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RAPID RECOMMENDATIONS

Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline

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ABSTRACT

Clinical question What are the benefits and harms of thyroid hormones for adults with subclinical hypothyroidism (SCH)? This guideline was triggered by a recent systematic review of randomised controlled trials, which could alter practice.

Current practice Current guidelines tend to recommend thyroid hormones for adults with thyroid stimulating hormone (TSH) levels >10 mIU/L and for people with lower TSH values who are young, symptomatic, or have specific indications for prescribing.

Recommendation The guideline panel issues a strong recommendation against thyroid hormones in adults with SCH (elevated TSH levels and normal free T4 (thyroxine) levels). It does not apply to women who are trying to become pregnant or patients with TSH >20 mIU/L. It may not apply to patients with severe symptoms or young adults (such as those ≤30 years old).

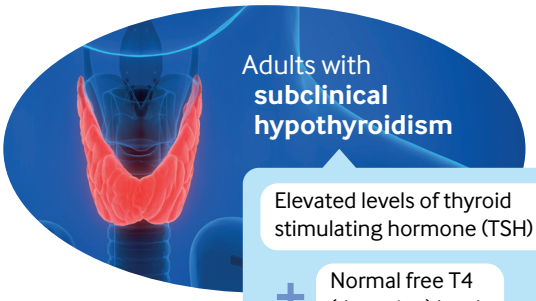
How this guideline was created A guideline panel including patients, clinicians, and methodologists produced this recommendation in adherence with standards for trustworthy guidelines using the GRADE approach.

The evidence The systematic review included 21 trials with 2192 participants. For adults with SCH, thyroid hormones consistently demonstrate no clinically relevant benefits for quality of life or thyroid related symptoms, including depressive symptoms, fatigue, and body mass index (moderate to high quality evidence). Thyroid hormones may have little or no effect on cardiovascular events or mortality (low quality evidence), but harms were measured in only one trial with few events at two years' follow-up.

Understanding the recommendation The panel concluded that almost all adults with SCH would not benefit from treatment with thyroid hormones. Other factors in the strong recommendation include the burden of lifelong management and uncertainty on potential harms. Instead, clinicians should monitor the progression or resolution of the thyroid dysfunction in these adults. Recommendations are made actionable for clinicians and their patients through visual overviews. These provide the relative and absolute benefits and harms of thyroid hormones in multilayered evidence summaries and decision aids available in MAGIC (https://app.magicapp.org/) to support shared decisions and adaptation of this guideline.

Visual summary of recommendation

Population



Adults with **subclinical hypothyroidism**

Elevated levels of thyroid stimulating hormone (TSH)

\+ Normal free T4 (thyroxine) levels

Including:

- ✔ Patients with no symptoms (diagnosed after screening)
- ✔ Patients with non-specific symptoms

May not apply to:

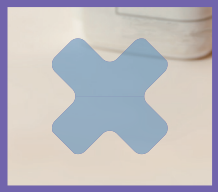
- ? Patients with severe symptoms
- ? Young adults (such as <30 years)

Does not apply to:

- ✖ Women who are or trying to become pregnant
- ✖ Patients with TSH above 20 mIU/L

Interventions compared

No thyroid hormones



or

Thyroid hormones

Levothyroxine

Recommendation

Strong | Weak | Weak | Strong

We recommend against thyroid hormone therapy for patients with subclinical hypothyroidism

Key practical issues

No thyroid hormones	Thyroid hormones
Regular visits and blood samples to monitor progression or resolution	Long-term regular visits and blood samples to monitor hormone levels
	Daily oral medication, normally tablets, often long-term treatment
	Overdosage can lead to hyperthyroidism symptoms
	Should be taken 4 hours apart from any products containing calcium or iron

TSH levels and symptoms

TSH levels may vary with stress, transient disease or with age. Elevated levels thus often revert to normal without treatment

There is no clear evidence on how to reliably attribute symptoms to subclinical hypothyroidism

Values and preferences

The panel expects little variability in how patients weigh the lack of benefit against the possible harms

Potential harms, and in particular risk of dying, may be valued differently by patients depending on their age, quality of life and comorbidities

Comparison of benefits and harms

For the elderly - about 65 years and older

Includes all the evidence, including from the largest TRUST trial conducted among an elderly population with comorbidities (see Figure 2)

