

Recommendation on screening adults for asymptomatic thyroid dysfunction in primary care

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This guideline from the Canadian Task Force on Preventive Health Care focuses on screening for thyroid dysfunction among asymptomatic nonpregnant adults in primary care beyond usual care and vigilance for signs and symptoms of thyroid dysfunction. Thyroid dysfunction is diagnosed based on abnormal levels of serum thyroid-stimulating hormone (TSH) and can be characterized as either hypo- or hyperthyroidism. Hypothyroidism results from impaired thyroid hormone production (i.e., thyroxine [T₄] or triiodothyronine [T₃]), leading to elevated levels of TSH. Hypothyroidism is often caused by autoimmune disorders (e.g., Hashimoto thyroiditis) or occurs as a sequela of hyperthyroidism treatment, which can render the thyroid gland nonfunctional.¹ Hyperthyroidism results from an overproduction of thyroid hormone, leading to the suppression of TSH.¹ Causes of hyperthyroidism include Graves disease, toxic multinodular goitre and toxic adenoma.²

Signs and symptoms of thyroid dysfunction are variable between patients and often nonspecific. For hypothyroidism, symptoms may include tiredness, sensitivity to cold, dry skin, hair loss, weight gain and slowed movements and thoughts.^{1,3-6} For hyperthyroidism, symptoms may include sinus tachycardia, atrial fibrillation, hyperactivity or irritability, intolerance to heat, tremor and weight loss.^{1,2,7} Some people with thyroid dysfunction are asymptomatic.⁸

If left untreated, hypothyroidism may increase the risk of cardiac dysfunction, hypertension, dyslipidemia, cognitive impairment and, in rare cases, myxedema coma.^{3,9} Untreated hyperthyroidism may increase the risk of cardiac conditions (e.g., atrial fibrillation, heart failure) or bone fractures, and could lead to thyroid storm, an uncommon, life-threatening condition associated with tachycardia, extreme fatigue, fever and nausea.^{2,10}

KEY POINTS

- The Canadian Task Force on Preventive Health Care strongly recommends against screening for thyroid dysfunction in asymptomatic nonpregnant adults.
- Screening for thyroid dysfunction in asymptomatic nonpregnant adults is not likely to confer clinical benefit, but could lead to unnecessary treatment for some patients and consume resources.
- Treating asymptomatic adults for screen-detected hypothyroidism may result in little to no difference in clinical outcomes.
- Clinicians should remain alert to signs and symptoms suggestive of thyroid dysfunction and investigate accordingly.

Minor variations in thyroid function as measured by abnormal levels of TSH are often self-limiting. Observational studies have reported that levels of TSH appear to revert to normal without treatment in 37%–62% of patients with initially elevated levels and 51% with initially low levels, particularly for milder cases of thyroid dysfunction (mean follow-up 32–60 mo).^{11,12}

Screening is intended to detect thyroid dysfunction in asymptomatic patients in order to prevent adverse consequences of untreated thyroid dysfunction.¹³ Screening is done by performing a blood test for TSH. Abnormal levels of TSH are followed up with additional diagnostic testing that often includes blood tests to measure thyroid hormone levels or other tests (e.g., ultrasound) as warranted. An estimated 10% of Canadians aged 45 years or older report that they have been diagnosed with thyroid dysfunction, and prevalence is higher in women (16%) than in men (4%).¹⁴ Prevalence has also been reported to be higher in adults older than 85 years (16%),¹⁴

although evidence suggests that concentrations of TSH increase with age even in the absence of obvious thyroid dysfunction, and that age-specific reference intervals for TSH should be used to avoid unnecessary treatment.¹⁵ In addition to female sex and older age, risk factors for thyroid dysfunction include medications that might affect thyroid hormone levels (e.g., lithium, amiodarone); other autoimmune diseases (e.g., type 1 diabetes mellitus, Addison disease); previous surgery or radiation therapy on the thyroid gland, head or neck area; and a family history of thyroid disease.^{1,5,9,16}

Thyroid hormone replacement medication is used to treat hypothyroidism,¹ whereas treatments for hyperthyroidism include antithyroid medication, radioiodine ablation or thyroid gland surgery.⁹

To make its recommendation, the task force considered evidence from systematic reviews on the benefits and harms of screening for asymptomatic thyroid dysfunction, treatment of asymptomatic thyroid dysfunction, and patient values and preferences.

