Subclinical thyroid disorders: significance and clinical impact

Salman Razvi,1,2 Jolanta U Weaver,1,3 Simon H S Pearce2,4

ABSTRACT
Subclinical thyroid diseases are defined by abnormal serum thyroid stimulating hormone (TSH) levels associated with normal thyroid hormone concentrations. The diagnosis of these conditions depends on defining the ‘normal’ euthyroid TSH range; in this review, arguments for and against lowering the upper limit of TSH are summarised. Although, subclinical hypothyroidism and subclinical hyperthyroidism are frequently encountered, their long-term consequences are debated due to conflicting results from many observational studies. The causes, effects and outcomes of treatment of both subclinical diseases are described, and the direction of future research in these conditions is outlined.

INTRODUCTION
Thyroid disorders are the second most common endocrine condition after diabetes mellitus; thus it is not surprising that each year 25% of the population have their thyroid function tests checked at an estimated cost of £30 million in the UK.1

The hypothalamic–pituitary–thyroid axis is regulated via a classic control loop: thyroid hormones (triiodothyronine (T3) and thyroxine (T4)) mediate the feedback loop of thyroid stimulating hormone (TSH) and thyroid releasing hormone (TRH) and determine the TSH set point for any given individual. A decrease of T4 or T3 leads to an increase in TSH as both hormones, T3 directly and T4 indirectly, contribute to hypothalamic and pituitary T3 levels via intra pituitary/cerebral conversion of T4 to T3. There is a linear relation between thyroid hormones and log TSH concentration reflecting that TSH is a sensitive indicator of thyroid status.

With highly sensitive and specific assays, increased frequency of testing and heightened awareness of subclinical conditions we are now able to detect ever more subtle degrees of thyroid dysfunction: non-thyroidal disease, subclinical hypothyroidism and subclinical hyperthyroidism. The increased frequency of thyroid testing and the ageing population is leading to more abnormal results being detected and can pose a challenge for clinicians and biochemists in its interpretation and clinical applications.

DEFINITION OF SUBCLINICAL THYROID CONDITIONS AND SERUM TSH REFERENCE RANGE
The subclinical states can be defined as normal serum levels of thyroid hormones in the presence of either elevated serum TSH (subclinical hypothyroidism or SHypo) or low/undetectable TSH concentrations (subclinical hyperthyroidism or SHyper). Thus, the diagnosis is based solely on the biochemical abnormality of serum TSH levels, and hence the normal range for serum TSH levels needs to be established. This task is proving to be quite challenging, especially defining the upper limit of the normal TSH reference range. This is because of a number of factors. First, it is important to note that circulating TSH displays two types of variations: pulsatile secretion with intervals between 1 h and 2 h, the amplitude of which is affected by fasting, surgery and illness.2–4 and circadian rhythm characterised by the surge of TSH before the onset of sleep. Thus the time of phlebotomy is important, because even in a healthy individual, the TSH level varies throughout the day, with early morning values greater than later ones, and is accentuated by sleep deprivation, strenuous exercise, or working during the night or evening shifts. Thus repeated measurements in the same individual may vary considerably over months. Second, other factors such as non-thyroidal illness or pregnancy may affect serum TSH as well as thyroid hormone levels. Finally, exogenous factors such as certain medications (amiodarone, lithium, glucocorticoids, anticonvulsants, etc) and iodine intake also influence thyroid function.

The reference TSH levels are generally derived from the 2.5th to 97.5th centile of individuals without evidence of thyroid dysfunction, positive thyroid antibodies, or medications affecting thyroid function.5 The limitation of this approach is that some individuals may have cytological evidence of lymphocytic infiltration while being negative for thyroid antibodies.5 Thus TSH levels have a skewed distribution at higher concentrations in healthy populations suggesting that some healthy people with subclinical disease are included in the upper limit of the reference range.7,8 For instance, inclusion of antibody-positive subjects significantly increases TSH 97.5th centile levels.5 The NHANES III survey in the USA measured TSH levels in non-pregnant people (n=13,544) aged 12 years or older, who were not on any medications known to affect thyroid hormone metabolism, and who had negative antithyroid peroxidase (TPO) antibodies; in this population, the reference range of TSH concentration (2.5th–97.5th centile) was 0.45–4.12 mIU/l, with a median value of 1.4 mIU/l.9

