

# Screening for Subclinical Thyroid Dysfunction in Nonpregnant Adults: A Summary of the Evidence for the U.S. Preventive Services Task Force

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**Background:** Subclinical thyroid dysfunction is a risk factor for developing symptomatic thyroid disease. Advocates of screening argue that early treatment can prevent serious morbidity in individuals who are found to have laboratory evidence of subclinical thyroid dysfunction.

**Purpose:** This article focuses on whether it is useful to order a thyroid function test for 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:** Controlled treatment studies that used thyroid-stimulating hormone (TSH) levels as an inclusion criterion and reported quality of life, symptoms, or lipid level outcomes were selected. Observational studies of the prevalence, progression, and consequences of subclinical thyroid dysfunction were also reviewed.

**Data Extraction:** The quality of each trial was assessed by

using preset criteria, and information about setting, patients, interventions, and outcomes was abstracted.

**Data Synthesis:** 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. No trials of treatment of subclinical hyperthyroidism have been done. Several small, randomized trials of treatment of subclinical hypothyroidism have been done, but the results are inconclusive except in patients who have a history of treatment of Graves disease, a subgroup that is not a target of screening in the general population. Data on the adverse effects of broader use of L-thyroxine are sparse.

**Conclusion:** It is uncertain whether treatment will improve quality of life in otherwise healthy patients who have abnormal TSH levels and normal free thyroxine levels.

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See related article on pp 125-127.

Hyperthyroidism and hypothyroidism are common conditions that have lifelong effects on health (1, 2). About 5% of U.S. adults report having thyroid disease or taking thyroid medication (1, 2). Consequences of untreated hyperthyroidism include atrial fibrillation, congestive heart failure, osteoporosis, and neuropsychiatric disorders. Hypothyroidism causes symptoms that reduce functional status and quality of life (3). Subclinical thyroid dysfunction, which can be diagnosed by thyroid function tests before symptoms and complications occur, is viewed as a risk factor for hyperthyroidism and hypothyroidism complications. The goal of screening is to identify and treat patients with subclinical thyroid dysfunction before they develop these complications (4–6).

The term *subclinical hyperthyroidism* describes conditions characterized by a low thyroid-stimulating hormone (TSH) level and normal levels of circulating thyroid hormones (thyroxine and triiodothyronine). Subclinical hyperthyroidism has the same causes as overt hyperthyroidism. These include excessive doses of L-thyroxine, Graves disease, multinodular goiter, and solitary thyroid nodule. Most studies of the course of subclinical hyperthyroidism concern patients whose history, physical examination, ultrasonogram, or thyroid scan suggests one of these causes. There are relatively few studies of patients who are found on screening to have an undetectable TSH level, normal free thyroxine ( $T_4$ ) level, and normal free triiodothyronine ( $T_3$ ) level and negative results on thyroid evaluation, although this is the largest group to be identified in a screen-

ing program. The prevalence of subclinical hyperthyroidism is about 1% (95% CI, 0.4% to 1.7%) in men older than 60 years of age and 1.5% (CI, 0.8% to 2.5%) in women older than 60 years of age (7).

The terms *subclinical hypothyroidism* and *mild thyroid failure* refer to patients who have an elevated TSH level and a normal free  $T_4$  level (Table 1) (6). Subclinical hypothyroidism is common, especially in older women (1, 2, 7–16). In an analysis of the Third National Health and Nutrition Examination Survey (NHANES III), a population-based survey of 17 353 people at least 12 years of age representing the U.S. population, the prevalence of subclinical hypothyroidism was 5.8% among white, non-Hispanic women; 1.2% among black, non-Hispanic women; and 5.3% among Mexican-American women (1). The prevalence of subclinical hypothyroidism was 3.4% among white men, 1.8% among black men, and 2.4% among Mexican-American men. In the Wickham survey, a large, good-quality, population-based study with 20-year follow-up, prevalence was 4% to 5% among women age 18 to 44 years, 8% to 10% among women age 45 to 74 years, and 17.4% among women older than age 75 years (17). The prevalence was 1% to 3% among men age 18 to 65 years and 6.2% among men older than age 65 years.

In this paper, I 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. I focus on whether screening should be aimed at

detection of subclinical thyroid dysfunction and whether individuals who have mildly abnormal TSH values can benefit.

## METHODS

In consultation with members of the U.S. Preventive Services Task Force (USPSTF) and an Institute of Medicine expert panel, I defined the population, interventions, and outcomes of interest and developed key questions to guide the literature review (18). The population of interest was asymptomatic, nonpregnant adults who did not have a goiter, nodule, proptosis, tremor, profound physical tiredness, or a history of thyroid disease (19). I also included elderly patients who reported 1 or 2 nonspecific or mild symptoms, such as cold intolerance, fatigue, weight gain, or constipation, because such patients are no more likely to have abnormal results on thyroid function tests than those who have no symptoms (20).

Previous systematic reviews have established that subclinical thyroid function is common and can be diagnosed easily by using a TSH test (7, 8, 21). In this article, I focus on the following questions:

1. What are the complications of subclinical thyroid dysfunction?
2. What are the benefits of earlier treatment of subclinical hypothyroidism and hyperthyroidism?
3. What are the adverse effects of treatment?

To find articles published before 1998, I searched the reference lists of previous reviews (6, 8, 9, 21–29) and my own files of over 1600 full-text articles from 1910 to 1998 (available at [www.ohsu.edu/epc/endnote/thyroidscreening](http://www.ohsu.edu/epc/endnote/thyroidscreening)). I then searched MEDLINE and EMBASE from 1996 to February 2002, PreMEDLINE in March 2002, and the Cochrane Library (2002, Issue 2) to identify recent articles relevant to each question.

