

Evidence-based Practice Center Systematic Review Protocol

Project Title: *Effectiveness of Screening and Treatment of Subclinical Hypothyroidism or Hyperthyroidism*

I. Background and Objectives for the Systematic Review

Condition Background

Condition definition

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 may include fatigue, feeling cold, weight gain, hair loss, poor concentration, dry skin, and constipation. 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.¹

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.¹

Subclinical thyroid dysfunction includes subclinical hypo- and hyperthyroidism. In these conditions, the serum TSH is either high or low, but free T4 and free T3 levels are normal and patients lack the signs and symptoms of overt thyroid dysfunction.¹

Subclinical hypothyroidism can be caused by poor adherence or under-treatment with levothyroxine, recent hospitalization for severe illness, previously treated Graves' disease, recovery from thyroiditis, and untreated adrenal insufficiency. Causes of subclinical hyperthyroidism are similar to overt hyperthyroidism and include Graves' disease, thyroiditis, thyroid nodule(s), and levothyroxine over-treatment.¹

Prevalence and burden of disease/illness

The prevalence of subclinical hypothyroidism ranges from 4 to 8.5%^{2,3} depending on the defined upper limit for TSH. In general the prevalence increases with age, and is higher among whites compared to blacks.² The prevalence of subclinical hyperthyroidism, excluding those with known thyroid disease, is 2%. Again estimates may vary based on whether a TSH threshold of 0.4 or 0.1 mIU/L is used for the definition of this condition. It has a higher prevalence in women, blacks, older individuals and those with low iodine intake.² Up to 20% of women over 60 years old have subclinical hypothyroidism.³

In the Colorado Thyroid Disease Prevalence Study, 0.4% of participants had hypothyroidism, and almost 30% of those reported no symptoms.³ The difference in the prevalence of symptoms between euthyroid controls (12.1%) and subjects with subclinical hypothyroidism (13.7%) was marginal.⁴ In another study of patients at a lipid clinic who did not carry a diagnosis of thyroid disease, seven female asymptomatic patients (2.8%) had frank biochemical hypothyroidism, and 11 patients (4.4%) had subclinical hypothyroidism.⁵

Etiology and natural history

It has been asserted that thyroid dysfunction is a continuum of subclinical disease to overt disease to life-threatening complications,⁶ and thus identification of those in the early stages can prevent morbidity and mortality. 2-5% of patients with subclinical hypothyroidism will progress to overt hypothyroidism. This however is proportional to the baseline TSH and occurs more frequently in those with anti-thyroid antibodies.² 1-2% of individuals with a TSH <0.1 mIU/L develop overt hyperthyroidism.²

Consequences of untreated subclinical hypothyroidism may include elevated total and LDL cholesterol, development of systemic hypothyroid symptoms, and neuropsychiatric symptoms.² 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.² While untreated thyroid dysfunction in pregnancy has possible association with increased miscarriage and neuropsychological complications in offspring, the adverse consequences of untreated subclinical thyroid dysfunction is less clear.^{2, 7, 8}

Risk factors

Risk factors for subclinical hypothyroidism include previous hyperthyroidism, type 1 diabetes mellitus, a family history of thyroid disease, Down's syndrome and treatment with external beam radiation for head and neck cancer.^{1, 2} Risk factors for subclinical hyperthyroidism are goiter, personal history of previous thyroid disease, family history of thyroid disease, atrial fibrillation, and ingestion of iodine-containing drugs, such as amiodarone.¹

Rationale for screening/screening strategies

Screening for both subclinical hypo- and hyperthyroidism is accomplished through serum TSH, with testing of serum free T4 and free T3 if the TSH falls outside of the normal range.¹ Additional testing is predicated on the results of this testing for diagnostic purposes and exclusion of other conditions.

