQoL and versions for other disorders. Domains are introduced by a hypothetical statement with five response options, e.g., If I did *not* have underactive thyroid, my working life would be . . . *very much better*, *much better*, *a little better*, *the same*, *worse* (the impact rating: scored from -3 to +1).

Respondents then rate how important that domain is to their QoL on a four-point Likert scale from *very important* to *not at all important* (the importance rating: scored from 3 to 0). A weighted domain impact score is obtained by multiplying the domain's impact rating by the corresponding importance rating. Weighted domain scores range from -9 to +3 (maximum negative to maximum positive impact of hypothyroidism on the domain). Similar to the ADDQoL, the ThyDQoL is individualised. It takes into account the relevance for the individual of each aspect of life covered in the questionnaire, by giving respondents the opportunity to indicate whether a particular domain, (e.g., *work* or *sex life*), is not applicable. In a "free comments" section at the end of the questionnaire, patients may describe any other ways in which underactive thyroid, and any treatment affect their QoL, allowing for the addition of further domains to the questionnaire in the future, as part of its continuing development.

The instructions on the finalised questionnaire make it clear to patients that they should consider their QoL from the point of view of the treated condition, if applicable. The 25 patients (those not participating in a reversed interview) who were asked how their QoL would be affected if they no longer had underactive thyroid, mentioned 18 areas of life specifically at this point. The key areas of life affected were: energy, weight, physical appearance, bodily discomfort (e.g., cold intolerance, aches and pains), and physical capabilities.

The selection of 18 domains was arrived at through the iterative interview process, taking particular account of the life domains that received spontaneous mentions, patients' marked responses, and comments while completing the ThyDQoL. Nine of the 18 domains have "not applicable" response options. Hypothyroidism was perceived as having a negative impact on applicable domains by 39% to 81% of patients, and the domains were important to most people. The most severely impacted domains were: energy, physical capabilities, motivation, physical appearance, and weight. However, for all 18 domains there were some patients who perceived hypothyroidism as having no impact on the domain, particularly for domains social life, future, and getting out and about. In the majority of domains there were no reports of any positive impact of hypothyroidism, as expected, but there was one woman who reported the positive impact of having the condition diagnosed and successfully treated, after some years of experiencing tiredness and other symptoms. Another patient

reported a positive impact in that she had become more understanding of people with health problems or disabilities. Although some domains received few spontaneous mentions, (sex life, relationship, future), they were included in the final version of the ThyDQoL because they received reports of negative impact on QoL when patients were completing the questionnaires, and were usually important when applicable. Item means are shown in table 37 for the 18 patients in the later interviews (by which stage mostly finer adjustments to items were being made but underlying concepts remained the same). This show the greatest negative weighted impact of hypothyroidism was perceived to be for bodily discomfort (-4.6 ± 3.95), energy (-4.17 ± 3.09) and motivation (-3.57 ± 3.03). Twelve of the final 18 domains on the ThyDQoL were derived from or are similar to domains on the ADDQoL (for diabetes). Additional domains not found on the ADDQoL were derived from other questionnaires: 2 from the HDQoL (for growth hormone deficiency) and 2 from the MacDQoL (for macular degeneration). Weight and depression are important further domains (not used in previous DQoL measures), because excessive weight gain and depression following onset of hypothyroidism were frequently mentioned as being particularly distressing. Of the 40 domains in the first draft ThyDQoL, 18 items were dropped over the course of interviews, for the reason that they were, for the majority of patients, not applicable or not important, and/or not negatively impacted by hypothyroidism, and/or there were no spontaneous mentions of the domain before the questionnaire item was presented. Items dropped were: feelings about fertility, physical stamina, bodily pain, local or long distance journeys, self-confidence, way people in general react to me, financial situation, depend on others, depend on medication, sleep, lose things, tolerance of stress, handle my personal affairs, shopping, do things for others, living conditions, spiritual/religious life, and people fuss or worry about me. In addition four items relating to specific symptoms of hypothyroidism (problems with memory, concentration, voice/speech, and appetite) were also dropped from the earlier drafts of the ThyDQoL because the majority of patients reported they were not applicable. They have been included, together with other more common symptoms mentioned by the patients, in a new short, 15-item Underactive Thyroid Symptom Checklist, suitable for self-completion.

Table 37.

ThyDQoL Item Means and standard deviations from final eighteen interviews.

Number	Abbreviation	Mean ± SD	N
QI	Present QoL	1.29 ± 0.99	17
QII	Hypothyroid-dependent QoL	-1.11 ± 0.96	18
1	Spare time	-1.39 ± 2.12	18
2	Working time	-2.56 ± 2.6	9
3	Holidays	-2.4 ± 3	15
4	Family life	-3 ± 3.43	18
5	Social life	-1.35 ± 2.47	17
6	Relationship	-2.25 ± 2.93	12
7	Sex life	-0.58 ± 1.24	12
8	Physical capabilities	-3.56 ± 3.37	18
9	Energy	-4.17 ± 3.09	18
10	Speed	-3.06 ± 3.65	18
11	Getting out and about	-2.83 ± 3.24	18
12	Household tasks	-2.78 ± 3.04	18
13	Physical appearance	-1.94 ± 2.41	17
14	Weight	-3.43 ± 3.16	14
15	Bodily discomfort	-4.6 ± 3.95	10
16	Depressed	-1.6 ± 1.67	5
17	Motivation	-3.57 ± 3.03	14
18	Future	-1.89 ± 3.09	18

ThyTSQ questionnaire

The first draft of the ThyTSQ was prepared after a review of the literature and discussions between clinicians and psychologists. Its design was based on the widely used Diabetes Treatment Satisfaction Questionnaire [DTSQ (Bradley and Lewis 1990)] and related questionnaires for people with renal disease [RTSQ (Barendse, *et al* 2005)], and human immunodeficiency virus [HIVTSQ (Woodcock and Bradley 2001)]. Instructions ask patients to consider their

experience of treatment for underactive thyroid over the previous few weeks. The first draft of the ThyTSQ comprised 10 questions including items concerning satisfaction with current treatment, convenience, and understanding of treatment, 6 of which were derived from the DTSQ questionnaire for people with diabetes. Patients respond to each item by circling a number on a scale from 6 to 0, indicating their degree of satisfaction with that aspect of treatment (e.g., from *very satisfied* to *very dissatisfied*) as in the following example:

How satisfied are you with the current treatment for your underactive thyroid?

very satisfied 6 5 4 3 2 1 0 **very dissatisfied**

Half the patients in the first sets of interviews (10/20) spontaneously reported negative experiences of treatment around the time of diagnosis. These related to delays in diagnosis, and/or in prescribing L-thyroxine treatment, and/or lack of information provided about the condition or the treatment. Even though patients' experiences of current treatment might be positive, in some cases these past negative experiences interfered with completion of questions about current treatment, because patients wanted to express their dissatisfaction with earlier treatment/mistreatment. A separate section was therefore drawn up, after half the interviews had been conducted, with questions covering satisfaction with past treatment, the ThyTSQ-Past. It is an extension of the main questionnaire, which was renamed the ThyTSQ-Present. Following the iterative process, the final version of the ThyTSQ-Present has seven items including questions about satisfaction with current treatment, control of symptoms of underactive thyroid, convenience, and patient understanding of treatment. Three items were dropped from the early draft ThyTSQ-Present concerning side effects, flexibility and safety of treatment, as these were not perceived to be relevant issues by the patients interviewed. Least satisfaction was found for patients' understanding of their condition (mean 4.58) and for how well the treatment was working (mean 4.97), but there were high means (5.0) for the other five items on satisfaction with present treatment (table 38). The ThyTSQ-Past has four items concerning satisfaction with the way doctors dealt with the patient or the thyroid condition around the time of diagnosis, and satisfaction with information provided about the condition and its treatment. Sixteen patients spontaneously

mentioned some dissatisfaction with past treatment before they saw the draft ThyTSQ. When draft questions about past treatment were being tested in later interviews, 8 of 18 patients expressed some degree of dissatisfaction with aspects of early treatment. Least satisfaction with past treatment was reported for information provided by doctors about the condition and about the treatment (both means less than 4.0). The wide range of responses selected for the majority of items in both treatment satisfaction measures is indicative of the likely responsiveness of these measures to different treatments.

Table 38.

ThyTSQ (present and past) item means from 36 patients.

Number	Abbreviation	Mean ± SD	N
ThyTSQ-Present			
1	Present satisfaction	5.17 ± 1.05	36
2	How well working	4.97 ± 1.11	36
3	Convenient	5.08 ± 1.44	36
4	Understanding of condition	4.58 ± 1.46	36
5	Encourage others	5.56 ± 1.16	36
6	Controlling symptoms	5.33 ± 0.78	12
7	Continue with treatment	5.53 ± 0.84	36
ThyTSQ-Past			
1	Past satisfaction	4.20 ± 2.35	10
2	Information of condition	3.36 ± 2.06	14
3	Information of treatment	3.43 ± 2.47	14
4	Taken seriously	4.85 ± 1.77	13

The Underactive Thyroid Symptom Checklist (ThySC)

When designing the ThyDQoL a number of symptoms were initially included in the measure, such as tiredness and voice problems. However, during the interviews with patients, the majority of these symptoms were found to be unsuitable for inclusion as ThyDQoL domains, being too specific in nature to be

important for many aspects or life, e.g. voice problems, or because some patients were unsure whether they were attributable to hypothyroidism. A total of 38 interviews were conducted with patients when designing the ThyDQoL, but as these progressed it was decided to develop a separate questionnaire, the Underactive Thyroid Symptom Checklist (ThySC), for completion by patients. ThySC design was influenced by design of the Diabetes Symptom Checklist (Grootenhuis, *et al* 1994) and the Asthma Symptoms Questionnaire (Steen and McColl 1995). Symptoms selected for inclusion were based 6 on the literature, consultations with endocrinologists, and were the most frequently mentioned symptoms in the interviews. The method used to design the ThySC was the same as for the ThyDQoL, and the ThySC was finalised and piloted in semi-structured interviews with 10 patients conducted at two centres (London and Surrey): 2 men and 8 women, [mean age 49 ± 14.3, range 32 – 67 years]. The checklist of 15 symptoms has a 4-point symptom bother scale measuring perceived symptom severity, and is introduced:

"This questionnaire asks you about symptoms that can be associated with underactive thyroid and that you may have experienced in recent weeks".

Respondents provide a bother rating for applicable symptoms, indicating how much the symptom bothers them from not at all, a little, quite a bit, very much (scoring 0, 1, 2 and 3 respectively). Any patient who reports that they do not have a symptom is given a symptom bother rating of zero (not at all bothered). The term 'in recent weeks', whilst not specific, has been found during interviews or in questionnaire development work to be interpreted as meaning the past three to six weeks. Although it would be possible to specify a time period (e.g. the past four weeks), in practice patients are not able to remember so precisely when symptoms occur and such specificity may give an illusion of precision that does not exist.

The ThySC was then further tested in a sample of hypothyroid patients (n=110) in whom the ThyDQoL and ThyTSQ were being validated. Table 39 describes the frequency of symptoms as well as mean bother scores.

Table 39.

Frequency and mean bother scores of symptoms of hypothyroidism (n=110).

Symptom	% (n)	Mean ± SD	Median
Tiredness	90 (99)	2.11 ± 0.77	2
Weight gain	59 (65)	2.22 ± 0.93	3
Feeling cold	53 (58)	2.12 ± 0.75	2
Constipation	42 (46)	1.74 ± 0.88	1.5
Hair	44 (48)	2.25 ± 0.86	3
Skin	60 (66)	2.00 ± 0.91	2
Nails	46 (51)	1.69 ± 0.84	2
Appetite	22 (24)	1.54 ± 0.98	1
Hearing	33 (36)	1.75 ± 1.05	1
Voice	24 (26)	1.58 ± 1.14	1
Speech	25 (27)	1.89 ± 0.89	2
Memory	54 (59)	2.00 ± 0.93	2
Concentration	56 (61)	2.07 ± 0.91	2
Feeling giddy	46 (51)	2.00 ± 0.88	2
Depression	73 (80)	2.13 ± 0.83	2

Discussion

The Thy-DQoL is an individualized patient-centred measure of the impact of hypothyroidism on QoL and the ThyTSQ measures satisfaction with treatment for this disorder. The ThyDQoL has two overview items to assess current QoL and overall impact of hypothyroidism on QoL, and 18 items covering specific domains of life that may be impacted by hypothyroidism, domains that were important to the great majority of interviewees. The ThyTSQ was divided into two separate and independent sections: the 7-item ThyTSQ-Present, which measures satisfaction with current treatment for hypothyroidism, and the 4-item ThyTSQ-Past measuring past satisfaction with treatment around the time of diagnosis. Over the course of the iterative interview process, many draft items were dropped from the early versions of the questionnaires, and new items inserted, or different forms of wording used. This has shown the importance of

developing condition-specific questionnaires rather than using generic measures, or making superficial modifications to questionnaires designed for other conditions.

There is considerable support for the domains selected for inclusion in the ThyDQoL. Patients who were asked what effect there would be on their QoL if they did not have underactive thyroid spontaneously mentioned all but 2 of the final 18 domains. The exceptions were holidays and depression, but these were often mentioned in other parts of the interviews. Despite treatment with L-thyroxine, hypothyroidism was found to have a negative impact on QoL, particularly for the domains of bodily discomfort, energy, motivation, physical capabilities, weight and physical appearance. This confirms the reports of continuing symptoms and effects of hypothyroidism on QoL that appear in newsletters produced by thyroid patient organisations (e.g., British Thyroid Foundation) and also recent discussion in the medical literature (Kaplan, *et al* 2003).

A problem for a measure of QoL in hypothyroidism is that patients may have treated comorbidities such as pernicious anaemia or diabetes, which often have diffuse symptoms that are indistinguishable from those caused by hypothyroidism. The advantage of the ThyDQoL, however, is that each item specifically mentions "underactive thyroid," encouraging the respondent to focus on this condition rather than any others that they might have. There is evidence that the related condition-specific questionnaire, the ADDQoL for diabetes, is more sensitive to the effects of diabetes in those with co morbidities than generic measures of health status (Woodcock, *et al* 2001), and we would expect the ThyDQoL to have similar properties. Furthermore the ThyDQoL is not designed to distinguish between people who are, for example, depressed for reasons unrelated to their hypothyroidism and those who are depressed owing to inadequate L-thyroxine replacement. However, it will distinguish between people who believe that their depression is caused by hypothyroidism and those that think that they have depression for other reasons (and who will indicate that underactive thyroid has had no impact on their feelings of depression). The overall total score for the ThyDQoL will provide the average weighted impact on QoL, for individual or group comparison with scores of other individuals or

groups. The next step was to validate the newly designed questionnaires and to assess their psychometric properties.

Validation of the questionnaires

This chapter concerns the evaluation of these questionnaire's psychometric properties.

Participants and Methods

In this cross-sectional study, the ThyDQoL, the ThyTSQ and ThySC questionnaires were completed by hypothyroid patients recruited from the diabetes and endocrinology clinic at Queen Elizabeth Hospital, Gateshead, UK (fewer than 5% of whom were attending the hospital for their primary hypothyroidism) and three local primary care practices in which all patients were approached who fitted the inclusion criteria. The age range was 18+ years (no upper limit), and all patients had a diagnosis of hypothyroidism based on two blood tests taken at least three months apart. People known to have mental health problems likely to render them incapable of understanding and completing the questionnaires were not included. The Gateshead Local Research Ethics Committee gave approval for the research, which was carried out in compliance with the Helsinki declaration.

The mean age of the sample was 55.1 years, and mean duration of hypothyroidism was 8.3 years. The ratio of women to men was 9:2, similar to the sex ratio of thyroid disease found in the general US population in a recent study (Hollowell, *et al* 2002). The great majority of patients had autoimmune hypothyroidism (N = 98, 89%) of which 11 patients had subclinical hypothyroidism. The great majority (N = 103, 94%) were receiving L-thyroxine replacement. Measurements of TSH levels were available for 95 patients (86%) (median 2.4 mIU/L) but in the case of free thyroxine (FT4) only 49 patients (45%) (mean 17.4 pmol/L).

Questionnaire completion rates

Healthcare professionals prompted patients recruited and respondents to complete any missed items on the questionnaires, or at the three primary care clinics (where patients were not prompted to complete missing data). The Flesch Reading Ease statistic was calculated to be 54.1 (ThyTSQ-Present) and 57.2 (ThyTSQ-Past). These are slightly less than the optimal 60-70 (in a possible score range of 0 to 100, where a higher score indicates greater reading ease).

