UK National Screening Committee

SCREENING FOR THYROID DISEASE

An evidence map to outline the volume and type of evidence related to screening for thyroid disease for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by the Department of Health and Social Care

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.

Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Blog: https://nationalscreening.blog.gov.uk/

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Summary

This document discusses the findings of the evidence map on screening for thyroid disease.

Evidence maps are a way of scanning published literature to look at the volume and type of the evidence base in relation to a specific topic. They inform whether the evidence is sufficient to commission further work on the topic under consideration.

Based on the findings of this evidence map, no further work on screening for thyroid disease should be commissioned at the present time. The UK National Screening Committee (UK NSC) will return to screening for thyroid disease in 3-years' time.

Introduction and approach

Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Screening for thyroid disease in adults is currently due for an updated external review.

The thyroid gland is responsible for the production of 2 hormones, thyroxine (T4) and tri-iodothyronine (T3). These hormones are essential for the normal maturation and metabolism of all tissues in the body and are regulated by the secretion of thyroid stimulating hormone (TSH) from the pituitary gland. Thyroid hormones are present in the blood in either protein bound forms (the majority) or the free and active (unbound) forms of the hormones. The amount of unbound T3 is referred to as 'free T3' (FT3) and unbound T4 as 'free T4' (FT4) [1,2,3].

There are 2 types of thyroid hormone dysfunction [1,2,3]:

- hypothyroidism, characterised by the under production of thyroid hormones
- hyperthyroidism, characterised by the over production of thyroid hormones

Hypothyroidism and hyperthyroidism can be further categorised into overt and subclinical disease. These are defined biochemically. Overt thyroid disease is defined by the presence of abnormal thyroid hormone levels (both TSH and free T4 or T3). Subclinical thyroid disease is diagnosed based on normal levels of thyroid hormones (free T3 and free T4) in the presence of abnormal levels of TSH [1,2,3].

Symptoms of overt hypothyroidism may be mild and non-specific, including fatigue, feeling cold, weight gain, hair loss, poor concentration, dry skin, and constipation, and therefore may go unrecognised. A life-threatening complication resulting from untreated or undertreated hypothyroidism is myxoedema coma, though rare it most often manifests in older people. Symptoms of overt hyperthyroidism include palpitations, heat intolerance, sweating, weight loss, hyperactivity, and fatigue. A life-threatening complication resulting from untreated or undertreated hyperthyroidism is thyroid storm, characterised by fever, delirium, seizures and coma [2,3]. Individuals with subclinical thyroid dysfunction may or may not experience symptoms [1,2].

Overt hypothyroidism is treated with thyroid replacement therapy (levothyroxine). Prolonged periods of over treatment with thyroid replacement therapy can lead to

symptoms of hyperthyroidism that may include nervousness, palpitations, atrial fibrillation, heart failure, exacerbation of angina pectoris, weight loss, and decreased bone mineral density leading to an increased risk of fractures. Subclinical hypothyroidism can also be treated with thyroid hormone replacement therapy, or a strategy of watchful waiting may be applied [2,4].

Overt hyperthyroidism is treated with anti-thyroid medication such as methimazole or propylthiouracil, or ablation therapy, such as radioactive iodine or surgical removal of part of the thyroid gland. One of the main risks of treatment for overt hyperthyroidism is the development of hypothyroidism. The treatment of subclinical hyperthyroidism is not recommended due to thyroiditis which typically resolves spontaneously [3,4].

Thyroid function tests are commonly used to detect both hypothyroidism and hyperthyroidism. A serum TSH assay is often used to screen for thyroid function disorders. Most reference laboratories use a normal range for TSH of between 0.45 and 4.5 mIU/L. Assays to measure FT4, and in some cases also FT3 tend to be used to evaluate abnormal TSH levels [2,3].

Current guidelines

In 2015, the U.S. Preventive Services Task Force (USPSTF) concluded that the current evidence was insufficient to recommend screening for thyroid disease in non-pregnant, asymptomatic adults and that more research is needed to assess the balance of benefits and harms associated with thyroid screening [5]. In 2019, the USPSTF conducted literature scans in MEDLINE, PubMed and the Cochrane Library for new evidence published from 2014 onwards. No systematic reviews or primary studies were identified on screening for thyroid dysfunction to support updating the systematic review behind the 2015 USPSTF recommendations [6].

In 2019, the Canadian Task Force on Preventive Health Care strongly recommended against screening for thyroid dysfunction in asymptomatic non-pregnant adults because screening for thyroid dysfunction is not likely to confer clinical benefit and could lead to unnecessary treatment for some patients [7]. The recommendation is based on a systematic review by Reyes Domingo *et al.* published in 2019 [4], which updated and adapted the searches for the previous USPSTF systematic review to July 2018. The systematic review found no studies on screening for thyroid dysfunction, treatment of subclinical hyperthyroidism, or patients' values and preferences for screening for thyroid dysfunction. Moderate to very low-quality evidence was found on the benefits and harms of treatment for subclinical hypothyroidism, with most of the evidence showing no benefit of treatment [4].

In the UK, the National Institute for Health and Care Excellence (NICE) published guidelines in 2019 on the diagnosis and treatment of people with thyroid disease. The

NICE guidelines make recommendations on diagnosis, treatment, long-term care and support of primary thyroid disease (related to the thyroid rather than the pituitary gland, and not thyroid cancer or thyroid disease in pregnancy) [8]. In 2015, the British Thyroid Association published a position statement on recommendations on the management of primary hypothyroidism [9].

