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CLINICAL GUIDELINE

Screening for Thyroid Dysfunction: U.S. Preventive Services Task Force Recommendation Statement

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Description: Update of the 2004 U.S. Preventive Services Task Force (USPSTF) recommendation on screening for thyroid disease.

Methods: The USPSTF reviewed the evidence on the benefits and harms of screening for subclinical and "overt" thyroid dysfunction without clinically obvious symptoms, as well as the effects of treatment on intermediate and final health outcomes.

Population: This recommendation applies to nonpregnant, asymptomatic adults.

Recommendation: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults. (I statement)

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The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendation and Evidence

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults. (I statement)

See the Clinical Considerations section for suggestions for practice regarding the I statement.

See the **Figure** for a summary of the recommendation and suggestions for clinical practice.

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

Rationale

Importance

Thyroid gland disorders are among the most common endocrine conditions evaluated and treated by clinicians. Thyroid dysfunction represents a continuum from asymptomatic biochemical changes to clinically symptomatic disease. In rare cases, it can produce life-threatening complications, such as myxedema coma or thyroid storm (1, 2).

Subclinical hypothyroidism is defined as an asymptomatic condition in which a patient has a serum thyroid-stimulating hormone (TSH) level exceeding the upper threshold of a specified laboratory reference interval (commonly but arbitrarily defined as 4.5 mIU/L) but a normal thyroxine (T4) level (3). Patients with subclinical hypothyroidism are often further classified as having TSH levels between 4.5 and 10.0 mIU/L or greater than 10.0 mIU/L.

Despite its name, "*overt*" *hypothyroidism* does not require the presence of symptoms and has been defined biochemically by an elevated TSH level and a low T4 level. As such, it encompasses a range of low T4 levels that may or may not be associated with a set of relatively subtle and nonspecific clinical symptoms, such as fatigue, feeling cold, weight gain, hair loss, and constipation.

Subclinical hyperthyroidism is defined as an asymptomatic condition in which a patient has a serum TSH level below the lower threshold of a specified laboratory reference interval (usually 0.4 mIU/L) but normal T4 and triiodothyronine (T3) levels. Patients with subclinical hyperthyroidism are further classified as having "low but detectable" (about 0.1 to 0.4 mIU/L) or "clearly low" or "undetectable" (<0.1 mIU/L) TSH levels (3).

Despite its name, "*overt*" *hyperthyroidism* does not require the presence of symptoms and has been defined biochemically by a low or undetectable TSH level and an elevated T4 or T3 level. When present, symp-

See also:

Editorial comment 1
Summary for Patients 2

Web-Only
Consumer Fact Sheet

* For a list of USPSTF members, see the **Appendix** (available at www.annals.org).

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Figure. Screening for thyroid dysfunction: clinical summary of U.S. Preventive Services Task Force recommendation.

Annals of Internal Medicine

U.S. Preventive Services TASK FORCE
www.USPreventiveServicesTaskForce.org

Population	Nonpregnant, asymptomatic adults
Recommendation	No recommendation. Grade: I statement (insufficient evidence)

Risk Assessment	Risk factors for an elevated thyroid-stimulating hormone (TSH) level include female sex, advancing age, white race, type 1 diabetes, Down syndrome, family history of thyroid disease, goiter, previous hyperthyroidism, and external-beam radiation in the head and neck area. Risk factors for a low TSH level include female sex; advancing age; black race; low iodine intake; personal or family history of thyroid disease; and ingestion of iodine-containing drugs, such as amiodarone.
Screening Tests	The primary screening test for thyroid dysfunction is serum TSH testing. Multiple tests over 3 to 6 mo should be performed to confirm or rule out abnormal findings. Follow-up testing of serum thyroxine (T4) levels in persons with persistently abnormal TSH levels can differentiate between subclinical (normal T4 level) and "overt" (abnormal T4 level) thyroid dysfunction.
Treatment and Interventions	Hypothyroidism is treated with oral T4 monotherapy (levothyroxine sodium). Consensus is lacking on the appropriate point for clinical intervention, especially for TSH levels <10.0 mIU/L. Hyperthyroidism is treated with antithyroid medications (e.g., methimazole) or nonreversible thyroid ablation therapy (e.g., radioactive iodine or surgery). Treatment is generally recommended for patients with a TSH level that is undetectable or <0.1 mIU/L, particularly those with overt Graves disease or nodular thyroid disease.
Balance of Benefits and Harms	The current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

toms are often relatively nonspecific (for example, weight loss, heart palpitations, heat intolerance, and hyperactivity).

