Project Title: Effectiveness of Screening and Treatment of Subclinical Hypo- or Hyperthyroidism

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Executive Summary

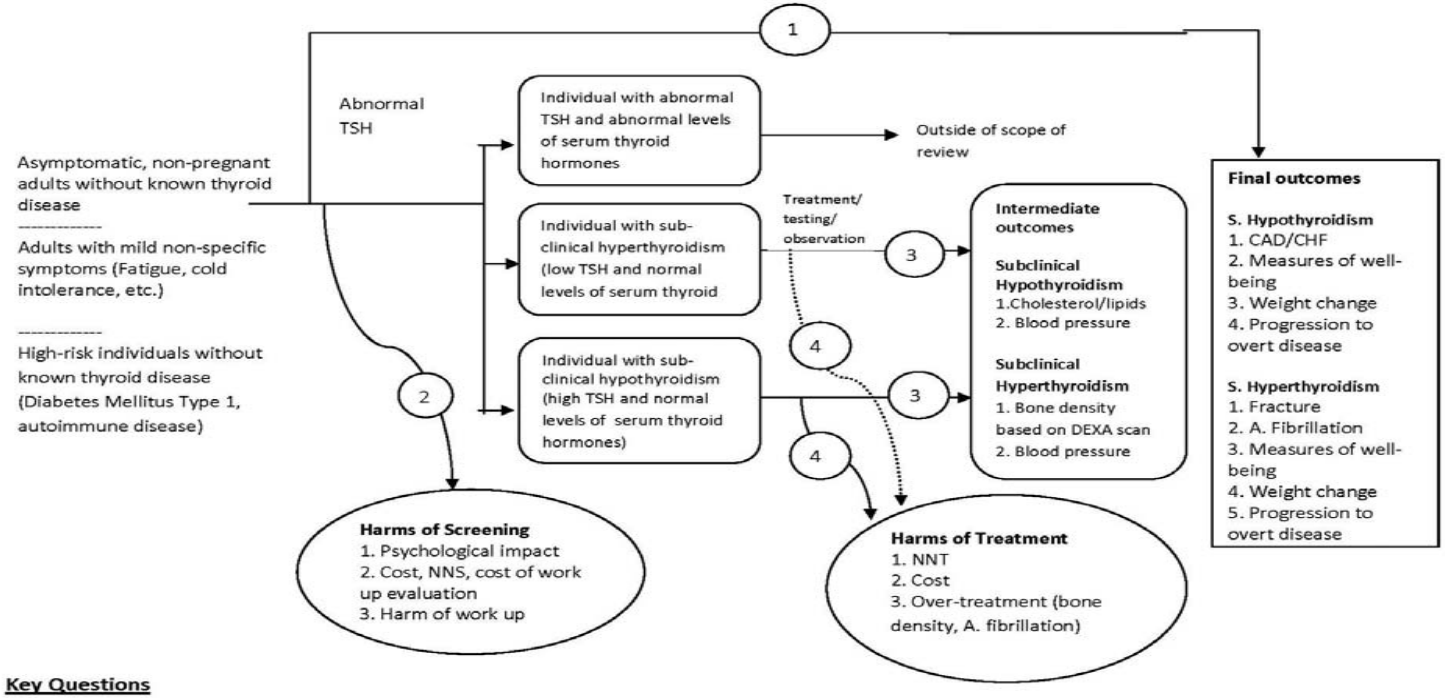
Background

Mildly elevated or decreased serum thyrotropin levels are the most common abnormalities related to thyroid function. It has been proposed that thyroid dysfunction is a continuum of subclinical disease to overt disease; thus, screening and treating for subclinical thyroid dysfunction might lead to earlier detection of overt thyroid disease and allow for the prevention of morbidity[23]. Subclinical thyroid dysfunction is a risk factor for the later development of overt thyroid disease[30]. In addition, a high thyroid stimulating hormone (TSH) level may be a risk factor for coronary events, and a low TSH level is a risk factor for atrial fibrillation and osteoporosis[1]. Evidence-based guidelines recommend against routine screening and treatment of subclinical thyroid dysfunction, but some experts argue that screening could decrease morbidity and mortality associated with progression and other complications.

<u>Topic Development</u>

This topic was nominated by the public as part of the Agency for Healthcare Research and Quality's (AHRQ) Effective Health Care (EHC) Program. The US Preventive Services Task Force (USPSTF) also expressed interest in updating its 2004 recommendations. We developed an analytic framework (Figure A) with the input of external technical experts and members of the USPSTF. We reviewed published studies to answer the following key questions:

Figure A. Analytic Framework



Key Questions

1a. Does screening for sub-clinical thyroid dysfunction reduce morbidity or mortality?
1b. Do screening high-risk groups for sub-clinical thyroid dysfunction reduce morbidity or mortality?
2. What are the harms of screening?
3. Does treatment make a difference in morbidity or mortality when sub-clinical hypothyroidism or hyperthyroidism is detected by screening?
4. What are the harms of treatment of sub-clinical hypothyroidism and sub-clinical hyperthyroidism?

Key Question 1:

a. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?

b. Does screening high-risk groups for subclinical thyroid dysfunction reduce morbidity or mortality?

Key Question 2:

What are the harms of screening? Specifically, how frequently and how severely do patients screened for subclinical thyroid dysfunction experience adverse psychological impacts or other harms of work-up from screening?

Key Question 3:

Does treatment make a difference in morbidity or mortality when subclinical hypothyroidism or hyperthyroidism is detected by screening? We were primarily interested in the comparative effectiveness of a strategy of routine treatment versus active surveillance to prevent the possible complications of untreated subclinical thyroid dysfunction.

Key Question 4:

What are the harms of treatment of subclinical hypothyroidism and subclinical hyperthyroidism? Specifically, what are the consequences of overtreatment, including effects on bone mineral density and incidences of atrial fibrillation, and how frequently do they occur?

Methods

Data Sources

A research librarian searched MEDLINE, the Cochrane Register Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects to identify systematic reviews of screening and treatment of subclinical hypothyroidism or subclinical hyperthyroidism, with no limits on dates. We also searched MEDLINE, AGELINE (AARP.org), EMBASE (embase.com) and the Cochrane Central Register of Controlled Trials to identify studies regarding screening and treatment of subclinical hypothyroidism or subclinical hyperthyroidism published from 2002 to June 2009. Additional materials were sought by searching for regulatory information, clinical trial registries, conference proceedings and other sources of grey literature. Additional studies were identified from citations in relevant articles, discussions with experts, and requests to pharmaceutical companies.

Because we found no U.S. studies either for screening for subclinical thyroid disease or treatment of screen-detected subclinical thyroid disease, we performed a supplementary search of the foreign language literature. For this search we included CINAHL and the World Health Organization Global Health Library.

Study Selection

We defined the target population as community-living, non-pregnant adults without history of thyroid disease or symptoms of overt hypothyroidism or hyperthyroidism, representative of primary care settings. Intermediate outcomes of interest for subclinical hypothyroidism were lipid levels and blood pressure; for subclinical hyperthyroidism intermediate outcomes of interest were bone mineral density and blood pressure. Final outcomes of interest for subclinical

hypothyroidism were weight change, measures of well-being including but not limited to cognition and memory, cardiovascular morbidity, and progression to overt disease. For subclinical hyperthyroidism, they were weight change, measures of well-being including but not limited to cognition and memory, cardiovascular morbidity, progression to overt disease, fractures, and atrial fibrillation.

The quality of each systematic review was assessed using the AMSTAR checklist. The quality of each study was assessed using criteria established by the USPSTF, and except for subclinical hyperthyroidism where no good or fair quality studies were found, poor quality studies were excluded from review. Information regarding the population, setting, treatments, and outcomes were all abstracted.

Data Synthesis

We assessed overall strength for each body of evidence addressing a particular outcome of each key question using the guidance from the Strength of Evidence chapter of the AHRQ Effective Health Care Program Methods Guide for Effectiveness and Comparative Effectiveness Reviews. To assign an overall strength of evidence (“high,” “moderate,” “low,” or “insufficient”) we considered the number, quality, and size of studies; consistency of results between studies; and directness of evidence.

Findings (Table A & Table B)

Key Question 1:

a. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?

b. Does screening high-risk groups for subclinical thyroid dysfunction reduce morbidity or mortality?

We identified no randomized controlled trials (RCTs) or observational studies comparing the outcomes of screening vs. not screening for subclinical hypothyroidism or subclinical hyperthyroidism in the general population.

Key Question 2:

What are the harms of screening? Specifically, how frequently and how severely do patients screened for subclinical thyroid dysfunction experience adverse psychological impacts or other harms of work-up from screening?

Information about the harms of screening remains sparse. We identified no RCTs or controlled observational studies that evaluated harms associated with screening for subclinical thyroid disease. Two natural history studies suggest that a significant number of subclinical thyroid individuals will have normal thyroid function if followed up at about 3 years [20, 70].

Key Question 3:

Does treatment make a difference in morbidity or mortality when subclinical hypothyroidism or hyperthyroidism is detected by screening?

Six trials of treatment for subclinical hypothyroidism were published from 2002-2009[78-83]. None of the trials evaluated long-term cardiovascular outcomes and none had more than 1 year of followup, the minimum time needed to compare immediate treatment to a strategy of active surveillance with annual testing. The largest trial included 120 patients[81]. The trials used different TSH cutoffs to diagnose subclinical thyroid dysfunction, different dosages of medication, and assessed effects over different time periods. None of the included studies were conducted on U.S. populations; most patients included in the studies were recruited from specialty clinics rather than from primary care settings.

Four trials evaluated the effect of treatment on lipids; they had inconsistent findings[79,81-83]. In two of the four studies, there were modest reductions in total cholesterol and Low Density Lipoprotein (LDL), but in two others, there were no improvement for any lipoproteins[79, 81-83]. Two other studies measured well-being[80,83]; two looked at blood pressure[82,83]; and four examined changes in weight or body mass index (BMI)[78,79,82,83]. Studies evaluating these measures consistently found no evidence of benefit.

Two controlled trials assessed the efficacy of treatment of subclinical hyperthyroidism[84,85]; both of these were of poor quality. Both assessed changes in blood pressure. One also evaluated changes in BMI[84], while the other evaluated patient-reported fatigue, nervousness, sweating, change in appetite, and tremors; lipids; and bone mineral density[85]. Evidence of efficacy was inconsistent.

Key Question 4:

What are the harms of treatment of subclinical hypothyroidism and subclinical hyperthyroidism? Specifically, what are the consequences of over-treatment, including effects on bone mineral density and incidences of atrial fibrillation, and how frequently do they occur?

None of the studies of treatment for either subclinical hypothyroidism or subclinical hyperthyroidism systematically reported on harms. In the randomized trials of treatment for subclinical hypothyroidism, the average TSH fell in the patients assigned to placebo control, indicating that overtreatment may have occurred.

Table A. Summary of evidence – subclinical hypothyroidism

Key Question	Study Type: Number of studies Number of subjects	Risk of Bias	Consistency	Directness	Precision	Comments	Magnitude of effect and *strength of evidence*
KQ1. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
KQ 2. What are the harms of screening for subclinical thyroid disease?	2 studies	N/A	No major inconsistency	Indirect Low to moderate applicability to primary care	N/A	No randomized controlled trials were identified; two natural history studies demonstrating indirect evidence of potential harm were included	***Insufficient***
KQ 3. Does treatment make a difference in morbidity or mortality when subclinical hypothyroidism is detected by screening?							
Cardiovascular events and coronary heart failure	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
Overall quality of life	RCT: 2 169	Fair	Consistent	Indirect Moderate applicability to primary care setting	Imprecise: Small studies of 100 and 69 subjects		No effect ***Low***

Changes in mood/cognition	RCT: 2 169	Fair	Consistent	Indirect Moderate applicability to primary care setting	Imprecise: Small studies of 100 and 69 subjects	No effect ***Low***
Weight/BMI changes	RCT: 4 305	Fair	Consistent	Indirect	Imprecise The largest study had 100 subjects; the smallest had 23	No effect ***Low***
Blood pressure changes	RCT: 2 195	Fair	Consistent	Indirect Low applicability to asymptomatic patients in primary care settings	Imprecise	No effect ***Low***
Changes in lipid levels	RCT: 4 379	Fair	Inconsistent	Indirect Low applicability to asymptomatic patients in U.S. primary care settings	Imprecise	Effect for LDL and total cholesterol ***Low***
KQ4. What are the harms of treatment of subclinical hypothyroidism and sub-clinical hyperthyroidism?	No Studies	N/A	N/A	N/A	N/A	***Insufficient***

Table B. Summary of evidence – subclinical hyperthyroidism

Key Question	Study Type: Number of studies Number of subjects	Risk of Bias	Consistency	Directness	Precision	Comments	Magnitude of effect and *strength of evidence*
KQ1. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
KQ 2. What are the harms of screening for subclinical thyroid disease?	No studies	N/A	N/A	N/A	N/A	N/A	No evidence ***Insufficient***
KQ 3. Does treatment make a difference in morbidity or mortality when subclinical hyperhyroidism is detected by screening?							
Cardiovascular events including angina, atrial fibrillation, and other clinically significant arrhythmias	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
Fractures	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
Overall quality of life Changes in mood/cognition	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***

Weight/BMI changes	Controlled trial: 1 14	High	N/A	Direct .	Imprecise	About 1% greater decrease in BMI in treated as compared to placebo group; absolute change in BMI in treated group of 0.5 kg/m^2 ***Insufficient***
Blood pressure changes	RCT: 1 20 Controlled trial: 1 14	High	Inconsistent	Indirect Treated subjects in one study included 2 patients with Graves disease and 8 with autonomous nodules	Imprecise	2.58 mmHG reduction daytime systolic BP from 1 study; no change in 2nd study ***Insufficient***
Changes in bone density (as measured by DEXA scan)	RCT: 1 20	High	N/A	Indirect Treated subjects included 2 patients with Graves disease and 8 with autonomous nodules	Imprecise	No effect ***Insufficient***

Changes in lipid levels	RCT: 1 20	High	N/A	Indirect Treated subjects included 2 patients with Graves disease and 8 with autonomous nodules	Imprecise	No effect ***Insufficient***
KQ4. What are the harms of treatment of subclinical hyperthyroidism and sub-clinical hyperthyroidism?	No studies	N/A	N/A	N/A	N/A	***Insufficient***

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Discussion

The findings of this review are consistent with those of a previous Cochrane review (2007)[67] and an older systematic review conducted for the USPSTF (2004)[1] and the Institute of Medicine (IOM) (2004)[34]. We found that the benefits and harms of screening for subclinical thyroid disease remain inadequately studied. We found no RCTs or observational studies assessing the benefits or harms of screening for thyroid dysfunction in the general population. The evidence is insufficient to assess or quantify the effect of screening on cardiovascular events and cardiac risk factors.