The 2018 UK NSC review noted that efforts to standardise TSH and free thyroid hormone reference ranges are being undertaken by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) [1]. The IFCC Committee for Standardisation of Thyroid Function Tests (C-STFT) was established in light of the prevalence of thyroid disease, the frequency of laboratory testing, and multiple reports on discrepant measurement results. The C-STFT has developed reference measurement systems for TSH harmonisation and FT4 standardisation and is now working with stakeholders to plan studies to define reference intervals [10,11,12].

The UK NSC does not currently recommend screening for thyroid disease in non-pregnant, asymptomatic adults. The Committee based this recommendation on the evidence provided by the 2018 UK NSC review carried out by Solutions for Public Health briefly described below.

Previous UK NSC review on screening for thyroid disease

The 2018 UK NSC review [1] looked for evidence published between January 2011 and January 2017, focusing on gaps identified by a previous UK NSC review in 2013. The 2018 review searched for evidence on the proportion of overt and subclinical thyroid disease that reverts to normal function without clinical intervention, whether a test cut-off suitable for population screening for overt and subclinical thyroid dysfunction had been identified and whether there was agreement on what is a healthy level of each of the T3, T4 and TSH hormones in non-pregnant adults, and the effectiveness of treatment for overt and subclinical thyroid disease.

The 2018 review concluded that the natural history of thyroid dysfunction remains unclear and that it was not possible to determine a cohort of people with subclinical or overt thyroid dysfunction whose thyroid status would be more or less likely to revert to normal without clinical intervention. The 2018 review did not identify any studies which outlined a consensus on the reference ranges and cut-off thresholds of TSH, finding that the TSH reference range varied across testing platforms impacting the number of people identified as eligible for treatment. No studies were found which focused on the cut-off thresholds for FT4 or FT3. The 2018 review also found a lack of consensus on what constitutes healthy levels of FT3, FT4 and TSH hormones and a lack of evidence that people with screen detected subclinical and overt thyroid disease would benefit from treatment [1].

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on screening for thyroid disease should be commissioned and to evaluate the volume and type of evidence on key issues related to screening for thyroid disease.

The aim was to address the following questions:

1. Has a test cut-off been identified which is suitable for population screening for overt and subclinical thyroid dysfunction?
2. Does early initiation of treatment for overt and subclinical thyroid dysfunction following screening or at a pre-symptomatic stage provide better outcomes compared to initiation of treatment following clinical detection or at a symptomatic stage?

The population of interest in this evidence map is non-pregnant, asymptomatic adults. The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on thyroid disease. The aim of this document is to present the information necessary for the UK NSC to decide this.

Search methods and results

The searches were conducted on 6 July 2021 on 3 databases: Medline, Embase and the Cochrane Library. The search period was restricted to January 2017 – July 2021. The search date was determined by the search period for the previous UK NSC review.

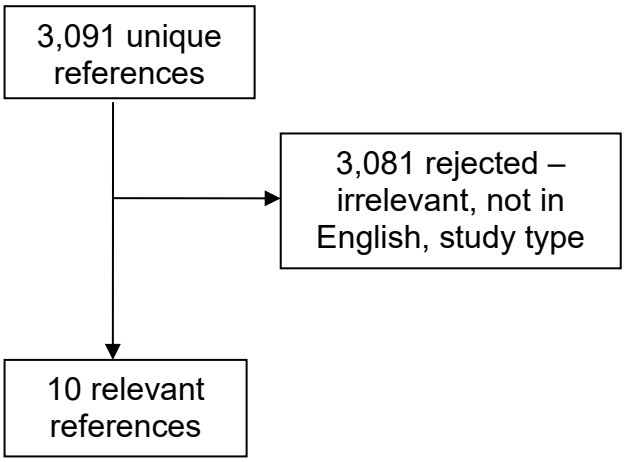
The detailed search strategies, including exclusion and inclusion criteria are available in Appendix 1. The searches returned a total of 3,091 unique references across the 2 questions which were initially sifted by an information scientist for potential relevance. One reviewer assessed 228 titles and abstracts for further appraisal and possible inclusion in the evidence map. Ten references were included in the final evidence map: no references in question 1, and 10 in question 2.

All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertainty. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

Abstract reporting tables are available in Appendix 2.

A flow diagram summarising the number of studies included and excluded is presented in Figure 1.

Figure 1: Summary of included and excluded publications



Summary of findings

Question 1: Has a test cut-off been identified which is suitable for population screening for overt and subclinical thyroid dysfunction?

No studies met the inclusion criteria for this question. The inclusion and exclusion criteria are summarised in Appendix 1.

Seventeen studies were identified as of potential interest to this question. Although they were not formally included in the evidence map because they did not meet the criteria for inclusion, they are briefly described below for information:

- 3 studies defined optimal TSH cut-off points for automatic referral for FT4 testing [13-15]. These studies were about rationalising the criteria for FT4 testing to reduce inappropriate laboratory test utilisation in the diagnostic testing of symptomatic populations in Spain, Australia and Canada. The studies did not consider suitable test cut-offs for screening populations
- one UK study [16] and 12 studies conducted in UK comparable countries [17-28] defined thyroid hormone normal reference ranges. The normal ranges varied depending on the laboratory, testing platform, lower and upper cut-offs used to define the range, and population under study. However, the studies did not define thresholds for thyroid dysfunction and therefore do not address the key question
- one study was conducted by members of the IFCC Committee for Standardization of Thyroid Function Tests. This focussed on the development of a global harmonisation approach for TSH measurements which may result in the adoption of a more uniform reference interval in the future [12]

No studies were identified that met the inclusion criteria for this question. Therefore, there is insufficient new evidence in this key area to justify commissioning an evidence summary.

