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**Systematic Evidence Review**

Number 23

## Screening for Thyroid Disease

**Prepared for:**

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U.S. Department of Health and Human Services  
540 Gaither Road  
Rockville, MD 20850  
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**Prepared by:**

Oregon Health & Science University  
Evidence-based Practice Center  
Portland, OR 97239

Mark Helfand, MD, MPH

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## Preface

The Agency for Healthcare Research and Quality (AHRQ) sponsors the development of Systematic Evidence Reviews (SERs) through its Evidence-based Practice Program. With guidance from the U.S. Preventive Services Task Force\* (USPSTF) and input from Federal partners and primary care specialty societies, the Evidence-based Practice Center at the Oregon Health Sciences University systematically review the evidence of the effectiveness of a wide range of clinical preventive services, including screening, counseling, and chemoprevention, in the primary care setting. The SERs—comprehensive reviews of the scientific evidence on the effectiveness of particular clinical preventive services—serve as the foundation for the recommendations of the USPSTF, which provide age- and risk-factor-specific recommendations for the delivery of these services in the primary care setting. Details of the process of identifying and evaluating relevant scientific evidence are described in the “Methods” section of each SER.

The SERs document the evidence regarding the benefits, limitations, and cost-effectiveness of a broad range of clinical preventive services and will help further awareness, delivery, and coverage of preventive care as an integral part of quality primary health care.

AHRQ also disseminates the SERs on the AHRQ Web site (<http://www.ahrq.gov/clinic/uspstfix.htm>) and disseminates summaries of the evidence (summaries of the SERs) and recommendations of the USPSTF in print and on the Web. These are available through the AHRQ Web site and through the National Guideline Clearinghouse (<http://www.ngc.gov>).

We welcome written comments on this SER. Comments may be sent to: Director, Center for Practice and Technology Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Suite 3000, Rockville, MD 20850.

Carolyn Clancy, M.D.  
Director  
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.  
Acting Director, Center for Practice and  
Technology Assessment  
Agency for Healthcare Research and Quality

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\*The USPSTF is an independent panel of experts in primary care and prevention first convened by the U.S. Public Health Service in 1984. The USPSTF systematically reviews the evidence on the effectiveness of providing clinical preventive services--including screening, counseling, and chemoprevention--in the primary care setting. AHRQ convened the USPSTF in November 1998 to update existing Task Force recommendations and to address new topics.

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# Structured Abstract

## Purpose

This article focuses on whether it is useful to order a thyroid function test in patients who have no history of thyroid disease and have few or no signs or symptoms of thyroid dysfunction.

## Data Sources

A MEDLINE® search, supplemented by searches of EMBASE® and the Cochrane Library, reference lists, and a local database of thyroid-related articles.

## Study Selection

We selected controlled studies of treatment that used thyroid-stimulating hormone (TSH) levels as an inclusion criterion and reported quality of life, symptoms, or lipid level outcomes. We also reviewed observational studies of the prevalence, progression, and consequences of subclinical thyroid dysfunction.

## Data Extraction and Synthesis

Using preset criteria, we assessed the quality of each trial and abstracted information about its setting, patients, interventions, and outcomes.

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## Results

The prevalence of unsuspected thyroid disease is lowest in men and highest in older women. Evidence regarding the efficacy of treatment in patients found by screening to have subclinical thyroid dysfunction is inconclusive. Several small, randomized trials of treatment for subclinical hypothyroidism have been done, but the results are inconclusive except in patients who have a history of treatment for Graves' disease, a subgroup that is not a target of screening in the general population. No trials of treatment for subclinical hyperthyroidism have been done. Data on the adverse effects of broader use of levothyroxine is sparse.

## Conclusion

Large randomized trials of treatment are needed to determine the likelihood that treatment will improve quality of life in otherwise healthy patients who have abnormal TSH levels and normal thyroxine (T4) levels.



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# 1. Introduction

## Burden of Illness

Hyperthyroidism and hypothyroidism are common conditions that have lifelong effects on health. About 5% of U.S. adults report having thyroid disease or taking thyroid medication.<sup>1,2</sup> In a cross-sectional study of 2,799 well-functioning adults aged 70-79, 9.7% of black women, 6% of white women, 3.2% of black men, and 2.2% of white men reported a history of hyperthyroidism.<sup>3</sup> In the same study, 6.2% of black women, 16.5% of white women, 1.7% of black men, and 5.6% of white men reported a history of hypothyroidism.

Hyperthyroidism has several causes. Graves' disease, the most common intrinsic cause, is an autoimmune disorder associated with the development of long-acting thyroid stimulating antibodies (LATS). Single or multiple thyroid nodules that produce thyroid hormones can also cause hyperthyroidism. The use of excessive doses of the thyroid hormone supplement levothyroxine is also a common cause.

The most common cause of hypothyroidism is thyroiditis due to antithyroid antibodies, a condition called "Hashimoto's thyroiditis." Another common cause of hypothyroidism is prior treatment for Graves' disease with surgery or radioiodine.

Consequences of untreated hyperthyroidism include atrial fibrillation, congestive heart failure, osteoporosis, and neuropsychiatric disorders. Both hyperthyroidism and hypothyroidism cause symptoms that reduce functional status and quality of life.

Subclinical thyroid dysfunction, which can be diagnosed by thyroid function tests before symptoms and complications occur, is viewed as a risk factor for developing hyperthyroidism and hypothyroidism complications. The goal of screening is to identify and treat patients with subclinical thyroid dysfunction before they develop these complications.

This article focuses on whether it is useful to order a thyroid function test for patients who have no history of thyroid disease when they are seen by a primary care clinician for other reasons. The review was used by 2 expert panels: the U.S. Preventive Services Task Force (USPSTF), which will make recommendations regarding screening in the general adult population, and the Institute of Medicine, which will focus on the Medicare population.

### Definition of Screening and Case-finding

Screening can be defined as “the application of a test to detect a potential disease or condition in a person who has no known signs or symptoms of that condition at the time the test is done.”<sup>4</sup> By this definition, screening with thyroid function tests may identify asymptomatic individuals as well as patients who have mild, nonspecific symptoms such as cold intolerance or feeling “a little tired.”

The symptoms associated with thyroid dysfunction are shown in Table 1.<sup>5,6</sup> When many of these symptoms and signs occur together, the clinician may have strong suspicion that the patient has thyroid disease. However, patients who complain of 1 or 2 of the symptoms in Table 1 may be no more likely to have abnormal thyroid function test than those who have no symptoms. In older patients<sup>7</sup> and in pregnant women, such symptoms are so common that it becomes meaningless to try to distinguish between “asymptomatic” patients and those who have symptoms that may or may not be related to thyroid status.

Studies of screening can be classified according to the setting in which the decision to screen takes place. In case finding, testing for thyroid dysfunction is performed among patients who come to their physicians for unrelated reasons. When the screening test is abnormal, the patient is called back for a detailed thyroid-directed history. Studies of case-finding programs provide the most realistic estimates of the effects and costs of screening in clinic or office practice.

Population-based studies of screening use special methods to recruit, contact, and follow patients in the context of an epidemiologic research effort. Such studies show the extent of unsuspected thyroid disease in a population sample of a particular geographic area, but do not reflect the yield or costs of screening in office-based practice.

## Classification of Thyroid Dysfunction

Thyroid dysfunction is a graded phenomenon, and progresses from early to more advanced forms. As better biochemical tests have come into use, classification of the grades of thyroid dysfunction has changed dramatically. Historically, clinical, biochemical, and immunologic criteria have been used to classify patients with milder degrees of thyroid dysfunction.<sup>8,9</sup> Today, the most common approach is to classify patients according to the results of thyroid function tests (Table 2). In this classification, “overt hypothyroidism” refers to patients who have an elevated thyrotropin (TSH) and a low thyroxine (T4) level. “Overt hyperthyroidism” refers to patients who have a low TSH and an elevated T4 or triiodothyronine (T3).

The primary rationale for screening is to diagnose and treat subclinical thyroid dysfunction.<sup>10-12</sup> This rationale views subclinical thyroid dysfunction as a risk factor for the later

development of complications and as a condition that may have symptoms that respond to treatment. Controversy centers on whether early treatment or close follow-up is warranted in apparently healthy people in whom the only indication of a thyroid disorder is an abnormal TSH result.

The terms “subclinical hypothyroidism” and “mild thyroid failure” refer to patients who have an elevated TSH and a normal thyroxine level (Table 2).<sup>12</sup> In some classification schemes, patients who have an elevated TSH and a normal thyroxine level are subclassified according to the degree of TSH elevation and the presence of symptoms, signs, and antithyroid antibodies.<sup>13</sup>

In the literature, the term “subclinical hypothyroidism” has been used to describe several conditions:

1. Patients who have subclinical hypothyroidism as a result of surgery or radioiodine treatment for Graves’ disease.
2. Patients who take inadequate doses of levothyroxine therapy for known thyroid disease.
3. Patients who have mildly elevated TSH levels, normal T4 levels, and non-specific symptoms that could be due to hypothyroidism.
4. Asymptomatic patients who are found by screening to have an elevated TSH and normal T4.

In this report, we are primarily concerned with the last 2 groups: patients who have no known history of thyroid disease and have no, or few, signs or symptoms.

The term “subclinical hyperthyroidism” is used to describe conditions characterized by a low TSH and normal levels of circulating thyroid hormones (thyroxine and triiodothyronine). Subclinical hyperthyroidism has the same causes as overt hyperthyroidism. These include excessive doses of levothyroxine, Graves’ disease, multinodular goiter, and solitary thyroid nodule. Most studies of the course of subclinical hyperthyroidism concern patients whose

history, physical examination, ultrasound, or thyroid scan suggests one of these causes. There are relatively few studies of patients found by screening to have a low TSH, normal T4 and T3 levels, and a negative thyroid evaluation, the largest group identified in a screening program.

