Screening for Thyroid Disease

A report for the
UK National Screening Committee

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Abbreviations

TFTs	Thyroid Function Tests
TSH	Thyroid Stimulating Hormone
T4	Thyroxine
FT4	Free Thyroxine
TT4	Total T4
T3	Tri-iodothyronine
FT3	Free Tri-iodothyronine
TT3	Total Tri-iodothyronine

Introduction

1. This report reviews screening for thyroid disease against the UK National Screening Committee criteria for appraising the viability, effectiveness and appropriateness of a screening programme (UK National Screening Committee 2003). It is based on a literature search conducted by the National Screening Committee in November 2011 (Coles 2011). Full details of the search strategy are set out in Appendix A.

2. The thyroid gland is responsible for the production of two hormones, thyroxine (T4) and tri-iodothyronine (T3). These thyroid hormones are essential for the normal maturation and metabolism of all tissues in the body. In health these hormones are tightly regulated by the secretion of thyroid stimulating hormone (TSH) from the pituitary gland in the brain. Thyroid hormones are present in the blood in either protein bound forms (the majority) or the free and active (unbound) forms of the hormones. The amount of unbound T3 is referred to as free T3 and unbound T4 as free T4. Currently, the majority of UK laboratories measure the free form of the hormones free T4 (FT4) or free T3 (FT3).

3. Thyroid dysfunction can be divided into hyperthyroidism (over production of thyroid hormones) and hypothyroidism (under production of thyroid hormones). Each of these can be further categorized into overt diagnosed, overt but un-diagnosed, and subclinical disease, yielding a total of six conditions that need to be considered:
   - Overt diagnosed hypothyroidism
   - Overt un-diagnosed hypothyroidism
   - Subclinical hypothyroidism
   - Overt diagnosed hyperthyroidism
   - Overt un-diagnosed hyperthyroidism
   - Subclinical hyperthyroidism

4. Overt thyroid dysfunction is defined biochemically, on the basis of abnormal levels of both TSH and T4 (or T3). A diagnosis of primary hypothyroidism is indicated by a high serum TSH and a low T4. A diagnosis of primary hyperthyroidism is indicated by a low serum TSH and a high T4 or T3 (Warrell et al 2010). Overt un-diagnosed thyroid disease represents a condition found in prevalence studies in which biochemical testing by researchers indentifies individuals who have overt disease, but who had not been previously diagnosed by their doctors.

5. Subclinical thyroid dysfunction is also defined biochemically, on the basis of an abnormal level of TSH in association with normal levels of thyroid hormones (Roberts et al 2006).

6. In 2004, the US Preventive Services Task Force (USPSTF) concluded the evidence is insufficient to recommend for or against routine screening for thyroid disease in adults. The USPSTF found fair evidence that TSH can detect subclinical thyroid disease in people without symptoms of thyroid dysfunction, but poor evidence that treatment improves clinically important outcomes in adults with screen detected thyroid disease (USPSTF 2004).

7. The US Agency for Healthcare Research and Quality (AHRQ) recently evaluated the effectiveness of screening and treatment of subclinical hypothyroidism and hyperthyroidism (Rugge et al 2011). Their report concluded that there were no studies that evaluated the benefits and harms of screening for subclinical thyroid dysfunction in the primary care setting, and that there is a lack of information on the potential harms of treatment.

8. UK Guidelines published jointly by the Association for Clinical Biochemistry (ACB), the British Thyroid Association (BTA) and British Thyroid Foundation (BTF) in 2006 state that screening for thyroid dysfunction in a healthy adult population is not warranted. A joint statement made in March 2011 by the BTA and the BTF states that there has not yet been an appropriately powered prospective, randomised, controlled, double blind interventional trial of either levothyroxine therapy for subclinical hypothyroidism, or antithyroid therapy for subclinical hyperthyroidism, in people identified through a screening programme (BTA/BTF 2011).

9. In 2010 a randomised double-blind cross-over trial investigating the efficacy of treatment for screen-detected adult hypothyroidism was published (Abu-Helalah et al 2010). The authors concluded that 'the results indicate that screening for hypothyroidism would be worthwhile. Approximately 1% of people screened would have a better quality of life. Pilot screening programmes for adult hypothyroidism are justified.' This conclusion was based on data from 15 participants, 11 of whom reported feeling better on thyroxine, with the other four reporting that they felt no better.

10. In January 2011 the BBC (http://www.bbc.co.uk/news/health-12252813) reported the following regarding the Abu-Helalah et al (2010) trial:

> Around 100,000 older people in the UK are missing out on thyroid medicine that could improve their lives, according to a study. The Journal of Medical Screening study examined women over 50 and men over 65 - and found 8% had underactive thyroids. But many were not getting treatment for symptoms, including lethargy and weight gain. Researchers, at the Wolfson Institute, said screening would improve lives.

11. In March 2011 the British Thyroid Association and British Thyroid Foundation (BTA/BTF 2011) released the following joint statement about screening for thyroid disorders in the elderly in response:

> There has been discussion in the media about the value of population screening for thyroid disorders in the elderly. The question of whether healthy adults living in the UK would benefit from screening for thyroid disease is controversial. To be effective, the benefit from a screening programme must outweigh the harm, both physical and psychological, caused by the test, diagnostic procedures and treatment. This was addressed in the UK national guidelines on testing thyroid function published in 2006
> .... In subclinical hypothyroidism, there is still debate as to what constitutes a normal Thyroid Stimulating Hormone (TSH) level, particularly in older people, since the reference range probably rises with healthy ageing. Although some people will progress to have overt hypothyroidism, recent study results suggest that a significant proportion of people with mild thyroid dysfunction revert to normal without treatment. Recent meta-analyses [*Rodondi et al 2010*] have suggested that there is an increased risk of heart problems in younger adults and in those with a TSH level above10mlU/L in their blood, but not in those with evidence of milder thyroid failure and a TSH level below 5mlU/L.

> If a patient has been identified through a screening programme and does not have symptoms, then it is reasonable to be cautious before recommending levothyroxine therapy, especially in those with only a slightly raised TSH level. People identified by positive screening tests do not always take their tablets regularly, particularly if their symptoms do not change or if they suffer from side effects. Treatment does appear to be justified in those who are symptomatic, pregnant or wishing to have children, aged 65 years or older, or who have evidence of heart failure [*Vanderpump 2010*]. However, for the vast majority of patients, adopting a 'wait and see' policy rather than intervention may avoid unnecessary treatment or the potential for harm.

12. These differences of opinion between the British Thyroid Association and British Thyroid Foundation and researchers at the Wolfson Institute (Abu-Helalah et al 2010) set the context within which this review has been prepared.