For question 1, I searched for studies of the causal relationship between subclinical thyroid dysfunction and any potential complication. Studies were included if they were conducted in the general adult population, in a demographic segment of the adult population, or among patients seen in the general clinic setting. Studies of screening for congenital or familial thyroid disorders and studies of screening in pregnant women, inpatients, institutionalized patients, and series of patients seen in specialized referral clinics for depression or obesity were excluded.

To examine the benefits and harms of treatment (questions 2 and 3), I included any controlled trial of oral L-thyroxine or triiodothyronine that used TSH levels as a criterion for entry in any sample, including patients with known thyroid disease. I also included recent observational (pretreatment–post-treatment and time series) studies that had not been included in previous meta-analyses (7, 9, 21, 30).

I reviewed abstracts and articles to identify studies that met the eligibility criteria and abstracted information

**Table 1. Classification of Thyroid Dysfunction**

Type	Biochemical Criteria	
	TSH Level	Thyroid Hormone Level
Overt hyperthyroidism	Low or undetectable	Elevated FT <sub>4</sub> or FT <sub>3</sub>
Subclinical hyperthyroidism	Low or undetectable	Normal FT <sub>4</sub> and FT <sub>3</sub>
Overt hypothyroidism	>5 mU/L	Low FT <sub>4</sub>
Subclinical hypothyroidism	>5 mU/L*	Normal FT <sub>4</sub>

\* Others use different cutoffs. FT<sub>4</sub> = serum free thyroxine; FT<sub>3</sub> = serum free triiodothyronine; TSH = thyroid-stimulating hormone.

about the setting, patients, interventions, and outcomes of each included trial using a standard template. Predefined criteria from the USPSTF were used to assess the internal validity of included studies (18), and the applicability of each study to screening was also rated.

This article is based on a larger evidence report that was funded by the Agency for Healthcare Research and Quality and the Institute of Medicine (available at [www.preventiveservices.ahrq.gov](http://www.preventiveservices.ahrq.gov)). Staff of both funding agencies, members of the USPSTF, and members of an Institute of Medicine expert panel reviewed the draft of the larger report and made editing suggestions.

## RESULTS

### Subclinical Hyperthyroidism

Advocates of screening for subclinical hyperthyroidism argue that early treatment might prevent later development of atrial fibrillation, osteoporotic fractures, and complicated overt hyperthyroidism. Other potential benefits 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.

#### Evidence on Potential Complications

**Atrial Fibrillation.** A good-quality cohort study in the Framingham population found that the risk for atrial fibrillation was 32% (CI, 14% to 71%) over 10 years in patients older than age 60 years who did not take L-thyroxine and had a serum TSH level of 0.1 mU/L or less (31). The risk for patients who had a normal TSH level was 8%. A more recent cross-sectional study of atrial fibrillation in overt and subclinical hyperthyroidism had serious flaws and was rated as poor quality (32). The clinical consequences of atrial fibrillation in patients who have a low TSH level have not been studied. In general, chronic atrial fibrillation is associated with stroke and other complications and with a higher risk for death (33).

**Mortality.** A population-based, 10-year cohort study of 1191 persons age 60 years or older found a higher mortality rate among those who had a low initial TSH level (34). The excess mortality was due primarily to cardiovascular diseases. In this study, the recruitment strategy and the statistical adjustment for potential confounders were inad-

equate; patients who had a low TSH level may have had a higher prevalence of other illnesses, but adjustment was done only for age and sex, not for comorbidity. Comorbidity adjustment would have been critical because acutely ill and chronically ill elderly patients often have falsely low TSH levels, presumably because of their illness (35). Thus, while it is possible that patients with a low initial TSH level had higher mortality because of their thyroid disease, it is also possible that patients who were ill to begin with had a low TSH level as a result of their illness.

**Osteoporosis and Fracture.** Most data about the risk for osteoporosis and fracture come from women who take thyroid hormones rather than from untreated women found by screening to have a low TSH level. Two meta-analyses of older studies (36, 37) suggest that women who have a low TSH level because they take thyroid hormones are at higher risk for osteoporosis. However, 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 but higher markers of bone turnover in women with a low TSH level (38).

In a more recent nested sample of cases and controls from SOF, the risk for hip fracture among women who had an undetectable TSH level was elevated but was of borderline statistical significance (adjusted hazard ratio, 3.6 [CI, 1.0 to 12.9]) (39). The risk for vertebral fracture among women who had an undetectable TSH level was significantly elevated when compared with 235 controls (odds ratio, 4.5 [CI, 1.3 to 15.6]). Among women who had a borderline low serum TSH level (0.1 to 0.5 mU/L), the risk for vertebral fracture (odds ratio, 2.8 [CI, 1.0 to 8.5]), but not hip fracture, was elevated.

This analysis has limited relevance to screening because the investigators were not able to obtain serum free T<sub>4</sub> or free T<sub>3</sub> tests, which could have distinguished between overt and subclinical hyperthyroidism. Also, among the 148 women with hip fractures, 22 had an undetectable serum TSH level (<0.1 mU/L), and of these, approximately 19 (86%) were taking thyroid hormones when their initial TSH measurement was obtained. Bauer and colleagues (39) stated that “thyroid hormone use was not associated with increased risk for . . . fracture,” but too few women with undetectable TSH levels were not taking thyroid hormone to make a valid comparison. Finally, at baseline, the participants with hip fracture were significantly older, weighed less, had lower bone density, were less healthy by self-report, and were twice as likely to have a history of hyperthyroidism than controls. The analysis could not exclude the possibility that some of the women with low TSH levels had several interacting risk factors and that other factors concomitant with age or socioeconomic status could have been confounders. Other studies of the risk for osteoporosis among patients not taking L-thyroxine concern small numbers of patients with nodular thyroid disease or Graves disease (40–43) rather than patients who have no obvious clinical signs of thyroid disease.