Scope

This recommendation provides guidance to clinicians, policy-makers and patients on screening for thyroid dysfunction among asymptomatic nonpregnant adults. These recommendations do not apply to patients with previously diagnosed thyroid disease or thyroid surgery; exposure to medications known to affect thyroid function; exposure to thyroid radioiodine therapy, or radiotherapy to the head or neck area; or pituitary or hypothalamic diseases.

Methods

The task force is an independent panel of clinicians and methodologists that makes recommendations on primary and secondary prevention in primary care (www.canadiantaskforce.ca). This recommendation was developed by a working group of 4 task force members (R.B., J.D., D.R. and B.T.) with scientific support from Public Health Agency of Canada staff.

The recommendation is based on systematic reviews¹⁷ on the effectiveness (i.e., benefits and harms) of screening for thyroid dysfunction in asymptomatic, nonpregnant adults; the effectiveness of treating screen-detected thyroid dysfunction in asymptomatic, nonpregnant adults; and patient values and preferences related to screening (see analytic framework, Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190395/-/DC2). The systematic reviews were based on a previous United States Preventive Services Task Force review¹⁸ with additional search terms included for patient values and preferences and all searches updated to July 25, 2018. We excluded studies if they recruited patients with clinically obvious hypothyroidism or hyperthyroidism (e.g., Graves disease), or patients who were recently admitted to hospital.

The protocol (PROSPERO: CRD42016033622), systematic reviews¹⁷ and draft guideline were externally peer reviewed. Two clinical experts engaged with Public Health Agency of Canada staff to address technical and clinical considerations. Clinical experts are external to the task force and did not participate in guideline

working group meetings or have input into, or vote on, task force recommendations.

The working group rated outcomes in accordance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.¹⁹ Clinical outcomes that were rated critical for assessment in the systematic reviews were mortality (all-cause or cardiovascular), cardiovascular events (fatal and nonfatal, atrial fibrillation), fractures, thyroid-specific quality of life, cognitive function and harms from treatment. Additional clinical outcomes rated as important included physical, mental, or general well-being; fatigue or tiredness; and harms from screening (e.g., psychological effects, harms of workup, overdiagnosis and overtreatment). Intermediate outcomes (i.e., physiologic measures related to the screening intervention but not clinical outcomes in and of themselves²⁰) rated as important were blood pressure, bone mineral density, cholesterol and weight change.¹⁷

We also used the GRADE approach to determine the certainty of the evidence and strength of the recommendation (Box 1).¹⁹ Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190395/-/DC2) provides the evidence-to-decision framework that the task force used to assess the balance between benefits and harms, patient values, resource use, feasibility, acceptability and equity in order to develop the recommendation. The entire task force reviewed and approved the recommendation.

The Knowledge Translation Program at St. Michael's Hospital (Toronto) developed the knowledge translation tool accompanying this guideline. The tool can be found on the task force website (www.canadiantaskforce.ca). The tool was informed by feedback from clinicians.

Management of competing interests

Funding for the task force is provided by the Public Health Agency of Canada. The task force does not consider the views of the funding body in developing its recommendations. All task force members and clinical experts are required to disclose financial and nonfinancial conflicts of interest, which are made available publicly on the task force website. All but 1 task force member declared no conflicts of interest for this guideline: R.G. declared a conflict related to the 2016 creation of non-industry-funded educational material on managing thyroid disease; he was not a member of the working group and chose not to vote on the guideline. Clinical experts are required to disclose any conflicts of interest at the outset of their participation, and annually thereafter. The 2 clinical experts (B.C. and A.Z.) involved with this guideline declared that they had no conflicts of interest for this guideline. Clinical experts did not participate in discussions on recommendations and did not vote on recommendations.

Recommendation

We recommend against screening asymptomatic nonpregnant adults aged 18 years and older for thyroid dysfunction in primary care settings (strong recommendation, low-certainty evidence).