No thyroid hormones	No important difference	Thyroid hormones	Evidence quality
After 1 year			
	EQ-5D score: -0.59-1 (High better)		
General quality of life	0.85	No important difference 0.83	★★★★ High
	Mean score: 0-100 (Low better)		
Thyroid-related symptoms	16.7	No important difference 16.5	★★★★ High
Fatigue / tiredness	28.6	No important difference 29.0	★★★★ High
	Mean score: 0-21 (Low better)		
Depressive symptoms	3.3	No important difference 3.6	★★★★ High
After 1.5 years			
	Mean score: 0-infinity (High better)		
Cognitive function	27.1	No important difference 28.1	★★★★ High
After 2 years			
	Events per 1000 people		
Mortality*	14	No important difference 27	★★☆☆ Low
Cardiovascular events*	54	No important difference 48	★★☆☆ Low
	Mean score: 0-100 (Low better)		
Side effects	10.3	No important difference 10.9	★★★☆ Moderate

For younger people (such as 65 and younger)

The results of the systematic review were dominated by the large TRUST trial, conducted among the elderly. Therefore, the panel examined the evidence without this trial whenever possible. However, TRUST was the only study reporting on harms.

No thyroid hormones	No important difference	Thyroid hormones	Evidence quality
After 1 year			
	EQ-5D score: -0.59-1 (High better)		
General quality of life	0.85	No important difference 0.82	★★★☆ Moderate
	Mean score: 0-100 (Low better)		
Thyroid-related symptoms	16.7	No important difference 16.4	★★★★ High
Fatigue / tiredness	28.6	No important difference 29.0	★★★☆ Moderate
	Mean score: 0-21 (Low better)		
Depressive symptoms	3.3	No important difference 3.6	★★★★ High
After 1.5 years			
	Mean score: 0-infinity (High better)		
Cognitive function	27.1	No important difference 29.7	★★☆☆ Low
After 2 years			
	Events per 1000 people		
Mortality	14	No important difference 27	★☆☆☆ Very low
Cardiovascular events	54	No important difference 48	★☆☆☆ Very low
	Mean score: 0-100 (Low better)		
Side effects	10.3	No important difference 10.9	★★☆☆ Low

* Only a few deaths were observed, in a single trial. For mortality, we are 95% confident that the difference is between 5 fewer to 62 more deaths per 1000 patients taking levothyroxine. For cardiovascular events, we are 95% confident that the difference is between 28 fewer to 62 more events per 1000 patients taking levothyroxine

Subclinical hypothyroidism (SCH) is a biochemical state. The thyroid stimulating hormone (TSH) level is elevated, but the free T4 (thyroxine) level is normal. Some people may experience symptoms linked to the abnormality. Other data have suggested links to overt hypothyroidism and adverse outcomes such as increased risk of coronary heart disease. So it is reasonable to ask whether treatment with thyroid hormones might help symptoms, prevent overt hypothyroidism, or avoid longer term heart problems. Box 1 extends and references this understanding.

This guideline was triggered by a systematic review,[15] summarising all studies on this question. It includes a large and new trial specifically in older people with TSH.[16] The results of the review might change practice. The main infographic provides an overview of the relative and absolute benefits and harms of treating SCH with thyroid hormones in standard GRADE format. Box 2 shows all of the articles and evidence linked in this Rapid Recommendation package.

Current practice

When to test for SCH

Historically, US guidelines recommended five-yearly screening of asymptomatic adults aged 35 years and older to identify thyroid dysfunction,[17] but it is uncertain if such screening has any clinical benefits.[18]

In clinical practice, thyroid function can be checked as part of routine screening or for diagnostic purposes in those with possible hypothyroidism based on physical or mental health signs and symptoms. In the UK about 25% of adults have thyroid function tests every year.[19] A recent overview showed an increase in the use of thyroid function tests over time.[20]

Patients and clinicians (general practitioners, internists, and endocrinologists) are commonly faced with abnormal thyroid function tests consistent with SCH. All parties collaboratively need to decide if and how to act.

WHAT YOU NEED TO KNOW

- Thyroid hormones should not be routinely offered to adults with SCH (strong recommendation according to GRADE).
- Thyroid hormones do not lead to important benefits for adults with SCH for quality of life or thyroid related symptoms including depressive symptoms and fatigue
- Taking a pill and attending periodic testing on an ongoing or lifelong basis is burdensome
- This recommendation builds on a recent systematic review and meta-analysis, which included the results of a new randomised controlled trial
- If implemented, this recommendation may substantially alter prescribing trends, which show that thyroid hormones are increasingly prescribed, most probably due to SCH

Box 1 | Overview of subclinical hypothyroidism (SCH)

What is SCH?