**Complicated Thyrotoxicosis and Progression to Overt Hyperthyroidism.** Overt thyrotoxicosis can be complicated by severe cardiovascular or neuropsychiatric manifestations requiring hospitalization and urgent treatment. No data link subclinical hyperthyroidism to later development of complicated thyrotoxicosis. Furthermore, 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 (44).

Progression from subclinical to overt 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 level and no thyroid signs. On the basis of sparse data from screening studies, a previous meta-analysis estimated that each year, 1.5% of women and 0% of men who have a low TSH level and normal free T<sub>4</sub> and free T<sub>3</sub> levels develop an elevated free T<sub>4</sub> or free T<sub>3</sub> level (7, 45, 46).

**Symptoms and Cardiac Effects.** In the setting of nodular thyroid disease, Graves disease, or long-term use of suppressive doses of L-thyroxine, subclinical hyperthyroidism has been associated with cognitive abnormalities, abnormalities in cardiac contractility, and exercise intolerance (47–52). However, the frequency of symptoms or myocardial contractility abnormalities in patients who have subclinical hyperthyroidism found by screening has not been studied, and no study has linked abnormalities in cardiac contractility or output to the development of clinically important heart disease.

#### **Efficacy of Treatment of Subclinical Hyperthyroidism**

No controlled trials of treatment of subclinical hyperthyroidism have been done. Small observational studies in patients with nodular thyroid disease not detected by screening have shown improvements in bone metabolism and hemodynamic measures after treatment (53–56).

#### **Subclinical Hypothyroidism**

##### **Evidence on Potential Complications**

**Progression to Overt Hypothyroidism.** There is good evidence from well-conducted longitudinal studies that subclinical hypothyroidism is a strong risk factor for later development of overt hypothyroidism. In addition to the TSH level, older age, antithyroid antibodies, and female sex are strong risk factors. In the Wickham survey, for a 50-year-old woman with a serum TSH level of 6 mU/L and positive antithyroid antibodies, the risk for overt hypothyroidism over 20 years was 57%; for a 50-year-old woman with a serum TSH level of 9 mU/L, the risk was 71% (57). A 50-year-old woman who had a normal TSH level and negative results on an antibody test had a risk of 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 level greater than 10 mU/L.

*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 that the prevalence and severity of symptoms and the quality of life differ in individuals who have mildly elevated TSH levels compared with those who do not (7, 20, 58). Since then, 2 cross-sectional studies in volunteers have addressed this question, with mixed results. An interview survey of 825 Medicare enrollees in New Mexico found no differences in age-adjusted frequency of self-reported symptoms between participants with elevated serum TSH levels (from 4.7 to 10 mU/L) and those with normal TSH concentrations (14). A larger survey from Colorado in 25 862 persons is less pertinent because patients who took L-thyroxine were included in the analysis of symptoms. That study also found that current symptoms did not differ between euthyroid patients and those with subclinical hypothyroidism but that “changed symptoms” were more common in the subclinical hypothyroid group (13.4% vs. 15.4%) (2).

Patients who have subclinical hypothyroidism, a TSH level greater than 10 mU/L, and a history of antithyroid treatment of Graves disease or nodular thyroid disease have a higher prevalence of symptoms than healthy controls (22, 59). This observation is probably 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 level and a history of antithyroid treatment. This is because euthyroid patients who have a history of treatment of hyperthyroidism also have a higher prevalence of anxiety, depression, and psychosocial dysfunction than healthy controls (60).

*Hyperlipidemia.* Overt hypothyroidism has long been known to be associated with elevated cholesterol levels (61), but patients in the earliest studies had very severe hypothyroidism. In more recent studies, there is a clinically important increase in total cholesterol level and low-density lipoprotein (LDL) cholesterol level among men (62) and women (63, 64) with overt hypothyroidism who have serum TSH levels higher than 20 mU/L.

In women with subclinical hypothyroidism, the relation between TSH level and total cholesterol or LDL cholesterol level is inconsistent. In the Whickham survey, there was no relationship between subclinical hypothyroidism and hyperlipidemia (17). In the Rotterdam Study (16) (later discussed in detail), lipid levels were significantly lower among women with subclinical hypothyroidism than among euthyroid women. The New Mexico Elder Health Survey, a fair-quality study of randomly selected Medicare recipients, found no differences in levels of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, or triglycerides between patients who had a serum TSH level less than 4.6 mU/L ( $n = 684$ ) and those who had a serum TSH level between 4.7 and 10 mU/L

( $n = 105$ ). There were nonsignificant increases in LDL cholesterol level (3.7 mmol [143 mg/dL] vs. 3.3 mmol/L [128 mg/dL];  $P = 0.08$ ) and HDL cholesterol level (1.07 mmol/L [41.6 mg/dL] vs. 1.23 mmol/L [47.5 mg/dL];  $P = 0.053$ ) among women who had a serum TSH level greater than 10 mU/L compared with euthyroid women (14).

Conversely, a recent cross-sectional study of 279 women older than age 65 years found a strong relationship between hyperlipidemia and serum TSH levels (65). Of the 279 women, 19 (6.8%) had a serum TSH level greater than 5.5 mU/L. After adjustment for age, weight, and estrogen use, women who had a serum TSH level greater than 5.5 mU/L had 13% (CI, 1% to 25%) higher LDL cholesterol levels and 13% (CI, -25% to 0%) lower HDL cholesterol levels than those with a normal serum TSH level (0.1 to 5.5 mU/L). However, 2 of the 19 women who had an elevated TSH level used L-thyroxine, suggesting that they had inadequately treated overt hypothyroidism. Because free  $T_4$  and free  $T_3$  levels were not measured, it is possible that others in this group had overt hypothyroidism as well.

