National Institute for Health and Care Excellence

Draft for Consultation

Thyroid disease: assessment and management

[B] Indications for testing

NICE guideline

Prognostic evidence review underpinning recommendations 1.2.1 to 1.2.6 in the guideline

June 2019

Draft for Consultation

This evidence review was developed by the National Guideline Centre

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1.1 Review question: Who should be tested for thyroid disease?

1.2 Introduction

Thyroid dysfunction affects many systems in the body, and the symptoms of thyroid disease are often non-specific. Most single common symptoms alone are not predictive of thyroid dysfunction. The decision to test or not is usually based on an overall clinical suspicion taking into account the nature and severity of symptoms, clinical signs and co-existing conditions.

Due to the non-specific nature of thyroid symptoms and the propensity of thyroid dysfunction to affect many other systems in the body, there are a wide range of possible indicators for testing. The committee hoped that that these recommendations would provide general guidance to support current practice.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	People without a previous diagnosis of thyroid disease
Prognostic variables under consideration	Any of the following, alone or in combination: • Co-existing conditions: ○ Obstructive sleep apnoea/hypopnea syndrome (OSAHS) ○ Osteoporosis ○ Autoimmune conditions (e.g. T1DM, RA) ○ Arrhythmia ○ T2DM ○ Congenital conditions (e.g. Turners/Downs/DiGeorge) • Symptoms or signs: ○ Dry skin ○ Hoarse voice ○ Cognitive impairment ○ Tremor ○ Palpitations ○ Muscle cramps ○ Weight loss/gain ○ Tiredness ○ Anxiety ○ Low mood/depression ○ Temperature disturbance ○ Abnormal menstrual cycle ○ Breathlessness ○ Bowel habit changes ○ Infertility/recurrent miscarriage ○ Eye symptoms • Other: ○ Family history of thyroid disease

Confounding factors	• Age • Sex • BMI • Smoking
Outcomes	Diagnoses of clinical or subclinical hypothyroidism or hyperthyroidism • RR or OR adjusted for key confounders • Sensitivity, specificity, PPV, NPV of risk factors
Study design	• Cross-sectional studies for accuracy type data • Cross-sectional or cohort studies for association type data

1.4 Clinical evidence

1.4.1 Included studies

Eight studies were included in the review;[6, 20-22, 39, 40, 42, 49] these are summarised in below Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix F:.

See the excluded studies list in Appendix J:.

1.4.2 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes
Almeida 2011[6]	n = 3,932 Australia Men, aged 69 to 87, community dwelling, randomly selected	Cross-sectional study Accuracy type data	Depression (self-rated by Geriatric Depression Scale, score of 7 or more) Depression prevalence 4.8%	Not applicable	Accuracy data for subclinical hypothyroidism and subclinical thyrotoxicosis SCH prevalence 10.8% SCT prevalence 1.0%
Canaris 2000[20]	n = 25,862 USA Participants in Colorado health fair, median age 56	Cross-sectional study Accuracy type data	Symptoms (self-assessed by survey): Hoarser voice Drier skin Feeling colder More tired Puffier eyes More muscle cramps More constipation Poorer memory	Not applicable	Accuracy data for combined subclinical hypothyroidism and clinical hypothyroidism SCH/hypothyroidism prevalence 9.5%
Canaris 2013[21]	n = 794 USA Participants in Michigan health fair, volunteers during	Cross-sectional study Accuracy type data	Symptoms (self-assessed by survey): Hoarser voice Drier skin	Not applicable	Accuracy data for hypothyroidism Hypothyroidism prevalence: 11.5%

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes
	Thyroid Awareness Week (excluding those with previously diagnosed thyroid disease from this analysis)		Feeling colder More tired Puffier eyes More muscle cramps More constipation More depressed Poorer memory		
Cappola 2006[22]	n = 3,233 USA Participants in CV health study (CHS), age >65, randomly selected from Medicare roster	Cross-sectional study Accuracy type data	Atrial fibrillation (self-reported or as assessed by baseline ECG): 5.2% Diabetes (fasting blood glucose >7mmol/L): 14%	Not applicable	Accuracy data for subclinical thyrotoxicosis, subclinical hypothyroidism and clinical hypothyroidism SCT prevalence: 1.5% SCH prevalence: 15.3% Hypothyroidism prevalence: 1.6%
Engum 2005[39]	n = 30,175 Norway Participants in HUNT2, age >20, all inhabitants in a county invited	Cross-sectional study Accuracy type data	Depression (HADS-D, score >8): 13.2% Anxiety (HADS-A, score >11): 16.7%	Not applicable	Accuracy data for thyroid autoimmunity (of which ~78% SCH, ~15% hypothyroidism) Autoimmunity prevalence: 3.3%
Feldthusen 2015[40]	n = 11,254 Denmark	Cross-sectional study Adjusted odds	Spontaneous miscarriage (self-reported in questionnaire): 21%	Age, menopause, BMI, smoking, diabetes, antiHTN medication, cholesterol lowering	Adjusted odds ratio for hypothyroidism and subclinical hypothyroidism