Interventions/treatment

After excluding other causes, treatment of subclinical hypothyroidism may include thyroid hormone replacement. Its use however is controversial in individuals with TSH between 4.5 and 10.⁶ The use of replacement therapy does not prevent progression to overt hypothyroidism, but it may prevent symptoms of overt disease in those who do progress.²

Hyperthyroidism is treated with anti-thyroid medications, such as propylthiouracil, or therapy such as radioactive iodine. However a consensus statement of three endocrine specialty societies did not recommend routine treatment in those whose TSH was between 0.1 and 0.45 mIU/L. For individuals with TSH <0.1 mIU/L, treatment was to be considered for those found to

have Graves or nodular thyroid disease because of the risk of atrial fibrillation or bone loss particularly in the elderly; however it was not recommended in those with thyroiditis, as most cases resolve spontaneously.²

Current clinical practice

A 2004 systematic review, conducted in follow-up to a Consensus Development Conference jointly 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.² The review found insufficient evidence to support population-based screening, and recommended against population-based screening for thyroid disease, though they did advocate aggressive case-finding in those considered high-risk, including pregnant women and women over 60 years old.

They recommended against routine treatment of patients with subclinical hypothyroidism with serum TSH levels of 4.5-10 mIU/L based on insufficient evidence; they did recommend repeating thyroid function tests at 6 to 12 month intervals for monitoring. A trial of treatment could be considered for those with symptoms compatible with hypothyroidism, with continued treatment based on symptomatic benefit. Treatment was reasonable for those with TSH level greater than 10 mIU/L, though the evidence was inconclusive but more compelling. The recommendation for subclinical hyperthyroidism was to observe and monitor patients with TSH in the range of 0.1-0.4 mIU/L, though treatment could be considered for elderly individuals. The panel recommended that treatment of patients with TSH <0.1 mIU/L due to Graves or nodular thyroid disease be considered despite the lack of intervention trials. Treatment could be considered in those over 60 years of age, those at increased risk for heart disease, osteopenia or osteoporosis, and those with symptoms consistent with hyperthyroidism.

A consensus statement about subclinical thyroid dysfunction was published by these same three groups in 2005 as a “counterbalance to the recommendations made by the consensus conference”;⁶ it favored routine screening for subclinical thyroid dysfunction in adults, and recommended routine screening with TSH in women during pregnancy evaluation or at the time pregnancy was diagnosed. The panel recommended that most patients with serum TSH levels of 4.5-10 mIU/L should be considered for treatment, with clinical judgment of the provider. The panel agreed with the recommendations from the consensus conference regarding treatment of subclinical hyperthyroidism.

A committee appointed by the Institute of Medicine in 2003 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.”⁹ They cited the absence of evidence in the “definition and physiological concomitants of early thyroid dysfunction; the effects of early dysfunction on target tissues and organs; the presence or absence of clinical manifestations in these early stages; the natural history of early dysfunction; and the net personal and population benefits and harms of long-term treatment.”⁹

The American College of Obstetricians and Gynecologists (ACOG) recommended against routine screening in its 2007 Committee Opinion for screening pregnant women for subclinical hypothyroidism. It stated that there is no evidence that identifying and treating pregnant women with subclinical hypothyroidism improved either maternal or infant outcomes.¹⁰

It cited a lack of data indicating maternal or fetal benefit of thyroxine treatment in women with subclinical hypothyroidism.

In 2004 the U.S. Preventive Services Task Force (USPSTF) reviewed the evidence surrounding the benefits and harms of screening for thyroid disease in the general adult, non-pregnant population.¹⁴ At that time they determined that the TSH test can detect subclinical thyroid disease in people without symptoms of thyroid dysfunction and that a substantial number of women with a TSH greater than 10 mIU/L will progress to symptomatic hypothyroidism over time. However, the evidence was insufficient to recommend for or against routine screening for thyroid disease in adults (I recommendation). For both subclinical hypothyroidism and subclinical hyperthyroidism, the evidence that asymptomatic individuals identified by screening benefit from early treatment was poor. It remained unclear whether treating subclinical thyroid disease, if detected, would have a beneficial effect to reduce morbidity.