Men with a mildly elevated TSH level generally do not have an increased risk for hyperlipidemia, but data on men are sparse. Men with hypercholesterolemia do not have a higher prevalence of subclinical hypothyroidism than men with normal lipid levels (66).

*Atherosclerosis.* The relationship between subclinical hypothyroidism and later development of atherosclerosis is unclear (14, 16, 67). The Whickham survey found no relationship between initial TSH levels and the subsequent development of ischemic heart disease over 20 years of follow-up (67).

A widely publicized population-based study of 1149 women age 55 years or older from Rotterdam came to a different conclusion (16). The main analysis in the paper was cross-sectional. In that analysis, after adjustment for age, body mass index, cholesterol level, blood pressure, and smoking status, a serum TSH level greater than 4.0 mU/L was associated with a history of myocardial infarction (odds ratio, 2.3 [CI, 1.3 to 4.2]) and with atherosclerosis of the abdominal aorta, which was diagnosed by blinded review of a lateral radiograph of the lumbar spine (odds ratio, 1.9 [CI, 1.2 to 3.1]). An analysis of incident myocardial infarction over 3 to 6 years of follow-up found a statistically nonsignificant increased risk in women with a serum TSH level greater than 4.0 mU/L (adjusted relative risk, 2.5 [CI, 0.7 to 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, however, the findings do not prove that an elevated TSH level precedes the development of atherosclerosis. The prospective part of the study adds little, because at baseline, the women who had an elevated TSH level had a higher prevalence of atherosclerotic disease and would be expected to have a

Table 2. Quality of Randomized Trials of Thyroxine Replacement Therapy\*

Study, Year (Reference)	Random Assignment?	Allocation Concealed?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Blinded?	Care Provider Blinded?
Cooper et al., 1984 (59)	Yes, by individual	Not stated	LT <sub>4</sub> patients were older (58.2 y vs. 50.2 y) 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 (76)	Sequential assignment using a predefined list; randomized by matched pairs	No	LT <sub>4</sub> patients had higher TSH levels (14.4 ± 1.7 mU/L vs. 11.3 ± 1.0 mU/L) and LDL cholesterol level (4.1 mmol/L vs. 3.7 mmol/L [158 mg/dL vs. 143 mg/dL]), but were otherwise similar for the whole groups (n = 66); comparisons were not presented for the analyzed group (n = 63)	Yes	Not stated	Yes
Caraccio et al., 2002 (78)	Yes, by individual	Not stated	Generally yes, but mean TSH level (6 vs. 4.9 mU/L) and LDL cholesterol level (3.6 vs. 3.3 mmol/L [139 vs. 114 mg/dL]) were higher in the LT <sub>4</sub> group	Yes	No	No
Jaeschke et al., 1996 (74)	Yes, by individual	Not stated	LT <sub>4</sub> patients had higher TSH level (12.1 vs. 9.4 mU/L) and slightly more symptoms (14 vs. 13) but were similar in age	Yes	Yes	One investigator was not blinded but was not involved in assessment or care
Kong et al., 2002 (79)	Yes, in blocks of 6	Yes	LT <sub>4</sub> patients were older (53 y vs. 45 y) and had lower FT <sub>4</sub> levels (0.9 vs. 1 mU/L), and higher TSH levels (8 vs. 7.3 mU/L)	Yes	Yes	One was not blinded but was not involved in care
Nystrom et al., 1988 (58)	Not stated	Not stated	No baseline data were given for the groups initially assigned to LT <sub>4</sub> and placebo	Yes	Yes	Yes
Michalopoulou et al., 1998 (75)	Yes, method not stated	Not stated	Inadequately described. LDL cholesterol level was higher in the 50-mg group (6.8 vs. 6.2 mmol/L [263 vs. 240 mg/dL])	Yes	Not stated	Not stated
Pollock et al., 2001 (77)	Yes, by coin toss in blocks of 4	No	No baseline data were given for the groups initially assigned to LT <sub>4</sub> and placebo	Yes	Not stated	Yes

\* Values reported with a plus/minus sign are means ± SD. FT<sub>4</sub> = serum free thyroxine; LDL = low-density lipoprotein; LT<sub>4</sub> = L-thyroxine; RCT = randomized, controlled trial; TSH = thyroid-stimulating hormone.

† Analysis based on assignment to treatment groups and includes all randomly assigned patients.

higher incidence of myocardial infarction over 3 to 6 years in any case. The prospective analysis would have been more consequential if patients who had atherosclerosis at baseline had been excluded.

In the Rotterdam Study, women with subclinical hypothyroidism had lower lipid levels than euthyroid women. This might be due to increased use of diet or other lipid-lowering therapy in women with known cardiovascular risk factors, but it also might suggest that atherosclerosis developed through another mechanism. One hypothesis is that elevations in both homocysteine and cholesterol levels may

contribute to the elevated risk for atherosclerosis in overt hypothyroidism. In cross-sectional studies, including an analysis of the sample from the Second National Health and Nutrition Examination Survey (NHANES II), patients with overt hypothyroidism had higher homocysteine levels than euthyroid patients (68, 69). The association between elevated homocysteine level and overt hypothyroidism appears to persist after controlling for serum folate levels, which are decreased in overt hypothyroidism (68–72). However, in the only study concerning patients who had *subclinical* hypothyroidism, there was no association (73).