Question 2: Does early initiation of treatment for overt and subclinical thyroid dysfunction following screening or at a pre-symptomatic stage provide better outcomes compared to initiation of treatment following clinical detection or at a symptomatic stage?

Ten studies met the inclusion criteria for this question. The inclusion and exclusion criteria are summarised in Appendix 1. The included studies are briefly described below and further information is provided in the abstract reporting tables in Appendix 2.

The 2018 UK NSC review found a lack of evidence that people with screen detected subclinical and overt thyroid disease would benefit from treatment. None of the studies identified by this evidence map compared the early initiation of treatment to later treatment for overt or subclinical thyroid dysfunction and therefore do not directly address the key question. In addition, no studies were identified on the early initiation of treatment for subclinical or overt hyperthyroidism.

Instead, the 10 studies that have been included all related primarily to the treatment of subclinical hypothyroidism. These were 7 systematic reviews [4, 29-34], 2 individual patient data meta-analyses [35,36], and one randomised controlled trial (RCT) (the TRUST trial) [37]. The RCT included some patients from the UK (number not reported). The systematic review by Reyes Domingo *et al.* (2019) [4] was the only included study that was specifically focusing on the treatment of screen-detected populations.

The most relevant systematic review, Reyes Domingo *et al.* (2019) [4], was conducted to inform the Canadian Task Force on Preventive Health Care recommendations on screening for thyroid dysfunction and assessed the benefits and harms of treating screen-detected thyroid dysfunction. Key points from this review were:

- included studies published up to July 2018
- found no studies on the benefits and harms of treatment compared to no treatment for screen-detected overt hypothyroidism, overt hyperthyroidism or subclinical hyperthyroidism in asymptomatic non-pregnant adults
- included 22 studies (19 RCTs and 3 cohort studies) in patients with screen-detected subclinical hypothyroidism. Meta-analyses were not conducted due to the heterogeneity of the studies
- assessed outcomes: mortality (all-cause and cardiovascular related), fatal and non-fatal cardiovascular events, atrial fibrillation, fractures, quality of life, cognitive function, intermediate outcomes (cholesterol, lipids, blood pressure, body mass index, weight, and bone density), and harms of screening
- did not find randomised evidence of treatment benefits or harms for subclinical hypothyroidism for any of the assessed outcomes with most of the included RCTs reporting very small effect sizes that were not statistically significant

Of the other included studies, only one systematic review considered both overt and subclinical hypothyroidism. Chen *et al.* (2020) [30], (searches to December 2019), assessed the impact of levothyroxine compared to placebo on thyroid hormone levels and cardiovascular morbidity measured in adults. However, the review was not limited to non-pregnant adults and it is not clear if any of the studies included patients with screen detected hypothyroidism. The review found 25 RCTs, 16 of which appear to be for subclinical hypothyroidism. No relevant RCTs on subclinical hypothyroidism that were published after the search date for Reyes Domingo *et al.* (2019) [4] were identified. The authors concluded that in the patients with overt hypothyroidism, compared with placebo, levothyroxine significantly increased FT4 levels and decreased TSH levels and in patients with subclinical hypothyroidism, compared with placebo, levothyroxine significantly decreased systolic blood pressure, TSH, T3 and total cholesterol and increased FT3 and FT4.

The most recent systematic review identified was Peng *et al.* (2021) [29], (searches to April 2020), which assessed the impact of thyroid hormone therapy compared to placebo or no therapy on mortality in non-pregnant adults with subclinical hypothyroidism. Two RCTs (TRUST & IEMO80+ trials[*]) and 5 observational studies were included but it is not clear if any of the studies included patients with screen detected hypothyroidism. The authors concluded that the studies showed no protective effects on mortality in adults treated for subclinical hypothyroidism overall, but subgroup analyses showed benefits on mortality in adults aged <65 to 70 years.

The 4 remaining systematic reviews, all with meta-analyses, were published before the systematic review by Reyes Domingo *et al.* (2019) [4] and where reported, had earlier search dates. These reviews assessed the impact of thyroid hormone replacement treatment compared to placebo or no therapy for subclinical hypothyroidism. It is not clear if any of the studies included patients with screen detected hypothyroidism. These reviews were:

- Li *et al.* (2017) [33] (search date July 2016) which included 12 RCTs and found significant improvements in total cholesterol and low-density lipoprotein
- Abreu *et al.* (2017) [34] (search date September 2015) which included 16 RCTs and found a significant, modest, decrease in serum thyroid-stimulating hormone and total and low-density lipoprotein cholesterol
- Feller *et al.* 2018 [32] (search date of July 2018) which included 21 RCTs and found no improvements in general quality of life or thyroid-related symptoms

[*] The IEMO80+ trial included participants aged 80 years and over from the Netherlands and Switzerland and was explicitly designed as an ancillary trial to the TRUST trial in order to conduct combined analyses of the TRUST and IEMO80+ trials [43]. The results of the IEMO80+ trial do not appear to have been published separately yet and are not included in the systematic review by Reyes Domingo *et al.* (2019) [4] but are included in the systematic review by Peng *et al.* (2021) [29]

- Swaid *et al.* (2019) [31] (search date not reported[†]) which included 7 RCTs and found significant improvement in flow-mediated dilation but not carotid intima media thickness

The 2 individual patient data meta-analyses included (Zijlstra *et al.* (2021) [35], Mooijaart *et al.* (2019) [36]) both assessed the effects of levothyroxine compared to placebo in older adults with subclinical hypothyroidism by pooling individual patient data from the TRUST trial and the IEMO80+ trial. Participants from both trials were identified from lists of patients with laboratory test results from hospitals and primary care practices and it is not clear if any were screen detected.

