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# Screening for and Treatment of Thyroid Dysfunction: An Evidence Review for the U.S. Preventive Services Task Force

**Prepared for:**
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540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

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**Prepared by:**
Pacific Northwest Evidence-based Practice Center
Oregon Health & Science University
Mail Code: BICC
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

**Investigators:**
J. Bruin Rugge, MD
Christina Bougatsos, MPH
Roger Chou, MD

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# Structured Abstract

**Background:** Screening may lead to detection and treatment of asymptomatic subclinical thyroid dysfunction or undiagnosed overt thyroid disease, potentially resulting in improved clinical outcomes.

**Purpose:** To update a 2004 review on screening for thyroid disease for the U.S. Preventive Services Task Force (USPSTF), expanded to include undiagnosed overt thyroid disease.

**Data Sources:** We searched Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from 2002 to July 2014 for subclinical hypothyroidism and hyperthyroidism, and without a prior date limitation for overt thyroid disease. Searches on electronic databases were supplemented by reviews of reference lists.

**Study Selection:** Randomized, controlled trials and controlled observational studies on the effects of screening for or treatment of subclinical or overt thyroid disease on clinical and intermediate outcomes.

**Data Extraction:** Information regarding the population, setting, treatments, and outcomes was abstracted. The quality of each study was assessed using the standard USPSTF criteria.

**Data Synthesis (Results):** No study directly assessed the benefits and harms of screening versus no screening. For subclinical hypothyroidism (thyroid-stimulating hormone [TSH] levels of 4 to 11 mIU/L), one fair-quality cohort study found that treatment of subclinical hypothyroidism was associated with decreased risk for coronary heart disease events versus no treatment. No studies found that treatment was associated with improved quality of life, cognitive function, blood pressure, or body mass index versus no treatment. Effects of treatment versus no treatment showed potential beneficial effects on lipid levels, but effects were inconsistent, not statistically significant in most studies, and of uncertain clinical significance (difference, -28 to 0 mg/dL for total cholesterol [nine studies] and -22 to 2 mg/dL for low-density lipoprotein cholesterol [10 studies]). Harms of treatment were poorly studied and sparsely reported. Two studies evaluated treatment of subclinical hyperthyroidism, but they were poor-quality and examined intermediate outcomes. No studies evaluated treatment versus no treatment for screen-detected, undiagnosed overt thyroid disease.

**Limitations:** We did not include non-English–language articles. None of the eligible studies were conducted in the United States. All studies were small and of short duration. Studies used varying TSH values to define subclinical disease and varying doses of thyroxine treatment. Few treatment studies were conducted in screen-detected populations.

**Conclusions:** Although screening can identify patients with subclinical thyroid dysfunction and undiagnosed overt thyroid disease, direct evidence on the benefits and harms of screening remains unavailable. More research is needed to understand how the effects of treatment of subclinical hypothyroidism on lipid parameters impacts clinical outcomes, and to determine the effects of identification and treatment of subclinical hyperthyroidism and undiagnosed overt thyroid disease.

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# Chapter 1. Introduction

## Scope and Purpose

An estimated 5 percent of women and 3 percent of men in the U.S. have subclinical thyroid dysfunction,[1] and about 0.5 percent of the population may have undiagnosed overt thyroid disease.[2,3] In some studies, subclinical hypothyroidism is associated with increased risk for coronary artery disease[4,5] and congestive heart failure,[6] and subclinical hyperthyroidism with increased risk for all-cause and coronary heart disease mortality, atrial fibrillation,[7] decreased bone density,[8] and potentially fractures.[9] Overt thyroid disease is associated with negative cardiovascular, musculoskeletal, dermatologic, gastrointestinal, and other effects, but clinical manifestations are highly variable and depend on the severity of the thyroid abnormality. Thyroid dysfunction represents a continuum from subclinical dysfunction to overt disease.

Approximately 2 to 5 percent of persons with subclinical hypothyroidism and 1 to 2 percent of those with subclinical hyperthyroidism develop overt thyroid disease.[10] However, as much as 40 percent of patients with subclinical thyroid dysfunction may revert to normal when followed over time.[11-13]

In 2004, the U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to recommend for or against screening for subclinical thyroid dysfunction in asymptomatic nonpregnant adults:[1,14,15]

- The USPSTF found fair evidence that the thyroid-stimulating hormone (TSH) test can detect subclinical thyroid dysfunction in persons without symptoms, but poor evidence that treatment improves clinically important outcomes in screen-detected adults.
- Although the yield of screening is greater in certain high-risk groups (e.g., postpartum women, persons with Down syndrome, and the elderly), the USPSTF found 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 evidence that overtreatment with levothyroxine occurs in a substantial proportion of patients, but the long-term harmful effects of overtreatment are not known.
- As a result, the balance of benefits and harms of screening in asymptomatic adults could not be determined.

The 2004 recommendation did not address effects of screening in or treatment of patients with undiagnosed overt thyroid disease.

A contemporaneous systematic review conducted for the American Thyroid Association, the American Association of Clinical Endocrinologists, and the Endocrine Society reached similar conclusions.[8] Nonetheless, thyroid medication prescription rates in the United States have increased dramatically, from an estimated 49.8 million in 2006 to 70.5 million in 2010.[16] Among community-dwelling persons older than age 65 years with subclinical hypothyroidism, the

proportion taking thyroid hormone has more than doubled, from 8.1 to 20 percent from 1989 to 2005.[17]

This report was commissioned by the USPSTF in order to update its 2004 recommendation on screening for thyroid disease. It builds upon a 2011 Comparative Effectiveness Review funded by the Agency for Health Care Research and Quality[18] and prior USPSTF reviews on identification and treatment of subclinical thyroid dysfunction.[1,15] Prior to updating its 2004 recommendation, the USPSTF determined that in addition to subclinical thyroid dysfunction, screening could also identify undiagnosed overt thyroid disease;[2,3] therefore, the decision to screen should also consider the potential benefits and harms of identifying and treating undiagnosed overt disease. This update therefore differs from prior USPSTF reviews and the 2011 review in that it also addresses identification and treatment of undiagnosed overt thyroid disease.

## Condition Definition

The thyroid gland is involved in metabolic homeostasis in adults through secretion of two hormones, thyroxine (T4) and triiodothyronine (T3), and is regulated by TSH, which is secreted by the anterior pituitary. Hypothyroidism is the undersecretion of T4 and T3, while hyperthyroidism is the oversecretion of these hormones. Current assays for TSH are extremely sensitive at detecting changes in thyroid homeostasis prior to changes in T4 and T3 levels. Subclinical thyroid dysfunction is defined as an elevated or low TSH test (normal reference range, 0.45 to 4.5 mIU/L) in the setting of normal thyroid hormone levels, and overt thyroid disease is defined by the presence of abnormal thyroid hormone (free T4, with or without T3) levels[8,19] (**Table 1**). Some recent data suggest that normal TSH ranges may require adjustment for age.[13,20-22]

Symptoms of overt hypothyroidism include fatigue, feeling cold, weight gain, hair loss, poor concentration, dry skin, and constipation (**Table 2**). Because a number of these symptoms are so common and nonspecific, they may be subtle and unrecognized. Myxedema coma is an uncommon but life-threatening complication of severe untreated or undertreated 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.[19] Symptoms of overt hyperthyroidism include palpitations, heat intolerance and sweating, weight loss, hyperactivity, and fatigue. Thyroid storm is a potentially life-threatening condition that results from an acute illness superimposed on undiagnosed or undertreated hyperthyroidism. It is accompanied by fever, delirium, seizures, and coma.[19]

## Prevalence and Burden of Disease

Subclinical thyroid dysfunction is more common than overt thyroid disease, and subclinical hypothyroidism is more common than subclinical hyperthyroidism. The National Health and Nutrition Examination Survey (NHANES) III found that 0.3 percent of the population had overt hypothyroidism, 4.6 percent had subclinical hypothyroidism, 0.5 percent had overt

hyperthyroidism, and 0.7 percent had subclinical hyperthyroidism.[2]

Prevalence estimates of subclinical hypothyroidism vary based on population factors and according to differences in the defined upper normal limit for TSH. In general, prevalence increases with age, is higher in whites than blacks, and is higher in women than men.[8] Cross-sectional studies have found that about 5 percent of women and 3 percent of men have subclinical hypothyroidism.[1] For women, estimates range from 1.2 percent in non-Hispanic black women to 5.8 percent in non-Hispanic white women in NHANES III (abnormal TSH defined as >4.5 mIU/L),[2] and from 4 percent in women ages 18 to 44 years to more than 17 percent in women older than age 75 years who participated in the Whickham Survey (abnormal TSH defined as >6.0 mIU/L).[23] For men, estimates from NHANES III range from 1.8 percent in non-Hispanic black men to 2.4 percent in Mexican American men; estimates from the Whickham Survey range from 1 percent in men ages 18 to 65 years to 6.2 percent in men age 65 years or older.[1]

When defined as an undetectable TSH level in a person with a normal free T4 level, the prevalence of subclinical hyperthyroidism is about 1 percent (95% confidence interval [CI], 0.4 to 1.7) in men and 1.5 percent (95% CI, 0.8 to 2.5) in women older than age 60 years.[1] Subclinical hyperthyroidism has a higher prevalence in women, blacks, the elderly, and persons with low iodine intake.[8]

Untreated subclinical hypothyroidism may increase risk for developing coronary artery disease, lipid disorders, hypertension, obesity, and memory or cognitive disorders; subclinical hyperthyroidism may increase risk for atrial fibrillation, osteoporosis, and osteoporotic fractures.[8,24-28] Although untreated subclinical hypothyroidism does not appear to increase risk for all-cause mortality, evidence on the association between subclinical hyperthyroidism and all-cause mortality is more mixed.[28,29]

Studies on subclinical thyroid dysfunction generally enrolled referral and other clinical populations rather than asymptomatic persons identified through screening. It is unclear whether otherwise healthy persons with subclinical thyroid disease identified by screening are at higher risk for adverse clinical outcomes compared with persons with normal thyroid function.[1]

## Etiology, Natural History, and Risk Factors

The most common cause of hypothyroidism in the United States is chronic autoimmune (Hashimoto's) thyroiditis. Other causes include previously treated thyroid dysfunction, poor adherence to or undertreatment with levothyroxine, external beam radiation in the head and neck area, and untreated adrenal insufficiency.[8,19] In addition to demographic risk factors described earlier, risk factors for hypothyroidism include type 1 diabetes mellitus, a family history of thyroid dysfunction, and Down syndrome.

Causes of hyperthyroidism include Graves' disease, autoimmune thyroiditis ("Hashitoxicosis"), functional thyroid nodules, and overtreatment with levothyroxine.[19] In addition to demographic risk factors described earlier, risk factors include a personal or family history of hyperthyroidism

and ingestion of iodine-containing drugs, such as amiodarone.

Some of the best data regarding the natural history of subclinical hypothyroidism comes from the Whickham Survey, which followed 2,779 British residents older than age 20 years. It found that, for a 50-year-old woman who had a serum TSH level of 6 mIU/L and positive antithyroid antibodies, the risk for developing overt hypothyroidism over 20 years was 57 percent; for a serum TSH level of 9 mIU/L, the risk was 71 percent. A 50-year-old woman who had a normal TSH level and negative antibody test had a risk of only 4 percent over 20 years.[1,23]

Subclinical hyperthyroidism is less common than subclinical hypothyroidism and not as well studied. However, it has been estimated that 1 to 2 percent of persons with a TSH level less than 0.1 mIU/L develop overt hyperthyroidism each year, with a low likelihood of progression for TSH levels between 0.1 and 0.45 mIU/L.[8]

## Rationale for Screening

The rationale for screening for subclinical thyroid dysfunction includes its relatively high prevalence and the potential for identification of affected persons to improve clinical outcomes through treatment prior to progression to overt disease or to mitigate adverse physiologic changes associated with adverse health outcomes later in life.[10] Screening could also identify persons with unrecognized overt thyroid disease or those with mild symptoms who have not sought care for their symptoms. Other factors in favor of screening include the low cost, wide availability, and acceptability of the screening test (serum TSH), as well as low-cost and widely available treatment (levothyroxine).[10,30]

## Treatment

Overt hypothyroidism is treated with thyroid hormone replacement therapy, while subclinical hypothyroidism can be treated with thyroid hormone replacement therapy or a strategy of watchful waiting. Most experts recommend treating persons with a TSH level of greater than 10 mIU/L, while treatment is more controversial for those with a TSH level between 4.5 and 10 mIU/L.[10] Replacement therapy is not thought to prevent progression to overt hypothyroidism, but may reduce risk for symptoms of overt disease in those who do progress.

Hyperthyroidism is treated with antithyroid medications, such as methimazole, or ablation therapy, such as radioactive iodine or surgery. Treatment is often recommended for persons who have an undetectable TSH level or a TSH level of less than 0.1 mIU/L, or who have Graves' disease or nodular thyroid disease, because of the risk for atrial fibrillation or bone loss, particularly in older adults. However, treatment is not recommended for subclinical hyperthyroidism due to thyroiditis, which typically resolves spontaneously.[8] Routine treatment is also not recommended in patients with a TSH level between 0.1 and 0.45 mIU/L.[8]

# Current Clinical Practice

Screening for both hypothyroidism and hyperthyroidism is accomplished through testing of serum TSH, with testing of serum free T4 (and in some cases T3) if the TSH level falls outside of the normal range.[19] Additional testing is not routinely performed but may be done depending on the results of initial tests and the need to exclude other associated conditions. Common symptoms of mild thyroid dysfunction, such as mild fatigue or weight changes, are nonspecific, very common, do not predict the presence of thyroid dysfunction, and may be unrecognized or unreported. Therefore, screening may also result in identification of persons with overt thyroid disease who are not technically asymptomatic.

# Recommendations of Other Groups

In 2002, a consensus panel sponsored by the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society found insufficient evidence to support population-based screening for thyroid dysfunction, although it recommended aggressive case-finding in those considered to be high risk, including pregnant women and women older than age 60 years.[31] Subsequently, a second panel appointed by the same three organizations reviewed the same evidence. While the panel acknowledged that the evidence does not support screening, it thought that a "lack of definitive evidence for a benefit does not equate to evidence for lack of benefit," and issued a separate dissenting consensus statement that recommended routine screening for subclinical hypothyroidism and hyperthyroidism in adults.[10] The American Thyroid Association also recommends screening in adults beginning at age 35 years and every 5 years thereafter.[30]

A committee appointed by the Institute of Medicine in 2003 examined screening for hypothyroidism and hyperthyroidism 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."[32] The American Academy of Family Physicians adopted the 2004 USPSTF recommendation.[33] The American College of Physicians does not have a current guideline (its 1998 guideline is inactive), but refers readers to the USPSTF recommendation.[34]

# CHAPTER 2. METHODS

## Key Questions and Analytic Framework

The analytic framework shown in the **Figure** was used to guide the literature review. It shows the populations, interventions, intermediate outcomes, and health outcomes examined in the review. The population of interest was asymptomatic adults or adults with mild, nonspecific symptoms (e.g., mild fatigue). We included patients with subclinical thyroid dysfunction as well as patients with overt thyroid disease but without clinically obvious symptoms. Key Questions 1 and 2 address direct evidence on the benefits and harms of screening for hypothyroidism and hyperthyroidism on clinical outcomes. Key Questions 3 and 4 address evidence on the benefits and harms of treating thyroid dysfunction.

The Key Questions are as follows:

1. Does screening for thyroid dysfunction reduce morbidity or mortality?
2. What are the harms of screening for thyroid dysfunction?

3a. Does treatment of screen-detected overt or subclinical thyroid dysfunction improve morbidity or mortality?

3b. Does treatment of screen-detected overt or subclinical thyroid dysfunction improve intermediate outcomes?

4. What are the harms of treatment of screen-detected thyroid dysfunction?

In addition, we addressed the following Contextual Questions:

1. Currently, are persons with mild TSH elevation being treated?
2. What are the cardiovascular consequences of untreated subclinical thyroid dysfunction?
3. What proportion of patients screened for thyroid dysfunction have overt thyroid disease?

Contextual Questions address background areas that the USPSTF deemed important for informing its recommendations. Contextual Questions are not reviewed using systematic review methodology, but rather summarize the evidence from key informative studies.

## Search Strategies

A research librarian searched MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews from 2002 to mid-July 2014 for subclinical hypothyroidism and subclinical hyperthyroidism and without a prior date limitation for overt thyroid disease, since it was not included in the prior review (**Appendix A1**). Additional studies were identified from review of reference lists of relevant articles and peer review suggestions.

## Study Selection

Two investigators independently evaluated each study at the title/abstract and full-text article stages to determine eligibility for inclusion (**Appendix A2**). Following the protocol, we included randomized trials and observational studies of thyroid screening versus no screening in adults (excluding pregnant women) without a history of thyroid dysfunction or obvious goiter, nodules, or symptoms, or treatment versus no treatment in adults with subclinical or overt thyroid dysfunction. Screening was based on TSH testing, with followup testing of thyroid hormone levels (free T4, with or without T3). Studies of patients with subclinical hypothyroidism due to Hashimoto's thyroiditis based on antibody testing were included if they did not describe enrollment of symptomatic patients. Clinical outcomes were cardiovascular end-points (cardiovascular disease, coronary artery disease/congestive heart failure, and atrial fibrillation), fractures, measures of quality of life or cognitive function, and harms, including harms related to overreplacement (such as negative effects on bone mineral density or atrial fibrillation). Intermediate outcomes were effects on lipid levels, blood pressure, weight change, and bone mineral density. We restricted inclusion to English-language articles and excluded studies published only as abstracts. The flow of studies from initial identification of titles and abstracts to final inclusion or exclusion using prespecified criteria is shown in **Appendix A3.** Excluded studies are listed in **Appendix A4**.