For the purposes of this recommendation, *thyroid dysfunction* is defined as a spectrum of disorders related to the thyroid gland. The spectrum begins with asymptomatic subclinical hypothyroidism and hyperthyroidism. In the middle of the spectrum are asymptomatic "overt" hypothyroidism and hyperthyroidism, defined biochemically by changes in serum TSH and T4 levels. At the end of the spectrum is thyroid disease, which is reserved for symptomatic "overt" hypothyroidism and hyperthyroidism (that is, persistently abnormal serum TSH and T4 levels and clearly associated clinical signs and symptoms that cannot be better explained by another condition).

In making its recommendations about clinical preventive services, the USPSTF focuses on asymptomatic populations that do not have known signs or symptoms of disease.

Detection

Early detection and treatment of asymptomatic persons with abnormal serum TSH levels with or without abnormal T4 levels may be beneficial because it may prevent longer-term morbidity and mortality from fractures, cancer, or cardiovascular disease. However, widespread screening and treatment of subclinical thyroid dysfunction can also result in harms due to labeling, false-positive results, and overdiagnosis and overtreatment.

The USPSTF found adequate evidence that screening can detect "abnormal" serum TSH levels in asymptomatic persons. However, what constitutes an abnormal TSH level is uncertain. Laboratory reference intervals are based on the statistical distribution of TSH levels across the general population (for example, using the 97.5th percentile as an upper boundary for normal) rather than according to the association of a TSH level with symptoms, adverse outcomes, or particular risk factors for disease (3). There is professional disagreement about the appropriate cut points for the lower and upper boundaries of normal TSH levels in the general population and in subgroups, such as older adults, where values differ from the overall population distribution (for example, shifting to a higher range of normal) (4–7).

Accurate interpretation of serum TSH levels is further complicated by measurement variability and the sensitivity of TSH secretion to conditions other than thyroid dysfunction. These issues have led many professional groups to recommend repeating thyroid function tests if the results fall above or below a specified reference interval for confirmation of persistent dysfunction (for example, over 3- to 6-month intervals) in

asymptomatic persons before making a diagnosis or considering any treatment strategies, unless the serum TSH level is greater than 10.0 or less than 0.1 mIU/L (3, 8, 9).

Benefits of Early Detection and Treatment

The USPSTF found inadequate evidence that screening for thyroid dysfunction in nonpregnant, asymptomatic adults leads to clinically important benefits. In particular, the USPSTF found inadequate evidence to determine whether screening for thyroid dysfunction reduces cardiovascular disease or related morbidity and mortality.

The USPSTF found adequate evidence that screening for and treatment of thyroid dysfunction in nonpregnant, asymptomatic adults does not improve quality of life or provide clinically meaningful improvements in blood pressure, body mass index (BMI), bone mineral density, or lipid levels. It also does not improve cognitive function, at least through the duration of available trials (≥1 to 2 years) (1, 2).

Harms of Early Detection and Treatment

The USPSTF found inadequate evidence on the harms of screening for and treatment of thyroid dysfunction. Indirect evidence points to the likelihood of important and frequent harms associated with screening in asymptomatic persons. Foremost among these are frequent false-positive results; the psychological effects of labeling; and a large degree of overdiagnosis and overtreatment of biochemically defined abnormal TSH levels (with or without abnormal serum T4 levels) that may revert to normal, not progress, or never result in health problems even if they do progress, particularly in persons with TSH levels less than 10 mIU/L.

USPSTF Assessment

The USPSTF concludes that the evidence is insufficient and that the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults cannot be determined.

If clinicians offer screening for thyroid dysfunction to asymptomatic persons, they should first ensure that patients clearly understand the uncertainties surrounding any potential clinical benefit of screening as well as the possibility of harm this choice may engender.

CLINICAL CONSIDERATIONS

Patient Population Under Consideration

This recommendation applies to nonpregnant, asymptomatic adults.

Suggestions for Practice Regarding the I Statement

Potential Preventable Burden

About 5% of women and 3% of men in the United States have subclinical hypothyroidism (4). Of note, several studies have shown that about 37% of persons with subclinical hypothyroidism spontaneously revert to a euthyroid state without intervention after several years (10, 11). About 2% to 5% of persons with subclinical hypothyroidism develop "overt" thyroid dysfunction (12).

One retrospective cohort study found that levothyroxine use in persons with subclinical hypothyroidism was associated with lower risk for ischemic heart disease events and overall mortality (13); however, the USPSTF did not identify any clinical trials that evaluated the causal relationship between treatment and subsequent cardiac events. The USPSTF did not identify any trials or observational studies that evaluated the effects of treatment of "overt" hypothyroidism (with or without symptoms) versus no treatment.

Subclinical hyperthyroidism is present in about 0.7% of the U.S. population and is more common in women than men (4). One quarter of persons with subclinical hyperthyroidism revert to a euthyroid state without medical intervention over time (10, 14). An estimated 1% to 2% of persons with TSH levels less than 0.1 mIU/L develop "overt" hyperthyroidism (with or without symptoms). Persons with TSH levels between 0.1 and 0.45 mIU/L are unlikely to progress to "overt" hyperthyroidism (8).