With regard to treatment for subclinical hypothyroidism, no RCTs have directly compared well-defined strategies for routine or selective treatment with a strategy of watchful waiting (active surveillance). No trials have tested the theory that early treatment of subclinical hypothyroidism can prevent coronary events or other heart disease. The applicability of these trials to decision-making in the primary care settings in the U.S was poor.

We considered the evidence insufficient to estimate an effect size or to draw conclusions with regard to benefits of treatment for lipids. For all other outcomes we assessed the reviewed studies as indicating that there is no benefit over watchful waiting of treatment for either subclinical hypothyroidism or subclinical hyperthyroidism and rated the quality of that evidence as low for subclinical hypothyroidism and insufficient for subclinical hyperthyroidism. Evidence is insufficient to assess the long-term harms of treatment for either subclinical hypothyroidism or subclinical hyperthyroidism.

Currently, it is unclear whether screening and early treatment for thyroid disease is better than watchful waiting. For patients who have been screened and have a mildly elevated TSH level, the balance of benefits and harms of treatment versus active surveillance is unclear. Recent ecological studies indicate that, in elderly individuals, a mildly high TSH is a predictor of longevity and possibly of better functional status[18-20]. A well designed, RCT or cohort study comparing the outcomes of well-defined alternative strategies—routine or selective treatment versus active surveillance—is needed to determine which strategy has better outcomes.

Chapter 1. Introduction

A mildly elevated thyroid stimulating hormone (TSH) concentration is the most common thyroid function test abnormality encountered in everyday practice. Most patients who have a mildly elevated TSH have a normal free T4 level. The treatment of such patients is controversial, particularly when they have few or no symptoms and no other clinical evidence of thyroid disease. Less frequently, clinicians encounter patients who have a low or undetectable serum TSH and normal T3 and free T4 levels. The management of these patients is also unclear.

The main purpose of this review is to compare the effectiveness of different strategies for managing individuals who have mildly elevated serum TSH concentrations and those who have mildly diminished TSH concentrations with normal free T3 and/or free T4. We also address whether the primary care physician should screen for thyroid function in patients who have no specific indication for thyroid testing and who come to the physician for other reasons. For the purposes of this review, we considered overt thyroid disease to be a well-defined clinical entity that has clear signs and symptoms, and thus, outside the scope of our review.

Description of Condition

Disorders of the thyroid gland are among the most common endocrine conditions that U.S. physicians evaluate and treat. Hyperthyroidism or hypothyroidism affects about five percent of adults in the United States. [1]

The thyroid gland is involved in metabolic homeostasis in adults. It accomplishes this through secretion of two hormones, thyroxine (T4) and triiodothyronine (T3), and is regulated by thyroid stimulating hormone (TSH), which is secreted by the anterior pituitary. Hypothyroidism is the

under-secretion of thyroid hormones, while hyperthyroidism is the over-secretion of these hormones.

Symptoms of hypothyroidism are subtle and nonspecific and may include fatigue, feeling cold, weight gain, hair loss, poor concentration, dry skin, and constipation (Table 1). Myxedema coma is a life-threatening complication of untreated or under-treated hypothyroidism, usually seen in the elderly. This condition may be precipitated by factors that impair respiration and is marked by hypothermia, hypoventilation, decreased level of consciousness, and sometimes seizures[2].

Table 1. Symptoms and Signs of Thyroid Dysfunction

	Hypothyroidism	**Hyperthyroidism**
Symptoms	Coarse, dry skin and hair	Nervousness & irritability
	Cold intolerance	Heat intolerance
	Constipation	Increased frequency of stools
	Deafness	Muscle weakness
	Diminished sweating	Increased sweating
	Physical tiredness	Fatigue
	Hoarseness	Blurred or double vision
	Paraesthesias	Erratic behavior
	Periorbital puffiness	Restlessness
		Heart palpitations
		Restless sleep
		Decrease in menstrual cycle
		Increased appetite
Signs	Slow cerebration	Distracted attention span
	Slow movement	Tremors
	Slowing of ankle jerk	Tachycardia
	Weight gain	Weight Loss
	Goiter	Goiter

Symptoms of hyperthyroidism may include palpitations, heat intolerance and sweating, weight loss, hyperactivity, and fatigue. Thyroid storm is a life-threatening condition that results from an acute illness superimposed on undiagnosed or under-treated hyperthyroidism. It is accompanied by fever, delirium, seizures, and coma[2].

Subclinical thyroid dysfunction includes subclinical hypo- and hyperthyroidism. Since the development of sensitive TSH assays, these conditions have been defined as follows (Table 2):

- High or low serum thyroid stimulating hormone (TSH) levels
- Normal free T4 and T3 levels
- The absence of signs and symptoms of overt thyroid dysfunction[2].

Patients with subclinical hypothyroidism are further categorized into those with mildly elevated TSH (4.5–10 mIU/liter), and those with markedly increased serum TSH levels (>10 mIU/liter). [3] Similarly, TSH levels below the lower reference limit can be classified as “low but detectable” (serum TSH 0.1-0.4mIU/L) and “clearly low serum TSH” (less than 0.1mIU/L).

Table 2. Classification of thyroid dysfunction

	Biochemical criteria		Comment
Overt hyperthyroidism	TSH Low or Undetectable	Thyroid hormones Elevated T4 or T3	
Overt hypothyroidism	>5 mIU/L	Low T4	
Subclinical hyperthyroidism	Low or Undetectable	Normal T4 and T3	
Subclinical hypothyroidism	>5 mIU/L	Normal T4	Some use lower or higher cutoffs for TSH

The biochemical definition has several limitations. First, the term “subclinical” usually implies that symptoms and signs are absent, whereas, in actual practice, the more common situation is that patients have nonspecific symptoms such as cold intolerance or feeling tired. As Cooper has noted, “Although subclinical hypothyroidism is the term most frequently used…, it is not necessarily apt, since on close questioning many patients disclose mild nonspecific symptoms. Mild hypothyroidism may be a more appropriate term for this very common syndrome, which is defined by an isolated elevated serum thyrotropin level in the setting of normal serum thyroid hormone levels, in the presence or absence of symptoms.” [4] Importantly, the presence of such symptoms does not mean they are related to the finding of an abnormal TSH test. In epidemiologic studies, individuals who had one or two nonspecific symptoms, such as cold intolerance or feeling “a little tired,” were no more likely to have subclinical thyroid disease than were asymptomatic individuals in the general population.[5-9]

Second, the biochemical, TSH-based definition of subclinical thyroid dysfunction does not take into account clinical factors that affect the natural history. Subclinical hypothyroidism can be caused by recent hospitalization for severe illness; previously treated Graves’ disease or nodular thyroid disease; thyroiditis and recovery from thyroiditis; or untreated adrenal insufficiency. The lack of clinical context has caused confusion about the applicability of evidence from patients with overt thyroid disease to asymptomatic, otherwise healthy individuals who have an abnormal TSH level. For example, a frequently cited randomized trial of treatment for subclinical hypothyroidism recruited patients who had undergone treatment for Graves’ disease. [10] Such patients predictably and rapidly progress to symptomatic hypothyroidism if not treated. While the study demonstrated quite convincingly that early treatment can prevent symptoms in patients who have undergone thyroid ablation, patients who have no history of thyroid disease and no clinical findings or symptoms attributable to the thyroid are unlikely to

progress as rapidly, so treatment has much less effect on symptoms in the short-term. The vast majority of patients identified by screening in the clinic or population-based settings are in the latter group.

Third, there is no consensus on what TSH level should be used as the cut-off to diagnose subclinical hypothyroidism or hyperthyroidism. Differences among assays make it difficult to establish a universal upper limit. [11] Most studies define an abnormal TSH test result as the upper and lower limits of the assay's 95% reference range, approximately 0.1 to 4.5 mIU/L.

This method, although widely used in laboratory medicine, is not appropriate for identifying a threshold for diagnosing or treating subclinical hypothyroidism.[12] As for other clinical measures, such as blood pressure, bone density, or serum lipid levels, the threshold should depend on the risk associated with a particular level as well as the balance of benefits and harms of treatment. Some have argued that the threshold for subclinical hypothyroidism should be raised above the upper limit of the reference range. The rationale is that otherwise healthy individuals who have a TSH in the range 4.5 mIU/L to 8 mIU/L or 9 mIU/L have not been shown to benefit from detection and treatment. Other experts argue that, because a TSH within the upper end of the usual reference range (2.5 to 4.5 mIU/L) confers some additional risk of progressing to overt hypothyroidism over time, the threshold for diagnosing subclinical hypothyroidism should be lowered to 2.5 mIU/L. [13-15] Approximately 9.7% of the US adult population, representing 20.6 million Americans, has a TSH in this range and would be identified as having subclinical hypothyroidism if this change were made. [3]

The appropriate level for decision-making can only be decided by better evidence about the adverse consequences in untreated individuals and the benefits and harms of treatment at

different TSH thresholds.[3, 12, 16, 17] For example, identification of subclinical hypothyroidism is unlikely to be beneficial in very elderly individuals, in whom an elevated TSH is associated with lower mortality and better mobility, and in whom treatment may be associated with worse outcomes.[18-20] Because it depends on the risk of complications in a particular population, the appropriate TSH cutoff for defining subclinical hypothyroidism might vary with age, gender, and race. [21]

Fourth, although the definition of subclinical thyroid dysfunction requires a "normal" free T4 level, the definition is not necessarily applicable to the individual patient. Some experts argue that, if a patient's TSH level is mildly elevated, then even if their thyroid hormone levels are within the normal range, they "are not truly normal for that individual."[22] Put differently, while higher levels of thyroid-stimulating hormone increase thyroid hormone production, the additional production does not fully compensate for the underlying deficiency. According to this view, subclinical hypothyroidism represents "early thyroid failure," that is, less than full compensation for the diminished function of the thyroid gland.

Prevalence and Course of Mild Thyroid Dysfunction

Using the upper limit of the reference range as a cut-off, approximately 5% of women and 3% of men have subclinical thyroid dysfunction.[16]. Approximately one in four of these individuals has a markedly elevated TSH concentration (>10 mIU/L). Such patients are likely to progress to overt hypothyroidism over 20 years.

The other 75% of individuals with subclinical hypothyroidism have mildly elevated TSH levels. In this group, age, sex, geographic region, and the presence of thyroid auto-antibodies are strong predictors of the course. From one-third to two-thirds of these individuals have

antithyroid antibodies. Depending on age, sex, and TSH level, 50-70% of these individuals will progress to overt disease over 20 years. In those who do not have antithyroid antibodies, the risk of progression is low.

In general, prevalence increases with age, is higher among whites compared with blacks, and higher in women compared with men.[23] Estimates of the prevalence of subclinical hypothyroidism vary based on demographic factors and differences in the defined upper normal limit for TSH. A systematic review and meta-analysis of good-quality cross-sectional studies,[16] estimated that the prevalence in women ranged from 1.2% among non-Hispanic, African-American women to 5.8% in non-Hispanic, white women and from 4% in women age 18-44 to over 17% in women over 75 years. In the NHANES sample, estimates ranged from 1.8% among non-Hispanic, African-American men to 2.4% among Mexican-American men. In a population-based epidemiological study in Whickham, England, the prevalence ranged from 1% among men 18-65 to 6.2% among men 65 or older. [24]

Strategies for Detecting and Managing Subclinical Thyroid Dysfunction

Screening Strategies. Screening can be defined as "the application of a test to detect a potential disease or condition in a person who has no known signs or symptoms of that condition at the time the test is done." [25] In case-finding, testing for thyroid dysfunction is performed among patients who come to their physicians for unrelated reasons. When the test is abnormal, the patient is called back for a detailed thyroid-directed history and confirmatory testing. Subclinical hypothyroidism is diagnosed if the TSH remains elevated and the free T4 remains normal when the patient is retested after 3 months of observation. While hypothyroidism and hyperthyroidism are distinctly different disorders, with different symptoms and potential complications, screening for both subclinical hypo- and hyperthyroidism is

accomplished through testing of serum TSH, with testing of serum free T4 if the TSH is high, and of T3 as well as free T4 if the TSH falls below the normal range. [2]

Management Strategies. For patients with subclinical hypothyroidism, the alternative management strategies are treatment with thyroid replacement versus watchful waiting. A detailed strategy for routine treatment is described elsewhere.[11] Treatment strategies vary, but all begin with repeat testing to confirm that the TSH is still elevated. If the TSH>10 mIU/L on repeat testing, treatment with levothyroxine is initiated. If the TSH is mildly elevated (above the reference range but below 10 mIU/L), some experts recommend routine treatment. Others recommend measurement of serum thyroid peroxidase antibodies and treatment with levothyroxine if antibody levels are high. All guidelines recommend levothyroxine rather than triiodothyronine or both as the drug of choice. The preference for levothyroxine is based on the generally negative results of randomized trials of levothyroxine alone versus combination therapy for patients with overt hypothyroidism.[26]

"Watchful waiting" encompasses two different strategies—"expectant management" or "active surveillance." Active surveillance means repeating thyroid function tests and a thyroid-directed history periodically to determine whether the patient progresses to have a markedly elevated TSH, decreased free T4, or new symptoms. While active surveillance is considered to be a reasonable approach, the appropriate period for retesting has not been established. A recent British guideline [27] offered the following typical strategy for active surveillance:

- If screening is performed, and a high serum TSH concentration and normal free T4 is found, repeat measurement 3-6 months later after excluding non-thyroidal illness and drug interference.