## Data Abstraction and Quality Rating

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, data analysis, and results, and another investigator verified data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF to rate the quality of each study as good, fair, or poor (**Appendix A5**).[35,36] Discrepancies in quality ratings were resolved by discussion and consensus. For all studies, we evaluated applicability to populations likely to be encountered in primary care screening settings.

## Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each Key Question qualitatively as "good," "fair," or "poor" using methods developed by the USPSTF, based on aggregate study quality, precision of estimates, consistency of results between studies, and directness of evidence.[35,36] Meta-analysis was not performed because of the methodological and clinical diversity among the included studies.

## External Review

An earlier draft of this report was reviewed by external experts not affiliated with the USPSTF (**Appendix A6**) and revised based on their comments.

# Chapter 3. Results

Fourteen studies (13 randomized, controlled trials and one cohort study) published since the prior USPSTF review[1,15] met inclusion criteria for this update. Twelve studies (in 15 publications) addressed treatment of subclinical hypothyroidism[37-51] and two studies addressed treatment of subclinical hyperthyroidism[52,53] (**Tables 3-7; Appendix B1**). No studies examined benefits or harms of screening and no studies addressed treatment versus no treatment of screen-detected, undiagnosed overt thyroid disease.

Three trials were rated as good quality,[42,47,48] six trials (reported in seven publications) were rated as fair quality[38-41,43,44,46] and four trials (in five publications) were rated as poor quality[37,50-53] (**Appendix B2**); the one retrospective cohort study was rated as fair quality (**Appendix B3**).[49] Most of the poor-quality studies were characterized by poor reporting of methods (e.g., methods of randomization, allocation concealment, blinding, and reporting of attrition) rather than clearly inadequate methods.

None of the trials were conducted in the United States. Twelve were conducted in Europe (the United Kingdom, Italy, Turkey, or Norway), two in Brazil, one in Kuwait, and one in Japan. The TSH values used to diagnose subclinical thyroid dysfunction at baseline varied among the studies; the threshold ranged from 4.1 to 11.0 mIU/L for subclinical hypothyroidism and from 0.06 to 0.23 mIU/L for subclinical hyperthyroidism. Mean patient age ranged from 32 to older than 70 years. Treatment of subclinical hypothyroidism was levothyroxine using different dosages and dosing regimens, and for subclinical hyperthyroidism was methimazole, propylthiouracil, or radioactive iodine. Study duration ranged from 4 to 12 months except for the cohort study, which analyzed data retrospectively, with up to 7.6 years of followup.[49] Sample sizes in the trials ranged from 14 to 120 patients; the cohort study analyzed 4,744 patients.[49] Two publications from the Tromsø Study reported different outcomes from the same population.[40,41] While most studies evaluated a placebo comparator, five used a no treatment comparison.[38,39,49,52,53]

Three trials (in four publications) evaluated screen-detected populations.[37,40,41,47] Most other trials did not clearly report how patients were identified, other than that they were recruited from outpatient clinics. Most trials reported that patients were newly diagnosed and excluded those with previous thyroid dysfunction or those previously taking antithyroid medications.

## Key Question 1. Does Screening for Thyroid Dysfunction Reduce Morbidity or Mortality?

As in the previous USPSTF report,[1,15] we found no studies of screening for subclinical dysfunction or biochemically overt thyroid disease versus no screening that reported clinical outcomes.

# Key Question 2. What Are the Harms of Screening for Thyroid Dysfunction?

No studies reported harms of thyroid screening versus no screening.

# Key Question 3a. Does Treatment of Screen-Detected Overt or Subclinical Thyroid Dysfunction Improve Morbidity or Mortality?

## Summary

The previous USPSTF review included no studies on effects of treatment of subclinical hypothyroidism on cardiovascular events. In one fair-quality retrospective cohort study of subclinical hypothyroid patients in the U.K. General Practice Research Database published since the prior USPSTF review, levothyroxine use was associated with lower risk for fatal or nonfatal ischemic heart disease events (4.2% vs. 6.6%; hazard ratio [HR], 0.61 [95% CI, 0.39 to 0.95]), all-cause mortality (3.4% vs. 6.4%; HR, 0.36 [95%, CI, 0.19 to 0.66]), death due to circulatory diseases (1.4% vs. 2.4%; HR, 0.54 [95% CI, 0.37 to 0.92]), and cancer mortality (1.2% vs. 2.2%; HR, 0.59 [95% CI, 0.21 to 0.88]) compared with no treatment among subjects ages 40 to 70 years, but there was no association among those older than age 70 years.[49]

Results regarding effects of treatment of subclinical hypothyroidism on clinical outcomes were consistent with findings from the prior USPSTF review in showing no clear effects on measures of quality of life or cognitive function. Five small randomized trials (N=40 to 100) published since the prior USPSTF review found no effect of treatment of subclinical hypothyroidism on various self-reported quality of life measures, and two trials (N=69 and 94) found no effect on measures of cognitive function.

No study of overt thyroid disease or subclinical hyperthyroidism reported clinical outcomes.

## Evidence

### Subclinical Hypothyroidism

We identified five trials (three good-quality,[42,47,48] one fair-quality,[41] and one poor-quality[37]) and one fair-quality retrospective cohort study[49] published since the prior USPSTF review that evaluated effects of treatment of subclinical hypothyroidism on clinical outcomes (**Tables 3 and 4; Appendixes B1, B2, and B3**).

*Cardiovascular events and mortality.* The previous USPSTF review[1,15] included no studies on the association between treatment of subclinical hypothyroidism and risk for cardiac events.

We identified one fair-quality retrospective cohort study conducted in 2001 that evaluated the

effects of treatment on risk for cardiac events[49] in 4,744 adults age 40 years or older with subclinical hypothyroidism (based on a single TSH level of >5.00 to 10.00 mIU/L; mean followup, 7.6 years) (**Table 3**). Analyses were stratified, based on an a priori categorization, by ages 40 to 70 years and older than age 70 years. The authors did not report analyses based on the whole cohort. The primary outcome was a composite of first incident fatal and nonfatal ischemic heart disease event. Secondary outcomes were first fatal and nonfatal cerebrovascular disease events and all-cause and cause-specific mortality identified during the study period. About half of the participants were treated with levothyroxine (average dose, 75 µg).

After adjustment for age, sex, body mass index, socioeconomic status, total cholesterol level, smoking status, history of diabetes mellitus, index serum thyrotropin level, levothyroxine use, and blood pressure, levothyroxine use was associated with lower risk for fatal or nonfatal ischemic heart disease events (4.2% vs. 6.6%; HR, 0.61 [95% CI, 0.39 to 0.95]), all-cause mortality (3.4% vs. 6.4%; HR. 0.36 [95% CI, 0.19 to 0.66]), death due to circulatory diseases (1.4% vs. 2.4%; HR, 0.54 [95% CI, 0.37 to 0.92]), and cancer mortality (1.2% vs. 2.2%; HR, 0.59 [95% CI, 0.21 to 0.88]) compared with no treatment in subjects ages 40 to 70 years.[49] In subjects older than age 70 years, there was no association between use of levothyroxine and ischemic heart disease events (HR, 0.99 [95% CI, 0.59 to 1.33]), all-cause mortality (35.2% vs. 40.5%; HR, 0.71 [95% CI, 0.56 to 1.08]), or cancer mortality (4.6% vs. 6.5%; HR, 0.51 [95% CI, 0.24 to 1.09]). Potential limitations include the lack of adjustment for medications that reduce risk for cardiovascular disease, though baseline data suggested no differences between treatment groups.

*Quality of life.* The prior USPSTF review[1,15] included five trials that evaluated the association between treatment of subclinical thyroid dysfunction and quality of life.[42,54-57] One of the trials found that treatment of subclinical hypothyroidism was associated with better quality of life in patients with recent Graves' disease.[54] The other four trials found no effect of treatment.[42,55-57] However, the applicability of these studies to screening appears limited, and three would have been excluded from this update because patients had previously been treated for thyroid dysfunction,[54,56] or because they included mostly enrolled euthyroid patients.[57]

We identified five trials (three good-quality,[42,47,48] one fair-quality,[41] and one poor-quality[37]) published since the prior USPSTF review on treatment of subclinical hypothyroidism (TSH thresholds varied from >3.5 to >5.5) using various doses of levothyroxine (mean, 50 to 109.7 µg/day) and effects on various measures of quality of life (36-Item Short-Form Health Survey [SF-36], General Health Questionnaire-30 [GHQ-30], Beck Depression Inventory, Hospital Anxiety and Depression Scale [HADS], and Underactive Thyroid-Dependent Quality of Life Questionnaire) in adults with mean ages ranging from 45 to 74 years (**Table 4**). Sample sizes were less than 100 in all trials, mean age ranged from 45 to 74 years, and followup ranged from 4 to 12 months. No differences were found between those receiving treatment and placebo in any study. Three of these treatment trials evaluated screen-detected populations.[37,41,47]

Of the three good-quality trials, one (N=40) found no difference in the mean change in the thyroxine group minus the mean change in the placebo group on the HADS anxiety score (1 [95% CI, -1 to 3]; p=not significant [NS]), the HADS depression score (-1 [95% CI, -3 to 1]; p=NS), or the GHQ-30 (2 [95% CI, -5 to 7]; p=NS) after 6 months.[42] One trial (N=94) found no

difference in HADS depression scores in the thyroxine versus placebo groups (mean score, 3.55 vs. 3.37; p=0.82) after 12 months,[47] and one crossover trial (N=100) found no differences in the Underactive Thyroid-Dependent Quality of Life Questionnaire (-1.1 vs. -1.2; p=0.24), the SF-36 sex component (-2.3 vs. -2.7; p=0.18), the SF-36 motivation component (-3.6 vs. -3.7; p=0.16), the SF-36 worries component (-2.5 vs. -2.8; p=0.23), or the average weighted effect of all 18 quality of life domains (-2.7 vs. -2.8; p=045) after 12 weeks.[48] The fair-quality study found no effects of treatment versus placebo on the GHQ-30 (1.9 vs. 1.2; p=NS) or the Beck Depression Inventory (4.3 vs. 3.3; p=NS).[41]

*Cognitive function.* Two trials included in the previous USPSTF review evaluated effects of treatment of subclinical hypothyroidism on cognitive function.[55,57] One trial that included euthyroid patients[57] found no effect, and the second trial found a statistically significant improvement in memory using a composite outcome in adults older than age 55 years that the authors described as "small and of questionable clinical importance."[55]

We identified one good-quality[47] and one fair-quality trial[41] published since the last USPSTF review that found no association between treatment with levothyroxine for subclinical hypothyroidism (defined as TSH >3.5 and <10[41] or TSH > 5.5[47]) versus placebo and various measures of cognitive function after 12 months (**Table 4**). Both studies appeared to evaluate screen-detected populations. Mean age was 62 to 63 years in one study (N=69),[41] and 74 years in the other (N=94).[47] The good-quality study[47] found no effects on cognitive skills and performance (Middlesex Elderly Assessment of Mental State, 11.67 vs. 11.60; p=0.57), cognitive status (Mini-Mental State Examination, 28.24 vs. 28.22; p=0.18), speed of cognitive processing and accounting (Speed and Capacity of Language Processing test, 1.29 vs. 0.84; p=0.59), psychomotor test of executive function (Trail Making A, 45.33 vs. 46.78; p=0.52), psychomotor test of executive function (Trail Making B, 100.65 vs. 114.11; p=0.95), or psychomotor test of executive function (Trail Making B-A, 54.55 vs. 67.27; p=0.86).

### Subclinical Hyperthyroidism

No studies evaluated benefits of treatments for subclinical hyperthyroidism on clinical outcomes.

### Overt Thyroid Disease

No studies reported effects of treatment of overt thyroid disease.

# Key Question 3b. Does Treatment of Screen-Detected Overt or Subclinical Thyroid Dysfunction Improve Intermediate Outcomes?

## Summary

We identified nine trials published since the prior USPSTF review on effects of treatment of subclinical hypothyroidism on intermediate outcomes. Like the prior USPSTF review, we found

some evidence that treatment is associated with lower total and low-density lipoprotein (LDL) cholesterol than placebo or no treatment. Across eight good- and fair-quality trials, mean differences between treatment and placebo or no treatment ranged from -28 to 0 mg/dL for total cholesterol and from -22 to 2 mg/dL for LDL cholesterol, with a statistically significant difference in three trials. Treatment was not associated with beneficial effects on blood pressure, high-density lipoprotein (HDL) cholesterol, triglyceride levels, or body mass index/weight.

Two small, poor-quality trials found no differences between treatment of subclinical hyperthyroidism and no treatment on blood pressure, body mass index, bone mineral density, or lipid levels.

No studies examined the effect of treatment of overt thyroid disease on intermediate outcomes.

## Evidence

### Subclinical Hypothyroidism

We identified nine trials (reported in 11 publications) published since the prior USPSTF review on the effects of treatment of subclinical hypothyroidism on blood pressure; total, LDL, and HDL cholesterol, triglycerides, and body mass index or weight (**Table 5; Appendices B1 and B2**).[38-40,42-46,48,50,51] Two trials were rated as good quality,[42,48] six trials as fair quality,[38-40,43,44,46] and one trial as poor quality.[50,51]

*Blood pressure.* The 2004 USPSTF review[1,15] included no studies on the effect of treatment of subclinical hypothyroidism on blood pressure.

We identified one good-quality[48] and two fair-quality[44,46] trials on the effects of treatment of subclinical hypothyroidism (defined as TSH > 3.6 [44] or >4.0[48] or TSH above the normal limit[46]) on blood pressure. None found a significant difference between groups. Across all three trials, differences in means between treatment and placebo groups in ranged from -3 to -2 mm Hg for systolic blood pressure and from -3 to 0 mm Hg for diastolic blood pressure (**Table 5**). In the good-quality trial (n=100), which was a crossover trial, the difference in means was -2 mm Hg (p=0.21) for systolic blood pressure and -1 mm Hg (p=0.16) for diastolic blood pressure after 12 weeks.[48]

*Lipids.* The prior USPSTF review included seven trials on the effect of treatment of subclinical hypothyroidism and effects on lipid profiles.[42,45,54-56,58,59] Six trials found no improvement in lipid parameters,[42,45,54-56,59] while one poor-quality trial in euthyroid patients found about a 5 percent improvement in LDL cholesterol with 50 µg/day of levothyroxine versus 25 µg/day.[58]

**Total cholesterol.** We identified two good-quality,[42,49] six fair-quality[38,39,43,44,46] and one poor-quality[50,51] trials published since the prior USPSTF review on the effects of treatment of subclinical hypothyroidism on total cholesterol (**Table 5**). TSH thresholds varied from >3.6 to >5, or "greater than the upper limit of normal".[46] In the eight good- and fair-quality trials, differences between treatment and no treatment in mean total cholesterol ranged from -28 to 0 mg/dL. Three of the trials (N=45, 100, and 120) reported statistically significant differences in

mean total cholesterol values of -12 mg/dL (p<0.03),[43] -28 mg/dL (p=0.03),[44] and -12 mg/dL (p<0001).[48] The poor-quality trial found that treatment was associated with slightly lower total cholesterol values (difference in means, -6 mg/dL; p=0.03).[50,51]

**LDL cholesterol.** Two good-quality,[42,48] six fair-quality,[38-40,43,44,46] and one poor-quality[50,51] trials published since the prior USPSTF review evaluated the effect of treatment of subclinical hypothyroidism on LDL values. In the eight good- and fair-quality trials, differences between treatment and no treatment in mean LDL cholesterol ranged from -22 to 2 mg/dL. Three of the trials (N=45, 100, and 120) reported statistically significant differences in mean LDL values of -8 mg/dL (p<0.001),[43] -22 mg/dL (p=0.03),[44] and -12 mg/dL (p<0.001).[48] The poor-quality trial found that treatment was associated with slightly lower LDL values (difference in means, -12 mg/dL; p=0.02).[50,51]

**HDL cholesterol.** We identified two good-quality,[42,48] six fair-quality,[38-40,43,44,46] and one poor-quality[50,51] trials published since the prior USPSTF review on the effect of treatment of subclinical hypothyroidism on HDL values (**Table 5**). In the eight good- and fair-quality trials, differences between treatment and no treatment in mean HDL cholesterol ranged from -4 to 4 mg/dL. None of the trials found a significant difference between treatment and control groups in HDL values. The two good-quality trials (N=40 and 100) reported differences in mean HDL values of -1 mg/dL (p=NS) after 6 months[42] and -4 mg/dL (p=NS) after 12 weeks.[48]

**Triglycerides.** We identified two good-quality,[42,48] six fair-quality,[38-40,43,44,46] and one poor-quality[50,51] trials on the effect of treatment of subclinical hypothyroidism on triglyceride values (**Table 5**). In the eight good- and fair-quality trials, differences in means ranged from -32 to 11 mg/dL. None of the trials found a significant difference between treatment and control groups in triglyceride values. The two good-quality trials (N=40 and 100) had differences in mean triglyceride values of 9 mg/dL (p=NS) after 6 months[42] and 0 mg/dL (p=NS) after 12 weeks.[48]

*Body mass index or weight.* None of the trials included in the previous USPSTF review assessed effects of treatment of subclinical thyroid dysfunction on body mass index or weight.