The Condition

The condition should be an important health problem

Overt hypothyroidism

13. In overt hypothyroidism the TSH level is raised and the circulating T4 is below the reference range. Clinical symptoms such as fatigue, weight gain, dry skin, lethargy, memory impairment and tiredness are likely to be present. In elderly populations symptoms such as memory disturbance, impaired mental state and depression may be seen. The United Kingdom has a reported annual incidence of primary hypothyroidism of 3.5 per 1,000 women and 0.6 per 1,000 men (Vaidya & Pearce 2008). The prevalence of hypothyroidism is reported to be about 20 per 1,000 across both sexes, and is 10 times more common in women (Vanderpump 2011). The major causes of primary hypothyroidism include auto immune destruction of the thyroid gland (Hashimoto's disease), radio-iodine treatment or surgical treatment of hyperthyroid disease, and iodine deficiency (the latter is less common in the Western World). Transient hypothyroidism may also be caused by medications such as lithium carbonate.

14. Overt un-diagnosed hypothyroidism represents a condition found in prevalence studies in which biochemical testing by researchers indentifies individuals who have overt disease, but these individuals had not been previously diagnosed by their doctors. Hypothyroidism often develops gradually, so the subtle and non-specific symptoms and signs may be mistakenly attributed to other illnesses.

15. A population-based study of 5,860 subjects in Birmingham, England aged 65 or over (excluding those with previous hyperthyroidism or those being treated for thyroid disease) found 0.4% had undiagnosed overt hypothyroidism (Wilson et al 2006).[1] We identified no studies of the natural history of undiagnosed overt hypothyroidism.

Subclinical hypothyroidism

16. Subclinical hypothyroidism is defined as a condition where the TSH is raised in the presence of a normal T4 (Vanderpump 2011).The prevalence of subclinical thyroid dysfunction has been evaluated in a number of studies. In the Birmingham population-based study 2.9% had subclinical hypothyroidism (Wilson et al 2006).

Overt hyperthyroidism

17. Overt hyperthyroidism is defined by a TSH below the reference range and an elevated T4. Clinical signs and symptoms such as fatigue, heat intolerance, sweating, palpitations and weight loss are likely to be present. Elderly patients may present with heart problems such as atrial fibrillation. The prevalence of overt hyperthyroidism in women is between 0.5 and

[1] All the prevalence figures obtained by Wilson et al (2006) are subject to the limitation that the 5,860 subjects studied were obtained from an eligible study population of nearly 16,000. The participation rate of well under 50% means that those studied may not be representative of the general population, and the true prevalence rates could be substantially higher or lower than the reported rates.

2% and it is ten times more common in women than in men in iodine replete communities (Vanderpump 2011).The major causes of primary hyperthyroidism include auto-immune Graves' disease, toxic multi-nodular goiter, excessive thyroxine treatment, thyroid adenoma and thyroiditis.

18. Overt un-diagnosed hyperthyroidism represents a condition found in prevalence studies in which biochemical testing by researchers indentifies individuals who have overt disease, but who had not been previously diagnosed by their doctors. In the Birmingham population-based study 0.3% of the population over 65 had undiagnosed overt hyperthyroidism (Wilson et al 2006). We identified no studies of the natural history of undiagnosed overt hyperthyroidism.

Subclinical hyperthyroidism

19. Subclinical hyperthyroidism is defined as a low serum TSH concentration and normal serum T3 and T4 concentrations in the absence of hypothalamic or pituitary disease, non-thyroidal illness or ingestion of drugs that inhibit TSH secretion (Vanderpump 2011). In the Birmingham population-based study 2.1% of the population over 65 had subclinical hyperthyroidism (Wilson et al 2006).

Table 1: Biochemical Classification and Prevalence of Thyroid Dysfunction

Condition	TSH level	Thyroid hormone levels	Prevalence (65 yrs +)
Overt Hypothyroidism	>4.5 mIU/L (elevated)	Low FT4	0.4% (undiagnosed)
Subclinical Hypothyroidism	> 10 mIU/L (markedly elevated)	Normal FT4	0.3%[2]
	4.5 - 10 mIU/L (mildly elevated)		2.6%
Overt Hyperthyroidism	<0.1 mIU/L or undetectable (low)	Elevated FT4 or FT3	0.3% (undiagnosed)
Subclinical Hyperthyroidism	< 0.1 mIU/L (clearly low)	Normal FT4 and FT3	0.4%
	0.1 - 0.4 mIU/L (low but detectable)		1.7%

Adapted from Rugge (2011) and Wilson et al (2006).

[2] Wilson et al (2006) found a 2.9% prevalence of subclinical hypothyroidism. They did not report the split between mildly and markedly elevated TSH, but the inter-quartile range for this group was 6.0-8.8 mIU/L. We have used this to estimate that approximately one tenth of the 2.9% had TSH > 10 mIU/L.

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Overt hypothyroidism

20. Overt hypothyroidism has been associated with a number of harmful effects including worsening of risk factors for coronary heart disease (CHD) such as dyslipidaemia and hypertension (McQuade et al 2011), low bone mineral density (Lee et al 2011) and cognitive decline (Hogervorst et al 2008). In cases where overt hypothyroidism is left un-treated then a life threatening myxoedema coma can develop (Rugge 2011).

21. We identified no studies of the effects of undiagnosed overt hypothyroidism. It therefore remains an assumption that the undiagnosed overt hypothyroidism has consequences similar to those of clinically diagnosed overt hypothyroidism.

Subclinical hypothyroidism

22. Spontaneous recovery has been described in subjects with subclinical hypothyroidism, although the frequency is not clear (Vanderpump 2011). Robust evidence regarding the natural history of screen-detected subclinical hypothyroidism should ideally be obtained from follow-up of individuals identified through population-based screening, in which an initial raised TSH level is confirmed by a second test a few weeks later (to exclude people with only a transiently raised TSH). The literature search for this review found no studies that meet these criteria. None of the identified population-based screening studies repeated the initial TSH measurement to exclude those who have only a transiently raised TSH (Table 2); and none of the studies that confirmed the initial raised TSH level identified their subjects through population-based screening (Table 3). Of the studies that repeated the initial TSH test, Diez & Iglesias (2004) comes closest to population-based screening, because none of the subjects had a known history of previous thyroid disease and they were not defined by having symptoms of thyroid disease. This study found that, among 117 patients aged over 55 years and followed up for between 6 and 32 months, 37% showed normalization of their TSH levels, while 27% showed progression to overt disease. Progression was more likely in the presence of symptoms, goitre and anti-thyroid auto antibodies. The substantial proportion that showed normalization of their TSH levels raises the possibility that many people with screen-detected subclinical hypothyroidism might return to normal without treatment.