A 2007 Cochrane review concluded that levothyroxine therapy for subclinical hypothyroidism did not result in improved survival, decreased cardiovascular morbidity, or improved health-related quality of life.¹¹

Some older recommendations

The American College of Physicians has a 1998 guideline, but refers visitors to their website to the USPSTF for guidelines regarding screening of thyroid disease (ACP guidelines more than 5 years old have been inactivated). In 2002, the clinical practice guideline on the management and treatment of thyroid disease from the American Association of Clinical Endocrinologists recommended treatment of subclinical hyperthyroidism in those with nodular thyroid disease, though there was no consensus about the management of subclinical hyperthyroidism. Treatment was recommended in those with TSH >10 mIU/L, and in those with TSH levels between 5 and 10 mIU/L with positive anti-thyroid peroxidase antibodies and/or goiter.¹² The American Thyroid Association has suggested screening all patients over 35 years of age every 5 years (more frequently if the patient is at increased risk), but has not updated their recommendation since 2000.¹³

Scope of review

This review will focus on evidence regarding the benefits and harms of screening and treatment for subclinical hypothyroidism and subclinical hyperthyroidism. A review of the literature on epidemiological studies of the complications of subclinical thyroid dysfunction is outside the scope of this update. Such a review was done as part of a previous systematic review for the USPSTF and other organizations.¹⁴

There remains uncertainty regarding the management and treatment of subclinical thyroid disease as reflected in the recommendations from various professional societies and other groups. This uncertainty impacts the decision-making for clinicians who are considering treatments for subclinical hypo- and hyperthyroidism, as well as those recommending screening approaches. A systematic review will inform both sets of stakeholders by synthesizing evidence around the effectiveness of management and treatment.

II. The Key Questions

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

Contextual Questions and Issues:

1. What is the current practice for treating those with mild elevations of TSH?
 - The treatment of asymptomatic patients with TSH between 4 and 10 mIU/L remains controversial.
 - Though treatment with thyroid replacement was not recommended in a joint statement of three specialty organizations, based on “available data and collective clinical experience” most of these patients should be “considered for treatment with the key determinant being the clinical judgment of the provider.”
2. What is the treatment for subclinical hyperthyroidism?
3. What are the consequences of untreated subclinical thyroid disease, in particular related to cardiovascular outcomes?

Population(s)

- 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.

Interventions

- Screening interventions: Serum TSH, with testing of serum free T4 and/or T3 if TSH is outside the decision threshold.
- Treatment interventions: Treatment of hypothyroidism includes levothyroxine or other acceptable options of thyroid replacement therapy, and may include inclusion of activities related to observation (e.g. repeat testing, additional testing for thyroid antibodies, etc). Treatment of hyperthyroidism includes antithyroid drugs and radioactive iodine treatment.
 - Hypothyroid Treatment:

- Drug Class: Synthetic version of thyroxine (T4); Generic Name: Levothyroxine sodium (Brand Name: Levo-T, Synthroid, Levotheroid, Levoxyl, Unithroid); All drugs are FDA-approved for this indication.
- Drug Class: Synthetic version of thyroxine (T4) and triiodothyronine (T3); Generic name: Liotrix (Brand name: Thyrolar) Thyrolar is FDA-approved for this indication.
- Drug/Biologic Class: Porcine thyroxine (T4) and triiodothyronine (T3); Generic name: Natural thyroid (Brand name: Armour, Bio-throid, Naturethroid, and Westroid); Porcine thyroxine is not FDA approved at this time.
- Hyperthyroid Treatment:
 - Drug Class: Methimazole - Inhibits the thyroid from using iodine to produce thyroid hormone; Generic Names: Methimazole (Brand name: Tapazole) and Carbimazole (Brand name: Neo-Mercazole)
 - Drug Class: Propylthiouracil (PTU) – inhibits the thyroid from using iodine to produce thyroid hormone, and inhibits T4 to T3 conversion.
 - Radioactive Iodine Treatment

Comparators

- For KQ 1 and 2, unscreened populations. For KQ 3 and 4, untreated populations with subclinical hyper- or hypothyroidism.