The USPSTF did not identify any studies that evaluated the benefits of treatment of subclinical hyperthyroidism on final health outcomes, such as fractures, cancer, or cardiovascular morbidity or mortality. Except for 1 small (n = 67) nonrandomized study that examined bone mineral density, no evidence was found on the effects of treatment of "overt" hyperthyroidism (with or without symptoms) (1, 2).

Potential Harms

The harms of treatment of thyroid dysfunction have not been well-studied. The most important potential harms are false-positive results, labeling, and overdiagnosis and overtreatment.

False-positive results occur because TSH secretion is highly variable and sensitive to several common factors, such as acute illness or certain medications. Ascertainment of true- versus false-positive results is further complicated by a lack of consensus on what constitutes a normal reference interval.

Consensus is also lacking on the appropriate point for clinical intervention, particularly for hypothyroidism. No clinical trial data support a treatment threshold to improve clinical outcomes. On the basis of expert opinion, a TSH level greater than 10.0 mIU/L is generally considered the threshold for initiation of treatment (in part because of the higher likelihood of progression to "overt"—even if still asymptomatic—thyroid dysfunction). The decision of whether and when to begin therapy in patients with TSH levels between 4.5 and 10.0 mIU/L is more controversial (3, 15). A large magnitude of overdiagnosis and overtreatment is a likely consequence of screening for thyroid dysfunction, particularly because the disorder is defined by silent biochemical parameters rather than a set of reliable and consistent clinical symptoms. The high variability of TSH secretion levels and the frequency of reversion to normal thyroid function without treatment underscore the importance of

not relying on a single abnormal laboratory value as a basis for diagnosis or the decision to start therapy.

Currently, it is not possible to differentiate persons who will have advancing thyroid dysfunction of clinical importance from those whose TSH levels will remain biochemically stable or even normalize. Treating the latter group (at a minimum) will not lead to benefit, and these persons may experience harms associated with antithyroid medications, ablation therapy, and long-term thyroid hormone therapy.

Current Practice

Although exact estimates are not available for the United States, screening for thyroid dysfunction by primary care providers seems to be a common practice (16). In the United Kingdom, an estimated 18% to 25% of the adult population receives thyroid function testing each year (17).

The annual number of dispensed prescriptions of levothyroxine sodium in the United States increased by 42% over a 5-year period, from 50 million in 2006 to 71 million in 2010 (18). In 2013, there were more than 23 million new prescriptions and refills for a single name brand of thyroid hormone in the United States, making it the most commonly prescribed drug in the country (19).

In 1996, a cross-sectional study of a U.S. population found that 39% of participants with TSH levels between 5.1 and 10.0 mIU/L received treatment (20). More recent evidence suggests that the median TSH level at initiation of thyroid hormone therapy has decreased over time; a retrospective cohort study in the United Kingdom found that the median TSH level at the time of first levothyroxine prescription decreased from 8.7 to 7.9 mIU/L between 2001 and 2009 (17).

Initiation and use of thyroid hormone therapy seem to be particularly common in older adults. Data from the CHS (Cardiovascular Health Study), a U.S. cohort of nearly 6000 community-dwelling adults aged 65 years or older, showed a steady increase in the overall percentage of older adults receiving thyroid hormone therapy (from 9% in 1989 to 20% in 2006) and a nonlinear probability of initiating levothyroxine therapy based on age; persons aged 85 years or older were more than twice as likely as those aged 65 to 69 years to begin thyroid hormone therapy (hazard ratio [HR], 2.34 [95% CI, 1.43 to 3.85]), independent of race or sex (21).

Data on the proportion of asymptomatic persons with thyroid dysfunction who receive thyroid hormone therapy are lacking. However, given the high number of prescriptions for levothyroxine dispensed in the United States and the low prevalence of "overt" hypothyroidism and hyperthyroidism among persons in the general population (0.3% and 0.5%, respectively [7], only a small fraction of whom are symptomatic), it is reasonable to conclude that many asymptomatic persons receive treatment. Clinicians seem to be treating more persons with thyroid dysfunction, at earlier times after initial diagnosis, and at TSH levels closer to normal.

Assessment of Risk

The most common cause of hypothyroidism in the United States is chronic autoimmune (Hashimoto) thyroiditis. Risk factors for an elevated TSH level include female sex, advancing age, white race, type 1 diabetes, Down syndrome, family history of thyroid disease, goiter, previous hyperthyroidism (possibly due in part to ablation therapy leading to iatrogenic thyroid dysfunction), and external-beam radiation in the head and neck area (1, 2).