- Zijlstra et al. (2021) determined the effects of levothyroxine on cardiovascular outcomes in adults aged 65 and over (737 adults aged ≥65 years from the TRUST trial and 105 adults ≥80 years from the IEMO80+ trial) and found no significant change in the risk of cardiovascular outcomes [35]
- Mooijaart et al. (2019), determined the effects of levothyroxine on quality of life in adults aged 80 years and over (105 adults ≥80 years from the IEMO80+ trial and 146 adults ≥80 years from the TRUST trial) and found no significant change in thyroid-related patient-reported quality of life [36]

In addition to the systematic reviews and meta-analyses, one paper on the TRUST RCT was included. The TRUST trial (Stott *et al.* 2017 [37]), assessed the effects of levothyroxine compared to placebo on quality of life, cognitive function, measures of cardiovascular morbidity and adverse events in 737 adults aged 65 years and older with subclinical hypothyroidism in the UK, the Netherlands and Switzerland. Participants were identified from clinical laboratory and general practice databases and records and it is not clear if any were screen detected. The authors concluded that levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism.

Five additional papers (Wildisen *et al.* 2021 [38]; Stuber *et al.* 2020 [39]; Gonzalez Rodriguez *et al.* 2020 [40]; Gencer *et al.* 2020 [41]; Blum *et al.* 2018 [42]) were identified that reported results on the TRUST trial with a focus on a particular outcome such as depressive symptoms, fatigue, bone mineral density and cardiovascular morbidity measures, and often in a subgroup of patients. These have not been formally included in this evidence map as the main trial findings are reported in Stott *et al.* (2017) [37] which includes all patients and outcomes.

In summary, 10 papers were identified that primarily compared standard care to placebo/no treatment for the treatment of subclinical hypothyroidism. The most relevant paper found was a systematic review with searches up to July 2018 (Reyes Domingo *et*

[†] This systematic review included studies published from 2004 to 2018. One paper was included that was published after the search date of the systematic review by Reyes Domingo *et al.* (2019). This paper, Blum *et al.* 2018 [42], reports on the TRUST trial. Blum *et al.* 2018 [42] was identified by the searches for this evidence map but was not formally included (see main body of the text for further details).

al. 2019 [4]) conducted to inform the Canadian Task Force on Preventive Health Care recommendations on screening for thyroid dysfunction in asymptomatic non-pregnant adults. New evidence identified (published after this systematic review or in the same year) included 2 systematic reviews and 2 individual patient data meta-analyses on thyroid hormone therapy compared to placebo or no therapy in subclinical hypothyroidism. One trial (IEMO80+) was not included in Reyes Domingo *et al.* 2019 [4] but was included by one of the systematic reviews and both individual patient data meta-analyses. The separate results of the IEMO80+ trial have not been published outside of these meta-analyses.

No studies were found for this evidence map that compared the early initiation of treatment to later treatment for overt and subclinical thyroid dysfunction. No studies were found on the early treatment of subclinical or overt hyperthyroidism.

Ten papers (7 systematic reviews, 2 meta-analyses, and one RCT) were included. They all compared standard care to placebo or no treatment for subclinical hypothyroidism. Only one of the systematic reviews identified considered overt hypothyroidism. However, this review was not limited to non-pregnant adults and it is not clear if any of the studies included patients with screen detected hypothyroidism. The most relevant paper was the systematic review (Reyes Domingo *et al.* 2019) conducted to inform the Canadian Task Force on Preventive Health Care recommendations on screening for thyroid dysfunction in asymptomatic non-pregnant adults. This found no evidence of treatment benefits or harms for subclinical hypothyroidism for any of the assessed outcomes.

One trial (IEMO80+) was not included in Reyes Domingo et al. 2019 but was included by one of the systematic reviews and by the 2 meta-analyses identified in this evidence map. Both meta-analyses found no significant changes in the outcomes assessed (cardiovascular outcomes in adults aged ≥65 years and quality of life in adults ≥80 years).

The volume and type of evidence on the treatment of subclinical hypothyroidism identified could be considered sufficient for more detailed consideration in an evidence summary. However, there is still an absence of evidence in relation to treatment for screen-detected overt hypothyroidism, as well as for subclinical and overt hyperthyroidism. Therefore, the conclusions that could be expected of an evidence summary in this key area would be limited. Hence, it is unlikely that a review of the available evidence relating to the treatment of subclinical hypothyroidism alone would lead to a change in the UK NSC’s current position.

Conclusions

Since the previous 2018 UK NSC review, no new studies were found reporting on suitable test cut-offs for population screening. A large volume of evidence was found on the treatment of subclinical hypothyroidism. None of the studies included in this evidence map compared the early initiation of treatment to later treatment for overt and subclinical thyroid dysfunction. In addition, there was an absence of evidence on screen-detected overt hypothyroidism, as well as in relation to subclinical and overt hyperthyroidism. It is therefore unlikely that a review of the available evidence in this area of treatment of subclinical hypothyroidism alone would lead to a change in the UK NSC's position.

With this in mind, commissioning a full, more sustained review of the evidence on screening for thyroid disease in non-pregnant, asymptomatic adults is not justified at the current time.

Recommendations

On the basis of this evidence map, no further work on screening for thyroid disease should be commissioned at the present time and the topic should be reconsidered in 3-years' time.