Outcomes

- Intermediate outcomes: lipid levels, osteoporotic fractures
- Health outcomes: quality of life, cognitive function, neuropsychiatric symptoms, cardiovascular morbidity (such as heart failure, atrial fibrillation, myocardial infarction or cerebrovascular accident), mortality.
- Adverse events
 - i. Psychological or social impact of false positive screening tests.
 - ii. Chemical effect of over- or undertreatment.
 - iii. Harms of thyroxine alone or thyroxine and triiodothyronine:
 - 1. Adverse reactions are usually due to therapeutic overdosage and resulting hyperthyroidism. Symptoms related to hyperthyroidism include:
 - a. Increased heart rate
 - b. Irregular heart rate
 - c. Chest pain
 - d. Increased blood pressure
 - e. Anxiety
 - f. Depression
 - g. Insomnia
 - h. Nausea
 - i. Vomiting
 - j. Diarrhea
 - k. Weight loss or gain
 - l. Tremor

- m. Fever
 - n. Sweating
 - o. Changes in menstrual cycle
 - p. Long-term overdosage could result in a decrease in bone density
- iv. Harms of antithyroid agents:
1. Antithyroid Drugs:
 - a. Mild temporary fever
 - b. Hives, skin rash, itching, allergic reaction
 - c. Abnormal hair loss
 - d. Upset stomach or nausea
 - e. Loss of taste or metallic taste
 - f. Abnormal sensations (tingling, prickling, burning, tightness and pulling)
 - g. Joint and muscle aches
 - h. Drowsiness
 - i. Dizziness
 - j. Liver problems
 - k. Agranulocytosis
 2. Radioactive Iodine Treatment:
 - a. Exposure to radiation and associated risks