### Accuracy of Screening Tests

Screening for thyroid dysfunction can be done using a history and physical examination, antithyroid antibodies, or thyroid function tests, including various assays for TSH and T4.

Today, the TSH test is usually proposed as the initial test in screening because of its ability to detect abnormalities before serum thyroxine and triiodothyronine levels are abnormal. When used to confirm suspected thyroid disease in patients referred to an endocrine specialty clinic, the sensitive TSH has a sensitivity above 98% and a specificity greater than 92% for the clinical and functional diagnosis.<sup>14</sup>

The accuracy of a TSH when used to screen primary care patients has proved difficult to evaluate. The greatest difficulty is in classifying a patient who has an abnormal TSH, normal T4 and T3 levels, and no evidence supporting thyroid disease on physical examination. Those who consider the TSH to be the “gold standard” determination of disease would define such a patient as a “true positive.” Others argue that patients who have an abnormal TSH, but never develop complications and never progress, should be considered “false positives.” They argue that these patients happen to have TSH levels outside the 95% reference limits for the general population, but never truly had a thyroid disorder to begin with.<sup>13</sup>

In screening programs and in the primary care clinic, many patients found to have an abnormal TSH revert to normal over time. In one randomized trial, for example, mildly elevated TSH levels reverted to normal in 8 of 19 patients given placebo.<sup>15</sup> In older subjects, only 59%

(range, 14%-87%) of patients with an undetectable TSH on initial screening had an undetectable TSH level when the TSH was repeated.<sup>16,17</sup> In the Framingham cohort, screening identified 41 people with an undetectable serum TSH ( $\leq 0.1$  mU/L) and a normal serum T4 level ( $< 129$  nmol/L).<sup>18</sup> After 4 years of follow-up, when 33 of these people were retested, 29 had higher serum TSH levels ( $> 0.1$  mU/L).

Nonthyroidal illness is an important cause of false positive TSH test results. In a recent systematic review of screening patients admitted to acute care and geriatric hospitals, the positive predictive value of a low serum TSH ( $< 0.1$  mU/L) was 0.24, meaning that approximately 1 in 4 patients proved to have hyperthyroidism.<sup>19</sup> For hypothyroidism, the predictive value of a serum TSH between 6.7 and 20 mU/L was 0.06.

The predictive value of a low TSH may also be low in frail or very elderly subjects.<sup>20-22</sup> One retrospective study reviewed the course of 40 female nursing home residents who had a low TSH and initially normal T4.<sup>21</sup> In 10 subjects (3 with low T3 levels and 7 who died) nonthyroidal illnesses probably caused the low TSH. In 18 other women, the TSH subsequently normalized, but the reason for the initially low TSH was not apparent. Only 3 subjects were later diagnosed to have thyroid disease as the cause of the low TSH (positive predictive value 0.075).

## Prevalence

In a population that has not been screened previously, the prevalence of the disease, along with the sensitivity of the screening test and follow-up tests, determine the potential yield of screening. These factors, along with the proportion of subjects who have a screening test and comply with follow-up testing if indicated, determine the actual yield of a screening program.



Over 40 studies reported the prevalence of thyroid dysfunction in defined geographic areas, health systems, primary care clinics, and at health fairs.<sup>1, 2, 23-33</sup>

In cross-sectional, population-based studies, a serum TSH  $\geq 4$  mU/L in conjunction with a normal thyroxine level (subclinical hypothyroidism) is found in about 5% of women and in up to 3% of men. In an analysis of the third National Health and Nutrition Examination Survey (NHANES-III), a population-based survey of 17,353 people aged 12 and older representing the U.S. population, subclinical hypothyroidism was defined as a serum TSH level above 4.5 mU/L and a serum T4  $\geq 57.9$  nmol/L.<sup>1</sup> Among those who did not have a history of thyroid disease, the prevalence of subclinical hypothyroidism was 5.8% among white, non-Hispanic females, 1.2% among black, non-Hispanic females, and 5.3% among Mexican Americans. For men, the prevalence was 3.4% among whites, 1.8% among blacks, and 2.4% among Mexican Americans. Older age and female sex are well-documented risk factors for subclinical hypothyroidism. In the NHANES-III survey, the overall prevalence of a serum TSH  $\geq 4.5$  mU/L was about 2% at ages 30-29, 6% at ages 50-59, 8% at ages 60-69, and 12% at ages 70-79. In a population-based study in Whickham, England, the prevalence (serum TSH  $\geq 6$  mU/L and normal T4) was 4% to 5% in women age 18 to 44, 8% to 10% in women age 45 to 74, and 17.4% in women over the age of 75.<sup>34</sup> The prevalence was 1% to 3% in men age 18 to 65 and 6.2% in men over the age of 65.

Population factors, such as iodine intake and ethnicity, affect the prevalence of subclinical hypothyroidism, but differences among studies are also due to differences in the definition of an abnormal TSH level and ascertainment of a history of thyroid disease or levothyroxine use.

The prevalence of subclinical hyperthyroidism (a low TSH in conjunction with normal T4 and T3 levels) depends on how a low TSH is defined. A meta-analysis found that, when defined as an undetectable TSH level in a person with a normal free thyroxine level, the prevalence of subclinical hyperthyroidism was about 1% (confidence interval [CI], 0.4% -1.7%) in men older than 60 and 1.5% (CI, 0.8%-2.5%) in women older than 60.<sup>25</sup> Other studies defined subclinical hyperthyroidism as a TSH below the lower limit of the normal range (about 0.4 mU/L) in a person with a normal T4 level. When defined in this way, the prevalence of subclinical hyperthyroidism in men and women aged 60 and older is as high as 12%.<sup>35</sup>

## Incidence

In a population that has been screened previously, the incidence of new cases of thyroid dysfunction is the most important factor in determining the yield of a second round of screening. In a 20-year follow-up of the Wickham population, the annual incidence of overt thyroid dysfunction was 4.9 per 1,000 in women (4.1 hypothyroid and 0.8 hyperthyroid) and 0.6 per 1,000 in men (all hypothyroid).<sup>36</sup> In most other studies, the incidence of hyperthyroidism is 0.3 to 0.4 per 1,000 in women and 0.01 to 0.1 per 1,000 in men.<sup>23</sup>

Within a given geographic region, older age, an elevated TSH level, antithyroid antibodies, and female sex are the strongest risk factors for developing overt hypothyroidism. In the Wickham survey, for a 50-year-old woman who has a serum TSH level of 6 mU/L and positive antithyroid antibodies, the risk for developing overt hypothyroidism over 20 years is 57%; for a serum TSH of 9 mU/L, the risk is 71%.<sup>36</sup> A 50-year-old woman who had a normal TSH and negative antibody test had a risk for only 4% over 20 years. The risk for progression

was not evenly distributed throughout the follow-up period. Nearly all women who developed hypothyroidism within 5 years had an initial serum TSH greater than 10 mU/L.

Exposure to ionizing radiation has also received attention as a potential risk factor for thyroid dysfunction. In general, studies of populations exposed to radioactive fallout have focused primarily on screening for thyroid cancer. A large cohort study of populations exposed to radiation from the Hanford nuclear facility provides the best-quality evidence about the risk for thyroid dysfunction. The study proved definitively that exposure to radioactive fallout from Hanford conferred no additional risk for hyperthyroidism or hypothyroidism compared to unexposed populations.<sup>37</sup> Specifically, the study found that there was no dose-response relationship between exposure to radioactive fallout and the incidence of thyroid disease. It also found that the rate of thyroid dysfunction in the Hanford region was no higher than that reported in areas which had not been exposed.

### **Evidence Regarding the Complications of Subclinical Hyperthyroidism**

Advocates of screening for subclinical hyperthyroidism argue that early treatment might prevent the later development of atrial fibrillation, osteoporotic fractures, and complicated overt hyperthyroidism. Other potential benefits of screening are earlier treatment of neuropsychiatric symptoms and prevention of the long-term consequences of exposure of the heart muscle to excessive stimulation from thyroid hormones.

*Atrial fibrillation.* A good-quality cohort study in the Framingham population found that, in subjects older than 60 who did not take levothyroxine and had a low TSH, the risk for atrial fibrillation was 32% (CI, 14%-71%) over 10 years.<sup>35</sup> The risk for subjects who had a normal

TSH level was 8%. Patients with low serum TSH values were stratified into 2 groups, those with serum TSH values  $\leq 0.1$  mU/L and those with values of  $> 0.1$  to  $0.4$  mU/L; only in the former group was the risk for atrial fibrillation increased. A more recent cross-sectional study of atrial fibrillation in overt and subclinical hyperthyroidism had serious flaws and was rated poor-quality.<sup>38</sup>

The clinical consequences of atrial fibrillation in patients who have a low TSH have not been studied. In general, chronic atrial fibrillation is associated with stroke, a higher risk for death, and other complications.<sup>39</sup>

*Mortality.* A population-based, 10-year cohort study of 1,191 people aged 60 and older found a higher mortality rate among patients who had a low TSH initially.<sup>40</sup> The excess mortality was due primarily to higher mortality from cardiovascular diseases. In this study, the recruitment strategy and the statistical adjustment for potential confounders were inadequate; patients who had a low TSH may have had a higher prevalence of other illnesses, but adjustment was done only for age and sex, and not for comorbidity. Such adjustment would be critical because acutely and chronically ill elderly patients have more false low TSH than relatively healthy patients, presumably as a result of their illness.<sup>19</sup> Thus, while it is possible that patients who had a low initial TSH had higher mortality because of their thyroid disease, it is also possible that patients who were ill to begin with had a low TSH as a result of their illness.