The definition of SCH varies. About 90% of all patients with SCH have TSH levels between 4 and 10 mIU/L.[1] TSH levels may increase with age,[2] and a slight increase of TSH may be normal for older people.

About 62% of TSH levels between 4 and 10 mIU/L normalise without intervention within five years.[3] There is biological variation in TSH levels. Levels may rise in response to stress and transient disease.[4] This biological variation in TSH values, means that one abnormal TSH level should be followed by a repeat blood test to confirm the diagnosis.[5]

According to the International Classification of Diseases (ICD), SCH does not have a separate code, but is typically labelled as "hypothyroidism, unspecified".

How common is it?

It affects 4-20% of the adult population.[6] This wide variation is due to poor consensus about the cut-off level for the diagnosis of SCH and regional variation between populations. It is more common in women, in older people, and those of white ethnicity.[6]

What are the symptoms?

Around 1 in 3 patients with SCH have no symptoms at all.[7] The type of symptoms people link to SCH include those of overt hypothyroidism: fatigue, muscle cramps, cold sensitivity, dry skin, voice changes, and constipation.[8] Other symptoms include poor memory, slowed thinking, weak muscles, puffy eyes, anxiety, and depression.[7-10] Many of these symptoms are not specific to hypothyroidism. Around 20-25% of people with normal TSH levels report one or two of these symptoms.[7] The relation between symptoms and biochemical TSH levels remains unclear.

What is the long term outlook?

The risk of progression to overt hypothyroidism ranges between 2% and 5% a year.[11] Presence of antibodies to thyroid peroxidase and, in particular, higher TSH levels increase this risk.[11-13]

Observational data suggest that SCH is associated with an increased risk of coronary heart disease, heart failure, and cardiovascular mortality, particularly in those with TSH levels >10 mIU/L.[1 14] Such associations were not found for most adults with TSH levels of 5-10 mIU/L.[1 14]

When to treat SCH

Guidelines generally recommend thyroid hormones for adults with TSH levels above 10 mIU/L. For those with lower TSH levels, most guidelines recommend treatment only when people are younger, symptomatic, or have other indications for prescribing (such as cardiovascular disease or antibodies to thyroid peroxidase). Table 1 summarises current guidance from various organisations.[5-22]

In many countries, the use of levothyroxine is increasing,[4] with a top ranking among the most prescribed drugs in the US in 2015.[23] Increasing treatment of SCH with thyroid hormone, and of levothyroxine in particular, is the most likely explanation for this increase. Research showed that prevalence of treated SCH has doubled from 1996 to 2006 and that people with TSH <10 mIU/L were prescribed levothyroxine 1.3 times more in 2009 than in 2001 in the UK.[19] This increased prevalence of treated SCH was confirmed in Norwegian population surveys, despite a stable prevalence of the condition itself.[24] Other evidence includes a study by Taylor[19] showing that a third of adults were offered treatment after a single TSH

Box 2 | Linked sources in this BMJ Rapid Recommendations cluster

- Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones for subclinical hypothyroidism: a clinical practice guideline. *BMJ* 2019;365:l2006
  - Summary of the results from the Rapid Recommendations process
- Feller M, Snel M, Moutzouri E, et al. Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. *JAMA* 2018;320:1349-59 doi:10.1001/jama.2018.13770
  - Review and meta-analysis of all available randomised trials that assessed thyroid hormones for subclinical hypothyroidism
- MAGICapp (https://app.magicapp.org/public/guideline/nyqWPn)
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

testing. Not all of these adults may actually have SCH as TSH levels fluctuate and may revert to normal without treatment.

Finally, some patients with symptoms may receive a trial of levothyroxine to evaluate improvement of symptoms, but in such an approach it is difficult to separate real from placebo effects. Once levothyroxine is started, most adults stay on the drug for several years.[19]

The evidence

The systematic review that triggered this guideline compared the effects of thyroid hormone treatment to that of no treatment or placebo in adults with SCH.[15] Figure 2 presents an overview of the characteristics of the randomised controlled trials (RCTs) and participants included in the review.