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes
	Women in GESUS, all individuals >30 in region of Denmark invited	ratio		medication, contraception, income, unemployment, education	Hypothyroidism prevalence: 9.4% SCH prevalence: 6.7%
Fleiner 2016[42]	n = 48,809 Norway Participants in HUNT3, age >20, all inhabitants in a county invited	Cross-sectional study Adjusted odds ratio and accuracy type data	Diabetes (self-reported) and classified into T2DM (3.1%) and autoimmune (0.5%)	Stratified by gender, adjusted for age, smoking and BMI	Adjusted odds ratio for hypothyroidism and hyperthyroidism, stratified by gender Accuracy data for genders combined Hypothyroidism prevalence: 6.8% Hyperthyroidism prevalence: 3.6%
Guimaraes 2009[49]	n = 1,249 Brazil Randomly selected sample of women in Rio de Janeiro	Cross-sectional study Adjusted odds ratio and accuracy type data	Depression symptoms (based on self-assessment with PRIME-MD): 45.7%	Restricted to women, adjusted for age, race, smoking, BMI	Adjusted odds ratio for hypothyroidism and SCH Accuracy data for hypothyroidism and SCH Hypothyroidism prevalence: 1.6% SCH prevalence: 8.2%

See Appendix D: for full evidence tables.

1.4.3 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: association data for spontaneous miscarriage

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
Spontaneous miscarriage and hypothyroidism	1	Adjusted OR: 1.02 (0.89 to 1.17)	Serious[a]	LOW[a,b] due to risk of bias, imprecision
Spontaneous miscarriage and subclinical hypothyroidism	1	Adjusted OR: 0.96 (0.79 to 1.17)	Serious[a]	MODERATE[a] due to imprecision

(a) Downgraded by 1 increment as the 95% CI crosses the null line
(b) Downgraded by 1 or 2 increments because evidence was at high or very high risk of bias as per QUIPS assessment, see appendix D for more information

Table 4: Clinical evidence summary: association data for depression symptoms

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
Depression symptoms and hypothyroidism	1	Adjusted OR: 8.05 (2.38 to 27.23)	Serious[a]	LOW[a,b] due to risk of bias, imprecision
Depression symptoms and subclinical hypothyroidism	1	Adjusted OR: 1.02 (0.60 to 1.73)	Serious[a]	LOW[a,b] due to risk of bias, imprecision

(a) Downgraded by 1 increment as the 95% CI crosses the null line or subjectively wide confidence intervals
(b) Downgraded by 1 or 2 increments because evidence was at high or very high risk of bias as per QUIPS assessment, see appendix D for more information

Table 5: Clinical evidence summary: depression, accuracy data

Predictor (outcome)	No of Participants (studies)	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
Depression (subclinical thyrotoxicosis)	3,932 (1 studies)	MODERATE[a] due to risk of bias	6% (1% to 21%)	95% (94% to 96%)	1.1%	99.2%
Depression (subclinical hypothyroidism)	34,107 (2 studies)	LOW[a] due to risk of bias	4% (2% to 6%) 12% (10% to 14%)	95% (94% to 96%) 87% (86% to 87%)	9.0% 2.9%	89.0% 96.6%
Depression (subclinical or clinical hypothyroidism)	1,249 (1 study)	HIGH	50% (40% to 59%)	55% (52% to 58%)	10.7%	90.8%
Feeling more depressed (subclinical or clinical hypothyroidism)	668 (1 studies)	MODERATE[a] due to risk of bias	22% (13% to 33%)	71% (67% to 75%)	9.1%	87.5%

(a) Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

Table 6: Clinical evidence summary: association data for diabetes mellitus

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
AIDM and hypothyroidism, in women	1	Adjusted OR: 2.15 (1.54 to 3.00)	None	HIGH
T2DM and hypothyroidism, in women	1	Adjusted OR: 1.09 (0.91 to 1.31)	Serious[a]	MODERATE[a] due to imprecision
AIDM and hyperthyroidism, in women	1	Adjusted OR: 0.89 (0.32 to 2.48)	Very serious[a]	LOW[a] due to

Risk factor and outcome (population)	Number of studies	Effect (95% CI)	Imprecision	GRADE Quality
				imprecision
T2DM and hyperthyroidism, in women	1	Adjusted OR: 1.09 (0.77 to 1.54)	Serious[a]	MODERATE[a] due to imprecision
AIDM and hypothyroidism, in men	1	Adjusted OR: 4.12 (2.49 to 6.82)	None	HIGH
T2DM and hypothyroidism, in men	1	Adjusted OR: 1.15 (0.84 to 1.57)	Serious[a]	MODERATE[a] due to imprecision
AIDM and hyperthyroidism, in men	1	Adjusted OR: 3.79 (1.75 to 8.21)	Serious[a]	MODERATE[a] due to imprecision
T2DM and hyperthyroidism, in men	1	Adjusted OR: 0.79 (0.45 to 1.39)	Serious[a]	MODERATE[a] due to imprecision