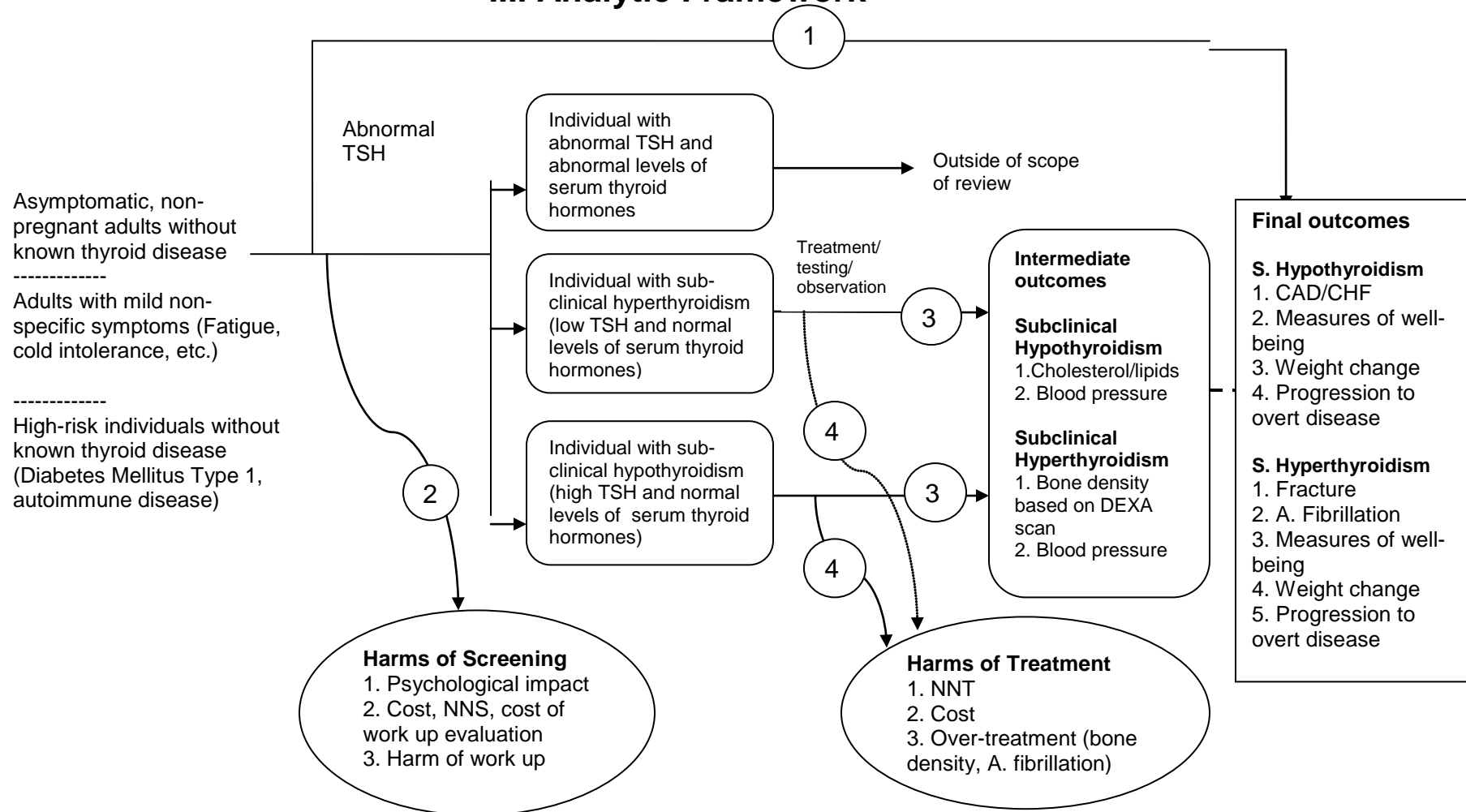
Timing

- No minimum threshold for duration of intervention will be used. However, study duration will affect assessment of the quality and applicability of the study.

Settings

- Primary care setting in populations in the US or similar to the US.

III. Analytic Framework



Key Questions:

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

IV. Methods

A. 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.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

Symbol	Concept	Search Strategy
SCTD	Subclinical Thyroid Disease	<ol style="list-style-type: none"> 1. Hyperthyroidism [mesh] 2. Hypothyroidism [mesh] 3. (hypothy* OR hypo-thyr* OR hyperthyr* OR hyper-thyr*) [tiab] 4. (thyroid deficien* OR thyroid insufficien* OR thyroid failure) [tiab] 5. 1 OR 2 OR 3 OR 4 6. (mild OR compens* OR subclinic* OR moderat* OR short-term) [tiab] 7. 5 AND 6 8. elevated tsh [tiab] 9. 7 OR 8
SCR	Screening	<ol style="list-style-type: none"> 1. Mass Screening [mesh] 2. Thyroid Function Tests [mesh] 3. (screening OR casefinding OR case finding) [tiab] 4. 1 OR 2 OR 3
TR-ER	Treatment for hyperthyroidism	<ol style="list-style-type: none"> 1. anti-thyroid [tiab] 2. methimazole [tiab] 3. Methimazole [mesh] 3. propylthiouracil [tiab] 4. Propylthiouracil [mesh] 5. radioactive thyroid treatment 6. 1 OR 2 OR 3 OR 4 OR 5
TR-O	Treatment for hypothyroidism	<ol style="list-style-type: none"> 1. T3 [tiab] 2. T4 [tiab] 3. thyroxine [tiab] 4. thyroxine [mesh] 5. levothyroxine [tiab] 6. triiodothyronine [tiab] 7. triiodothyronine[mesh] 8. liothyronine [tiab] 9. thyrolar 10. OR 1-9 11. therapeutic use [sh] 12. treatment [tiab] 13. therapy [tiab] 14. OR 11-13 15. 14 AND 10
TR-G	Treatment in general	((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
H	Harms	<ol style="list-style-type: none"> 1. adverse effects [sh] 2. poisoning [sh] 3. toxicity [sh] 4. contraindications [sh] 5. complications [sh] 6. 1 OR 2 OR 3 OR 4 OR 5 7. (safe OR safety OR side-effect\$ OR undesirable effect\$ OR treatment emergent OR tolerability OR toxicity) [tw] 8. adverse [tiab] 9. (effect\$ OR reaction\$ OR event\$ OR outcome\$) [tiab] 10. 8 AND 9 11. 10 OR 7 OR 6
P	Patient issues of	1. Patient Satisfaction[Mesh]