23. Potential consequences of subclinical hypothyroidism include cardiac dysfunction, cardiovascular mortality, elevated cholesterol and neuropsychiatric disorders (Surks et al 2004), but the strength of evidence for these associations is variable.

Table 2: Studies of the natural history of subclinical hypothyroidism in cohorts derived from population-based screening

Source of sample	Age at start of follow-up (years)	Criteria for defining baseline TSH as raised	Mean duration of follow-up (months)	Thyroid antibodies present?	Sample size	Number (%) that returned to normal TSH	Number (%) that progressed to overt hypothyroidism	Comments	Reference
Screening via GP lists in Wickham, UK	49 (mean)	Single TSH > 6 mU/1	48	No	36	50% (approx., see comment)	0 (0)	• Mean TSH levels tended to return to normal over four years (mean TSH after 4 yrs = 5.1 mU/l). The range of initial TSH levels in this group was 6 to 10 mU/l and rose above this subsequently in only one subject.	Tunbridge (1981)
				Yes	40	1 (3)	10 (25)	• The range of initial TSH levels in this group was 6-24 mU/l; the level fell in only one subject, in whom it had initially been about 6 mU/l.	
			240	No	<36	Not stated	15% if baseline TSH = 5 mU/l; 36% if baseline TSH = 9 mU/l	• 20-year risk of developing overt hypothyroidism rises in proportion to initial TSH level and initial age, and is higher if thyroid antibodies are present. Risks stated here are for women with initial age of 55 yrs.	Vanderpump (1995)
				Yes	<40	Not stated	52% if baseline TSH = 5 mU/l; 77% if baseline TSH = 9 mU/l		
Population-based screening of women in Gothenburg, Sweden	51-73	Single TSH 4.0-15 mU/1, and TSH increased by > 30 mU/l when given thyroliberin	6-12	No	9	3 (33)	Not stated	• The natural history data are from the 6-12 month period between recruitment and the start of this cross-over RCT. • The 3 women who returned to normal TSH all had high titres of anti-microsomal antibodies.	Nystrom (1988)
				Yes	8	0 (0)	Not stated		
Screening via one GP list in Birmingham, UK	60+	Single TSH > 5 mU/1	12	No	32	3 (10)	3 (10)	• All subjects who returned to normal TSH had initial TSH < 10 mU/l. • Subjects who had anti-thyroid antibodies were more likely to progress to overt hypothyroidism.	Parle (1991)
				Yes	41	1 (2)	10 (25)		
Population-based screening in Australia	69 (mean)	Single TSH > 4 mU/1	60	Yes	35	Not stated	7 (20)		Gopinath (2010)

Table 3: Studies of the natural history of subclinical hypothyroidism in cohorts NOT derived from population-based screening

Source of sample	Age (years)	Criteria for defining baseline TSH as raised	Mean follow-up (months)	Sample size	Number (%) that returned to normal TSH	Number (%) that progressed to overt hypothyroidism	Comments	Reference
Selected hospital patients with symptomless autoimmune thyroiditis, defined as: • Raised level of thyroglobulin antibodies **or** • Raised level of thyroid microsomal antibodies **or** • Evidence of thyroiditis on fine needle biopsy	14-61	Single TSH > 5.0 mU/1	62	11	5 (45)	6 (55)	• All those who returned to normal TSH had initial TSH < 10mU/l • 5/6 who progressed to overt hypothyroidism had initial TSH > 10mU/l	Gordin (1981)
Women who had been treated for hyperthyroidism at Massachusetts General Hospital.	32-71	Single TSH > 3.5 mU/1	12	16	0 (0)	0 (0)	• The natural history data are from the placebo arm of this RCT.	Cooper (1984)
Unclear, but not representative of a screen-detected sample because only 5 of the 30 subjects lacked a clinical reason for checking TSH levels: • 11 had neck surgery or neck radiotherapy • 9 had previous treatment with radioiodine or surgery for hyperthyroidism • 4 had Hashimoto's thyroiditis • 1 had long-term lithium therapy	25-79	TSH > 5 mU/1 on 3 occasions, and TSH increased by > 25 mU/l when given thyroliberin	98	30	0 (0)	16 (53)	• 14 (47%) showed persistently raised TSH but maintained normal levels of T4 and T3.	Kabadi (1993)
Unclear, but most had symptoms consistent with hypothyroidism, so they may not be representative of a screen-detected sample.	55+	TSH > 6 mU/1 on 2 occasions, ≥ 1 month apart	10	19	*8* *(42)*	0 (0)	• The natural history data are from the placebo arm of this RCT. • In 8 of 19 patients TSH fell within the normal range on at least one visit during follow-up	Jaeschke (1996)
All subjects had presented to their GP with thyroid-related symptoms.	45 (mean)	Single TSH 5-10 mU/1	6	15	4 (27)	Not stated	• . The natural history data are from the placebo arm of this RCT.	Kong (2002)
Most subjects had underlying thyroid disorders: • 42 had Graves' disease (32 treated with radioiodine and 10 with surgery) • 29 had autoimmune thyroiditis (2 had surgery and 27 were untreated) • 11 had nontoxic goitre (all had surgery)	51 (mean)	TSH 4-6 mU/1 on 2 occasions	110	21	3 (14)	0 (0)	• The figures for progression to overt hypothyroidism are estimates from Kaplan-Meier curves.	Huber (2002)
		TSH >6-12 mU/1 on 2 occasions		36	0 (0)	(43)		
		TSH >12 mU/1 on 2 occasions		25	0 (0)	(77)		
None of the subjects had a known history of previous thyroid disease, but they had all been referred to an endocrine clinic after an incidental raised TSH was found by a hospital specialist (46%) or a GP (54%).	55-83	TSH > 5 mU/1 on 2 occasions, 1-3 months apart	32	107	40 (37)	28 (27)	• Among those with initial TSH of 5-10mU/l, 52% returned to normal TSH levels.	Diez and Iglesias (2004)

24. In 2004 a panel sponsored by three professional thyroid groups reviewed data regarding the natural history of subclinical thyroid disease, and the benefits and harms of treating it. The results are summarised in table 4.

25. Subsequent to this 2004 review, the AHRQ review (Rugge et al 2011) found four meta-analyses evaluating the association between subclinical thyroid disorder and cardiac and all cause mortality. It found that these meta-analyses produced mixed results and that overall the epidemiological studies included had serious limitations. For example, many studies included individuals who had known thyroid disease, ischaemic heart disease or TSH levels within the reference range; many included subjects who underwent treatment with levothyroxine during the follow-up period; and most studies did not adequately control for potential confounders, such as lipid levels and blood pressure (Rugge et al 2011).