The Flesch statistic takes into account the average number of syllables per word and words such as our recruitment sources might create artifactual correlations in the combined sample, if the subgroup mean scores differed consistently across items. This was investigated by converting the scores to standardised z-scores within each subgroup before combining the sub-sets of scores. Such standardisation renders group means identical and thereby removes the possibility of correlations caused by subgroup differences (a method adopted when developing the ADDQoL). Forced one-factor solutions on the raw scores, and then on the z-scores, produced two sets of factor loadings that were then compared using correlation and regression analyses. There was no significant difference between loadings of standardised and raw scores: the correlation of 0.998 was close to 1, the constant was 0.0, and the slope of the regression line (1.001) did not differ significantly from 1, [t (15) = 60.28, p >0.05]. Thus initial analyses demonstrated that the four recruitment groups could be treated as one sample for reliability and factor analyses (for which larger N is desirable).

Statistical analyses

No data from respondents selecting a N/A response option on the ThyDQoL would normally be included in factor and reliability analyses. N/A responses are treated as missing by the statistical package used (SPSS for Windows, Release 10.0). Furthermore, if the SPSS default of listwise deletion of missing data is used, all cases that have any missing values across all 18 items are lost to analysis, so considerable data could be lost. From 3 to 50% of volunteers selected N/A on items where the option was available, N/A responses were therefore coded as zero for factor and reliability analyses, with pair wise deletion of data missing for other reasons, as in the original development of the ADDQoL. Normality of distributions was determined through investigation of histograms and z (skew) scores (comparing the skewness value with zero using the z distribution), where z (skew) scores between ±2.58 are indicative of normality . The minimum acceptable Cronbach's alpha coefficient of internal consistency reliability was taken as 0.8 and acceptable item-total correlations were >0.2. Factor structure was explored using Principal Components as an extraction method with Varimax rotation, with salient loadings taken as > 0.4.

The ThyDQoL

Descriptive statistics

Domains reported as most severely (and negatively) impacted by hypothyroidism were: motivation (mean weighted impact = -4.84), weight (-4.51), and depression (-4.36), (maximum possible range -9 to +3) (table 40). The majority of respondents (71%) perceived that hypothyroidism had had a negative impact on overall QoL (mean QII:Thyroid dependent QoL was -1.25), and Present QoL was rated as between good and neither good nor bad (mean 0.89). Transformations of any non-normal distributions left three items with slightly skewed distributions [z (skew) ranging from 2.8 to 4.0].

Table 40. ThyDQoL item descriptive statistics in validation study (n=108).

Number	Abbreviation	Mean ± SD	N
QI	Present QoL	0.89 ± 1.02	108
QII	Hypothyroid-dependent QoL	-1.25 ± 0.99	108
1	Spare time	-2.49 ± 2.71	107
2	Working time	-3.46 ± 3.3	54
3	Holidays	-2.37 ± 2.63	90
4	Family life	-2.74 ± 2.93	105
5	Social life	-2.00 ± 2.57	106
6	Relationship	-2.91 ± 3.18	88
7	Sex life	-2.69 ± 3.12	75
8	Physical capabilities	-3.23 ± 2.82	105
9	Energy	-4.21 ± 3.11	107
10	Speed	-2.78 ± 2.52	108
11	Getting out and about	-2.60 ± 2.90	108
12	Household tasks	-3.37 ± 2.89	106
13	Physical appearance	-3.24 ± 3.24	108
14	Weight	-4.51 ± 2.97	86
15	Bodily discomfort	-4.29 ± 2.81	89
16	Depressed	-4.36 ± 2.73	76
17	Motivation	-4.84 ± 2.79	95
18	Future	-2.87 ± 2.86	107
	Average Weighted Impact 18	-3.11 ± 2.2	108

Reliability and factor analyses and correlations

The 18-item ThyDQoL had very high internal consistency reliability [Cronbach's alpha =0.949, standardised item alpha = 0.95, N = 97 (N/A responses coded as zero)]. All corrected item-total correlations were satisfactory (>0.2, range 0.49 to 0.88), the lowest being the item 'depression' which also detracted slightly from overall scale alpha (0.95). A forced 1-factor analysis showed all 18 items had satisfactory loadings (>0.5) on the single factor (accounting for 55.4% of the variance), indicating that all applicable domains could be combined into an overall Average Weighted Impact score (AWI-18), reflecting a maximum of 18 weighted domain impact scores. The AWI-18 mean score of -3.11 (2.2) indicated overall negative perceived impact of hypothyroidism on QoL. To assess the effects of missing data on ThyDQoL reliability, reliability analyses were run sequentially, deleting the strongest item each time, (i.e. deleting the item having the lowest 'alpha if item deleted' and therefore contributing most to the scale's internal reliability). Calculation of ThyDQoL AWI-18 was reliable at alpha = 0.9 with a maximum of five items missing and reliable at alpha = 0.8 with a maximum 10 missing items. It is therefore reasonable to calculate AWI-18 providing at least half of the items (i.e. domain-specific items) have been completed.

The correlation between AWI-18 and QII:*Thyroid-dependent QoL,* [r = 0.69, p <0.001, N =108], was sufficiently high for QII to replace the full ThyDQoL for some purposes. With respect to AWI-18 and overview items, no significant sub-group differences were found in treatment (noting that only 6.5% of patients were untreated), nor a significant correlation with TSH levels was noted. However, the difference in QII:Thyroid-dependent QoL between those with overt and subclinical hypothyroidism approached significance (Bonferroni correction required p value 0.05/3 = 0.017).

The ThyTSQ

Descriptive statistics

Non-normality, (negative skew towards high satisfaction with treatment) was found in most ThyTSQ items and was dealt with successfully by conducting reflect and log transformations, leaving two items with a small degree of non-normality [z (skew) = 4.2]. ThyTSQ-Present item means indicate that overall

patients were satisfied with all aspects of their treatment (table 41). Patients were most satisfied with convenience of treatment (item 3, mean 5.24), and least satisfied with their understanding of their condition (item 4, mean 4.19). Mean Present Satisfaction was 32.5 (7.8) (maximum possible range 0 – 42). Of the six patients (5.9%) who had Present Satisfaction scores of < 21 (expressing dissatisfaction with current treatment) five had available TSH measurements: mean 1.64, range 0.12 to 3.53, i.e. were being treated so that their TSH levels were within the laboratory reference range of 0.4 to 4.0 mIU/L. Patients were more satisfied than dissatisfied with all four aspects measured by the ThyTSQ-Past, but had least satisfaction with information provided about the condition or its treatment at time of diagnosis. Mean Past Satisfaction was 17.5 (6.1) (maximum possible range 0 – 24). Nineteen patients (18.4%) had Past Satisfaction scores < 12 indicating overall dissatisfaction with past treatment.

Table 41.

ThyTSQ item means in validation study (n-=110)

Number	Abbreviation	Mean ± SD	N
ThyTSQ-Present			
1	Present satisfaction	4.89 ±1.27	103
2	How well working	4.22 ± 1.47	102
3	Convenient	5.24 ± 1.18	103
4	Understanding of condition	4.19 ± 1.73	103
5	Encourage others	5.1 ± 1.26	103
6	Controlling symptoms	4.36 ± 1.27	103
7	Continue with treatment	4.52 ± 1.43	103
ThyTSQ-Past			
1	Past satisfaction	4.72 ± 1.68	103
2	Information of condition	3.94 ± 1.8	103
3	Information of treatment	4.2 ± 1.72	103
4	Taken seriously	4.59 ± 1.78	103

Correlations

ThyTSQ-Present no.7: "continue with treatment" correlated negatively with BMI (rho = -0.23, p = 0.03, N = 92), no.3: "convenient" correlated with TSH levels (rho = -0.22, p = 0.4, N = 88) indicating that those with high BMI were more dissatisfied to continue their present treatment, and those with high TSH levels were more dissatisfied with convenience of treatment. Variables 1:present satisfaction, 2:how well working, 6:controlling symptoms and 7:continue all correlated positively with age (rho values range from 0.32 to 0.40, $p \leq 0.001$, N ranging 102 to 103), and ThyTSQ-Past 1:past satisfaction, 2:information-condition also correlated with age (rho = 0.23 and 0.21 respectively, $p < 0.05$) indicating improved satisfaction with increasing age. There were no significant correlations between the Satisfaction scores and the number of co-morbid conditions that patients had or duration of hypothyroidism.

Sub-group differences in ThyTSQ variables

The only significant sub-group difference found was a sex difference: women had higher satisfaction with the control of their hypothyroid symptoms, median 5, compared with men, median 4 (U = 528.5, p = 0.034) There were no significant differences in ThyTSQ-Present or Past Satisfaction scores, between respondents whose TSH levels were within the reference range of 0.4 to 4.0 mIU/L, (N = 46), and those below (N = 12), and above this range (N = 29) (p = 0.092), nor between those who had autoimmune hypothyroidism (N = 91) and those with hypothyroidism caused by treatment (N = 12).

Reliability and factor analyses

The 7-item ThyTSQ-Present had very high internal consistency reliability [Cronbach's alpha = 0.907, standardised item alpha = 0.914, (N = 102)]. All corrected item-total correlations were satisfactory, the lowest being 0.504 (item 4: understanding of condition), which was also the only item to increase overall scale alpha if deleted (alpha if item deleted was 0.925) and therefore detract slightly from the scale reliability while broadening the content. The 4-item ThyTSQ-Past had high internal consistency reliability [Cronbach's alpha = 0.896, standardised item alpha = 0.896, (N = 103)]. All corrected item-total

correlations were satisfactory, the lowest being 0.692 (item 1: past satisfaction). No item detracted from the ThyTSQ-Past scale alpha.

An unforced principal components analysis, conducted on the 11 items, (transformed to near normality), of the Satisfaction score (range 0 to 42) and all four ThyTSQ-Past items could be summed into a separate ThyTSQ-Past Satisfaction score (range 0 to 24). A lower score indicates greater dissatisfaction with treatment, and a higher score indicates greater satisfaction with treatment. We do not recommend summing the Present and Past Satisfaction scores into an overall Treatment Satisfaction score for the two sections combined. The correlation between the Past and Present Satisfaction scores was rho = 0.649, p< 0.001; Cronbach's alpha = 0.8 with no more than one item of missing data.

The ThySC

Descriptive statistics

The most common reported symptoms were tiredness (90% of respondents), feeling depressed or low, and skin problems. The mean number of symptoms reported per patient was 7.4 (3.2), N = 107, with six patients indicating they had 13 or more symptoms. Almost one third reported being very much bothered by symptoms of tiredness, weight gain or depression when applicable. The highest mean bother ratings were for hair, weight gain, depressed, and cold. When data were examined from the 57 respondents who had either no co-morbidities (N = 42), or whose only co-morbidities were likely to be perceived by patients as symptomless (hypertension and hypercholesterolaemia, N = 15), the picture was only a little different: the most common reported symptoms were tiredness, depression, problems with concentration and skin, weight gain, memory and cold (full results not reported).

Reliability and factor analyses

Exploratory psychometric analyses were performed on the ThySC scale formed by the symptom bother ratings although the checklist, being a number of disparate symptoms, was not expected to have high internal consistency reliability or any particular factor structure.

ThySC internal consistency reliability was unexpectedly high: Cronbach's alpha = 0.808, standardised alpha = 0.81, N = 95, with all corrected item-total correlations >0.2. Only two items would increase alpha if deleted from the scale (5:hair and 9:hearing), and by no more than 0.002 (full results not shown). Results of unforced and forced factor analyses were unclear, with insufficient evidence of satisfactory subgroups of symptoms that could produce reliable subscale scores. Forced one factor analyses showed 12/15 items loaded >0.44 but constipation, hair and hearing fell short of this (0.35 to 0.28) indicating that a total score is not fully justified. This result was not unexpected.

Correlations and subgroup differences

Chi-Square tests found no significant differences in symptom frequency of thyroxine treated and untreated patients. The only correlations between TSH (a tissue marker for severity of hypothyroidism) and ThySC bother ratings to approach significance were for constipation [rho = -0.43, p = 0.009, N = 36] and depression [rho = -0.35, p = 0.0035, N = 68] (the required significance after a Bonferroni correction is 0.0033).

Relationships between the ThySC and ThyDQoL questionnaires

When both ThyDQoL and ThySC questionnaires are administered to patients it would be prudent, if analysing relationships between ThyDQoL AWI and ThySC symptom bother ratings, to exclude patients' responses to the four ThyDQoL symptom domains (energy, weight, bodily discomfort and depression) from the calculation of the AWI score, i.e. a maximum of 14 items should be included in the AWI-14 score. Analyses showed a very high internal consistency reliability of the 14-item ThyDQoL (Cronbach's alpha = 0.944, N = 99), with lowest corrected item-total correlation of 0.57. All loadings on a forced 1-factor analysis were >0.6. This provided evidence for the reliability and validity of calculating overall AWI-14. Mean ThyDQoL AWI-14 for the sample was -2.86 (2.22), slightly less negative than -3.11 (2.2) for the full 18-item AWI-18, as expected. When correlating AWI-14 with ThySC bother ratings, the strongest significant negative correlations were found (in decreasing order) with tiredness, concentration, depressed, weight gain, cold, speech and skin, indicating that increased symptom bother was associated with greater negative

impact of hypothyroidism on QoL. The correlations with AWI-14 were very similar to those with the full 18-item ThyDQoL AWI-18, indicating that concerns about spuriously high correlations between ThySC and AWI-18 were not supported. Correlations between symptoms and AWI scores were low to moderate (range -0.1 to -0.6), an indication that symptoms and QoL are distinct and separate patient-reported outcomes. A stepwise multiple regression analysis was conducted to evaluate how well the bother ratings for the five symptoms with the highest correlations with QI:Present QoL i.e. tiredness, depressed, cold, concentration and giddy, predicted Present QoL. Only tiredness was a significant predictor of Present QoL: [$F(1,98) = 31.1$, $p < 0.001$]. The sample multiple correlation coefficient was 0.49, indicating that 24% of variance in QI could be accounted for by tiredness: the greater the bother rating for tiredness, the worse the present QoL. Moderate significant negative correlations were found between the number of applicable symptoms and ThyDQoL overview items QI: Present QoL ($r = -0.42$), and QII: Thyroid dependent QoL ($r = -0.43$) ($p < 0.001$, $N = 105$) indicating decreased Present QoL, and greater negative impact of hypothyroidism on QoL with increasing numbers of symptoms.

Discussion

The ThyDQoL is a individualised measure of the perceived impact of hypothyroidism on QoL, with high completion rates indicating good acceptability to respondents. Internal consistency reliability was excellent and factor analyses highly supportive of the combination of all 18 weighted domains into a single average score, the ThyDQoL AWI-18 score, which indicated moderately severe perceived negative impact of hypothyroidism on QoL in this sample. Useful information can be elicited from the single overview items. On average, respondents' Present QoL (QI) was perceived to be between good and neither good nor bad and QII, concerning impact of hypothyroidism on QoL, could provide an approximate substitute for the full ThyDQoL for some purposes, (e.g. when respondent burden is of particular concern), as the correlation between QII and overall ThyDQoL AWI-18 was high ($r = 0.69$). Analysing individual domains can obtain rich information separately. For example, it was found that, despite most patients receiving L-thyroxine replacement to normalise TSH levels, hypothyroidism still had a marked

negative impact, particularly on motivation, weight, feelings of depression, bodily discomfort and energy, which may well impact on several other domains, such as spare time activities or work.

Over 70% of respondents reported feeling depressed or having bodily discomfort in recent weeks. Content validity was supported, as no new ThyDQoL domains emerged when analysing the free comments section, and all existing domains detected negative impact of hypothyroidism with mean weighted domain impact scores of -2 or less.

The ThyTSQ-Present measures satisfaction with present treatment, and the ThyTSQ-Past measures satisfaction with treatment around the time of diagnosis, but treatment in the broader sense of the term, to include medical care and interactions with healthcare professionals. Use of the ThyTSQ-Past is recommended to avoid any negative experiences of past treatment interfering with completion of questions about current treatment, though if it were used in a clinical trial it might only be completed once, at baseline, (in the present study they were used together). Use of the ThyTSQ-Present alone without the ThyTSQ-Past would need further psychometric evaluation. The measure is short and quick to complete, with minimal respondent burden, and the very high completion rates indicating good acceptability to respondents. The factor structure was clear. When the 11 items of both sections were combined in one unforced factor analysis, two clean factors emerged, with Past and Present items loading on separate factors. Unforced analyses performed on each separate section produced one factor each, with very high factor loadings, which lent support for summing the individual item scores into Present and Past Satisfaction scores. The internal consistency reliability of each section was also excellent. The moderate correlation between the total scores of the two parts is an indication that they are measuring different but related constructs.