- If the TSH is mildly elevated (above the reference range but below 10 mIU/L), obtain serum thyroid peroxidase antibodies.
- If antibody levels are high, repeat measurement of TSH annually. If they are low, repeat measurement of TSH every 3 years. Initiate treatment if the TSH level is greater than 10 mIU/L or the patient develops clinical findings of hypothyroidism.

Practice styles vary widely. A well-conducted chart review study of 500 patients with subclinical hypothyroidism seen at the Mayo Clinic in 1995-1996 found that clinicians treated 38.7% of patients who had a TSH between 5.1 and 10.0 mIU/L. [28] Unfortunately, more recent data on practice patterns are not available.

For subclinical hyperthyroidism, some experts [23, 29] recommend repeating thyroid function tests after 3 months and, if the TSH remains suppressed, obtaining ultrasonography and a 24 hour Radioactive Iodine Uptake (RAIU) thyroid scan. These guidelines recommend antithyroid treatment if the patient has a persistent TSH levels less than 0.1 mIU/L and is found to have Graves' or nodular thyroid disease. Treatments include medications, such as propylthiouracil, or ablation with radioactive iodine or surgery. The guideline recommended against routine treatment in those whose TSH was between 0.1 and 0.45 mIU/L.

Guidelines on Early Detection and Treatment

A review of the history of guidelines for subclinical thyroid dysfunction provides insight into the reason for practice variation (See also Appendix Table D3). In 1990 and again in 1998, the American College of Physicians found "it is reasonable to screen women older than 50 years of age for unsuspected but symptomatic thyroid disease." The guideline specified that the goal of routine testing was to find overt, but overlooked, thyroid dysfunction, not subclinical

hypothyroidism. Because the clinical significance of mildly elevated TSH test results was uncertain, the guideline recommended obtaining a free T4 test only when the TSH level was undetectable or 10 mU/L or more. The ACP guideline panel used a systematic review of the literature to arrive at their recommendations [30]. These guidelines expired in 2003.

In 1999, the American Association of Clinical Endocrinologists recommended screening asymptomatic women over the age of 60. [36] The American Thyroid Association recommended screening all patients over 35 years of age every 5 years (more frequently if the patient is at increased risk), but has not updated the recommendation since 2000[32]. These organizations used a consensus process to develop guidelines and did not use systematic reviews in arriving at their recommendations.

In 2003, the Institute of Medicine (IOM) published a volume entitled "Medicare Coverage of Routine Screening for Thyroid Disease," which examined the issue of screening for thyroid dysfunction in the Medicare population and concluded that "there is insufficient evidence to recommend periodic, routine screening for thyroid dysfunction among asymptomatic persons using serum TSH levels." [33] In 2004, the USPSTF determined that the evidence was poor that treatment of screen-detected adults, in either the general population or in specific high-risk groups, improves clinically important outcomes and concluded that there was insufficient evidence to recommend for or against screening for thyroid disease in adults. These groups used essentially identical systematic reviews to arrive at their recommendations. [16, 33] The USPSTF issued an "I" recommendation, indicating that the evidence was insufficient to recommend for or against routine screening for thyroid disease in adults [34]. The conclusions about the evidence were:

- There is fair evidence that the thyroid stimulating hormone (TSH) test 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.
- Although the yield of screening is greater in certain high-risk groups (e.g., postpartum women, people with Down's syndrome, and the elderly), there is poor evidence that screening these groups leads to clinically important benefits.
- There is the potential for harm caused by false positive screening tests; however, the magnitude of harm is not known.
- There is good evidence that over-treatment with levothyroxine occurs in a substantial proportion of patients, but the long-term harmful effects of over-treatment are not known. As a result, the balance of benefits and harms of screening asymptomatic adults for thyroid disease could not be determined.

In 2004, a panel sponsored by the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society evaluated data regarding the management of subclinical thyroid dysfunction[23]. Unlike the older AACE and ATA guidelines, the panel used systematic reviews of the evidence to arrive at its recommendations.[35] The panel found insufficient evidence to support population-based screening and recommended against population-based screening for thyroid disease, though it did advocate aggressive case-finding in those considered high-risk, including pregnant women and women older than 60. They also recommended against routine treatment of patients with subclinical hypothyroidism with serum TSH levels of 4.5 – 10.0 mIU/L. Specifically, the panel found insufficient evidence to support routine treatment of individuals who have a mildly elevated TSH (Table 3). The findings about

the evidence regarding the complications of subclinical hypothyroidism and the effects of treatment agreed with those of the IOM and USPSTF.

Table 3. Findings of the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society Panel.

Complication	Strength of Evidence	Benefits and Harms of Treatment
Progression to overt hypothyroidism	Good	Variable
Adverse cardiac end points	Insufficient	No evidence
Elevation in serum cholesterol and LDL-C levels	Insufficient	Insufficient
Cardiac dysfunction	Insufficient	Insufficient
Symptoms of hypothyroidism	No clear evidence	Insufficient
Psychiatric symptoms	No clear evidence	Insufficient

(Adapted from JAMA [23].)

In 2005, the three professional societies that sponsored the evidence-based panel issued a consensus statement rejecting its recommendations.[36] While acknowledging that the independent review panel found insufficient evidence to recommend treatment of patients with subclinical hypothyroidism in the range of 4.5 – 10.0 mIU/L, the societies counter argued that "lack of definitive evidence for a benefit does not equate to evidence for lack of benefit" and recommended that most patients with TSH levels between 4.5 and 10.0 mIU/L should be considered for treatment. Their rationale for recommending screening despite gaps in the evidence about treatment is discussed in detail in the next section of this report ("Rationale for Screening and Treatment").

In 2006, three British professional associations (Association for Clinical Biochemistry, the British Thyroid Association, and the British Thyroid Foundation) published guidelines for using thyroid function tests. [27] The guideline panel found that "screening for thyroid dysfunction in a healthy

adult population is not warranted." It recommended against routine treatment of patients who have a TSH concentration above the reference range but below 10 mIU/L but said that "a therapeutic trial of thyroxine [should be considered] on an individual patient basis." The British panel noted that that there was growing evidence against the use of thyroxine in elderly patients, in whom an elevated TSH concentration "may reflect an adaptive mechanism to prevent excessive catabolism." Like the ACP and AACE guidelines, the British panel recommended aggressive case-finding in women with non-specific symptoms. The panel used systematic reviews in their process for developing guidelines. [37]

In 2007, The American College of Obstetricians and Gynecologists (ACOG) recommended against routine screening in pregnant women. It stated that there is no evidence that identifying and treating pregnant women with subclinical hypothyroidism improved either maternal or infant outcomes[38].

Rationale for screening and treatment.

Although there is wide agreement that the long-term benefits of early treatment of subclinical thyroid dysfunction have not been proven, there is disagreement about what to do until better evidence is available. This disagreement reflects differing views of the clinical relevance of research about the complications of subclinical thyroid dysfunction.

Proponents argue that thyroid dysfunction is common and associated with significant morbidity. Additionally, a serum TSH test is relatively inexpensive, accurate, readily available, and generally a very acceptable test for patients to undergo [32, 36]. Symptoms of overt thyroid dysfunction also can be vague and at times difficult to diagnose, and therefore, thyroid screening may allow the diagnosis of overt disease earlier in the clinical course, thus reducing morbidity. [32, 36, 39] For subclinical hypothyroidism, treatment with levothyroxine is noninvasive

and inexpensive. Finally, proponents argue that the potential harms are small in relation to the potential benefits: "Because the potential harm of early detection and treatment appear to be so minor and preventable, it seems prudent to err on the side of early detection and treatment until there is sufficient data to address these issues definitively."[36]

Since 2005, the most important, widely cited argument for early treatment of thyroid dysfunction is the association of untreated subclinical hypothyroidism with other risk factors for heart disease and with incident coronary disease later in life. Subclinical hypothyroidism may be a risk factor for atherosclerosis and myocardial infarction, but epidemiologic studies of this question have had mixed results. [40-44] Four recent meta-analyses have evaluated the association of subclinical thyroid disorder on cardiac mortality or all cause mortality.

One included six cohort studies and found that those with subclinical hypothyroidism had a relative risk (RR) of 1.533 (1.312-1.7.91) of having coronary artery disease (CAD) at baseline. [45] Subclinical hypothyroidism was associated with a RR of 1.188 (1024-1.379) of developing CAD in follow up (included studies follow up ranged from 4 to 20 years), but was not found to be associated with all cause mortality.[45] The second review found no association with subclinical hyperthyroidism and circulatory or all-cause mortality.[46] With regard to subclinical hypothyroidism, the association with circulatory mortality was not statistically significant, but a hazard ratio of 1.25 (1.3-1.53) was found for all-cause mortality. [46] The third review found no overall statistically significant association between either subclinical hypothyroidism or subclinical hyperthyroidism and total mortality or coronary morbidity or mortality.[47] A statistically significant, but small increased risk for heart disease was found for individuals younger than 65.[47] The last meta-analysis included 15 studies with 2,531 subclinical hypothyroid participants and 26,491 euthyroid individuals. [48] Five studies provided longitudinal data on the risk of

coronary events; in these, overall there was no difference in incident ischemic heart disease (IHD) in subclinical hypothyroid participants and euthyroid participants (OR 1.27 (95% CI 0.95–1.69); *P*=0.11). In a subgroup analysis, in studies of subjects younger than 65 years, the odds ratio was 1.68 (1.27–2.23), but for older subjects, there was no relationship between subclinical hypothyroidism and incident IHD (OR 1.02 (0.85–1.22)).[48]

The epidemiological studies included in these reviews had serious limitations. Many included individuals who had known thyroid disease, ischemic heart disease or TSH levels within the reference range. Many included subjects who underwent treatment with levothyroxine during the follow-up period. In general, the studies did not adequately control for potential confounders, such as lipid levels and blood pressure.

The most recent research, a reanalysis of the Whickham study, addresses some of the limitations of previous studies.[49] Unlike the earlier report from the Whickham study, [50] the new analysis included only subjects who had mildly elevated TSH levels, excluded subjects who had known thyroid disease or ischemic heart disease, stratified subjects according to whether they were treated with thyroxine during the follow-up period, and adjusted for several cardiovascular risk factors as well as socioeconomic status. Because of these improvements in delineating the sample, this analysis provides the best estimates of the relationship between a mildly elevated TSH level and the risk of incident coronary events over 20 years. After adjustment for baseline age, gender, social class, body weight, history of cerebrovascular disease, diabetes mellitus, smoking, systolic and diastolic blood pressure, serum cholesterol levels, and levothyroxine use during follow-up as covariates, subclinical hypothyroidism was associated with a higher risk of coronary events over 20 years (hazard ratio 1.76 (1.15–2.71); *P* <0.01.) When levothyroxine use during follow-up was not controlled for, the relationship was weaker (hazard ratio 1.53

(0.97–2.45); p=0.07). This finding suggests that previous analyses that did not adjust for treatment during follow-up may have underestimated the association. Among the 91 subjects who had subclinical hypothyroidism, 2 of 20 who were treated with levothyroxine during the course of the study died, versus 22 of 71 who did not receive levothyroxine. Despite the low number of events, the authors reported a hazard ratio of 0.20 (0.05–0.89) for all-cause mortality after adjustment for age, gender, and total serum cholesterol.

While it is much stronger than previous evidence, this analysis also had weaknesses. First, the description of the methods for ascertaining cardiac events are not clear, and, specifically, it is not clear what events were considered in addition to documented myocardial infarction or death from coronary disease. In the context of risk factor epidemiology, for a broadly defined composite endpoint, the hazard ratios are low, making it more likely that confounding or methodological factors account for the observed differences. Second, the study did not control for the use of lipid-lowering medications during the follow-up period. It is possible that the better outcomes of subjects treated with levothyroxine could be due to other interventions introduced by their physicians. Finally, the study was conducted before the era of statins and other aggressive cardiac risk management techniques. It is possible that, in current practice, the association between subclinical hypothyroidism and subsequent cardiovascular outcomes would become negligible in the context of current cardiac disease management.