26. Two further cohort studies were also included in the AHRQ review. The prospective cohort Cardiovascular Health Study found no relationship between an elevated TSH and cardiovascular outcomes among 3,233 individuals aged over 65 and older and followed for an average of 12.5 years (Cappola et al 2006). The second study reviewed previous data from an original cohort study conducted between 1972 and 1974 involving 2,779 adults in Wickham, England (Vanderpump et al 1996). This found that subclinical hypothyroidism was associated with a higher risk of CHD events over 20 years. However, this study concerns events that pre-date the introduction of statins, and the AHRQ review concluded that it was possible that the association between subclinical hypothyroidism and subsequent cardiovascular outcomes would become negligible in the context of current management of raised cholesterol (Rugge et al 2011).

Table 4: Evidence for the association of subclinical hypothyroidism (TSH 4.5-10 mIU/L) and adverse health outcomes and quality of evidence for risks and benefits of treatment: Findings of the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society Panel (2004)

Complication	Strength of evidence for association with complications	Strength of evidence regarding benefits and harms of treatment
Progression to overt hypothyroidism	Good[a]	Not applicable
Adverse cardiac end points	Insufficient[b]	No evidence
Elevation in serum cholesterol and LDL-C levels	Insufficient[c]	Insufficient
Cardiac dysfunction	Insufficient[c]	Insufficient
Symptoms of hypothyroidism	No evidence	Insufficient
Psychiatric symptoms	No evidence	Insufficient

Source: Rugge et al (2011)

[a]Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes

[b]Insufficient: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

[c]Data did not distinguish between serum TSH concentrations between 4.5-10mIU/L and >10mIU/L.

27. The AHRQ review also identified a subsequent analysis of the Cardiovascular Health Study (Rodondi et al 2008) and an analysis of the Health, Aging and Body Composition Study cohort (n=2,730) (Rodondi et al 2005) which indicated that an isolated raised TSH might be a risk factor for the development of congestive heart failure (CHF), particularly for those

with a TSH >10 mIU/L. The AHRQ review concluded that this association requires further study and that it is unknown whether thyroid replacement therapy would modify this risk (Rugge et al 2011).

28. A further meta-analysis, published after the AHRQ review concluded that subclinical hypothyroidism is associated with an increased risk of CHD events and CHD mortality in those with higher TSH levels, particularly in those with a TSH concentration of10 mIU/L or greater (Rodondi et al 2010). This meta-analysis was based on individual participant data extracted from other studies in order to evaluate the risk of subclinical hypothyroidism on CHD outcomes. It aimed to overcome some of the problems with confounding variables in previous studies.

29. A recent retrospective cohort study (n=6,048) examined the association between subclinical hypothyroidism and mortality (McQuade et al 2011). The authors concluded that overt hypothyroidism and moderate (TSH 6.1 – 10), but not mild (TSH 3.1 -6.0), subclinical hypothyroidism are associated with increased CHD mortality and all cause mortality. However, members of the study cohort had all been referred to a preventative cardiology service in the USA because of known CHD, strong family history of CHD or difficulty managing one or more CHD risk factors. The results may therefore not be applicable to the general population.

30. Other studies have postulated a link between subclinical hypothyroidism and cognitive decline. One cross sectional study (Roberts et al 2006) found that, after controlling for confounding effects, subclinical thyroid dysfunction was not associated with depression, anxiety or cognition.

Overt hyperthyroidism

31. Overt hyperthyroidism causes symptoms that reduce functional status and reduce quality of life. The consequences of untreated hyperthyroidism include atrial fibrillation, congestive cardiac failure, osteoporosis and neuropsychiatric disorders (Vanderpump 2011b). Atrial fibrillation is an independent risk factor for cardiovascular events and stroke (Gammage et al 2007).

32. We identified no studies of undiagnosed overt hyperthyroidism. It therefore remains an assumption that the undiagnosed overt hyperthyroidism has consequences similar to those of clinically diagnosed overt hyperthyroidism.

Subclinical hyperthyroidism

33. The natural history of subclinical hyperthyroidism has been studied less frequently than that of hypothyroidism, so less is known about it. The AHRQ review indentified that cross-sectional studies have shown that untreated subclinical hyperthyroidism is associated with tachycardia, increased left ventricular mass leading to diastolic dysfunction, atrial arrhythmias and a decline in bone mass density. However, cross-sectional studies are not able to establish cause and effect. The only association that has been demonstrated in longitudinal studies, which are better able to establish cause and effect, is between subclinical hyperthyroidism and atrial fibrillation (Rugge et al 2011).

34. Among people with subclinical hyperthyroidism, spontaneous reversion to normality appears to be much more common than progression to overt hyperthyroidism. A retrospective cohort study of 2,024 Scottish adults with subclinical hyperthyroidism found that 36% reverted to normal during a median follow up period of 51 months, while only 6% progressed to overt hyperthyroidism (Vadiveloo et al 2011).

35. A prospective community-based study in Australian found that out of four individuals over 55 years with subclinical hypothyroidism at baseline, two (50%) progressed to overt disease and one (25%) reverted to normality after 5 years (Gopinath et al 2010).These numbers are too small to allow any useful conclusions.

All the cost-effective primary prevention interventions should have been implemented as far as practicable

36. Iodine is essential for the production of thyroid hormones (FSA 2008). The UK has previously been considered to be iodine sufficient by the International Council for Control of Iodine Deficiency Disorders. However, recent research assessing the median urinary iodine excretion in 664 14-15 year old girls throughout the UK indicated mild iodine deficiency in the UK (Vanderpump et al 2011).

37. Vanderpump et al (2011) suggest that this iodine deficiency is related to a fall in milk consumption, as milk contributes 41% of the total iodine intake in the UK through the supplementation of animal feed with iodine (FSA 2008).

38. Some European Countries (e.g. Switzerland) and the USA have national salt iodisation programmes, but this has never been the case in the UK. Vanderpump et al (2011) therefore call for a comprehensive investigation of UK iodine status and evidence-based recommendations on the need to implement a policy of iodine prophylaxis.