When the free comments were analysed, they showed that the areas of dissatisfaction mentioned were, for the most part, already covered by the items of the questionnaire, suggesting that respondents were emphasising or explaining dissatisfaction already reflected in existing items. Insufficient numbers of patients specified particular issues to justify the addition of new items, hence the measure would appear to have good content validity, however,

the measure is still at a relatively early stage of development, and new items may be added in the future when more data become available. Construct validity was not assessed in this exploratory study as no prior hypotheses were formulated. The only significant sub-group difference found was that women had higher satisfaction than men with the control of their hypothyroid symptoms. Satisfaction improved with increasing age for both Past and Present scores, perhaps because people expect to have more health problems, as they grow older and, with lower expectations of treatment, are more likely to be satisfied with treatment.

Generally high satisfaction rates were found, but a small proportion of patients were dissatisfied, giving support to anecdotal reports from clinicians. More patients expressed dissatisfaction with their present understanding of the condition and with information provided about the condition in the past than any other item on the ThyTSQ-Present and Past respectively. Although dissatisfaction with L-thyroxine therapy has been defined in relation to persistence of symptoms (Walsh 2002), it is clear, not only from interviews conducted when developing this questionnaire but also from the analyses presented here, that symptoms are not the only aspect causing dissatisfaction. This study has found support for having the section on satisfaction with past treatment, as scores on Past Satisfaction tended to be lower than those for Present Satisfaction with treatment, and some patients clearly welcomed the opportunity to report their dissatisfaction as evidenced by the larger number of patients using the free comments section of the ThyTSQ-Past.

This study has shown that more consideration needs to be given to the interaction between patient and doctor at the time of diagnosis. More consultation time may be required at the point when a patient is first told that they have a condition that requires life-long treatment. Patients may be too distressed at the time they are first told they have hypothyroidism, to absorb much of the information they are given, especially as cognitive functioning of people with untreated hypothyroidism is reduced in some cases (del Ser Quijano, *et al* 2000). They may welcome information leaflets that they can take home and study in their own time. Whilst the daily tablet regimen in itself is not

complicated, some patients may not understand why their dosage must be increased slowly until equilibrium is reached between hypo and hyperthyroidism. Others may be despondent if treatment does not return them to their previous state before onset, and not fully adhere to the tablet treatment regimen. Thus it is possible that increased adherence to treatment would result if patients understood their treatment better. Use of the ThyTSQ questionnaire will pinpoint lack of understanding in individual patients, who can then receive more help from healthcare professionals.

Although further studies will be needed in the future to assess test-retest reliability, sensitivity to change (ThyTSQ-Present only), and construct validity, the questionnaire is ready to be used in clinical trials of treatments for hypothyroidism. It can be used also with individual patients, completed questionnaires forming the basis for discussion between patients and health care professionals.

The Underactive Thyroid Symptom Checklist measures both symptom frequency and the degree to which patients are bothered by symptoms associated with hypothyroidism. All 15 symptoms were experienced recently by at least some patients and there was a wide spread of frequencies of responses from not at all bothered to very much bothered. Internal consistency reliability was unexpectedly high, but factor analysis did not support the calculation of a total symptom bother score. Analysis of the most frequently reported symptoms (tiredness, depression, weight gain, and problems with skin, concentration and memory) and bother ratings, confirmed the typical picture of hypothyroidism: physiological symptoms connected with slowing of the metabolism and also reduced psychological well-being and impaired cognitive functioning. Although measures of health status are often and erroneously described as QoL measures, in this study symptoms (an aspect of health status) and QoL were distinct and separate patient-reported outcomes, as indicated by low to moderate correlations between symptom bother ratings and ThyDQoL AWI.

The ThyDQoL includes four symptom items that are also covered on the ThySC symptom measure, namely energy, weight, bodily discomfort and depression. It is recommend that these four items be excluded from the calculation of ThyDQoL AWI when the questionnaire is administered with the ThySC, to

avoid duplication and spurious correlations between the two questionnaires. The equivalent symptoms on the ThySC (tiredness, depressed, weight gain and cold) still had some of the strongest correlations with AWI-14, suggesting that the impact of those symptoms on QoL is reflected in ratings of many domains, and symptom-specific domains are not required in the ThyDQoL, although they are likely to increase face and content validity where no symptom measure is used. If troublesome symptoms can be reduced, QoL of patients may be improved. The data suggested that patients were most bothered by hair problems, weight gain, depression, feeling cold, and tiredness and that healthcare professionals could direct their efforts to alleviating these symptoms if they wish to improve the QoL of their patients. Symptoms can be selected for the ThySC to suit the purposes of a particular clinical trial. Further symptoms may need to be added if required (e.g. side effects of a new drug under evaluation), although the rationale of any deletions or additions would need to be justified.

In conclusion, the ThyDQoL, ThyTSQ and ThySC are new condition-specific questionnaires measuring the perceived impact of hypothyroidism on QoL, satisfaction with treatment and bother ratings for 15 symptoms respectively, and allowing multidimensional assessments of the effects of treatment in hypothyroidism. All questionnaires perform well with good acceptability to the great majority of respondents, and have excellent internal consistency reliability. Domains can be analysed separately if required and an overall score calculated for ThyDQoL and ThyTSQ. Additional symptoms may be added to the ThySC to suit the requirements of different studies. Sensitivity to change of all measures now needs to be evaluated in clinical trials.

RESULTS (B)

Baseline characteristics of patient-reported outcomes.

Baseline parameters of patient reported outcomes are outlined in tables 42 – 44.

Table 42.

Baseline scores of perceived health status as measured by SF-36v2 (n=100).

Domains	**Mean score (SD)**
Physical-Functioning	71.4 (26.4)
Role-Physical	64.6 (28.7)
Bodily Pain	64.6 (27.4)
General Health	59.3 (22.2)
Vitality	39.1 (22.6)
Social Functioning	69.6 (28.0)
Role-Emotional	70.5 (27.7)
Mental Health	63.8 (19.4)
Physical Component Summary Score	45.9 (10.6)
Mental Component Summary Score	41.9 (12.2)

As can be seen above, the most impacted perceived health status domain was vitality. The SF-36 v2 scores were then compared with normative population scores to assess the degree of impairment in health status, as seen in next chapter.

Table 43.

Baseline QoL scores as measured by ThyDQoL (n=100).

Domains	**Mean scores (SD)**
General QoL	0.89 (1.0)
Thyroid-dependent QoL	-1.24 (1.0)
Spare time	-3.0 (2.4)
Work life	-3.1 (2.7)
Holidays	-2.6 (2.6)
Family life	-3.2 (3.0)
Social life	-2.4 (2.4)
Close relationship	-2.9 (2.9)
Sex life	-2.6 (2.5)
Physical capabilities	-3.4 (2.9)
Energy levels	-4.3 (3.1)
Speed of doing things	-2.7 (2.4)
Getting out and about	-2.7 (2.9)
Household tasks	-3.0 (2.9)
Physical appearance	-2.5 (2.6)
Weight	-3.5 (2.7)
Bodily discomfort	-3.6 (2.9)
Depressed	-3.7 (2.8)
Motivation	-4.4 (2.8)
Worries about future	-3.1 (3.2)
Average Weighted Impact-18	-3.0 (2.9)

Overall QoL was perceived to be good by the SCH patients but hypothyroidism was thought to have a negative impact on QoL. The two domains of motivation and energy were perceived to have been most negatively influenced by SCH. The rest of the domains showed varying degrees of negative impact of SCH.

Table 44.

Baseline frequency and bother scores of symptoms of hypothyroidism (n=100).

Symptoms	Frequency (%)	Bother scores (SD)
Tiredness	93	2.0 (0.9)
Depression	71	1.7 (0.9)
Weight gain	53	2.0 (0.8)
Feeling cold	52	1.8 (0.8)
Hair problems	36	1.9 (0.9)
Skin problems	52	1.8 (0.8)
Nail problems	42	1.4 (0.8)
Constipation	31	1.5 (0.9)
Voice change	23	1.6 (0.8)
Speech change	24	2.1 (0.8)
Suppressed Appetite	17	1.0 (0.6)
Hearing problems	29	1.8 (0.8)
Memory impairment	49	2.0 (0.8)
Concentration impairment	54	1.7 (0.9)
Dizziness	47	1.8 (0.9)

Tiredness was reported by a large number of patients and depression by many. Bother-scores were similar for tiredness, weight gain, speech and memory impairment.

Amongst these questionnaires, only the SF 36 v2 is a generic instrument whereas all the others are disease-specific ones. Therefore, only the SF 36 v2 scores can be compared with other populations to gauge the impact of SCH on perceived health status. This was therefore done by comparing scores of patients aged 18-65 years (n=71) with those of the UK normative working age population.

Perceived health status in patients with subclinical hypothyroidism compared to normative UK population.

The presence of symptoms of hypothyroidism in patients with SCH when compared with the general population is controversial due to the non-specific nature of many hypothyroid symptoms, which are also common to many other conditions, and due to the different types of patient samples studied (Canaris, *et al* 1997) (Canaris, *et al* 2000) (Nystrom, *et al* 1988) (Eden, *et al* 1988) (Zulewski, *et al* 1997) (Cooper, *et al* 1984).

The lifetime prevalence of depression in patients with SCH is double that of the general population and has been reported to reduce the efficacy of antidepressant treatment (Saddock and Saddock 2000); it is associated with anxiety (Sait Gonen, *et al* 2004) and changes in mood and cognitive functioning (Hendrick, *et al* 1998). There is also evidence that exercise capacity may be impaired due to significant reduction of exercise-related stroke volume, cardiac index, vital capacity and reduced anaerobic thresholds (Kahaly 2000). All these factors may affect subjective perception of health status.

Subjective health status is a key component in the evaluation of any medical condition and therapeutic intervention. In patients with SCH, symptoms may contribute to perceived impairment of health-related quality of life (Jaeschke, *et al* 1994). Health status can be measured by the widely used generic Short Form-36 (SF-36) questionnaire. As there have been some concerns about the wording and layout of the original SF-36, the developers have designed a second version – the SF-36v2. The normative data for the SF-36v2 in the UK was obtained from a postal survey of patients randomly selected from general practitioner records, which achieved a response rate of 64.4% (n = 8889). The SF-36v2 was shown to have improved reliability and reduced floor and ceiling effects compared with the previous version of the SF-36 (Jenkinson, *et al* 1999). Respondents were also asked to report demographic details and any long-term illnesses, and 36.6% reported a chronic long-standing illness. Therefore the health status of people with SCH using the SF-36v2 was compared to UK normative population scores.

Patients

Only 71 patients, mean age (SD) 48.7 years (9.67), range 23–64; 15 males, in the 18 to 64 year age group were considered for comparison with the UK SF-36v2 normative data, as normative data are not available for older adults. The mean (SD) TSH concentration was 6.6 (2.5) mIU/L, range 4.1–16 and the FT4 concentration was 13.9 (1.9) pmol/L, range 10.3–19. The frequency of other chronic diseases was: hypertension 9.5%, hypercholesterolaemia 1.3% and arthritis (osteoarthritis, gout or rheumatoid arthritis) 21.9%. Results of two participants found to be on treatment for asthma were not included in the analyses. The results of 27 participants aged 65 to 80 years were used for within-SCH group comparisons.

SF-36v2

Perceived health status was evaluated by the SF-36v2 questionnaire. The questionnaire is composed of 36 items, 35 of which are classed into eight scales of varying length. For each SF-36v2 dimension, raw item scores are coded, summed and transformed on to a scale ranging from 0 (worst possible perceived health status) to 100 (best possible health status). The single item on perceived changes in health status over the previous 12 months was not considered. The degree of divergence from the scores for the normative population of an individual patient or specific patient population can be measured using a z transformation, taking into account the effects of age and gender. For each SF-36v2 scale, a z-score was calculated by subtracting the mean scale score of the normative population sample (matched for age and sex) from the scale score of the study group and dividing this difference by the standard deviation of the normative population sample. This was carried out individually for each participant for each scale and the overall group mean was calculated. A z-score value of 0 corresponds to the mean value of the normal population, a z-score value of –1 or –2 corresponds to one or two standard deviations below the normal population respectively. Z-scoring was preferred to the 0–100 based scoring algorithm to compare with the UK normative scores because it provides a basis for meaningful comparison across scales and for easier interpretation

(Ware, *et al* 2000b) (Garratt, *et al* 1993). Control values were obtained in relatively large numbers from random samples of the UK population aged between 18 and 64 years (n = 8889), as described above. This procedure has previously been used in the UK in the study of health status in patients with different diseases such as Parkinson's disease and multiple sclerosis (Riazi, *et al* 2003); heart failure and left ventricular systolic dysfunction (Hobbs, *et al* 2002) and low back pain, menorrhagia, suspected peptic ulcer and varicose veins (Garratt, *et al* 1993), and elsewhere in thyroid disease (Bianchi, *et al* 2004).

Statistical analyses

Means (SD) were used to report descriptive data and 95% confidence intervals (95% CI) were used to report the difference in the means between the study participants and the normative population. Student's unpaired *t*-test was used to compare the subgroup means. Z-scores were also used to report transformed scores as discussed previously. A mean z-score <0.2 was considered clinically non-significant, between 0.2 and 0.5 as a small difference, between 0.5 and 0.8 as a moderate difference and >0.8 as a large difference (Kazis, *et al* 1989).

Correlation analysis (Spearman's rho for non-parametric data or Pearson's r for parametric data) was used to assess the relationship between each SF-36 scale measured and biochemical and demographic parameters. Internal consistency reliability - that is, the extent to which there is a correlation between items on a scale – was assessed by Cronbach's alpha, an inter-item correlation statistic, with a value range of 0–1 (Cronbach LJ 1951). Levels of >0.9 are usually agreed to signify excellent internal consistency reliability. A *P* value of <0.05 was taken as statistically significant. SPSS version 11.0 was utilised for computing the statistics (SPSS Inc., Chicago, IL, USA).

Results

In comparison with a large UK population reference group, scores on all eight scales of the SF36v2 were significantly reduced (Table 45). The difference was attenuated but still significant when people with SCH and other chronic diseases (e.g. arthritis, hypertension and hypercholesterolaemia) were excluded from the analyses (n = 24). Z-scores for all 71 participants studied were significantly

lower than the normative data for all scales of the SF-36 but only the vitality (VT) scale showed a large difference, that is >0.8 (Fig. 17).