*Osteoporosis and fracture.* A good-quality study from the Study of Osteoporotic Fractures (SOF) cohort found similar bone loss among women with undetectable, low, and normal TSH levels.<sup>41</sup> Two meta-analyses of older studies<sup>42, 43</sup> suggest that women who have a low TSH because they take thyroid hormones are at a higher risk for developing osteoporosis. Other studies of the risk for osteoporosis concern small numbers of subjects with nodular thyroid

disease or Graves' disease<sup>44-47</sup> rather than patients who have no obvious clinical signs of thyroid disease.

Among women in the SOF population, a history of treated hyperthyroidism is associated with an increased risk for having a hip fracture later in life.<sup>48</sup> A more recent nested sample of cases and controls from SOF examined the relationship between fractures and a low TSH in a broader group of women who had been followed for 6 years.<sup>49</sup> The sample consisted of 148 women with hip fractures, 149 with vertebral fractures, and 304 women without fracture who were selected as controls. The subjects were classified according to their initial TSH level. Among the 148 women with hip fractures, 22 had an undetectable serum TSH (<0.1 mU/L). At baseline, the cases were significantly older, weighed less, and were less likely to be healthy by self-report than controls. They were also twice as likely to have a history of hyperthyroidism and had lower bone density at baseline. After adjustment for all of these confounding factors, the risk for hip fracture among women who had an undetectable TSH was elevated, but the value was of borderline statistical significance (adjusted relative hazard ratio 3.6; CI, 1.0-12.9). Similarly, after adjustment for confounders the risk for vertebral fracture among women who had an undetectable TSH was significantly elevated when compared with 235 controls (odds ratio [OR], 4.5; CI, 1.3-15.6). Among women who had a borderline low serum TSH (0.1-0.5 mU/L), the risk for vertebral fracture (OR, 2.8; CI, 1.0-8.5), but not hip fracture, was elevated.

This analysis has limited relevance to screening because the investigators were not able to obtain serum FT4 or FT3 tests, which could have distinguished between overt and subclinical hyperthyroidism. Also, among the 148 women with hip fractures, 22 had an undetectable serum TSH (< 0.1 mU/L); approximately 19 of these (86%) took thyroid hormones when their initial TSH measurement was made. Bauer and colleagues stated that "thyroid hormone use was not

associated with increased risk for...fracture,” but there were not enough women with undetectable TSH levels not taking thyroid hormones to make a valid comparison.<sup>49</sup> The analysis could not exclude the possibility that some of the women with low TSH levels had multiple, interacting risk factors and that other factors concomitant with age or socioeconomic status could have been confounders.

*Complicated thyrotoxicosis and progression to overt hyperthyroidism.* Thyrotoxicosis can be complicated by severe cardiovascular or neuropsychiatric manifestations requiring hospitalization and urgent treatment. There are no data linking subclinical hyperthyroidism to the later development of complicated thyrotoxicosis. Such a link is unlikely to be made because 1) complicated thyrotoxicosis is rare, 2) one-half of cases occur in patients with known hyperthyroidism, and 3) complications are associated with social factors, including insurance status, that may also affect access to screening and follow-up services.<sup>50</sup>

Progression from subclinical hyperthyroidism is well-documented in patients with known thyroid disease (goiter or nodule), but not in patients found by screening to have a low TSH and no thyroid signs. Based on the sparse data from screening studies, each year 1.5% of women and 0% of men who have a low TSH and normal T4 and T3 levels develop an elevated T4 or T3.<sup>16, 25,</sup>  
<sup>51</sup> In one population-based study (n = 2,575), 33 of 41 patients who had an initially low TSH had a serum TSH higher than 0.1 mU/L on repeat testing 4 years later.<sup>18</sup> Two patients developed overt hyperthyroidism during the follow-up period. In another population-based study, screening in 886 85-year-olds found 6 women and 2 men who had an undetectable TSH and were not already taking levothyroxine.<sup>51</sup> After 3 years of follow-up, 2 women were diagnosed to have hyperthyroidism: one was apparently healthy initially, while the other had atrial fibrillation on the initial examination.

*Dementia.* In the Rotterdam study, a population-based, longitudinal study with 2-year follow-up (discussed in detail below), people with reduced TSH levels at baseline had a more than threefold increased incidence of dementia (RR = 3.5; 95% CI, 1.2-10.0) and of Alzheimer's disease (RR = 3.5; 95% CI, 1.1-11.5), after adjustment for age and sex.<sup>52</sup> With respect to this result, Kalmijn et al stated that the results were similar “when controlling for the effects of atrial fibrillation or excluding subjects taking beta-blockers.” These results are not reported, however, and it is unclear whether they were statistically significant. Later, after presenting several other results, they stated that “adjustments for education, symptoms of depression, cigarette smoking, or apolipoprotein ε4 did not alter any of these findings,”<sup>52</sup> but it is not clear whether this statement pertains to the main result.

*Symptoms and cardiac effects.* Untreated or inadequately treated hyperthyroid patients who have neuropsychiatric symptoms or congestive heart failure may respond to treatment. In the setting of nodular thyroid disease, Graves' disease, or the long-term use of suppressive doses of levothyroxine, subclinical hyperthyroidism has also been associated with cognitive abnormalities, abnormalities in cardiac contractility, and exercise intolerance.<sup>53-58</sup> However, the frequency of symptoms or myocardial contractility abnormalities in patients who have subclinical hyperthyroidism found by screening is not well-studied, and no study has linked abnormalities in cardiac contractility or output to the development of clinically important heart failure.

## Evidence Regarding the Complications of Subclinical Hypothyroidism

The best-studied potential complications of hypothyroidism are hyperlipidemia, atherosclerosis, symptoms, and (for subclinical disease) progression to overt hypothyroidism. In pregnancy, subclinical hypothyroidism confers additional risks to both mother and infant.

*Hyperlipidemia.* Overt hypothyroidism has long been known to be associated with elevated levels of cholesterol;<sup>59</sup> however, patients in the earliest studies had very severe hypothyroidism. In more recent studies, there is a clinically important increase in total cholesterol and low-density lipoprotein (LDL) cholesterol among men<sup>60</sup> and women<sup>61, 62</sup> with overt hypothyroidism, who usually have serum TSH levels higher than 20 mU/L.

In women with milder forms of hypothyroidism, the relation between TSH and total cholesterol or LDL cholesterol is inconsistent. About 1 in 4 patients with subclinical hypothyroidism has a total cholesterol concentration higher than 6.2 mmol/L. The Whickham survey found no relationship between subclinical hypothyroidism and hyperlipidemia.<sup>34</sup> Recent, cross-sectional, population-based studies of the relation between TSH and lipid levels in women have had mixed results. In the Rotterdam study<sup>33</sup> (discussed in detail below), lipid levels were significantly lower among women with subclinical hypothyroidism than among euthyroid women. A fair-quality study of randomly selected Medicare recipients found no differences in total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, or triglycerides between subjects who had a serum TSH < 4.6 (n = 684) and those who had a serum TSH between 4.7 and 10 (n = 105). There were non-significant increases in LDL cholesterol and HDL cholesterol among women who had a serum TSH >10 (LDL cholesterol 143 vs 128 in euthyroid women,  $P = 0.08$ ; HDL cholesterol 41.6 vs 47.5,  $P = 0.053$ ).<sup>31</sup>



Conversely, a cross-sectional, population-based study from the Netherlands found that the prevalence of subclinical hypothyroidism was correlated with lipid levels; the prevalence was 4% among women with a total cholesterol level < 5 mmol/l; 8.5% when total cholesterol was 5 to 8 mmol/l; and 10.3% when total cholesterol was > 8 mmol/l.<sup>63</sup> Another recent cross-sectional study of 279 women over the age of 65 found a strong relationship between hyperlipidemia and serum TSH levels.<sup>64</sup> Of the 279 women, 19 (6.8%) had a serum TSH > 5.5 mU/L. After adjustment for age, weight, and estrogen use, women who had a serum TSH > 5.5 mU/L had 13% higher LDL cholesterol (95% CI, 1%-25%) and 13% lower HDL cholesterol (CI, -25%-0%) than women with a normal serum TSH (0.1-5.5 mU/L). However, 2 of the 19 women who had an elevated TSH used thyroxine, suggesting that they had inadequately treated overt hypothyroidism. Because T4 and T3 levels were not measured, it is possible that others in this group had overt hypothyroidism as well. Moreover, only 1 of the 19 women (6%) took estrogen replacement therapy, whereas 32 of 250 women in the euthyroid group used estrogen. The analysis was adjusted for estrogen use, but not for other factors, such as socioeconomic status, that is associated with lipid levels and is also known to be associated with estrogen use.

Men with a mildly elevated TSH generally do not have an increased risk for hyperlipidemia, but data on men are sparse. Hypercholesterolemic men do not have a higher prevalence of subclinical hypothyroidism than men with low lipid levels.<sup>63</sup>

Another cross-sectional study of 2,799 adults age 70-79 illustrates some of the difficulties in determining whether subclinical hypothyroidism is associated with hypercholesterolemia, especially in men.<sup>3</sup> For the entire group, a serum TSH > 5.5 mU/L was associated with a 9 mg/dL (0.23 mmol/L) higher total cholesterol after adjustment for age, sex, race, body mass index, tobacco, alcohol, and estrogen use, and diabetes. Among men, the association was

statistically significant for a cutoff serum TSH  $\geq 7.0$  mU/L, but not for a serum TSH  $\geq 5.5$  mU/L. About 23% of white subjects and 14% of black subjects took lipid-lowering medication and a substantial proportion took thyroid hormones (eg, 18% of white women, 6.1% of white men). Among subjects taking thyroid hormones but not lipid-lowering medication, a serum TSH  $\geq 5.5$  mU/L was associated with 15 mg/dL higher total cholesterol. However, the results for subjects not taking either medication were not reported.