If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

39. Not applicable for thyroid disease

The Test

There should be a simple, safe, precise and validated screening test. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

40. Current guidelines jointly produced by the British Thyroid Association, British Thyroid Foundation and the Association for Clinical Biochemistry (ACB/BTA/BTF 2006) state that the measurement of TSH in a blood sample by a sensitive immunometric assay provides the single most sensitive, specific and reliable test of thyroid status in both overt and subclinical primary thyroid disorders. However, the 2006 guidelines also note that the use of TSH as a solitary first line test will fail to indentify some patients with thyroid disorders. They note that measurement of TSH with free T4 (FT4) should allow detection of almost all causes of thyroid dysfunction, as long as the results of both the tests are correctly interpreted (ACB/BTA/BTF 2006).

41. The BTF guidelines (2006) give the following as typical serum reference ranges:

Table 5: Serum reference ranges

TSH	0.4-4.5 mIU/L		
FT4	9.0-25 pmol/L	**TT4**	60-160 nmol/L
FT3	3.5 – 7.8 nmol/L	**TT3**	1.2 – 2.6 nmol/L

42. Reference ranges for TFTs are derived from a reference population that comprises a large group of healthy subjects who do not have thyroid disease. Conventionally, a reference range includes 95% of a reference population. Therefore 2.5% of 'normal' individuals will fall above the reference range and 2.5% will fall below the range (ACB/BTA/BTF 2006).

43. Considerable variation exists in published studies between the levels of thyroid hormones that are considered to be abnormal. A review of cohort studies evaluating subclinical thyroid dysfunction and mortality (Haentjens et al 2008) showed variation in the cut off levels used to define subclinical thyroid disease. The TSH cut off levels for subclinical hypothyroidism varied between >4.0mIU/L and >5.10mIU/L. For subclinical hyperthyroidism, the TSH cut off varied between <0.3mIU/L and <0.5mIU/L. These variations mean that a test undertaken in one laboratory may indicate the presence of disease, while the same result may be considered normal in a different setting.

44. The secretion of TSH is pulsatile. Low levels of serum TSH are found during the daytime with a characteristic rise at night of up to 100%, peaking after midnight. These fluctuations contribute to the width of the reference range (Anderson et al 2003). The concentrations of FT4 and FT3 in blood change little during a single day but, like TSH, they do change throughout the year. These natural fluctuations have the potential to affect whether an individual is categorized as having abnormal TFTs (Anderson et al 2003). Abu-Helalah et al (2010) reported that the within-person standard deviation of serum TSH when not taking thyroxine was 1.7mU/L meaning that a single measurement could lead to people whose TSH level is not usually high being selected as having a high TSH.

45. A study carried out to evaluate the effect of age on TSH found that TSH distribution progressively shifts toward higher concentrations with age. The authors concluded that the prevalence of subclinical hypothyroidism may be significantly overestimated unless an age-specific range for TSH is used (Surks & Hollowell 2007). A recent statement jointly published by the BTA and the BTF (BTA/BTF 2011) stated that in subclinical hypothyroidism there is still debate as to what constitutes a normal TSH level, particularly in older people, since the reference range probably rises with healthy ageing.

Performance of TSH as a screening test for overt thyroid disease

46. A UK guideline states that, in unselected populations, measurement of serum TSH has a sensitivity of 89% to 95% and specificity of 90% to 96% for overt thyroid dysfunction, as compared to cases confirmed by history, examination and additional testing (ACB/BTA/BTF 2006). However, the study from which these figures are derived (de los Santos et al 1989) is likely to have exaggerated the performance of serum TSH in population-based screening. The ideal sample for a study of screening test accuracy is a consecutive or randomly selected series of individuals from the target screening population (Centre for Reviews and Dissemination 2009:113). The study population in de los Santos et al (1989) comprised two distinct groups of subjects rather than a consecutive or randomly selected series of individuals from the target screening population. There were 'study subjects', who were all patients being seen in a hospital clinic, regardless of their apparent clinical thyroid status; and 'controls', who were normal subjects recruited from various sources. Out of a total study population of 544 individuals, 27 (5.0%) had untreated overt hyperthyroidism and 23 (4.2%) had untreated overt hypothyroidism. Their study population therefore had a prevalence of untreated overt thyroid disease about ten times greater than would likely be found in a UK screening programme (see Table 1 above). This selective inclusion of cases with thyroid disease approximates to a 'two-gate' study design, which is likely to lead to over estimation of test sensitivity (see Centre for Reviews and Dissemination 2009:119 for further details).

Performance of TSH as a screening test for subclinical thyroid disease

47. The literature search for the current report did not identify any published data that explicitly define the performance characteristics of TSH as a whole population screening test for subclinical thyroid disease. However, Abu-Helalah et al (2010) argue that a symptomatic response to thyroxine is a necessary diagnostic criterion of hypothyroidism, and if their argument is accepted their data can be used to estimate the sensitivity, specificity and predictive values of various TSH cut-off values when used for population-based screening for subclinical hypothyroidism. For this purpose:

    - true positives are defined as people who BOTH have a TSH measurement that could indicate hypothyroidism AND who feel better when taking thyroxine

    - true negatives are defined as people who EITHER have entirely normal TSH measurements OR have a TSH measurement that could indicate hypothyroidism but do not feel better when taking thyroxine.

On this basis the sensitivity, specificity and predictive values of population-based screening for subclinical hypothyroidism can be estimated (see Table 6) for the various TSH cut-off values used by Abu-Helalah et al (2010):

Table 6: Sensitivity, specificity, positive predictive value and negative predictive values calculated using the results from Abu-Helalah et al (2010)

Cut-off level	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Using one TSH measurement only:				
>4.5 mU/L	100%	95%	38%	100%
>5.0 mU/L	81%	97%	44%	99%
>5.5 mU/L	57%	98%	41%	99%
>6.0 mU/L	52%	98%	42%	99%
Using two TSH measurements, initial >4.0 mU/L and repeat:				
>4.0 mU/L	57%	98%	52%	99%
>4.5 mU/L	52%	99%	73%	99%

48. In their discussion section Abu-Helalah et al (2010) favour screening using an initial cut-off of TSH >4.0 mU/L and repeat TSH cut-off using a of >4.5 mU/L. This approach would result in an estimated sensitivity of 52% and positive predictive value of 73%, and an estimated specificity and negative predictive value of 99%.

49. We found no study that describes the performance of TSH or any other test in population-based screening for subclinical hyperthyroidism.

The test should be acceptable to the population

50. No studies identified by the literature search directly assessed the acceptability of the test. Taking venous blood for population-based screening is accepted by women as part of routine antenatal care, but no other population-based screening programme in the UK involves taking venous blood samples.

51. A cross sectional study inviting patients from 20 general practices in central England found that only 14.6% of patients aged over 85 years agreed to take part in the study (Roberts 2006).