We identified two good-quality[42,48] and four fair-quality[39,40,44,46] trials published since the prior USPSTF review on the effect of treatment of subclinical hypothyroidism (TSH thresholds varied from >3.5 to >5, or "greater than the normal range"[46]) on body mass index or weight (**Table 5**). Of the five trials reporting body mass index, differences in means between treatment and placebo groups ranged from -1 to 1 $kg/m^2$. Of the two trials reporting weight, one found a difference in means of -1 kg,[48] and one found a 0.1 difference in the percentage of lean body weight.[42] None of the trials found a significant difference between treatment and control groups in body mass index or weight. Of the good-quality trials, one (N=40) reported a difference in mean body mass index of -0.3 $kg/m^2$ (p=NS) and a difference in mean percentage of lean body weight of 0.1 after 6 months (p=NS);[42] the other (N=100) reported a difference in mean weight of -1 kg after 12 weeks.[48]

## Subclinical Hyperthyroidism

We identified two small poor-quality trials (N=14 and 20) on effects of treatment of subclinical hyperthyroidism on blood pressure, body mass index, and bone mineral density (**Table 6; Appendixes B1 and B2**).[52,53] In both studies, treatment was compared with no treatment, and subjects were not blinded to treatment status. One trial included adults (mean age, 57 to 59 years) with mean TSH levels of 0.06 mIU/L who took 10 to 15 mg of methimazole for 12 months.[52] The other trial included younger adults (mean age, 34 to 39 years) with mean TSH levels of 0.21 to 0.23 mIU/L who took 150 mg of propylthiouracil or radioactive iodine (one patient) for 6 months.[53]

*Blood pressure.* Two small poor-quality trials (N=14 and 20) reported no differences between treatment of subclinical hyperthyroidism and no treatment on either systolic or diastolic blood pressure after 6[53] and 12[52] months of followup. Across both trials, differences in means between treatment and placebo groups ranged from -2 to 10 mm Hg for systolic blood pressure and from -3 to 0 mm Hg for diastolic blood pressure (**Table 6**).

*Body mass index.* One small poor-quality trial (N=14) found no difference in body mass index between treatment of subclinical hyperthyroidism and no treatment after 12 months.[52] The difference in means between treatment and placebo groups in body mass index was 0 $kg/m^2$ (**Table 6**).

*Bone mineral density.* One small poor-quality trial (N=20) found no difference in femur neck or lumbar vertebral bone mineral density between treatment of subclinical hyperthyroidism and no treatment after 6 months.[53] The difference in means between treatment and placebo groups was -0.042 $g/cm^2$ for femur neck bone mineral density and 0.03 $g/cm^2$ for lumbar vertebra bone mineral density (**Table 6**).

*Lipids.* One small poor-quality trial (n=20) found no differences between treatment of subclinical hyperthyroidism and no treatment groups in total, LDL, or HDL cholesterol or triglycerides after 6 months.[53] The difference in means between treatment and placebo groups was 26 mg/dL for total cholesterol, 15 mg/dL for LDL cholesterol, 0 mg/dL for HDL cholesterol, and -36 mg/dL for triglycerides (**Table 6**).

## Overt Thyroid Disease

No studies examined the effect of treatment of overt thyroid disease on intermediate outcomes. One nonrandomized study (N=67) evaluated effects of treatment of hyperthyroidism on bone mineral density but was excluded because it was published in French.[60]

# Key Question 4. What Are the Harms of Treatment of Screen-Detected Thyroid Dysfunction?

## Summary

Studies of treatment of subclinical thyroid dysfunction assessed and reported harms poorly, precluding reliable conclusions. In addition, the studies were not designed or powered to assess long-term harms or harms associated with thyroid hormone overreplacement. No studies reported harms of treatment of overt thyroid disease.

## Evidence

### Subclinical Hypothyroidism

The previous USPSTF report found very limited evidence on harms related to treatment of subclinical hypothyroidism. One good-quality trial of patients who developed subclinical hypothyroidism after treatment of Graves' disease found that four of 17 persons randomized to thyroxine felt worse compared with six of 15 who were given placebo (p=0.33).[54] Other studies reported one case of angina,[55] one case of atrial fibrillation,[55] worsened anxiety scores,[42] worsened SF-36 vitality scores,[57] and two withdrawals due to adverse events.[59]

Five trials (in six publications) published since the prior USPSTF review reported harms, but harms were assessed and reported poorly, precluding reliable conclusions (**Table 7**).[37,46-48,50,51] In addition, the studies were not designed or powered to assess long-term or serious harms, or harms related to overtreatment. One study reported "no indication of harms,"[37] and another study stated that none of the patients reported side effects that required withdrawal or dose reduction.[46] One study reported no difference between treatment and placebo groups in risk for withdrawal due to side effects after 12 months (9.6% vs. 14.3%; p=0.49).[47] Two other trials (N=100 and 60) reported none[48] or two cases[50,51] of withdrawals due to adverse events in patients treated for subclinical hypothyroidism.

### Subclinical Hyperthyroidism

One study (N=14) of patients with subclinical hyperthyroidism reported no harms with methimazole treatment.[52]

### Overt Thyroid Disease

No studies reported harms of treatment of overt thyroid disease.

# Contextual Question 1. Currently, Are Persons With Mild TSH Elevation Being Treated?

One cross-sectional study of 500 patients in Rochester, MN, conducted from 1995 to 1996 found

that about 39 percent of patients with a TSH level between 5.1 and 10 mIU/L were treated.[61] More recent data indicate that the number of thyroid hormone prescriptions have increased substantially in the United States, from 49.8 million in 2006 to 70.5 million in 2010, although the proportion of patients with mild TSH elevation was not reported.[16] Similarly, a recent prospective study of community-dwelling adults older than age 65 years in Toronto, Canada found that the proportion taking thyroid hormone increased from 8.9 to 20 percent from 1989 to 2005.[17] However, some data suggests that increases in prescribing may be related in part to a lower threshold for treatment over time. One study analyzing TSH levels in the U.K. Clinical Practice Research Database from 2001 and 2009 found that the median TSH level decreased from 8.7 to 7.9 mIU/L, and the adjusted odds for prescribing levothyroxine at TSH levels of less than 10.0 mIU/L was 1.30 (95% CI, 1.19 to 1.42; p<0.001).[62]

# Contextual Question 2. What Are the Cardiovascular Consequences of Untreated Subclinical Thyroid Dysfunction?

## Subclinical Hypothyroidism

A recent meta-analysis of 11 prospective cohorts (n=55,287) found some evidence of an association between severity of hypothyroidism and risk for cardiovascular events.[4] Among patients with TSH values of 4.5 to 6.9, 7.0 to 9.9, and 10 to 19.9 mIU/L, respectively, the HR for a cardiac event was 1.00 (95% CI, 0.86 to 1.18), 1.17 (95% CI, 0.96 to 1.43), and 1.89 (95% CI, 1.28 to 2.80) (p<0.001 for trend). The HR for cardiac mortality was 1.09 (95% CI, 0.91 to 1.30), 1.43 (95% CI, 1.03 to 1.95), and 1.58 (95% CI, 1.10 to 2.27) (p=0.005 for trend). One challenge in interpreting these findings is that the cohort studies included some persons with a prior history of heart disease and may have been subject to residual confounding, despite attempts to control for cardiovascular risk factors. Other systematic reviews were somewhat inconsistent in finding an association between presence of subclinical hypothyroidism and cardiovascular risk, but did not perform analyses stratified by TSH level.[28,63] One meta-analysis reported an association between presence of subclinical hypothyroidism and risk for cardiovascular events in younger (age <65 years) adults (relative risk [RR], 1.7 [95% CI, 1.3 to 2.2]) but not in older adults (RR, 1.0 [95% CI, 0.90 to 1.2]).[5]

Four meta-analyses found no clear association between presence of subclinical hypothyroidism and risk for all-cause mortality.[4,5,28,29,63] One other meta-analysis found no association between subclinical hypothyroidism and mortality in community cohorts (HR, 1.03 [95% CI, 0.78 to 1.35]), but increased risk in patients with comorbid conditions (HR, 1.76 [95% CI, 1.36 to 2.30]).[29]

One meta-analysis of six prospective cohorts in the United States and Europe (n=25,390) found no association between the presence of subclinical hypothyroidism and congestive heart failure after adjustment for age and sex, although heterogeneity was present (HR, 1.26 [95% CI, 0.91 to 1.74]; $I^2$=77%).[6]

## Subclinical Hyperthyroidism

One meta-analysis of 10 prospective cohort studies (median followup, 8.8 years; N=52,674) found that subclinical hyperthyroidism was associated with increased risk for all-cause mortality (HR, 1.24 [95% CI, 1.06 to 1.46]), coronary heart disease mortality (HR, 1.29 [95% CI, 1.02 to 1.62]) and atrial fibrillation (HR, 1.68; 95% CI, 1.16 to 2.43), but not coronary heart disease events (HR, 1.21 [95% CI, 0.99 to 1.46]).[7] Persons with a TSH level of less than 0.10 mIU/L were at highest risk. Another, much smaller (N=290) meta-analysis of seven cohorts also found an association between subclinical hyperthyroidism and increased risk for all-cause mortality (HR, 1.41 [95% CI, 1.12 to 1.79]).[29] A meta-analysis of six cohort studies (n=25,390) found no association between presence of subclinical hyperthyroidism and risk for congestive heart failure after adjustment for age and sex (HR, 1.46 [95% CI, 0.94 to 2.27]; $I^2$=61%).[6]

Challenges in interpreting these meta-analyses are the inclusion of studies that enrolled persons with known thyroid dysfunction, ischemic heart disease, or a TSH level within the euthyroid reference range, and the failure of some included studies to adequately control for potential confounders such as lipid levels, blood pressure, and thyroid hormone use during the followup period. In addition, none of the studies evaluated whether treatment improved outcomes.

# Contextual Question 3. What Proportion of Patients Screened for Thyroid Dysfunction Have Overt Thyroid Disease?

While no studies directly answered this question, two large population-based cross-sectional studies reported similar findings regarding the prevalence of unrecognized overt thyroid disease. NHANES III found that about 0.8 percent of persons without a history of thyroid dysfunction or thyroid medication use had overt thyroid disease.[2] Because NHANES III did not assess for presence of thyroid symptoms, it is not possible to determine what proportion of persons with overt thyroid disease had clinically apparent disease. A second large population-based survey (N=25,862) based in Colorado found that about 0.5 percent of persons had undiagnosed overt thyroid disease.[3] This study included a 14-question survey that assessed if symptoms of hypothyroidism were currently present or had changed in the past year.[3] Persons with overt and subclinical hypothyroidism reported a greater number of hypothyroid symptoms than those who were euthyroid, although sensitivities (range, 2.9% to 28%) and positive predictive values (range, 8% to 12%) for presence of symptoms and overt hypothyroidism were low.

# Chapter 4. Discussion

## Summary of Review Findings

The findings of this review are summarized in **Table 8**.

As in the 2004 USPSTF report, we found no direct evidence on effects of thyroid screening compared with no screening on clinical outcomes. The scope of this update was expanded to include detection and treatment of screen-detected, undiagnosed overt thyroid disease, but we found no studies of treatment versus no treatment.

Evidence on benefits and harms of treatment was largely restricted to patients with subclinical hypothyroidism. Despite the potential association between subclinical hypothyroidism and cardiovascular disease and congestive heart failure[4-6] there is no clear evidence that treatment improves clinical outcomes. Although one fair-quality retrospective cohort study found that treatment of subclinical hypothyroidism associated with decreased risk for cardiac events, cancer, and all-cause mortality in adults ages 40 to 70 years,[49] it was an observational study with potential methodological limitations, including failure to adjust for some important confounders

As in the 2004 USPSTF review, evidence from newer trials found no clear improvement in quality of life or measures of cognitive function, but they were few in number, enrolled small samples, and may have been underpowered.[37,41,42,47,48]

Findings regarding intermediate outcomes were also consistent with the 2004 USPSTF review. Trials found no clear benefits of treatment of subclinical hypothyroidism on blood pressure, bone mineral density, or body mass index. Although treatment of subclinical hypothyroidism might have some beneficial effects on total and LDL cholesterol levels, differences were small and of uncertain clinical significance (range, -28 to 0 mg/dL for total cholesterol and -22 to 2 mg/dL for LDL cholesterol) and were not statistically significant in most studies.[38-40,42-46,48,50,51] No studies evaluated treatment of subclinical hypothyroidism with higher TSH levels, which may be associated with increased risk for adverse clinical outcomes.

Only two poor-quality studies evaluated treatment of subclinical hyperthyroidism, precluding reliable conclusions.[52,53] While a recent systematic review of observational studies found that subclinical hyperthyroidism might be associated with an increased risk for fractures, it only found trends, not statistically significant effects.[9]

The harms of screening remain poorly studied and sparsely reported. Potential harms of screening for subclinical hypothyroidism include false-positive test results, anxiety related to test results, and harms of treatment (including overreplacement or overtreatment), but evidence is too limited to estimate effects on any of these outcomes. Two prospective cohort studies suggest that approximately 40 percent of persons with subclinical hypothyroidism were biochemically euthyroid after 3 years of watchful waiting, and subsequent overtreatment could be a potential issue.[11,13]

# Limitations

Our review has several limitations. We did not include non-English–language articles. However, some studies have found that excluding non-English–language articles does not lead to biased estimates for noncomplementary interventions,[64] and a number of the studies included in our review were published in non-English–speaking countries. We were also unable to assess for publication bias using graphical or statistical methods because of the small numbers of studies for different outcomes.[65] We included poor-quality studies, but focused on results from higher-quality studies and performed sensitivity analyses in which poor-quality studies were excluded. Inclusion of poor-quality studies did not change any conclusions.

The evidence on thyroid screening was also limited. Direct evidence on benefits and harms of screening remains unavailable. In addition, the applicability of the evidence on benefits and harms of treatment of subclinical thyroid dysfunction to screening is uncertain. Few trials evaluated screen-detected populations.[37,40,41,47] Other trials did not clearly describe methods for identifying patients, except to report that they were recruited from outpatient clinics. In addition, no treatment study was conducted in the U.S., most trials were small (n<120), criteria for abnormal TSH and free T4 varied, treatment regimens varied, and followup in most studies was relatively brief (4 to 12 months).

We identified no trials of treatment versus no treatment of biochemically overt thyroid disease. This may be because treatment is recommended in clinical practice guidelines[10,30,31] and considered the standard of care. Although some trials have evaluated treatment of clinically overt thyroid disease (e.g., Graves' disease), such studies are not directly relevant for screening and were outside the scope of this report.

# Emerging Issues and Future Research

Trials of thyroid screening versus no screening would provide the most direct evidence on benefits and harms of screening. Prior to conducting trials of screening, however, it may be prudent to conduct well-designed trials of treatment versus placebo or no treatment, as effective treatments are a necessary prerequisite for effective screening interventions. For treatment trials to be most informative, they should enroll clearly defined samples of patients, clearly describe treatment protocols (e.g., doses and target TSH levels), and be designed to evaluate important clinical outcomes, including both benefits and harms and short- and long-term outcomes. Trials that enroll screen-detected asymptomatic patients would be the most directly applicable for informing screening decisions.

Research is also needed on the prevalence of unrecognized overt thyroid disease and on the effects of treatment in such patients in order to better understand the potential impact of screening. Observational studies could help provide important information on effects of screening and treatment, but should be conducted in well-defined populations and account for important confounders (e.g., patient demographics, medical and psychiatric comorbidities, risk factors for cardiovascular disease, and concomitant medication use) in their design and analysis. More research is needed to understand potential effects of treatment of subclinical

hypothyroidism on cancer risk.[49]

Another emerging area with implications for screening is research suggesting that subclinical hypothyroidism might be protective in older persons[13,20,21] and that the reference ranges for TSH should be adjusted upward in older adults.[22,66] Additional research to clarify criteria for abnormal thyroid function would obviously have implications for defining the target populations and impact of screening.

# Conclusion

Although screening can identify patients with subclinical hypothyroidism, subclinical hyperthyroidism, or unrecognized or undiagnosed overt thyroid disease, direct evidence on benefits and harms of screening versus no screening remains unavailable. Trials of treatment of subclinical hypothyroidism suggest a possible beneficial effect on total and LDL cholesterol levels, but the magnitude of effect appears small and of uncertain clinical significance. The only study showing a beneficial effect of treatment on cardiovascular events was observational and susceptible to residual confounding. Trials on the effects of treatment of subclinical hypothyroidism on other clinical and intermediate outcomes showed no clear beneficial effects, and data on harms were poor. More research is needed to understand effects of treatment of subclinical thyroid dysfunction and screen-detected, undiagnosed overt thyroid disease.

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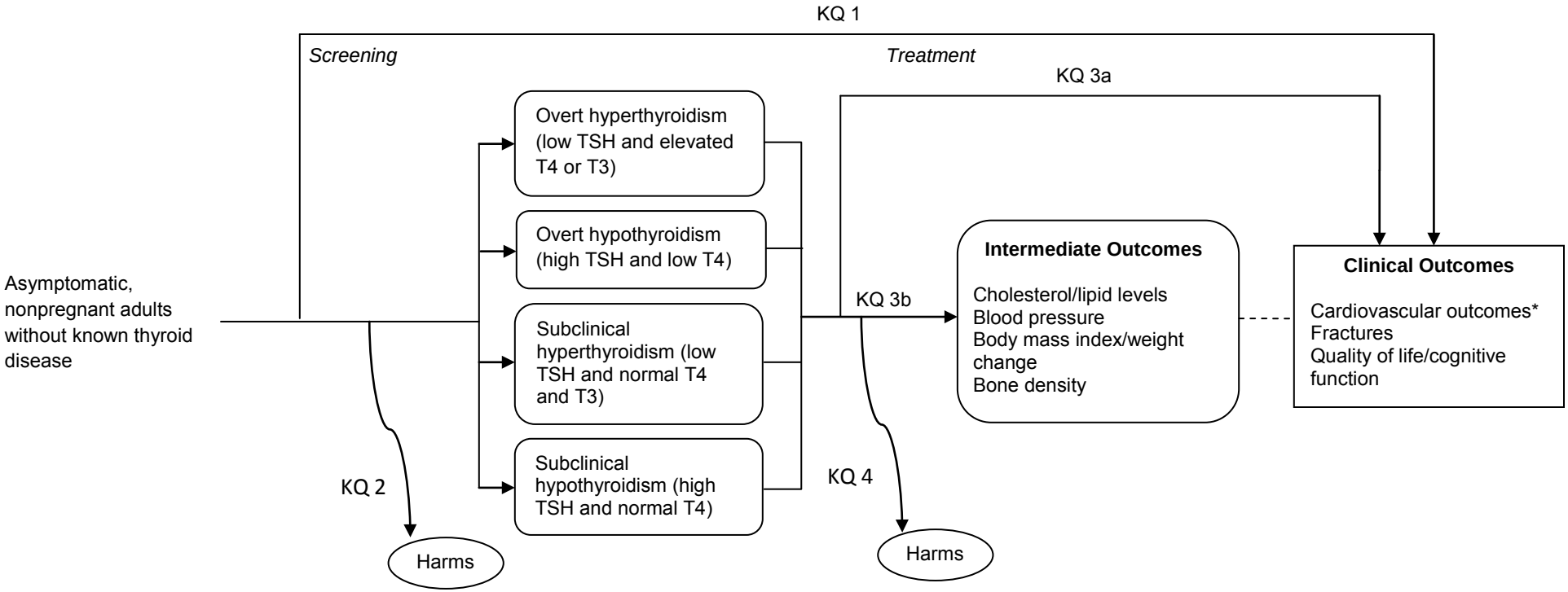
**Figure. Analytic Framework**




*Includes cardiovascular disease, coronary artery disease/congestive heart failure, and atrial fibrillation.