The Helfand (2004) review found that evidence regarding mildly elevated TSH levels and hyperlipidemia and atherosclerosis were inconsistent.[16] The recent reanalysis of the Whickham study data provides the best available estimates of the association of thyroid status with cardiac risk factors at baseline. Compared at baseline with euthyroid individuals, subjects with subclinical hypothyroidism had higher systolic blood pressure (139.5± 24.7 mm Hg vs 146.9

±26.4 mm Hg) and total cholesterol levels (5.9 ±1.2 vs 6.2 ±1.3 mmol/L) and were slightly less likely to smoke. After adjustment for age, gender, weight, smoking, and relevant medications, however, systolic blood pressure was associated with subclinical hypothyroidism, but total cholesterol was not. In other cross-sectional studies, subclinical hypothyroidism was weakly associated with total and LDL cholesterol, blood pressure, abnormalities of cardiac function, and subcutaneous fat.[51, 52]

Untreated subclinical hyperthyroidism may lead to tachycardia, increased left ventricular mass leading to diastolic dysfunction, atrial arrhythmias, atrial fibrillation, and a decline in bone mass density increasing the risk of fractures.[16, 23] In a recent longitudinal study of 102 women who had a TSH between 0.1 to 0.4 mIU/L, three progressed to overt hyperthyroidism and 24 reverted to a normal TSH. [53]

In summary, progression to overt disease is the best established complication of subclinical thyroid dysfunction. Epidemiologic data suggest that subclinical hypothyroidism is associated with cardiovascular disease in subjects younger than 65 years, but the magnitude of risk is low. Evidence about the relationship of a mildly elevated TSH to symptoms and to other cardiac risk factors, including the metabolic syndrome, is weak.

Scope of Review

The main question addressed in this review was whether individuals who have mildly abnormal TSH values will either benefit from or be harmed by treatment. We also addressed the question of whether the primary care physician should screen for thyroid function in patients seen in general medical practice who have no specific indication for thyroid testing and who come to the physician for other reasons. For the purposes of this review, we considered overt thyroid

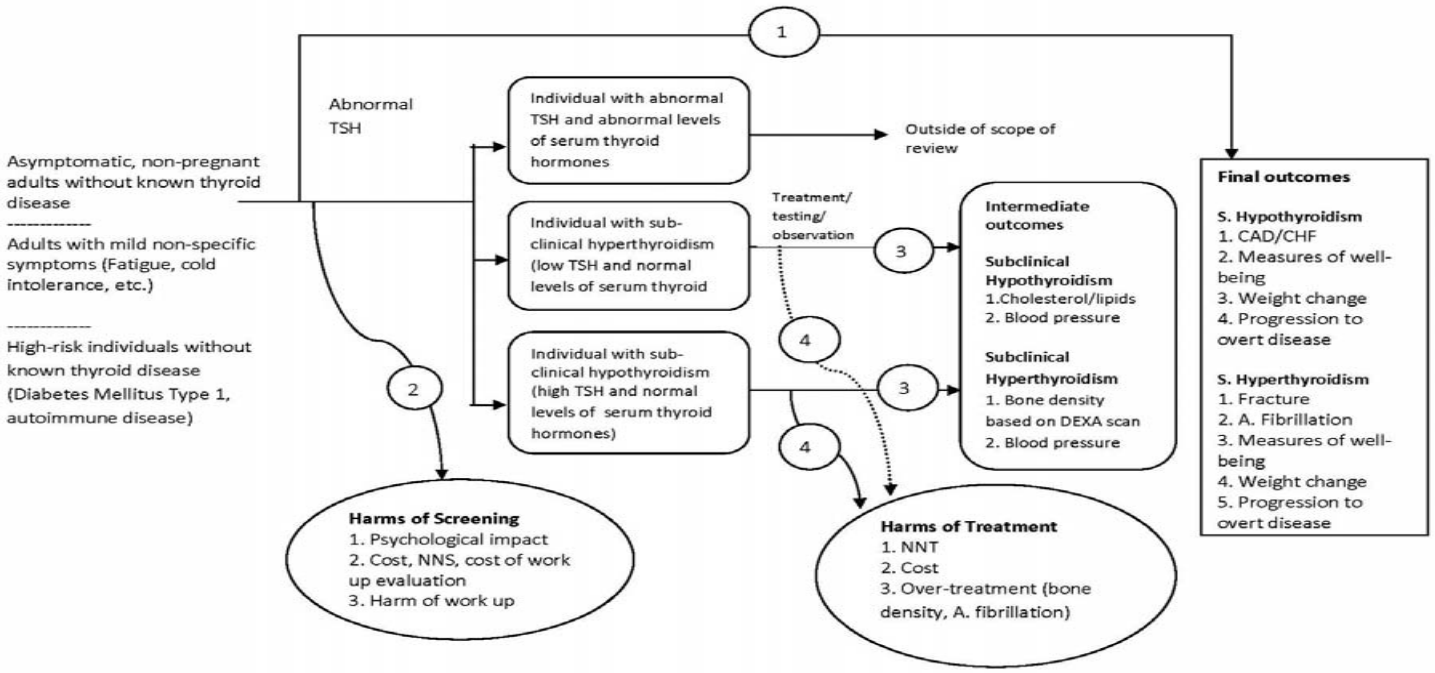
disease to be a well-defined clinical entity that has clear signs and symptoms, and thus, outside the scope of our review.

In order for a condition to be a good candidate for screening in the general population, several conditions need to be met. First, the condition needs to be relatively prevalent, having a significant impact on the health of the population or an easily identified special population. Second, there needs to be a test that is readily available to the general population that is of reasonable cost, accuracy, and is acceptable to individuals to undergo. Finally, there needs to be an intervention that is of reasonable cost and tolerability that when administered in a timely fashion will alter the disease state to prevent morbidity and/or morality.

The 2004 review established that subclinical thyroid disease is quite prevalent; may be responsible for morbidity; and that the serum TSH test is a readily available, reliable, and acceptable test to detect the condition with a sensitivity above 98% and specificity greater than 92%[16]. However, in 2004, it remained unclear whether, if detected, treating subclinical thyroid disease would have a beneficial effect to reduce morbidity.

As evidence of prevalence, test yield, and test performance have already been adequately established [16], this current review focuses on whether new evidence demonstrates that treatment improves clinically important outcomes in adults with screen-detected thyroid disease.

Figure 1. Analytic Framework



Key Questions

1a. Does screening for sub-clinical thyroid dysfunction reduce morbidity or mortality?
1b. Do screening high-risk groups for sub-clinical thyroid dysfunction reduce morbidity or mortality?
2. What are the harms of screening?
3. Does treatment make a difference in morbidity or mortality when sub-clinical hypothyroidism or hyperthyroidism is detected by screening?
4. What are the harms of treatment of sub-clinical hypothyroidism and sub-clinical hyperthyroidism?

Key Questions and Analytic Framework

The key questions for this review were:

Key Question 1:

a. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?

b. Does screening high-risk groups for subclinical thyroid dysfunction reduce morbidity or mortality?

Key Question 2:

What are the harms of screening? Specifically, how frequently and how severely do patients screened for subclinical thyroid dysfunction experience adverse psychological impacts or other harms of work-up from screening?

Key Question 3:

Does treatment make a difference in morbidity or mortality when subclinical hypothyroidism or subclinical hyperthyroidism is detected by screening?

Key Question 4:

What are the harms of treatment of subclinical hypothyroidism and subclinical hyperthyroidism? Specifically, what are the consequences of over-treatment, including effects on bone mineral density and incidence of atrial fibrillation, and how frequently do they occur?

We developed the final analytic framework shown in Figure 1 to guide the literature review. The analytic framework shows the populations, classification, intermediate outcomes, and health outcomes we examined in the review. We defined the target population as community-living,

non-pregnant adults, without a history of thyroid disease or symptoms of overt hypothyroidism or hyperthyroidism, representative of primary care settings.

Arrows 1 and 2 represent the ability of screening to detect unsuspected thyroid dysfunction, the harms of the screening tests, and the symptom status of the patients diagnosed by screening. Key questions related to Arrows 3 and 4 focus on evidence about the benefits and harms of treating early thyroid dysfunction. Outcomes of interest for subclinical hypothyroidism were cardiovascular morbidity and mortality, measures of well-being including but not limited to cognition and memory, weight change, blood pressure changes, and changes in lipid levels. For subclinical hyperthyroidism, outcomes of interest were cardiovascular morbidity and mortality, osteoporitic fractures, measures of well-being including but not limited to cognition and memory, weight changes, blood pressure changes, changes in bone mineral density, and changes in lipid levels.

Chapter 2. Methods

This topic was nominated by the public as part of AHRQ's EHC Program. The USPSTF also expressed interest in updating its 2004 recommendations. Using the methods of the EHC Program [54] and the USPSTF[55] and with members of the USPSTF as well as external technical experts, we developed a preliminary analytic framework and Key Questions (KQs) to guide our literature search and review. We sought input from a representative of the nominating organization, experts in thyroid disease, and members of the USPSTF to refine the clinical logic and PICOTS (Population, Intervention, Comparators, Outcome, Timing, and Setting) and to understand the rationale for screening. Draft key questions were posted for public comment on the EHC Program Web site.

Data Sources

A research librarian searched MEDLINE, the Cochrane Register Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects to identify systematic reviews regarding screening and treatment of subclinical hypothyroidism or subclinical hyperthyroidism, with no limits on dates (search strategies are described in Appendix Tables B1A through B1C). As described in detail below, the systematic reviews we identified examined all relevant studies published prior to 2004. Therefore, we searched MEDLINE, AGELINE (AARP.org), EMBASE (embase.com) and the Cochrane Central Register of Controlled Trials to identify studies regarding screening and treatment of subclinical hypothyroidism or subclinical hyperthyroidism published from 2002 (thereby allowing an overlap with all previous reviews) to June 2009. In addition to searching bibliographic databases, we sought additional materials by searching for regulatory information, clinical trial registries, conference proceedings, and other sources of grey literature. Additional studies were identified from citations in relevant articles, discussions with experts, and requests to pharmaceutical companies.

Because we found no U.S. studies either of screening for subclinical thyroid disease or treatment of screen-detected subclinical thyroid disease, we performed a supplementary search of bibliographic databases that have a higher concentration of non-English language articles. For this search we included CINAHL and the World Health Organization (WHO) Global Health Library which includes African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Latin American and Caribbean Health Sciences Literature, Pan American Health Organization Database, WHO Library Database, and WHO Western Pacific Region Database. We reviewed our original search and found 114 abstracts of foreign language studies and conducted an additional search that found 48 new non-English language citations for review.

Selection of Systematic Review

Two reviewers evaluated each review at the title/abstract and full-text article stages to determine eligibility for inclusion. Only reviews that 1) included studies of screening and treatment for subclinical thyroid disease in asymptomatic individuals, 2) included studies that met the design and quality criteria of this current study, and 3) considered outcomes included in the analytic framework of the current study were included.

Data Abstraction and Quality Rating of Systematic Reviews

Data from the included systematic reviews were abstracted according to the guidance provided in the chapter on “Using Existing Systematic Reviews to Replace de Novo Processes in CERs” from the AHRQ EHC Program Methods Guide for Effectiveness and Comparative Effectiveness Reviews available at: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318 (Table 4). Abstracted data includes the

TABLE 4. INCLUDED SYSTEMATIC REVIEWS

Author Year; n studies	Study types, n	Total participants	SR assessment of quality of primary literature	Overlapping studies n*†	Quality of SR	Comments
Helfand 2004; 8	RCT, 8; Metanalyses of observational studies, 2	RCT, 291+	Screening Benefits: N/A Screening Harms: Poor Yield: Good Treatment Benefits: Poor Treatment Harms Osteoporosis: Good Overtreatment: Good Other: Poor	Danese: 2 Villar: 6	Good AMSTAR 9/11	
Villar 2007; 12	RCT, 12	RCT, 461+	Maximum Jadad score of 5; median score of 12 studies was 4 with a range of 3 to 5	Danese: 2 Helfand: 6	Good AMSTAR 10/11	Assessed the quality of the individual studies using the Jadad and Schulz criteria, but did not assess the overall strength of the evidence of the body of literature

+ One study did not report n

* 2 studies (Cooper 1984; Jaeschke 1996) were common to all three reviews

† See Table N Study Concordance for details

author and year of the review; the number of included studies and their type (RCT, observational, etc.); total study participants; the reviews assessment of the quality of the body of evidence if available; the overlap of studies among the reviews; and the quality of the systematic review. The quality of each study was assessed using the assessment of multiple systematic reviews (AMSTAR) measurement tool.[56]

Individual Study Selection

Two reviewers evaluated each study at the title/abstract and full-text article stages to determine eligibility for inclusion. Studies that included patients with Hashimoto's disease were included if those patients were asymptomatic and likely were diagnosed as a result of screening for antibodies during the study. Because few studies included patients identified through screening in primary care settings, we included studies of patients from endocrine clinics and from laboratory database studies in which testing of thyroid function was done for a variety of reasons. For Key Question 1 we included RCTs and observational studies of screening or case-finding for subclinical thyroid dysfunction. For Key Question 2 we did not restrict our search to any particular study design but searched for any harms, including those related to treatment as well as those related to patient issues and concerns about testing, screening, or case-finding for subclinical thyroid dysfunction. For Key Question 3, we restricted our search to RCTs of treatment for subclinical hypothyroidism. However, because of the paucity of studies, in addition to RCTs, we included controlled trials, cohort studies, case-control, or other studies that looked at treatment of subclinical hyperthyroidism. For Key Question 4 we again did not restrict our search to any particular study design but searched for any articles reporting harms due to treatment for subclinical hypothyroidism or subclinical hyperthyroidism, including RCTs, controlled trials, cohort studies, and case-control studies. (Table 5) Appendix Figure B1A provides a flow diagram illustrating the selection of included systematic reviews; Appendix

Figure B1B provides the diagram for selection of individual studies; Appendix Figure B1C provides a flow diagram for the selection of foreign language studies.