Table 2—Continued

Patient Unaware of Treatment?	Intention-To-Treat Analysis†	Maintenance of Comparable Groups?	Reporting of Attrition, Cross-overs, Adherence, and Contamination?	Differential Loss to Follow-up or Overall High Loss to Follow-up?	Statistical Analysis Appropriate?	Score
Yes—not verified	No	The number of patients randomly assigned appears to be 41; 33 patients were analyzed. It is not clear to which group the other 8 patients belonged	Partially	Unclear, probably not	Yes, except it did not address dropouts	Good
Yes—not verified	No	Yes	No	No	No—analyzed as RCT, but reported primarily as a before–after study	Poor
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
Yes—not verified	No	Probably, 3 dropouts in each group	Partially	Overall, 6 of 40 dropped out	Yes, except it did not address dropouts	Fair
Yes—not verified	No	Unknown	Yes	Yes, especially for lipid comparison	Yes, except it did not address dropouts	Poor
Probably aware—verified	No	Yes	No	No	No—no baseline comparisons or results provided about the first assignment	Poor
Not stated	Probably	Yes	No	No	No—analyzed as before–after	Poor
Yes—verified	No	Probably, but all 3 dropouts were from the LT <sub>4</sub> group	No	No	Yes	Fair

### Efficacy of Treatment

I identified 14 randomized trials of L-thyroxine therapy, 8 of which met the inclusion criteria (58, 59, 74–79). Six involved patients with elevated TSH levels, 1 (75) concerned hyperlipidemic patients with high-normal TSH levels, and the last trial (77) concerned patients with normal TSH levels who had symptoms of hypothyroidism.

Randomized trials of L-thyroxine treatment in subclinical hypothyroidism and in symptomatic patients who had normal TSH levels are described in Table 2 (quality ratings) and Table 3 (description and results). The first 2 trials in the tables concerned patients followed in thyroid specialty clinics. In both trials, patients had a mean serum TSH level above 10 mU/L. The first trial, by Cooper and

colleagues (59), concerned patients who had been treated for Graves disease and whose TSH levels were increasing relatively quickly. 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 L-thyroxine 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 1 symptom and partial relief of a second symptom per patient. Eight of 17 treated patients (47%) reported reduced or milder symptoms, 4 felt worse, and 5 reported no change in symptoms. In the placebo group, 3 of 16 patients (19%) 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,  $-0.09$  to  $0.65$ ), indicating that the number needed to treat to benefit 1 patient was 3.5 (59). Treatment had no effect on lipid levels. The internal validity of this trial was rated as good quality; it was the highest-quality trial of the group.

The second trial, by Meier and colleagues (76), concerned patients with thyroiditis or a history of Graves disease. Treatment with L-thyroxine had no effect on symptoms. In reporting results, the authors emphasized that LDL cholesterol level decreased significantly in the L-thyroxine group (from  $4.0$  to  $3.7$  mmol/L [ $154$  mg/dL to  $143$  mg/dL];  $P = 0.004$ ) but not in the placebo group. The difference appears to be related to an imbalance in the groups at baseline. Pretreatment LDL cholesterol level was  $4.0$  mmol/L ( $154$  mg/dL) in the treatment group versus  $3.7$  mmol/L ( $143$  mg/dL) in the placebo group. In fact, mean post-treatment LDL cholesterol level ( $\pm$ SD) was the same in both groups ( $3.7 \pm 0.2$  mmol/L [ $143 \pm 7$  mg/dL];  $P = 0.11$ ). When the results were analyzed as a randomized trial, the difference between lipid levels in the treatment and control group was not significant. The discrepancy suggests that randomization may have been flawed.

These 2 studies were rated as having low relevance to screening. The study by Cooper and colleagues (59) supports treatment in patients with a history of treated Graves disease, especially if the serum TSH level is above  $10$  mU/L. However, 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 recruited patients known to have Hashimoto thyroiditis, positive antithyroid antibodies, and mildly elevated TSH levels (78). When the results were analyzed as a randomized trial, the L-thyroxine and placebo groups did not differ significantly in any lipid variable. When the results were analyzed as a pretreatment–post-treatment study, there was a statistically significant reduction in LDL cholesterol levels ( $3.6$  mmol/L [ $139$  mg/dL] to  $3.1$  mmol/L [ $120$  mg/dL]) in the L-thyroxine group but not in the control group. The study appeared to be unblinded, which is a major flaw. 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 relevant to screening; the mean TSH level was only slightly elevated, and patients who have antithyroid antibodies and a modestly elevated TSH level are commonly found in screening programs.

The next 3 studies may have had more relevance to screening or primary care: They generally concerned patients, mostly women, who had subclinical hypothyroidism and 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 (74), 37 patients with subclinical hypothyroidism were recruited from the outpatient clinics of a com-

munity hospital and randomly assigned to L-thyroxine treatment or placebo. Patients given placebo did as well or better than those given L-thyroxine. After 6 months, 8 patients in the L-thyroxine group improved, 3 worsened, and 5 remained the same, according to the Cooper Questionnaire. In the placebo group, 11 patients improved, 1 worsened, and 4 remained the same. After 11 months, patients treated with L-thyroxine had a small but statistically significant improvement in short-term memory, but treatment did not improve general health status as measured by the Sickness Impact Profile, a standardized questionnaire. The other negative trial was too small to achieve balance in the compared groups and had a high rate of loss to follow-up (79).

A small crossover trial (58) involved women identified by screening in the general population. The 20 patients were older than age 50 years and had an initial serum TSH level 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 1 symptom per patient. As judged by subjective improvement and cognitive measures, 4 of the 19 patients who received L-thyroxine (24%) improved, while 2 (12%) felt worse with treatment.

The last 2 studies listed in Table 3 concern patients who had TSH levels in the normal range. In the study by Michalopoulou and colleagues (75), L-thyroxine,  $50$   $\mu$ g, reduced LDL cholesterol levels from  $6.8$  to  $5.9$  mmol/L ( $262$  to  $228$  mg/dL) in patients with elevated total cholesterol levels ( $>7.5$  mmol/L [ $>290$  mg/dL]) and normal TSH levels. In the study by Pollock and colleagues (77), L-thyroxine was ineffective in patients who had symptoms of hypothyroidism but normal TSH and free  $T_4$  levels. The latter study, designed as a crossover study, found that L-thyroxine significantly reduced the Short Form-36 vitality score in healthy patients and documented a clinically important and statistically significant effect of placebo.