The systematic review includes 21 studies; the largest of which is the TRUST trial. This study examined the effects of thyroid hormone for SCH in over 700 elderly people aged 65-93 years.[16] Many participants had common comorbidities: 14% had ischaemic heart disease, 12% atrial fibrillation, 51% hypertension, 16% diabetes, and 12% had osteoporosis,[16] representative of a general elderly population. Because of its size, results of the TRUST trial dominate the results of the systematic review. For that reason, and to estimate the effect in younger patients, the guideline panel also looked at the results of the systematic review excluding the TRUST trial (see below).

The evidence applies to a broad range of adults with SCH as included in the systematic review. Some adults consulted physicians because of symptoms, others did not and were diagnosed after routine screening. The severity of symptoms, reported in seven studies (1263 adults) was mild to moderate. No studies included only patients with severe symptoms. For younger people (that is, those <30 years of age) and for patients with unusually high TSH levels (>20 mIU/L with normal T4 levels) the evidence remains more indirect, although this concerns only a small minority of patients.

Table 1 | Current guidance on thyroid hormone treatment for subclinical hypothyroidism

Organisation	Recommendation
National Institute for Health and Care Excellence (NICE) CKS guidelines, 2018[21]	• TSH >10 mIU/L: - Age <70 years, treat - Age ≥70 years, watch and wait • TSH 4-10 mIU/L: - Age <65 years with symptoms, consider trial - Age ≥65 years, watch and wait
European Thyroid Association (ETA), 2013[5]	• Age <70 years: - TSH >10 mIU/L, treat - TSH <10 mIU/L with symptoms, start trial - TSH <10 mIU/L without symptoms, observe • Age >70 years: - TSH <10 mIU/L, observe - TSH >10 mIU/L, consider treatment if clear symptoms or high cardiovascular risk
American Thyroid Association (ATA), 2012[8]	• TSH >10 mIU/L, consider treatment • TSH <10 mIU/L, consider treatment if symptoms suggestive of hypothyroidism, positive antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or risk factors for these diseases
UpToDate, 2018[22]	• TSH <7 mIU/L: - Age >65/70 years, observe - Age <65/70 years, treat if symptoms, observe without symptoms • TSH 7-10 mIU/L: - Age >65/70 years, treat if symptoms, observe without symptoms - Age <65 years, treat • TSH >10 mIU/L: treat

Box 3 | Exceptions to this *BMJ* Rapid Recommendation

This recommendation does not apply to

- Women who are trying to become pregnant. Such women were excluded from the studies. A systematic review of observational studies suggests that pregnant women with SCH may be at increased risk of adverse outcomes for both mother and baby.[25] Guidelines recommend levothyroxine for pregnant women depending on TSH level and presence of antibodies to thyroid peroxidase[26]
- Those with very high TSH levels (>20 mIU/L) and with normal T4 (thyroxine) levels. These findings could suggest overt hypothyroidism but would affect only a few patients

This recommendation may not apply to

- Those with severe symptoms, as few were included in the studies reviewed. However, there is no clear evidence on how to attribute symptoms to SCH reliably, even with severe symptoms
- Very young adults (such as ≤30 years old). Few of these patients were included in the studies, probably because SCH is so uncommon at younger ages
- Women at risk of unplanned pregnancy. Clinicians may consider offering thyroid hormones because pregnant women with SCH may be at increased risk of adverse outcomes for mother and baby[25]
- Patients who already take thyroid hormones. The evidence presented here looked at the effect of starting medication and only indirectly informs stopping it

Understanding the recommendation

Who does it apply to?

The recommendation applies to most adults, with SCH after at least two consecutive thyroid function tests, with or without mild to moderate symptoms, who are considering initiating thyroid hormone treatment. Box 3 shows situations where the guideline does not or may not apply.

Absolute benefits and harms

The panel made a strong recommendation against thyroid hormones for SCH, because there were no important benefits from treatment. In addition, we cannot rule out the possibility of harms.

Fig 2| Characteristics of participants and trials included in the systematic review of the effects of thyroid hormone treatment for subclinical hypothyroidism (SCH)

For older people (≥65 years)

There was high certainty that there is little to no difference in general quality of life (QoL), thyroid related symptoms, depressive symptoms, fatigue, cognitive function, muscle strength, and body mass index (BMI). The results are consistent across these outcomes, which strengthens our confidence that there really is a lack of benefit (see main infographic).