Common causes of hyperthyroidism include Graves disease, Hashimoto thyroiditis, and functional thyroid nodules. Risk factors for a low TSH level include female sex; advancing age; black race; low iodine intake; personal or family history of thyroid disease; and ingestion of iodine-containing drugs, such as amiodarone (1, 2).

The USPSTF found no direct evidence that treatment of thyroid dysfunction based on risk level alters final health outcomes.

Screening Tests

The serum TSH test is the primary screening test for thyroid dysfunction. Multiple tests should be done over a 3- to 6-month interval to confirm or rule out abnormal findings. Follow-up testing of serum T4 levels in persons with persistently abnormal TSH levels can differentiate between subclinical (normal T4 levels) and "overt" (abnormal T4 levels) thyroid dysfunction.

Screening Interval

The optimal screening interval for thyroid dysfunction (if one exists) is unknown.

Interventions

The principal treatment for hypothyroidism is oral T4 monotherapy (levothyroxine sodium).

Hyperthyroidism is treated with antithyroid medications (such as methimazole) or nonreversible thyroid ablation therapy (for example, radioactive iodine or surgery). Although definitive data are lacking, treatment is generally recommended for patients with a TSH level that is undetectable or less than 0.1 mIU/L, particularly those with overt Graves disease or nodular thyroid disease. Treatment is typically not recommended for patients with TSH levels between 0.1 and 0.45 mIU/L or when thyroiditis is the cause (1, 2).

OTHER CONSIDERATIONS

Research Needs and Gaps

Although detection and treatment of abnormal TSH levels (with or without abnormal T4 levels) in asymptomatic persons is common practice, evidence that this clinical approach improves important health outcomes is lacking. Long-term randomized, blinded, and controlled trials of screening for thyroid dysfunction would provide the most direct evidence on any potential benefits of this widespread practice. Serum TSH levels that define eligibility for enrollment, particularly based on age-specific ranges, are needed. Impor-

tant clinical outcomes include cardiovascular- and cancer-related morbidity and mortality, as well as falls, fractures, functional status, and quality of life. Intermediate biochemical outcomes are less important; they are not reliable evidence of treatment effectiveness, and the effects of treatment of thyroid dysfunction on important clinical outcomes may be independent of any known intermediate outcomes.

Before conducting screening trials, it may be more feasible for researchers to conduct well-designed treatment trials of either subclinical or asymptomatic "overt" thyroid dysfunction versus watchful waiting (including intervention if "overt" dysfunction becomes symptomatic), using final health outcomes, such as cardiovascular-related morbidity and mortality, as the end points of interest. For such trials to be most informative, they should have clearly defined patient populations; intervention protocols (for example, treatment doses and target TSH levels); and study outcomes, including short- and long-term benefits and harms.

Long-term observational studies are needed to better understand the natural history of untreated, asymptomatic thyroid dysfunction based on different serum TSH and T4 levels, as well as outcomes in persons with common but nonspecific symptoms. Useful information might be available from ongoing studies that collect biochemical samples; detailed demographic data; and information on functional status, quality of life, and other final health outcomes.

Currently, the evidence does not show important benefits of treatment of subclinical thyroid dysfunction on blood pressure, BMI, lipid levels, cognitive function, or quality of life. Although treatment is associated with harms, it could have important long-term benefits on final health outcomes (such as reduced bone fractures and cardiovascular- and cancer-related morbidity and mortality) that may be independent of known intermediate outcomes. For example, evidence indicates that if treatment is effective for fractures or cardiovascular disease prevention, it is due to factors other than improvements in bone mineral density or lipid levels (13, 22). The need for randomized trials that evaluate the effect of treatment of subclinical thyroid dysfunction on cardiac outcomes has been emphasized (13). Given the increasingly popular clinical practice of routine identification and treatment of asymptomatic persons with thyroid dysfunction and the treatment of those with vague and nonspecific symptoms, these trials are warranted.

Studies that evaluate the harms of screening for and treatment of thyroid dysfunction are critically lacking. The USPSTF believes that false-positive results, labeling, and overdiagnosis and overtreatment are important harms of any screening and prevention program and that these harms should be minimized. Additional evidence is needed on how to best communicate the clinical complexity surrounding screening for and treatment of asymptomatic thyroid dysfunction so that patients and their providers can make informed decisions.

DISCUSSION

Burden of Condition

Disorders of the thyroid gland are among the most common endocrine conditions evaluated and treated by clinicians. According to data from NHANES (National Health and Nutrition Examination Survey), about 46 per 1000 persons in the United States have subclinical hypothyroidism, 7 per 1000 have subclinical hyperthyroidism, 3 per 1000 have "overt" hypothyroidism, and 5 per 1000 have "overt" hyperthyroidism (4).