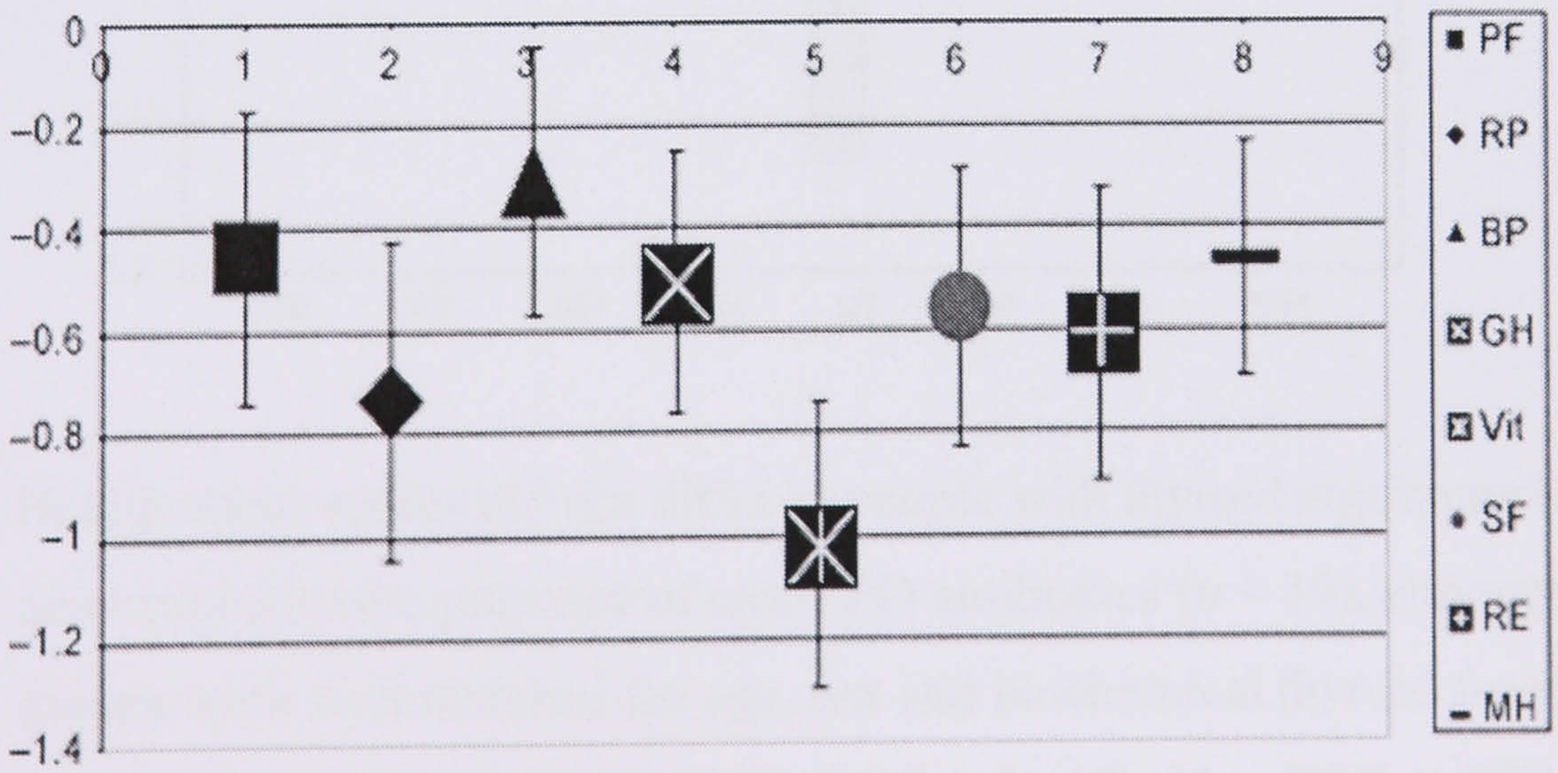
Table 45.

Differences in absolute SF-36 scores in patients with SCH compared with age- and sex-matched normative data.

	SCH patients Mean score (SD); n=71	UK normative Mean score (SD); n=8660	Difference in means (95% CI)
Physical functioning	76.0 (25.0)	88.0 (19.7)	11.9 (7.4 – 16.5)
Role physical	68.3 (29.7)	87.2 (22.0)	18.9 (13.8 – 23.9)
Bodily pain	68.6 (27.0)	78.8 (23.0)	10.2 (4.9 – 15.5)
General health	60.1 (22.3)	71.1 (20.4)	11.0 (6.3 – 15.7)
Vitality	37.2 (23.8)	58.0 (19.6)	20.9 (16.4 – 25.4)
Social-functioning	69.5 (27.5)	82.8 (23.2)	13.3 (7.9 – 18.6)
Role emotional	72.5 (26.8)	85.8 (21.2)	13.3 (8.4 – 18.2)
Mental health	63.4 (18.9)	71.9 (18.1)	8.6 (4.4 – 12.8)

SF-36 score range: 0 to 100 (poor to excellent health status).

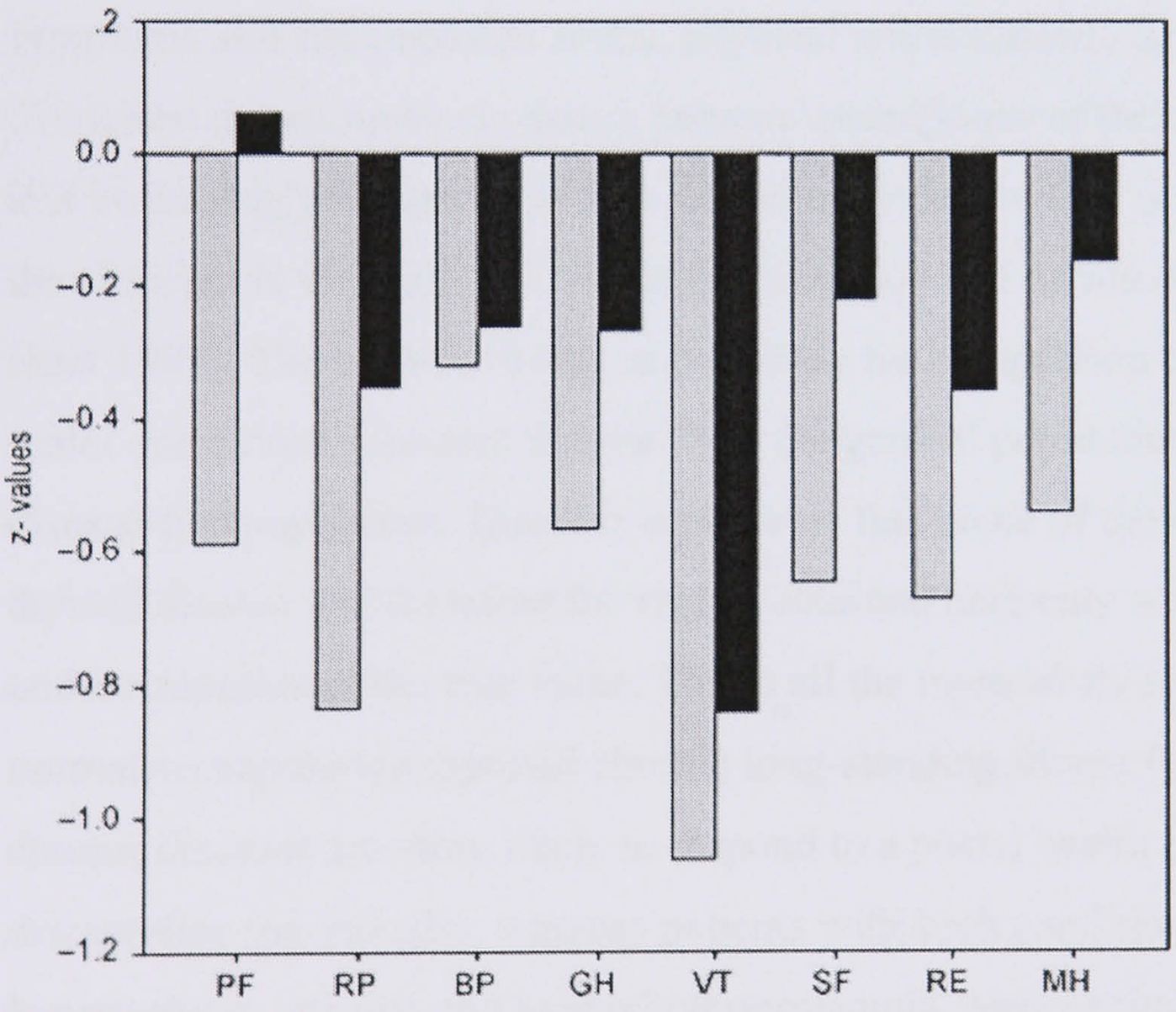
Figure 17. SF-36v2 scale scores of patients with SCH (mean with 95% confidence interval) compared with age- and sex-matched controls in a UK cohort (zero line). Note: a negative z-score indicates lower health status in the SCH group compared with normative data. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.



The rest of the z-scores showed either moderate (role physical (RP), general health (GH), social functioning (SF) and role emotional (RE)) or small (physical functioning (PF), bodily pain (BP) and mental health (MH)) differences. When analysed separately for men (n = 15) and women (n = 56), the results of the z-score analysis showed that women tended to have lower scores for all scales compared with men, although not significantly so (figure 18). Men had significantly lower z-scores in all scales except PF when compared with men from the UK norms whereas women had significantly lower scores on all scales.

Figure 18.

Sex differences in z-scores for each SF-36 scale for patients with SCH (n = 71). Solid bars, males; shaded bars, females. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.



Health status scores did not differ in people with thyroid autoimmunity, as determined by the presence of anti-TPO antibodies (n = 39), although the two groups were well matched for age, sex and biochemical thyroid function tests. None of the scales of the SF-36v2 correlated with either TSH or FT4 levels. As

expected, TSH values correlated significantly with FT4 ($r = –0.238$, $P = 0.04$). The z-scores for the VT scale correlated significantly with age ($r = 0.35$, $P = 0.002$). This was statistically significant even if Bonferroni correction requiring a p value of 0.006 (0.05/8) was applied. Comparison of absolute scores of older people with SCH (aged 65–80 years) ($n = 27$) with the younger group studied ($n = 71$) showed that the older group had significantly impaired health status only for the PF, RP and BP scales (difference in means (95% CI): 17.72 (6.4 – 29.04), 13.93 (1.32 – 26.54) and 14.93 (2.97 – 26.89) respectively).

Cronbach's alpha coefficient ranged from 0.91 to 0.93 signifying excellent internal consistency reliability for all eight SF-36 scales in this sample of patients with SCH.

Discussion

Perceived health status is more than just the presence or absence of disease or symptoms and encompasses social, physical and emotional dimensions. Clinicians do not routinely assess patients' perceptions of their health status, but it is increasingly being argued that the patient's perspective is as valid as that of the clinician in evaluation of a medical condition and its outcomes (Leplege and Hunt 1997). The normative data in this study for comparison of scores for all scales comprised a random sample from the general population and not a disease-free population. Hence it is probable that some of these individuals had thyroid disease and therefore the results obtained here may well be an underestimation of the true value. This is all the more likely since 36.6% of the normative population reported chronic long-standing illness (patients with chronic diseases are more likely to respond to a postal health survey than disease-free individuals), whereas patients with such conditions, apart from hypertension, arthritis and hypercholesterolaemia, were excluded in the present study.

Bianchi and colleagues recently reported that there were no differences in perceived health status (as measured by the SF-36 and the Nottingham Health Profile instruments) between their Italian patients with SCH, and age- and sex-

matched Italian population norms (Bianchi, *et al* 2004). The results reported here are different from their observations. This may be due to the different population and normative data used in the analysis as well as the fact that the comparison sample in the present study was younger owing to the lack of normative data for people older than 64 years in the UK.

Limitations of this study are that patients were not identified from a screening programme and were recruited from primary care practices. Thus patients with presence of symptoms at the higher end of the scale and/or with other co-morbidities were more likely to have been studied. However, the results obtained still remain significantly different from the normative scores even when data were analysed after excluding people with other chronic conditions. It is quite possible that some conditions such as hypertension and hypercholesterolaemia are 'silent' and hence affect health status the least (Stewart, *et al* 1989). Also, it would seem that men with SCH tend not to have any impairment of physical functioning as compared with normative scores for men of the same age. There is no direct explanation for this and further research is required. Also, older people (>64 years) with SCH have significantly lower scores on the physical scales (PF, RP and BP) when compared with younger people. This was not an unexpected finding as others have obtained significant age gradients in some SF-36 subscales (Brazier, *et al* 1992), but the lack of normative data for comparison with this older group is disappointing, especially since SCH is more prevalent in older people. Although it is clear from this study that people with SCH have impaired perceived health status, it is yet to be clarified whether normalizing serum TSH level would improve it.

In conclusion, this comparison has shown that perceived health status is significantly impaired in people presenting with SCH and this should be considered when managing this condition.

Effect of L-thyroxine on QoL, symptoms of hypothyroidism, perceived health status and satisfaction with treatment.

The baseline data suggested that patients with SCH have an impaired QoL, perceived health status as well as a considerable number of symptoms. The following tables 46 - 53 document the response to intervention with L-thyroxine and compare it to placebo. Satisfaction with treatment was also assessed in all patients.

Perceived health status:

Table 46.

Effect of L-thyroxine on perceived health status, as measured by the SF 36v2 in patients with SCH compared to placebo (n=100).

	L-thyroxine Mean (SD)	**Placebo Mean (SD)**	**Adjusted difference (95% CI) †**	**p value**
Physical-Functioning	72.9 (25.2)	71.3 (26.9)	1.9 (-1.7 to 5.5)	0.15
Role-Physical	69.3 (29.3)	68.6 (31.3)	0.6 (-5.8 to 7.0)	0.78
Bodily Pain	66.4 (27.1)	64.8 (28.1)	1.7 (-3.2 to 6.6)	0.34
General Health	61.3 (19.5)	59.7 (19.8)	1.5 (-2.5 to 5.4)	0.32
Vitality	47.1 (22)	43.7 (22.7)	3.4 (-2.5 to 9.3)	0.11
Social Functioning	75.1 (27.4)	74.9 (25.3)	0.2 (-6.4 to 6.9)	0.92
Role-Emotional	74.1 (28)	75.5 (25.1)	-1.7 (-8.9 to 5.4)	0.50
Mental Health	67.3 (20)	66.2 (17.8)	1.0 (-3.9 to 6.0)	0.56
Physical Component Summary Score	46.7 (9.9)	45.7 (11.2)	0.83 (0 to 1.66)	0.15
Mental Component Summary Score	44.8 (12.1)	44.7 (10.4)	0.04 (-1.4 to 1.5)	0.97

† Adjusted for subject and period effects.

Table 47.

Effect of L-thyroxine on perceived health status, as measured by the SF 36v2 in patients with SCH with discordant TFTs excluded (n=71).

	L-thyroxine Mean (SD)	Placebo Mean (SD)	Adjusted difference (95% CI) †	p value
Physical-Functioning	74.6 (25.4)	73.1 (25.8)	1.9 (-2.3 to 6.1)	0.23
Role-Physical	70.4 (30.1)	70.5 (31.1)	-0.3 (-7.6 to 7.0)	0.90
Bodily Pain	67.6 (26.9)	65.5 (27.9)	2.1 (-3.6 to 7.8)	0.31
General Health	61.1 (19.7)	60.5 (21)	0.6 (-4.7 to 5.9)	0.75
Vitality	47.4 (23.2)	44 (23.1)	3.5 (-3.4 to 10.4)	0.17
Social Functioning	78 (26.5)	77.6 (24.6)	0.64 (-6.4 to 7.6)	0.80
Role-Emotional	75 (28.8)	78.5 (23.8)	-3.1(-11.8 to 5.6)	0.33
Mental Health	68.9 (19.8)	67.2 (18.3)	1.8 (-4.0 to 7.5)	0.39
Physical Component Summary Score	46.2 (10.1)	45.5 (10.9)	0.8 (-1.0 to 2.5)	0.27
Mental Component Summary Score	43.9 (11.8)	43.8 (12.2)	0.2 (-3.4 to 3.9)	0.86

† Adjusted for subject and period effects.

SF-36v2 subscales: 0 to 100 (poor to good health status).

There was no significant difference in either the individual domains of the SF 36v2 or the summary scores on L-thyroxine as compared to placebo. There was a trend towards improvement, but the sign test statistic failed to reach significance (p=0.07) in favour of L-thyroxine. One of the explanations could be that the study was not powered to detect a significant change in this instrument. It is calculated that to reach statistical significance, the number of patients randomised would have needed to be much higher. For example, to detect a significant improvement in Vitality (the subscale that showed the most improvement in the SF-36 v2), we calculate that a much larger sample would have been needed (n=310).

Hypothyroid specific Quality of life:

Table 48.

Effect of L-thyroxine on QoL, as measured by the ThyDQoL in all patients with SCH compared to placebo (n=100).