	testing	<ol style="list-style-type: none"> 2. Perception"[Mesh] 3. Family[Mesh] 4. Stress, Physiological[Mesh] 5. Attitude to Health"[Mesh] 6. False Positive Reactions [Mesh] 7. patient preference* [tiab] 8. consequence* [tiab] 9. cost [tiab] OR costs [tiab] 10. false positive* [tiab] 11. acceptability [tiab] 12. worry [tiab] 13. OR 1-12
RCT	RCTs	<ol style="list-style-type: none"> 1. randomized controlled trial [pt] 2. controlled clinical trial [pt] 3. randomized [tiab] 4. placebo [tiab] 5. clinical trials as topic [mesh: noexp] 6. randomly [tiab] 7. trial [ti] 8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 9. animals [MeSH] not (humans [MeSH] and animals [MeSH]) 10. 8 NOT 9

[MeSH] = exploded term, all subterms and subtrees included

[mesh: noexp] = non-exploded term, no subterms or subtrees included

[tiab] = in title and abstract

[tw] = word anywhere in the record

[pt] = publication type

* = truncation

all searches were limited to publication date 2004 or later

PubMed:

KQ1 Screening for Subclinical Thyroid Disease
SCTD AND SCR AND RCT

KQ2 Harms of Screening
(H OR P) AND SCTD AND SCR

KQ3a treatment hyper
SCTD AND TR-ER AND TR-G

KQ3b treatment hypo
SCTD AND TR-O AND RCT

KQ 4 harms of treatment
(TR-ER OR TR-O) AND H AND SCTD

Other sources to be searched:

Cochrane Register of Controlled Trials

EMBASE

Scientific Information Packet (SIP) for levothyroxine

Gray Literature

C. Data Abstraction and Data Management

All abstracts were dual-reviewed and disagreements resolved through discussion with the full project team. Abstracts were all coded as (I)nclude or (E)xclude and recorded in an EndNote database. Full-text articles of included abstracts were then dual reviewed for a final inclusion decision. Again all disagreements were resolved through discussion at the full team level. Full-text articles were coded as (I)nclude or (E-N)xclude where N was a number indicating the reason for exclusion (e.g. wrong population, no data by design, no data, not relevant to key questions, etc.).

A standard data abstraction form will be used by all team members. The form allows for abstraction of the following information:

Extractor, First Author (Last name, First name), Year of publication, Language, Study design, Direction of Investigation, Patients, Age, Gender, Other population characteristics, Eligibility Criteria, Inclusion criteria, Exclusion criteria, Baseline TSH, Number screened/eligible/enrolled, Number withdrawn/analyzed, Setting, Interventions (dose, duration) , Control, Outcomes assessed/when assessed, Adverse effects, Results

D. Assessment of Methodological Quality of Individual Studies

Each team member was asked to rate the quality all of the included studies. Quality ratings will be reviewed at a project meeting and disagreements resolved through discussion with the team. Quality will be assessed following the guidance in the current USPSTF Manual as described in Section 4 and Appendix 7.¹⁵

For all studies we will assess:

Sources of funding, whether adverse effects were assessed, and whether statistical analysis appropriate

For RCTs we will assess:

Exclusion criteria, how outcomes assessed, randomization method, allocation concealed, outcome assessors blinded, care provider blinded, patient unaware of treatment, groups similar at baseline, differential loss to follow-up or overall high loss to follow-up, intention-to-treat analysis

For observational studies we will assess:

Case definition explicit, nonbiased selection of cases/controls, valid definition, ascertainment/definition of exposure applied equally between cases and controls, maintenance of comparable groups, whether confounders were mentioned, whether adjustments were made to control for confounders, consideration of inception cohorts

E. Data Synthesis

Evidence will be summarized by Key Question and will include an introduction summarizing the definition of the condition, prevalence and burden, etiology and natural history, the rationale for screening, a description of the interventions and treatment, a discussion of current clinical practice related to subclinical thyroid dysfunction, a brief discussion of recommendation of other groups and of the previous USPSTF recommendation.