**Abbreviations:** KQ=key question; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

**Table 1. Classification of Thyroid Dysfunction: Biochemical Definition**

| Condition | TSH Level | Thyroid Hormones | Comments |
|---|---|---|---|
| Overt hyperthyroidism | <0.1 mIU/L or undetectable | Elevated T4 or T3 | |
| Overt hypothyroidism | >4.5 mIU/L | Low T4 | |
| Subclinical hyperthyroidism | <0.1 mIU/L<br>0.1 to 0.4 mIU/L | Normal T4 and T3<br>Normal T4 and T3 | Clearly low serum TSH<br>Low but detectable |
| Subclinical hypothyroidism | 4.5 to 10 mIU/L<br>≥10 mIU/L | Normal T4<br>Normal T4 | Mildly elevated TSH<br>Markedly elevated TSH |

Source: Jameson 2008,[19] Surks 2004[8]

**Abbreviations:** T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone.

**Table 2. Symptoms and Signs of Overt Thyroid Disease**

| Hypothyroidism | Hyperthyroidism |
|---|---|
| **Symptoms** | |
| Coarse, dry skin and hair<br>Cold intolerance<br>Constipation<br>Deafness<br>Diminished sweating<br>Physical tiredness<br>Hoarseness<br>Paresthesia<br>Periorbital puffiness | Nervousness and irritability<br>Heat intolerance<br>Increased frequency of stools<br>Muscle weakness<br>Increased sweating<br>Fatigue<br>Blurred or double vision<br>Erratic behavior<br>Restlessness<br>Heart palpitations<br>Restless sleep<br>Decrease in menstrual cycle<br>Increased appetite |
| **Signs** | |
| Decreased mental function<br>Slow movement<br>Slowing of ankle jerk<br>Weight gain<br>Goiter<br>Slow pulse | Distracted attention span<br>Tremors<br>Tachycardia<br>Weight loss<br>Goiter<br>Hyperreflexia<br>Proptosis |

**Table 3. Subclinical Hypothyroidism Cardiovascular Events and Mortality**

| Study, Year Study Design Study Duration | Country Age TSH Level | Intervention, n | Outcome | Treated vs. Nontreated | | | | | | Quality |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Ages 40–70 Years | | | Age >70 Years | | | |
| | | | | Events in Treated vs. Nontreated Groups (%) | HR (95% CI)[a] | Age- and Sex-Adjusted HR (95% CI) | Events in Treated vs. Nontreated Groups (%) | HR (95% CI)[a] | Age- and Sex-Adjusted HR (95% CI) | |
| Razvi 2012[49]<br><br>Retrospective cohort study (database analysis)<br><br>Median for 40–70 age group: 7.6 years<br>Median for >70 age group: 5.2 years | United Kingdom<br><br>Age ≥40 years<br><br>TSH: 5.01 to 10.00 mIU/L | *Ages 40-70 years*<br>LT4, 75 µg/d (median): 1634<br>Not treated: 1459<br><br>*Age >70 years*<br>LT4, 75 µg/d (median): 819<br>Not treated: 832 | Fatal and nonfatal ischemic heart disease events | 4.2% vs. 6.6% | **0.61 (0.39–0.95)** | **0.64 (0.41–0.89)** | 12.7% vs. 10.7% | 0.99 (0.59–1.33) | 1.03 (0.98–1.83) | Fair |
| | | | All-cause mortality | 3.4% vs. 6.4% | **0.36 (0.19–0.66)** | **0.43 (0.30–0.78)** | 35.2% vs. 40.5% | 0.71 (0.56–1.08) | 0.91 (0.65–1.14) | |
| | | | Death due to circulatory diseases[b] | 1.4% vs. 2.4% | **0.54 (0.37–0.92)** | **0.61 (0.37–0.91)** | 17.1% vs. 18.3% | 0.91 (0.56–1.46) | 0.87 (0.43–1.37) | |
| | | | Death due to ischemic heart disease events | 1.0% vs. 1.7% | 0.43 (0.19–2.05) | 0.55 (0.38–1.19) | 5.5% vs. 6.3% | 1.04 (0.56–1.93) | 1.12 (0.66–2.05) | |
| | | | Death due to malignant neoplasms | 1.2% vs. 2.2% | **0.59 (0.21–0.88)** | **0.61 (0.36–0.95)** | 4.6% vs. 6.5% | 0.51 (0.24–1.09) | 0.73 (0.34–1.16) | |
| | | | Fatal and nonfatal cerebrovascular accident | 3.4% vs. 3.0% | 1.03 (0.51–2.13) | 1.09 (0.75–1.89) | 17.7% vs. 17.9% | 0.81 (0.31–2.12) | 1.11 (0.45–2.01) | |
| | | | Atrial fibrillation | 2.0% vs. 2.3% | 0.76 (0.26–1.73) | 0.87 (0.59–1.44) | 8.1% vs. 7.7% | 0.98 (0.54–1.76) | 1.23 (0.69–1.58) | |

[a] Multivariate adjusted for age, sex, body mass index, socioeconomic deprivation score, total cholesterol, TSH level, smoking status, history of diabetes mellitus, systolic and diastolic blood pressure, and levothyroxine use as a time-dependent covariate.
[b] Circulatory events include ischemic heart disease, cerebrovascular accident, and peripheral vascular disease.
Bold=significant difference.

**Abbreviations:** HR=hazard ratio; CI=confidence interval; LT4=levothyroxine; TSH=thyroid-stimulating hormone.

**Table 4. Subclinical Hypothyroidism Quality of Life and Cognitive Function**

| Study, Year<br>Study Design<br>Study Duration<br>Country | Mean Age<br>Mean TSH Level<br>(LT4 vs. Placebo) | Intervention and Duration, n | Results, LT4 vs. Placebo | Quality |
|---|---|---|---|---|
| **Quality of life** | | | | |
| Abu-Helalah 2010[37]<br>RCT crossover (at 2 months)<br>4 months<br>United Kingdom | 58 years overall<br>(NR by group)<br>4.1 to 9.0 mIU/L<br>(mean NR) | LT4 72 µg (mean) for 2 months: 33<br>Placebo: 31 | QOL: odds of feeling better after taking thyroxine than placebo<br>TSH >4.0 mIU/L: 21 vs.16 patients; odds, 1.3<br>TSH >4.5 mIU/L: 17 vs. 7 patients; odds, 2.4<br>TSH >5.0 mIU/L: 12 vs. 5 patients; odds, 2.4<br>TSH >5.5 mIU/L: 11 vs. 4 patients; odds, 2.8<br>TSH >6.0 mIU/L: 8 vs. 2 patients; odds, 4.0 | Poor |
| Jorde 2006[41]<br>RCT<br>12 months<br>Norway | 62 vs. 63 years<br>5.8 vs. 5.3 mIU/L | LT4 109.7 µg for 12 months (mean): 36<br>Placebo: 33 | GHQ-30: 1.9 ± 3.3 vs. 1.2 ± 2.0; p=NS<br>BDI: 4.3 ± 3.6 vs. 3.3 ± 4.0; p=NS | Fair |
| Kong 2002[42]<br>RCT<br>6 months<br>United Kingdom | 53 vs. 45 years<br>8.0 vs. 7.3 mIU/L | LT4 (mean NR) for 6 months: 23<br>Placebo: 17 | Mean change in thyroxine group minus mean change in placebo group:<br>HADS–anxiety: 1 (95% CI, −1 to 3); p=NS<br>HADS–depression: −1 (95% CI, −3 to 1); p=NS<br>GHQ-30: 2 (95% CI, −5 to 7); p=NS | Good |
| Parle 2010[47]<br>RCT<br>12 months<br>United Kingdom | 73.5 vs. 74.2 years<br>6.6 vs. 6.6 mIU/L | LT4 50 µg (median) for 12 months: 52<br>Placebo: 42 | HADS–depression: 3.55 (0.27) vs. 3.37 (0.31); p=0.82 | Good |
| Razvi 2007[48]<br>RCT crossover (at 2.8 months)<br>5.5 months<br>United Kingdom | 53.5 vs. 54.2 years<br>5.4 vs. 5.3 mIU/L | LT4100 µg for 12 weeks: 50<br>Placebo: 50 | ThyDQoL: −1.1 ± 1 vs. −1.2 ± 0.9; p=0.24<br>SF-36–sex: −2.3 ± 2.7 vs. −2.7 ± 2.8; p=0.18<br>SF-36–motivation: −3.6 ± 2.7 vs. −3.7 ± 2.7; p=0.16<br>SF-36–worries: −2.5 ± 3 vs. −2.8 ± 2.9; p=0.23<br>Average weighted impact of all 18 QOL domains: −2.7 ± 2.4 vs. −2.8 ± 2.3; p=0.45 | Good |
| **Cognitive function** | | | | |
| Jorde 2006[41]<br>RCT<br>12 months<br>Norway | 62 vs. 63 years<br>5.8 vs. 5.3 mIU/L | LT4 109.7 µg for 12 months (mean): 36<br>Placebo: 33 | Composite cognitive function score: 1.5 ± 3.7 vs. −0.9 ± 4.8; p=NS<br>Trail Making A–psychomotor test of executive function: 39.0 ± 14.8 vs. 44.1 ± 17.7; p=NS<br>Trail Making B–psychomotor test of executive function: 94 ± 62 vs. 103 ± 49; p=NS | Fair |
| Parle 2010[47]<br>RCT<br>12 months<br>United Kingdom | 73.5 vs. 74.2 years<br>6.6 vs. 6.6 mIU/L | LT4 50 µg (median) for 12 months: 52<br>Placebo: 42 | MEAMS–cognitive skills and performance: 11.67 (0.09) vs. 11.60 (0.11); p=0.57<br>MMSE–cognitive status: 28.24 (0.38) vs. 28.22 (0.43); p=0.18<br>SCOLP–speed of cognitive processing and accounting: 1.29 (0.30) vs. 0.84 (0.35); p=0.59<br>Trail Making A–psychomotor test of executive function: 45.33 (2.63) vs. 46.78 (3.05); p=0.52<br>Trail Making B–psychomotor test of executive function: 100.65 (7.75) vs. 114.11 (9.07); p=0.95<br>Trail Making B-A–psychomotor test of executive function: 54.55 (6.80) vs. 67.27 (7.97); p=0.86 | Good |

**Abbreviations:** BDI=Beck Depression Inventory; CI=confidence interval; GHQ-30=General Health Questionnaire; HADS=Hospital Anxiety and Depression Scale; LT4=levothyroxine; MEAMS=Middlesex Elderly Assessment on Mental State; MMSE=Mini-Mental State Examination; NR=not reported; NS=not significant; QOL=quality of life; RCT=randomized, controlled trial; SCOLP=Speed and Capacity of Language Processing; SF-36=36-Item Short-Form Health Survey; TSH=thyroid-stimulating hormone.

**Table 5. Subclinical Hypothyroidism Intermediate Outcomes**

| Study, Year<br>Study Design<br>Study Duration<br>Country | Mean Age<br>Mean TSH Level<br>(LT4 vs. Placebo) | Intervention and Duration, n | Results, LT4 vs. Placebo | Difference in Means (Treatment vs. Control)[a] | Quality |
|---|---|---|---|---|---|
| **Blood pressure** | | | | | |
| Monzani 2004[44]<br>RCT<br>10.5 months<br>Italy | 37 years (NR by group)<br>6.03 vs. 5.68 mIU/L | LT4 70 µg (mean) for 6 months: 23<br>Placebo: 22 | SBP: 112 ± 15 vs. 114 ± 13 mm Hg; p=NS<br>DBP: 69 ± 9 vs. 72 ± 8 mm Hg; p=NS | SBP: −2 mm Hg<br>DBP: −3 mm Hg | Fair |
| Nagasaki 2009[46]<br>RCT<br>5 months<br>Japan | 64 vs. 66 years<br>7.3 vs. 7.3 mIU/L | LT4 25.8 µg (average) for 5 months: 48/NR<br>Placebo: 47/NR | SBP: 129 ± 4 vs. 132 ± 4 mm H; p=NS<br>DBP: 73 ± 2 vs. 73 ± 2 mm Hg; p=NS | SBP: −3 mm Hg<br>DBP: 0 mm Hg | Fair |
| Razvi 2007[48]<br>RCT crossover (at 12 weeks)<br>24 weeks<br>United Kingdom | 53.5 vs. 54.2 years<br>5.4 vs. 5.3 mIU/L | LT4 100 µg for 12 weeks: 50/50<br>Placebo: 50/49 | SBP: 133 ± 23 vs. 135 ± 23 mm Hg; p=0.21<br>DBP: 79 ± 10 vs. 80 ± 10 mm Hg; p=0.16 | SBP: −2 mm Hg<br>DBP: −1 mm Hg | Good |
| **Total cholesterol** | | | | | |
| Cabral 2011[38]<br>RCT<br>12 months<br>Brazil | 43 vs. 47 years<br>6.79 vs. 6.77 mIU/L | LT4 (median, 44.23 µg) for 12 months: 14<br>No treatment: 18 | TC: 208 ± 37 vs. 228 ± 37 mg/dL; p=NS | TC: −20 mg/dL | Fair |
| Duman 2007[39]<br>RCT<br>8 months<br>Turkey | 36 vs. 35 years<br>10.9 vs. 11.0 mIU/L | LT4 (all patients reached dose of 100 µg [mean NR] for 8 months): 22<br>No treatment: 19 | TC: 202 ± 28 vs. 202 ± 28 mg/dL; p=NS | TC: 0 mg/dL | Fair |
| Iqbal, 2006[40]<br>RCT<br>12 months<br>Norway | 63 vs. 61 years<br>5.8 vs. 5.4 mIU/L | LT4 96 to 97 µg (mean) for 12 months: 32/32<br>Placebo: 32/32 | TC: 220 ± 43 vs. 224 ± 35 mg/dL; p=NS | TC: −4 mg/dL | Fair |
| Kong 2002[42]<br>RCT<br>6 months<br>United Kingdom | 53 vs. 45 years<br>8.0 vs. 7.3 mIU/L | LT4 (mean NR) for 6 months: 23<br>Placebo: 17 | NR | Mean change in thyroxine group minus mean change in placebo group, TC: −8 mg/dL (95% CI, −28 to 20); p=NS | Good |
| Mikhail 2008[43]<br>RCT<br>12 months<br>Kuwait | 32 vs. 32 years<br>6.4 vs. 6.3 mIU/L | LT4 72 µg (mean) for 12 months: 60<br>Placebo: 60 | TC: 183 ± 34 vs. 195 ± 26 mg/dL; p<0.029 | TC: −12 mg/dL | Fair |
| Monzani 2004[44]<br>RCT<br>10.5 months<br>Italy | 37 years (NR by group)<br>6.03 vs. 5.68 mIU/L | LT4 70 µg (mean) for 6 months: 23<br>Placebo: 22 | TC: 192 ± 33 vs. 220 ± 49 mg/dL; p=0.03 | TC: −28 mg/dL | Fair |

**Table 5. Subclinical Hypothyroidism Intermediate Outcomes**

| Study, Year<br>Study Design<br>Study Duration<br>Country | Mean Age<br>Mean TSH Level<br>(LT4 vs. Placebo) | Intervention and Duration, n | Results, LT4 vs. Placebo | Difference in Means (Treatment vs. Control)[a] | Quality |
|---|---|---|---|---|---|
| Nagasaki 2009[46]<br>RCT<br>5 months<br>Japan | 64 vs. 66 years<br>7.3 vs. 7.3 mIU/L | LT4 25.8 µg (average) for 5 months: 48/NR<br>Placebo: 47/NR | TC: 201 ± 6 vs. 206 ± 9 mg/dL; p=NS | TC: −5 mg/dL | Fair |
| Razvi 2007[48]<br>RCT crossover (at 12 weeks)<br>24 weeks<br>United Kingdom | 53.5 vs. 54.2 years<br>5.4 vs. 5.3 mIU/L | LT4 100 µg for 12 weeks: 50/50<br>Placebo: 50/49 | TC: 220 ± 39 vs. 232 ± 39 mg/dL; p<0.001 | TC: −12 mg/dL | Good |
| Teixeira 2008[50,51]<br>RCT<br>12 months<br>Brazil | 48.9 vs. 47.5 years<br>7.5 vs. 7.7 mIU/mL | LT4 (mean NR) for 12 months: 35<br>Placebo: 25 | TC: 197 ± 29 vs. 203 ± 41 mg/dL; p=0.032 | TC: −6 mg/dL | Poor |
| **Low-density lipoprotein** | | | | | |
| Cabral 2011[38]<br>RCT<br>12 months<br>Brazil | 43 vs. 47 years<br>6.79 vs. 6.77 mIU/L | LT4 (median, 44.23 µg) for 12 months: 14<br>No treatment: 18 | LDL: 133 ± 38 vs. 151 ± 35 mg/dL; p=NS | LDL: −18 mg/dL | Fair |
| Duman 2007[39]<br>RCT<br>8 months<br>Turkey | 36 vs. 35 years<br>10.9 vs. 11.0 mIU/L | LT4 (all patients reached dose of 100 µg [mean NR] for 8 months): 22<br>No treatment: 19 | LDL: 130 ± 32 vs. 128 ± 25 mg/dL; p=NS | LDL: 2 mg/dL | Fair |
| Iqbal 2006[40]<br>RCT<br>12 months<br>Norway | 63 vs. 61 years<br>5.8 vs. 5.4 mIU/L | LT4 96 to 97 µg (mean) for 12 months: 32/32<br>Placebo: 32/32 | LDL: 139 ± 35 vs. 139 +/0 39 mg/dL; p=NS | LDL: 0 mg/dL | Fair |
| Kong 2002[42]<br>RCT<br>6 months<br>United Kingdom | 53 vs. 45 years<br>8.0 vs. 7.3 mIU/L | LT4 (mean NR) for 6 months: 23<br>Placebo: 17 | NR | Mean change in thyroxine group minus mean change in placebo group, LDL: −4 mg/dL (95% CI, −23 to 15); p=NS | Good |
| Mikhail 2008[43]<br>RCT<br>12 months<br>Kuwait | 32 vs. 32 years<br>6.4 vs. 6.3 mIU/L | LT4 72 µg (mean) for 12 months: 60<br>Placebo: 60 | LDL: 112 ± 23 vs. 120 ± 30 mg/dL; p<0.001 | LDL: −8 mg/dL | Fair |
| Monzani 2004[44]<br>RCT<br>10.5 months<br>Italy | 37 years (NR by group)<br>6.03 vs. 5.68 mIU/L | LT4 70 µg (mean) for 6 months: 23<br>Placebo: 22 | LDL: 119 ± 28 vs. 141 ± 39 mg/dL; p=0.03 | LDL: −22 mg/dL | Fair |