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

52. British guidelines (ACB/BTA/BTF 2006) give the following recommendations for the further investigation of individuals with an abnormal TSH level on initial testing:

- Subclinical hypothyroidism should be confirmed by repeat thyroid function testing 3-6 months after the original result
- The measurement of thyroid antibodies in subjects with subclinical hypothyroidism helps to define the risk of developing overt hypothyroidism

- The finding of a low serum TSH should prompt consideration of the cause. If non-thyroidal illness and relevant drug therapies have been excluded then repeat measurement of TSH (with serum FT4 and FT3) should be performed, to exclude progression to overt hyperthyroidism and to determine if the biochemical abnormality is persistent. The timing of repeat assessment should be based on the clinical picture; more frequent testing may be appropriate if the subject is elderly or has underlying vascular disease, otherwise repeat biochemical testing after 3-6 months may be appropriate.

If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out

53. Not applicable to thyroid disease

The Treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

Overt Hypothyroidism

54. Treatment of overt hypothyroidism requires the use of levothyroxine (British National Formulary 2011). The goal of treatment is to restore and maintain serum TSH within the reference range (ACB/BTA/BTF 2006). Prolonged periods of over treatment with thyroxine can lead to symptoms of hyperthyroidism with associated features of atrial fibrillation and osteoporosis.

Subclinical Hypothyroidism

55. A Cochrane review of RCTs of levothyroxine replacement therapy for the treatment of subclinical hypothyroidism (Villar et al 2007) indentified 11 RCTs evaluating levothyroxine against placebo and one comparing levothyroxine with no treatment. The duration of these trials varied from six to 14 months and involved a total of 350 participants.

56. Seven RCTs evaluated symptoms, mood and quality of life and did not demonstrate any statistically significant differences between groups, though one study showed a statistically significant improvement in cognitive function with levothyroxine. None of the RCTs assessed cardiovascular mortality or morbidity. Six studies assessed serum lipids and they found no statistically significant difference in total cholesterol levels, however there was a trend towards a reduction in some parameters following treatment with levothyroxine. Nine studies assessed impact on TSH levels and found statistically significant reductions in TSH levels with levothyroxine, however there was considerable heterogeneity between trials (Villar et al 2007).

57. The Rugge et al (2011) review assessed whether treating patients with subclinical hypothyroidism detected by screening affects outcomes. The authors stated that six RCTs of treatment for subclinical hypothyroidism were published between 2002 and 2010, with the largest involving 120 patients and none of which followed patients for more than one year. Two of the six RCTs were also included in the Cochrane review (Villar et al 2007).

58. Four RCTs evaluated the effect of treatment on lipids with two showing modest reductions in total cholesterol and low density lipoprotein and two showing no improvement for any lipoproteins. There was no evidence of benefit in two studies measuring well-being, two measuring blood pressure and four examining changes in weight and body mass index (BMI) (Rugge et al 2011). The summary table on the evidence for subclinical hypothyroidism produced by Rugge et al (2011) is re-produced in appendix B.

59. We identified two further RCTs published since the Villar and Rugge reviews (Parle et al 2010, Abu-Helalah et al 2010).

60. Parle et al (2010) conducted a double-blind RCT comparing the effect of thyroxine or placebo on cognitive function in 94 patients aged ≤65 years who had been identified as having subclinical hypothyroidism over a two-year period of recruitment into a community-based prevalence study. Participants received either placebo or sufficient thyroxine to achieve and maintain a TSH level within the reference range (0.4 – 5.5 mU/L) over 12 months. There were no statistically significant differences between the groups on any of the measures of cognitive function used. This result remained non-significant when adjusted for depression and smoking status and for a sub-group analysis of participants who had achieved euthyroidism for at least six months at the time of the cognitive assessment.

61. Abu-Helalah et al (2010) conducted a randomised double-blind cross-over trial on the efficacy of thyroxine treatment for adults with screen-detected sub-clinical hypothyroidism. The primary outcome measure was the number of participants who felt better on thyroxine, felt no different, or felt better on placebo. The results were analyzed with patients grouped according to various cut-off TSH values that could potentially be used to define eligibility for treatment, using either a single TSH measurement, or two TSH measurements about seven weeks apart.

62. The 56 cross-over RCT participants (49 women and 7 men) were identified from 341 healthy people who were found to have a TSH level above 4.0mU/L on attending a general health assessment offered by BUPA. Participants were aged 50-79 years (women), 65-79 years (men) or 35-49 years (women with a family history of thyroid disease). Participants were randomised into two groups, with the first group taking thyroxine for four months followed by placebo for four months and the second group placebo for four months followed by thyroxine for four months. Participants were monitored monthly, with the thyroxine dose increased up to 100µg if necessary to achieve a target TSH range of between 0.6 and 2.0mU/L. Before blinding was broken participants were asked to report whether they felt better during the first four-month period, better during the second four-month period or no better (the primary outcomes).

63. The odds of feeling better on thyroxine rather than on placebo were greatest when the cut-off used to define eligibility for treatment was an initial TSH >4.0 followed by a repeat TSH >4.5mU/L (11/15 participants felt better on thyroxine, Table 7).

64. Secondary outcomes were based on:

- Data from a questionnaire asking whether they felt better with respect to 14 common symptoms associated with hypothyroidism during one four-month period compared with the other
- The SF-36 questionnaire data on quality of life completed after each of the four-month periods
- General Health Questionnaire (GHQ-30) data
- Examination findings in respect of physical signs of hypothyroidism blood pressure, pulse rate and body weight.
- Zulewski scores (which is based on seven symptoms and five clinical signs of hypothyroidism)
- Billewicz index scores (which is another index of the clinical features of hypothyroidism).

65. With one exception, none of these secondary outcomes measures showed any significant difference between the end of the placebo period and the end of the thyroxine period. The one exception was that the 11 participants who had a repeat TSH measurement of >4.5mU/L and felt better on thyroxine showed a significant improvement in the Zulewski score on thyroxine compared to placebo (0.3 vs. 2.4, P=0.002). This suggests that their sense of feeling better on thyroxine (the primary outcome) is attributable to an improvement in their thyroid status.

66. The authors concluded that screening for hypothyroidism would be worthwhile but acknowledge that this was based on a small number of participants (11 of 15 who reported feeling better on thyroxine, with the other four reporting feeling no better).