Appendix 1 — Search strategy for the evidence map

SOURCES SEARCHED: Medline, Embase and Cochrane Library

DATES OF SEARCH: January 2017 to 6 July 2021

SEARCH STRATEGIES

Medline search question 1			**Embase search question 1**		
2	Hypothyroidism/	27852	1	Hypothyroidism/	62179
3	Hyperthyroidism/	26274	2	Hyperthyroidism/	34044
4	((overactive or underactive) adj thyroid).tw.	43	3	((overactive or underactive) adj thyroid).tw.	80
5	(thyroid adj (dysfunction or disease or deficiency or failure)).tw.	15177	4	(thyroid adj (dysfunction or disease or deficiency or failure)).tw.	21697
6	(hyperthyroid* or hypothyroid*).tw. or thyroid.ti.	156784	5	(hyperthyroid* or hypothyroid*).tw.	178505
7	2 or 3 or 4 or 5 or 6	172543	6	1 or 2 or 3 or 4 or 5	211558
8	Thyroid Function Tests/	14941	7	Thyroid Function Test/ or Thyroxine test kit/	12368
9	thyroid function test$.tw.	3906	8	thyroid function test$.tw.	6666
10	Immunoassay/	31144	9	Immunoassay/	71644
11	immunometric assay.tw.	533	10	immunometric assay.tw.	788
12	thyrotrophin assay.tw.	7	11	thyrotrophin assay.tw.	7
13	8 or 9 or 10 or 11 or 12	48615	12	7 or 8 or 9 or 10 or 11	85981
14	exp "Sensitivity and Specificity"/	611709	13	"sensitivity and specificity"/ or diagnostic accuracy/ or predictive value/	701401
15	(Sensitiv$ or specific$).tw.	4E+06	14	(Sensitiv$ or specific$).tw.	5369221
16	((Positive or negative) adj predictive value$).tw.	69667	15	((Positive or negative) adj predictive value$).tw.	103500
17	(PPV or NPV).tw.	22456	16	(PPV or NPV).tw.	41637
18	((False or true) adj (negative$ or positive$)).tw.	84884	17	((False or true) adj (negative$ or positive$)).tw.	116119
19	14 or 15 or 16 or 17 or 18	5E+06	18	13 or 14 or 15 or 16 or 17	5762039
20	thyroid status.tw.	2253	19	thyroid status.tw.	2824
21	(Thyroid stimulating hormone or TSH).tw.	37323	20	(Thyroid stimulating hormone or TSH).tw.	54785
22	(Thyroxine or T4 or free T4 or FT4).tw.	69037	21	38 not 39	91863
23	(tri-iodothyronine or T3 or triiodothyronine or free T3 or FT3).tw.	60274	22	(tri-iodothyronine or T3 or triiodothyronine or free T3 or FT3).tw.	85552
24	serum thyrotropin.tw.	1124	23	serum thyrotropin.tw.	1287
25	antithyroid antibod$.tw.	993	24	antithyroid antibod$.tw.	1379
26	20 or 21 or 22 or 23 or 24 or 25	121513	25	19 or 20 or 21 or 22 or 23 or 24	162979
27	Mass Screening/	108432	26	Mass Screening/ or Screening/ or Screening Test/	305969
28	(screen$3 or detect$3 or test or tests or testing).tw.	5E+06	27	(screen$3 or detect$3 or test or tests or testing).tw.	6576295

29	27 or 28	5E+06	28	26 or 27	6617929
30	7 and 13 and 19 and 26	1057	29	6 and 12 and 18 and 25	1229
31	7 and 13 and 26 and 29	3346	30	6 and 12 and 25 and 28	4589
32	(screen$ and (hypothyroidism or hyperthyroidism or thyroid dysfunction or thyroid disease or thyroid deficiency or thyroid failure)).ti.	985	31	(screen$ and (hypothyroidism or hyperthyroidism or thyroid dysfunction or thyroid disease or thyroid deficiency or thyroid failure)).ti.	1319
33	Reference Values/	161763	32	Reference Values/	69278
34	((reference or normal) adj (rang$ or value$ or interval$)).tw.	101545	33	((reference or normal) adj (rang$ or value$ or interval$)).tw.	86103
35	(cut-off or cutoff).tw.	115623	34	(cut-off or cutoff).tw.	43869
36	33 or 34 or 35	355162	35	32 or 33 or 34	192454
37	7 and 26 and 36	4508	36	6 and 25 and 35	6034
38	30 or 31 or 32 or 37	8135	37	29 or 30 or 31 or 36	7991
39	limit 38 to (english language and yr="2017 -Current")	1383	38	limit 37 to (english language and yr="2017 -Current")	2490
			39	conference*.pt.	4892778
			40	38 not 39	1506
Medline search question 2			**Embase search question 2**		
1	Hypothyroidism/	27852	1	Hypothyroidism/	62179
2	Hyperthyroidism/	26274	2	Hyperthyroidism/	34044
3	((overactive or underactive) adj thyroid).tw.	43	3	((overactive or underactive) adj thyroid).tw.	80
4	(thyroid adj (dysfunction or disease or deficiency or failure)).tw.	15177	4	(thyroid adj (dysfunction or disease or deficiency or failure)).tw.	21697
5	(hyperthyroid* or hypothyroid*).tw. or thyroid.ti.	156784	5	(hyperthyroid* or hypothyroid*).tw. or thyroid.ti.	178505
6	1 or 2 or 3 or 4 or 5	172543	6	1 or 2 or 3 or 4 or 5	211558
7	Hormone Replacement Therapy/	10513	7	hormone substitution/	38321
8	thyroid hormone replacement.tw.	1001	8	thyroid hormone replacement.tw.	1479
9	Thyroxine/tu [Therapeutic Use]	6025	9	thyroxine/dt	6239
10	(levothyroxine or L-thyroxine or thyroxin$).tw.	34427	10	(levothyroxine or L-thyroxine or thyroxin$).tw.	39756
11	Carbimazole/	1101	11	Carbimazole/	4210
12	carbimazole.tw.	914	12	carbimazole.tw.	1288
13	(radio-iodine or radioactive iodine or I-131 or RAI).tw.	12774	13	(radio-iodine or radioactive iodine or I-131 or RAI).tw.	15527
14	Thyroid Gland/su [Surgery]	2887	14	Thyroid Gland/su [Surgery]	352
15	(surgery or surgical intervention$).tw.	1254058	15	(surgery or surgical intervention$).tw.	1749361
16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	1312624	16	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	1840703
17	Treatment outcome/	1038731	17	Treatment outcome/	885756
18	Mortality/	46989	18	Mortality/	790888
19	Morbidity/	31498	19	Morbidity/	363288
20	Health Status Indicators/	23848	20	Health Status Indicator/	3204
21	"Quality of Life"/	215615	21	"Quality of Life"/	513315
22	("quality of life" or qol or hrqol).tw.	308321	22	("quality of life" or qol or hrqol).tw.	493657
23	(questionnaire$ or survey$ or index$).tw.	1935594	23	(questionnaire$ or survey$ or index$).tw.	2674031
24	((physical or psychological or health) adj status).tw.	71984	24	((physical or psychological or health) adj status).tw.	93170
25	all cause mortality.tw.	39399	25	all cause mortality.tw.	63403
26	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	3188420	26	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	4719191
27	6 and 16 and 26	6955	27	6 and 16 and 26	6321