Currently, the most common argument in favor of early treatment of thyroid dysfunction is the possible associations among untreated subclinical hypothyroidism, risk factors for heart disease, and subsequent coronary disease or heart failure. However, the epidemiologic evidence for this argument is mixed, and the available studies (including several meta-analyses) had important methodological limitations, precluding certainty in their findings (3, 23–28). If early treatment is effective in preventing coronary disease or heart failure, the current evidence suggests that it is probably through mechanisms other than mediation of blood pressure and lipid levels.

Recently, 2 prospective studies—Health ABC (Health, Aging, and Body Composition Study) (29) and CHS (30)—showed a correlation between subclinical hypothyroidism and congestive heart failure, particularly in persons with a serum TSH level greater than 10.0 mIU/L (HRs, 3.26 [CI, 1.37 to 7.77] and 1.88 [CI, 1.05 to 3.34], respectively). This possible association warrants further study; however, it is not known whether thyroid replacement therapy would modify this potential risk (3).

Scope of Review

The USPSTF commissioned a systematic evidence review to update its 2004 recommendation on screening for thyroid disease. The review assessed the evidence on the benefits and harms of screening for subclinical and "overt" thyroid dysfunction without clinically obvious symptoms, as well as the effects of treatment of screen-detected subclinical and "overt" thyroid dysfunction on intermediate and final health outcomes. The review also evaluated the proportion of patients screened for thyroid dysfunction who have clinically apparent disease, the proportion with TSH levels of 10 mIU/L or less who are treated in current practice, and the cardiovascular consequences of untreated subclinical thyroid dysfunction.

Accuracy of Screening Tests

When used to confirm clinically suspected thyroid disease in patients referred to an endocrinologist, the serum TSH test has a sensitivity of about 98% and a specificity of about 92% (31). However, its accuracy is more challenging to ascertain when it is used to screen asymptomatic persons for thyroid dysfunction, for several reasons. First, there is no consensus on the appropriate TSH cutoff for a diagnosis of subclinical hypothyroidism or hyperthyroidism. Most laboratories define an abnormal TSH test result by using the upper and

lower limits of the 95% reference interval for a particular assay (generally about 0.4 to 4.5 mIU/L) (3). However, laboratories use varying types of assays (32). More important, this threshold is arbitrary; it is not based on the risk for an adverse health outcome but simply a normal population distribution of values.

Second, TSH secretion varies among different subpopulations, such as those defined by race/ethnicity, sex, and age. For example, 12% of persons aged 80 years or older with no evidence of thyroid disease have been found to have TSH levels greater than 4.5 mIU/L (33). Therefore the "standard" population reference interval for older adults is probably inappropriate (10, 34, 35).

Third, TSH secretion is highly sensitive to factors other than thyroid disorders. For example, serum TSH is frequently suppressed during phases of acute illness (3). Levels of TSH may also be affected by the administration of drugs or substances, such as iodine, dopamine, glucocorticoids, octreotide, or bexarotene (1, 15). Adrenal insufficiency, pregnancy (particularly during the first trimester), anorexia nervosa, certain autoimmune diseases, and pituitary adenomas can also interfere with normal circulating levels of TSH (3, 15).

Fourth, serum TSH levels can vary by as much as 50% of mean values on a day-to-day basis, with up to 40% variation of values obtained from serial TSH measurements performed at the same time of day (36, 37).

All of this confirms the importance of not relying on a single TSH value to establish a diagnosis of thyroid dysfunction. Serial TSH measurements are an essential step in establishing that a thyroid disorder is real and persistent.

Effectiveness of Early Detection and Treatment

Early Detection

No studies directly evaluated the effects of screening for thyroid dysfunction on morbidity (including quality of life and functional status) or mortality in the general population (1, 2).

Treatment of Hypothyroidism

Three trials (n = 239) found no statistically significant effect of treatment of subclinical hypothyroidism on blood pressure (1, 2) through 10.5 months of follow-up. Similarly, 6 trials (n = 385) found no statistically significant effect of treatment on BMI or weight (1, 2) through 1 year of follow-up.

Evidence on the effect of treatment of subclinical hypothyroidism on lipid levels is mixed. Several trials suggested potential beneficial effects, but the results are inconsistent and of uncertain clinical importance. In 8 good- or fair-quality trials (n = 597), 3 of which reported statistically significant results, differences between the treatment and control groups ranged from −0.7 to 0 mmol/L (−28 to 0 mg/dL) for mean total cholesterol level and from −0.6 to 0.1 mmol/L (−22 to 2 mg/dL) for mean low-density lipoprotein cholesterol level (1, 2). No studies reported statistically significant differences in levels of high-density lipoprotein cholesterol or triglycerides (1, 2). Whether changes in these intermediate outcomes due to treatment are adequate surrogates for cardiovascular morbidity or mortality is not known, and no trials directly evaluated the effects of treatment of subclinical hypothyroidism on final health outcomes, such as cardiac morbidity or mortality.