*Atherosclerosis.* The relationship of subclinical hypothyroidism to the later development of atherosclerosis is unclear.<sup>31, 33, 65</sup> The Wickham survey found no relationship between initial TSH levels and the subsequent development of ischemic heart disease over 20 years of follow-up.<sup>65</sup>

A widely publicized population-based study of 1,149 women age 55 or older, from Rotterdam, came to a different conclusion.<sup>33</sup> The main analysis in the paper was cross-sectional. In that analysis, after adjustment for age, body mass index, cholesterol level, blood pressure, and tobacco use, a serum TSH  $>4.0$  mU/L was associated with a history of myocardial infarction (OR, 2.3; CI, 1.3-4.2) and with atherosclerosis of the abdominal aorta, diagnosed by blinded review of a lateral radiograph of the lumbar spine (OR, 1.9; CI, 1.2-3.1). An analysis of incident myocardial infarction over 3 to 6 years of follow-up found a statistically non-significant increased risk in women with a serum TSH  $> 4.0$  mU/L (adjusted relative risk 2.5; CI, 0.7-9.1).

The strengths of the Rotterdam study are the relatively large sample size, adjustment for some potential confounders, and validated, blinded assessment of outcomes. Because the study was primarily cross-sectional, the findings do not prove that an elevated TSH precedes the development of atherosclerosis. The prospective part of the study adds little because, at baseline, women who had an elevated TSH had a higher prevalence of atherosclerotic disease; they would

be expected to have a higher incidence of myocardial infarction over 3 to 6 years, in any case. The prospective analysis would have been more consequential if subjects who had atherosclerosis at baseline were excluded. In contrast, the long follow-up period in the Whickham study reduces the chance that baseline differences in the prevalence of coronary disease affected the results.<sup>65</sup> None of the cross-sectional studies adequately adjusted for several factors that may influence rates of cardiovascular disease, such as socioeconomic status, diet, diabetes, estrogen use, and other health practices. The relation of these factors to the development of subclinical hypothyroidism has not been well studied, so it is possible that 1 or more of them are confounders.

In the Rotterdam study,<sup>33</sup> women with subclinical hypothyroidism had lower lipid levels than euthyroid women; this might be a result of higher use of diet or other lipid-lowering therapy in women with known cardiovascular risk factors, but it also might suggest that the women developed atherosclerosis by another mechanism. One hypothesis is that elevations in both homocysteine and cholesterol may contribute to the elevated risk for atherosclerosis in overt hypothyroidism. In cross-sectional studies, including an analysis of the second National Health and Nutrition Examination Survey (NHANES-II) sample, patients who had overt hypothyroidism had higher homocysteine levels than euthyroid subjects.<sup>66,67</sup> Although no single study has adjusted statistically for all potential confounders, the association of elevated homocysteine and hypothyroidism appears to persist after controlling for serum folate levels, which are decreased in hypothyroidism.<sup>66-70</sup> In overtly hypothyroid patients, homocysteine levels decreased after treatment with levothyroxine in small, observational studies.<sup>69-73</sup> The association of homocysteine levels with subclinical hypothyroidism has not yet been established.

*Symptoms, mood, and quality of life.* In its 1998 review and guideline, the American College of Physicians concluded that, in the general population, it was not clear if the prevalence and severity of symptoms and quality of life differs for individuals who have mildly elevated TSH levels.<sup>7, 74</sup> Since then, 2 cross-sectional studies in volunteers have addressed this question, with mixed results. A cross-sectional interview survey of 825 Medicare enrollees in New Mexico found no differences in the age-adjusted frequency of self-reported symptoms between participants with serum TSH elevations from 4.7 to 10 mU/L and those with normal TSH concentrations.<sup>31</sup> A larger survey from Colorado (n = 25,862) is less pertinent because it included subjects who took levothyroxine in the analysis of symptoms. It also found no difference between euthyroid subjects and those with subclinical hypothyroidism in current symptoms, but found a higher percentage of “changed symptoms” in the subclinical hypothyroid group (13.4% vs 15.4%).<sup>2</sup>

Patients who have subclinical hypothyroidism and a history of antithyroid treatment for Graves’ disease or nodular thyroid disease have a higher prevalence of symptoms than healthy controls.<sup>75, 76</sup> It is likely that this observation is valid, but an important limitation of the evidence should be noted: the appropriate comparison group is not healthy volunteers, but patients who have a normal TSH and a history of antithyroid treatment. The reason is that euthyroid patients who have a history of treatment for hyperthyroidism also have a higher prevalence of anxiety, depression, and psychosocial dysfunction than healthy controls.<sup>77</sup>

*Pregnancy complications.* Three recent reports from a cohort study of pregnant women have linked TSH levels in pregnancy to poor obstetric outcomes and to poor cognitive development in children. In the first report, among 9,403 women with singleton pregnancies, serum TSH measurements were 6 mU/l or greater in 209 women (2.2%).<sup>78</sup> The rate of fetal

death was significantly higher in those pregnancies (3.8%) than in the women with serum TSH less than 6 mU/l (0.9%, OR, 4.4; 95% CI, 1.9-9.5). In the second report, the children of women who had a high serum TSH (mean  $13.2 \pm 0.3$  mU/L) in the first trimester of pregnancy had lower IQ scores than matched controls (mean serum TSH  $1.4 \pm 0.2$  mU/L) when they were 7 to 9 years of age.<sup>79</sup> The average difference in IQ was 7 points; 19% of the children of hypothyroid mothers had IQ scores of 85 or less. Although no statistical adjustment for baseline differences was done, at baseline, age, socioeconomic status, and other risk factors for low IQ were similar in the 2 groups. Results for the subgroup who had subclinical hypothyroidism were not broken out, but most of the women fell into this category (that is, they had normal T4 levels).

The third report from these authors analyzed TSH levels by outcomes. Fifty percent of the children of 20 mothers who had a TSH equal to or higher than the 99.85 percentile had IQ scores greater than 1 standard deviation (SD) below the control mean. Fifteen percent of the children of controls, and 21 percent of the children of women who had a TSH between the 98 and 99.85 percentile, had IQ scores this low.<sup>80</sup>

## Prior Recommendations

In 1996, the USPSTF recommended against routine screening for thyroid disease in asymptomatic adults (D recommendation).<sup>81</sup> They found insufficient evidence to recommend for or against routine screening with thyroid function tests in the elderly, but recommended screening based on the higher prevalence of disease and the increased likelihood that symptoms of thyroid disease will be overlooked (C recommendation). At that time, 2 randomized trials of treatment for subclinical hypothyroidism had been done. The Task Force found that one of them<sup>75</sup> was not relevant to screening, because the subjects had a known history of thyroid

disease. They found the other trial to be methodologically flawed.<sup>74</sup> There were no trials of treatment for subclinical hyperthyroidism.

## Analytic Framework and Key Questions

In this paper we address whether the primary care physician should screen for thyroid function in patients seen in general medical practice who have no specific indication for thyroid testing and who come to the physician for other reasons. We focus on whether screening should be aimed at detection of subclinical thyroid dysfunction and whether individuals who have mildly abnormal TSH values can benefit.

We used the analytic framework in Figure 1 to guide the literature review. The population of interest was adults who are seeing a primary care clinician, have no history of thyroid disease, and have no or few signs or symptoms of thyroid dysfunction.

Arrow 1 represents direct evidence of health benefits from controlled studies of screening; no such studies have been done. Arrows 2 and 3 represent the ability of screening to detect unsuspected thyroid dysfunction, the false positive rate of the screening tests, and the symptom status of the patients diagnosed by screening. These issues, summarized above, were reviewed in detail elsewhere.<sup>14,25</sup> In this article, we address key questions related to Arrows 4 and 5, focusing primarily on evidence about the benefits and harms of treating early thyroid dysfunction. Specifically, we addressed:

1. What are the benefits of earlier treatment of a) subclinical hyperthyroidism and b) hypothyroidism?
2. What are the adverse effects of treatment?

A thorough review of the adverse effects of antithyroid drugs, radioiodine therapy, thyroid surgery, and thyroid replacement therapy was beyond the scope of this review. Instead, we emphasize the frequency of adverse effects in trials of levothyroxine therapy for subclinical hypothyroidism and the potential adverse effects of long-term treatment with levothyroxine.





## 2. Methods

### Search Strategy

We identified articles published before 1998 from the reference lists of previous reviews<sup>9, 12, 13, 23, 24, 76, 82-87</sup> and by searching our own files of over 1,600 full-text articles from the period 1910 to 1998. We then searched MEDLINE® and EMBASE® from 1996 to February 2002, PREMEDLINE March 2002, and the Cochrane Library (2002, Issue 2) to identify additional articles. In a MEDLINE® search, the medical subject headings (MeSH) *thyroid function tests* and *thyroid diseases* were combined with the term *mass screening*, and the text words *screening* or *case-finding*. We conducted a separate search for controlled studies of the effect of thyroid-directed treatments on potential complications of subclinical thyroid disease, using the word *levothyroxine* in title, abstract, or keywords combined with terms for clinical trials. We also searched MEDLINE® from 1966-May 2002 for articles about the adverse effects of thyroid hormone replacement. Periodic hand searching of endocrinologic and major medical journals, review of the reference lists of retrieved articles, and suggestions from peer reviewers of earlier versions of this article supplemented the electronic searches.