Many observational studies have examined the effects of treatment in patients with subclinical hypothyroidism. A recent meta-analysis of both observational and randomized studies found that total cholesterol level decreased by  $0.14$  mmol/L ( $5.6$  mg/dL) in previously untreated patients (80). Another review concluded that L-thyroxine treatment might reduce serum cholesterol level by 8% in selected patients who have both a serum TSH level of  $10$  mU/L or greater and an elevated total cholesterol level of  $6.2$  mmol/L or greater ( $\geq 240$  mg/dL) (7). About 7% of persons with subclinical hypothyroidism meet these criteria.

The studies on which these analyses are based have important limitations (21). Many were before–after studies in which reductions in serum lipid levels could have been due to regression toward the mean. 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 just that these studies are observational but also that many of them are of poor quality.

Table 3. Description and Results of Randomized Trials of Thyroxine Replacement Therapy\*

Study, Year (Reference)	Patients	Setting	Age and Sex	Eligibility Criteria	Other Sample Characteristics	Exclusion Criteria
<b>Known history of thyroid disease</b>						
Cooper et al., 1984 (59)	Previously treated Graves disease, stage C subclinical hypothyroidism	Thyroid specialty clinic, Boston, MA	32 women and 1 man; mean age, 55 y	TSH level >3.5 mU/L on 2 occasions	History of Graves disease	None stated
Meier et al., 2001 (76)	Autoimmune thyroiditis (n = 33), previously treated Graves disease (n = 22), previously treated goiter (n = 7)	Thyroid specialty clinic, Switzerland	63 women; mean age, 58.5 ± 1.3 y	Women age 18–75 y; TSH level >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	Coronary heart disease, lipid-lowering drugs, history of poor adherence (estrogen therapy allowed)
Caraccio et al., 2002 (78)	Hashimoto thyroiditis (n = 48) or Graves disease (n = 1)	Medical school internal medicine clinic, Italy	42 premenopausal women, 7 men	TSH level >3.6 mU/L for >6 mo, + atP and anti-Tg, good general health	Patients had higher total cholesterol, LDL cholesterol, and apolipoprotein B levels than healthy controls	Diabetes, renal or liver disease, total cholesterol level >7.8 mmol/L (>301 mg/dL)
<b>No known history or not stated</b>						
Jaeschke et al., 1996 (74)	Diagnosis of subclinical hypothyroidism	Unclear setting, Ontario, Canada	28 women and 9 men older than age 55 y; mean age, 68 y	TSH level >6 mU/L on 2 occasions	None stated	Medications that interfere with thyroid function test results; serious medical conditions
Kong et al., 2002 (79)	Women with a diagnosis of subclinical hypothyroidism	Referrals from GPs for thyroid function tests, London, U.K.	45 women; mean age, ~49 y	Women age >18 y; TSH level 5 to <10 mU/L	Most patients were referred because of symptoms	History of thyroid disease, psychiatric disorder, anticipated pregnancy
Nystrom et al., 1988 (58)	Women identified by screening	Population-based screening study, Gothenburg, Sweden	20 women age 51–73 y	Women >age 18 y; TSH level 4 to <15 mU/L, exaggerated TSH response to TRH	Symptoms did not differ between patients and healthy controls	History of or signs of thyroid disease, history of cardiovascular disease
<b>Biochemically euthyroid patients</b>						
Michalopoulou et al., 1998 (75)	Patients referred for lipid assessment	Preventive medicine (lipid) hospital-based clinic, Greece	Not stated	Total cholesterol level >7.5 mmol/L (>290 mg/dL); TSH level 0.4–4.0 mU/L	None stated	Conditions and medications that affect lipid profiles
Pollock et al., 2001 (77)	Symptomatic patients with normal serum free thyroxine and TSH levels	Referrals from GPs, hospital clinic, and response to newspaper advertisement, Glasgow, U.K.	25 symptomatic and 19 asymptomatic patients, sex and age not given	Recent thyroid function tests within the reference range plus >3 symptoms of hypothyroidism (tiredness, lethargy, weight gain, or 3 others) or no symptoms	Symptomatic patients weighed more and had worse memory and psychological function than healthy controls	Current medical disorders

\* Values presented with a plus/minus sign are means ± SD. anti-TG = anti-thyroglobulin; atP = antithyroid-peroxidase; ECG = electrocardiogram; GHQ = General Health Questionnaire; GP = general practitioner; HADS = Hospital Anxiety and Depression Questionnaire; LDL = low-density lipoprotein; LT<sub>4</sub> = L-thyroxine; NA = not applicable; NNT<sub>B</sub> = number needed to treat for benefit; NR = not reported; SF-36 = Medical Outcomes Study Short Form; SIP = Sickness Impact Profile; TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

† Symptomatic group only.