A single fair-quality retrospective cohort study by Razvi and colleagues examined the association between treatment of subclinical hypothyroidism and risk for cardiac events (13). The study identified 4735 persons aged 40 years or older with subclinical hypothyroidism (based on a single TSH value of 5.01 to 10.0 mIU/L) from the U.K. General Practice Research Database. Mean follow-up was 7.6 years, and participants were categorized a priori into 2 age groups (40 to 70 years or >70 years). After adjustment for age, sex, BMI, socioeconomic status, blood pressure, total cholesterol level, smoking status, history of diabetes mellitus, levothyroxine use, and index serum TSH level, levothyroxine use in the younger age group was associated with lower risk for fatal or nonfatal ischemic heart disease events (4.2% vs. 6.6%; HR, 0.61 [CI, 0.39 to 0.95]), death due to circulatory diseases (1.4% vs. 2.4%; HR, 0.54 [CI, 0.37 to 0.92]), and all-cause mortality (1.2% vs. 2.2%; HR, 0.59 [CI, 0.21 to 0.88]). There were no statistically significant associations between treatment and cardiovascular outcomes in the older age group.

One limitation of this study is that it did not adjust for the use of medications that reduce risk for cardiovascular disease, such as aspirin or lipid-lowering therapy. Residual confounding for these and other variables could be present, although baseline data did not show differences between the treatment groups (13). Although the results are promising and justify the prioritization of further research in this area, this study is ultimately hypothesis-generating rather than proof of effect.

Razvi and colleagues' study also reported an association between use of levothyroxine and reduced risk for any cancer death in persons aged 40 to 70 years (1.2% vs. 2.2%; HR, 0.59 [CI, 0.21 to 0.88]) (13). The authors noted that this was an unexpected finding that should therefore be interpreted with caution, particularly because it was not the primary study outcome. This finding further underscores the probable presence of residual confounding and emphasizes the need for experimental research to ascertain the true effect of treatment of subclinical hypothyroidism on cardiovascular outcomes.

In 2004, the USPSTF identified 5 trials that evaluated the effects of treatment on quality of life in persons with subclinical hypothyroidism. Only 1 trial, in patients with recent Graves disease, found a positive effect of treatment (38). Since then, 4 good- or fair-quality trials (n = 327) have been published, and none found a difference between persons receiving treatment and those receiving placebo through 1 year of follow-up (1, 2).

Since the previous USPSTF review, 1 good-quality (n = 94) and 1 fair-quality (n = 69) trial have each found no effect of treatment of screen-detected subclinical

hypothyroidism on various measures of cognitive function (such as cognitive skills and performance, cognitive status, speed of cognitive processing, and psychomotor tests of executive function) after 1 year (39, 40).

No studies evaluated the effects of treatment of "overt" hypothyroidism (with or without symptoms) versus no treatment on any outcome (1).

Treatment of Hyperthyroidism

No fair- or good-quality studies evaluated the benefits of treatment of subclinical hyperthyroidism (1, 2). Two small (n = 14 and 20) poor-quality trials found no differences between treatment of subclinical hyperthyroidism and no treatment on blood pressure, BMI, bone mineral density, or lipid levels (1, 2).

The only identified evidence relevant to "overt" hyperthyroidism was 1 small (n = 67) nonrandomized study that evaluated the effects of treatment on bone mineral density (41). This study did not meet inclusion criteria and was not formally assessed as part of the systematic evidence review.

No trials evaluated the effects of treatment of hyperthyroidism (subclinical or "overt") versus no treatment on final health outcomes.

Potential Harms of Early Detection and Treatment

Screening

No studies directly examined the harms of screening for thyroid dysfunction. However, screening clearly has potential harms, the most important of which are false-positive results, psychological effects of disease labeling, and overdiagnosis and overtreatment.

False-positive results on serum TSH tests are common due to several factors. Secretion of TSH is sensitive to multiple factors unrelated to thyroid conditions; varies across time intervals, sometimes as short as a day; and varies depending on the population being considered (average TSH values may differ by age, sex, and race/ethnicity). In addition, there is no universally agreed-on "normal" TSH reference value, in part because it is not linked to the risk for actual adverse health outcomes.

Reliable estimates of the frequency of false-positive results from serum TSH tests are not available. A prospective observational study followed a cohort of 599 older adults after a single baseline TSH test, with repeated testing of 376 participants at the end of the study. It found that 37% (11 of 30) of participants with an initially elevated TSH level and 29% (5 of 17) with an initially low TSH level reverted to normal thyroid function after 3 years without intervention. Limitations of this study include the small number of affected participants, high loss to follow-up, and inability to distinguish between false-positive results and overdiagnosis with the methodological approach (10).