28	((treat$ or manage$ or therap$) and (hypothyroidism or hyperthyroidism)).ti.	4735	28	((treat$ or manage$ or therap$) and (hypothyroidism or hyperthyroidism)).ti.	4739
29	27 or 28	7914	29	27 or 28	14357
30	limit 29 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")	204	30	limit 29 to (meta analysis or "systematic review" or "reviews (maximizes specificity)")	330
31	randomized controlled trial.pt.	536578	31	(randomised controlled trial/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or (random* or ((singl* or doubl*) adj (blind* or mask*)) or crossover or cross over or factorial* or latin square or assign* or allocat* or volunteer*).ti,ab.) not ((exp animals/ or nonhuman/) not human/)	2150818
32	controlled clinical trial.pt.	94267	32	29 and 31	1172
33	randomized.ab.	525623	33	30 or 32	1371
34	placebo.ab.	219437	34	conference*.pt.	4892778
35	drug therapy.fs.	2343875	35	33 not 34	1135
36	randomly.ab.	360830	36	limit 35 to (english language and yr="2017 -Current")	339
37	trial.ab.	558341			
38	groups.ab.	2215402			
39	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	5050973			
40	exp animals/ not humans.sh.	4855957			
41	39 not 40	4391690			
42	29 and 41	4750			
43	30 or 42	4828			
44	limit 43 to (english language and yr="2017 -Current")	908			

Cochrane search	
#1	MeSH descriptor: [Hypothyroidism] this term only
#2	MeSH descriptor: [Hyperthyroidism] this term only
#3	("overactive thyroid" OR "underactive thyroid"):ti,ab,kw OR ("thyroid dysfunction" OR "thyroid disease" OR "thyroid deficiency" OR "thyroid failure"):ti,ab,kw OR (hyperthyroid* or hypothyroid*):ti
#4	#1 or #2 or #3

Results by database

Medline	**2291**
Embase	**1844**
Cochrane Library	**557**
Total	**4692**

After the exclusion of duplicates, 3,091 references remained.

An additional search for guidelines was conducted on the TRIPdatabase, NICE Evidence Search and using an internet search engine. Returns were sifted by a reviewer for potential relevance.

Inclusions and exclusions

Publications not in the English language or published prior to January 2017, case reports, conference abstracts, trial protocols and comment/editorials/letters were excluded.

Eligibility for inclusion in the map

Question 1

- population: non-pregnant, asymptomatic adults
- index test: any thyroid function test (for example, TSH, T4 and T3)
- comparator: none or any
- reference standard: any other specific “gold standard”, as determined by the study itself
- target condition: overt and subclinical thyroid dysfunction
- outcomes: sensitivity, specificity, positive and negative predictive values, likelihood ratios, area under the curve, incidental findings, for example, other conditions detected by the test
- study design: studies in randomly assigned or consecutively enrolled populations and systematic reviews of these should be prioritised. If none or few of these designs are found, other study designs should be reported, for example case-control studies

Question 2

- population: non-pregnant adults
- intervention: standard care for overt and subclinical dysfunction, for example:
  - for hypothyroidism: levothyroxine
  - for hyperthyroidism: anti-thyroid medications, radioactive iodine or surgical intervention

  With particular focus on whether any of these interventions are administered at an early, pre-symptomatic stage
- comparator: later treatment of individuals identified through clinical presentation/ at a symptomatic stage with any of the interventions listed above or no comparator
- outcomes: TSH levels, cognitive function, measures of cardiovascular morbidity (for example, blood pressure, cholesterol etc.), improved physical and psychological health status (for example, via commonly used thyroid disease indexes, general health questionnaires etc.), harms of treatments, any other outcome as outlined by each study
- study design: studies in screen detected and asymptomatic populations should be prioritised as well as randomised controlled trials, cohort studies or systematic reviews of these. If none or few of these designs are found, other study designs can be reported. Also, studies with a comparator (e.g. early vs late / presymptomatic vs symptomatic) should be prioritised. However, in the

absence of such studies or in the presence of a low volume of such studies, studies without a comparator can be reported

Appendix 2 – Abstract reporting tables

Question 1 – Has a test cut-off been identified which is suitable for population screening for overt and subclinical thyroid dysfunction?