There has been a debate whether the upper limit of the reference range for serum TSH should be reduced. The improved sensitivity and specificity of current antibody-based immunometric assays, together with improvement in thyroid antibody tests used for pre-screening subjects over the last
Best practice

20 years, has led to a steady decline of the upper reference limit for TSH from about 10 mIU/l to approximately 4.0–4.5 mIU/l. 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 OR of developing hypothyroidism over the next 20 years, especially if thyroid antibodies were present. An increased risk for hypothyroidism was even seen in antibody-negative subjects with a TSH over 2.0 mIU/l. It is likely that a proportion of 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. Even the current sensitive anti-TPO immunoassays may not identify all individuals with low-grade thyroid autoimmunity. 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 mIU/l and 2.5 mIU/l. There are data indicating that African Americans, who have a 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. The American Association of Clinical Endocrinologists has recommended that the TSH upper limit should be 3.0 mIU/l. On the other hand, it has been argued that there is no evidence for associated adverse outcomes in people with TSH values between 2.50 mIU/l and 4.0 mIU/l and that some of these TSH levels may be due to technical reasons with the TSH assay (abnormal TSH isoforms and heterophile antibodies). The variability of the TSH upper limit reported for different populations may be related to variance in hidden thyroid pathology, sampling time of day, TSH and antibody assay characteristics. In particular, data from UK quality assessment schemes indicate that TSH reference ranges quoted by diagnostic companies (and adopted by many laboratories) were not related to assay bias. More recently it has been confirmed that 50% of cases of abnormal TSH levels are normalised on repeat testing, thus introducing an additional challenge to interpretation of TSH results.

Finally, TSH reference intervals are population dependent and assay dependent, and statistical methodology dependent. We provide the example of three neighbouring hospitals that could provide care to one individual patient. There was a difference in reference range between three of them, potentially giving the patient a different diagnosis depending which hospital performed thyroid function tests (TFTs) (table 1). Hospitals 1 and 2 use the same assay (ElectroChemiLuminescence immunoassay; Roche Diagnostics, Burgess Hill, UK) but have adopted different reference ranges. The third hospital uses a similar assay but manufactured by Siemens.

### Table 1  Thyroid function test reference ranges in three neighbouring hospitals

<table>
<thead>
<tr>
<th>Thyroid function test</th>
<th>Hospital 1</th>
<th>Hospital 2</th>
<th>Hospital 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mIU/l)</td>
<td>0.4–4.0</td>
<td>0.3–3.8</td>
<td>0.3–4.7</td>
</tr>
<tr>
<td>Free T4 (pmol/l)</td>
<td>9–25</td>
<td>12.0–22.0</td>
<td>9.5–21.5</td>
</tr>
<tr>
<td>Free T3 (pmol/l)</td>
<td>2.8–7.5</td>
<td>3.1–6.8</td>
<td>3.5–6.5</td>
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</tbody>
</table>

*American Thyroid Association guidelines (2002).
†Roche assay reference range.
‡Siemens assay reference range.
TSH, thyroid stimulating hormone; T4, thyroxine.