A summary of the recommendation is available in Box 2.

Box 1: Grading of recommendations

Recommendations are graded according to the Grading of Recommendations Assessment, Development and Evaluation system (GRADE).¹⁹ Whether a recommendation is strong or conditional* will depend on considerations such as certainty in estimated effects of an intervention, including magnitude, as well as estimates of how patients value and prioritize outcomes, variability of these estimates and wise use of resources.

Strong recommendations

Strong recommendations are those for which the Canadian Task Force for Preventive Health Care is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most people will be best served by the recommended course of action.

Strong recommendations are typically based on high-certainty evidence (i.e., high confidence in the estimate of the effect of an intervention). Strong recommendations may recommend in favour of an intervention (when there is high confidence of net benefit) or against an intervention (when there is high confidence of net harm). However, there are circumstances in which a strong recommendation may be considered based on low- or very low-certainty evidence or when there is absence of evidence or low-certainty evidence of benefit.²¹

When there is an absence of evidence to provide confidence that there is benefit from implementing a new prevention service or when a conclusion of possible benefit requires a high level of speculation on linkages of uncertain evidence, but there is high certainty that some patients would be harmed or scarce health care resources expended, the task force may make a strong recommendation against service implementation. This is consistent with the GRADE approach, in which strong recommendations are sometimes made with low-certainty evidence combined with high certainty of harm or resource implications, and with the value that the task force places on using scarce primary care resources wisely.

Conditional recommendations

Conditional recommendations are those for which the desirable effects probably outweigh the undesirable effects (conditional recommendation in favour of an intervention) or undesirable effects probably outweigh the desirable effects (conditional recommendation against an intervention) but appreciable uncertainty exists. Conditional recommendations are made when the certainty of evidence is lower, when the margin between desirable and undesirable consequences is small and the balance depends on patient values and preferences, or when there is high variability in the values and preferences of patients. Conditional recommendations may also be applied when the balance of cost and benefits is ambiguous, key stakeholders differ about the acceptability or feasibility of the implementation, or the effects on health equity are unclear.

In certain cases where a conditional recommendation for an intervention is made, clinicians are encouraged to engage in shared decision-making, to recognize that different choices will be appropriate for individual patients, and to help each person arrive at a management decision consistent with their values and preferences. Clinicians should recognize that different choices will be appropriate for different patients and that decisions must be consistent with each patient's values and preferences.

Knowledge translation tools are available on the task force website (www.canadiantaskforce.ca) to facilitate decisions that are evidence informed and aligned with an individual's priorities.

Evidence is graded as high-, moderate-, low- or very low-certainty, based on how likely further research is to change the task force's confidence in the estimate of effect.

*The task force previously used the term "weak recommendation," but has replaced this with the term "conditional recommendation," to improve understanding and facilitate implementation of guidance, based on feedback from clinician knowledge users. One reason for this change was the value that the task force places on shared decision-making, together with a need to clarify better when implementation of a recommendation depends on circumstances such as patient values, resource availability or other contextual considerations. Conditional recommendations based on patient values and preferences require clinicians to recognize that different choices will be appropriate for different patients and those decisions must be consistent with each patient's values and preferences.

Screening for thyroid dysfunction

The systematic reviews conducted to support the guideline did not find any eligible studies that directly assessed the benefits or harms of screening for thyroid dysfunction compared with not screening in asymptomatic nonpregnant adults.¹⁷

Treatment of screen-detected thyroid dysfunction

Because the task force found no studies comparing screening to no screening for thyroid dysfunction, we considered indirect evidence on the effectiveness of the treatment of asymptomatic thyroid dysfunction.¹⁷ The systematic review on treatment included studies that screened for thyroid dysfunction and followed only those participants who screened positive. In total, there were 22 eligible studies, including 19 randomized controlled trials (RCTs) and 3 cohort studies. In 14 RCTs (16 publications), nonpregnant adults who screened positive for hypothyroidism were randomized to receive either levothyroxine treatment or placebo,²²⁻³⁷ and 5 RCTs³⁸⁻⁴² and 3 cohort studies⁴³⁻⁴⁵ compared levothyroxine treatment to no treatment. The length of follow-up ranged from 3 to 36 months for the RCTs and between 5.0 and 7.6 years (median)