Table 3—Continued

Funding Sources	Interventions	Control	Baseline TSH Level	Patients Screened/Eligible/Enrolled	Patients Withdrawn/Analyzed	Outcomes Assessed and When Assessed	How Were Symptoms Assessed (e.g., Scales Used)?
U.S. Public Health Service (Armour supplied LT <sub>4</sub> )	LT <sub>4</sub> , 50 µg, then titrated up	Placebo	Mean, 11 mU/L (range, 3.6–55.3 mU/L); mean TSH level in control group increased to ~15 mU/L by the end of the study	656/91/41	8/33	Symptoms, lipid profile at 1 y	Symptom change scores (Cooper Questionnaire)
Swiss Research Foundation, Henning Berlin, Sandoz, Roche	LT <sub>4</sub> titrated over 6 months (mean final dose, 85.5 ± 4.3 µg), with similar visits and changes in control group. Total follow-up, 50 wk	Placebo	Mean, 12.8 mU/L (range, 5–50 mU/L)	NR/NR/66	3/63	Symptoms, lipid profile at 1 y	Thyroid symptom questionnaire
Grant from university	LT <sub>4</sub> , 25 µg, then titrated up	Placebo	Mean, 5.43 mU/L (range, 3.65–15 mU/L)	NR/NR/49	0/49	Lipid profile at 6 months for placebo group vs. about 11 months for LT <sub>4</sub> group	Not assessed
Ontario Ministry of Health, Boots Pharmaceuticals	LT <sub>4</sub> , 25 µg, then titrated up (final dose, 68 ± 21 µg)	Placebo	Mean, 9.4 mU/L (range, 6–32 mU/L)	NR/NR/37	6/31	Quality of life, symptoms, lipid profile at 6 months	Chronic Thyroid Questionnaire, Cooper Questionnaire, SIP, cognitive tests
Medical Research Council	LT <sub>4</sub> , 50 µg, then titrated up to 100 µg if TSH level >6 mU/L	Placebo	Mean, ~7.7 mU/L	NR/52/45	10/34 for quality of life, 18/27 for lipids	Quality of life, symptoms, lipid profile at 6 months	Thyroid symptom questionnaire, GHQ-30, HADS
Nonindustry grants (Nyegaard supplied LT <sub>4</sub> )	LT <sub>4</sub> , 50 µg, for 2 wk, then 100 µg for 2 wk, then 150 µg/d	Placebo	Mean, ~7.7 mU/L (range, 2.9–16.3 mU/L)	1192/22/20	3/17	Quality of life, symptoms, psychometric tests, vital signs, ECG, lipid profile at 6 months	Thyroid symptom questionnaire, reaction time, Bingley memory test
Not stated	LT <sub>4</sub> , 50 µg	LT <sub>4</sub> , 25 µg	Stratified: mean, 1.0 mU/L or ~2.6 mU/L	NR/NR/110	0/110	Lipid profile	Not assessed
Association of Clinical Biochemists	LT <sub>4</sub> , 100 µg	Placebo	Mean, 1.9 mU/L	NR/NR/25†	3/22†	Symptoms, vital signs, biochemical tests after 14 weeks	SF-36 and validated cognitive-memory testing

Table 3—Continued

Results in LT <sub>4</sub> Group vs. Placebo Group	Before-After Results	Adverse Effects Assessed?	Adverse Effects	Quality Rating	Relevance to Screening	Comments and Questions
Improved symptoms (−1.2 vs. 2.1) in LT <sub>4</sub> group. 47% improved in LT <sub>4</sub> group vs. 19% in placebo group (NNT <sub>B</sub> = 3.6). No difference in lipid profiles	Placebo group's TSH level and symptoms increased during the year, suggesting the patients had rapidly advancing subclinical hypothyroidism profiles	Only through symptom scores	4 patients in LT <sub>4</sub> group felt worse vs. 6 in placebo group	Good	Low	Well-conducted trial, but patients had known thyroid disease and the study is not relevant to screening. What proportion of all patients who had elevated TSH levels and normal FT <sub>4</sub> levels were eligible for the study?
Post-treatment LDL cholesterol level was the same in both groups (3.7 ± 0.2 mmol/L [143 ± 8 mg/dL]; <i>P</i> = 0.11), and symptom scores were not significantly different ( <i>P</i> > 0.2)	LDL cholesterol level decreased from 4.0 to 3.7 mmol/L (154 to 143 mg/dL) in the LT <sub>4</sub> group ( <i>P</i> = 0.004), and there were borderline improvements in symptom scores ( <i>P</i> = 0.02). Placebo group TSH level was stable	No	Not assessed	Poor	Low	The discrepancy between before-after results and LT <sub>4</sub> vs. placebo results suggests that randomization was probably flawed. Were patients informed of their LDL cholesterol levels?
No significant differences between LT <sub>4</sub> and placebo groups in any lipid variable	LT <sub>4</sub> group's total cholesterol level decreased from 5.5 to 5.0 mmol/L (212 to 193 mg/dL); LDL cholesterol level decreased from 3.6 to 3.1 mmol/L (139 to 120 mg/dL)	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 patients in each group had a total cholesterol level >6.2 mmol/L (>239 mg/dL)?
No improvement in symptoms or lipids; improved memory in LT <sub>4</sub> group (mean difference of 0.58 on z-score scale, described as "small and of questionable clinical importance")	Placebo group's TSH level increased from 9.42 to 10.32 mU/L over 6 months	Only through dropouts	1 case of atrial fibrillation and 1 case of angina in the LT <sub>4</sub> group	Fair	Fair	Description of recruitment was inadequate. Were patients referred from family practitioners? Were patients who had a history of thyroid disease included?
No improvement in symptoms or lipids	Placebo group's TSH level decreased from 7.3 to 5.6 mU/L over 6 months	Only through symptom scores	Anxiety scores were higher in the LT <sub>4</sub> group	Poor	Fair	High dropout rate, but patients were relevant to primary care: symptomatic with borderline TSH values
No difference in lipids	Symptom scores improved by the equivalent of 1 symptom per patient ( <i>P</i> < 0.001), and 4 patients felt better with LT <sub>4</sub> than with placebo	Only through dropouts	In LT <sub>4</sub> group, 1 patient 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
LDL cholesterol level decreased from 6.2 to 6.1 mmol/L (240 to 236 mg/dL) in 25-μg group and from 6.8 to 5.9 mmol/L (263 to 228 mg/dL) in 50-μg group	LDL cholesterol level decreased significantly in 50-μg group	No	Not assessed	Poor	Fair	Description of recruitment was inadequate. Were patients referred from family practitioners? Were patients who had a history of thyroid disease included?
Among symptomatic patients ( <i>n</i> = 22), there were no important differences between LT <sub>4</sub> and placebo groups in any SF-36, memory, or cognitive measures	Placebo significantly improved SF-36 general health and physical health scores	Not assessed, except for SF-36 scores	In asymptomatic patients, LT <sub>4</sub> significantly reduced SF-36 vitality scores	Fair	NA	Too small; authors note that it is only a "pilot study." Placebo effect, adverse effect of LT <sub>4</sub> in healthy patients, and baseline differences in cholesterol levels (6.3 vs. 5.2 mmol/L [243 vs. 201 mg/dL]) between symptomatic and asymptomatic patients deserve more study