No studies identified

Question 2 – Does early initiation of treatment for overt and subclinical thyroid dysfunction following screening or at a pre-symptomatic stage provide better outcomes compared to initiation of treatment following clinical detection or at a symptomatic stage?

Systematic reviews

TITLE	
Citation	Peng *et al.* (2021) [29]
BACKGROUND	
Study type	Systematic review and meta-analysis
Objectives	To summarise the impact of thyroid hormone therapy on mortality in adults with subclinical hypothyroidism
Components of the study	Population – non-pregnant adults with subclinical hypothyroidism (n=21,055) Intervention – thyroid hormone therapy Comparator – placebo or no therapy Study designs – RCTs (n=2) and observational studies (n=5) Search date – April 2020 [full-text checked]
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • any other outcome as outlined by each study (all-cause mortality and cardiovascular mortality) Outcomes specified by the commissioning document that are not reported include TSH levels, cognitive function, measures of cardiovascular morbidity, physical and psychological health status, and harms of treatments
Conclusions	The authors concluded that the use of thyroid hormone therapy does not provide protective effects on mortality in older adults with subclinical hypothyroidism

TITLE	
Citation	Chen *et al.* (2020) [30]
BACKGROUND	
Study type	Systematic review and meta-analysis
Objectives	To review relevant randomised controlled trials in order to determine the clinical efficacy of levothyroxine in the treatment of overt or subclinical hypothyroidism
Components of the study	Population – individuals with overt or subclinical hypothyroidism (n=1,735) Intervention – levothyroxine monotherapy or combined with other drugs Comparator – placebo or levothyroxine monotherapy Study designs – RCTs (n=25) Search date – December 2019 [full-text checked]
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • TSH levels • measures of cardiovascular morbidity (systolic and diastolic blood pressure, total cholesterol, triglycerides, high density lipoprotein, low density lipoprotein) • any other outcome as outlined by each study (triiodothyronine (T3), free triiodothyronine (FT3), and free thyroxine and body mass index) Outcomes specified by the commissioning document that are not reported include cognitive function, physical and psychological health status, and harms of treatments
Conclusions	The authors concluded that in the patients with overt hypothyroidism, compared with placebo, levothyroxine significantly increased FT4 levels and decreased TSH levels and in patients with subclinical hypothyroidism, compared with placebo, levothyroxine significantly decreased systolic blood pressure, TSH, T3 and total cholesterol and increased FT3 and FT4 [full-text checked]

TITLE	
Citation	Reyes Domingo *et al.* (2019) [4]
BACKGROUND	
Study type	Systematic review
Objectives	To inform the Canadian Task Force on Preventive Health Care recommendations on screening for thyroid dysfunction. The review sought to answer key questions on the benefits and harms of screening for thyroid dysfunction, patients' values and preferences for screening, and the benefits and harms of treating screen-detected thyroid dysfunction
Components of the study	For the benefits and harms of treating screen-detected thyroid dysfunction: Population – screen-detected thyroid dysfunction among asymptomatic non-pregnant adults Intervention – thyroid hormone replacement (e.g., levothyroxine), antithyroid medications (e.g., methimazole), ablation therapy (e.g., radioactive iodine), and/or surgery Comparator – placebo or observation Study designs – RCTs (n=5 on clinical outcomes; n=15 on intermediate outcomes and n=7 on harms) and controlled observational studies (n=3 on clinical outcomes) Search date – July 2014 to July 2018 [full-text checked]
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • measures of cardiovascular morbidity (non-fatal cardiovascular events, atrial fibrillation, cholesterol and lipid levels, and blood pressure • cognitive function • physical and psychological health status (quality of life) • any other outcome as outlined by each study (all-cause mortality, deaths due to cardiovascular diseases, body mass index or weight change, fractures, and bone density) • harms of treatments (adverse events and withdrawal due to adverse events) Outcomes specified by the commissioning document that are not reported include TSH levels

	[full-text checked]
Conclusions	The review found moderate to very low-quality evidence on the benefits and harms of treatment for subclinical hypothyroidism, with most of the evidence showing no benefit of treatment

TITLE	
Citation	Swaid *et al.* (2019) [31]
BACKGROUND	
Study type	Systematic review and meta-analysis
Objectives	To determine the effect of levothyroxine treatment in individuals with subclinical hypothyroidism on surrogate markers of atherosclerosis
Components of the study	Population – individuals with subclinical hypothyroidism (n=541) Intervention – levothyroxine Comparator – placebo Study designs – RCTs (n=7) Search date – not reported (included studies were published between 2004 and 2018) [full-text checked]
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • measures of cardiovascular morbidity (carotid intima media thickness (CIMT) and flow-mediated dilation (FMD)) Outcomes specified by the commissioning document that are not reported include TSH levels, cognitive function, physical and psychological health status, and harms of treatments
Conclusions	The authors concluded that among patients with subclinical hypothyroidism, levothyroxine treatment was associated with significant improvement in FMD but not CIMT

TITLE	
Citation	Feller *et al.* (2018) [32]
BACKGROUND	
Study type	Systematic review and meta-analysis
Objectives	To conduct a meta-analysis of the association of thyroid hormone therapy with quality of life and thyroid-related symptoms in adults with subclinical hypothyroidism