Box 2: Summary of recommendation for clinicians, policy-makers and patients

We recommend against screening asymptomatic nonpregnant adults aged 18 years and older for thyroid dysfunction in primary care settings (strong recommendation, low-certainty evidence).*

This recommendation does not apply to adults who have the following risk factors for thyroid dysfunction:

- Individuals who have had a previously diagnosed thyroid disease or surgery;
- Individuals receiving thyroid medications or medications that may affect thyroid function (i.e., lithium, amiodarone);
- Individuals with previous or ongoing exposure to thyroid radioiodine therapy or head and neck radiotherapy; or
- Individuals with pituitary or hypothalamic diseases.

*Screening refers to measuring levels of thyroid-stimulating hormone (TSH) in patients with no apparent signs or symptoms of thyroid dysfunction. Screening differs from measuring levels of TSH among patients who are experiencing signs and symptoms (e.g., fatigue, weight gain, menstrual irregularities, goitre) or are at risk for thyroid dysfunction due to secondary causes (e.g., pituitary or hypothalamic diseases) to investigate possible thyroid dysfunction.

for the cohort studies. Patients were recruited via population-based screening in 3 of the RCTs,^{24,25,32,42} and in the remainder of the trials and cohort studies, participants were from primary care as well as specialized and nonspecified outpatient clinics. Studies took place in Europe, the Middle East, South America and Asia. We did not identify any studies reporting on treatment for screen-detected hyperthyroidism. We synthesized data narratively because of the clinical and methodological variability among the included studies, similar to the approach used in the United States Preventive Services Task Force review.¹⁸

Clinical outcomes

Mortality (all-cause and cardiovascular) and cardiovascular events

One RCT ($n = 737$)³⁴ assessed the effect of treatment in participants aged 65 years and older on mortality (all-cause or cardiovascular; low- and very low-certainty evidence, respectively), and cardiovascular events (fatal and nonfatal, atrial fibrillation; low-certainty evidence) and reported no statistically significant differences between treatment and placebo (Appendix 3, Supplemental Table 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.190395/-/DC2). Very low-certainty evidence on adults aged 40–70 years and younger than 65 years from 2 cohort studies was used to inform outcomes for younger adults.^{43,45} These 2 studies^{43,45} reported a minimal reduction in all-cause mortality and equivocal results for cardiovascular outcomes (Appendix 3, Supplemental Table 1). Two cohort studies^{43,44} reported no statistically significant differences in all-cause mortality or cardiovascular events for women or men between those treated and not treated with levothyroxine for screen-detected hypothyroidism.

Cognitive function

Low-certainty evidence from 3 RCTs ($n = 759$)^{25,32,34} reported on 22 cognitive function outcome analyses, stemming from 20 unique tests (i.e., 2 tests were included in 2 separate RCTs). Only 2 tests (the Composite Cognitive Score and the Speed and Capacity of Language Processing Test) showed statistically significant treatment effects over placebo (Appendix 3, Supplemental Table 1).

Fractures and quality of life measures

The task force found no statistically significant differences between treatment and no treatment or placebo for any of the remaining clinical outcomes: fractures (low-certainty evidence from 1 RCT),³⁴ thyroid-specific quality of life (moderate-certainty evidence from 1 RCT),³⁴ mental well-being (moderate-certainty evidence from 4 RCTs),^{25,31–33} physical well-being (moderate-certainty evidence from 1 RCT),³⁴ general well-being (moderate-certainty evidence from 3 RCTs),^{25,33,34} or fatigue or tiredness (moderate-certainty evidence from 1 RCT)³⁴ (Appendix 3, Supplemental Table 1).

Intermediate outcomes

Blood pressure

There were no statistically significant differences for blood pressure in 8 studies that included that outcome (moderate-certainty evidence).^{26,28–30,34,37,41,42}

Bone mineral density

We found no studies that addressed bone mineral density.