Labeling someone with a diagnosis of disease may have adverse psychological consequences, particularly in the case of an otherwise asymptomatic condition. Although the patient may have previously felt healthy, being informed that he or she has a disorder that requires medical surveillance or intervention can result in anxiety or changes to the patient's sense of well-being. A cross-sectional study of almost 34 000 persons aged 40 to 70 years found that women with known hypothyroidism were less likely to report good self-rated health compared with those without thyroid dysfunction (adjusted odds ratio, 0.49 [CI, 0.41 to 0.59]) (42).

Overdiagnosis of thyroid dysfunction is probably common, in part because the condition is defined biochemically rather than clinically and because disagreements persist about the appropriate cut points for classification of disease. The exact proportion of thyroid dysfunction diagnoses that are overdiagnoses is not known. However, many persons labeled with hypothyroidism or hyperthyroidism spontaneously revert to a euthyroid state over time; others never progress to noticeable health problems, especially those who are asymptomatic and have "mildly elevated" (4.5 to 10.0 mIU/L) TSH levels.

In 1 prospective study, 102 women aged 60 years or older with subclinical hyperthyroidism (defined as a TSH level of 0.1 to 0.4 mIU/L, as measured at baseline and 12 weeks after study entry) but normal T3 and T4 levels were followed for a mean of 41 months without intervention. At the end of the study, 24 women (24%) had TSH levels that had spontaneously normalized (14). A second prospective study evaluated the natural history of subclinical hypothyroidism. The study followed 107 persons aged 55 years or older with newly diagnosed subclinical hypothyroidism (defined as a TSH level >5.0 mIU/L on 2 serial measurements before study entry) for a mean of 32 months without intervention. After this time, 40 participants (37%) had reverted to a euthyroid state. Of note, nearly half of the persons in this population had been referred to the study clinic by their general practitioner because of the incidental discovery of an elevated TSH level during routine "analytical lab checking." Forty-four percent also reported 1 or more symptoms commonly associated with hypothyroidism (11).

Overdiagnosis is of concern because it leads to the psychological consequences of labeling and unnecessary treatment. It is a fundamental harm that should be avoided in disease prevention and health promotion.

Treatment

As with screening, limited evidence is available to assess the harms of treatment of thyroid dysfunction.

Levothyroxine therapy is a synthetic preparation of a natural hormone found in the body. Treatment of hypothyroidism with levothyroxine generally lasts for many years. Despite its previous widespread use in the United States, levothyroxine sodium was not approved by the U.S. Food and Drug Administration until 2000. However, its approval process did not include studies that evaluated short- or long-term adverse effects. The product label cites possible adverse effects on bone mineral density and the cardiovascular system, such as

angina, arrhythmia, and increased cardiac wall thickness (3).

The previous review found that one quarter of patients who received levothyroxine were inadvertently maintained on doses high enough to make TSH levels undetectable. Although the ultimate effect of long-term overdosing with levothyroxine is unknown, it could increase risk for osteoporosis, fractures, abnormal cardiac output, or ventricular hypertrophy (31).

Five trials published since the previous review assessed the harms of treatment of hypothyroidism with levothyroxine and generally reported no indication of harms or no or minimal (n = 0 to 2) withdrawals from treatment due to adverse effects. However, harms were poorly assessed and reported, and the studies were not designed or powered to evaluate long-term or serious harms or harms related to overtreatment (1, 2).

In the case of asymptomatic hyperthyroidism, overtreatment may be of even greater concern given that one treatment option is ablation of the thyroid gland followed by thyroid replacement therapy. Patients who are overdiagnosed and overtreated could develop iatrogenic hypothyroidism and become dependent on lifelong thyroid hormone therapy. Overtreatment is also of concern because it can introduce opportunity costs; clinicians and patients may spend time focused on certain areas of health at the expense of other conditions or care needs that are of higher priority for the patient's overall well-being.

Estimate of Magnitude of Net Benefit

The USPSTF found no direct evidence on the benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults and therefore considered the indirect evidence on screening accuracy, benefits of early treatment, and harms. There is adequate evidence that the serum TSH test can identify abnormal levels of the hormone; however, substantial debate surrounds what constitutes an abnormal TSH level. Thresholds vary for different populations, such as older adults. Although a single fair-quality observational study found a possible association between treatment of subclinical hypothyroidism with levothyroxine and reduced risk for cardiac events, there is no evidence from randomized trials to prove that early treatment of thyroid dysfunction leads to clinically important benefits. The harms of screening for and treatment of thyroid dysfunction have been poorly studied. However, screening and treatment have real potential harms, and these harms are probably common. Overall, the USPSTF was unable to estimate the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.