On top of the absence of benefit, the panel were concerned about a signal of harm in those treated. There were between five fewer and 62 more deaths per year in the treatment group (this is the 95% confidence interval). This interval includes the possibility of benefit (5 fewer deaths) as well as harm (62 more deaths). Additionally, these deaths were evaluated in only one trial with a two year follow-up.[16] For these reasons, the panel had low cer-

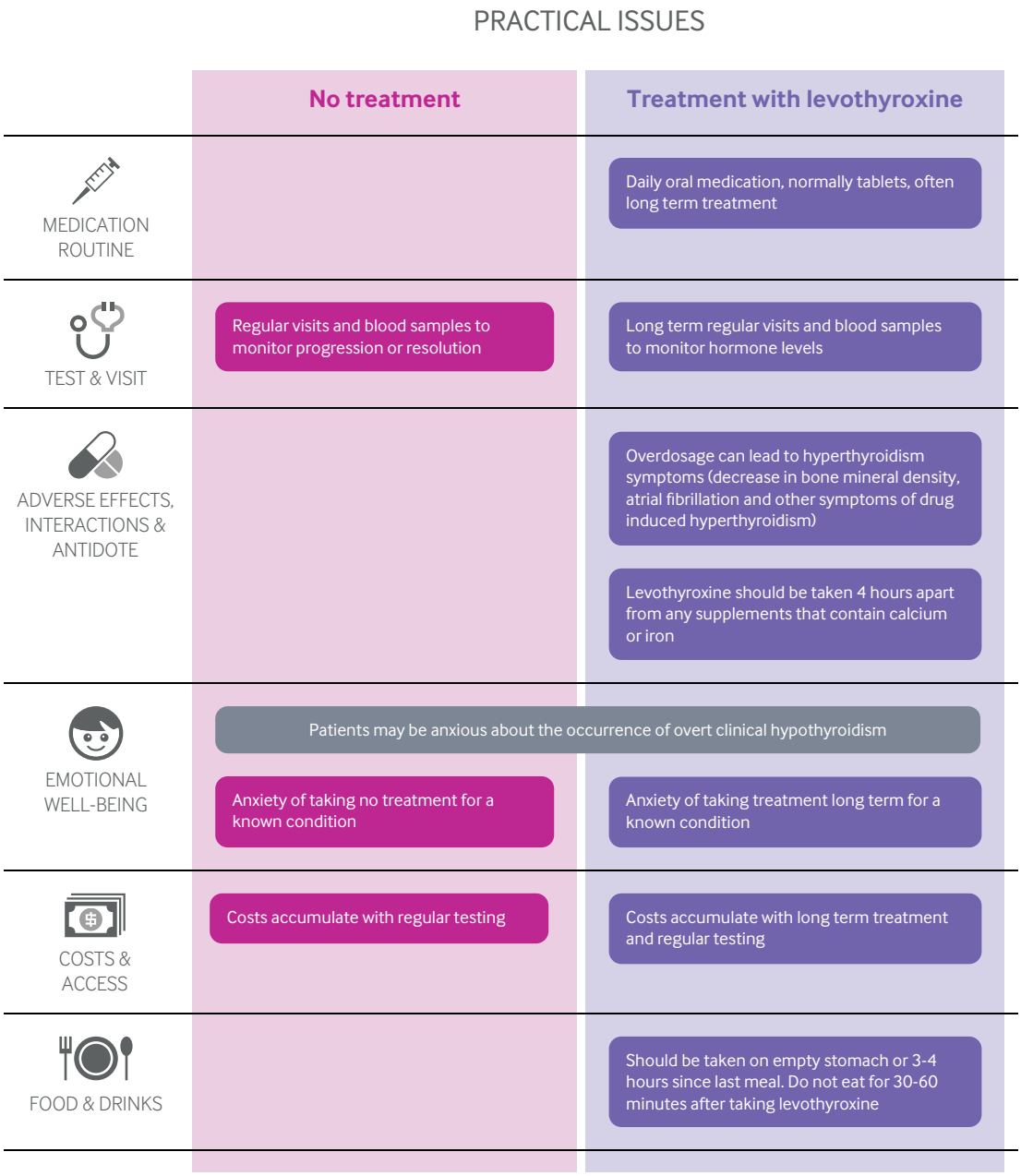


Fig 3| Practical issues about the use or non-use of thyroid hormones for subclinical hypothyroidism (SCH)

tainty in this estimate. None the less, the panel agreed that the possibility of harms contributes towards the strong recommendation.

For younger people (such as <65)

There was no important benefit shown in younger groups. However, the panel's certainty in the estimates was slightly lower. There is moderate to high certainty that such patients experience little or no benefit from thyroid hormone therapy for SCH.