### Inclusion Criteria

We selected controlled trials of treatment of thyroid dysfunction that reported at least one health outcome (symptoms, cognitive function, or quality of life) or lipid levels. Broad inclusion criteria were used to get a picture of the benefits and adverse effects of treatment on

patients with different degrees of thyroid dysfunction. Specifically, we included any trial that used TSH levels as a criterion for entry, in any population, including patients with known thyroid disease. We also identified observational studies of treatment for subclinical thyroid dysfunction; we included recent studies that had not been included in previous meta-analyses.<sup>13, 24, 25, 88</sup>

To assess the prevalence of thyroid disease and the causal relationships between thyroid dysfunction and potential complications, we used the following sources:

- Previous meta-analyses and systematic reviews.
- More recent cross-sectional, cohort, and case-control studies of the prevalence of overt or subclinical thyroid dysfunction.
- Cross-sectional and longitudinal studies of the relationship between an elevated or low TSH to potential complications of subclinical hypothyroidism or subclinical hyperthyroidism.

For these categories of studies, we included studies in the general adult population, a demographic segment of the adult population, or among patients seen in the general clinic setting. We excluded studies of screening for congenital or familial thyroid disorders and studies of screening in inpatients, institutionalized patients, and series of patients seen in specialized referral clinics for depression or obesity.

Finally, we identified observational studies of the long-term adverse effects of levothyroxine therapy. We excluded studies of suppressive doses of thyroxine; to be included, the study had to include at least some patients that were taking replacement doses of thyroxine.

### Data Extraction

We used predefined criteria from the USPSTF to assess the internal validity of trials, which we rated as “good,” “fair,” or “poor.” We also rated the applicability of each study to screening. The rating system is described in detail elsewhere.<sup>89</sup> (The criteria are listed as column headings in Table 3.) We also abstracted information about its setting, patients, interventions, and outcomes. When possible, we recorded the difference between the probability of a response in the treatment and control groups for each complication studied.



## 3. Results

### Efficacy of Treatment for Subclinical Hyperthyroidism

No controlled trials of treatment for subclinical hyperthyroidism have been done. Small observational studies of patients with nodular thyroid disease not detected by screening have shown improvements in bone metabolism and hemodynamic measures after treatment.<sup>53, 90-92</sup>

### Efficacy of Treatment for Subclinical Hypothyroidism

We identified 14 randomized trials of levothyroxine therapy. We excluded 2 trials that compared levothyroxine to levothyroxine plus triiodothyronine in patients with overt hypothyroidism,<sup>93, 94</sup> 1 trial of different levothyroxine preparations,<sup>95</sup> and 1 of levothyroxine suppressive therapy for solitary nodules.<sup>96</sup> Two trials of levothyroxine treatment in patients with subclinical hypothyroidism reported no clinical outcomes or lipid results; one of these concerned bone density<sup>97</sup> and the other, cardiac function parameters from Doppler echocardiography and videodensitometric analysis.<sup>98</sup> These trials are not included in evidence tables but are discussed briefly.

Of the 8 included trials,<sup>15, 74, 75, 99-103</sup> 6 concerned patients with elevated TSH levels. One concerned hyperlipidemic patients with high-normal TSH levels,<sup>99</sup> and the last trial concerned patients with a normal TSH who had symptoms of hypothyroidism.<sup>101</sup>

Randomized trials of levothyroxine treatment in subclinical hypothyroidism and in symptomatic patients who have a normal TSH are described in Table 3 (quality ratings) and in

Table 4 (description and results). The first 2 trials in Table 4 concerned patients followed in thyroid specialty clinics. In both trials, subjects had a mean serum TSH above 10 mU/L. The first trial (Cooper et al) concerned patients who had been treated for Graves' disease in whom TSH was rising relatively quickly.<sup>75</sup> Symptoms were rated on the "Cooper Questionnaire," a 24-point scale that records how 6 symptoms of hypothyroidism change over time. After 1 year, patients taking levothyroxine improved by 2.1 points, while patients taking placebo deteriorated by 1.2 points ( $P=0.037$ ). The difference (3.3 points) is roughly equivalent to complete relief of one symptom and partial relief of a second symptom per patient. Eight (47%) of 17 treated patients reported reduced or milder symptoms; 4 felt worse; and 5 reported no change in symptoms. In the placebo group, 3 (19%) of 16 patients felt better, 6 felt worse, and 7 reported no change. The difference between the proportion of patients who felt better in each group was 0.28 (CI, -0.09-0.65), indicating that 1 patient improved for every 3.5 patients treated with levothyroxine.<sup>75</sup> Treatment had no effect on lipid levels. The internal validity of this trial was rated "good-quality;" it was the highest-quality trial of the group.

The second trial (Meier et al) concerned patients with thyroiditis or a history of Graves' disease.<sup>100</sup> In this trial, treatment with levothyroxine had no effect on symptoms. In reporting results, the authors emphasized that there was a significant reduction in LDL cholesterol in the levothyroxine-treated group from 4.0 to 3.7 mmol/L ( $P=0.004$ ) and no significant reduction in the placebo group. The difference appears to be related to an imbalance in the groups at baseline: pre-treatment LDL cholesterol was 4.0 mmol/L in the treatment group versus 3.7 mmol/L in the placebo group. In fact, post-treatment LDL cholesterol was the same in both groups ( $3.7 \pm 0.2$ ,  $P=0.11$ ). When analyzed as a randomized trial, the difference between the

treatment and control groups in lipid levels was not significant. The discrepancy suggests that randomization may have been flawed.

We rated the relevance of these 2 studies to screening and found it to be “low.” The Cooper study supports treatment in patients with a history of treated Graves’ disease, especially if the serum TSH is above 10 mU/L, but it has little relevance to screening because the natural history of treated Graves’ disease differs from the natural history of spontaneous hypothyroidism in the general population.

The third trial, in patients known to have Hashimoto’s thyroiditis and positive antithyroid antibodies who had mildly elevated TSH levels, had a similar flaw.<sup>102</sup> When analyzed as a randomized trial, there were no significant differences between levothyroxine-treated and placebo groups in any lipid parameter. When analyzed as a pre-/post-treatment study, there was a statistically significant reduction in LDL cholesterol levels (3.6-3.1 mmol/L) in the levothyroxine-treated group, but not in the control group. The study appeared to be unblinded; this could be a major flaw, since differential attention to lipid levels in the treatment and control groups could lead to different behavioral approaches to reducing lipid levels. If the results are valid, they would be fairly relevant to screening; the mean TSH was only slightly elevated, and patients who have antithyroid antibodies and a modestly elevated TSH are found commonly in screening programs.

The next 3 studies may have had more relevance to screening or primary care: they generally concerned patients, mostly women, with subclinical hypothyroidism who were not previously treated for Graves’ disease or nodular thyroid disease. However, 2 of the 3 studies had poor internal validity. In the fair-quality trial by Jaeschke and colleagues, 37 patients with subclinical hypothyroidism were recruited from the outpatient clinics of a community hospital

and randomized to levothyroxine treatment or placebo.<sup>15</sup> Patients given placebo did as well or better than those given levothyroxine. After 6 months, in the levothyroxine group, 8 patients improved, 3 were worse, and 5 were the same according to the “Cooper Questionnaire.” In the placebo group, 11 patients improved, 1 was worse, and 4 were the same. After 11 months, patients treated with levothyroxine had a small but statistically significant improvement in short-term memory, but treatment did not improve general health status as measured by a standardized questionnaire, the Sickness Impact Profile (SIP). In that study, the mean SIP score in patients with subclinical hypothyroidism recruited from a general medical clinic was initially 3.1 out of 10. On this scale, a score of 3.0 is usually interpreted as the border between no disability and mild disability. A random sample of healthy older adults had a similar mean SIP of 3.4.

The other negative trial was too small to achieve balance in the compared groups and had high loss to follow-up.<sup>103</sup>

A small crossover trial<sup>74</sup> concerned women identified by screening in the general population. The 20 subjects were women aged 50 and older who had an initial serum TSH between 4 and 15 mU/L. After 6 months of treatment, the mean symptom score improved by 1.81 units, equivalent to complete relief of one symptom per patient. As judged by subjective improvement and cognitive measures, 4 (24%) of the 19 patients who received levothyroxine improved, while 2 (12%) felt worse with treatment.

The last 2 studies listed in Table 4 concern patients who have TSH levels in the normal range. In 1 of these, 50 micrograms of levothyroxine therapy reduced LDL cholesterol levels from 6.8 to 5.9 mmol/L in patients with elevated total cholesterol levels (>7/5 mmol/L) and normal TSH levels.<sup>99</sup> In the other study, levothyroxine was ineffective in patients who had symptoms of hypothyroidism but normal TSH and T4 levels.<sup>101</sup> The latter study, designed as a



crossover study, found that levothyroxine significantly reduced SF-36 vitality score in healthy subjects and also documented a clinically important and statistically significant effect of placebo.

Many observational studies have examined the effects of treatment in patients with subclinical hypothyroidism. One meta-analysis of these observational studies found that treatment reduced LDL cholesterol levels by 0.4 mmol/L, and a more recent meta-analysis of both observational and randomized studies found that, in previously untreated patients, total cholesterol was reduced by 0.14 mmol/L (-5.6 mg/dL).<sup>104</sup> Another review concluded that levothyroxine treatment might reduce serum cholesterol by 8% in selected patients who have both a serum TSH  $\geq 10$  mU/L and an elevated total cholesterol ( $\geq 6.2$  mmol/L).<sup>25</sup> About 7% of individuals with subclinical hypothyroidism meet these criteria.

Most of the studies on which these analyses are based have important limitations.<sup>13, 25, 104</sup> Many of these studies were before/after studies in which reductions in serum lipids could have been due to regression toward the mean. In most, samples were small, selection of patients was poorly described, clinicians and patients were aware of the treatment and of the need to lower lipid levels, and outcome assessment may have been biased. That is, the problem is not that these studies are observational, but that many of them are poor-quality observational studies.