### Table 2  Causes of SHypo and raised TSH levels

<table>
<thead>
<tr>
<th>Causes</th>
<th>Details</th>
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<tbody>
<tr>
<td>Autoimmune hypothyroidism</td>
<td>Usually associated with positive thyroid autoantibodies and/or hypothyroidic appearance on ultrasound</td>
</tr>
<tr>
<td>Previously treated thyroid or neck disease</td>
<td>History of radioiodine or surgical treatment</td>
</tr>
<tr>
<td>Drugs</td>
<td>Lithium, amiodyarone, anticonvulsants (due to increased T4 metabolism), interferon, suntininb</td>
</tr>
<tr>
<td>Inadequate treatment of thyroid disease</td>
<td>Non-compliance, undertreatment with thyroid hormones, malabsorption, interaction with other substances (iron, calcium); overtreatment with antithyroid drugs</td>
</tr>
<tr>
<td>Transiently raised TSH levels</td>
<td>Non-thyroidal illness (recovery phase)</td>
</tr>
<tr>
<td>Systemic diseases with thyroid involvement</td>
<td>Sarcoiiosis, amyloidosis, lymphoproliferative disorders, haemochromatosis</td>
</tr>
<tr>
<td>TSH receptor gene mutations</td>
<td>Several loss of function gene mutations have been found in non-autoimmune SHypo</td>
</tr>
</tbody>
</table>
| Pituitary tumours secreting low bioactivity TSH | SHypo, subclinical hyperthyroidism; TSH, thyroid stimulating hormone; T4, thyroxine. (Hashimoto disease) and previously treated thyroid disease. The causes of SHypo and elevated serum TSH levels are outlined in table 2. It is important to differentiate between SHypo and other reasons for a raised TSH level, SHypo should be confirmed by repeat tests after 3–6 months, at which time transiently raised TSH levels (eg, caused by non-thyroidal illness) will have normalised.

### Prevalence

The prevalence of SHypo has been noted to be between 4% and 20% depending on the gender and the age of the population studied. In the Whickham survey, SHypo (TSH >6.0 mIU/l) was prevalent in 7.5% of women and 2.8% of men. In the much larger NHANES III study in the USA, the prevalence of SHypo (TSH >4.6 mIU/l) was 4.3% of the population; this reduced to 3.9% when individuals with thyroid disease or positive thyroid antibodies were excluded. This study also showed that subclinical thyroid diseases are more prevalent in white and Mexican–American populations than in African Americans. Furthermore, analysis of the NHANES III data also showed that serum TSH levels increased with age and in women; individuals aged between 12 years and 39 years were less likely to have elevated serum TSH levels (≈2%) compared with age groups 60–69 years (≈7%) and 80+ years (≈14%). The large Colorado Health Fair study found the prevalence of SHypo to be much higher at 8.5%, but it was not strictly population-based; the sample was recruited from health fair visitors and included individuals on medications affecting thyroid function. Nevertheless, the age-related and gender-related increases in prevalence of elevated serum TSH were also detected in this study. As discussed above, it is quite probable that serum TSH concentrations increase progressively with age even in healthy individuals, thus the prevalence of SHypo may be being overestimated. Therefore, there is a need to investigate whether age-specific TSH reference ranges would provide better decision making and improved patient outcomes.

### Implications of SHypo

#### Progression of disease

The risk of progression of SHypo to overt hypothyroidism is based on the level of TSH, age, female sex as well as positive thyroid antibody status. In the 20-year follow-up of the Whickham study, the annual rate of progression to overt...
hypothyroidism was 4.3% in women who had raised TSH as well as positive thyroid autoantibodies, 3% if TSH alone was raised, and 2% for those with positive thyroid autoantibodies only. Other studies have reported similar results. Conversely, the rate of spontaneous normalisation of elevated serum TSH is also well recognised. In a prospective study of patients with SHypo aged 55 years or more, nearly 40% normalised their TSH values, of which 67% normalised in the first 2 years of follow-up. In an observational study using the computerised database of a large healthcare organisation, a one-off raised TSH level between 5.6 mIU/l and 10 mIU/l normalised in 62% of patients, whereas levels higher than 10 mIU/l normalised in 27% of patients. There is evidence that increased frequency of testing and the lower limit of the T4 reference range influence patients being categorised as SHypo or euthyroid. In that study of 21 patients with SHypo confirmed on two occasions prior to inclusion, and who went on to have monthly thyroid function tests for 15 months, 29% of participants remained in SHypo state on all visits, while 67% had variable diagnosis ranging from euthyroid, SHypo and overt hypothyroidism. In summary, individuals with a single raised TSH level should not be classed as being SHypo and should be monitored after 5–6 months. In individuals who normalise their TSH levels, further monitoring up to a year after the index test may be appropriate.