Weight change

Ten RCTs^{22–24,26,28–30,34,37,39} found no differences in weight change, 1 RCT⁴² did not report the difference between groups, and 1 RCT³⁶ reported a mean increase in body mass index measurement among the treatment group (moderate-certainty evidence).

Cholesterol

Cholesterol outcomes were reported separately as total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides (moderate-certainty evidence). Six RCTs^{22,24,30,35,38,39} reported no differences in total cholesterol levels, and 4 RCTs^{26,27,29,42} reported a decrease in total cholesterol levels among those treated compared with the control group. Nine RCTs^{22,24,26,27,29,30,35,38,39} reported no differences in high-density lipoprotein and 1 RCT⁴² did not report the difference between groups. Eight RCTs^{22,24,26,27,30,35,38,39} reported no differences in low-density lipoprotein levels, 1 RCT⁴² did not report the difference between groups, and 1 RCT²⁹ reported that treatment for subclinical hypothyroidism led to a mean decrease in low-density lipoprotein levels. Nine RCTs^{22,24,26,27,29,30,35,38,42} reported no differences in triglyceride levels and 1 RCT³⁹ reported a decrease in mean triglyceride levels in the treatment group.

Although there were few statistically significant reductions in lipid markers, the point estimate mean differences in levels of total cholesterol, low-density lipoprotein and triglycerides suggest some improvement with treatment in 23 of 27 analyses¹⁶ (point estimate ranges for total cholesterol: -1.07 to 0.00 mmol/L; low-density lipoprotein: -1.23 to 0.11 mmol/L; triglycerides: -1.94 to 0.12 mmol/L).

Harms of treatment

Low-certainty evidence from 7 RCTs^{26,30,32,34,35,40,42} reported no statistically significant differences in adverse outcomes (e.g., adverse events, symptoms, adverse effects) of treatment between groups, treated and not treated, for screen-detected hypothyroidism. Furthermore, the proportion of withdrawals owing to adverse outcomes was similar between the control (0%–14.3%) and intervention groups (0%–9.6%).^{26,32,35,42}

Patient values and preferences

The systematic reviews identified no studies that reported on patients' values and preferences related to screening for thyroid dysfunction.¹⁷

Resource use

The total resource requirements of screening asymptomatic adults for thyroid dysfunction were not evaluated via systematic review, but would include the unit costs of laboratory tests for TSH (about \$5–14 each)^{46–48} and additional financial costs borne by patients and the provinces and territories related to diagnostic tests, provider fees, treatment, monitoring and lifelong medical follow-up for cases of identified thyroid dysfunction. The task force did not assess the cost-effectiveness of screening for thyroid dysfunction. In the judgment of the task force, given the

lack of evidence of clinical effectiveness, financial costs of screening asymptomatic adults would represent an undesirable consequence for the health care system.

Feasibility, acceptability and equity

No formal programs exist in Canada to screen for thyroid dysfunction among adults, although many clinicians routinely order TSH tests for asymptomatic patients. One study from Toronto found that 71% of 135 243 patients (aged 20 yr or older) without known thyroid disease and not on thyroid medication had their levels of TSH tested at least once over a 2-year period, and 92% of these tests came back normal.⁴⁹ A recommendation against screening for thyroid dysfunction may represent a change in current practice for some clinicians; in the judgment of the task force, this would reduce unnecessary tests and burden on patients. Given the lack of evidence of benefit, in the judgment of the task force, this recommendation is feasible and acceptable to most clinicians, policy-makers and patients and would neither increase nor decrease equity.

Rationale

The task force found no studies that directly evaluated the benefits and harms of screening for thyroid dysfunction among asymptomatic nonpregnant adults. We identified no studies that reported on treatment for screen-detected hyperthyroidism. On balance, evidence on the treatment of screen-detected hypothyroidism did not indicate improvement for the clinical outcomes examined. The task force placed greater value on low-certainty evidence from 1 RCT indicating no effect on all-cause mortality than on very low-certainty evidence from 2 cohort studies, which showed a very small reduction in mortality among people aged 40–70 years and younger than 65 years, and 1 cohort study that showed no benefit.