The hazards of relying on observational studies of the effect of drug therapy is illustrated by a large (n = 139) open study of levothyroxine to treat symptoms of hypothyroidism in patients who had normal thyroid function tests. This study found that the mean number of signs and symptoms of hypothyroidism decreased from 13 to 3 following 6 months or more of treatment; 76% of patients had improvement or disappearance of over 12 findings.<sup>105</sup> Whether or not these effects are real, they illustrate that only well-controlled trials can determine the effects of thyroxine therapy in patients with subclinical hypothyroidism.

In summary, treatment of subclinical hypothyroidism appears to reduce symptoms in the subset of patients who have a history of Graves' disease and a serum TSH > 10 mU/L. In other subgroups of patients with subclinical hypothyroidism, there is insufficient evidence to determine whether or not treatment is effective in reducing symptoms. Most trials found there was no effect on lipid levels, but because of the number of subjects and the limited quality of the trials, the evidence from randomized trials is insufficient to determine whether treatment has a clinically important effect. No trials of treatment for subclinical hypothyroidism in pregnant patients were identified.

### Other Benefits

One randomized trial of levothyroxine versus placebo used Doppler echocardiography and videodensitometric analysis to assess myocardial structure and parameters of myocardial contractility in 20 patients followed for 1 year.<sup>98</sup> We excluded this trial because it did not report any clinical outcome measures.

Another benefit of treating subclinical hypothyroidism is to prevent the spontaneous development of overt hypothyroidism, diagnosed when a patient with subclinical hypothyroidism develops a low FT4 level (see Table 2). This potential benefit has not been studied in randomized trials, so it is necessary to estimate it based on data from observational studies. Based on data from the Wickham study, a previous analysis estimated that, if 1,000 women age 35 and over are screened, 80 will be diagnosed to have subclinical hypothyroidism, and 43 will have a mildly elevated TSH and positive antithyroid antibodies. If these 43 individuals are treated with levothyroxine, by 5 years overt hypothyroidism would be prevented in 3 women ([number needed to treat] NNT = 14.3), while 40 will have taken medication for 5 years without

a clear benefit. By 20 years, overt hypothyroidism would be prevented in 29 (67%) of the 43 women, but 14 otherwise healthy women will have taken medication for 20 years.

In assessing the balance of benefits and harms, the key uncertainties are:

1) Without screening or prophylaxis, how long would overt hypothyroidism be undetected?

2) How much morbidity would undiagnosed overt hypothyroidism cause while undetected?

3) What are the harms of treatment in those who do not progress?

No studies have measured the severity of symptoms or degree of disability in newly diagnosed hypothyroid patients or the length of time spent in that state. There are no published data on the effect of careful follow-up on health outcomes in patients with subclinical hypothyroidism. The case for treatment to prevent progression of subclinical hypothyroidism would be greatly strengthened by data showing that this progression is associated with significant burden of illness that could be prevented by earlier treatment.

## Adverse Effects of Levothyroxine

Adverse effects of replacement doses of levothyroxine include nervousness, palpitations, atrial fibrillation, and exacerbation of angina pectoris. Adverse effects were not assessed carefully in the randomized trials listed in Table 4, although some reported them incidentally. In 1 of the trials, 2 of 20 (10%) patients taking levothyroxine quit the protocol because of nervousness and a sense of palpitations.<sup>74</sup> In another, 2 of the 18 (11%) patients assigned to levothyroxine withdrew because of complications: 1 because of an increase in angina, and 1

because of new onset atrial fibrillation.<sup>15</sup> In a third, anxiety scores were higher in the levothyroxine group.<sup>103</sup>

A systematic review of observational studies published from 1966 to 1997 found that replacement doses of levothyroxine have not been associated with osteoporosis or with any other serious long-term adverse effects.<sup>106</sup> A short-term randomized trial of levothyroxine for subclinical hypothyroidism confirms this view.<sup>97</sup> By contrast, thyroid hormone to suppress TSH because of thyroid cancer, goiters, or nodules contributed to osteoporosis in postmenopausal women.<sup>106</sup>

Overtreatment with levothyroxine, indicated by an undetectable TSH, is another potential risk. About one-fourth of patients receiving levothyroxine for primary hypothyroidism are maintained unintentionally on doses sufficient to cause the TSH to be undetectable.<sup>2,35</sup> Data from the Framingham cohort suggest that 1 excess case of atrial fibrillation might occur for every 114 patients treated with doses of levothyroxine sufficient to suppress the TSH.<sup>35</sup> As mentioned above, 2 meta-analyses of older studies and a recent nested case-control study from SOF suggest that, in patients taking levothyroxine, a low TSH is associated with an increased risk for osteoporosis<sup>42, 43</sup> and of osteoporotic fractures.<sup>49</sup> Another potential risk for overtreatment with levothyroxine is left ventricular hypertrophy and abnormalities of cardiac output,<sup>54, 58</sup> but there is insufficient evidence for these effects in patients inadvertently overtreated for hypothyroidism.

## 4. Summary

The results of this review are summarized in Table 5. The ability of screening programs to detect subclinical thyroid dysfunction has been demonstrated in good-quality cohort studies, and some of the complications of subclinical thyroid dysfunction are well-documented. The main gap in the evidence is the lack of convincing data from controlled trials that early treatment improves outcomes for patients with subclinical hypothyroidism and subclinical hyperthyroidism detected by screening.



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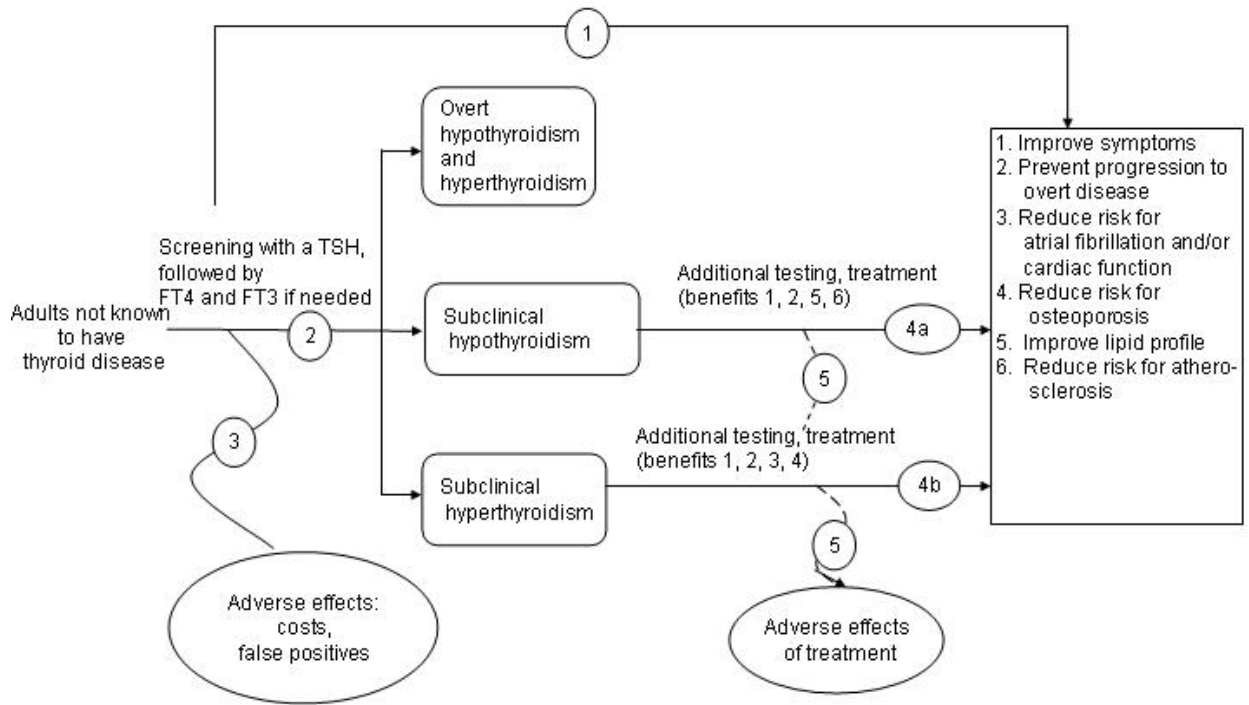
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Figure 1. Screening with Thyroid Function Tests Analytic Framework



\*FT4, free thyroxine; FT3, free triiodothyronine.

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**Table 1. Symptoms and Signs of Thyroid Dysfunction**

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

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**Table 2. Classification of Thyroid Dysfunction**

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	<b>Biochemical Criteria</b>	
	<b><u>TSH</u></b>	<b><u>Thyroid Hormones</u></b>
<b>Overt hyperthyroidism</b>	Low or undetectable	Elevated T4 or T3
<b>Subclinical hyperthyroidism</b>	Low or undetectable	Normal T4 and T3
<b>Overt hypothyroidism</b>	> 5 mU/L	Low T4
<b>*Subclinical hypothyroidism</b>	> 5 mU/L	Normal T4

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\*Some use lower or higher cutoffs for TSH.

T3, triiodothyronine; T4, normal thyroxine; TSH, thyroid-stimulating hormone.