TABLE 5. Criteria for Inclusion/Exclusion of Studies in the Review

- KQ 1a and 1b: RCT
- KQ 2: RCT, controlled trials, cohort studies, case-control studies, and observational databases.
- KQ 3: RCT, controlled trials, cohort studies, and case-control studies.
- KQ 4: RCT, controlled trials, cohort studies, case-control studies and observational databases.

Costs: A discussion of the costs or cost-effectiveness of screening is not within the scope of this review.

Target Population: Community living adults, without history of thyroid disease or symptoms of overt hypothyroidism or hyperthyroidism, representative of primary care settings. Hospitalized or recently hospitalized participants are to be excluded as these individuals may have elevated TSH levels.

Date Range: Publications from 2002 to the present will be included in the study. This start date was chosen to provide a small period of overlap with the publication date range used in the prior 2004 review.

Non-English language studies will be considered for inclusion in the review, and a search for relevant grey literature will be conducted.

Data Abstraction and Quality Rating of Individual Studies

We abstracted details about the patient population, study design, data analysis, and results. One author abstracted data and another author verified data abstraction for accuracy. We used predefined criteria developed by the USPSTF to assess the internal validity (quality) of studies (Appendix Table B3). Two authors independently rated the internal validity of each study as "good," "fair," or "poor". For all studies, we evaluated applicability to populations likely to be encountered in primary care screening settings. Discrepancies in quality ratings were resolved by discussion and consensus.

The quality of each study was assessed using criteria established by the USPSTF, and except for subclinical hyperthyroidism where no good or fair quality studies were found, poor quality studies were excluded from review.

Data Synthesis

We assessed overall strength for each body of evidence addressing a particular key question or part of a key question (for example, different treatments or screening tests) using guidance from the Strength of Evidence chapter of the AHRQ EHC Program Methods Guide for Effectiveness and Comparative Effectiveness Reviews.

To assign an overall strength of evidence (“high,” “moderate,” “low,” or “insufficient”) we considered the number, quality, and size of studies; consistency of results between studies; and directness of evidence.

External Review

We distributed this draft of the report for review by external experts not affiliated with AHRQ or the USPSTF, and will revise the report based on their comments as well as on comments received during the public review period.

Chapter 3. Results

Systematic Reviews

Our search identified 74 unique reviews whose abstracts were reviewed for inclusion (Appendix Table D5). After review, 18 where pulled for full-text review. Of those 18 reviews, four were not systematic reviews[57-60]; six did not address the key questions of this review[11, 45, 47, 61-63]; and two fell outside the timeframe for included reviews[64, 65]. The studies included in the six remaining reviews are compared in Table D6 (see Appendix) [16, 23, 66-69].

Three of these reviews examined the effect of treating subclinical hypothyroidism on lipids.[66, 68, 69] All of these demonstrated an improvement in lipids with treatment, but they had serious flaws that have already been described: they did not distinguish between studies of otherwise healthy patients from those who acquired hypothyroidism after treatment for hyperthyroidism, or they included poorly done observational studies.

A recent, good-quality Cochrane review provided the best information about several relevant outcomes, including cardiovascular mortality and morbidity, symptom improvement, and health-related quality-of-life.[67] That review also examined all-cause mortality, lipid levels, systolic and diastolic heart function, and adverse effects of levothyroxine. The review concluded that while there might be some short-term improvement in lipid profiles and left ventricular function with treatment, trials of thyroid hormone therapy for subclinical hypothyroidism were not suited to assess survival or cardiovascular morbidity. These trials did not demonstrate that treatment improved health-related quality of life or symptoms. [67]

The earlier reviews[16, 23] addressed screening and treatment of both subclinical hypothyroidism and hyperthyroidism. As seen in Table 6, there was considerable overlap in the trials reviewed by these earlier reviews and the Cochrane review. A total of 14 trials were included in one or more of these reviews. The conclusions of the two earlier reviews largely agreed with those of the more recent Cochrane review. Because of the convergence of findings from these disparate reviews, we considered the evidence considered by these three reviews to adequately reflect the state of the evidence through 2006 (the most recent search date for the Cochrane review.)

Individual Studies

The current review includes eight trials, six of which were not examined in previous systematic reviews. Four were studies of treatment for subclinical hypothyroidism, and two were studies of treatment for subclinical hyperthyroidism. The flow of studies from initial identification of titles and abstracts to final inclusion or exclusion using pre-specified criteria (Appendix Table B3) is diagrammed in Appendix Figure B1B. Our original search found a total of 941 individual articles published from 2002 to 2009. This search also included 113 English abstracts of non-English articles. Our supplementary foreign language search found a total of 48 new non-English language articles published between 2002 and 2009. These 161 foreign language abstracts were also reviewed. After the abstracts were reviewed, 295 articles from our original search were found to meet criteria for full article review. In addition, six articles from our foreign language search met the criteria for full article review. However, none of the foreign language articles met inclusion criteria for quality or study design, and all six were excluded from the analysis. The flow of studies from this supplementary search is diagrammed in Figure B1C. Excluded studies are described in Appendix Tables C15 and C16. No controlled trials of the benefits or harms of screening (Key Questions 1 and 2) were identified, but two observational studies relevant to the harms of screening were identified. Six trials assessed one or more

relevant outcomes of treatment for subclinical hypothyroidism (Key Question 3), but none of them assessed harms systematically.

Several aspects of these trials make their applicability to a US primary care population problematic. None of the studies was conducted in the US. Most of the studies recruited subjects from specialty clinics, rather than from the primary care setting. Additionally, the studies were relatively short, the longest lasting 12 months. A longer duration would be needed to compare early treatment with annual retesting, the main alternative in practice.

A meta-analysis was not performed due to the methodological and clinical diversity among the included studies. The TSH value that was used to diagnose subclinical thyroid disease varied among the studies. Different dosages of medications were used in the different trials.

Key Question 1. a) Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?; b) Does screening high-risk groups for subclinical thyroid dysfunction reduce morbidity or mortality?

In 2004, Helfand[16] did not find any studies that evaluated the impact of screening for thyroid disease on morbidity or mortality. We also identified no controlled trials of screening for subclinical hypothyroidism or subclinical hyperthyroidism in the general population.

Key Question 2. What are the harms of screening for subclinical thyroid disease?

Information about the harms of screening is still sparse. We identified no RCTs or controlled observational studies that evaluated harms associated with screening for subclinical thyroid

disease. Overdiagnosis is a potential harm because the TSH level returns to the reference range in a substantial proportion of individuals.

Potential harms of screening for subclinical hypothyroidism include false positive test results, anxiety related to test results, and overdiagnosis. There is little direct evidence about these potential adverse effects of screening.

In the context of screening for subclinical hypothyroidism, overdiagnosis can be defined as diagnosing subclinical hypothyroidism in a patient who cannot benefit from the diagnosis. Overdiagnosis is relevant to screening for subclinical hypothyroidism because many individuals who have a mildly elevated TSH level and a normal free T4 never develop complications and, in some, the TSH reverts spontaneously to a value below the upper reference limit.

Spontaneous reversion of mildly elevated TSH levels was observed in the Whickham study, other natural history studies, and in trials of levothyroxine therapy. Recent studies suggest that it is more frequent than previously thought and that it can occur after a long period of persistent elevation (Table 7). An observational, population-based study followed elderly patients living in Leiden, Netherlands, screening for thyroid disease at age 85 and then rechecking thyroid function at age 88[20]. Twenty-one subjects were initially found to have subclinical hypothyroidism (all were 85 years old). Three years later, none of the subjects had progressed to overt hypothyroidism, eight continued to have subclinical hypothyroidism, two had developed subclinical hyperthyroidism, and 11 subjects now had normal thyroid function tests. In the same study, 12 subjects were initially found to have subclinical hyperthyroidism. Three years later, one had progressed to overt hyperthyroidism while five continued to have subclinical

TABLE 7. SCREENING EVIDENCE TABLE

Author, year Duration	Country and population	Study design	Sample size Begun/Completed	Results	Quality Score
Gussekloo., 2004	Born in 1912-1914, and living in Leiden, the Netherlands, between Sep 1997 and Sep 1999	Uncontrolled observational study	558	In follow-up group at age 88, 21/30 with subclinical hypothyroid were reassessed: 0 had overt hypothyroid, 8 had subclinical, 11 had normal thyroid, and 2 had overt hyperthyroid. 12/17 with subclinical hyperthyroid were reassessed: one had overt hyperthyroid, 5 had subclinical hyperthyroid and 5 had normal thyroid and 1 had subclinical hypothyroid	**Not rated**
Diez, 2004	Patients with "spontaneous" subclinical hypothyroidism referred to an endocrinology clinic	Uncontrolled observational study	107	28 patients (26.2%) developed overt thyroid failure during follow-up (mean 31.7 months). 40 patients (37.4%) showed normal TSH at the end of follow-up period. Normal TSH levels more common in those with nonautoimmune hypothyroidism (61.5%) and with lower TSH level at start.	**Not rated**

hyperthyroidism, five individuals had normal thyroid function, and one subject had developed subclinical hypothyroidism.

In a natural history study, 107 patients age 55 to 83 with newly diagnosed and untreated subclinical hypothyroidism referred from general practice and other specialty clinics to an endocrinology clinic were followed for a mean period of 32 months [70]. All patients had two measurements of TSH above 5.0 mIU/liter and free T4 in the normal range of 0.75-2.0 ng/dl one to three months prior to entering the study. During the 32 month follow-up period a total of 40 patients (37.4%) reverted back to normal TSH levels without treatment. While this is only a natural history study, it suggests that overdiagnosis may occur unless treatment is withheld until repeat testing over 1-2 years confirms persistent and progressive elevations.

Key Question 3. Does treatment make a difference in morbidity or mortality when subclinical hypothyroidism or hyperthyroidism is detected by screening?

Subclinical Hypothyroidism

An earlier systematic review conducted for the USPSTF appraised 8 trials of treatment for subclinical hypothyroidism. [16] These studies are summarized in Appendix Table D7. Three of the studies[10, 71, 72] included individuals with known thyroid disease, making them less relevant to a population identified by screening. Only one of these studies was rated as a good quality study[10]. Cooper found that patients with a history of Graves' disease had a modest improvement in hypothyroid symptoms following one year of therapy with levothyroxine, but no improvement in lipid levels. Another three studies included individuals without a history of thyroid disease[73-75], thus are likely more relevant to primary care. However, only one was considered of fair quality[73] (the others were rated poor[74, 75]) and that study only found improvement in short term memory, and failed to find improvement in the Sickness Impact Profile (SIP). The final two studies

included individuals who were euthyroid but either had a TSH in the 4 to 4.5 mIU/L range[76] or had at least 3 symptoms of hypothyroidism[77]. One study was rated as poor (Michalopoulou, 1998). [76] The fair quality study, Pollock (2001),[77] found a reduced SF-36 vitality score in euthyroid patients treated with levothyroxine.

A 2007 Cochrane review[67] provides the most recent, good-quality review and meta-analysis of levothyroxine treatment for subclinical hypothyroidism. The review included 12 studies, five of which were not included in the reviews by Surks[23] or Helfand[16] (see Table 6). None of the trials assessed cardiovascular mortality or morbidity, and seven evaluated symptoms, mood, and quality of life, and found no statistically significant improvement. The authors also noted methodological deficiencies in previous meta-analyses of the effect of levothyroxine on cholesterol levels and other lipids. In their systematic review, six of the trials measured plasma cholesterol or LDL cholesterol. They noted baseline differences in cholesterol levels in several of the trials, and conducted two analyses finding: 1) the post-treatment difference of the means favored treatment, but 2) analysis of changes from baseline favored placebo.

Our review includes six trials that were not included in the 2004 USPSTF review[78-83], four of which were not include the Cochrane review. [79, 81-83] (See Table 6, Table 8, and Tables 8a – 8g) These studies were not included because they were published after the literature searches were performed for the earlier reviews and/or due to differences in inclusion/exclusion criteria. The largest enrolled 120 individuals, and four enrolled fewer than 70 individuals. The follow-up period ranged from 5 to 12 months. Five of the trials did not report their method for allocation concealment; [78-82]; four did not report their method of randomization; [78-80, 82] and three reported the number of patients enrolled at baseline but not at study conclusion, and did not indicate that intention-to-treat analysis was followed. [79, 81, 82]. These studies were rated fair quality.