Symptoms and quality of life

Most patients found by screening to have subclinical hypothyroidism have at least one symptom that could be related to this diagnosis. Symptoms include muscle cramps, dry skin, intolerance to cold, constipation, poor energy levels, fatigue and mental slowness. Baseline data in people with SHypo from a study by Cooper et al showed an increased prevalence of hypothyroid symptoms and cognitive impairments as compared to euthyroid controls. The Colorado cross-sectional study of 2586 participants reported increased prevalence of hypothyroid symptoms in response to a validated survey. The 2536 subjects who were identified as having SHypo, more often reported having dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramps, cold intolerance, puffy eyes, constipation, and voice hoarseness than did euthyroid subjects. It is important to note that, whereas euthyroid subjects experienced a mean of 12.1% of all listed symptoms, overt hypothyroid subjects had 16.6% of these symptoms (p<0.05 versus euthyroid group), and subjects with SHypo reported an intermediate 13.7% of the symptoms (p<0.05 versus euthyroid group). This suggests a ‘dosage effect’ between the degree of thyroid failure and symptoms. Consistent with these findings, a Swiss study involving 352 women with hypothyroidism reported that 24% of the 95 subjects with mild thyroid failure exhibited typical symptoms of hypothyroidism. Another study that compared SHypo patients with age-matched and gender-matched UK general population found that all scales of the health status questionnaire SF-36 were reduced; this finding was consistent with reduced health. Some experts have argued that these are not population-based studies and that some studies have also included people with undertreated hypothyroidism. Other cross-sectional studies have demonstrated evidence of specific neurobehavioral and neuromuscular dysfunction in patients with SHypo. Depression, memory loss, cognitive impairment and a range of neuromuscular complaints have been reported to occur more frequently in patients with this condition. 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. The association of SHypo 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. Additionally, the mere association between SHypo and psychiatric disorders should not lead to the conclusion that SHypo brings about these associated disorders. The four large epidemiological studies that examined cognitive and affective scores in SHypo subjects found few or no significant differences overall, and none in those with TSH between 5 mIU/l and 10 mIU/l.

Cardiovascular risk and mortality

The association of SHypo with cardiovascular (CV) disease has been quite controversial. One of the earliest case–control studies showed a strong association between SHypo (as defined by exaggerated response to thyrotropin releasing hormone) and angiographically demonstrated coronary artery disease. Since then, there have been several community-based cross-sectional and longitudinal studies that have assessed this relationship. However, there has been no large-scale randomised controlled trial of treatment with SHypo in assessing CV disease. The cross-sectional component of the Rotterdam study demonstrated a twofold excess of myocardial infarction and aortic atherosclerosis in SHypo women aged 55 years or more, with a vascular risk attributable to SHypo comparable with that associated with diabetes mellitus, smoking and hypercholesterolaemia. However, the longitudinal component of this study (follow-up period of 4.6 years), did not demonstrate this association, but this may have lacked power as total CV events were quite low. The cross-sectional Whickham study showed a weak association between minor ECG changes and SHypo in women, independent of other variables. A 20-year follow-up study of the cohort did not reveal an association between autoimmune thyroid disease and CV disease. But many patients with SHypo in the original survey received L-thyroxine replacement therapy and the analysis did not differentiate between SHypo and euthyroid people with positive antibodies. A Japanese study showed that SHypo was associated with prevalent CV disease and incident all-cause mortality independent of all other variables in men but not in women. 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 SHypo, although it did not differentiate between treated and untreated patients. Similarly, the prevalence of CV disease was not increased in SHypo patients in a cross-sectional survey of 3410 elderly people in Maryland, USA. 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 was >10 mIU/l. A recent study, with cross-sectional and longitudinal arms, of people aged between 70 years and 79 years reported no association between SHypo and CV disease at baseline, but there was an increased incidence of congestive heart failure after 4 years of follow-up in the moderate and severe SHypo groups (TSH 7–9.9 mIU/l and >10 mIU/l, respectively), but not in the mild SHypo group. 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 as follow-up. 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.
Thus, there have been a number of cross-sectional as well as longitudinal studies that have assessed the risk of ischaemic heart disease (IHD) in people with SHypo, 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 SHypo. The most likely cause of the difference, however, is likely to be due to the age groups of the SHypo patients studied: younger patients are more likely to have an increased IHD risk compared with older patients.47