	L-thyroxine Mean (SD)	Placebo Mean (SD)	Adjusted difference (95% CI) †	p value
General QoL	0.95 (0.91)	0.88 (0.94)	0.1 (-0.3 to 0.5)	0.43
T-QoL	-1.1 (1)	-1.2 (0.9)	0.2 (0.02 to 0.36)	0.04
Spare-time	-2.6 (2.5)	-2.9 (2.7)	0.3 (-0.1 to 0.7)	0.21
Work-life	-2.7 (3)	-2.8 (2.7)	0.1 (-0.5 to 0.6)	0.82
Holidays	-2.8 (2.9)	-2.7 (2.9)	0 (-0.4 to 0.5)	0.87
Family-life	-3.1 (3.1)	-3.1 (2.9)	0 (-0.4 to 0.4)	0.95
Social-life	-2.5 (2.7)	-2.5 (2.6)	0 (-0.4 to 0.4)	0.96
Close relationship	-2.7 (2.9)	-2.9 (3)	0.1 (-0.3 to 0.5)	0.67
Sex-life	-2.3 (2.7)	-2.7 (2.8)	0.3 (0.02 to 0.7)	0.03
Physical capabilities	-3.1 (2.9)	-3.1 (2.8)	0 (-0.4 to 0.4)	0.87
Energy levels	-3.5 (2.8)	-3.6 (2.8)	0.1 (-0.3 to 0.6)	0.56
Speed of doing things	-2.4 (2.5)	-2.3 (2.4)	-0.1 (-0.5 to 0.3)	0.63
Getting out and about	-2.2 (2.7)	-2 (2.5)	-0.1 (-0.5 to 0.2)	0.44
Household tasks	-2.6 (2.8)	-2.8 (2.7)	0.1 (-0.2 to 0.5)	0.50
Physical appearance	-2.3 (2.9)	-2.5 (2.8)	0.2 (-0.2 to 0.6)	0.29
Weight	-3.1 (2.8)	-3.2 (2.6)	0 (-0.5 to 0.5)	0.86
Bodily discomfort	-3.2 (2.8)	-3.6 (2.6)	0.2 (-0.5 to 1)	0.50
Depressed	-4.3 (2.8)	-4.5 (2.7)	0.5 (-0.4 to 1.5)	0.25
Motivation	-3.6 (2.7)	-3.7 (2.7)	0.4 (-0.4 to 0.9)	0.16
Worries about future	-2.5 (3)	-2.8 (2.9)	0.2 (-0.2 to 0.7)	0.23
AWI-18	-2.7 (2.4)	-2.8 (2.3)	0.1 (-0.3 to 0.5)	0.45

† Adjusted for subject and period effects.

Table 49.

Effect of L-thyroxine on QoL, as measured by the ThyDQoL in patients with SCH with discordant TFTs excluded (n=71).

	L-thyroxine Mean (SD)	Placebo Mean (SD)	Adjusted difference (95% CI) †	p value
General QoL	1.0 (0.9)	1.0 (1)	0.1 (-0.0 to 0.2)	0.51
T-QoL	-1 (0.9)	-1.2 (1)	0.3 (0.08 to 0.52)	0.01
Spare-time	-2.3 (2.4)	-2.7 (2.6)	0.4 (-0.3 to 1.1)	0.12
Work-life	-2 (2.5)	-2.5 (2.5)	0.5 (-0.3 to 1.3)	0.15
Holidays	-2.1 (2.7)	-2.5 (2.8)	0.3 (-0.4 to 1.0)	0.23
Family-life	-2.5 (2.8)	-2.9 (2.8)	0.2 (-0.4 to 0.8)	0.38
Social-life	-2 (2.5)	-2.4 (2.7)	0.4 (-0.3 to 1.1)	0.73
Close relationship	-2.1 (2.8)	-2.4 (2.8)	0.1 (-0.5 to 0.7)	0.25
Sex-life	-1.9 (2.6)	-2.4 (2.9)	0.3 (0.05 to 0.7)	0.01
Physical capabilities	-2.8 (2.9)	-3 (2.8)	0.1 (-0.5 to 0.7)	0.68
Energy levels	-3.1 (2.8)	-3.5 (2.9)	0.4 (-0.3 to 1.1)	0.21
Speed of doing things	-2 (2.3)	-2.1 (2.2)	0.1 (-0.5 to 0.7)	0.66
Getting out and about	-1.7 (2.5)	-1.8 (2.4)	0 (-0.6 to 0.6)	0.91
Household tasks	-2.1 (2.6)	-2.5 (2.6)	0.4 (-0.2 to 1.0)	0.11
Physical appearance	-2.1 (2.9)	-2.5 (2.9)	0.4 (-0.2 to 1.0)	0.13
Weight	-2.8 (2.7)	-3.2 (2.8)	0.3 (-0.2 to 0.8)	0.22
Bodily discomfort	-2.6 (2.7)	-3.4 (2.5)	0.4 (-0.4 to 1.2)	0.38
Depressed	-4.2 (2.9)	-4.7 (2.7)	0.9 (-0.3 to 2.1)	0.11
Motivation	-3.1 (2.8)	-3.8 (2.8)	0.9 (0.1 to 1.7)	0.009
Worries about future	-2 (2.9)	-2.6 (3)	0.4 (-0.2 to 1.1)	0.07
AWI-18	-2.3 (2.3)	-2.7 (2.3)	0.3 (0.01 to 0.6)	0.01

† Adjusted for subject and period effects.

Maximum score range: ThyDQoL individual QoL domains: -9 to +3, TQoL (Hypothyroid-dependent QoL) score range: -3 to +1 (maximum negative to maximum positive perceived weighted impact of hypothyroidism on QoL). AWI-18 (Average weighted impact of all 18 domains) score range –9 to +3, provides a total summative score, the more negative the score, the greater the perceived negative impact of hypothyroidism on QoL.

Hypothyroid-dependent quality of life (QoL), therefore showed a significant improvement overall as shown by TQoL. The domain on sex-life also showed a significant improvement on L-thyroxine. When individuals with discordant TFTs were excluded from analyses, then additionally motivation and AWI-18 became significantly improved.

Symptoms of hypothyroidism:

The symptoms associated with hypothyroidism as assessed by the ThySC were investigated to observe if L-thyroxine improved them. The frequencies of the different symptoms are reported in table 50 for all one hundred patients. Table 51 reports the frequencies of hypothyroid symptoms in patients with discordant results excluded.

Table 50.

Effect of L-thyroxine on reported frequency of hypothyroid symptoms (n=100).

Symptoms (%)	L-thyroxine	Placebo	Adjusted difference†	P value
Tiredness	78	89	11	0.005
Depression	52	62	11	0.08
Weight gain	37	44	6	0.32
Feeling cold	29	36	6	0.16
Hair problems	38	36	-7	0.11
Skin problems	38	45	7	0.18
Nail problems	37	36	-1	0.82
Constipation	25	27	2	0.69
Voice change	24	21	-3	0.47
Speech change	23	21	-2	0.56
Suppressed Appetite	12	16	3	0.32
Hearing problems	27	24	-4	0.47
Memory impairment	45	45	0	0.99
Concentration impairment	49	46	-3	0.56
Dizziness	39	38	-1	0.83

† Adjusted for subject and period effects.

Table 51.

Effect of L-thyroxine on hypothyroid symptoms in patients with SCH after excluding discordant TFTs (n=71).

Symptoms (%)	L-thyroxine	Placebo	Adjusted difference†	P value
Tiredness	75	87	15	0.007
Depression	48	58	10	0.11
Weight gain	37	41	3	0.68
Feeling cold	27	34	6	0.25
Hair problems	35	32	-5	0.56
Skin problems	34	45	12	0.04
Nail problems	37	39	3	0.59
Constipation	27	27	0	0.99
Voice change	23	21	-3	0.78
Speech change	23	23	0	0.99
Suppressed Appetite	13	14	1	0.76
Hearing problems	27	23	-4	0.36
Memory impairment	41	44	2	0.48
Concentration impairment	46	45	-1	0.81
Dizziness	30	31	2	0.79

† Adjusted for subject and period effects.

This showed that L-thyroxine reduced significantly the number of people complaining of tiredness. In addition, when people with discordant results were excluded, then the symptom of skin problems also reduced significantly. It is estimated that the NNT (number needed to treat for one person to benefit) is 9.1 for tiredness.

For all other symptoms, the sign test did not show any significant improvement (p=0.6). The symptoms bother score did not show any significant difference for any symptom.

Treatment satisfaction:

Satisfaction with treatment with L-thyroxine was assessed by the ThyTSQ and compared to placebo. The ThyTSQ-Past was used but not reported since it would not be expected to be influenced by current treatment. It did not show any change.

Table 52.

Effect of L-thyroxine on satisfaction with treatment for SCH (n=100).

	L-thyroxine Mean (SD)	Placebo Mean (SD)	Adjusted difference (95%CI)†	P value
Satisfaction	4.2 (1.7)	4.2 (1.7)	0.0 (-0.3 to 0.3)	0.98
Treatment working	3.3 (1.8)	3.0 (1.7)	0.21 (-0.1 to 0.5)	0.35
Convenient	5.3 (1.2)	5.3 (1)	-0.0 (-0.2 to 0.2)	0.90
Understanding of problem	4.1 (1.7)	4.2 (1.6)	-0.2 (-0.4 to 0.1)	0.40
Encourage others	4.5 (1.6)	4.5 (1.8)	0.0 (-0.3 to 0.3)	0.91
Control symptoms	3.2 (1.8)	3.2 (1.7)	0.2 (-0.2 to 0.5)	0.49
Continue with treatment and dose	3.6 (2)	3.5 (1.9)	0.1 (-0.2 to 0.4)	0.68
Total score	28.1 (8.7)	27.7(8.9)	0.4 (-1.6 to 2.3)	0.70

† Adjusted for subject and period effects.

Table 53.

Effect of L-thyroxine on satisfaction with treatment with discordant TFTs excluded (n=71).

	L-thyroxine Mean (SD)	Placebo Mean (SD)	Adjusted difference (95%CI)†	P value
Satisfaction	4.3 (1.7)	4.3 (1.6)	-0.0 (-0.5 to 0.4)	0.91
Treatment working	3.4 (1.8)	3.1 (1.7)	0.3 (-0.0 to 0.6)	0.18
Convenient	5.2 (1.2)	5.4 (0.9)	-0.3 (0.0 to –0.6)	0.19
Understanding of problem	4.2 (1.6)	4.3 (1.5)	-0.1 (-0.3 to 0.1)	0.36
Encourage others	4.5 (1.6)	4.6 (1.6)	-0.0 (-0.3 to 0.3)	0.69
Control symptoms	3.3 (1.8)	3.2 (1.7)	0.1 (-0.3 to 0.5)	0.42
Continue with treatment and dose	3.8 (2.0)	3.6 (1.9)	0.3 (-0.1 to 0.7)	0.50
Total score	29.1 (8.7)	28.4 (8)	0.6 (-1.5 to 2.7)	0.60

† Adjusted for subject and period effects.

ThyTSQ: range 0 to 42 (higher scores indicating greater satisfaction with present treatment).

Patients with SCH did not notice any significant difference between L-thyroxine and placebo in terms of satisfaction with treatment. The sign test too did not show any significant trends (p=0.68).

The effect of thyroid autoantibodies and serum TSH levels at baseline on various parameters after treatment

Forty-nine patients had positive anti-TPO antibodies (titre > 50). The results were then compared in all 100 patients with regards to positive versus negative antibody status. This showed no significant changes between individuals who were anti-TPO positive compared to anti-TPO negative with regards to patient-reported outcomes.

Participants were then compared with regards to their baseline TSH levels. Sixty-two individuals had TSH < 6.1 mIU/L (the mean TSH of the group) and the remaining 38 had TSH > or = 6.1 mIU/L. There was no difference in any aspect of patient-reported outcomes in either group.

DISCUSSION (B)

Synopsis of study findings

This randomised controlled study shows that treatment of SCH with L-thyroxine provides significant improvement in some patient-reported outcomes. Unique disease-specific questionnaires assessing QoL, symptom-bother and satisfaction with treatment were designed and validated with good effect. At baseline, perceived health status was found to be impaired as compared to a normative population. In the prospective crossover trial, assessment of patient-reported outcomes utilising these questionnaires as well as the widely used SF-36 showed that QoL and the frequency of tiredness significantly improved by treatment with L-thyroxine, although there was no significant change in satisfaction with treatment or perceived health status.

Possible mechanisms and explanations of findings

The effect of L-thyroxine treatment on patient-reported outcomes was mixed. The perceived negative impact of hypothyroidism on QoL and on sex-life was reduced (as measured by the disease-specific ThyDQoL). However, although all subscales of the generic health status measure, the SF-36 v2, (apart from Role-emotional), tended towards an improvement with L-thyroxine therapy, none reached statistical significance. This is not surprising given that generic instruments are less sensitive than disease-specific ones in assessing response to treatment, but could also be due to the fact that the study was not designed to detect a significant difference in patient-reported outcomes. For example, to detect a significant improvement in Vitality (the subscale that showed the most improvement in the SF-36 v2), it is calculated that a much larger sample would have been needed (n=310). However, health status of patients with SCH (as assessed by a disease-specific instrument) was not improved by L-thyroxine in the study by Jaeschke and colleagues (Jaeschke, *et al* 1996), but the disadvantage of that study was that treated patients' mean TSH was not optimal (4.6 mIU/L). The effect of L-thyroxine on reducing perceived negative impact of hypothyroidism on sex-life is interesting and warrants further research into the underlying mechanism. This may be due to the effect of thyroid hormones on psychological aspects (e.g. reducing tiredness) as well as on other hormones (e.g. reducing prolactin levels). L-thyroxine has been shown to improve

impaired sexual function and performance in men with hypothyroidism (Carani, *et al* 2005). The present study indicates that fewer patients reported tiredness following L-thyroxine therapy although patients' scores for symptom severity did not improve. The increased prevalence of tiredness in SCH could be due to a direct result of thyroid hormones on skeletal muscle (Argov, *et al* 1988). It could also be due to a more central effect on mood (Sait Gonen, *et al* 2004). The reason for the lack of improvement in any symptom bother scores is unclear and may be due to patients having adapted to their symptoms.

Comparison with relevant findings from other published studies

This is the first RCT to have assessed QoL and treatment satisfaction in patients with SCH. This study has shown that overall QoL improves with L-thyroxine treatment in SCH but also that the domains that improve significantly are sex-life and motivation. In comparison, other studies have assessed health status (Jaeschke, *et al* 1996), symptoms and mood (Cooper, *et al* 1984) (Nystrom, *et al* 1988) (Meier, *et al* 2001) (Kong, *et al* 2002) (Jorde, *et al* 2006). Symptoms of tiredness improved significantly in the present study. Other RCTs have shown inconsistent results. Other studies have used tools to assess symptoms that report a total mean score. This makes it difficult to analyse, which individual symptoms improve, if any. For example, the Basel thyroid study, conducted by Meier and colleagues, found a significant reduction in symptoms only in the subgroup of patients with TSH levels above 12 mIU/L (Meier, *et al* 2001). It is difficult to find out which of the symptoms measured (by Billewicz and Zulewski questionnaires) actually improved. The reason for these inconsistent results may be that some hypothyroid symptoms improve with L-thyroxine treatment in patients with SCH whereas others do not. The other reason for the significant result in the present study (where most patient's TSH levels were below 10 mIU/L) could be the relatively large number of patients studied that has detected a significant improvement in symptoms which other smaller studies failed to identify.

Limitations of the study

The limitations of the present study are that patients were not identified from a population sample, the length of treatment was only twelve weeks, and the dose of L-thyroxine was a fixed 100 mcg per patient. Twelve weeks may be insufficient time for some benefits (such as perceptible reduction in some symptoms and psychological factors) to become apparent to patients.

Summary

Treatment with L-thyroxine reduces perceived negative impact of hypothyroidism on QoL and improves tiredness. There is improvement in sex-life and motivation, the mechanism of which needs to be elucidated.

REFERENCES (B)

(1995) The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med,* **41,** 1403-1409.

(2002) American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract,* **8,** 457-469.

Argov, Z., Renshaw, P.F., Boden, B., Winokur, A. & Bank, W.J. (1988) Effects of thyroid hormones on skeletal muscle bioenergetics. In vivo phosphorus-31 magnetic resonance spectroscopy study of humans and rats. *J Clin Invest,* **81,** 1695-1701.

Bahemuka, M. & Hodkinson, H.M. (1975) Screening for hypothyroidism in elderly inpatients. *Br Med J,* **2,** 601-603.

Baldini, I.M., Vita, A., Mauri, M.C., Amodei, V., Carrisi, M., Bravin, S. & Cantalamessa, L. (1997) Psychopathological and cognitive features in subclinical hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry,* **21,** 925-935.

Barendse, S.M., Speight, J. & Bradley, C. (2005) The Renal Treatment Satisfaction Questionnaire (RTSQ): a measure of satisfaction with treatment for chronic kidney failure. *Am J Kidney Dis,* **45,** 572-579.

Barker, D.J. & Bishop, J.M. (1969) Computer-based screening system for patients at risk of hypothyroidism. *Lancet,* **2,** 835-838.

Beyer, I.W., Karmali, R., Demeester-Mirkine, N., Cogan, E. & Fuss, M.J. (1998) Serum creatine kinase levels in overt and subclinical hypothyroidism. *Thyroid,* **8,** 1029-1031.