TABLE 8. TREATMENT EVIDENCE TABLE (SUBCLINICAL HYPOTHYROIDISM)

Author, year Duration	Country and population	Study design	Sample size Begun/Completed	Results[a]		Quality Score
1. Caraccio, 2005 6 months	Italy. Patients recruited from outpatient clinic. All suffered from Hashimoto's thyroiditis and had positive antibodies TSH > 3.6 mIU/L	Randomized, placebo-controlled trial. Randomization method not stated. Allocation concealment not described.	LT4: 12/12 Placebo: 11/11	BMI	⇔	**Fair**
2. Iqbal, 2006 12 months	Norway. SCH patients found from general health survey. 3.5 < TSH < 10 mIU/L	Randomized placebo-controlled trial. Randomization method not stated. Blinding and allocation concealment not described.	LT4: 32/? Placebo: 32/?	Total Cholesterol LDL HDL Triglycerides BMI	⇔ ⇔ ⇔ ⇔ ⇔	**Fair**
3. Jorde, 2006 12 months	Norway. SCH patients found from general health survey. 3.5 < TSH < 10 mIU/L	Randomized placebo-controlled trial. Randomization method not stated. Allocation concealment not described.	LT4: 36/36 Placebo: 33/32	Cognitive General Health Depression	⇔ ⇔ ⇔	**Fair**
4. Mikhail, 2008 52 weeks	Kuwait. Patients, age 15-60, from endocrinology outpatient clinic. 4 < TSH < 10 mIU/L	Double-blind, Placebo-controlled trial. Blinding stated but not described; allocation concealment not stated.	LT4: 60/? Placebo: 60/?	Total Cholesterol LDL HDL Triglycerides	⇧ p < 0.03 ⇧ p < 0.001 ⇔ ⇔	**Fair**

5. Nagasaki, 2009 5 months	Japan. Newly diagnosed patients with SCH due to chronic thyroiditis with positive antibodies TSH "above the normal upper limit"	Randomized, placebo-controlled study. Randomization method not described. Blinding of patients but not caretakers or assessors described. Allocation concealment not described.	LT4: 48/? Placebo: 47/?	Total Cholesterol LDL HDL Triglycerides Blood Pressure BMI	⇔ ⇔ ⇔ ⇔ ⇔ ⇔	**Fair**
6. Razvi, 2007 24 weeks	United Kingdom. Patients from urban, general practice settings identified through laboratory database, not through screening. TSH > 4 mIU/L	Randomized, placebo-controlled cross-over (12-week) trial	LT4:50/50 Placebo: 50/49	Total Cholesterol LDL HDL Triglycerides Blood pressure Weight QoL	⇧ $p < 0.001$ ⇧ $p < 0.001$ ⇔ ⇔ ⇔ ⇔ ⇔	**Good**

LT4: Levothyroxine

1 **TABLE 8a. QUALITY OF LIFE**

Jorde, 2006 (Norway)	**Thyroxine**	**N**	**Placebo**	**N**
Dosage	109.7 mcg/day (avg)			
Cognitive Before	1.8 +/- 3.4	34	-1.1 +/- 4.7	31
Cognitive After	1.5 +/- 3.7	35	-0.9 +/- 4.8	30
Difference	n.s.		n.s.	
GHQ-30 Before	1.5 +/- 2.3	36	0.7 +/- 1.3	33
GHQ-30 After	1.9 +/- 3.3	36	1.2 +/- 2.0	32
Difference	n.s.		n.s.	
BDI Before	4.4 +/- 3.7	36	3.7 +/- 3.8	33
BDI After	4.3 +/- 3.6	36	3.3 +/- 4.0	33
Difference	n.s.		n.s.	

Razvi, 2007 (UK)					**Delta Mean Difference**	**P**
	Thyroxine	**N**	**Placebo**	**N**		
Dosage	100 mcg/day for 12 weeks					
T-QoL After	-1.1 +/- 1	50	-1.2 +/- 0.9	50	0.2 (0.02 to 0.36)	n.s.
Sex life After	-2.3 +/- 2.7	50	-2.7 +/- 2.8	50	0.3 (0.02 to 0.7)	n.s.
Motivation After	-3.6 +/- 2.7	50	-3.7 +/- 2.7	50	0.4 (-0.4 to 0.9)	n.s.
Worries After	-2.5 +/- 3	50	-2.8 +/- 2.9	50	0.2 (-0.2 to 0.7)	n.s.
AWI* After	-2.7 +/- 2.4	50	-2.8 +/- 2.3	50	0.1 (-0.3 to 0.5)	n.s.

2 *AWI: Average weighted impact of all 18 domains

TABLE 8b. WEIGHT (kg)/BMI (kg/m^2) (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	P
Caraccio, 2005 (Italy)		BMI	BMI				
Thyroxine	65 mcg (avg) for 6 months	22.8 +/- 0.9	22.3 +/- 0.9	-0.5	n.s.		
Placebo		22.6 +/- 0.6	22.7 +/- 0.6	0.1	n.s.		
						-0.6†	n.s.
Quality: Fair							
Iqbal, 2006 (Norway)		BMI	BMI				
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	28.7 +/- 5.7	28.4 +/- 5.8	-0.3	n.s.		
Placebo		27.1 +/- 3.7	27.0 +/- 4.1	-0.1	n.s.		
						-0.2†	n.s.
Quality: Fair							
Nagasaki, 2009 (Japan)		BMI	BMI				
Thyroxine	Not stated for 5 months	22.0 +/- 0.48	21.8 +/- 0.48	-0.2	n.s.		
Placebo		22.2 +/- 0.51	22.1 +/- 0.50	-0.1	n.s.		
						-0.1†	n.s.
Quality: Fair							
Razvi, 2007 (UK)		WEIGHT	WEIGHT				
Thyroxine	100 mcg/day for 12 weeks	75.9 +/- 15.9	75.8 +/- 16.5	-0.1	n.s.		
Placebo		77.0 +/- 16.9	76.5 +/- 16.7	-0.5	n.s.		
						-0.6 (-1.1 to -0.1)	n.s.
Quality: Good							

†Difference calculated from numbers provided

TABLE 8c. BLOOD PRESSURE (mmHg) (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	P
Nagasaki, 2009 (Japan)		Systolic	Systolic				
Thyroxine	Not stated for 5 months	132.8 +/- 3.9	128.8 +/- 3.8	-4.0	n.s.		
Placebo		133.1 +/- 3.4	132.2 +/- 3.5	-0.9	n.s.		
						-3.1†	n.s.
		Diastolic	Diastolic				
Thyroxine		74.3 +/- 2.9	72.7 +/- 2.2	-1.6	n.s.		
Placebo		75.7 +/- 1.9	72.8 +/- 2.0	-2.9	n.s.		
						1.3†	n.s.
Quality: Fair							
Razvi, 2007 (UK)		Systolic	Systolic				
Thyroxine	100 mcg/day for 12 weeks	135.7 +/- 22.6	132.8 +/- 22.8	-2.9	n.s.		
Placebo		129.4 +/- 20.1	134.6 +/- 22.9	5.2	n.s.		
						-1.8 (-4.6 to 1.0)	n.s.
		Diastolic	Diastolic				
Thyroxine		80.8 +/- 8.3	78.8 +/- 10.3	-2.0	n.s.		
Placebo		79.1 +/- 10.0	79.9 +/- 9.6	0.8	n.s.		
						-1.1 (-2.8 to 0.5)	n.s.
Quality: Good							

†Difference calculated from numbers provided

TABLE 8d. TOTAL CHOLESTEROL (mg/dL)* (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	p
Iqbal, 2006 (Norway)							
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	227.7 +/- 42.5	220.0 +/- 42.5	-7.7	n.s.		
Placebo		223.9 +/- 30.9	223.9 +/- 34.7	0	n.s.		
						-7.7†	n.s.
Quality: Fair							
Mikhail, 2008 (Kuwait)							
Thyroxine	72+/-3.8 mcg/day (avg) for 52 weeks	194.9 +/- 37.8	183.0 +/0 33.6	-11.9	< 0.001		
Placebo		192.6 +/- 27.8	194.5 +/- 25.9	1.9	n.s.		
						-13.8†	0.03
Quality: Fair							
Nagasaki, 2009 (Japan)							
Thyroxine	Not stated for 5 months	215.8 +/- 10.4	200.3 +/- 6.2	-15.5	n.s.		
Placebo		213.5 +/- 9.7	205.7 +/- 9.3	-7.8	n.s.		
						-7.7†	n.s.
Quality: Fair							
Razvi, 2007 (UK)							
Thyroxine	100 mcg/day for 12 weeks	235.5 +/- 34.7	220.0 +/- 38.6	-15.5			
Placebo		231.6 +/- 54.0	231.6 +/- 38.6	0		-13.5 (-19.3 to -7.72)	< 0.001
Quality: Good							

*Converted from mmol/liter by multiplying by 38.6

†Difference calculated from numbers provided

TABLE 8e. LDL (mg/dL)* (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	p
Iqbal, 2006 (Norway)							
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	142.8 +/- 34.7	139.0 +/- 34.7	-3.8	n.s.		
Placebo		139.0 +/0 30.9	139.0 +/0 38.6	0	n.s.		
						-3.8†	n.s.
Quality: Fair							
Mikhail, 2008 (Kuwait)							
Thyroxine	72+/-3.8 mcg/day (avg) for 52 weeks	127.4 +/- 34.7	111.6 +/- 22.8	-15.8	< 0.01		
Placebo		107.7 +/- 23.2	120.0 +/- 29.7	+12.3	< 0.001		
						-28.1†	< 0.001
Quality: Fair							
Nagasaki, 2009 (Japan)							
Thyroxine	Not stated for 5 months	138.2 +/- 8.5	121.2 +/- 11.2	-17.0	n.s.		
Placebo		137.4 +/- 7.7	129.7 +/- 7.3	-7.7	n.s.		
						-9.3†	
Quality: Fair							
Razvi, 2007 (UK)							
Thyroxine	100 mcg/day for 12 weeks	139.0 +/- 30.9	131.2 +/- 30.9	-7.8			
Placebo		139.0 +/- 46.3	142.8 +/- 34.7	+3.8			
						-7.7 (-15 to -3.9)	<0.001
Quality: Good							

*Converted from mmol/liter by multiplying by 38.6

†Difference calculated from numbers provided

TABLE 8f. HDL (mg/dL)* (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	P
Iqbal, 2006 (Norway)							
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	57.9 +/- 15.4	57.9 +/- 15.4	0.0	n.s		
Placebo		57.9 +/- 23.2	57.9 +/- 19.3	0.0	n.s.	0†	n.s.
Quality: Fair							
Mikhail, 2008 (Kuwait)							
Thyroxine	72+/-3.8 mcg/day (avg) for 52 weeks	46.3 +/- 12.7	45.9 +/- 12.4	-0.4	n.s.		
Placebo		44.4 +/- 8.9	42.5 +/- 9.7	-1.9	n.s.		
						1.5†	n.s.
Quality: Fair							
Nagasaki, 2009 (Japan)							
Thyroxine	Not stated for 5 months	54.4 +/- 1.9	54.4 +/- 3.1	0.0	n.s.		
Placebo		53.3 +/- 2.3	53.7 +/- 2.3	0.4	n.s.	-0.4†	n.s.
Quality: Fair							
Razvi, 2007 (UK)							
Thyroxine	100 mcg/day for 12 weeks	65.6 +/- 19.3	61.8 +/- 19.3	-3.8			
Placebo		61.8 +/- 15.4	65.6 +/- 19.3	3.8			
						-2.3 (-3.9 to -0.4)	n.s.
Quality: Good							

*Converted from mmol/liter by multiplying by 38.6

†Difference calculated from numbers provided

TABLE 8g. TRIGLYCERIDES (mg/dL)* (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	P
Iqbal, 2006 (Norway)							
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	132.9 +/- 79.7	132.9 +/- 88.6	0	n.s.		
Placebo		141.8 +/- 79.7	141.8 +/- 62.0	0	n.s.		
						0†	n.s.
Quality: Fair							
Mikhail, 2008 (Kuwait)							
Thyroxine	72+/-3.8 mcg/day (avg) for 52 weeks	104.5 +/- 62.9	84.2 +/- 47.0	-20.3	< 0.002		
Placebo		89.5 +/- 58.5	93.9 +/- 52.3	4.4	n.s.		
						-24.7†	n.s.
Quality: Fair							
Nagasaki, 2009 (Japan)							
Thyroxine	Not stated for 5 months	118.7 +/- 12.4	132.9 +/- 14.2	14.2	n.s.		
Placebo		121.4 +/- 11.5	122.3 +/- 12.4	.9	n.s.		
						13.3†	n.s.
Quality: Fair							
Razvi, 2007 (UK)							
Thyroxine	100 mcg/day for 12 weeks	106.3 (62.0 to 327.8)	115.2 (44.3 to 363.3)	8.9	n.s.		
Placebo		106.3 (44.3 to 274.7)	115.2 (35.4 to 451.9)	8.9	n.s.		
						-5.3 (-17.7 to -8.9)	n.s.
Quality: Good							

*Converted from mmol/liter by multiplying by 88.6

†Difference calculated from numbers provided

Cardiac Events

None of the studies evaluated the effect on cardiovascular morbidity or mortality from treatment of subclinical hypothyroidism with levothyroxine.

Quality of Life (QoL)

Two studies, with a total of 169 subjects, evaluated the effect of treatment on measures of quality of life. One good-quality, 12-week cross-over study (Razvi) enrolled 100 participants from 322 patients from urban, general practices in the United Kingdom identified as eligible from thyroid function tests from a laboratory database.[83]. Of the 322 patients originally identified as eligible, 63% had been tested either for symptoms attributable to hypothyroidism (n=179) or because of familial history of thyroid disease (n=24). Fifty of the enrollees were given 100 mcg of levothyroxine without dose titration and 50 were given placebo for 12 weeks. Patients then switched treatment arms without a wash-out period. (The half-life of thyroxine is estimated to be 5 – 9 days.) While the absence of a washout period could introduce bias, it would bias the study towards the null, i.e. decrease the likelihood of demonstrating a treatment effect. The primary endpoints of this study were improved brachial artery flow-mediated dilatation (as a marker of vascular endothelial function) and total cholesterol. Secondary endpoints assessed were changes in weight (as measured by body mass index), patient-reported outcomes including perceived health status, hypothyroidism-specific quality of life and hypothyroid symptoms (as assessed by questionnaires). This trial found no improvement in overall quality of life measures; health status, as measured by the SF-36v2, or treatment satisfaction.

The other trial (Jorde, n=69) recruited subjects who had a TSH level between 3.5 and 10 mU/L from a population-based sample in Norway. Asymptomatic subjects who had no history of

thyroid disease were invited to participate in a 12-month trial of levothyroxine treatment. After 12 months, there was no significant improvement in cognitive or emotional function or in hypothyroid symptoms.