Response to Public Comment

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from 28 October to 24 November 2014. In response to the comments received, the USPSTF clarified some of the terminology used in this statement (for example, "reference interval" instead of "reference range" and "Hashimoto thyroiditis" instead of "Hashitoxicosis") and added a reference for initiation and use of thyroid hormone therapy in older adults. The USPSTF also clarified that the systematic evidence review searched for studies on the treatment of thyroid dysfunction that used placebo or no treatment as the comparator.

Some comments noted that it would be unacceptable for clinicians to allow patients with "overt" thyroid dysfunction to participate in a trial with a placebo group (and that this therefore explains the lack of current evidence on the topic), but the USPSTF disagrees with this position. There are no high-quality data showing that treatment of "overt" thyroid dysfunction in asymptomatic persons affects important health outcomes, such as cardiovascular- and cancer-related morbidity and mortality, fractures, or quality of life and functional status. Given the widespread practice of screening for and treatment of thyroid dysfunction in asymptomatic persons and the absence of high-quality evidence on the effectiveness of this approach, a pressing research need for this field is well-designed randomized treatment trials of subclinical and "overt" thyroid dysfunction versus watchful waiting (with the important caveat that patients would be provided therapy if they became notably symptomatic).

It is clear from the comments received that the current terminology used to describe disorders of the thyroid generates substantial confusion, not only among the public but among clinicians and researchers as well. The terms "thyroid dysfunction" and "thyroid disease" are frequently used interchangeably to encompass all forms of hypothyroidism and hyperthyroidism, regardless of whether the patient has clinical signs or adverse consequences of illness. The term "overt thyroid dysfunction" is particularly misleading given that an "overt" (meaning "done or shown openly; plainly or readily apparent" [43]) condition is usually associated with obvious signs and symptoms of disease. In the case of thyroid dysfunction, "overt" dysfunction has been defined by biochemical parameters (serum TSH and T4 levels) that may not be associated with clinically evident symptoms or adverse health outcomes. The USPSTF believes that alternative terms are needed to more accurately describe thyroid dysfunction—reserving the term "overt thyroid disease" to describe symptomatic patients who also have persistently abnormal serum TSH and T4 levels.

UPDATE OF PREVIOUS USPSTF RECOMMENDATION

This recommendation replaces the 2004 USPSTF recommendation on screening for thyroid disease. In this update, the USPSTF has restricted its definition of thyroid disease to symptomatic "overt" hypothyroidism and hyperthyroidism (that is, persistently abnormal serum TSH and T4 levels and clearly associated clinical signs and symptoms that cannot be better explained by another condition). There is a broad spectrum of thyroid disorders, and the USPSTF recognizes that screening with the serum TSH test can detect changes along any point in this spectrum. Thus, the USPSTF changed

the scope of its recommendation statement to screening for thyroid dysfunction to emphasize that screening can detect biochemical abnormalities as well as potentially clinically important disease. Despite this change, the USPSTF's ultimate assessment is the same as in the previous recommendation; the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults (I statement).

Recommendations of Others

The American Thyroid Association and the American Association of Clinical Endocrinologists recommend considering screening for hypothyroidism in patients older than 60 years, as well as "aggressive case finding" (but not universal screening) in persons who are at increased risk for hypothyroidism and in women who are planning pregnancy (15). In 2006, three British professional associations (the Association for Clinical Biochemistry, the British Thyroid Association, and the British Thyroid Foundation) jointly recommended against routine screening for thyroid dysfunction in a healthy adult population, although the panel favors aggressive case finding in women with nonspecific symptoms (44). The American Academy of Family Physicians has endorsed the USPSTF recommendation (45).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

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Appendix: U.S. Preventive Services Task Force

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Michael L. LeFevre, MD, MSPH, *Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Kirsten Bibbins-Domingo, PhD, MD, MAS, *Co-Vice Chair* (University of California, San Francisco, San Francisco, California); Linda Ciofu Baumann, PhD, RN, APRN (University of Wisconsin, Madison, Wisconsin); Karina W. Davidson, PhD, MASc (Columbia University, New York, New York); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Matthew Gillman, MD, SM (Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Alex R. Kemper, MD, MPH, MS (Duke University, Durham, North Carolina); Alexander H. Krist, MD, MPH (Fairfax Family Practice, Fairfax, and Virginia Commonwealth University, Richmond, Virginia); Ann E. Kurth, PhD, RN, MSN, MPH (New York University, New York, New York); Douglas K. Owens, MD, MS (Veterans Affairs Palo Alto Health Care System, Palo Alto, and Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); Maureen G. Phipps, MD, MPH (Brown University, Providence, Rhode Island); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/Page/Name/our-members.

Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.