**Table 3. Quality of Randomized Trials of Thyroxine Replacement Therapy**

Study, Year	Random Assignment?	Allocation concealed?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Blinded?	Care Provider Blinded?
Cooper et al, 1984(75)	Yes, by individual	Not stated	LT4 subjects were older (58.2 vs 50.2) and had fewer symptoms (2.1 vs 2.4) but otherwise similar	Yes	Yes	Probably (1 of 2 investigators is said to be blinded)
Meier et al, 2001(100)	Sequential assignment using a predefined list; randomized by matched pairs	No	LT4 subjects had higher TSH (14.4±1.7 vs 11.3±1.0) and LDLc (4.1 vs 3.7) but groups were otherwise similar for the whole groups (n = 66); comparisons were not presented for the analyzed group (n = 63)	Yes	Not stated	Yes
Meier et al, 2001(100)	Yes, by individual	Not stated	Generally yes, but mean TSH (6 vs 4.9) and LDLc (3.6 vs 3.3) were higher in LT4 group	Yes	No	No
Jaeschke et al, 1996(15)	Yes, by individual	Not stated	LT4 subjects had higher TSH (12.1 vs 9.4) and slightly more symptoms (14 vs 13) but similar in age	Yes	Yes	1 investigator was not blinded but was not involved in assessment or care
Kong et al, 2002(103)	Yes, in blocks of 6	Yes	LT4 subjects were older (53 vs 45 years), had lower FT4 (.9 vs 1), and higher TSH (8 vs 7.3)	Yes	Yes	1 investigator was not blinded but was not involved in care
Nystrom et al, 1988(74)	Not stated	Not stated	No baseline data were given for the groups initially assigned LT4 and placebo	Yes	Yes	Yes
Michalopoulou et al, 1998(99)	Yes, method not stated	Not stated	Inadequately described. LDL was higher in 50 mg group (6.8 vs 6.2)	Yes	Not stated	Not stated
Pollock et al, 2001(101)	Yes, by coin toss in blocks of 4	No	No baseline data were given for the groups initially assigned LT4 and placebo	Yes	Not stated	Yes

\*Analysis based on assignment to treatment groups AND includes all randomized subjects.

FT4, free thyroxine; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; LT4, levothyroxine; RCT, randomized controlled trial; TSH, thyroid-stimulating hormone.

**Table 3. Quality of Randomized Trials of Thyroxine Replacement Therapy (continued)**

Study, Year	Patient Unaware of Treatment?	Intention-to-Treat Analysis?*	Maintenance of Comparable Groups?	Reporting of Attrition, Crossovers, Adherence, and Contamination?	Differential Loss to Follow-up or Overall High Loss to Follow-up?	Statistical Analysis Appropriate?	Score (Good/Fair/Poor)
Cooper et al, 1984(75)	Yes, not verified	No	The number of patients randomized appears to be 41; 33 patients were analyzed. It is not clear which group the other 8 belonged to	Partially	Unclear, probably not	Yes, except it did not address dropouts	Good
Meier et al, 2001(100)	Yes, not verified	No	Yes	No	No	No, analyzed as RCT, but reported primarily as a before/after study	Poor
Meier et al, 2001(100)	Probably were aware, since dosing and length of follow-up differed. It is not clear whether patients were informed of their lipid levels.	Yes, assuming that completion of study was not a criterion for inclusion	Probably	No	No	Yes, when analyzed as an RCT	Poor
Jaeschke et al, 1996(15)	Yes, not verified	No	Probably, 3 dropouts in each group	Partially	Overall 6 out of 40 dropped out	Yes, except it did not address dropouts	Fair
Kong et al, 2002(103)	Yes, not verified	No	Unknown	Yes	Yes, especially for lipid comparison	Yes, except it did not address dropouts	Poor
Nystrom et al, 1988(74)	Probably aware, verified	No	Yes	No	No	No, no baseline comparisons or results provided about the first assignment	Poor
Michalopoulou et al, 1998(99)	Not stated	Probably yes	Yes	No	No	No, analyzed as before/after	Poor
Pollock et al, 2001(101)	Yes, verified	No	Probably, but all 3 dropouts were from the LT4 group	No	No	Yes	Fair

\*Analysis based on assignment to treatment groups AND includes all randomized subjects.

FT4, free thyroxine; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; LT4, levothyroxine; RCT, randomized controlled trial; TSH, thyroid-stimulating hormone.

**Table 4. Description and Results of Randomized Trials of Thyroxine Replacement Therapy**

<b>Study, Year</b>	<b>Patients</b>	<b>Setting</b>	<b>Age, Gender</b>	<b>Eligibility Criteria</b>	<b>Other Population Characteristics</b>
<b>Known history of thyroid disease</b>					
Cooper et al, 1984(75)	Previously treated Graves' disease, stage c subclinical hypothyroidism	Thyroid specialty clinic, Boston	32 women and 1 man, mean age 55 yrs	TSH > 3.5 mU/L on 2 occasions	History of Graves' disease
Meier et al, 2001(100)	Autoimmune thyroiditis (n = 33), previously treated Graves' disease (n = 22), previously treated goiter (7)	Thyroid specialty clinic, Switzerland	63 women, mean age 58.5 ± 1.3 yrs	Women 18-75 yrs; TSH > 6.0 mU/L on 2 occasions; exaggerated TSH response to TRH; good general health	History of autoimmune thyroiditis (n = 33), Graves' disease (n = 22), goiter (n = 7), only 4 had idiopathic subclinical hypothyroidism
Caraccio et al, 2002(102)	Hashimoto's thyroiditis (48) or Graves' disease (1)	Medical school internal medicine clinic, Italy	42 premenopausal women, 7 men	TSH > 3.6 mU/L for > 6 mos, + atP and anti-Tg, good general health	Subclinical hypothyroid patients had higher TC, LDL, and ApoB levels than healthy controls
<b>No known history or not stated</b>					
Jaeschke et al, 1996(15)	Diagnosis of subclinical hypothyroidism	Unclear setting, Ontario	28 women and 9 men over age 55, mean age 68 yrs	TSH > 6 mU/L on 2 occasions	None stated
Kong et al, 2002(103)	Women with a diagnosis of subclinical hypothyroidism	Referrals from GPs for thyroid function tests, London	45 women, mean age ~49 yrs	Women over 18 years; 5 < TSH < 10 mU/L	Most patients were referred because of symptoms
Nystrom et al, 1988(74)	Women identified by screening	Population-based screening study, Gothenburg	20 women, aged 51-73	Women over 18 years; 4 < TSH < 15 mU/L, exaggerated TSH response to TRH	Symptoms did not differ between subjects and healthy controls
<b>Biochemically euthyroid patients</b>					
Michalopoulou et al, 1998(99)	Patients referred for lipid assessment	Preventive Medicine (Lipid) hospital-based clinic, Greece	Not stated	TC > 7.5 mmol/L and TSH 0.4-4.0 mU/L	
Pollock et al, 2001(101)	Symptomatic patients with normal TSH and FT4	Referrals from GPs, hospital clinic, and response to newspaper ad, Glasgow	25 symptomatic and 19 asymptomatic subjects, sex and age not given	"Recent thyroid function tests within the reference range" plus (a) at least 3 symptoms of hypothyroidism (tiredness, lethargy, weight gain, or 3 others) or (b) no symptoms	Symptomatic subjects weighed more and had worse memory and psychological function than healthy controls

\* Symptomatic group only.

anti-TG, anti-thyroglobulin; ApoB, Apolipoprotein B; atP, antithyroid-peroxidase; ECG, electrocardiogram; GHQ, General Health Questionnaire; GP, general practitioner; HADS, Hospital Anxiety and Depression Questionnaire; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; LT4, levothyroxine; SF=36, Medical Outcomes Study short form; SIP, Sickness Impact Profile; TC, total cholesterol; FT4, free thyroxine; TFT, thyroid function test; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

**Table 4. Description and Results of Randomized Trials of Thyroxine Replacement Therapy (continued)**

Study, Year	Exclusion Criteria	Funding Sources and Role of Funder	Interventions (Dose, Duration)	Control	Baseline TSH	Screened/Eligible/Enrolled	Number Withdrawn/Analyzed
<b>Known history of thyroid disease</b>							
Cooper et al, 1984(75)	None stated	U.S. Public Health Service (Armour supplied LT4)	LT4 50 micrograms then titrated up	Placebo	11 (mean) 3.6-55.3 (range) mean TSH in control group increased to ~15 by the end of the study	656/91/41	8/33
Meier et al, 2001(100)	Coronary heart disease, lipid-lowering drugs, history of poor compliance. (Estrogen therapy allowed.)	Swiss Research Foundation, Henning Berlin, Sandoz, Roche	LT4 titrated over 6 mos (mean final dose 85.5 ± 4.3), with similar visits and changes in control group, total follow-up 50 wks	Placebo	12.8 (mean) 5-50 (range)	NR/NR/66	3/63
Caraccio et al, 2002(102)	Diabetes, renal or liver disease, TC > 7.8 mmol/L	Grant from University	LT4 25 then titrated up	Placebo	5.43 (mean) 3.65-15 (range)	NR/NR/49	0/49
<b>No known history or not stated</b>							
Jaeschke et al, 1996(15)	Medications that interfere with TFTs; serious medical conditions	Ontario Ministry of Health, Boots Pharmaceuticals	LT4 25 then titrated up (mean final dose 68±21)	Placebo	9.4 (mean) 6-32 (range)	NR/NR/37	6/31
Kong et al, 2002(103)	History of thyroid disease, psychiatric disorder, anticipated pregnancy	Medical Research Council	LT4 50 then titrated up to 100 if TSH > 6 mU/L.	Placebo	~7.7 (mean)	NR/52/45	10/34 for quality of life, 18/27 for lipids
Nystrom et al, 1988(74)	History of or signs of thyroid disease, history of cardiovascular disease	Non-industry grants (Nyegaard supplied LT4)	LT4 50 for 2 wks, then 100 mg for 2 wks, then 150 daily	Placebo	~7.7 (mean) 2.9-16.3 (range)	1,192/22/20	3/17
<b>Biochemically euthyroid patients</b>							
Michalopoulou et al, 1998(99)	Conditions and medications that affect lipid profiles	Not stated	LT4 50	LT4 25 mg	stratified: 1.0 (mean) or ~2.6 (mean)	NR/NR/110	0/110
Pollock et al, 2001(101)	Current medical disorders	Association of Clinical Biochemists	LT4 100	Placebo	1.9 (mean)	NR/NR/25 (symptomatic group only)	3/22 (symptomatic group only)