Pregnancy
The prevalence of SHypo in pregnancy is 2.5%.48 49 This relative thyroid hormone deficiency can affect maternal and fetal outcomes. Several poor outcomes have been reported with SHypo on the mother, including increased fetal death50 and increased maternal hypertension.51 The fetus does not develop secretion of cortisol by 0.26 mmol/l.63 64 There has been no reported beneficial effect of L-thyroxine on cardiac function that have shown a beneficial effect.34 55–59

Studies that have investigated the effect of L-thyroxine on serum lipids is variable.24 55

Several randomised, prospective, placebo-controlled trials of L-thyroxine therapy in SHypo published so far, have assessed symptoms of hypothyroidism or health status.24 34 55–59 Cooper et al14 and Nystrom et al55 reported significant improvements in symptoms of hypothyroidism. Jaeschke and colleagues did not find any improvement in health status (general or disease specific) in their patients with SHypo, apart from some improvement in a composite psychometric memory score57 That study has been criticised because of insufficient treatment of the SHypo patients—the mean TSH levels of the treated patients were 4.61 mIU/l. Meier and colleagues concluded that physiological mean L-thyroxine replacement therapy in people with SHypo (the mean TSH at baseline in this group was 12.1 mIU/l at baseline) improves clinical symptoms of hypothyroidism.59 On the other hand, Kong et al did not find any significant improvement in their patients with mild SHypo, in terms of symptom scores. In fact, there was a significant worsening in anxiety scores on L-thyroxine therapy.23 The patients in this study were not recruited by population screening and did not have stable SHypo, and had a rigid dosing regimen (50 µg/day or 100 µg/day) leading to a treated TSH level of 3.4 mIU/l (towards upper limit of normal range). Two recent studies came to the opposite conclusions: one found no significant improvement in symptoms or other psychological parameters after L-thyroxine therapy,55 whereas our group found a significant improvement in certain parameters of a disease-specific quality of life questionnaire.56

The effects of L-thyroxine on cognitive function and memory are not clear. Some studies have shown a beneficial effect whereas others have not.27 28 34 55 57

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 than those with higher TSH levels. This would mean that 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 with 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 12 mIU/l (n=18).77 This fact was amply illustrated in the largest RCT to date (n=100) that showed significant improvements in lipid levels and quality of life even in patients with mild SHypo (TSH <10 mIU/l).56

In the USA, a consensus statement of three societies concluded that there was no evidence that routine treatment of SHypo should be recommended in patients with serum TSH levels below 10 mIU/l.1 The societies sponsoring the consensus statement disagreed with this recommendation and recommend treatment of mild SHypo.74 A clinically reasonable position is that individuals with SHypo and TSH <10 mIU/l can be offered a 3-month or 4-month trial of T4 therapy if they have symptoms suggestive of hypothyroidism; the decision about continuation of T4 depending upon symptomatic benefits.75

**SUBCLINICAL HYPERTHYROIDISM**

**Definition**
SHyper is defined as a serum TSH that is below the reference range, with free T3 and free T4 concentrations within the reference range (table 3). There is an important distinction within SHyper, related to whether the serum TSH is low

**Best practice**

Effects of treatment
The potential benefits and risks of treating SHypo 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 quality of life, and a potentially decrease in 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 surrogate CV risk factors. RCTs of L-thyroxine in SHypo show that the effect of L-thyroxine on serum lipids is variable.24 55–62 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 mmol/l to 0.4 mmol/l, and low-density lipoprotein cholesterol by 0.26 mmol/l.63 64 There has been no reported beneficial effect on high-density lipoprotein cholesterol or triglycerides. There have also been studies investigating the effect of L-thyroxine on cardiac function that have shown a beneficial effect.24 55 65–72 A few trials that studied endothelial dysfunction found that L-thyroxine had a beneficial effect.56 73

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(0.1–0.4 mU/l) or completely suppressed to <0.1 mU/l or <0.05 mU/l. The former pattern of results (grade I SHyper) is typical of non-thyroidal illness or drug effects and not consistent with endogenous hyperthyroidism; some individuals with the latter pattern of investigations (suppressed TSH; grade II SHyper) will have endogenous hyperthyroidism. By definition, many individuals with SHyper do not have symptoms, although weight loss, anxiety, tremulousness and palpitations are occasionally seen.