**Table 5. Subclinical Hypothyroidism Intermediate Outcomes**

| Study, Year<br>Study Design<br>Study Duration<br>Country | Mean Age<br>Mean TSH Level<br>(LT4 vs. Placebo) | Intervention and Duration, n | Results, LT4 vs. Placebo | Difference in Means (Treatment vs. Control)[a] | Quality |
|---|---|---|---|---|---|
| Nagasaki 2009[46]<br>RCT<br>5 months<br>Japan | 64 vs. 66 years<br>7.3 vs. 7.3 mIU/L | LT4 25.8 µg (average) for 5 months: 48/NR<br>Placebo: 47/NR | LDL: 121 ± 11 vs. 130 ± 7 mg/dL; p=NS | LDL: −9 mg/dL | Fair |
| Razvi 2007[48]<br>RCT crossover (at 12 weeks)<br>24 weeks<br>United Kingdom | 53.5 vs. 54.2 years<br>5.4 vs. 5.3 mIU/L | LT4 100 µg for 12 weeks: 50/50<br>Placebo: 50/49 | LDL: 131 ± 31 vs. 143 ± 35 mg/dL; p<0.001 | LDL: −12 mg/dL | Good |
| Teixeira 2008[50, 51]<br>RCT<br>12 months<br>Brazil | 48.9 vs. 47.5 years<br>7.5 vs. 7.7 mIU/mL | LT4 (mean NR) for 12 months: 35<br>Placebo: 25 | LDL: 118 ± 24 vs. 130 ± 35 mg/dL; p=0.024 | LDL: −12 mg/dL | Poor |
| **High-density lipoprotein** | | | | | |
| Cabral 2011[38]<br>RCT<br>12 months<br>Brazil | 43 vs. 47 years<br>6.79 vs. 6.77 mIU/L | LT4 (median, 44.23 µg) for 12 months: 14<br>No treatment: 18 | HDL: 54 ± 12 vs. 50 ± 10 mg/dL; p=NS | HDL: 4 mg/dL | Fair |
| Duman 2007[39]<br>RCT<br>8 months<br>Turkey | 36 vs. 35 years<br>10.9 vs. 11.0 mIU/L | LT4 (all patients reached dose of 100 µg [mean NR] for 8 months): 22<br>No treatment: 19 | HDL: 53 ± 16 vs. 53 ± 9 mg/dL; p=NS | HDL: 0 mg/dL | Fair |
| Iqbal 2006[40]<br>RCT<br>12 months<br>Norway | 63 vs. 61 years<br>5.8 vs. 5.4 mIU/L | LT4 96 to 97 µg (mean) for 12 months: 32/32<br>Placebo: 32/32 | HDL: 58 ± 16 vs. 58 ± 19 mg/dL; p=NS | HDL: 0 mg/dL | Fair |
| Kong 2002[42]<br>RCT<br>6 months<br>United Kingdom | 53 vs. 45 years<br>8.0 vs. 7.3 mIU/L | LT4 (mean NR) for 6 months: 23<br>Placebo: 17 | NR | Mean change in thyroxine group minus mean change in placebo group, HDL: −1 mg/dL (95% CI, −8 to 4); p=NS | Good |
| Mikhail 2008[43]<br>RCT<br>12 months<br>Kuwait | 32 vs. 32 years<br>6.4 vs. 6.3 mIU/L | LT4 72 µg (mean) for 12 months: 60<br>Placebo: 60 | HDL: 46 ± 12 vs. 43 ± 10 mg/dL; p=NS | HDL: 3 mg/dL | Fair |
| Monzani 2004[44]<br>RCT<br>10.5 months<br>Italy | 37 years (NR by group)<br>6.03 vs. 5.68 mIU/L | LT4 70 µg (mean) for 6 months: 23<br>Placebo: 22 | HDL: 55 ± 7 vs. 58 ± 12 mg/dL; p=NS | HDL: −3 mg/dL | Fair |

**Table 5. Subclinical Hypothyroidism Intermediate Outcomes**

| Study, Year<br>Study Design<br>Study Duration<br>Country | Mean Age<br>Mean TSH Level<br>(LT4 vs. Placebo) | Intervention and Duration, n | Results, LT4 vs. Placebo | Difference in Means (Treatment vs. Control)[a] | Quality |
|---|---|---|---|---|---|
| Nagasaki 2009[46]<br>RCT<br>5 months<br>Japan | 64 vs. 66 years<br>7.3 vs. 7.3 mIU/L | LT4 25.8 µg (average) for 5 months: 48/NR<br>Placebo: 47/NR | HDL: 55 ± 3 vs. 54 ± 2 mg/dL; p=NS | HDL: 1 mg/dL | Fair |
| Razvi 2007[48]<br>RCT cross-over (at 12 weeks)<br>24 weeks<br>United Kingdom | 53.5 vs. 54.2 years<br>5.4 vs. 5.3 mIU/L | LT4 100 µg for 12 weeks: 50/50<br>Placebo: 50/49 | HDL: 62 ± 19 vs. 66 ± 19 mg/dL; p=0.12 | HDL: −4 mg/dL | Good |
| Teixeira 2008[50, 51]<br>RCT<br>12 months<br>Brazil | 48.9 vs. 47.5 years<br>7.5 vs. 7.7 mIU/mL | LT4 (mean NR) for 12 months: 35<br>Placebo: 25 | HDL: 55 ± 18 vs. 49 ± 10 mg/dL; p=0.180 | HDL: 6 mg/dL | Poor |
| **Triglycerides** | | | | | |
| Cabral 2011[38]<br>RCT<br>12 months<br>Brazil | 43 vs. 47 years<br>6.79 vs. 6.77 mIU/L | LT4 (median, 44.23 µg/d) for 12 months: 14<br>No treatment: 18 | TG: 106 ± 37 vs. 137 ± 56 mg/dL;, p=NS | TG: −31 mg/dL | Fair |
| Duman 2007[39]<br>RCT<br>8 months<br>Turkey | 36 vs. 35 years<br>10.9 vs. 11.0 mIU/L | LT4 (all patients reached dose of 100 µg [mean NR] for 8 months): 22<br>No treatment: 19 | TG: 96 ± 37 vs. 128 ± 58 mg/dL; p=NS | TG: −32 mg/dL | Fair |
| Iqbal 2006[40]<br>RCT<br>12 months<br>Norway | 63 vs. 61 years<br>5.8 vs. 5.4 mIU/L | LT4 96 to 97 µg (mean) for 12 months: 32/32<br>Placebo: 32/32 | TG: 133 ± 89 vs. 142 ± 62 mg/dL; p=NS | TG: −9 mg/dL | Fair |
| Kong 2002[42]<br>RCT<br>6 months<br>United Kingdom | 53 vs. 45 years<br>8.0 vs. 7.3 mIU/L | LT4 (mean NR) for 6 months: 23<br>Placebo: 17 | NR | Mean change in thyroxine group minus mean change in placebo group, TG: 9 mg/dL (95% CI, −26 to 44); p=NS | Good |
| Mikhail 2008[43]<br>RCT<br>12 months<br>Kuwait | 32 vs. 32 years<br>6.4 vs. 6.3 mIU/L | LT4 72 µg (mean) for 12 months: 60<br>Placebo: 60 | TG: 84 ± 47 vs. 94 ± 52 mg/dL; p=NS | TG: −10 mg/dL | Fair |
| Monzani 2004[44]<br>RCT<br>10.5 months<br>Italy | 37 years (NR by group)<br>6.03 vs. 5.68 mIU/L | LT4 70 µg (mean) for 6 months: 23<br>Placebo: 22 | TG: 88 ± 30 vs. 103 ± 53 mg/dL; p=NS | TG: −15 mg/dL | Fair |

**Table 5. Subclinical Hypothyroidism Intermediate Outcomes**

| Study, Year<br>Study Design<br>Study Duration<br>Country | Mean Age<br>Mean TSH Level<br>(LT4 vs. Placebo) | Intervention and Duration, n | Results, LT4 vs. Placebo | Difference in Means (Treatment vs. Control)[a] | Quality |
|---|---|---|---|---|---|
| Nagasaki 2009[49]<br>RCT<br>5 months<br>Japan | 64 vs. 66 years<br>7.3 vs. 7.3 mIU/L | LT4 25.8 µg (average) for 5 months: 48/NR<br>Placebo: 47/NR | TG: 133 ± 14 vs. 122 ± 12 mg/dL; p=NS | TG: 11 mg/dL | Fair |
| Razvi 2007[46]<br>RCT cross-over (at 12 weeks)<br>24 weeks<br>United Kingdom | 53.5 vs. 54.2 years<br>5.4 vs. 5.3 mIU/L | LT4 100 µg for 12 weeks: 50/50<br>Placebo: 50/49 | TG: 115 (44 to 363) vs. 115 (35 to 452) mg/dL; p=0.26 | TG: 0 mg/dL | Good |
| Teixeira 2008[50, 51]<br>RCT<br>12 months<br>Brazil | 48.9 vs. 47.5 years<br>7.5 vs. 7.7 mIU/mL | LT4 (mean NR) for 12 months: 35<br>Placebo: 25 | TG: 105 ± 59 vs. 123 ± 59 mg/dL; p=0.384 | TG: −18 mg/dL | Poor |
| **Body mass index or weight** | | | | | |
| Duman 2007[39]<br>RCT<br>8 months<br>Turkey | 36 vs. 35 years<br>10.9 vs. 11.0 mIU/L | LT4 (all patients reached dose of 100 µg [mean NR] for 8 months: 22<br>No treatment: 19 | BMI: 25 ± 3 vs. 26 ± 9 kg/m$^2$; p=NS | BMI: −1 kg/m$^2$ | Fair |
| Iqbal 2006[40]<br>RCT<br>12 months<br>Norway | 63 vs. 61 years<br>5.8 vs. 5.4 mIU/L | LT4 96 to 97 µg (mean) for 12 months: 32/32<br>Placebo: 32/32 | BMI: 28 ± 6 vs. 27 ± 4 kg/m$^2$; p=NS | BMI: 1 kg/m$^2$ | Fair |
| Kong 2002[42]<br>RCT<br>6 months<br>United Kingdom | 53 vs. 45 years<br>8.0 vs. 7.3 mIU/L | LT4 (mean NR) for 6 months: 23<br>Placebo: 17 | NR | Mean change in thyroxine group minus mean change in placebo group:<br>BMI: −0.3 kg/m$^2$ (95% CI, 0.9 to 0.4); p=NS<br>% lean body weight: 0.1 (95% CI, 1.6 to 1.7); p=NS | Good |
| Monzani 2004[44]<br>RCT<br>10.5 months<br>Italy | 37 years (NR by group)<br>6.03 vs. 5.68 mIU/L | LT4 70 µg (mean) for 6 months: 23<br>Placebo: 22 | BMI: 24 ± 4 vs. 25 ± 4 kg/m$^2$; p=NS | BMI: −1 kg/m$^2$ | Fair |
| Nagasaki 2009[46]<br>RCT<br>5 months<br>Japan | 64 vs. 66 years<br>7.3 vs. 7.3 mIU/L | LT4 25.8 µg (average) for 5 months: 48/NR<br>Placebo: 47/NR | BMI: 22 ± 0.5 vs. 22 ± 0.5 kg/m$^2$; p=NS | BMI: 0 kg/m$^2$ | Fair |

**Table 5. Subclinical Hypothyroidism Intermediate Outcomes**

| Study, Year<br>Study Design<br>Study Duration<br>Country | Mean Age<br>Mean TSH Level<br>(LT4 vs. Placebo) | Intervention and Duration, n | Results, LT4 vs. Placebo | Difference in Means (Treatment vs. Control)[a] | Quality |
|---|---|---|---|---|---|
| Razvi 2007[48]<br>RCT crossover (at 12 weeks)<br>24 weeks<br>United Kingdom | 53.5 vs. 54.2 years<br>5.4 vs. 5.3 mIU/L | LT4 100 µg for 12 weeks: 50/50<br>Placebo: 50/49 | Weight: 76 ± 17 vs. 77 ± 17 kg; p=0.12 | Weight: −1 kg | Good |

[a] Negative values favor treatment for BMI, SBP, DBP, total cholesterol, LDL, and triglycerides; positive values favor treatment for HDL.

**Abbreviations:** BMI=body mass index; CI=confidence interval; DBP=diastolic blood pressure; HDL=high-density lipoprotein; LDL=low-density lipoprotein; LT4=levothyroxine; NR=not reported; NS=not significant; RCT=randomized, controlled trial; SBP=systolic blood pressure; TC= total cholesterol; TG=triglycerides; TSH=thyroid-stimulating hormone.

**Table 6. Subclinical Hyperthyroidism Intermediate Outcomes**

| Study, Year<br>Study Design<br>Study Duration<br>Country | Mean Age<br>Mean TSH Level (Intervention vs. No Treatment) | Intervention, n | Results, Intervention vs. No Treatment | Difference in Means (Treatment vs. Control)[a] | Quality |
|---|---|---|---|---|---|
| **Blood pressure** | | | | | |
| Buscemi 2007[52]<br>RCT<br>12 months<br>Italy | 59 vs. 57 years<br>0.06 vs. 0.06 mIU/L | Methimazole 10 to 15 mg for 12 months: 7<br>No treatment: 7 | SBP: 136 ± 4 vs. 126 ± 11 mm Hg; p=NS<br>DBP: 78 ± 3 vs. 80 ± 3 mm Hg; p=NS | SBP: 10 mm Hg<br>DBP: −2 mm Hg | Poor |
| Yonem 2002[53]<br>RCT<br>6 months<br>Turkey | 38.7 vs. 33.5 years<br>0.23 vs. 0.21 mIU/L | Propylthiouracil 150 mg for 6 months: 9<br>Radioactive iodine for 6 months: 1<br>No treatment: 10 | SBP day: 112 ± 3 vs. 114 ± 3 mm Hg; p=NS<br>DBP day: 69 ± 2 vs. 72 ± 2 mm Hg; p=NS<br>SBP night : 100 ± 2 vs. 102 ± 2 mm Hg; p=NS<br>DBP night: 62 ± 1 vs. 62 ± 3 mm Hg; p=NS | SBP day: −2 mm Hg<br>DBP day: −3 mm Hg<br>SBP night: −2 mm Hg<br>DBP night: 0 mm Hg | Poor |
| **Body mass index** | | | | | |
| Buscemi 2007[52]<br>RCT<br>12 months<br>Italy | 59 vs. 57 years<br>0.06 vs. 0.06 mIU/L | Methimazole 10 to 15 mg for 12 months: 7<br>No treatment: 7 | BMI: 28 ± 1 vs. 28 ± 1 kg/m$^2$; p=NS | BMI: 0 kg/m$^2$ | Poor |
| **Bone mineral density** | | | | | |
| Yonem 2002[53]<br>RCT<br>6 months<br>Turkey | 38.7 vs. 33.5 years<br>0.23 vs. 0.21 mIU/L | Propylthiouracil 150 mg for 6 months: 9<br>Radioactive iodine for 6 months: 1<br>No treatment: 10 | BMD femur neck: 0.826 ± 0.042 vs. 0.868 ± 0.019 g/cm$^2$; p=NS<br>BMD lumbar vertebra: 0.998 ± 0.048 vs. 0.968 ± 0.030 g/cm$^2$; p=NS | BMD femur neck: −0.042 g/cm$^2$<br>BMD lumbar vertebra: 0.03 g/cm$^2$ | Poor |
| **Lipid levels** | | | | | |
| Yonem 2002[53]<br>RCT<br>6 months<br>Turkey | 38.7 vs. 33.5 years<br>0.23 vs. 0.21 mIU/L | Propylthiouracil 150 mg for 6 months: 9<br>Radioactive iodine for 6 months: 1<br>No treatment: 10 | TG: 40 ± 24 vs. 76 ± 14 mg/dL; p=NS<br>TC: 183 ± 9 vs. 157 ± 7 mg/dL; p=NS<br>LDL: 106 ± 7 vs. 91 ± 6 mg/dL; p=NS<br>HDL: 48 ± 4 vs. 48 ± 4 mg/dL; p=NS | TG: −36 mg/dL<br>TC: 26 mg/dL<br>LDL: 15 mg/dL<br>HDL: 0 mg/dL | Poor |

[a] Negative values favor treatment for BMD, BMI, SBP, DBP, TC, LDL, and TG; positive values favor treatment for HDL.