The panel re-analysed the data without TRUST (the largest trial, performed exclusively in older people). The panel examined the age distribution of each study's participants. The results in younger people remain consistent: probably no evidence of any benefits, and possibly little or no difference in risk for harms. For some outcomes, uncertainty increased: for example, for fatigue, certainty was rated down to moderate due to indirectness (the evidence only comes from older adults). There is low certainty about the lack of effect on cognitive function, but the panel recognises that this outcome is less relevant to younger, healthier patients.

The same is true for harms. However, the panel was concerned about the burden of lifelong treatment and the limited evidence about possible long term harms of thyroid hormones (such as adverse cardiovascular effects). In addition, patients may experience a delay in diagnosis of another condition (such as mood disorder).

HOW WAS THIS RECOMMENDATION CREATED?

Our international panel included methodologists, general practitioners, internists, endocrinologists, and patient partners with subclinical hypothyroidism (SCH) (see appendix 1 on bmj.com for details of panel members). They decided on the scope of the recommendation and identified patient-important outcomes to inform the recommendations.

The panel met online to discuss the evidence and formulate a recommendation. No member had a financial conflict of interest; intellectual and professional conflicts were minimised and are transparently described (appendix 2 on bmj.com). The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,[27] including using the GRADE approach to critically appraise the evidence and create recommendations (appendix 3 on bmj.com).[28] The panel considered the benefits, harms, and burdens and other practical issues related to thyroid hormones in the context of SCH, as well as expected variations in patient values and preferences.[29] Within the GRADE approach, recommendations can be either strong or weak (also known as conditional), and for or against a specific course of action.[30]

Values and preferences

The panel expects little variability in how patients perceive the lack of benefit. Harms may be more important as SCH is not a fatal disease, and most people are reasonably well when they are diagnosed. In addition, potential harms, and in particular risk of dying, may be valued differently by patients depending on their quality of life and comorbidities.

Practical issues

Figure 3 outlines the key practical issues about the use or non-use of thyroid hormones. The option to treat is more burdensome for patients as treatment requires daily and possibly long term medication, follow-up, and blood tests. Both treating and not treating may result in anxiety.

Cost and resources

Although we did not take costs and resources into account beyond direct costs to patients (such as out-of-pocket costs), thyroid hormones cannot be cost effective given the lack of important benefit, potential for harm, and associated costs.

Uncertainty

Future research could explore whether there is an unidentified subgroup of patients who do benefit from treatment. No evidence of a potential subgroup or even a trend was observed in the current body of evidence, consistently across outcomes. Such research could consider whether there is more benefit in groups of people for whom there is less direct evidence and therefore more uncertainty, such as

- Younger people (about ≤30 years old)
- People with more severe symptoms.

There is uncertainty about potential harms, as these were studied only in the TRUST trial, which found only a few events after a follow-up of only two years. However, this uncertainty becomes important only when there is evidence of benefit.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Two people with lived experience of subclinical hypothyroidism were members of the panel and participated in the whole process. They identified and rated outcomes, and helped lead the discussion on values and preferences in a videoconference and in email discussions with the full panel. They noted patients may feel anxious about deteriorating or developing overt hypothyroidism when no treatment was given. To address this, regular follow-up is very important. They also mentioned that it is difficult for patients to make a decision when feeling unwell. We thank them for their contribution.

Updates to this article

Table 2 shows the evidence that has emerged since the publication of this article. As new evidence is published, a group will assess this new evidence and make a judgment on the extent that it is expected to alter the recommendation.

At the time of publication, we identified one new trial in trial registries:

- IEMO, assessing the effect of thyroid hormones versus placebo in elderly aged 80 years with SCH, 80-plus thyroid trial (NTR3851 in Netherlands Trial Register).

Table 2 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

Competing interests All authors have completed the *BMJ Rapid Recommendations* interests disclosure form and a detailed, contextualised description of all disclosures is reported in appendix 2 on bmj.com. As with all *BMJ Rapid Recommendations*, the executive team and *The BMJ* judged that no panel member had any relevant financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions. M Feller, M Snel, E Moutzouri, and N Rodondi participated in writing the systematic review that formed the evidence base for this guideline. JP Brito and N Singh Ospina wrote an editorial about the overuse of levothyroxine.

Funding This guideline was not funded.

Transparency: G E Bekkering affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

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