Aetiology

In more than half of cases, a single reduced serum TSH measurement will revert to within the reference range on a repeat test.76 Of individuals with a sustained reduction in serum TSH, the commonest cause for SHyper is overtreatment of hyperthyroidism as the cause of their low TSH, re-instatement of CT scan contrast media. Non-thyroidal systemic illness, which may take many forms, may lead to an isolated reduction or complete suppression of the serum TSH concentration (either grade I or II SHyper). An isolated reduction in serum TSH is also commonly found as a normal feature of the first trimester of pregnancy, as well as in extreme old age.27 Lastly, a few people have mild but true endogenous hyperthyroidism as the cause of their low TSH, reflecting overproduction of thyroid hormones generally owing to indolent multinodular goitre or mild Graves disease (box 1).

<table>
<thead>
<tr>
<th>Table 3 Degrees of hyperthyroidism</th>
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<tbody>
<tr>
<td>Overt hyperthyroidism</td>
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<tr>
<td>TSH (reference range 0.4–4.0 mU/l)</td>
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<tr>
<td>Free T4</td>
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<td>Free T3</td>
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</table>

SHyper, subclinical hyperthyroidism; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

Prevalence

SHyper affects about fivefold fewer people than subclinical hypothyroidism. The NHANESIII survey found that 1% of people between the ages of 60 years and 80 years had subclinical hyperthyroidism, as defined by a serum TSH <0.4 mU/l on a single blood test. In people above the age of 80 years, the prevalence rose to 3%.9 Three quarters of individuals with SHyper have a serum TSH that is low (0.1–0.4 mU/l), and the remainder, about 0.3–1% of unselected populations, have a suppressed TSH concentration (below 0.1 mU/l). Due to the transient nature of SHyper, these numbers are likely to over-represent the prevalence, and the number of individuals with sustained SHyper is likely to be substantially lower than this. There is a slight preponderance of women, (women:men 1.5:1). In our hospital-based series, the average age was 77 years.

Implications of SHyper

Progression

The risk of progression to overt hyperthyroidism is largely dependent upon serum TSH concentration and aetiology. Individuals with Graves disease are more likely to progress. In Grade I SHyper, the risk of progression is low.76 However, if the TSH is suppressed to below 0.1 mIU/l, the risk of progression to overt thyrotoxicosis is between 2% and 5% per year.7

Cardiovascular risk and mortality

Data from Framingham show that an undetectable TSH concentration (<0.1 mU/l) is associated with a threefold increase in the risk of subsequent atrial fibrillation.78 Similarly, the atrial fibrillation prevalence was doubled in individuals with SHyper in the Cardiovascular Health Study, examining patients older than 65 years over 15 years of follow-up.43 Retrospectively acquired data from an acute general hospital setting show that there is almost no difference in the atrial fibrillation rate in overt thyrotoxicosis compared with that found in SHyper.79 A 10-year observational study of patients over 60 years old from Birmingham, UK, also demonstrated that all-cause mortality was excess in patients with the lowest quintile of TSH, predominantly due to circulatory (cardiovascular and cerebrovascular) mortality in the first 5 years of follow-up.45 In this important community-based survey, circulatory deaths were maximal (2.3-fold excess; 95% CI 1.3 to 4.0) after 5 years of observation, with a circulatory mortality of 25% in the group with a TSH <0.5 mU/l, compared with 15% in the group with normal TSH.45 Similarly, the prospective Leiden ‘85-plus’ study confirmed that the excess mortality associated with a low TSH extends right across the range of elderly subjects, with an increased risk of cardiovascular mortality over 4 years of follow-up in these subjects: a sex-adjusted HR of 1.5 (95% CI 1.0 to 2.1) per SD decrease in serum TSH.46 Nevertheless, this has not been the conclusion of all studies, particularly those examining younger population cohorts.44 A recently published meta-analysis of eight studies that examined mortality with relationship to thyroid status showed that there was an overall HR for mortality of 1.4 (95% CI 1.1 to 1.8) in SHyper cohorts as compared with euthyroid groups.80 Thus, SHyper should, at least, be considered as a marker for circulatory disease and adverse outcome.