Bianchi, G.P., Zaccheroni, V., Solaroli, E., Vescini, F., Cerutti, R., Zoli, M. & Marchesini, G. (2004) Health-related quality of life in patients with thyroid disorders. *Qual Life Res,* **13,** 45-54.

Billewicz, W.Z., Chapman, R.S., Crooks, J., Day, M.E., Gossage, J., Wayne, E. & Young, J.A. (1969) Statistical methods applied to the diagnosis of hypothyroidism. *Q J Med,* **38,** 255-266.

Biondi, B., Palmieri, E.A., Lombardi, G. & Fazio, S. (2003) The importance of using strict inclusion criteria in subclinical hypothyroid studies. *Am J Med,* **114,** 76; author reply 77.

Botella-Carretero, J.I., Galan, J.M., Caballero, C., Sancho, J. & Escobar-Morreale, H.F. (2003) Quality of life and psychometric functionality in

patients with differentiated thyroid carcinoma. *Endocr Relat Cancer,* **10,** 601-610.

Bowling, A., Bond, M., Jenkinson, C. & Lamping, D.L. (1999) Short Form 36 (SF-36) Health Survey questionnaire: which normative data should be used? Comparisons between the norms provided by the Omnibus Survey in Britain, the Health Survey for England and the Oxford Healthy Life Survey. *J Public Health Med,* **21,** 255-270.

Bradley, C. (1997) Design of a renal-dependent individualized quality of life questionnaire. *Adv Perit Dial,* **13,** 116-120.

Bradley, C. (2001) Importance of differentiating health status from quality of life. *Lancet,* **357,** 7-8.

Bradley, C. & Lewis, K.S. (1990) Measures of psychological well-being and treatment satisfaction developed from the responses of people with tablet-treated diabetes. *Diabet Med,* **7,** 445-451.

Bradley, C., Todd, C., Gorton, T., Symonds, E., Martin, A. & Plowright, R. (1999) The development of an individualized questionnaire measure of perceived impact of diabetes on quality of life: the ADDQoL. *Qual Life Res,* **8,** 79-91.

Brazier, J.E., Harper, R., Jones, N.M., O'Cathain, A., Thomas, K.J., Usherwood, T. & Westlake, L. (1992) Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *Bmj,* **305,** 160-164.

Bunevicius, R., Kazanavicius, G., Zalinkevicius, R. & Prange, A.J., Jr. (1999) Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. *N Engl J Med,* **340,** 424-429.

Canaris, G.J., Manowitz, N.R., Mayor, G. & Ridgway, E.C. (2000) The Colorado thyroid disease prevalence study. *Arch Intern Med,* **160,** 526-534.

Canaris, G.J., Steiner, J.F. & Ridgway, E.C. (1997) Do traditional symptoms of hypothyroidism correlate with biochemical disease? *J Gen Intern Med,* **12,** 544-550.

Carani, C., Isidori, A.M., Granata, A., Carosa, E., Maggi, M., Lenzi, A. & Jannini, E.A. (2005) Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. *J Clin Endocrinol Metab,* **90,** 6472-6479.

Chu, J.W. & Crapo, L.M. (2001) The treatment of subclinical hypothyroidism is seldom necessary. *J Clin Endocrinol Metab,* **86,** 4591-4599.

Clyde, P.W., Harari, A.E., Getka, E.J. & Shakir, K.M. (2003) Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. *Jama,* **290,** 2952-2958.

Cook, D.J., Guyatt, G.H., Juniper, E., Griffith, L., McIlroy, W., Willan, A., Jaeschke, R. & Epstein, R. (1993) Interviewer versus self-administered questionnaires in developing a disease-specific, health-related quality of life instrument for asthma. *J Clin Epidemiol,* **46,** 529-534.

Cooper, D.S. (2001) Clinical practice. Subclinical hypothyroidism. *N Engl J Med,* **345,** 260-265.

Cooper, D.S., Halpern, R., Wood, L.C., Levin, A.A. & Ridgway, E.C. (1984) L-Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Ann Intern Med,* **101,** 18-24.

Crevenna, R., Zettinig, G., Keilani, M., Posch, M., Schmidinger, M., Pirich, C., Nuhr, M., Wolzt, M., Quittan, M., Fialka-Moser, V. & Dudczak, R. (2003) Quality of life in patients with non-metastatic differentiated thyroid cancer under thyroxine supplementation therapy. *Support Care Cancer,* **11,** 597-603.

Danese, M.D., Powe, N.R., Sawin, C.T. & Ladenson, P.W. (1996) Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. *Jama,* **276,** 285-292.

del Ser Quijano, T., Delgado, C., Martinez Espinosa, S. & Vazquez, C. (2000) [Cognitive deficiency in mild hypothyroidism]. *Neurologia,* **15,** 193-198.

Dow, K.H., Ferrell, B.R. & Anello, C. (1997) Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. *Thyroid,* **7,** 613-619.

Eden, S., Sundbeck, G., Lindstedt, G., Lundberg, P.A., Jagenburg, R., Landahl, S. & Svanborg, A. (1988) Screening for thyroid disease in the elderly. Serum concentrations of thyrotropin and 3,5,3'-triiodothyronine in a representative population of 79-year-old women and men. *Compr Gerontol [A],* **2,** 40-45.

Eggertsen, R., Petersen, K., Lundberg, P.A., Nystrom, E. & Lindstedt, G. (1988) Screening for thyroid disease in a primary care unit with a thyroid stimulating hormone assay with a low detection limit. *Bmj,* **297,** 1586-1592.

Escobar-Morreale, H.F., Botella-Carretero, J.I., Gomez-Bueno, M., Galan, J.M., Barrios, V. & Sancho, J. (2005) Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. *Ann Intern Med,* **142,** 412-424.

Ganguli, M., Burmeister, L.A., Seaberg, E.C., Belle, S. & DeKosky, S.T. (1996) Association between dementia and elevated TSH: a community-based study. *Biol Psychiatry,* **40,** 714-725.

Garratt, A.M., Ruta, D.A., Abdalla, M.I., Buckingham, J.K. & Russell, I.T. (1993) The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *Bmj,* **306,** 1440-1444.

Gavin, L.A. (1988) The diagnostic dilemmas of hyperthyroxinemia and hypothyroxinemia. *Adv Intern Med,* **33,** 185-203.

Goldberg, D. & Williams, P. (1988) A user's guide to the General Health Questionnaire. *NFER-Nelson, Windsor,UK.*

Goldberg, D.P., Rickels, K., Downing, R. & Hesbacher, P. (1976) A comparison of two psychiatric screening tests. *Br J Psychiatry,* **129,** 61-67.

Golger, A., Fridman, T.R., Eski, S., Witterick, I.J., Freeman, J.L. & Walfish, P.G. (2003) Three-week thyroxine withdrawal thyroglobulin stimulation screening test to detect low-risk residual/recurrent well-differentiated thyroid carcinoma. *J Endocrinol Invest,* **26,** 1023-1031.

Goulis, D.G., Tsimpiris, N., Delaroudis, S., Maltas, B., Tzoiti, M., Dagilas, A. & Avramides, A. (1998) Stapedial reflex: a biological index found to be abnormal in clinical and subclinical hypothyroidism. *Thyroid,* **8,** 583-587.

Griffin, J.E. (1990) Hypothyroidism in the elderly. *Am J Med Sci,* **299,** 334-345.

Grootenhuis, P.A., Snoek, F.J., Heine, R.J. & Bouter, L.M. (1994) Development of a type 2 diabetes symptom checklist: a measure of symptom severity. *Diabet Med,* **11,** 253-261.

Guyatt, G.H. & Jaeschke, R.J. (1997) Reassessing quality-of-life instruments in the evaluation of new drugs. *Pharmacoeconomics,* **12,** 621-626.

Guyatt, G.H., Naylor, C.D., Juniper, E., Heyland, D.K., Jaeschke, R. & Cook, D.J. (1997) Users' guides to the medical literature. XII. How to use articles about health-related quality of life. Evidence-Based Medicine Working Group. *Jama,* **277,** 1232-1237.

Guyatt, G.H., Veldhuyzen Van Zanten, S.J., Feeny, D.H. & Patrick, D.L. (1989) Measuring quality of life in clinical trials: a taxonomy and review. *Cmaj,* **140,** 1441-1448.

Haddow, J.E., Palomaki, G.E., Allan, W.C., Williams, J.R., Knight, G.J., Gagnon, J., O'Heir, C.E., Mitchell, M.L., Hermos, R.J., Waisbren, S.E., Faix, J.D. & Klein, R.Z. (1999) Maternal thyroid deficiency during

pregnancy and subsequent neuropsychological development of the child. *N Engl J Med,* **341,** 549-555.

Haggerty, J.J., Jr., Stern, R.A., Mason, G.A., Beckwith, J., Morey, C.E. & Prange, A.J., Jr. (1993) Subclinical hypothyroidism: a modifiable risk factor for depression? *Am J Psychiatry,* **150,** 508-510.

Harrison, L.C., Buckley, J.D. & Martin, F.I. (1977) Use of a computer-based postal questionnaire for the detection of hypothyroidism following radioiodine therapy for thyrotoxicosis. *Aust N Z J Med,* **7,** 27-32.

Hayes, V., Morris, J., Wolfe, C. & Morgan, M. (1995) The SF-36 health survey questionnaire: is it suitable for use with older adults? *Age Ageing,* **24,** 120-125.

Helfand, M. (2004) Screening for subclinical thyroid dysfunction in nonpregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med,* **140,** 128-141.

Helfand, M. & Crapo, L.M. (1990) Screening for thyroid disease. *Ann Intern Med,* **112,** 840-849.

Hendrick, V., Altshuler, L. & Whybrow, P. (1998) Psychoneuroendocrinology of mood disorders. The hypothalamic-pituitary-thyroid axis. *Psychiatr Clin North Am,* **21,** 277-292.

Herrmann, C. (1997) International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res,* **42,** 17-41.

Hobbs, F.D., Kenkre, J.E., Roalfe, A.K., Davis, R.C., Hare, R. & Davies, M.K. (2002) Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. *Eur Heart J,* **23,** 1867-1876.

Hollowell, J.G., Staehling, N.W., Flanders, W.D., Hannon, W.H., Gunter, E.W., Spencer, C.A. & Braverman, L.E. (2002) Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab,* **87,** 489-499.

Hunt, S.M., McEwen, J. & McKenna, S.P. (1985) Measuring health status: a new tool for clinicians and epidemiologists. *J R Coll Gen Pract,* **35,** 185-188.

Indra, R., Patil, S.S., Joshi, R., Pai, M. & Kalantri, S.P. (2004) Accuracy of physical examination in the diagnosis of hypothyroidism: a cross-sectional, double-blind study. *J Postgrad Med,* **50,** 7-11; discussion 11.

Jaeschke, R., Guyatt, G., Cook, D., Harper, S. & Gerstein, H.C. (1994) Spectrum of quality of life impairment in hypothyroidism. *Qual Life Res,* **3,** 323-327.

Jaeschke, R., Guyatt, G., Gerstein, H., Patterson, C., Molloy, W., Cook, D., Harper, S., Griffith, L. & Carbotte, R. (1996) Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *J Gen Intern Med,* **11,** 744-749.

Jaeschke, R., Guyatt, G.H. & Cook, D. (1992) Quality of life instruments in the evaluation of new drugs. *Pharmacoeconomics,* **1,** 84-94.

Jenkinson, C., Fitzpatrick, R. & Argyle, M. (1988) The Nottingham Health Profile: an analysis of its sensitivity in differentiating illness groups. *Soc Sci Med,* **27,** 1411-1414.

Jenkinson, C., Stewart-Brown, S., Petersen, S. & Paice, C. (1999) Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health,* **53,** 46-50.

Joffe, R.T. & Levitt, A.J. (1992) Major depression and subclinical (grade 2) hypothyroidism. *Psychoneuroendocrinology,* **17,** 215-221.

Jorde, R., Waterloo, K., Storhaug, H., Nyrnes, A., Sundsfjord, J. & Jenssen, T.G. (2006) Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *J Clin Endocrinol Metab,* **91,** 145-153.

Joyce, C.R. (1994) Requirements for the assessment of individual quality of life. In: *Quality of Life following renal failure: Psychosocial challenges accompanying high technology medicine.* (ed. by C. Bradley), pp. 43-54. Harwood Academic Publishers, Chur, Switzerland.

Kahaly, G.J. (2000) Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid,* **10,** 665-679.

Kaplan, M.M., Sarne, D.H. & Schneider, A.B. (2003) In search of the impossible dream? Thyroid hormone replacement therapy that treats all symptoms in all hypothyroid patients. *J Clin Endocrinol Metab,* **88,** 4540-4542.

Kazis, L.E., Anderson, J.J. & Meenan, R.F. (1989) Effect sizes for interpreting changes in health status. *Med Care,* **27,** S178-189.

Kent, G.N., Stuckey, B.G., Allen, J.R., Lambert, T. & Gee, V. (1999) Postpartum thyroid dysfunction: clinical assessment and relationship to psychiatric affective morbidity. *Clin Endocrinol (Oxf),* **51,** 429-438.

Kind, P. & Carr-Hill, R. (1987) The Nottingham health profile: a useful tool for epidemiologists? *Soc Sci Med,* **25,** 905-910.

Kong, W.M., Sheikh, M.H., Lumb, P.J., Naoumova, R.P., Freedman, D.B., Crook, M., Dore, C.J. & Finer, N. (2002) A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *Am J Med,* **112,** 348-354.

Ladenson, P.W. (2002) Psychological wellbeing in patients. *Clin Endocrinol (Oxf),* **57,** 575-576.

Ladenson, P.W., Singer, P.A., Ain, K.B., Bagchi, N., Bigos, S.T., Levy, E.G., Smith, S.A., Daniels, G.H. & Cohen, H.D. (2000) American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Intern Med,* **160,** 1573-1575.

Larisch, R., Kley, K., Nikolaus, S., Sitte, W., Franz, M., Hautzel, H., Tress, W. & Muller, H.W. (2004) Depression and anxiety in different thyroid function states. *Horm Metab Res,* **36,** 650-653.

Larsen, P.R. & Ingbar, S.H. (1992) The thyroid gland. In: *William's Textbook of Endocrinology* (ed. by J.D. Wilson & D.W. Foster), pp. 357-487. WB Saunders Co, Philadelphia.

Leplege, A. & Hunt, S. (1997) The problem of quality of life in medicine. *Jama,* **278,** 47-50.

Lindeman, R.D., Schade, D.S., LaRue, A., Romero, L.J., Liang, H.C., Baumgartner, R.N., Koehler, K.M. & Garry, P.J. (1999) Subclinical hypothyroidism in a biethnic, urban community. *J Am Geriatr Soc,* **47,** 703-709.

Luboshitzky, R., Oberman, A.S., Kaufman, N., Reichman, N. & Flatau, E. (1996) Prevalence of cognitive dysfunction and hypothyroidism in an elderly community population. *Isr J Med Sci,* **32,** 60-65.

Manciet, G., Dartigues, J.F., Decamps, A., Barberger-Gateau, P., Letenneur, L., Latapie, M.J. & Latapie, J.L. (1995) The PAQUID survey and correlates of subclinical hypothyroidism in elderly community residents in the southwest of France. *Age Ageing,* **24,** 235-241.

McGee, H.M., O'Boyle, C.A., Hickey, A., O'Malley, K. & Joyce, C.R. (1991) Assessing the quality of life of the individual: the SEIQoL with a healthy and a gastroenterology unit population. *Psychol Med,* **21,** 749-759.

McMillan, C.V., Bradley, C., Gibney, J., Healy, M.L., Russell-Jones, D.L. & Sonksen, P.H. (2003) Psychological effects of withdrawal of growth hormone therapy from adults with growth hormone deficiency. *Clin Endocrinol (Oxf),* **59,** 467-475.

McNeil, B.J., Weichselbaum, R. & Pauker, S.G. (1981) Speech and survival: tradeoffs between quality and quantity of life in laryngeal cancer. *N Engl J Med,* **305,** 982-987.

Meier, C., Staub, J.J., Roth, C.B., Guglielmetti, M., Kunz, M., Miserez, A.R., Drewe, J., Huber, P., Herzog, R. & Muller, B. (2001) TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). *J Clin Endocrinol Metab,* **86,** 4860-4866.

Meier, C., Trittibach, P., Guglielmetti, M., Staub, J.J. & Muller, B. (2003) Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey. *Bmj,* **326,** 311-312.

Misiunas, A., Niepomniszcze, H., Ravera, B., Faraj, G. & Faure, E. (1995) Peripheral neuropathy in subclinical hypothyroidism. *Thyroid,* **5,** 283-286.