**Abbreviations:** BMD=bone mineral density; BMI=body mass index; DBP=diastolic blood pressure; HDL=high-density lipoprotein; LDL=low-density lipoprotein; NS=not significant; RCT=randomized, controlled trial; SBP=systolic blood pressure; TC=total cholesterol; TG=triglycerides; TSH=thyroid-stimulating hormone.

**Table 7. Adverse Effects of Treatment**

| Study, Year | Duration | Adverse Effects Reported | Quality |
|---|---|---|---|
| **Subclinical hypothyroidism** | | | |
| Abu-Helalah 2010[37] | 4 months | "No indication of harms" | Poor |
| Nagasaki 2009[46] | 5 months | None of the patients required withdrawal of treatment due to side effects | Fair |
| Parle 2010[47] | 12 months | Withdrawal due to side effects: 9.6% (5/52) intervention vs. 14.3% (6/42) placebo; p=0.49 | Good |
| Razvi 2007[48] | 5.5 months | 1 person in the placebo group discontinued because of "perceived side effects and personal problems" | Good |
| Teixeira 2008[50,51] | 12 months | Levothyroxine group: 1 patient withdrew because of Hashitoxicosis, 1 patient withdrew because of symptomatic tachycardia | Poor |
| **Subclinical hyperthyroidism** | | | |
| Buscemi 2007[52] | 12 months | "No adverse effect" was observed in the treatment group | Poor |

**Table 8. Summary of Evidence**

| Prior Report Findings | Studies Identified in Update | Limitations | Consistency | Applicability | Summary of Findings | Overall Quality |
|---|---|---|---|---|---|---|
| **KQ 1. Does screening for thyroid dysfunction reduce morbidity or mortality?** | | | | | | |
| No studies | No studies | - | - | - | - | - |
| **KQ 2. What are the harms of screening for thyroid dysfunction?** | | | | | | |
| No studies | No studies | - | - | - | - | - |
| **KQ 3a. Does treatment of screen-detected overt or subclinical thyroid dysfunction improve morbidity or mortality?** | | | | | | |
| **Subclinical hypothyroidism** | | | | | | |
| *Cardiovascular events, coronary artery disease, and heart failure* | | | | | | |
| No studies | 1 retrospective cohort study | Did not adjust for use of aspirin, lipid-lowering therapy, or cardiovascular medications | NA | Study population in United Kingdom | 1 fair-quality retrospective cohort study found that treatment of subclinical hypothyroidism was associated with decreased risk for cardiac events, cancer, and all-cause mortality in adults ages 40–70 years, but not in those age >70 years. However, this study had methodological limitations, including failure to adjust for some important confounders. The findings could represent a true effect or a spurious association as a result of residual confounding | Poor |
| *Overall quality of life* | | | | | | |
| Only 1 of 5 trials found improvement in quality of life; most studies evaluated patients previously treated for Graves' disease | 5 RCTs | Trials were small and of short duration | Consistent | Study populations in Norway and United Kingdom | Thyroxine was associated with no effect on quality of life using various measures | Fair |
| *Changes in cognition* | | | | | | |
| 1 of 2 trials found a statistically significant improvement in memory in patients older than age 55 years that the authors described as "small and of questionable clinical importance" | 2 RCTs | Trials were small and of short duration | Consistent | Study populations in Norway and United Kingdom | Thyroxine was associated with no effect on cognitive function using various measures | Poor |
| **Subclinical hyperthyroidism** | | | | | | |
| No studies | No studies | - | - | - | - | - |
| **Overt thyroid disease**[a] | | | | | | |
| Not assessed | No studies | - | - | - | - | - |

**Table 8. Summary of Evidence**

| Prior Report Findings | Studies Identified in Update | Limitations | Consistency | Applicability | Summary of Findings | Overall Quality |
|---|---|---|---|---|---|---|
| **KQ 3b. Does treatment of screen-detected overt or subclinical thyroid dysfunction improve intermediate outcomes?** | | | | | | |
| **Subclinical hypothyroidism** | | | | | | |
| *Changes in blood pressure* | | | | | | |
| No studies | 3 RCTs | Studies were small, of limited duration, used different cutoffs for TSH, and used different dosing protocols | Consistent | Study populations in Italy, Japan, and United Kingdom | Thyroxine was associated with no effect on systolic blood pressure (difference ranged from −3 to −2 mm Hg) or diastolic blood pressure (difference ranged from −3 to 0 mm Hg) | Poor |
| *Changes in lipid levels* | | | | | | |
| 1 of 7 studies found a slight improvement in LDL cholesterol with treatment of 50 µg/d of levothyroxine vs. 25 µg/d | 9 RCTs | See above | Inconsistent | Study populations in United Kingdom, Brazil, Italy, Turkey, Norway, Kuwait, and Japan | 3 of 8 good- and fair-quality trials found that treatment was associated with lower total and LDL cholesterol, and other trials also reported a slight trend toward beneficial effects for total cholesterol, although nonsignificant. However, differences were small (−28 to 0 mg/dL for total cholesterol and −22 to 2 mg/dL for LDL). Treatment of subclinical hypothyroidism was not associated with beneficial effects on HDL (−4 to 4 mg/dL) or triglyceride (−32 to 11 mg/dL) levels | Fair |
| *Changes in BMI or weight* | | | | | | |
| No studies | 6 RCTs | See above | Consistent | | Thyroxine was associated with no effect on BMI (difference ranged from −1 to 1 $kg/m^2$) or weight (difference of −1 kg in one study) | Fair |
| **Subclinical hyperthyroidism** | | | | | | |
| *Changes in blood pressure* | | | | | | |
| No studies | 2 RCTs | Studies were very small, of limited duration, and used different treatment protocols | Consistent | Study populations in Italy and Turkey | Thyroxine was associated with no effect on systolic blood pressure (difference ranged from −2 to 10 mm Hg) or diastolic blood pressure (difference ranged from −3 to 0 mm Hg) | Poor |
| *Changes in bone density* | | | | | | |
| No studies | 1 RCT | See above | NA | Study populations in Turkey | Thyroxine was associated with no effect on femur neck (difference was −0.042 $g/cm^2$) or lumbar vertebra BMD (difference was 0.03 $g/cm^2$) | Poor |

**Table 8. Summary of Evidence**

| Prior Report Findings | Studies Identified in Update | Limitations | Consistency | Applicability | Summary of Findings | Overall Quality |
|---|---|---|---|---|---|---|
| *Changes in lipid levels* | | | | | | |
| No studies | 1 RCT | See above | NA | Study populations in Turkey | Thyroxine was associated with no effect on total (difference was 26 mg/dL), LDL (difference was 15 mg/dL), or HDL cholesterol (difference was 0 mg/dL), or triglycerides (difference was −36 mg/dL) | Poor |
| *Changes in BMI* | | | | | | |
| No studies | 1 RCT | See above | NA | Study population in Italy | Thyroxine was associated with no effect on BMI (difference was 0 $kg/m^2$) | Poor |
| **Overt thyroid disease[a]** | | | | | | |
| Not assessed | No studies | - | - | - | - | - |
| **KQ 4. What are the harms of treatment of screen-detected thyroid dysfunction?** | | | | | | |
| Incidental findings included low percentage of nervousness, anxiety, palpitations, and withdrawals due to complications | 5 RCTs for subclinical hypothyroidism; 1 RCT for subclinical hyperthyroidism | Only 1 trial directly compared harms between treated and not treated adults; all other reported ad hoc adverse effects | Not able to assess | Study populations in United Kingdom, Japan, Brazil, and Italy | Only 1 trial in patients with subclinical hypothyroidism directly compared harms between treated and not treated adults and found no difference in withdrawals due to side effects; all other trials reported ad hoc adverse effects | Poor |

[a] Asymptomatic or mildly symptomatic patients with biochemically overt thyroid disease.

**Abbreviations:** BMD=bone mineral density; BMI=body mass index; HDL=high-density lipoprotein; KQ=key question; LDL=low-density lipoprotein; NA=not applicable; TSH=thyroid-stimulating hormone; RCT=randomized, controlled trial.

**Appendix A1. Search Strategies**

## Screening

Database: Ovid MEDLINE® and Ovid OLDMEDLINE®
Search Strategy:
1 thyroid diseases/ or hyperthyroidism/ or hypothyroidism/
2 (thyroid and disease$).mp.
3 (hypothyroid$ or hyperthyroid$).mp.
4 or/1-3
5 Mass Screening/
6 4 and 5
7 Pregnancy/
8 (pediatric$ or newborn or neonat$ or child$ or infan$).mp.
9 6 not (7 or 8)
10 limit 9 to english language
11 limit 9 to abstracts
12 10 or 11
13 limit 12 to humans

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 thyroid diseases/ or hyperthyroidism/ or hypothyroidism/
2 (thyroid and disease$).mp.
3 (hypothyroid$ or hyperthyroid$).mp.
4 or/1-3
5 Mass Screening/
6 screen$.mp.
7 5 or 6
8 4 and 7

## Treatment

Database: Ovid MEDLINE® and Ovid OLDMEDLINE®
1 Thyroid Diseases/
2 Hyperthyroidism/
3 Hypothyroidism/
4 (hyperthyroid$ or hypothyroid$).ti.
5 ("thyroid deficien*" or "thyroid insufficien*" or "thyroid failure").mp.
6 or/1-5
7 exp Antithyroid Agents/
8 (anti-thyroid or methimazole or propylthiouracil or radioiodine or "radioactive iodine").ti,ab.
9 exp Thyronines/
10 exp Thyroxine/
11 (t3 or t4 or thyroxine or levothyroxine or triiodothyronine or liothyronine or thyrolar or liotrix).ti,ab.
12 or/7-11
13 6 and 12
14 6 and pc.fs.

15 6 and dt.fs.
16 6 and th.fs.
17 or/14-16
18 13 or 17
19 Pregnancy/
20 (child$ or pediatric$ or infan$ or newborn or neonat$ or toddler).mp.
21 grave's.ti.
22 18 not (19 or 20 or 21)
23 limit 22 to humans
24 limit 23 to english language
25 limit 23 to abstracts
26 24 or 25
27 limit 26 to (clinical trial, all or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 Thyroid Diseases/
2 Hyperthyroidism/
3 Hypothyroidism/
4 (hyperthyroid$ or hypothyroid$).ti. (413)
5 ("thyroid deficien*" or "thyroid insufficien*" or "thyroid failure").mp.
6 or/1-5
7 exp Antithyroid Agents/
8 (anti-thyroid or methimazole or propylthiouracil or radioiodine or "radioactive iodine").ti,ab.
9 exp Thyronines/
10 exp Thyroxine/
11 (t3 or t4 or thyroxine or levothyroxine or triiodothyronine or liothyronine or thyrolar or liotrix).ti,ab.
12 or/7-11
13 6 and 12
14 6 and pc.fs.
15 6 and dt.fs.
16 6 and th.fs.
17 or/14-16
18 13 or 17
19 Pregnancy/
20 (child$ or pediatric$ or infan$ or newborn or neonat$ or toddler).mp.
21 grave's.ti.
22 18 not (19 or 20 or 21)

### All Key Questions

Database: Ovid MEDLINE® Without Revisions
1 Thyroid Diseases/
2 Hyperthyroidism/
3 Hypothyroidism/

4 (hyperthyroid$ or hypothyroid$).ti.
5 ("thyroid deficien*" or "thyroid insufficien*" or "thyroid failure").mp.
6 or/1-5
7 exp Antithyroid Agents/
8 (anti-thyroid or methimazole or propylthiouracil or radioiodine or "radioactive iodine").ti,ab.
9 exp Thyronines/
10 exp Thyroxine/
11 (t3 or t4 or thyroxine or levothyroxine or triiodothyronine or liothyronine or thyrolar or liotrix).ti,ab.
12 or/7-11
13 6 and 12
14 13 not (pregnan$ or pediatric$ or newborn or neonat$ or child$ or infan$).ti.
15 limit 14 to evidence based medicine reviews

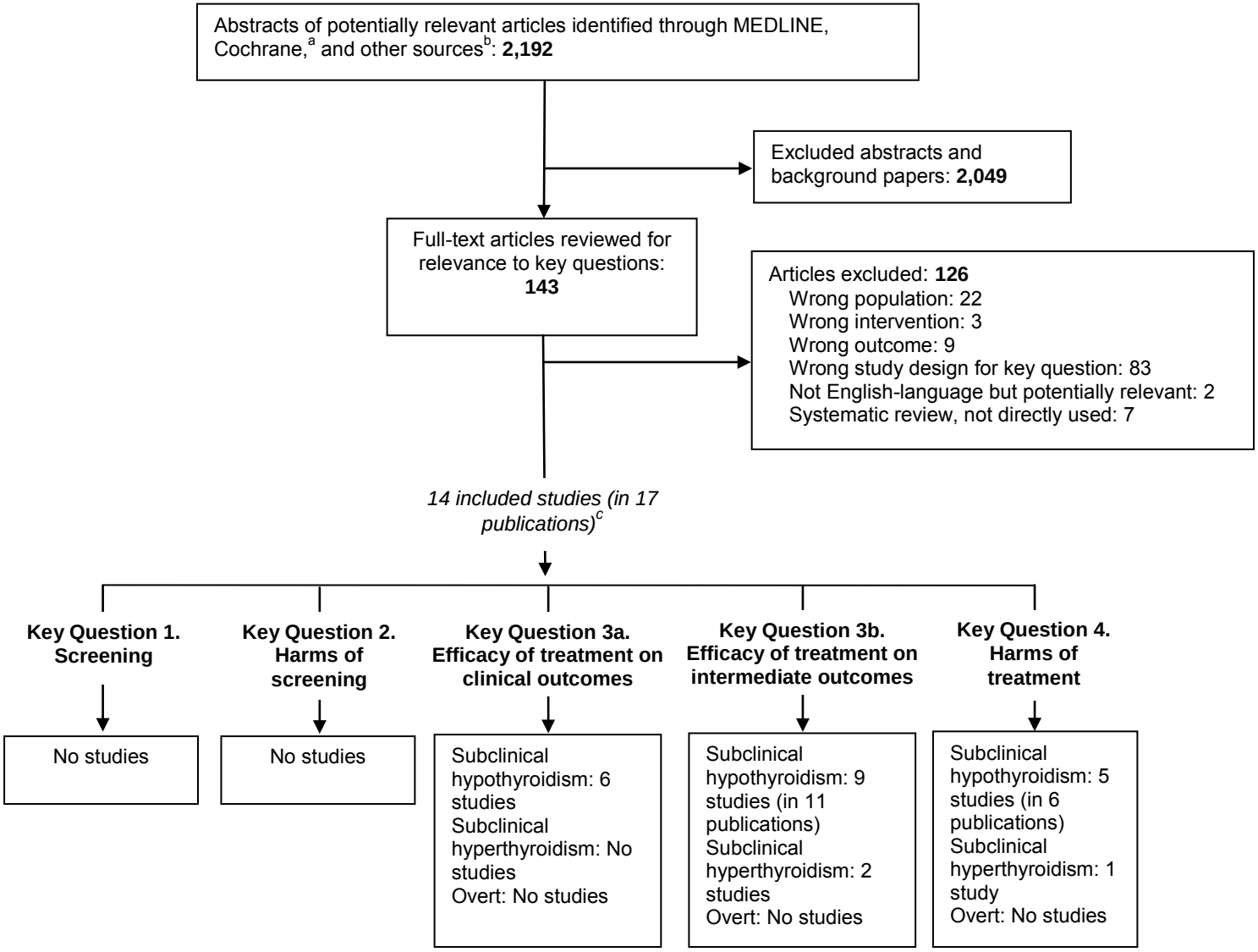
Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 (thyroid or hypothyroid$ or hyperthyroid$).ti.
2 pregnan$.ti.
3 1 not 2
4 limit 3 to full systematic reviews

**Appendix A2. Inclusion Criteria**

| PICOS | Include | Exclude |
|---|---|---|
| Populations | • Community-living, nonpregnant adults without a history of thyroid disease or clear symptoms of overt hypothyroidism or hyperthyroidism who were screened or treated for thyroid disease<br>• Patients with subclinical hypothyroidism in studies that do not clearly describe enrollment of symptomatic patients | • Patients with clinically obvious hypothyroidism or hyperthyroidism (e.g., Graves' disease)<br>• Hospitalized or recently hospitalized participants, as they may have elevated TSH levels |
| Interventions | **KQs 1, 2:** Screening<br><br>**KQs 3a, 3b, 4:** Treatment of overt thyroid disease, subclinical hypothyroidism, and subclinical hyperthyroidism, including hormone replacement therapy, antithyroid medications (i.e., methimazole), and ablation therapy (i.e., radioactive iodine, surgery) | |
| Comparators | **KQ 1:** No screening<br><br>**KQs 3a, 3b:** No treatment or observation | |
| Outcomes | **KQs 1, 3a:** Clinical outcomes, including cardiovascular outcomes (cardiovascular disease, coronary artery disease/congestive heart failure, atrial fibrillation), fractures, and measures of quality of life or cognitive function<br><br>**KQ 2:** Psychological effects, harms of workup<br><br>**KQ 3b:** Intermediate outcomes, including cholesterol/lipid levels, blood pressure, weight change, and bone density<br><br>**KQ 4:** Harms of treatment | |
| Settings | Representative of primary care | |
| Study designs | Randomized, controlled trials or controlled observational studies | |

**Abbreviations:** KQ=key question; PICOS=Populations, Interventions, Comparators, Outcomes, Settings; TSH=thyroid-stimulating hormone.

**Appendix A3. Literature Flow Diagram**




[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
[b] Other sources include prior reports, reference lists of relevant articles, and systematic reviews.
[c] Some studies are included for more than one key question.