Weight/Body Mass Index (BMI)

Four studies with a total of 305 subjects looked at either weight or BMI. Study periods ranged from five [82] to 12 months [79]. Three were rated fair quality[78, 79, 82]; one was rated good quality [83]. None found any significant improvement in either weight or BMI after five months [82], 24 weeks [83], 6 months [78], or one year [79].

Blood Pressure

Two studies, with a total of 195 subjects looked at blood pressure. One five month study (n=95) was rated fair quality [82] the other (n=100), a 12-week cross-over study was rated good. [83] Neither found significant improvement in blood pressure.

Lipids

Four studies with a total of 379 subjects evaluated the impact of treatment on lipids. Two found improvements to lipids; two found no improvement.

The good quality randomized, controlled 12-week, cross-over trial showed modest improvement in total cholesterol and LDL [83]. The study also reported results for changes in LDL, HDL, and triglycerides. Razvi found a significant decrease in total cholesterol of 5.8% (from 235.5 mg/dL to 220.0 mg/dL; p = <0.001) and a significant 5.6% decline in LDL (from 139.0 mg/dL to 131.2 mg/dL; p=<0.05).

We also found one fair-quality RCT that demonstrated improvement in total cholesterol and LDL from treatment for subclinical hypothyroidism. [81] While this study described itself as a double-blinded randomized, placebo-controlled trial, blinding was not described nor was allocation concealment. In addition, the number of enrolled patients was described at baseline, but not at the end of the study and there was no mention of intention to treat analysis. This study of 120 patients from an endocrinology outpatient clinic in Kuwait found a significant decline in LDL of 12.4% (from 127.38 mg/dL to 111.55 mg/dL; $p<0.01$) and a significant 6.1% decline in total cholesterol (194.9 mg/dL to 183.0 mg/dL; $p< 0.0001$).

Iqbal 2006, [79] a fair quality study with 64 subjects did a post hoc analysis and found a significant decline in total cholesterol and LDL in the subgroup of 23 patients with serum TSH at the end of the 12 month study within the range 0.2 – 2.0 mIU/L but no difference in lipids when considering the full study sample. This study reported the number of patients enrolled at baseline but not at study conclusion, and did not indicate that intention-to-treat analysis was followed. Nagasaki 2008, [82] a fair quality study of 95 subjects found no improvement in any lipids. Like Iqbal, Nagasaki reported the number of patients enrolled at baseline but not at study conclusion, and did not indicate that intention-to-treat analysis was followed.

Subclinical Hyperthyroidism

No controlled trials for the treatment of subclinical hyperthyroidism were found in the Helfand 2004 systematic review for the USPSTF [16]. We identified two poor quality controlled trials that assessed the effect of treatment of subclinical hyperthyroidism[84, 85]. (See Table 9 and Tables 9a – 9d) Buscemi (2007)[84] (n=14) was designed to assess the effects of treatment of subclinical hyperthyroidism on the heart as measured by blood pressure, basal heart rate, 24-hour heart rate, and atrial and ventricular premature beats; on bone turnover; and on bone density as

measured by heel ultrasonometry (Stiffness Index). That study found a small, but significant weight gain (BMI 27.3 +/- 1.3 kg/m^2 to 27.8 +/- 1.4 kg/m^2 in treated patients vs. 27.9 +/- 1.2 kg/m^2 to 28.1 +/- 1.0 kg/m^2 in untreated controls; $p < 0.05$) after 12 months of treatment with methimazole. However, this study was weakened by failure to conceal allocation (alternating assignment) and lack of blinding (patients were given the option of changing their randomly assigned group; blinding of assessors was not described). In Yonem (2002)[85] (n=20), 10 patients with subclinical hyperthyroidism randomized to treatment with propylthiouracil (nine patients) or radioiodine (one patient) were compared with 10 patients randomized to no treatment and found no change in bone mineral density or lipids, a small, but significant decrease in mean daytime systolic blood pressure (from 115.00 +/- 2.78 mmHg to 112.42 +/- 2.66 mmHg in treated patients vs. from 114.50 +/- 3.21 to 113.70 +/- 2.62 mmHg in untreated controls; $p < 0.05$), and inconsistent findings with regard to patient-reported outcomes. Of the 10 patients randomized to treatment nine received propylthiouracil and one received radioactive iodine and the analysis did not distinguish between treatments. In addition, patients randomized to control received no treatment and so the study was not adequately blinded.

TABLE 9. TREATMENT EVIDENCE TABLE (SUBCLINICAL HYPERTHYROIDISM)

Author, year Duration	Country and population	Study design	Sample size Begun/Completed	Results[a]		Quality Score
1. Buscemi, 2007 12 months	Italy. Newly diagnosed patients. TSH < 0.49 mIU/L	Controlled trial. Treatment allocation through alternate assignment. Patients given option of changing assigned group (none did). Not blinded.	Methimazole: 7/7 No treatment: 7/7	BMI Blood Pressure	⇧ ⇔	**Poor**
2. Yonem, 2002 6 months	Turkey. Patients with SCH for 6 – 60 months. 2 patients with Graves disease and 8 with autonomous nodule. TSH < 0.4 mIU/L	Randomized controlled trial. Randomization method not stated. Not blinded. Allocation concealment not described. Multiple treatments not analyzed separately	Propylthiouracil: 9/? Radioactive Iodine: 1/? No Treatment: 10/? Treatments not analyzed separately	Total Cholesterol LDL HDL Triglycerides Bone Mineral Density Blood Pressure	⇔ ⇔ ⇔ ⇔ ⇔ ⇧	**Poor**

[a] For details see separate results tables by outcome – Tables 7a-7d
⇔: No evidence of benefit
⇧: Evidence of benefit

TABLE 9a. BMI (kg/m^2) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Buscemi, 2007 (Italy)							
Methimazole	TSH > 0.01: 10 mg/day TSH <= 0.01: 15 mg/day for 12 months	27.3 +/- 1.3	27.8 +/- 1.4	0.5	<0.05		
No Treatment		27.9 +/- 1.2	28.1 +/- 1.0	0.2	n.s.		
						0.3	?
Quality: Poor							

†Difference calculated from numbers provided

TABLE 9a. BMI (kg/m^2) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Buscemi, 2007 (Italy)							
Methimazole	TSH > 0.01: 10 mg/day TSH <= 0.01: 15 mg/day for 12 months	27.3 +/- 1.3	27.8 +/- 1.4	0.5	<0.05		
No Treatment		27.9 +/- 1.2	28.1 +/- 1.0	0.2	n.s.		
						0.3	?
Quality: Poor							

†Difference calculated from numbers provided

TABLE 9b. BLOOD PRESSURE (mmHg) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Buscemi, 2007 (Italy)		Systolic	Systolic				
Methimazole	TSH > 0.01: 10 mg/day TSH <= 0.01: 15 mg/day for 12 months	139 +/- 6	136 +/- 4	-3	n.s.		
No Treatment		136 +/- 8	126 +/- 11	-10	n.s.		
						7	n.s.
		Diastolic	Diastolic				
Methimazole		79 +/- 3	78 +/- 3	-1	n.s.		
No Treatment		78 +/- 3	80 +/- 3	+2	n.s.		
						-3	n.s.
Quality: Poor							
Yonem, 2002 (Turkey)		Daytime Systolic	Daytime Systolic				
Propylthiouracil or Radioactive Iodine	Propylthiouracil 150 mg/day Radioactive Iodine not stated for 6 months	115.00 +/- 2.78	112.42 +/- 2.66	-2.58	<0.05		
No Treatment		114.50 +/- 3.21	113.70 +/- 2.62	-0.80	n.s.		
						-1.78	?
		Daytime Diastolic	Daytime Diastolic				
Propylthiouracil or Radioactive Iodine		71.10 +/- 2.37	69.40 +/- 1.78	-1.70	n.s.		
No Treatment		72.70 +/- 2.00	72.10 +/- 2.37	-0.60	n.s.		
						-1.1	
		Nighttime Systolic	Nighttime Systolic				
Propylthiouracil or Radioactive Iodine		98.50 +/- 2.96	100.10 +/- 2.25	1.60	n.s.		
No Treatment		100.60 +/- 2.29	101.60 +/- 1.96	1.00	n.s.		
						0.6	n.s.
		Nighttime Diastolic	Nighttime Diastolic				
Propylthiouracil or Radioactive Iodine		62.80 +/- 1.95	61.50 +/- 1.40	-1.30	n.s.		
No Treatment		62.30 +/- 1.71	61.80 +/- 2.80	-0.50	n.s.		
						-0.8	n.s.

Quality: Poor

[†]Difference calculated from numbers provided

TABLE 9c. BONE MINERAL DENSITY (g/cm^2) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Yonem, 2002 (Turkey)		Femur Neck	Femur Neck				
Propylthiouracil or Radioactive Iodine	Propylthiouracil 150 mg/day Radioactive Iodine not stated for 6 months	0.828 +/- 0.038	0.826 +/- 0.042	-0.002	n.s.		
No Treatment		0.848 +/- 0.017	0.868 +/- 0.019	0.020	n.s.		
						-0.022	n.s.
		Lumbar Vertebra	Lumbar Vertebra				
Propylthiouracil or Radioactive Iodine		0.991 +/- 0.046	0.998 +/- 0.048	0.007	n.s.		
No Treatment		0.968 +/- 0.030	0.968 +/- 0.030	0.000	n.s.		
Quality: Poor						.007	n.s.

†Difference calculated from numbers provided

TABLE 9d. LIPIDS (mg/dL) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Yonem, 2002 (Turkey)		TOTAL CHOLESTEROL	TOTAL CHOLESTEROL				
Propylthiouracil or Radioactive Iodine	Propylthiouracil 150 mg/day Radioactive Iodine not stated for 6 months	183.0 +/- 12.0	182.6 +/- 8.9	-0.4	n.s.		
No Treatment		161.7 +/- 10.0	157.1 +/- 6.6	-4.6	n.s.		
						4.2	n.s.
		LDL	LDL				
Propylthiouracil or Radioactive Iodine		110.0 +/- 8.8	105.8 +/- 6.6	-4.2	n.s.		
No Treatment		86.9 +/- 6.9	91.1 +/- 5.8	4.2	n.s.		
						-8.4	n.s.
		HDL	HDL				
Propylthiouracil or Radioactive Iodine		54.4 +/- 4.6	47.5 +/- 3.9	-6.9	n.s.		
No Treatment		52.5 +/- 5.8	48.3 +/- 3.5	-4.2	n.s.		
						-2.7	n.s.
		TRIGLYCERIDES	TRIGLYCERIDES				
Propylthiouracil or Radioactive Iodine		124.0 +/- 15.9	39.9 +/- 23.9	-84.1	?		
No Treatment		93.9 +/- 10.6	76.2 +/- 14.2	-17.7	n.s.		
Quality: Poor						-66.4	n.s.

*Converted total cholesterol, LDL, and HDL from mmol/liter by multiplying by 38.6 and triglycerides by 88.6

†Difference calculated from numbers provided

Key Question 4. What are the harms of treatment of subclinical hypothyroidism and subclinical hyperthyroidism?

Until August, 2000, levothyroxine sodium was an unapproved marketed drug. In August 1997, the FDA declared levothyroxine sodium tablets a "new drug", requiring manufacturers to submit a new drug approval to continue manufacturing it. The first product was approved in August, 2000. The product label mentions adverse effects on bone mineral density and the cardiovascular system, such as provocation of angina and arrhythmias and increased cardiac wall thickness. The FDA's medical reviewer cited the following evidence regarding the safety of levothyroxine:

- Elderly patients >= 60 years, with TSH suppressed to <= 0.1 mIU/L due to either subclinical hyperthyroidism or overtreatment with levothyroxine had approximately a 3-fold increased incidence of atrial fibrillation over a 10-year period compared to those with normal TSH levels;[86]
- Two systematic reviews found that long-term suppression therapy with levothyroxine led to decreases in bone mass in post-menopausal women. No adverse effect was found in men.[64, 65]

The approval was conducted without requiring manufacturers to conduct studies to estimate the actual risks of short-term or long-term adverse effects. Consequently, scant information regarding the adverse effects of thyroid replacement is available. The 2004 review[16] and the Cochrane review both mentioned that information about the frequency and severity of side effects when levothyroxine is used to treat subclinical hypothyroidism is lacking.

Three of the studies reviewed by Helfand (2004) provided some information on harms.[71, 72, 76] In one study,[10] out of 33 individuals, four treated with levothyroxine (and 6 with placebo) "felt

worse." Another study reported that out of 37 total individuals, one developed atrial fibrillation, and one developed angina.[73] A third study found anxiety scores to be higher in the levothyroxine treated group.[74] In another study of 20 individuals, two in the treatment arm dropped out, one for "nervousness" and another for "a sense of tachycardia."[75] The final study reported that within the treatment group a reduction in SF-36 vitality scores was found.[77]

None of newer studies of treatment for either subclinical hypothyroidism or subclinical hyperthyroidism systematically reported on harms. Of the six studies of treatment of subclinical hypothyroidism included in the current review only one reported on harms, stating that none of the patients reported side effects that would have required withdrawal or dose reduction[82]. One[83] of the other five reported that one participant withdrew from the study after reporting side effects from 12 days of placebo treatment; a second[80] reported that one subject in the placebo group dropped out after six months because of serious disease unrelated to thyroid function.

The long-term adverse effects of levothyroxine therapy may depend on careful clinical and laboratory monitoring and adjustment of dosage accordingly. The previous systematic review demonstrated that overtreatment with levothyroxine leading to undetectable TSH levels is common in practice [1]. We did not identify more recent data to estimate the frequency of overtreatment in current practice.