Table 7: Results from Abu-Helalah et al (2010)

	Percent of population	Numbers feeling:			Odds of feeling better on thyroxine than placebo
		Better on thyroxine	No different	Better on placebo	
Using one TSH measurement only:					
>4.0 mU/L	8%	21 (38%)	19 (34%)	16 (29%)	1.3 (21/16)
>4.5 mU/L	6%	17 (44%)	15 (38%)	7 (18%)	2.4 (17/7)
>5.0 mU/L	4%	12 (41%)	12 (41%)	5 (17%)	2.4 (12/5)
>5.5 mU/L	3%	11 (42%)	11 (42%)	4 (15%)	2.8 (11/4)
>6.0 mU/L	2%	8 (50%)	6 (38%)	2 (13%)	4.0 (8/2)
Using two TSH measurements, initial >4.0 mU/L and repeat:					
>4.0 mU/L	3%	12 (52%)	8 (35%)	3 (13%)	4.0 (12/3) (p=0.04)
>4.5 mU/L	2%	11 (73%)	4 (27%)	0 (0%)	∞ (11/0) (p=0.001)

67. As table 7 demonstrates, the proportion of patients feeling better on thyroxine was around 40% for a cut off level on one measurement of between >4.0mU/L and >5.5mU/L, reaching 50% or better with a cut-off TSH level using one measurement of >6.0mU/L or when TSH level was >4.0mU/L at two measurements taken about seven weeks apart.

68. The performance of these TSH cut-off levels for identifying people who benefit from thyroxine treatment needs to be confirmed in an hypothesis-testing study in a different group of patients.

Overt Hyperthyroidism

69. Options for the treatment for overt hyperthyroidism include the anti-thyroid drug carbimazole, radio-iodine, and surgical removal of part of the thyroid gland. One of the main risks of treatment for overt hyperthyroidism is the development of hypothyroidism (ACB/BTA/BTF 2006).

Subclinical Hyperthyroidism

70. The AHRQ review (Rugge et al 2011) found one RCT (n=20) and one controlled trial (n=14) assessing the efficacy of treatment of subclinical hyperthyroidism. Change in blood pressure was assessed by both trials; BMI, patient-reported fatigue, nervousness, sweating, lipids, bone mineral density and change in appetite and tremors were assessed by one trial. Evidence of efficacy was inconsistent. The summary table on the evidence for subclinical hyperthyroidism produced by Rugge et al (2011) is re-produced in appendix B.

71. A second review (Vanderpump 2011b) concluded that there are no appropriately powered prospective randomised, controlled, double blind interventional trials of anti-thyroid therapy for subclinical hyperthyroidism.

There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

72. Current UK guidelines (ACB/BTA/BTF 2006) describe established treatments for overt thyroid disease, and make the following recommendations regarding subclinical disease:
    - In sub-clinical hypothyroidism with serum TSH >10mU/L, treatment with thyroxine is recommended.
    - In sub-clinical hypothyroidism with serum TSH <10mU/L, thyroxine therapy is not recommended as a routine therapy. However, thyroxine may be indicated in non-pregnant patients with goitre, and in patients who are seeking pregnancy.
    - Persistent subclinical hyperthyroidism should prompt referral to a specialist, who may seek evidence of underlying thyroid disease and consider treatment with radioiodine or thionamides.

The Screening Programme

There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity

73. Neither our search nor the AHRQ review (Rugge et al 2011) identified any RCTs of a screening programme for subclinical thyroid disease in the general population.

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

74. The participants in the Abu-Helalah (2010) RCT were all UK residents who had attended a general health assessment at one of five BUPA wellness centres. Of the 110 who were judged eligible for the trial, 64 agreed to take part and 56 completed the trial. The reasons provided for the eight participants who did not complete the trial included loss of interest (5) and headache (3).

The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

75. Villar et al (2007) reported that adverse effects were inadequately addressed in most of the RCTs included in their Cochrane review. Rugge et al (2011) concluded that there was a lack of any formal data on the harms of treatment and that further research is needed to determine if treating subclinical thyroid dysfunction is beneficial or harmful.

The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money).

76. This review did not identify any studies on the cost-effectiveness of screening for thyroid disease.

All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

77. The literature search for this review did not identify any studies relevant to this criterion, but 2010/11 QOF data show that for England as a whole 95.9% of patients with hypothyroidism had received a thyroid function test within the previous 15 months. QOF does not measure the proportion of these patients who are receiving the correct dose of thyroxine.

Implications for policy

It is not appropriate to start a screening programme for thyroid disease because:

- There is a lack of consensus about the TSH cut-off value or values for defining which patients should receive treatment, and what constitutes a normal TSH level is still a matter of debate (British Thyroid Association and the British Thyroid Foundation 2011).
- Two systematic reviews on RCTs on treatment of subclinical thyroid disease have concluded that there is insufficient evidence of benefit and that the potential adverse effects from treatment have not been adequately studied.
- It is unclear what proportion of people with screen-detected subclinical hypothyroidism would revert to normal without treatment, but it could be a substantial minority.
- The apparent short-term (four month) benefits of treating screen-detected subclinical hypothyroidism that were demonstrated in 15 subjects by Abu-Helalah et al (2010) need to be confirmed in a larger study with longer follow-up.
- There have been no RCTs of screening for thyroid disease.

Based on data from studies that have been conducted in diverse populations and that have used slightly different cut-offs to define disease categories, the balance between the benefits of detection and treatment and the harms caused by detection of abnormalities for which management in uncertain appears to be finely balanced. For example, if a UK population of 10,000 people aged 65 years and over were screened for thyroid disease using serum TSH measurement, the following consequences might be expected:

- Approximately 100 individuals would be found to have a form of thyroid disease for which there is an agreed, evidence based treatment. This group would comprise 40 people with undiagnosed overt hypothyroidism, 30 with marked subclinical hypothyroidism (TSH > 10 mIU/L), and 30 with undiagnosed overt hyperthyroidism.

- Approximately 260 individuals would be found to have mild subclinical hypothyroidism, the management of which is somewhat controversial. 165 of them might feel better if treated with thyroxine (Abu-Helalah et al 2010) and there is clinical support for treatment for individuals in this group if they have symptoms (BTA/BTF 2011). However, a significant minority of these individuals might revert to normal within 3 years without any treatment (Diez & Iglesias 2004), and the extent of overlap between this group and the 165 who might feel better on thyroxine is unknown.

- Approximately 210 individuals would be found to have subclinical hyperthyroidism, the consequences of which are poorly understood, and the management of which lacks an adequate evidence base. About a third of them would probably revert to normal within 7 years without any treatment (Vadiveloo et al 2011).

Implications for research

An investigation of UK iodine status may be needed to help determine whether a policy of iodine prophylaxis should be implemented (Vanderpump et al 2011).