A narrative synthesis will be produced and after assessing heterogeneity, if appropriate a quantitative analysis will be included; based on fair and good quality studies.

We will include a review of and, if appropriate, a separate discussion of findings for patients in the high risk groups such as those with Type 1 Diabetes Mellitus.

F. Grading the Evidence for Each Key Question

We will use the Grading the Strength of a Body of Evidence when Comparing Medical Interventions chapter of the AHRQ Effective Health Care 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>.



V. References

1. Jameson J. Chapter 335. Disorders of the Thyroid Gland. In: Fauci A, Braunwald E, Kasper D, Houser S, Longo D, Jameson J, editors. *Harrison's Principles of Internal Medicine*. New York: The McGraw-Hill Companies, Inc.; 2008. p. 2224-46.
2. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004; 292: 228-38.
3. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado Thyroid Disease Prevalence Study. *Arch Intern Med* 2000;160:526-34.
4. Brabant G, Beck-Peccoz P, Jarzab B, et al. Is there a need to redefine the upper normal limit of TSH? *Eur J Endocrinol* 2006;154(5):633-7.
5. Tsimihodimos V, Bairaktari E, Tzallas C, et al. The Incidence of Thyroid Function Abnormalities in Patients Attending an Outpatient Lipid Clinic. *Thyroid*. 1999;9:365-8.
6. Gharib H, Tuttle R, Baskin H, et al. Consensus statement: subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. *Journal of Clinical Endocrinology & Metabolism* 2005;90:581-5.
7. Haddow JE, Palomaki GE, Allan WC, et al. Maternal Thyroid Deficiency during Pregnancy and Subsequent Neuropsychological Development of the Child. *N Engl J Med* 1999;341:549-55.
8. Abalovich M, Gutierrez S, Alcaraz G, et al. Overt and subclinical hypothyroidism complicating pregnancy. *Thyroid* 2002; 12: 63-8.
9. Stone M, Wallace R. Medicare coverage of routine screening for thyroid dysfunction: Washington, DC: National Academies Press; 2003.
10. Committee on Patient S, Quality I, Committee on Professional L. ACOG Committee Opinion No. 381: Subclinical hypothyroidism in pregnancy. *Obstet Gynecol*. 2007; 110: 959-60.
11. Villar HC, Saconato H, Valente O, et al. Thyroid hormone replacement for subclinical hypothyroidism. *Cochrane Database Syst Rev*. 2007 p. CD003419.
12. Baskin HJ, Cobin RH, Duick DS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract*. 2004; 10: 457-69.
13. Ladenson PW, Singer PA, Ain KB, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. *Arch Int Med* 2000;160:1573-5.
14. Helfand M. Screening for Thyroid Disease. Rockville, MD: U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality; 2004; Available from: <http://www.ahrq.gov/downloads/pub/prevent/pdfser/thyrser.pdf>.
15. U.S. Preventive Service Task Force Procedure Manual. AHRQ Publication No. 08-05118-EF. Rockville, MD: Agency for Healthcare Research and Quality; July 2008 [cited 2010 January 6th]; Available from: www.ahrq.gov/clinic/uspstf08/methods/procmanual.htm.

VI. Definition of Terms

1. Subclinical hypothyroidism: A TSH above the decision threshold with free T4 and free T3 levels within the accepted range. The upper threshold for TSH will be defined using the limits defined in the literature. Multiple limits may be considered.
2. Subclinical hyperthyroidism. A TSH below the decision threshold with free T4 and free T3 levels within the accepted range. The lower threshold for TSH will be defined using the limits defined in the literature. Multiple limits may be considered.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.



It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.