For subclinical hyperthyroidism, one of the two studies of treatment reported that they "did not find any increase in confusion, myopathy, atrial fibrillation, and deep tendon reflexes incidence" in either the treatment or observation group before or after treatment/observation[85].The second study[84] did not discuss harms.

Chapter 4. Discussion

Summary of Review Findings

Tables 10A and 10B summarize our findings by key question.

Table 10A. Summary of evidence – Subclinical Hypothyroidism

Key Question	Study Type: Number of studies Number of subjects	Risk of Bias	Consistency	Directness	Precision	Comments	Magnitude of effect and *strength of evidence*
KQ1. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
KQ 2. What are the harms of screening for subclinical thyroid disease?	2 studies	N/A	No major inconsistency	Indirect Low to moderate applicability to primary care	N/A	No randomized controlled trials were identified; two natural history studies demonstrating indirect evidence of potential harm were included	***Insufficient***
KQ 3. Does treatment make a difference in morbidity or mortality when subclinical hypothyroidism is detected by screening?							
Cardiovascular events and coronary heart failure	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
Overall quality of life	RCT: 2 169	Fair	Consistent	Indirect Moderate applicability to primary care setting	Imprecise: Small studies of 100 and 69 subjects		No effect ***Low***

Changes in mood/cognition	RCT: 2 169	Fair	Consistent	Indirect Moderate applicability to primary care setting	Imprecise: Small studies of 100 and 69 subjects	No effect ***Low***
Weight/BMI changes	RCT: 4 305	Fair	Consistent	Indirect	Imprecise The largest study had 100 subjects; the smallest had 23	No effect ***Low***
Blood pressure changes	RCT: 2 195	Fair	Consistent	Indirect Low applicability to asymptomatic patients in primary care settings	Imprecise	No effect ***Low***
Changes in lipid levels	RCT: 4 379	Fair	Inconsistent	Indirect Low applicability to asymptomatic patients in U.S. primary care settings	Imprecise	Effect for LDL and total cholesterol ***Low***
KQ4. What are the harms of treatment of subclinical hypothyroidism and sub-clinical hyperthyroidism?	No Studies	N/A	N/A	N/A	N/A	***Insufficient***

Table 10B. Summary of evidence – Subclinical Hyperthyroidism

Key Question	Study Type: Number of studies Number of subjects	Risk of Bias	Consistency	Directness	Precision	Comments	Magnitude of effect and *strength of evidence*
KQ1. Does screening for subclinical thyroid dysfunction reduce morbidity or mortality?	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
KQ 2. What are the harms of screening for subclinical thyroid disease?	No studies	N/A	N/A	N/A	N/A	N/A	No evidence ***Insufficient***
KQ 3. Does treatment make a difference in morbidity or mortality when subclinical hyperhyroidism is detected by screening?							
Cardiovascular events including angina, atrial fibrillation, and other clinically significant arrhythmias	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
Fractures	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***
Overall quality of life Changes in mood/cognition	No studies	N/A	N/A	N/A	N/A		No evidence ***Insufficient***

Weight/BMI changes	Controlled trial: 1 14	High	N/A	Direct .	Imprecise	About 1% greater decrease in BMI in treated as compared to placebo group; absolute change in BMI in treated group of 0.5 kg/m^2 ***Insufficient***
Blood pressure changes	RCT: 1 20 Controlled trial: 1 14	High	Inconsistent	Indirect Treated subjects in one study included 2 patients with Graves disease and 8 with autonomous nodules	Imprecise	2.58 mmHG reduction daytime systolic BP from 1 study; no change in 2nd study ***Insufficient***
Changes in bone density (as measured by DEXA scan)	RCT: 1 20	High	N/A	Indirect Treated subjects included 2 patients with Graves disease and 8 with autonomous nodules	Imprecise	No effect ***Insufficient***

Changes in lipid levels	RCT: 1 20	High	N/A	Indirect Treated subjects included 2 patients with Graves disease and 8 with autonomous nodules	Imprecise	No effect ***Insufficient***
KQ4. What are the harms of treatment of subclinical hyperthyroidism and sub-clinical hyperthyroidism?	No studies	N/A	N/A	N/A	N/A	***Insufficient***

1

Benefits of screening/treatment

No comparative studies have evaluated the benefits of screening for thyroid disease versus watchful waiting (Key Question 1). Thus, it remains unknown if screening the general population with a serum TSH test will improve outcomes. The rationale for screening is based on the premise that subclinical hypothyroidism and hyperthyroidism have an inherent detrimental effect on health. We did not systematically review the literature concerning the relationship between mildly elevated TSH levels and long-term cardiovascular and cognitive effects. In previous systematic reviews, the relationship between subclinical hypothyroidism and risk factors for coronary disease was inconsistent. More recent studies, in particular, the re-analysis of the Whickham data, suggest that subclinical hypothyroidism may be associated with increased cardiovascular morbidity over 20 years, but the validity and practical value of this observation is unclear. For example, whether a mildly elevated TSH confers additional risk for coronary events in the current era of widespread screening and treatment of hyperlipidemia is unclear, and the new data do not permit any estimate of the additional predictive ability of a TSH level above that of widely used risk assessment instruments based on the Framingham study. Based on the relative risks that these studies do provide, and even assuming that treatment has a reversible effect on the disease process, the additional benefit of screening and treatment for subclinical hypothyroidism is likely to be low.

Additionally, it is still unknown if treating individuals found to have subclinical thyroid dysfunction through population-based screening is beneficial. In attempting to demonstrate the benefit of treatment, the literature contained a fair number of rigorous studies that looked at a variety of physiological parameters. These studies represent potentially important work that might someday help explain all the effects of thyroid hormone within the body and help explain why

thyroid hormone is beneficial. However, we found only six trials of good or fair quality that reported outcomes that were in our analytic framework. No studies assessed effects on cardiac events. None of the studies found an improvement in patient-centered outcomes. Within the included studies, BMI/weight and measures of well-being were the only patient-centered outcomes evaluated, and improvement with treatment was not found. Four studies evaluated changes in intermediate outcomes that were included in our analytic framework. The findings regarding lipids were inconsistent, with two of the four studies finding some improvement and two finding no change[79, 81-83]. Neither of the two studies evaluating blood pressure found an improvement[82, 83].

The literature surrounding subclinical hyperthyroidism was particularly sparse; we only found two poor quality controlled trials. One found a slight improvement in weight gain after 12 months of treatment with methimazole, but no change in blood pressure. The other study found a small decrease in the mean daytime systolic blood pressure[84, 85].

Harms of Screening/Treatment (Key Questions #2 and #4)

The harms of screening are still poorly studied. Indirect evidence appears to indicate that overdiagnosis, and thus, over-treatment could be a potential problem.

The harms of treatment also remain insufficiently studied. We found no studies that primarily focused on the harms of treatment. Of the studies that evaluated the benefits of treating subclinical hypothyroidism, only one reported that no subjects had side effects that required withdrawal or dose reduction[82]. One study that evaluated the benefits of subclinical hyperthyroidism, reported simply that there was no “increase in confusion, myopathy, atrial fibrillation and deep tendon reflexes” with treatment.[85]

Strength of Evidence

The EPC strength of evidence assessment involves assessing the body of literature based on four domains: risk of bias, consistency, directness, and precision.

Risk of Bias

The possibility of bias or error within the studies that evaluated the benefits of treating subclinical hypothyroidism is moderate. Of the six trials that evaluated the benefits of treating subclinical hypothyroidism, one study was judged to be of good quality[83], the other five, fair quality. The fair quality studies, did not adequately describe their randomization, allocation, and/or blinding[78-82].

The possibility of bias within the studies that evaluated the benefits of treating subclinical hyperthyroidism is high. Both of these studies were of poor quality; assigning treatment or placebo via alternate assignment and offering the patients the options of switching arms once assigned[84], and not describing randomization, allocation concealment or blinding[85]. Additionally, in one study different treatments were used in the treatment arm[85].

Consistency

The four trials that evaluated the effect of thyroid replacement therapy on lipids in subjects with subclinical hypothyroidism were inconsistent. Two trials demonstrated improvement in lipids[81, 83], while another two trials showed no improvement[79, 82]. Blood pressure changes with thyroid replacement were also evaluated, and two studies were consistent in demonstrating no improvement[82, 83].

Of the two patient-centered outcomes evaluated in trials evaluating the benefits of treatment, four studies were consistent in showing no benefit of weight/BMI change[78, 79, 82, 83], and two studies were consistent in failing to show improvement in measures of well-being[80, 83].

Of the two studies evaluating the benefits of treating subclinical hyperthyroidism, both looked at blood pressure. One study found improvement in the mean, daytime systolic blood pressure[85] while the other did not[84].

Directness

For the purposes of this report, directness refers to both the applicability of a study to the population specified for this review (i.e. asymptomatic, non-pregnant individuals seen in primary care settings) and to the degree to which one can directly associate the intervention to a patient-centered outcome. As defined by our analytic framework, these include: coronary artery disease, congestive heart failure, measures of well-being, weight change, progression to overt disease, osteoporotic fractures, and atrial fibrillation. None of the trials included in this review found improvement in these outcomes.

The only benefit found was for lipids, an intermediate outcome for which results were inconsistent.

Applicability

Because 1) the topic was nominated with regard to a particular practice setting (primary care); 2) the key questions address a specific population (asymptomatic, non-pregnant individuals); and 3) this review will be used by a body, the USPSTF, to make a recommendation regarding screening for subclinical thyroid disease,, this review considers directness to include the domain

of applicability. Several aspects of these trials make their applicability to the general U.S. population a concern. First, none of the studies occurred in the U.S. Most of the studies recruited subjects from specialty clinics, rather than from the primary care setting. Additionally, the studies were relatively short, the longest lasting 12 months. The applicability of studies of this duration to a condition that is generally life-long is unclear.

Precision

The studies included in the review were small. Among studies of subclinical hypothyroidism, the largest contained 120 individuals[81], with the smallest having only 23 subjects[78]. Of the two studies of subclinical hyperthyroidism one had 20 subjects[85] and one 14[84]. Due to the small sample size, none of the included studies were judged to provide a precise estimation of the effect of treatment.

Limitations

In addition to the above regarding the possibility of bias, consistency, directness, and precision, we are also concerned that the included studies used different lab values as the cutoff for an abnormal TSH and used different doses of levothyroxine, making comparisons between studies difficult. Because of this clinical heterogeneity, a meta-analysis was not conducted.

Strength of Evidence

As in 2004, there remains insufficient evidence directly linking screening of asymptomatic individuals for subclinical thyroid disease to improvements in morbidity or mortality. However a growing body of evidence, which this review rates as low quality, continues to suggest that

treating sub-clinical hypothyroidism is not any more beneficial than watchful waiting for overall quality of life, mood or cognition, weight/BMI or blood pressure changes. Studies regarding lipids remain inconsistent, small, and of varying quality. We, therefore, regard the evidence concerning lipids as insufficient to determine if treatment is more beneficial than watchful waiting. Larger trials of treatment that are longer in duration would be helpful in improving the quality of evidence for all of these outcomes.

The following information from this report can be helpful to the practicing clinician:

- We know that subclinical thyroid disease is not uncommon, with prevalence somewhere in the range of 5% for the general population.
- It is still unclear if subclinical thyroid disease has any impact on patient outcomes. Systematic reviews regarding all-cause mortality and coronary artery disease mortality are inconsistent, and indicate that even if treatment is effective, a clinician would need to screen and treat a large number of patients before seeing a benefit to any individual patient.
- We know that there is some evidence that as many as 37% of patients initially diagnosed with subclinical hypothyroidism may test normal within the three years following initial screening.
- We know, therefore, that there is potential for serious harms, including atrial fibrillation and angina, from unnecessary treatment or overtreatment of subclinical thyroid disease, although in most cases reported harms appear to be minor, such as increased anxiety and nervousness, and are likely to improve with discontinuation of therapy.
- The quality of evidence is low that treating subclinical hypothyroidism will lead to improvement in quality of life, mood, cognition, weight/BMI, or blood pressure when compared with watchful waiting.

- Finally we know that the current evidence is inconsistent with regards to the benefits of treatment for lipids, that improvement is likely to be modest at best, and is likely to be of little clinical significance.

As in all cases, this evidence should be considered, along with the physician's knowledge of the individual, in making clinical judgments about the appropriate care for each patient. For instance, one might consider levothyroxine therapy in an individual with both subclinical hypothyroidism and dyslipidemia, who also reports several symptoms of thyroid dysfunction, but who is at low risk for atrial fibrillation and other possible side effects. However, an individual at higher risk of atrial fibrillation, who has no or few hypothyroid symptoms, or who is known to be prone to anxiety might not be a good candidate for treatment.

Emerging issues/Next steps

One issue that might emerge in the near future concerns the clinical significance of a mildly elevated TSH in the elderly population. Two ecological studies indicate that a mildly high TSH is a predictor of longevity[19, 20]. Another recent study indicates that older individuals with subclinical hypothyroidism might have a slight functional benefit[18]. Thus, not treating subclinical hypothyroidism, at least in the elderly population might be advantageous.

Future Research

Because the prevalence of subclinical thyroid dysfunction in the general population may be as high as 7% in women and 5% in men,[16] determining the harms and benefits of screening and treating thyroid disease has the potential to significantly impact the health of many. Many experts who favor early treatment acknowledge the need for appropriately powered randomized

controlled trials comparing early treatment with thyroxine therapy to active surveillance or expectant management in patients who have a mildly increased serum TSH level. The trial should follow subjects for at least 3 years. Such a trial should recruit subjects who were identified by screening. The power of such a trial can be increased by requiring a longer pre-randomization period to ensure that subjects have persistently high TSH levels, and by including subjects who have serologic evidence of autoimmunity

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