A population-based study of screening for thyroid disease could generate patient populations for an RCT that should provide better answers to the following questions:

- What is the natural history of screen-detected subclinical hypothyroidism? In particular, what proportion of people with screen-detected subclinical hypothyroidism will revert to normal if observed over a period of years?
- Do the apparent short-term (4 month) benefits of treating subclinical hypothyroidism with thyroxine persist when treatment is continued for years?

Appendix A

Knowledge update on screening for thyroid dysfunction
Paula Coles, Information Scientist
November 2011

BACKGROUND: In 2004, the US Preventive Services Task Force concluded that "…the evidence is insufficient to recommend for or against routine screening for thyroid disease in adults."
US Preventive Services Task Force. (2004) *Screening for Thyroid Dysfunction*. http://www.uspreventiveservicestaskforce.org/uspstf/uspsthyr.htm **[accessed 14 November 2011]**

For this recommendation, the evidence was reviewed up until February/March 2002. Therefore, for the purposes of this 2011 review, the searches covered January 2002 to October 2011.

SOURCES SEARCHED: Medline (OvidSP), Embase, Cinahl, and the Cochrane Library.
DATES OF SEARCH: January 2002 – October 2011
SEARCH STRATEGY:
1. (hyperthyroidism or hypothyroidism).tw. (32331)
2. (thyroid adj (dysfunction or disease)).tw. (8532)
3. 1 or 2 (38243)
4. Mass screening/ (73310)
5. screen$3.ti. (97457)
6. Thyroid diseases/di [Diagnosis] (3792)
7. 4 or 5 or 6 (138054)
8. 3 and 7 (2006)
9. Thyroid Function Tests/ (11833)
10. (serum adj (TSH or thyroid stimulating hormone)).tw. (3515)
11. ((TSH or thyroid stimulating hormone) adj (assay$ or level$ or measurement$ or value$)).tw. (5410)
12. 9 or 10 or 11 (18154)
13. (screen$3 or detect$3 or test or tests or testing).tw. (2613386)
14. 12 and 13 (5443)
15. 8 and 14 (540)
16. incidence/ or prevalence/ (289327)
17. (prevalence or incidence).ti. (131592)
18. 16 or 17 (353877)
19. 3 and 18 (1898)
20. Thyroxine/ (31902)
21. Triiodothyronine/ (22908)
22. thyroxine or triiodothyronine).tw. (28382)
23. Thyroid disease/th [Therapy] (640)
24. 20 or 21 or 22 or 23 (49941)
25. 3 and 24 (11361)
26. randomized controlled trial/ (320214)
27. Random Allocation/ (73347)
28. (random* adj5 (alloca* or assign* or control*)).tw. (190235)
29. double-blind method/ or single-blind method/ (128465)
30. exp clinical trial/ (664848)
31. (clinical adj5 trial*).tw. (180599)
32. ((singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)).tw. (115429)

33. (placebo* or random* or crossover).tw. (649724)
34. (compar* adj5 (report* or stud* or trial*)).tw. (350574)
35. systematic review.tw. (27337)
36. meta-analys?s.tw. (38133)
37. consensus statement.ti. (1370)
38. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (1453701)
39. 25 and 38 (996)
40. 15 or 19 or 39 (3260)
41. limit 40 to yr="2002 -Current" (1630)

Similar searches were also carried out in Embase, Cinahl, and the Cochrane Library. All searches carried out on 21 October 2011

Medline	1630
Embase	2702
Cochrane Library	309
Cinahl	452
Total	**5138**

Inclusions and exclusions
The above search strategies retrieved 5138 references in total. After duplicate references were removed a total of 3507 potentially relevant references were left. The title and abstracts of these remaining citations were scanned for relevance to screening for thyroid dysfunction, focusing on the following:

Inclusions
• adults
• subclinical thyroid dysfunction (hypo- and hyperthyroidism)
• detection of subclinical (or asymptomatic) disease
• treatment in subclinical dysfunction
• progression of subclinical disease to overt disease

Exclusions
• children
• in pregnancy
• congenital hypothyroidism
• autoimmune thyroid dysfunction
• thyroid dysfunction as a result of medication/treatment
• treatment for overt thyroid dysfunction

434 references were deemed to be relevant. These references were passed onto the expert reviewer for further sifting and appraisal for possible inclusion into the review.

Appendix B

Table 1: Summary of the evidence for the treatment of subclinical hypothyroidism detected by screening (Rugge et al 2011)

Outcome	Study type; number of studies; number of subjects	Risk of bias	Consistency	Precision	Magnitude of effect (strength of evidence)
Cardiovascular events, coronary artery disease and heart failure	No studies	N/a	N/a	N/a	No evidence (insufficient)
Overall quality of life	2 RCTs N = 169	Medium	Consistent	Imprecise: small studies of 100 and 69 subjects	No effect (low)
Changes in mood/ cognition	2 RCTs N = 169	Medium	Consistent	Imprecise: small studies of 100 and 69 subjects	No effect (low)
Weight/ BMI changes	4 RCTs N = 305	Medium	Consistent	Imprecise: the largest study had 100 subjects; the smallest had 23	No effect (low)
Blood pressure changes	2 RCTs N = 195	Medium	Consistent	Imprecise	No effect (low)
Changes in lipid levels	4 RCTs N = 379	Medium	Inconsistent	Imprecise	Small effect for LDL and total cholesterol (low)

Table 2: Summary of the evidence for the treatment of subclinical hyperthyroidism detected by screening (Rugge et al 2011)

Outcome	Study type; number of studies; number of subjects	Risk of bias	Consistency	Precision	Magnitude of effect (strength of evidence)
Cardiovascular events, including angina, atrial fibrillation, and other clinically significant arrhythmias	No studies	N/a	N/a	N/a	No evidence (insufficient)
Fractures	No studies	N/a	N/a	N/a	No evidence (insufficient)
Overall quality of life	No studies	N/a	N/a	N/a	No evidence (insufficient)
Changes in mood/ cognition	No studies	N/a	N/a	N/a	No evidence (insufficient)
Weight/ BMI changes	1 Controlled trial N=14	High	N/a	Imprecise	About 1% greater decrease in BMI in treated compared with placebo group; absolute change in BMI in treated group of 0.5kg/m^2 (insufficient)
Blood pressure changes	1 RCT N=20 1 Controlled trial N=14	High	Inconsistent	Imprecise	2.58 mmHG reduction in daytime systolic blood pressure from 1 study; no change in 2nd study (insufficient)
Changes in bone density (as measured by DEXA scan)	1 RCT N=20	High	N/a	Imprecise	No effect (Insufficient)
Changes in lipid levels	1 RCT N=20	High	N/a	Imprecise	No effect (Insufficient)

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