Mitchell, J. & Bradley, C. (2004) Design of an individualised measure of the impact of macular disease on quality of life (the MacDQoL). *Qual Life Res,* **13,** 1163-1175.

Monzani, F., Caraccio, N., Del Guerra, P., Casolaro, A. & Ferrannini, E. (1999) Neuromuscular symptoms and dysfunction in subclinical hypothyroid patients: beneficial effect of L-T4 replacement therapy. *Clin Endocrinol (Oxf),* **51,** 237-242.

Monzani, F., Caraccio, N., Siciliano, G., Manca, L., Murri, L. & Ferrannini, E. (1997) Clinical and biochemical features of muscle dysfunction in subclinical hypothyroidism. *J Clin Endocrinol Metab,* **82,** 3315-3318.

Monzani, F., Del Guerra, P., Caraccio, N., Pruneti, C.A., Pucci, E., Luisi, M. & Baschieri, L. (1993) Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clin Investig,* **71,** 367-371.

Nystrom, E., Caidahl, K., Fager, G., Wikkelso, C., Lundberg, P.A. & Lindstedt, G. (1988) A double-blind cross-over 12-month study of L-thyroxine treatment of women with 'subclinical' hypothyroidism. *Clin Endocrinol (Oxf),* **29,** 63-75.

O'Brien, B.J., Banner, N.R., Gibson, S. & Yacoub, M.H. (1988) The Nottingham Health Profile as a measure of quality of life following combined heart and lung transplantation. *J Epidemiol Community Health,* **42,** 232-234.

Parle, J.V., Franklyn, J.A., Cross, K.W., Jones, S.C. & Sheppard, M.C. (1991) Prevalence and follow-up of abnormal thyrotrophin (TSH)

concentrations in the elderly in the United Kingdom. *Clin Endocrinol (Oxf),* **34,** 77-83.

Petersen, K., Bengtsson, C., Lapidus, L., Lindstedt, G. & Nystrom, E. (1990) Morbidity, mortality, and quality of life for patients treated with levothyroxine. *Arch Intern Med,* **150,** 2077-2081.

Philp, J.R., Duthie, M.B. & Crooks, J. (1968) A follow-up scheme for detecting hypothyroidism in thyrotoxic patients treated with radioiodine. *Lancet,* **2,** 1336-1338.

Pollock, M.A., Sturrock, A., Marshall, K., Davidson, K.M., Kelly, C.J., McMahon, A.D. & McLaren, E.H. (2001) Thyroxine treatment in patients with symptoms of hypothyroidism but thyroid function tests within the reference range: randomised double blind placebo controlled crossover trial. *Bmj,* **323,** 891-895.

Razvi, S., McMillan, C.V. & Weaver, J.U. (2005) Instruments used in measuring symptoms, health status and quality of life in hypothyroidism: a systematic qualitative review. *Clin Endocrinol (Oxf),* **63,** 617-624.

Riazi, A., Hobart, J.C., Lamping, D.L., Fitzpatrick, R., Freeman, J.A., Jenkinson, C., Peto, V. & Thompson, A.J. (2003) Using the SF-36 measure to compare the health impact of multiple sclerosis and Parkinson's disease with normal population health profiles. *J Neurol Neurosurg Psychiatry,* **74,** 710-714.

Roberts, N.D. (1996) *Psychological problems in thyroid disease.* In: British Thyroid Foundation News Letter., Vol. 18.

Saddock, B.J. & Saddock, V. (2000) Psychological factors affecting medical conditions. In: *Kaplan and Saddock's Comprehensive Textbook of Psychiatry.* (ed. by J.S. McDaniel), pp. 1765-1888. Lippincott Williams and Wilkins, Philadelphia.

Sait Gonen, M., Kisakol, G., Savas Cilli, A., Dikbas, O., Gungor, K., Inal, A. & Kaya, A. (2004) Assessment of anxiety in subclinical thyroid disorders. *Endocr J,* **51,** 311-315.

Saravanan, P., Chau, W.F., Roberts, N., Vedhara, K., Greenwood, R. & Dayan, C.M. (2002) Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. *Clin Endocrinol (Oxf),* **57,** 577-585.

Saravanan, P., Simmons, D.J., Greenwood, R., Peters, T.J. & Dayan, C.M. (2005) Partial substitution of thyroxine (T4) with tri-iodothyronine in patients on T4 replacement therapy: results of a large community-based randomized controlled trial. *J Clin Endocrinol Metab,* **90,** 805-812.

Sawin, C.T., Chopra, D., Azizi, F., Mannix, J.E. & Bacharach, P. (1979) The aging thyroid. Increased prevalence of elevated serum thyrotropin levels in the elderly. *Jama,* **242,** 247-250.

Sawka, A.M., Gerstein, H.C., Marriott, M.J., MacQueen, G.M. & Joffe, R.T. (2003) Does a combination regimen of thyroxine (T4) and 3,5,3'-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. *J Clin Endocrinol Metab,* **88,** 4551-4555.

Schectman, J.M., Kallenberg, G.A., Shumacher, R.J. & Hirsch, R.P. (1989) Yield of hypothyroidism in symptomatic primary care patients. *Arch Intern Med,* **149,** 861-864.

Seshadri, M.S., Samuel, B.U., Kanagasabapathy, A.S. & Cherian, A.M. (1989) Clinical scoring system for hypothyroidism: is it useful? *J Gen Intern Med,* **4,** 490-492.

Singer, P.A., Cooper, D.S., Levy, E.G., Ladenson, P.W., Braverman, L.E., Daniels, G., Greenspan, F.S., McDougall, I.R. & Nikolai, T.F. (1995) Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Standards of Care Committee, American Thyroid Association. *Jama,* **273,** 808-812.

Smith, K.W., Avis, N.E. & Assmann, S.F. (1999) Distinguishing between quality of life and health status in quality of life research: a meta-analysis. *Qual Life Res,* **8,** 447-459.

Sonino, N. & Fava, G.A. (1998) Psychological aspects of endocrine disease. *Clin Endocrinol (Oxf),* **49,** 1-7.

Spencer, C.A., Takeuchi, M. & Kazarosyan, M. (1996) Current status and performance goals for serum thyrotropin (TSH) assays. *Clin Chem,* **42,** 140-145.

Staub, J.J., Althaus, B.U., Engler, H., Ryff, A.S., Trabucco, P., Marquardt, K., Burckhardt, D., Girard, J. & Weintraub, B.D. (1992) Spectrum of subclinical and overt hypothyroidism: effect on thyrotropin, prolactin, and thyroid reserve, and metabolic impact on peripheral target tissues. *Am J Med,* **92,** 631-642.

Steen, N. & McColl, E. (1995) Developing and testing symptom-based outcome measures. In: *Health Outcomes for Primary and Outpatient Care.* (ed. by C.L. Riccalton). Harwood Academic Publishers., Chur, Switzerland.

Stewart, A.L., Greenfield, S., Hays, R.D., Wells, K., Rogers, W.H., Berry, S.D., McGlynn, E.A. & Ware, J.E., Jr. (1989) Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. *Jama,* **262,** 907-913.

Surks, M.I., Ortiz, E., Daniels, G.H., Sawin, C.T., Col, N.F., Cobin, R.H., Franklyn, J.A., Hershman, J.M., Burman, K.D., Denke, M.A., Gorman, C., Cooper, R.S. & Weissman, N.J. (2004) Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *Jama,* **291,** 228-238.

Tachman, M.L. & Guthrie, G.P., Jr. (1984) Hypothyroidism: diversity of presentation. *Endocr Rev,* **5,** 456-465.

Tappy, L., Randin, J.P., Schwed, P., Wertheimer, J. & Lemarchand-Beraud, T. (1987) Prevalence of thyroid disorders in psychogeriatric inpatients. A possible relationship of hypothyroidism with neurotic depression but not with dementia. *J Am Geriatr Soc,* **35,** 526-531.

Terwee, C.B., Gerding, M.N., Dekker, F.W., Prummel, M.F. & Wiersinga, W.M. (1998) Development of a disease specific quality of life questionnaire for patients with Graves' ophthalmopathy: the GO-QOL. *Br J Ophthalmol,* **82,** 773-779.

Toft, A.D. & Beckett, G.J. (2003) Thyroid function tests and hypothyroidism. *Bmj,* **326,** 295-296.

Vanderpump, M.P., Ahlquist, J.A., Franklyn, J.A. & Clayton, R.N. (1996) Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism. The Research Unit of the Royal College of Physicians of London, the Endocrinology and Diabetes Committee of the Royal College of Physicians of London, and the Society for Endocrinology. *Bmj,* **313,** 539-544.

Walsh, J.P. (2002) Dissatisfaction with thyroxine therapy - could the patients be right? *Curr Opin Pharmacol,* **2,** 717-722.

Walsh, J.P., Shiels, L., Lim, E.M., Bhagat, C.I., Ward, L.C., Stuckey, B.G., Dhaliwal, S.S., Chew, G.T., Bhagat, M.C. & Cussons, A.J. (2003) Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. *J Clin Endocrinol Metab,* **88,** 4543-4550.

Walsh, J.P., Ward, L.C., Burke, V., Bhagat, C.I., Shiels, L., Henley, D., Gillett, M.J., Gilbert, R., Tanner, M. & Stuckey, B.G. (2006) Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being or quality of life: results of a double blind, randomized clinical trial. *J Clin Endocrinol Metab,* **91**, 2624-2630.

Ware, J.E., Kosinski, M. & Gandek, B. (2000a) *SF-36 Health Survey: Manual & Interpretation Guide.* QualityMetric Incorporated, Lincoln,RI.

Ware, J.E.J., Kosinski, M. & Gandek, B. (2000b) *SF-36 Health Survey: Manual and Interpretation Guide.* QualityMetric Incorporated., Lincoln, RI.

Wiklund, I., Romanus, B. & Hunt, S.M. (1988) Self-assessed disability in patients with arthrosis of the hip joint. Reliability of the Swedish version of the Nottingham Health Profile. *Int Disabil Stud,* **10,** 159-163.

Wilson, I.B. & Cleary, P.D. (1995) Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. *Jama,* **273,** 59-65.

Woodcock, A. & Bradley, C. (2001) Validation of the HIV treatment satisfaction questionnaire (HIVTSQ). *Qual Life Res,* **10,** 517-531.

Woodcock, A., Bradley, C., Plowright, R., ffytche, T., Kennedy-Martin, T. & Hirsch, A. (2004) The influence of diabetic retinopathy on quality of life: interviews to guide the design of a condition-specific, individualised questionnaire: the RetDQoL. *Patient Educ Couns,* **53,** 365-383.

Woodcock, A.J., Julious, S.A., Kinmonth, A.L. & Campbell, M.J. (2001) Problems with the performance of the SF-36 among people with type 2 diabetes in general practice. *Qual Life Res,* **10,** 661-670.

Zulewski, H., Muller, B., Exer, P., Miserez, A.R. & Staub, J.J. (1997) Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls. *J Clin Endocrinol Metab,* **82,** 771-776.

Acknowledgments

I am extremely grateful to my research and educational supervisor, Dr Jola Weaver who was instrumental in helping, pushing, encouraging and highly accessible throughout the duration of this project and beyond. Thanks Jola!

I would not have been able to complete this work without the hard work of two people – Lorna and Rachel, from the Diabetes Centre, QE Hospital, Gateshead, who worked as hard (almost!) to complete this project.

Other individuals without whom this project would have never seen the light of day and who deserve a mention are Dr Graham Handley (Consultant Biochemist, QE Hospital, Gateshead), Pat Dobson (Lead Pharmacist, Chainbridge Medical Centre, Blaydon), Lyndsey (Trials Pharmacist, QE Hospital, Gateshead), Penny Williams and rest of the staff at R&D at QE, Gateshead, Prof. Matthews (Department of Medical Statistics, University of Newcastle upon Tyne) and all the people who willingly took part in this research at their own peril.

Finally, this mission would never have been accomplished (and in such good spirits!) without the support and understanding of my wife. Zarine – thanks a lot for putting up with the late nights, phone calls to volunteers from home, early mornings, weekend dashes to work and everything else that time has made me forget.

Publications arising from this thesis

1. McMillan CV, Bradley C, Woodcock A, Razvi S, Weaver JU. Design of new questionnaires to measure quality of life and treatment satisfaction in hypothyroidism. Thyroid 2004;14(11):916-925.
2. Razvi S, Ingoe LE, McMillan CV, Weaver JU. Health status in patients with sub-clinical hypothyroidism. European Journal of Endocrinology 2005;152(5):713-717.
3. Razvi S, McMillan CV, Weaver JU. Instruments used in measuring symptoms, health status and quality of life in hypothyroidism: a systematic qualitative review. Clinical Endocrinology 2005;63 (6):617-624.
4. McMillan CV, Bradley C, Razvi S, Weaver JU. Psychometric evaluation of a new questionnaire measuring treatment satisfaction in hypothyroidism:the ThyTSQ. Value Health 2006;9(2):132-139.
5. Razvi S, Weaver JU. Subclinical hypothyroidism and cardiovascular risk. Thyroid 2004;14:870.
6. Razvi S, Ingoe L, Keeka G, Oates C, Weaver JU. Cardiovascular risk factors are reduced by L-thyroxine therapy in subclinical hypothyroidism. British Thyroid Association, London 2005.
7. Razvi S, Manian UD, Weaver JU. Factors influencing treatment of subclinical hypothyroidism. British Thyroid Association, London 2005.
8. Razvi S, Ingoe L, Oates C, Tong J, Weaver JU. Increased free T4 levels determine improvement in endothelial function in subclinical hypothyroidism. Society for Endocrinology, London 2005.
9. Razvi S, Ingoe L, Keeka G, Oates G, Weaver JU. Cardiovascular risk factors in subclinical hypothyroidism. International Thyroid Congress, Buenos Aires 2005.
10. Razvi S, McMillan CV, Weaver JU. Quality of life, health status, symptoms and treatment satisfaction in subclinical hypothyroidism: double blind, 12-week, crossover study of L-thyroxine versus placebo. Endocrine Abstracts (2006) 11 P790
11. McMillan CV, Bradley C, Razvi S, Weaver JU. Psychometric validation of new measures of hypothyroid-dependent quality of life (QoL) and symptoms. Endocrine Abstracts (2005) 9 P151.

12. Razvi S, McMillan CV, Weaver JU. Health status is impaired in people with subclinical hypothyroidism. Endocrine Abstracts (2005) 9 P164
13. Razvi S, McMillan CV, Weaver JU. Quality of life is impaired in people on Levothyroxine therapy and untreated people with sub-clinical hypothyroidism. Endocrine Abstracts (2005) 9 P171.
14. McMillan CV, Razvi S, Bradley C, Weaver JU. Design and validation of new questionnaires assessing quality of life and treatment satisfaction in hypothyroidism. British Thyroid Association, London 2004.

Appendices

SF 36v2

Your Health and Well-Being

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

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

3. **The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
c. Lifting or carrying groceries	☐	☐	☐
d. Climbing several flights of stairs	☐	☐	☐
e. Climbing one flight of stairs	☐	☐	☐
f. Bending, kneeling, or stooping	☐	☐	☐
g. Walking more than a mile	☐	☐	☐
h. Walking several hundred yards	☐	☐	☐
i. Walking one hundred yards	☐	☐	☐
j. Bathing or dressing yourself	☐	☐	☐

4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐	☐	☐	☐	☐
b. Accomplished less than you would like	☐	☐	☐	☐	☐
c. Were limited in the kind of work or other activities	☐	☐	☐	☐	☐
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐	☐	☐	☐	☐

5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐	☐	☐	☐	☐
b. Accomplished less than you would like	☐	☐	☐	☐	☐
c. Did work or other activities less carefully than usual	☐	☐	☐	☐	☐

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐	☐	☐	☐	☐	☐

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

SF-36v2™ Health Survey © 1996, 2000 by QualityMetric Incorporated and Medical Outcomes Trust. All Rights Reserved.
SF-36® is a registered trademark of Medical Outcomes Trust.
(SF-36v2 Standard, US Version 2.0)

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks –**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐	☐	☐	☐	☐
b. Have you been very nervous?	☐	☐	☐	☐	☐
c. Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐
d. Have you felt calm and peaceful?	☐	☐	☐	☐	☐
e. Did you have a lot of energy?	☐	☐	☐	☐	☐
f. Have you felt downhearted and depressed?	☐	☐	☐	☐	☐
g. Did you feel worn out?	☐	☐	☐	☐	☐
h. Have you been happy?	☐	☐	☐	☐	☐
i. Did you feel tired?	☐	☐	☐	☐	☐

10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

11. **How TRUE or FALSE is each of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b. I am as healthy as anybody I know	☐	☐	☐	☐	☐
c. I expect my health to get worse	☐	☐	☐	☐	☐
d. My health is excellent	☐	☐	☐	☐	☐

THANK YOU FOR COMPLETING THESE QUESTIONS!