The hazards of relying on observational studies of the effect of drug therapy is illustrated by a large open study of L-thyroxine to treat symptoms of hypothyroidism in 139 patients who had normal results on thyroid function tests. This study found that the mean number of signs and symptoms of hypothyroidism decreased from 13 to 3 after at least 6 months of treatment; 76% of patients had improvement or resolution of more than 12 findings (81). Regardless of whether these effects are real (a subsequent randomized trial had negative results [Table 3] but was too small to exclude a clinically significant effect), they illustrate that only well-controlled trials can determine the effects of thyroxine therapy in patients with subclinical hypothyroidism.

### Adverse Effects of L-Thyroxine Treatment

Adverse effects of replacement doses of L-thyroxine include nervousness, palpitations, atrial fibrillation, and exacerbation of angina pectoris. Adverse effects were not assessed carefully in the randomized trials listed in Table 3, although some reported them incidentally. In 1 of the trials (58), 2 of 20 patients taking L-thyroxine (10%) quit the protocol because of nervousness and a sense of palpitations. In another (74), 2 of the 18 patients assigned to L-thyroxine (11%) withdrew because of complications, 1 because of an increase in angina and the second because of new-onset atrial fibrillation. In a third study (79), anxiety scores were higher in the L-thyroxine group.

A systematic review of observational studies published from 1966 to 1997 found that replacement doses of L-thyroxine (restoring TSH to normal levels) have not been associated with osteoporosis or with any other serious long-term adverse effects (82). A short-term randomized trial of L-thyroxine for subclinical hypothyroidism confirms this view (83).

The harms of overtreatment with L-thyroxine, indicated by an undetectable TSH level, are uncertain. About one fourth of patients receiving L-thyroxine for primary hypothyroidism are maintained unintentionally on doses sufficient to cause an undetectable TSH level (2, 31). Data from the Framingham cohort suggest that 1 excess case of atrial fibrillation might occur for every 114 patients treated with doses of L-thyroxine sufficient to suppress TSH (31). As mentioned earlier, some information suggests that an undetectable TSH level in patients taking L-thyroxine is associated with an increased risk for osteoporosis (36, 37) and fractures (39). Other studies, however, have found no difference in bone density (38) or hip fracture rates (84). Suppressive doses of L-thyroxine can temporarily increase heart rate and left ventricular mass (85), but there is no evidence that this causes long-term complications.

Another potential harm is treatment of healthy patients based on false-positive test results. In screening programs and in the primary care clinic, many patients found to have an abnormal TSH level revert to normal values over time. In 1 randomized trial, for example, mildly ele-

vated TSH level reverted to normal in 8 of 19 patients given placebo (74). In older patients, only 59% (range, 14% to 87%) of patients with an undetectable TSH level on initial screening had an undetectable TSH level when the test was repeated (45, 86). In the Framingham cohort, screening identified 41 people with undetectable serum TSH levels ( $\leq 0.1$  mU/L) and normal serum free  $T_4$  levels ( $< 129$  nmol/L) (87). After 4 years of follow-up, when 33 of these persons were retested, 29 had higher serum TSH levels ( $> 0.1$  mU/L).

### DISCUSSION

The ability of screening programs to detect subclinical thyroid dysfunction has been demonstrated in good-quality cohort studies. There is also good evidence that, in the general population, an undetectable TSH level is a risk factor for later development of atrial fibrillation. However, there have been no studies of early treatment to prevent this complication.

An elevated TSH level—even a mildly elevated one—is a risk factor for later development of overt hypothyroidism. Early treatment would prevent this progression, but the balance of benefits and harms is unclear. The key uncertainties are as follows. First, without screening or prophylaxis, how long would overt hypothyroidism be undetected? Second, how much morbidity would undiagnosed overt hypothyroidism cause while undetected? Third, what are the harms of treatment in those who do not progress? Data showing that progression to overt disease is associated with significant burden of illness would strengthen the case for preemptive treatment. Other potential harms of subclinical thyroid dysfunction are not well established. Data on osteoporosis, fracture, hyperlipidemia, and atherosclerotic disease are inconsistent, and most data come from patients who take L-thyroxine or have clinically evident thyroid disease.

Not surprisingly, experts give conflicting advice about the treatment of subclinical hypothyroidism (6, 21, 26, 28). Good evidence shows that L-thyroxine reduces symptoms (but not lipid levels) in patients who have a markedly elevated TSH level ( $> 10$  mU/L) following surgery or radioiodine treatment. However, in apparently healthy patients who have mildly elevated TSH levels (4 to 7 mU/L), the largest group identified by screening, the frequency of hyperlipidemia and symptoms may be no different from that in euthyroid individuals. The main gap in the evidence is the lack of convincing data from controlled trials that early treatment reduces lipid levels, symptoms, or the risk for cardiovascular disease in patients with mild thyroid dysfunction detected by screening.

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