Components of the study	Population – non-pregnant adults with subclinical hypothyroidism Intervention – thyroid hormone therapy Comparator – placebo or no therapy Study designs – RCTs (n=21) Search date – July 2018
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • physical and psychological health status (general quality of life) • any other outcome as outlined by each study (thyroid-related symptoms) Outcomes specified by the commissioning document that are not reported include TSH levels, cognitive function, measures of cardiovascular morbidity, and harms of treatments
Conclusions	The authors concluded that among non-pregnant adults with subclinical hypothyroidism, the use of thyroid hormone therapy was not associated with improvements in general quality of life or thyroid-related symptoms

TITLE	
Citation	Li *et al.* (2017) [33]
BACKGROUND	
Study type	Systematic review and meta-analysis
Objectives	To clarify the lipid-lowering effect of substitution treatment with levothyroxine in patients with subclinical hypothyroidism
Components of the study	Population – non-pregnant patients with subclinical hypothyroidism (n=940) Intervention – replacement therapy including triiodothyronine, thyroxine, or both Comparator – placebo or observation Study designs – RCTs (n=12) Search date – July 2016 [full-text checked]
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported:

	• measures of cardiovascular morbidity (total cholesterol, low-density lipoprotein and high-density lipoprotein cholesterol and triglycerides) Outcomes specified by the commissioning document that are not reported include TSH levels, cognitive function, physical and psychological health status, and harms of treatments [full-text checked]
Conclusions	The authors concluded that levothyroxine treatment has clear benefits on total cholesterol and low-density lipoprotein in patients with subclinical hypothyroidism, including those with mild disease

TITLE	
Citation	Abreu *et al.* (2017) [34]
BACKGROUND	
Study type	Systematic review and meta-analysis
Objectives	To assess whether subclinical hypothyroidism treatment is of clinical relevance based on cardiovascular risk parameters correction
Components of the study	Population – individuals with subclinical hypothyroidism (n=867) Intervention – levothyroxine Comparator – placebo Study designs – RCTs (n=16) Search date – September 2015 [full-text checked]
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • TSH levels • measures of cardiovascular morbidity (total, high-density lipoprotein and low-density lipoprotein, cholesterol, triglycerides, apolipoprotein A, apolipoprotein B, and lipoprotein(a)) • any other outcome as outlined by each study (FT4 and FT3 levels) Outcomes specified by the commissioning document that are not reported include cognitive function, physical and psychological health status, and harms of treatments

	[full-text checked]
Conclusions	The authors found a significant, modest, decrease in serum thyroid-stimulating hormone and total and low-density lipoprotein cholesterol with levothyroxine therapy which could be significant in terms of reduction of the incidence of coronary artery disease

Individual patient data meta-analyses

TITLE	
Citation	Zijlstra *et al.* (2021) [35]
BACKGROUND	
Study type	Individual patient data meta-analysis of 2 RCTs (TRUST & IEMO80+ trials)
Objectives	To determine the effects of levothyroxine treatment on cardiovascular outcomes in older adults with subclinical hypothyroidism
Components of the study	Population – adults aged ≥65 years for TRUST trial (n=737) and ≥80 years for IEMO80+ trial (n=105) with subclinical hypothyroidism (n=867) Intervention – levothyroxine Comparator – placebo
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • measures of cardiovascular morbidity (cardiovascular events, atrial fibrillation and heart failure) • harms of treatments • any other outcome as outlined by each study (all-cause mortality) Outcomes specified by the commissioning document that are not reported include TSH levels, cognitive function, physical and psychological health status
Conclusions	The authors concluded that treatment with levothyroxine does not significantly change the risk of cardiovascular outcomes in older adults with subclinical hypothyroidism, irrespective of a history of cardiovascular disease and age

TITLE	
Citation	Mooijaart *et al.* (2019) [36]
BACKGROUND	
Study type	Individual patient data meta-analysis of one RCT (IEMO80+ trial) and one RCT subgroup (TRUST trial)
Objectives	To determine the association of levothyroxine treatment for subclinical hypothyroidism with thyroid-related quality of life in adults aged 80 years and older
Components of the study	Population – adults aged 80 years and older with subclinical hypothyroidism (n=251) Intervention – levothyroxine Comparator – placebo
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • physical and psychological health status (Thyroid-Related Quality of Life Patient-Reported Outcome measure (ThyPRO) Hypothyroid Symptoms score and Tiredness score) • harms of treatments Outcomes specified by the commissioning document that are not reported include TSH levels, cognitive function, and measures of cardiovascular morbidity
Conclusions	The authors concluded that in adults aged 80 years and older with subclinical hypothyroidism, treatment with levothyroxine compared with placebo, was not significantly associated with improvement in hypothyroid symptoms or fatigue

Individual randomised controlled trial

TITLE	
Citation	Stott *et al.* (2017) [37]
BACKGROUND	
Study type	Randomised controlled trial (the TRUST trial)
Objectives	To determine whether there are clinical benefits from levothyroxine replacement in older persons with subclinical hypothyroidism

Components of the study	Population – adults aged 65 years and older with subclinical hypothyroidism (n=737) Intervention – levothyroxine Comparator – placebo
OUTCOMES	
Outcomes reported	Outcomes specified by the commissioning document that are reported: • physical and psychological health status (Thyroid-Related Quality of Life Patient-Reported Outcome measure (ThyPRO) Hypothyroid Symptoms score and Tiredness score; and generic health-related quality of life (EQ-5D)) • cognitive function • measures of cardiovascular morbidity (systolic and diastolic blood pressure and fatal and nonfatal cardiovascular events) • harms of treatments (adverse events) • any other outcome as outlined by each study (weight, body mass index, waist circumference and Instrumental Activities of Daily Living score) Outcomes specified by the commissioning document that are not reported include TSH levels [full-text checked]
Conclusions	The authors concluded that levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism

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