The task force believes that asymptomatic adults would be unlikely to choose to be screened for thyroid dysfunction if they were aware of the lack of evidence of clinical effectiveness beyond usual care and vigilance; the potential for overdiagnosis, meaning the diagnosis of transient thyroid dysfunction or dysfunction that would never manifest in symptoms; the need for follow-up testing and long-term monitoring; and increased treatment burden.⁵⁰ Therefore, the task force recommends against screening asymptomatic nonpregnant adults for thyroid dysfunction given the lack of demonstrated benefit on critical and important clinical outcomes, along with the financial costs to patients and the health care system.

Implementation

This recommendation applies only to screening asymptomatic nonpregnant adults for thyroid dysfunction. Clinicians should be aware of symptoms, signs and conditions associated with thyroid dysfunction so patients with these can be tested, particularly symptomatic postmenopausal women (given the higher prevalence of hypothyroidism in that population),⁹ and those with atrial fibrillation, when hyperthyroidism may be suspected. We did not find evidence on the effectiveness of screening for thyroid dysfunction specifically among patients with other chronic conditions, but there may be different reasons to test their levels of TSH to optimize management of their primary condition. These recommendations do not apply to patients with previously diagnosed thyroid disease or thyroid surgery; exposure to medications known to affect thyroid function (e.g., lithium, amiodarone); exposure to thyroid radioiodine therapy, or radiotherapy to the head or neck area; or pituitary or hypothalamic diseases.

Monitoring and evaluation

Indicators of the uptake of this recommendation against screening asymptomatic nonpregnant adults for thyroid dysfunction could be clinician awareness of this recommendation and reduction in regular tests for TSH among asymptomatic patients presenting for periodic health assessments. The task force will monitor evidence related to this guideline and will update the recommendation if new evidence becomes available that could influence its direction or strength.

Other guidelines

Variation currently exists among guidelines from other organizations (Table 1). The British Columbia Ministry of Health⁵¹ and Toward Optimized Practice⁵² from Alberta recommend against testing for TSH in asymptomatic patients. The United States Preventive Services Task Force did not provide a recommendation either for or against screening for thyroid dysfunction because of its determination that there was insufficient evidence to assess the balance of benefits and harms.⁵ A joint recommendation by the American Thyroid Association and American Association of Clinical Endocrinologists suggests that screening for hypothyroidism should be considered in patients older than 60 years.⁵³

Table 1: National and international recommendations on screening for thyroid dysfunction

Guideline group	Recommendation
British Columbia Ministry of Health ⁵¹	Routine thyroid function testing is not recommended in asymptomatic adults. However, testing may be indicated when nonspecific signs and symptoms are present in patients at risk for thyroid disease.
Toward Optimized Practice ⁵²	Do not test patients who are asymptomatic, seemingly healthy, having a periodic exam.
United States Preventive Services Task Force ⁵	The United States Preventive Services Task Force concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.
American Thyroid Association and American Association of Clinical Endocrinologists ⁵³	Screening for hypothyroidism should be considered in patients older than age 60 years. This recommendation was downgraded because there is strong evidence that hypothyroidism is common in this group but insufficient evidence of benefit or cost-effectiveness.

Gaps in knowledge

Despite the frequency of testing for TSH in Canada, there are no trials that directly assess the benefits and harms of screening for thyroid dysfunction versus not screening in asymptomatic nonpregnant adults. In addition, the task force found no evidence on the effectiveness of specifically screening patients with other concomitant conditions (e.g., cardiovascular diseases, type 1 diabetes mellitus or other autoimmune diseases).

Conclusion

The task force found no trial evidence on screening versus not screening asymptomatic nonpregnant adults for thyroid dysfunction. Low-certainty evidence suggests that treatment of screen-detected hypothyroidism among nonpregnant adults is unlikely to provide meaningful improvement on clinical outcomes reviewed by the task force. Screening will also result in overuse of resources without a demonstrated benefit. Therefore, the task force strongly recommends against screening for thyroid dysfunction in asymptomatic nonpregnant adults.

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