Bone mass, fracture risk, muscle function and dementia

In addition to the association with adverse vascular outcomes, SHyper is also associated with several other degenerative problems. Many studies show a reduced bone mineral density (BMD)
**Take-home messages**

### SUBCLINICAL HYPOTHYROIDISM

- Common causes are inadequately treated and autoimmune hypothyroidism.
- Progression to overt hypothyroidism is directly related to serum thyroid stimulating hormone (TSH) levels, female gender and presence of thyroid autoantibodies, although up to half of these individuals may normalise TSH levels.
- There is little evidence for impaired quality of life in these individuals, but there is good evidence that the condition may be associated with poor vascular outcomes, especially in younger individuals.
- There is good evidence that, in pregnancy, it is associated with poor fetal and maternal outcomes.
- Treatment may improve surrogate markers of cardiovascular disease and some aspects of quality of life, but no trial of treatment has been performed investigating ‘hard’ vascular outcomes.
- We suggest treatment of individuals with persistent TSH levels above 10 mIU/l, and considering a trial of treatment in those with persistent levels ≤10 mIU/l and with symptoms of hypothyroidism.

### SUBCLINICAL HYPERTHYROIDISM

- Common causes are overtreatment with thyroxine, nodular and autoimmune thyroid disease, and non-thyroidal illness.
- Progression to overt hyperthyroidism is dependent on initial serum TSH levels; those with lower levels are more likely to progress, as are those with Graves disease.
- There is good evidence that it is associated with increased incidence of osteoporosis, fractures, atrial fibrillation and vascular events, and mortality, especially in older individuals.
- There is no trial of treatment that has investigated vascular or skeletal outcomes in these individuals.
- We suggest treating those individuals who have atrial fibrillation or to consider treating those with persistent TSH levels <0.1 mIU/l and with signs of hyperthyroidism.

### Interactive multiple choice questions

This JCP best practice article has an accompanying set of multiple choice questions (MCQs). To access the questions, click on BMJ Learning: Take this module on BMJ Learning from the content box at the top right and bottom left of the online article. For more information please go to: http://jcp.bmj.com/site/about/education.xhtml Please note: the MCQs are hosted on BMJ Learning—the best available learning website for medical professionals from the BMJ Group. If prompted, subscribers must sign into JCP with their journal’s username and password. All users must also complete a one-time registration on BMJ Learning and subsequently log in (with a BMJ Learning username and password) on every visit.

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**Effects of treatment**

The effects of treatment on the long-term outcome of SHyper are largely unknown. There have been three small controlled trials of treatment of SHyper, with BMD as the main outcome indicator. The first study used radiiodine in a non-randomised fashion in 16 postmenopausal women with SHyper, BMD at the spine and hip was significantly better in the radiiodine-treated women compared with the untreated group, largely because of the continued decline in BMD in the untreated individuals. The second study randomised 16 postmenopausal women with endogenous grade II SHyper to methimazole treatment or placebo. BMD at distal radius was improved in the active treatment group by the second year of the study. Last, a beneficial effect of methimazole was found on non-invasive indices of cardiac function and on BMD in seven Italian women with SHyper compared with placebo-treated subjects. Overall, these studies provide little evidence to guide practice in individuals with SHyper, and a case by case approach has to be taken. Surveys of UK and North American thyroidologists have shown that many do treat individuals with SHyper, with atrial fibrillation being a strong indication for treatment, but with goitre, reduced BMD and symptoms as additional factors.

**CONCLUSION**

Subclinical thyroid disorders are very common, being more prevalent than diabetes. Despite this, there is no clear consensus of how these disorders should be managed due to conflicting results from various observational studies and a real lack of good randomised treatment studies examining hard endpoints or important outcomes. For SHypo, the available evidence so far suggests that treatment of these disorders should be considered if the TSH abnormality is persistent, if the person is less than 65 years old and has symptoms compatible with hypothyroidism. For SHyper, atrial fibrillation is a strong indicator to treat. In the presence of sinus rhythm, individuals with persistent grade II SHyper, with symptoms, goitre or osteoporosis, should be considered for treatment. Randomised controlled trials of treatment are required to provide good evidence on effects of long-term cardiovascular and mortality outcomes to guide practice.

**Competing interests** None.

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