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## Criteria for Assessing Internal Validity of Individual Studies

The USPSTF Methods Workgroup developed a set of criteria by which the internal validity of individual studies could be evaluated. The USPSTF accepted the criteria, and the associated definitions of quality categories, that relate to internal validity at its September 1999 meeting.

This appendix describes the criteria relating to internal validity and the procedures that topic teams follow for all updates and new assessments in making these judgments.

All topic teams use initial "filters" to select studies for review that deal most directly with the question at issue and that are applicable to the population at issue. Thus, studies of any design that use outdated technology or that use technology that is not feasible for primary care practice may be filtered out before the abstraction stage, depending on the topic and the decisions of the topic team. The teams justify such exclusion decisions if there could be reasonable disagreement about this step. The criteria below are meant for those studies that pass this initial filter.

Presented below are a set of minimal criteria for each study design and then a general definition of three categories: "good," "fair," and "poor," based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a good-quality study is one that meets all criteria well. A fair-quality study is one that does not meet (or it is not clear that it meets) at least one criterion, but has no known "fatal flaw." Poor-quality studies have at least one fatal flaw.

### Randomized, Controlled Trials and Cohort Studies

*Criteria:*

Initial assembly of comparable groups:

- For randomized, controlled trials (RCTs): adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
- For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.

Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination).

Important differential loss to followup or overall high loss to followup.

Measurements are equal, reliable, and valid (includes masking of outcome assessment).

Clear definition of interventions.

All important outcomes considered.

Analysis includes adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs.

*Definition of ratings based on above criteria:*

**Good:** Meets all criteria: comparable groups are assembled initially and maintained throughout the study (followup ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and there is appropriate attention to confounders in analysis. In addition, for RCTs, intention-to-treat analysis is used.

**Fair:** Any or all of the following problems occur, without the fatal flaws noted below: generally comparable groups are assembled initially, but some question remains whether some (although not major) differences occurred with followup; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention-to-treat analysis is done for RCTs.

**Poor:** Any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention-to-treat analysis is lacking.

### Case-Control Studies

*Criteria:*
Accurate ascertainment of cases.
Nonbiased selection of cases/controls with exclusion criteria applied equally to both.
Response rate provided.
Diagnostic testing procedures applied equally to each group.
Measurement of exposure accurate and applied equally to each group.
Appropriate attention to potential confounding variables.

*Definition of ratings based on criteria above:*
**Good:** Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements are accurate and applied equally to cases and controls; and there is appropriate attention to confounding variables.

**Fair:** Recent, relevant, without major apparent selection or diagnostic workup bias, but response rate is less than 80 percent or there is attention to some but not all important confounding variables.

**Poor:** Major selection or diagnostic workup biases, response rate less than 50 percent, or inattention to confounding variables.

### Systematic Reviews

*Criteria:*
Comprehensiveness of sources considered/search strategy used.
Standard appraisal of included studies.
Validity of conclusions.
Recency and relevance are especially important for systematic reviews.

*Definition of ratings from above criteria:*
**Good:** Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

**Fair:** Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

**Poor:** Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

**Appendix A6. Reviewers of the Draft Report**

Douglas Bauer, MD, Professor of Medicine and Epidemiology and Biostatistics, University of California, San Francisco

Joseph Chin, MD, MSc, Medical Officer, Centers for Medicare & Medicaid Services

Hossein Gharib, MD, MACP, MACE, Professor of Medicine, Mayo Clinic College of Medicine

Valerie J. King, MD, MPH, Associate Professor, Oregon Health and Science University

Linda Kinsinger, MD, MPH, Chief Consultant for Preventive Medicine, Office of Patient Care Services, Veterans Health Administration

Martin Surks, MD, MACP, Professor of Medicine and Pathology, Montefiore Medical Center and the Albert Einstein College of Medicine

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Study Design | Study Duration | How Patients in the Trial Were Identified | Eligibility Criteria | Mean Age, Intervention vs. Control | TSH Level at Baseline, Intervention vs. Control |
|---|---|---|---|---|---|---|
| ***Subclinical hypothyroidism*** | | | | | | |
| Abu-Helalah 2010[37]<br><br>United Kingdom | RCT crossover | 4 months (at 2 months) | Screening-based<br><br>Healthy adults attending a general health assessment at 5 centers where TSH is routinely measured in all women ages 50–79 years, women ages 35–49 years with a family history of thyroid disease, and all men ages 65–79 years | Ages 35–79 years<br><br>TSH >4.0 mIU/L<br><br>Excluded if did not live or work in or near study area; did not speak English; had known thyroid, pituitary, adrenal, or cardiovascular disease; or were taking drugs that affect thryoxine or serum concentrations of TSH or free T4 | 58 years overall (NR by group) | 4.1 vs. 9.0 mIU/L (mean NR) |
| Cabral 2011[38]<br><br>Brazil | RCT | 12 months | Women recruited from outpatient clinic with mild subclinical hypothyroidism | Female patients with subclinical hypothyroidism who attended outpatient clinic of university hospital and had TSH >4.0 to <12 mIU/L with normal free T4 (at least 2 measurements 6 weeks apart). Patients had no previous history of thyroid disease; were not taking any drug that could interfere with thyroid, lipoprotein, or endothelial function; and had no history of recent hospitalization<br><br>Excluded if had a history of alcohol use or current cardiovascular disease or nonthyroid illness (e.g., obesity, diabetes, hypertension) | 43 vs. 47 years | 6.79 vs. 6.77 mIU/L |
| Duman 2007[39]<br><br>Turkey | RCT | 8 months | Women newly diagnosed with subclinical hypothyroidism | Women with newly diagnosed subclinical hypothyroidism (TSH >4.2 mIU/L) who were premenopausal with regular menses, not pregnant, and not taking medication<br><br>Excluded if smoker, obese, or had diabetes mellitus, coronary artery disease, renal or hepatic failure, or familial hypercholesteremia | 36 vs. 35 years | 10.9 vs. 11.0 mIU/mL |

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Study Design | Study Duration | How Patients in the Trial Were Identified | Eligibility Criteria | Mean Age, Intervention vs. Control | TSH Level at Baseline, Intervention vs. Control |
|---|---|---|---|---|---|---|
| Iqbal 2006[40]<br><br>Tromsø Substudy<br><br>Norway | RCT | 12 months | All men and women age >29 years living in Tromsø were invited to complete a health questionnaire that included use of thyroxine, nonfasting blood samples were drawn and analyzed for serum TSH and persons with subclinical hypothyroidism were invited to participate | Patients ages 30–80 years with subclinical hypothyroidism identified from general health survey<br><br>TSH 3.5 to 10 mIU/L<br><br>Excluded if had a history of coronary infarction, angina pectoris, or stroke; using thyroid or lipid-lowering medication; or age >80 years | 63 vs. 61 years | 5.8 vs. 5.4 mIU/L |
| Jorde 2006[41]<br><br>Tromsø Substudy<br><br>Norway | RCT | 12 months | All men and women age >29 years living in Tromsø were invited to complete a health questionnaire that included use of thyroxine, nonfasting blood samples were drawn and analyzed for serum TSH and persons with subclinical hypothyroidism were invited to participate | Patients ages 30–80 years with subclinical hypothyroidism identified from general health survey<br><br>TSH 3.5 to 10 mIU/L<br><br>Excluded if had a history of coronary infarction, angina pectoris, or stroke; using thyroid or lipid-lowering medication; or age >80 years | 62 vs. 63 years | 5.8 vs. 5.3 mIU/L |
| Kong 2002[42]<br><br>United Kingdom | RCT | 6 months | Consecutive women who were referred for thyroid function tests by their general practitioner over a 12-month period based on self-reported symptoms (except for 2 women who were having issues with fertility) | Women age >18 years referred for thyroid function tests by their general practitioner to investigate subfertility or symptoms of thyroid disease and found to have subclinical hypothyroidism (TSH 5 to 10 mIU/L and T4 0.8 to 16 ng/dL)<br><br>Excluded if had history of previous thyroid disease, psychiatric disorder, or anticipated pregnancy | 53 vs. 45 years | 8.0 vs. 7.3 mIU/L |
| Mikhail 2008[43]<br><br>Kuwait | RCT | 12 months | Recruited patients from outpatient clinic | Mostly premenopausal women ages 15–60 years from endocrinology outpatient clinic<br><br>TSH 4 to 10 mIU/L<br><br>Excluded if had previously diagnosed thyroid disease; received radioiodine or any thyroid medication; had known dyslipidemia or used lipid-lowering agents in the year before enrollment; had coronary artery disease, diabetes, renal or hepatic failure, or other systemic diseases; or smoker | 32 vs. 32 years | 6.4 vs. 6.3 mIU/L |

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Study Design | Study Duration | How Patients in the Trial Were Identified | Eligibility Criteria | Mean Age, Intervention vs. Control | TSH Level at Baseline, Intervention vs. Control |
|---|---|---|---|---|---|---|
| Monzani 2004[44]<br><br>Also see Caraccio 2002[45]<br><br>Italy | RCT | Median, 10.5 months | Patients with subclinical hypothyroidism recruited from outpatient clinic | Patients age <55 years recruited from internal medicine outpatient clinic with TSH >3.6 mIU/L for at least 6 months prior to trial. Women were premenopausal, with regular menses, and not pregnant. No patients were on medication<br><br>Excluded if age >55 years, obese, smoker, or had hypertension, diabetes mellitus, renal or hepatic failure, or other systemic disease | 37 years (NR by group) | 6.03 vs. 5.68 mIU/L |
| Nagasaki 2009[46]<br><br>Japan | RCT | 5 months | Newly diagnosed with subclinical hypothyroidism | Newly diagnosed patients with subclinical hypothyroidism due to chronic thyroiditis with positive antibodies<br><br>TSH “above the normal upper limit”<br><br>Excluded if in recovery from a nonthyroid illness; had a major disease, such as hypertension, hyperlipidemia, or diabetes mellitus; receiving other hormone replacement therapy or taking any drugs that affect the lipid profile and atherosclerosis, such as antihypertension agents, lipid-lowering drugs, antiplatelet drugs, and bisphosphonates, including etidronate | 64 vs. 66 years | 7.3 vs 7.3 mIU/L |
| Parle 2010[47]<br><br>United Kingdom | RCT | 12 months | Patients with subclinical hypothyroidism recruited from a community-based cross-sectional study (Birmingham Elderly Thyroid Study), registered with 1 of 20 family practices; those identified as having subclinical hypothyroidism over the 2-year recruitment period were invited | Patients age ≥65 years in primary care setting (20 family practices)<br><br>TSH >5.5 mIU/L<br><br>Excluded if taking T4 therapy or antithyroid medications or had recent treatment for hyperthyroidism | 73.5 vs. 74.2 years | 6.6 vs. 6.6 mIU/L |

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Study Design | Study Duration | How Patients in the Trial Were Identified | Eligibility Criteria | Mean Age, Intervention vs. Control | TSH Level at Baseline, Intervention vs. Control |
|---|---|---|---|---|---|---|
| Razvi 2012[49]<br><br>United Kingdom | Retrospective cohort study (UK General Practice Research Database retrospective analysis) | Median of 7.6 years for age 40–70 subgroup<br><br>Median of 5.2 years for age >70 subgroup | Retrospectively identified patients with subclinical hypothyroidism from case records from large UK General Practice Research Database | Primary care patients age ≥40 years with subclinical hypothyroidism<br><br>TSH 5.01 to 10 mIU/L<br><br>Excluded if treated with thyroid hormones or antithyroid drugs, had history of ischemic heart or cerebrovascular disease, did not have at least 12 months of predefined data leading up to the index elevated thyrotropin level, had poor-quality records, treated at any time before the index elevated thyrotropin level with amiodarone hydrochloride or lithium carbonate, or treated in the previous year with an oral corticosteroid | Age 40–70 subgroup: 55.9 vs. 55.9 years<br><br>Age >70 subgroup: 79.4 vs. 79.9 years | Age 40–70 subgroup: 6.74 vs. 6.32 mIU/L; p<0.001<br><br>Age >70 subgroup: 6.77 vs. 6.32 mIU/L; p<0.001 |
| Razvi 2007[48]<br><br>United Kingdom | RCT crossover | 24 weeks (crossover at 12 weeks) | Patients from 27 general practices with subclinical hypothyroidism identified from a laboratory database | Patients ages 18–80 years from urban, general practice settings identified through laboratory database<br><br>TSH >4 mIU/L<br><br>Excluded if taking medications that could cause thyroid hormone dysfunction or had previous thyroid disease and treatment; or had diabetes mellitus, serum creatinine >1.36 mg/dL, vascular disease, psychiatric conditions and treatment, or current or previous pregnancy in the last 2 years | 53.5 vs. 54.2 years | 5.4 vs. 5.3 mIU/L |
| Teixeira 2008[50,51]<br><br>Brazil | RCT, stratified by TSH | 12 months | Recruited from 2 outpatient clinics | Patients from 2 outpatient clinics with TSH >4.0 mIU/L and free T4 0.9 to 1.8 ng/dL (at least 2 measurements 6 weeks apart)<br><br>Excluded if had disease or used medication that influences thyroid function or lipid profile; if patient developed subclinical hypothyroidism after treatment of hyperthyroidism, confirmation of biochemical euthyroidism for at least 1 year before the development of subclinical hypothyroidism was necessary | 48.9 vs. 47.5 years (in all randomized)<br><br>53.8 vs. 46.6 years (in those who completed trial) | 7.5 vs. 7.7 mIU/L (in all randomized)<br><br>8.0 vs. 8.4 mIU/L (in those who completed trial) |

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Study Design | Study Duration | How Patients in the Trial Were Identified | Eligibility Criteria | Mean Age, Intervention vs. Control | TSH Level at Baseline, Intervention vs. Control |
|---|---|---|---|---|---|---|
| ***Subclinical hyperthyroidism*** | | | | | | |
| Buscemi 2007[52]<br><br>Italy | RCT (patients given option of changing assigned group, although none did) | 12 months | Consecutively and newly diagnosed outpatients with subclinical hyperthyroidism | Newly diagnosed patients<br><br>TSH <0.4 mIU/L<br><br>Excluded if had Graves' disease and positive serum antithyroidperoxidase, antithyroglobulin, and anti-TSH–receptor antibodies; history of hepatic or renal disorders, alcoholism, or other major medical conditions; or taking any medications that might affect thyroid function or calcium metabolism | 59 vs. 57 years | 0.06 vs. 0.06 mIU/mL |
| Yonem 2002[53]<br><br>Turkey | RCT | 6 months | Not reported | Patients with subclinical hyperthyroidism for 6 to 60 months<br><br>TSH <0.4 mIU/L<br><br>Patients had normal liver and kidney function tests, and none had diabetes mellitus or pituitary, psychiatric, or other acute or chronic systemic disease. None used thyroxine or antithyroid drugs for hyperthyroidism treatment, beta-blocking agents, or drugs related to the etiology or treatment of osteoporosis | 38.7 vs. 33.5 years | 0.23 vs. 0.21 mIU/mL |

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Interventions and Duration, n (Began/Completed) | Between-Group Results (Intervention vs. Placebo) | Adverse Effects | Quality |
|---|---|---|---|---|
| ***Subclinical hypothyroidism*** | | | | |
| Abu-Helalah 2010[37]<br><br>United Kingdom | LT4 72 µg (mean) for 2 months: 33/30<br>Placebo: 31/26 | QOL: Odds of feeling better taking thyroxine than placebo<br>TSH >4.0 mIU/L: 21 vs. 16 patients; odds, 1.3<br>TSH >4.5 mIU/L: 17 vs. 7 patients; odds, 2.4<br>TSH >5.0 mIU/L: 12 vs. 5 patients; odds, 2.4<br>TSH >5.5 mIU/L: 11 vs. 4 patients; odds, 2.8<br>TSH >6.0 mIU/L: 8 vs. 2 patients; odds, 4.0 | "No indication of harms" | Poor |
| Cabral 2011[38]<br><br>Brazil | LT4 44.23 µg/d (median) for 12 months: 14/14<br>No treatment: 18/18<br><br>Patients were advised to reduce fat in their diet, increase fish consumption, and minimize intake of sugar and salt | TC: 208.4 ± 36.7 vs. 227.6 ± 36.9 mg/dL; p=NS<br>HDL: 54.36 ± 12.3 vs. 49.61 ± 9.74 mg/dL; p=NS<br>LDL: 132.8 ± 37.5 vs. 150.6 ± 34.74 mg/dL; p=NS<br>TG: 106.0 ± 36.7 vs. 137.0 ± 56.06 mg/dL; p=NS<br><br>Article states that no significant changes were observed in BMI at the end of the study (data not shown)<br><br>When patients were subdivided as low (TSH, 4 to <8 mIU/L) or high (TSH, 8 to <12 mIU/L), there were no differences in metabolic or vascular parameters (data not shown) | NR | Fair |
| Duman 2007[39]<br><br>Turkey | LT4 (all patients reached dose of 100 µg [mean NR] for 8 months): 22/20<br>No treatment: 19/19 | BMI: 24.8 ± 3.2 vs. 25.5 ± 3.8 kg/m$^2$; p=NS<br>TC: 202 ± 28 vs. 202 ± 28 mg/dL; p=NS<br>LDL: 130 ± 32 vs. 128 ± 25 mg/dL; p=NS<br>HDL: 53.0 ± 16 vs. 53.08 ± 8.6 mg/dL; p=NS<br>TG: 96 ± 37 vs. 128 ± 58 mg/dL; p=NS | NR for LT4 | Fair |
| Iqbal 2006[40]<br><br>Tromsø Substudy<br><br>Norway | LT4 96 to 97 µg (mean) for 12 months: 32/32<br>Placebo: 32/32 | BMI: 28.4 ± 5.8 vs. 27.0 ± 4.1 kg/m$^2$; p=NS<br>TC: 220.0 ± 42.5 vs. 224.3 ± 34.8 mg/dL; p=NS<br>TG: 132.9 ± 88.6 vs. 141.8 ± 62.0 mg/dL; p=NS<br>HDL: 58.0 ± 15.5 vs. 58.0 ± 19.3 mg/dL; p=NS<br>LDL: 139.2 ± 34.8 vs. 139.2 ± 38.7 mg/dL; p=NS | NR | Fair |
| Jorde 2006[41]<br><br>Tromsø Substudy<br><br>Norway | LT4 109.7 µg/d (mean) for 12 months: 36/36<br>Placebo: 33/32 | Composite cognitive function score: 1.5 ± 3.7 vs. −0.9 ± 4.8; p=NS<br>Trail Making A, psychomotor test of executive function: 39.0 ± 14.8 vs. 44.1 ± 17.7; p=NS<br>Trail Making B, psychomotor test of executive function: 94 ± 62 vs. 103 ± 49; p=NS<br>GHQ-30: 1.9 ± 3.3 vs. 1.2 ± 2.0; p=NS<br>BDI: 4.3 ± 3.6 vs. 3.3 ± 4.0; p=NS | NR | Fair |