ThyDQoL

This questionnaire asks about your quality of life and how it has been affected by underactive thyroid.

Your quality of life is how good or bad you feel your life to be.

There are no right or wrong answers.

Section A

The questions on this page are overview questions.

Please tick the box that best indicates your response.

The first question asks about your general quality of life.

I) **In general, my present quality of life is:**

☐ excellent	☐ very good	☐ good	☐ neither good nor bad	☐ bad	☐ very bad	☐ extremely bad

The next question asks about the impact of your underactive thyroid and any thyroid treatment on your quality of life *in recent weeks*.

II) **If I did *not* have underactive thyroid, my quality of life would be:**

☐ very much better	☐ much better	☐ a little better	☐ the same	☐ worse

Section B

The following questions are about how underactive thyroid has affected different aspects of your life ***in recent weeks***. If you are currently being treated for underactive thyroid, please consider the effects of ***the treated condition***.

Part **(a)**: Tick **one** box to show how underactive thyroid and any treatment affect this aspect of your life.

Part **(b)**: Tick **one** box to show how important this aspect of life is to your quality of life.

1 (a)	**If I did *not* have underactive thyroid, I would enjoy the things I do in my spare time:**					
	☐ very much more	☐ much more	☐ a little more	☐ the same	☐ less	
(b)	**The things I do in my spare time are:**					
	☐ very important	☐ important	☐ somewhat important	☐ not at all important		

2	**Are you currently working?** Yes ☐ No ☐				
	If no, do you want to work? Yes ☐ No ☐				
	If ***yes*** to either question, complete **(a)** and **(b)**.				
	If ***no*** to both questions, go straight to **Question 3**.				
(a)	**If I did *not* have underactive thyroid, my working life would be:**				
	☐ very much better	☐ much better	☐ a little better	☐ the same	☐ worse
(b)	**For me, working life is:**				
	☐ very important	☐ important	☐ somewhat important	☐ not at all important	

3	**Do you ever want to go on holiday?**				
	Yes ☐ If ***yes***, complete **(a)** and **(b)**.				
	No ☐ If ***no***, go straight to **Question 4**.				
(a)	**If I did *not* have underactive thyroid, my holidays would be:**				
	☐ very much better	☐ much better	☐ a little better	☐ the same	☐ worse
(b)	**For me, holidays are:**				
	☐ very important	☐ important	☐ somewhat important	☐ not at all important	

4	**Do you have family / relatives?** **Yes** ☐ If ***yes***, complete **(a)** and **(b)**. **No** ☐ If ***no***, go straight to **Question 5**.
(a)	**If I did *not* have underactive thyroid, my family life would be:** ☐ very much better ☐ much better ☐ a little better ☐ the same ☐ worse
(b)	**My family life is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

5 (a)	**If I did *not* have underactive thyroid, my social life would be:** ☐ very much better ☐ much better ☐ a little better ☐ the same ☐ worse
(b)	**My social life is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

6	**Are you married or in a close personal relationship?** Yes ☐ No ☐ **If no, would you like to have a close personal relationship?** Yes ☐ No ☐ If ***yes*** to either question, complete **(a)** and **(b)**. If ***no*** to both questions, go straight to **Question 7.**
(a)	**If I did *not* have underactive thyroid, my closest personal relationship would be:** ☐ very much better ☐ much better ☐ a little better ☐ the same ☐ worse
(b)	**For me, having a close personal relationship is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

7	**Do you have a sex life?** Yes ☐ No ☐ **If no, would you like to have one?** Yes ☐ No ☐ If ***yes*** to either question, complete **(a)** and **(b)**. If ***no*** to both questions, go straight to **Question 8.**
(a)	**If I did *not* have underactive thyroid, my sex life would be:** ☐ very much better ☐ much better ☐ a little better ☐ the same ☐ worse
(b)	**For me, a sex life is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

8 (a)	**If I did *not* have underactive thyroid, physically I could do:** ☐ very much more ☐ much more ☐ a little more ☐ the same ☐ less
(b)	**For me, how much I can do physically is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

9 (a)	**If I did *not* have underactive thyroid, my energy levels would be:** ☐ very much higher ☐ much higher ☐ a little higher ☐ the same ☐ lower
(b)	**My energy levels are:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

10 (a)	**If I did *not* have underactive thyroid, the speed I could do things would be:** ☐ very much faster ☐ much faster ☐ a little faster ☐ the same ☐ slower
(b)	**The speed I can do things is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

11 (a)	If I did ***not*** have underactive thyroid, getting out and about (e.g. shopping, short trips) would be: ☐ very much easier ☐ much easier ☐ a little easier ☐ the same ☐ more difficult
(b)	For me, getting out and about is: ☐ very important ☐ important ☐ somewhat important ☐ not at all important

12 (a)	If I did ***not*** have underactive thyroid, I could handle my household tasks: ☐ very much better ☐ much better ☐ a little better ☐ the same ☐ worse
(b)	Handling household tasks is: ☐ very important ☐ important ☐ somewhat important ☐ not at all important

13 (a)	If I did ***not*** have underactive thyroid, my physical appearance would be: ☐ very much better ☐ much better ☐ a little better ☐ the same ☐ worse
(b)	My physical appearance is: ☐ very important ☐ important ☐ somewhat important ☐ not at all important

14	Do you consider yourself to be underweight? Yes ☐ No ☐ Do you consider yourself to be overweight? Yes ☐ No ☐ If ***yes*** to either question, complete **(a)** and **(b)**. If ***no*** to both questions, go straight to **Question 15**.
(a)	If I did ***not*** have underactive thyroid, my weight would be: ☐ very much better ☐ much better ☐ a little better ☐ the same ☐ worse
(b)	For me, my weight is: ☐ very important ☐ important ☐ somewhat important ☐ not at all important

15	**Have you had any bodily discomfort (e.g. aches, feeling cold, constipation) in recent weeks?** **Yes** ☐ If ***yes***, complete **(a)** and **(b)**. **No** ☐ If ***no***, go straight to **Question 16**.
(a)	**If I did *not* have underactive thyroid, my experience of bodily discomfort would be:** ☐ very much less ☐ much less ☐ a little less ☐ the same ☐ greater
(b)	**For me, not having bodily discomfort is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

16	**Have you felt depressed or low in recent weeks?** **Yes** ☐ If ***yes***, complete **(a)** and **(b)**. **No** ☐ If ***no***, go straight to **Question 17**.
(a)	**If I did *not* have underactive thyroid, I would feel depressed or low:** ☐ very much less ☐ much less ☐ a little less ☐ the same ☐ more
(b)	**For me, not feeling depressed or low is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

17	**Do you ever lack motivation (e.g. feel you can't be bothered to do things)?** **Yes** ☐ If ***yes***, complete **(a)** and **(b)**. **No** ☐ If ***no***, go straight to **Question 18**.
(a)	**If I did *not* have underactive thyroid, my motivation to do things would be:** ☐ very much greater ☐ much greater ☐ a little greater ☐ the same ☐ less
(b)	**My motivation to do things is:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

18 (a)	**If I did *not* have underactive thyroid, my feelings about the future (e.g. worries, hopes) would be:** ☐ very much better ☐ much better ☐ a little better ☐ the same ☐ worse
(b)	**My feelings about the future are:** ☐ very important ☐ important ☐ somewhat important ☐ not at all important

Are there any other ways in which underactive thyroid and any treatment affect your quality of life, that have ***not*** been covered by the questionnaire?

Yes ☐ **No** ☐

If ***yes***, please describe in the box provided.

Thank you for completing this questionnaire.

The Hypothyroidism Treatment Satisfaction Questionnaire: ThyTSQ- Present

The following questions are concerned with the treatment for your underactive thyroid (including blood monitoring and any medication) and your experience over the past few weeks. Please answer each question by circling a number on each of the scales.

1. How satisfied are you with the current treatment for your underactive thyroid?

   very satisfied 6 5 4 3 2 1 0 very dissatisfied

2. How well do you feel the treatment is working?

   very well 6 5 4 3 2 1 0 very badly

3. How convenient have you found your treatment to be recently (e.g. remembering to take the medication, getting prescriptions)?

   very convenient 6 5 4 3 2 1 0 very inconvenient

4. How satisfied are you with your understanding of your underactive thyroid?

   very satisfied 6 5 4 3 2 1 0 very dissatisfied

5. Would you encourage someone else with underactive thyroid to have your kind of treatment?

   Yes, I would definitely encourage them 6 5 4 3 2 1 0 No, I would definitely not encourage them

6. How well do you feel that the treatment is controlling symptoms of underactive thyroid?

   very well 6 5 4 3 2 1 0 very badly

7. How satisfied would you be to continue with your present treatment and dose?

   very satisfied 6 5 4 3 2 1 0 very dissatisfied

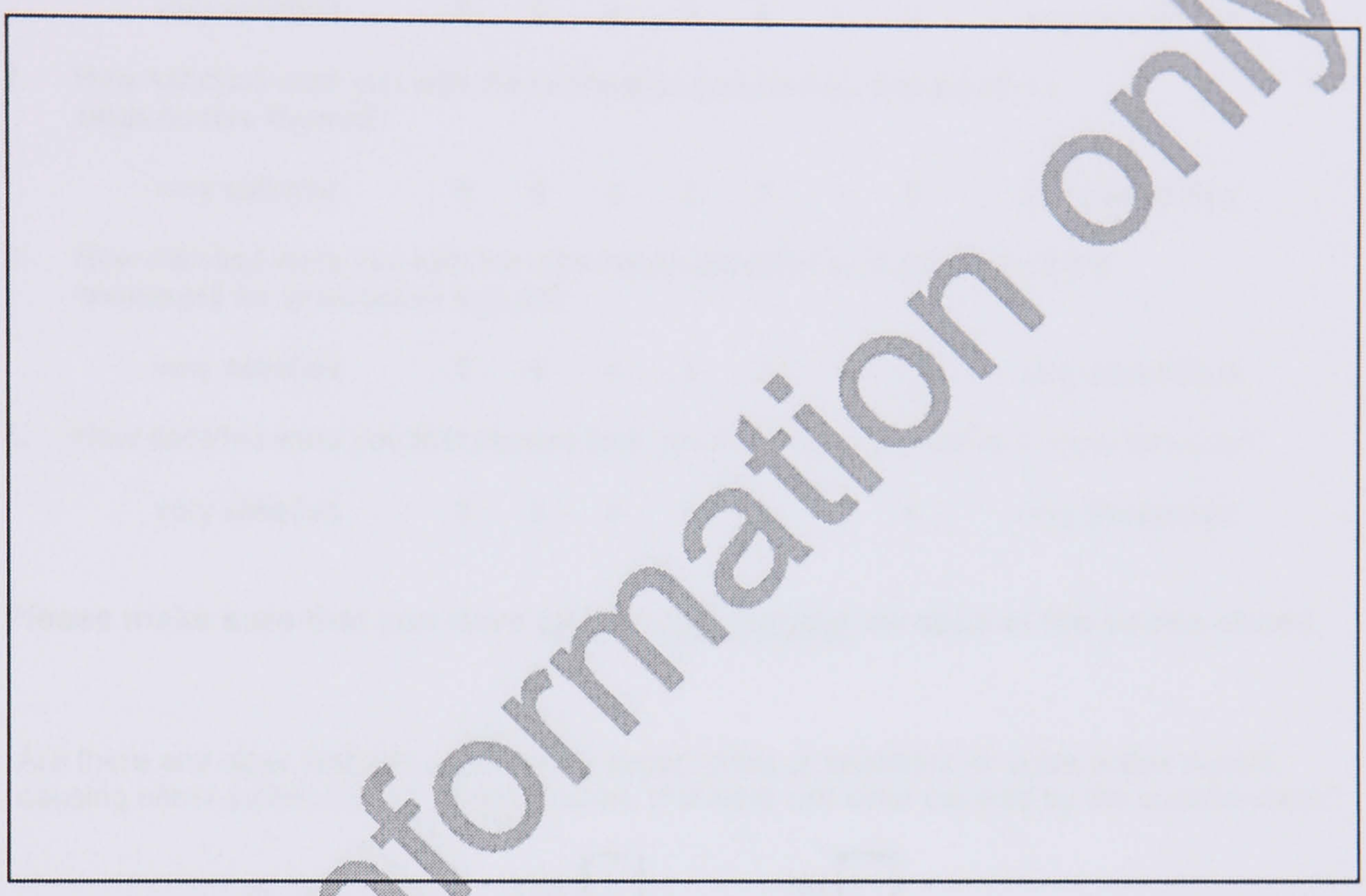
Please make sure that you have circled one number on each of the scales above.

Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK

Are there any other features of your recent treatment for underactive thyroid, causing either satisfaction or dissatisfaction, that have ***not*** been covered by the questionnaire?

Yes ☐ No ☐

If ***yes***, please describe in the box provided.



Thank you for completing this questionnaire.

The Hypothyroidism Treatment Satisfaction Questionnaire: ThyTSQ- Past

The following questions are concerned with your early experiences both before and after you were told you had underactive thyroid.
Please answer each question by circling a number on each of the scales.

1. How satisfied were you with the way doctors dealt with your underactive thyroid around the time it was first diagnosed?

   very satisfied 6 5 4 3 2 1 0 very dissatisfied

2. How satisfied were you with the information provided by doctors about **underactive thyroid**?

   very satisfied 6 5 4 3 2 1 0 very dissatisfied

3. How satisfied were you with the information provided by doctors about the **treatment** for underactive thyroid?

   very satisfied 6 5 4 3 2 1 0 very dissatisfied

4. How satisfied were you that doctors took you and your underactive thyroid seriously?

   very satisfied 6 5 4 3 2 1 0 very dissatisfied

Please make sure that you have circled one number on each of the scales above.

Are there any other features of your early experiences of treatment for underactive thyroid, causing either satisfaction or dissatisfaction, that have ***not*** been covered by the questionnaire?

Yes ☐ No ☐

If ***yes***, please describe in the box provided.

Please continue overleaf if necessary.

Thank you for completing this questionnaire.

Hypothyroid Symptom Checklist

This questionnaire asks you about symptoms that can be associated with underactive thyroid and that you may have experienced in recent weeks.

For each question - if you answer ***yes*** to part (a) please complete part (b) of that question

- if you answer ***no*** to part (a), go straight to the next question.

Please tick the box that best indicates your response.

1(a)	Have you felt tired in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much does feeling tired bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

2(a)	Have you gained weight in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much does your weight gain bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

3(a)	Have you felt colder than other people in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much does feeling cold bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

4(a)	Have you had constipation in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much does constipation bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

5(a)	Have you had hair problems in recent weeks (e.g. hair loss, coarseness)?			Yes ☐	No ☐
(b)	If ***yes***, how much do hair problems bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

6(a)	Have you had skin problems in recent weeks (e.g. dryness, coarseness)?			Yes ☐	No ☐
(b)	If ***yes***, how much do skin problems bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

7(a)	Have you had nail problems in recent weeks (e.g. brittleness, flaking)?			Yes ☐	No ☐
(b)	If ***yes***, how much do nail problems bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

8(a)	Have you had loss of appetite in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much does loss of appetite bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

9(a)	Have you had hearing problems in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much do hearing problems bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

10(a)	Have you had voice problems in recent weeks (e.g. hoarseness, huskiness)?			Yes ☐	No ☐
(b)	If ***yes***, how much do voice problems bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

11(a)	Have you had speech problems in recent weeks (e.g. slowness, inaccuracy)?			Yes ☐	No ☐
(b)	If ***yes***, how much do speech problems bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

12(a)	Have you had memory problems in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much do memory problems bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

13(a)	Have you had problems with your concentration in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much do concentration problems bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

14(a)	Have you felt giddy or dizzy in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much does giddiness or dizziness bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

15(a)	Have you felt depressed or low in recent weeks?			Yes ☐	No ☐
(b)	If ***yes***, how much do feelings of depression bother you?	☐ not at all	☐ a little	☐ quite a bit	☐ very much

Thank you for completing this questionnaire.