\* Symptomatic group only.  
 anti-TG, anti-thyroglobulin; ApoB, Apolipoprotein B; atP, antithyroid-peroxidase; ECG, electrocardiogram; GHQ, General Health Questionnaire; GP, general practitioner; HADS, Hospital Anxiety and Depression Questionnaire; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; LT4, levothyroxine; SF=36, Medical Outcomes Study short form; SIP, Sickness Impact Profile; TC, total cholesterol; FT4, free thyroxine; TFT, thyroid function test; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

**Table 4. Description and Results of Randomized Trials of Thyroxine Replacement Therapy (continued)**

Study, Year	Outcomes Assessed/ When Assessed	How Outcomes Assessed (eg, Scales Used)	LT4 vs Placebo Group Results	Before/After Results
<b>Known history of thyroid disease</b>				
Cooper et al, 1984(75)	Symptoms, lipid profile at 1 yr	Symptom change scores ("Cooper questionnaire")	Improved symptoms (-1.2 vs +2.1) in LT4 group, 47% improved in LT4 group vs 19% in placebo group (NNT = 3.6), no difference in lipid profiles	Placebo group's TSH and symptoms rose during the year, suggesting the patients had rapidly advancing subclinical hypothyroidism
Meier et al, 2001(100)	Symptoms, lipid profile at 1 yr	Thyroid symptom questionnaire	Post-treatment LDLc was the same in both groups (3.7±0.2, p = 0.11), and symptoms scores were not significantly different (p = .53)	LDLc reduced from 4.0- 3.7 in the LT4 group (p = 0.004) and there were borderline improvements in symptom scores (p = 0.02), placebo group TSH was stable
Caraccio et al, 2002(102)	Lipid profile at 6 mos for placebo group vs about 11 mos for LT4 group	Biochemical tests	There were no significant differences between LT4 and placebo groups in any lipid parameter	LT4 group: TC reduced from 5.5-5.0, LDLc from 3.6-3.1
<b>No known history or not stated</b>				
Jaeschke et al, 1996(15)	Quality of life, symptoms, lipid profile at 6 mos	Chronic Thyroid Questionnaire, Cooper questionnaire, SIP, cognitive tests	No improvement in symptoms or lipids, improved memory in LT4 group (mean difference of .58 on z score scale, described as "small and of questionable clinical importance")	Placebo group's TSH rose from 9.42-10.32 over 6 mos
Kong et al, 2002(103)	Quality of life, symptoms, lipid profile at 6 mos	Thyroid symptom questionnaire, GHQ-30, HADS	No improvement in symptoms or lipids	Placebo group's TSH dropped from 7.3-5.6 over 6 mos
Nystrom et al, 1988(74)	Quality of life, symptoms, psychometric tests, vital signs, ECG, lipid profile at 6 mos	Thyroid symptom questionnaire, Bingley's memory test	No difference in lipids.	Symptom scores improved by the equivalent of 1 symptom per subject (P < 0.001), and 4 patients felt better with LT4 than with placebo
<b>Biochemically euthyroid patients</b>				
Michalopoulou et al, 1998(99)	Lipid profile	Not assessed	LDL reduced from 6.2-6.1 in 25 mg group and from 6.8-5.9 in 50 mg group	LDLc reduction was significant in 50 mg group
Pollock et al, 2001(101)	Symptoms, vital signs, biochemical tests after 14 weeks	SF-36 plus validated cognitive/ memory testing	Among symptomatic patients (n = 22), there were no important differences between LT4 and placebo groups in any SF-36, memory, or cognitive measures	Placebo significantly improved SF-36 general health and physical health scores

\* Symptomatic group only. anti-TG, anti-thyroglobulin; ApoB, Apolipoprotein B; atP, antithyroid-peroxidase; ECG, electrocardiogram; GHQ, General Health Questionnaire; GP, general practitioner; HADS, Hospital Anxiety and Depression Questionnaire; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; LT4, levothyroxine; SF=36, Medical Outcomes Study short form; SIP, Sickness Impact Profile; TC, total cholesterol; FT4, free thyroxine; TFT, thyroid function test; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.



**Table 4. Description and Results of Randomized Trials of Thyroxine Replacement Therapy (continued)**

Study, Year	Adverse Effects Assessed?	Adverse Effects	Quality Rating (Good/Fair/Poor)	Relevance to screening	Comments	Questions
<b>Known history of thyroid disease</b>						
Cooper et al, 1984(75)	Only through symptom scores	4 patients in LT4 group felt worse, vs 6 in placebo group	Good	Low	Well-conducted trial, but subjects had known thyroid disease and the study is not relevant to screening	What proportion of all patients who had elevated TSH and normal FT4 were eligible for the study?
Meier et al, 2001(100)	No	Not assessed	Poor	Low	The discrepancy between before/after results and LT4 vs placebo results suggests that randomization was probably flawed	Were patients informed of their LDLc levels?
Caraccio et al, 2002(102)	No	Not assessed	Poor	Fair	Analyzed as an open, uncontrolled study	Was completion of the study a criterion for inclusion in the analysis? How many patients were screened, eligible, enrolled, and randomized? Were patients and providers aware of treatment? How was randomization done? Were baseline differences statistically significant? What proportion of subjects in each group had a TC > 6.2?
<b>No known history or not stated</b>						
Jaeschke et al, 1996(15)	Only through dropouts	1 case of atrial fibrillation and 1 case of angina in LT4 group	Fair	Fair	Description of recruitment was inadequate	Were patients referred from family practitioners? Were patients who had a history of thyroid disease included?
Kong et al, 2002(103)	Only through symptom scores	Anxiety scores were higher in the LT4 group	Poor	Fair	High dropout rate, but patients were relevant to primary care: symptomatic with borderline TSH values	
Nystrom et al, 1988(74)	Only through dropouts	In LT4 group, 1 subject dropped out because of nervousness, 1 because of a sense of tachycardia	Poor	Good	The flaws in analyzing data make the study uninterpretable, but the patients are most like those encountered in screening	
<b>Biochemically euthyroid patients</b>						
Michalopoulou et al, 1998(99)	No	Not assessed	Poor	Fair	Randomization was probably flawed, and blinding is not reported	
Pollock et al, 2001(101)	Not assessed, except for SF-36 scores	In asymptomatic patients, LT4 sign, reduced SF-36 vitality scores	Fair	N/A	Too small; authors note that it is only a "pilot study." Placebo effect, adverse effect of LT4 in healthy subjects, and baseline difference in cholesterol levels (6.3 vs 5.2) between symptomatic and asymptomatic subjects deserve more study	

\* Symptomatic group only.  
 anti-TG, anti-thyroglobulin; ApoB, Apolipoprotein B; atP, antithyroid-peroxidase; ECG, electrocardiogram; GHQ, General Health Questionnaire; GP, general practitioner; HADS, Hospital Anxiety and Depression Questionnaire; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; LT4, levothyroxine; SF=36, Medical Outcomes Study short form; SIP, Sickness Impact Profile; TC, total cholesterol; FT4, free thyroxine; TFT, thyroid function test; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

**Table 5. Summary of Findings of Systematic Review**

Arrow*	Question	Level and Type of Evidence	Overall Evidence for the Link	Findings
1	Is there direct evidence from controlled studies linking screening to improved health outcomes?	None	N/A	No controlled studies links screening directly to health outcomes.
2	What is the yield of screening with a TSH test?	II-2. Well-designed cohort studies	Good	Screening detects symptomatic, overt thyroid dysfunction in 4-8 per 1,000 adult women, up to 14 per 1,000 elderly women, and 0-4 per 1,000 adult men. It also detects unsuspected subclinical hyperthyroidism in 5-20 per 10,000 adults. Subclinical hypothyroidism is found in 5% of women and 3% of men; the yield varies with age and is highest in elderly women.
3	What are the adverse effects of screening (false positives)?	II-2. Well-designed cohort studies (for frequency of false positive results)	Poor for consequences of false positive screening test results	Some consider positive TSH test results in patients who never develop complications to be "false positives." A false positive TSH test result can be harmful if it leads to anxiety or labelling, or if it leads to a treatment that has adverse effects.
4a	Is treatment effective for subclinical hypothyroidism found by screening?	Small, poor-to-fair-quality trials, most of limited relevance to screening, and 1 good-quality trial in a population not relevant to screening.	Poor	The efficacy of treatment for reducing lipids or improving symptoms is inconsistent. A good-quality trial found treatment improved symptoms and had no effect on lipid levels in patients with a history of treatment for Graves' disease. In an overview of observational studies thyroxine reduced total cholesterol by 0.14 mmol/L (5.6 mg/dL) in previously untreated patients, but the quality of the observational studies was generally poor.
4b	Is treatment effective for subclinical hyperthyroidism found by screening?	None	Poor	Subclinical hyperthyroidism is a risk factor for developing atrial fibrillation, but no studies have been done to determine whether screening and early treatment are effective in reducing the risk.
5	What are the adverse effects of treatment?	II-3. Cross-sectional studies (for osteoporosis and overtreatment). For short-term complications and long-term cardiac effects, there are only incidental findings from randomized trials.	Good (for osteoporosis and overtreatment), Poor (for other complications)	Replacement doses of levothyroxine have not been shown to have any serious long-term adverse effects. Cross-sectional studies consistently find no adverse effect of replacement doses on bone mineralization. Overtreatment with levothyroxine is present in about one-fourth of patients, but the duration and long-term consequences of inadvertent overtreatment have not been established. Evidence regarding the incidence of serious short-term complications of levothyroxine therapy (ie, atrial fibrillation, angina, myocardial infarction) is poor.

\*See Figure 1, Analytical Framework.

II-2, Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than 1 center or research group.; II-3, Evidence obtained from multiple time series with or without the intervention.; TSH, thyroid stimulating hormone.