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Interventions and Duration, n (Began/Completed) | Between-Group Results (Intervention vs. Placebo) | Adverse Effects | Quality |
|---|---|---|---|---|
| Kong 2002[42]<br><br>United Kingdom | LT4 (mean NR) for 6 months: 23/20 for QOL, 16 for metabolic outcomes<br>Placebo: 17/14 for QOL, 11 for metabolic outcomes | *Mean change in thyroxine group minus mean change in placebo group*<br>HADS–anxiety: 1 (95% CI, −1 to 3); p=NS<br>HADS–depression: −1 (95% CI, −3 to 1); p=NS<br>GHQ-30: 2 (95% CI, −5 to 7); p=NS<br>TC: −8 mg/dL (95% CI, −28 to 20); p=NS<br>TG: 9 mg/dL (95% CI, −26 to 44); p=NS<br>LDL: −4 mg/dL (95% CI, −23 to 15); p=NS<br>HDL: −1 mg/dL (95% CI, −8 to 4); p=NS<br>BMI: −0.3 (95% CI, −0.9 to 0.4) kg/m$^{2;}$, p=NS<br>% lean body weight: 0.1 (95% CI, −1.6 to 1.7); p=NS | NR | Good |
| Mikhail 2008[43]<br><br>Kuwait | LT4 72 µg/d (mean) for 12 months: 60/NR<br>Placebo: 60/NR | TC: 183.3 ± 33.6 vs. 194.9 ± 25.9 mg/dL; p<0.029<br>LDL: 111.8 ± 22.8 vs. 120.3 ± 29.8 mg/dL; p<0.001<br>HDL: 46.0 ± 12.4 vs. 42.5 ± 9.7 mg/dL; p=NS<br>TG: 84.1 ± 46.9 vs. 93.9 ± 52.3 mg/dL; p=NS | NR | Fair |
| Monzani 2004[44]<br><br>Also see Caraccio 2002[45]<br><br>Italy | LT4 70 µg (mean) for 6 months: 23/23<br>Placebo: 22/22 | BMI: 23.7 ± 3.5 vs. 24.9 ± 3.8 kg/m$^2$; p=NS<br>SBP: 112 ± 15 vs. 114 ± 13 mm Hg; p=NS<br>DBP: 69 ± 9 vs. 72 ± 8 mm Hg; p=NS<br>TC: 191.6 ± 32.5 vs. 219.6 ± 48.9 mg/dL; p=0.03<br>HDL: 54.7 ± 7.4 vs. 57.8 ± 11.6 mg/dL; p=NS<br>LDL: 119.2 ± 27.8 vs. 141.3 ± 38.6 mg/dL; p=0.03<br>TG: 88.1 ± 30.0 vs. 102.7 ± 53.1 mg/dL; p=NS | NR | Fair |
| Nagasaki 2009[46]<br><br>Japan | LT4 25.8 µg (average) for 5 months: 48/NR<br>Placebo: 47/NR | SBP: 128.8 ± 3.8 vs. 132.2 ± 3.5 mm Hg; p=NS<br>DBP: 72.7 ± 2.2 vs. 72.8 ± 2.0 mm Hg; p=NS<br>BMI: 21.8 ± 0.48 vs. 22.1 ± 0.50 kg/m$^{2;}$ p=NS<br>TC: 200.7 ± 6.2 vs. 206.1 ± 9.3 mg/dL; p=NS<br>LDL: 121.4 ± 11.2 vs. 129.9 ± 7.3 mg/dL; p=NS<br>HDL: 54.5 ± 3.1 vs. 53.8 ± 2.3 mg/dL; p=NS<br>TG: 132.9 ± 14.2 vs. 122.2 ± 12.4 mg/dL; p=NS | None of the patients required withdrawal of treatment because of side effects | Fair |
| Parle 2010[47]<br><br>United Kingdom | LT4 50 µg/d (median) for 12 months: 52/49<br>Placebo: 42/36 | HADS–depression: 3.55 (0.27) vs. 3.37 (0.31); p=0.82<br>MEAMS–cognitive skills and performance: 11.67 (0.09) vs. 11.60 (0.11); p=0.57<br>MMSE–cognitive status: 28.24 (0.38) vs. 28.22 (0.43); p=0.18<br>SCOLP–speed of cognitive processing and accounting: 1.29 (0.30) vs. 0.84 (0.35); p=0.59<br>Trail Making A, psychomotor test of executive function: 45.33 (2.63) vs. 46.78 (3.05); p=0.52<br>Trail Making B, psychomotor test of executive function: 100.65 (7.75) vs. 114.11 (9.07); p=0.95<br>Trail Making B-A, psychomotor test of executive function: 54.55 (6.80) vs. 67.27 (7.97); p=0.86 | Withdrawal due to side effects: 9.6% (5/52) intervention vs. 14.3% (6/42) placebo; p=0.49 | Good |

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Interventions and Duration, n (Began/Completed) | Between-Group Results (Intervention vs. Placebo) | Adverse Effects | Quality |
|---|---|---|---|---|
| Razvi 2012[49]<br><br>United Kingdom | *Age 40–70 subgroup*<br>LT4 75 µg/d (median): 1634<br>Not treated: 1459<br><br>*Age >70 subgroup*<br>LT4 75 µg/d (median): 819<br>Not treated: 823 | *HR (95% CI): Multivariate-adjusted results presented, followed by age- and sex-adjusted results*<br><br><u>Age 40–70 subgroup:</u><br>Fatal/nonfatal ischemic heart disease events: 4.2% vs. 6.6%; HR, 0.61 (0.39 to 0.95); HR, 0.64 (0.41 to 0.89)<br>All-cause mortality: 3.4% vs. 6.4%; HR, 0.36 (0.19 to 0.66); HR, 0.43 (0.30 to 0.78)<br>Death due to circulatory diseases: 1.4% vs. 2.4%; HR, 0.54 (0.37 to 0.92); HR, 0.61 (0.37 to 0.91)<br>Death due to ischemic heart disease events: 1.0% vs. 1.7%; HR, 0.43 (0.19 to 2.05); HR, 0.55 (0.38 to 1.19)<br>Death due to malignant neoplasms: 1.2% vs. 2.2%; HR, 0.59 (0.21 to 0.88); HR, 0.61 (0.36 to 0.95)<br>Fatal/nonfatal cerebrovascular accident: 3.4% vs. 3.0%; HR, 1.03 (0.51 to 2.13), HR, 1.09 (0.75 to 1.89)<br>Atrial fibrillation: 2.0% vs. 2.3%; HR, 0.76 (0.26 to 1.73); HR, 0.87 (0.59 to 1.44)<br><br><u>Age >70 subgroup:</u><br>Fatal/nonfatal ischemic heart disease events: 12.7% vs. 10.7%; HR, 0.99 (0.59 to 1.33); HR, 1.03 (0.98 to 1.83)<br>All-cause mortality: 35.2% vs. 40.5%; HR, 0.71 (0.56 to 1.08); HR, 0.91 (0.65 to 1.14)<br>Death due to circulatory diseases: 17.1% vs. 18.3%; HR, 0.91 (0.56 to 1.46); HR, 0.87 (0.43 to 1.37)<br>Death due to ischemic heart disease events: 5.5% vs. 6.3%; HR, 1.04 (0.56 to 1.93); HR, 1.12 (0.66 to 2.05)<br>Death due to malignant neoplasms: 4.6% vs. 6.5%; HR, 0.51 (0.24 to 1.09); HR, 0.73 (0.34 to 1.16)<br>Fatal/nonfatal cerebrovascular accident: 17.7% vs. 17.9%; HR, 0.81 (0.31 to 2.12); HR, 1.11 (0.45 to 2.01)<br>Atrial fibrillation: 8.1% vs. 7.7%; HR, 0.98 (0.54 to 7.76); HR, 1.23 (0.69 to 1.58) | NR | Fair |

**Appendix B1. Evidence Table of Studies of Subclinical Hypothyroidism and Hyperthyroidism**

| Study, Year Country | Interventions and Duration, n (Began/Completed) | Between-Group Results (Intervention vs. Placebo) | Adverse Effects | Quality |
|---|---|---|---|---|
| Razvi 2007[48]<br><br>United Kingdom | LT4 100 µg/d for 12 weeks: 50/50<br>Placebo: 50/49 | ThyDQoL: −1.1 ± 1 vs. −1.2 ± 0.9; p=0.24<br>SF-36 Sex: −2.3 ± 2.7 vs. −2.7 ± 2.8; p=0.18<br>SF-36 Motivation: −3.6 ± 2.7 vs. −3.7 ± 2.7; p=0.16<br>SF-36 Worries: −2.5 ± 3 vs. −2.8 ± 2.9;, p=0.23<br>Average weighted effect of all 18 QOL domains: −2.7 ± 2.4 vs. −2.8 ± 2.3; p=0.45<br>TC: 220.4 ± 38.7 vs. 232.0 ± 38.7 mg/dL; p<0.001<br>LDL: 131.2 ± 30.9 vs. 142.8 ± 34.7 mg/dL; p<0.001<br>HDL: 61.9 ± 19.3 vs. 65.7 ± 19.3 mg/dL; p=0.12<br>TG: 115.1 (44.3 to 363.2) vs. 115.1 (35.4 to 451.7) mg/dL; p=0.26<br>Weight: 75.8 ± 16.5 vs. 76.5 ± 16.7 kg; p=0.12<br>SBP: 132.8 ± 22.8 vs. 134.6 ± 22.9 mm Hg; p=0.21<br>DBP: 78.8 ± 10.3 vs. 79.9 ± 9.6 mm Hg; p=0.16 | 1 person in the placebo group discontinued because of "perceived side effects and personal problems" | Good |
| Teixeira 2008[50,51]<br><br>Brazil | LT4 (mean NR) for unreported duration (evaluated for 12 months post-euthyroid state): 35/11<br>Placebo: 25/15 | TC: 197.0 ± 28.7 vs. 202.7 ± 40.5 mg/dL; p=0.032<br>HDL: 54.8 ± 17.5 vs. 48.5 ± 9.9 mg/dL; p=0.180<br>LDL: 118.3 ± 24.2 vs. 129.7 ± 35.2 mg/dL; p=0.024<br>TG: 105.0 ± 58.7 vs. 122.7 ± 58.5 mg/dL; p=0.384 | LT4 group: 1 patient withdrew because of Hashitoxicosis, 1 withdrew because of symptomatic tachycardia | Poor |
| ***Subclinical hyperthyroidism*** | | | | |
| Buscemi 2007[52]<br><br>Italy | Methimazole 10 to 15 mg for 12 months: 7/7<br>No treatment: 7/7 | SBP: 136 ± 4 vs. 126 ± 11 mm Hg; p=NS<br>DBP: 78 ± 3 vs. 80 ± 3 mm Hg; p=NS<br>BMI: 27.8 ± 1.4 vs. 28.1 ± 1.0 kg/m$^2$; p=NS | "No adverse effect" was observed in the treatment group | Poor |
| Yonem 2002[53]<br><br>Turkey | Propylthiouracil 150 mg for 6 months: 9/NR<br>Radioactive iodine for 6 months: 1/NR<br>No treatment: 10/NR | BMD femur neck : 0.826 ± 0.042 vs. 0.868 ± 0.019 g/cm$^2$; p=NS<br>BMD lumbar vertebra: 0.998 ± 0.048 vs. 0.968 ± 0.030 g/cm$^2$; p=NS<br>TG: 39.9 ± 23.9 vs. 76.2 ± 14.2 mg/dL; p=NS<br>TC: 182.9 ± 8.9 vs. 157.4 ± 6.6 mg/dL; p=NS<br>LDL: 106.0 ± 6.6 vs. 91.3 ± 5.8 mg/dL; p=NS<br>HDL: 47.6 ± 3.9 vs. 48.3 ± 3.5 mg/dL; p=NS<br>SBP day: 112.42 ± 2.66 vs. 113.70 ± 2.62 mm Hg; p=NS<br>DBP day: 69.40 ± 1.78 vs. 72.10 ± 2.37 mm Hg; p=NS<br>SBP night: 100.10 ± 2.25 vs. 101.60 ± 1.96 mm Hg; p=NS<br>DBP night: 61.50 ± 1.40 vs. 61.80 ± 2.80 mm Hg; p=NS | NR | Poor |

**Abbreviations:** BDI=Beck Depression Inventory; BMD=bone mineral density; BMI=body mass index; CI=confidence interval; DBP=diastolic blood pressure; GHQ-30=General Health Questionnaire; HADS=Hospital Anxiety and Depression Score; HDL=high-density lipoprotein; HR=hazard ratio; LDL=low-density lipoprotein; LT4= levothyroxine; MEAMS=Middlesex Elderly Assessment of Mental State; MMSE=Mini-Mental State Examination; NR=not reported; NS=not significant; QOL=quality of life; RCT=randomized, controlled trial; SBP=systolic blood pressure; SCOLP=Speed and Capacity of Language Processing; SF-36=36-Item Short-Form Health Survey; TC=total cholesterol; TG= triglycerides; ThyDQoL=Underactive Thyroid-Dependent Quality of Life; TSH=thyroid-stimulating hormone.

**Appendix B2. Quality Assessment of Trials**

| Author, Year | Randomization Adequate? | Allocation Concealment Adequate? | Groups Similar at Baseline? | Eligibility Criteria Specified? | Outcome Assessors Masked? | Care Provider Masked? | Patient Masked? | Attrition and Withdrawals Reported? | Loss to Followup Differential/ High? | Analyzed Persons in the Groups in Which They Were Randomized? | Quality Rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Subclinical Hypothyroidism*** | | | | | | | | | | | |
| Abu-Helalah 2010[37] | Unclear | Unclear | Unclear | Yes | Yes | No | Yes | Yes | No/No | No | Poor |
| Cabral 2011[38] | Yes | Yes | Yes | Yes | No | No | No | Yes | No/No | Yes | Fair |
| Duman 2007[39] | Unclear | Unclear | Yes | Yes | No | No | No | Yes | No/No | Yes | Fair |
| Iqbal 2006[40] Tromsø Substudy | Unclear | Unclear | Yes | Yes | Unclear | Unclear | Yes | Yes | No/No | Yes | Fair |
| Jorde 2006[41] Tromsø Substudy | Unclear | Unclear | Yes | Yes | Unclear | Unclear | Yes | Yes | No/No | Yes | Fair |
| Kong 2002[42] | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No/no for overall completion and QOL outcome; Yes/no for metabolic outcomes | Yes | Good |
| Mikhail 2008[43] | Yes | Unclear | Yes | Yes | Unclear | Unclear | Unclear | Yes | No/No | Yes | Fair |
| Monzani 2004[44] | Unclear | Unclear | Yes | Yes | Unclear | No | Yes | Yes | No/No | Yes | Fair |
| Nagasaki 2009[46] | Unclear | Unclear | Yes | Yes | Unclear | Unclear | Yes | Yes | No/No | Yes | Fair |
| Parle 2010[47] | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | No/No | Yes | Good |
| Razvi 2007[48] | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | No/No | Yes | Good |
| Teixeira 2008[50,51] | Unclear | Unclear | No; BMI slightly higher in treatment group | Yes | Yes | No | Yes | Yes | Yes/Yes | Yes | Poor |
| ***Subclinical Hyperthyroidism*** | | | | | | | | | | | |
| Buscemi 2007[52] | Unclear | Unclear | Yes | Yes | Unclear | No | No | Yes | No/No | Yes | Poor |
| Yonem 2002[53] | Unclear | Unclear | Yes | Yes | Unclear | No | No | Unclear | Unclear | Unclear | Poor |

**Abbreviations:** BMI=body mass index; QOL=quality of life.

**Appendix B3. Quality Assessment of Cohort Study**

| Author, Year | Did the Study Attempt to Enroll All (or a Random Sample of) Patients Meeting Inclusion Criteria, or a Random Sample? | Were the Groups Comparable at Baseline on Key Prognostic Factors? | Did the Study Maintain Comparable Groups Through the Study Period? | Did the Study Use Accurate Methods for Ascertaining Exposures and Potential Confounders? | Were Outcome Assessors and/or Data Analysts Blinded to the Exposure Being Studied? | Did the Article Report Attrition? | Did the Study Perform Appropriate Statistical Analyses on Potential Confounders? | Is There Important Differential or Overall High Loss to Followup? | Were Outcomes Prespecified and Defined, and Ascertained Using Accurate Methods? | Quality Rating |
|---|---|---|---|---|---|---|---|---|---|---|
| Razvi 2012[49] | Yes | No; thyrotropin level was significantly different between treated and nontreated groups | Unclear | Did not adjust for use of aspirin, lipid-lowering therapy, or cardiovascular medications | Not applicable | Not applicable | Did not adjust for use of aspirin, lipid-lowering therapy, or cardiovascular medications | Not applicable | Yes | Fair |