(a) Downgraded by 1 increment as the 95% CI crosses the null line or subjectively wide confidence intervals, downgraded by 2 increments if the 95% CI crosses the null line and subjectively wide confidence intervals

Table 7: Clinical evidence summary: diabetes, accuracy data

Predictor (outcome)	No of Participants (studies)	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
Diabetes (subclinical thyrotoxicosis)	3,233 (1 study)	MODERATE[a] due to risk of bias	23% (12% to 38%)	86% (85% to 87%)	2.4%	98.7%
Diabetes (subclinical or clinical hypothyroidism)	3,233 (1 study)	MODERATE[a] due to risk of bias	15% (12% to 18%)	86% (85% to 87%)	17.8%	83.2%

Predictor (outcome)	No of Participants (studies)	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
AIDM (hypothyroidism)	48,809 (1 study)	HIGH	1% (1% to 2%)	100% (99% to 100%)	16.4%	93.2%
T2DM (hypothyroidism)	48,809 (1 study)	HIGH	5% (4% to 6%)	97% (97% to 97%)	10.6%	93.3%
AIDM (hyperthyroidism)	48,809 (1 study)	HIGH	1% (0% to 1%)	100% (99% to 100%)	5.5%	96.4%
T2DM (hyperthyroidism)	48,809 (1 study)	HIGH	3% (3% to 5%)	97% (96% to 97%)	3.7%	96.3%

(a) Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

Table 8: Clinical evidence summary: anxiety, accuracy data

Predictor (outcome)	No of Participants (studies)	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
Anxiety (subclinical hypothyroidism)	30,175 (1 study)	LOW[a] due to risk of bias	16% (14% to 19%)	83% (83% to 84%)	3.2%	96.7%

(a) Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

Table 9: Clinical evidence summary: symptoms, accuracy data

Predictor (outcome)	No of Participants (studies)	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
Hoarser voice (subclinical or clinical hypothyroidism)	26,530 (2 studies)	MODERATE[a] due to risk of bias	6% (5% to 6%) 6% (2% to 15%)	95% (95% to 95%) 90% (87% to 92%)	10.3% 7.7%	90.6% 88.0%
Drier skin (subclinical or clinical hypothyroidism)	26,530 (2 studies)	MODERATE[a] due to risk of bias	28% (27% to 30%) 30% (20% to 41%)	75% (74% to 75%) 66% (63% to 70%)	10.5% 10.4%	90.9% 87.9%
Feeling colder (subclinical or clinical hypothyroidism)	26,530 (2 studies)	MODERATE[a] due to risk of bias	15% (13% to 16%) 13% (6% to 23%)	88% (88% to 89%) 84% (81% to 87%)	11.5% 9.8%	90.8% 88.1%
More tired (subclinical or clinical hypothyroidism)	26,530 (2 studies)	LOW[a,b] due to risk of bias, inconsistency	18% (17% to 20%) 34% (23% to 45%)	84% (84% to 84%) 59% (55% to 63%)	10.7% 9.9%	90.8% 87.4%
Puffier eyes (subclinical or clinical hypothyroidism)	26,530 (2 studies)	MODERATE[a] due to risk of bias	11% (10% to 13%) 14% (7% to 24%)	90% (90% to 91%) 82% (79% to 85%)	10.8% 9.7%	90.7% 88.1%
More muscle cramps (subclinical or clinical hypothyroidism)	26,530 (2 studies)	MODERATE[a] due to risk of bias	18% (16% to 19%) 18% (10% to 29%)	85% (84% to 85%) 78% (74% to 81%)	10.9% 9.8%	90.8% 88.0%
More constipation (subclinical or clinical hypothyroidism)	26,530 (2 studies)	MODERATE[a] due to risk of bias	6% (5% to 7%) 9% (4% to 18%)	95% (95% to 95%) 90% (88% to 93%)	11.3% 11.0%	90.6% 88.4%
Poorer memory (subclinical or clinical hypothyroidism)	26,530 (2 studies)	MODERATE[a] due to risk of bias	24% (23% to 26%) 26% (17% to 37%)	79% (79% to 80%) 68% (64% to 72%)	10.9% 9.6%	90.9% 87.6%

(a) Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias

(b) Inconsistency was assessed by inspection of the sensitivity and specificity plots. Particular attention was placed on the sensitivity threshold set by the committee as an acceptable level to recommend a test. The evidence was downgraded by 1 increment if the individual study values varied across 2 areas: where values of individual studies are both above and below 50%, or both above and below the acceptable threshold 90%, downgraded by 2 increments if the individual study values varied across 3 areas, where values of individual studies are above and below 50%, and also above and below the acceptable threshold 90%

Table 10: Clinical evidence summary: atrial fibrillation, accuracy data

Predictor (outcome)	No of Participants (studies)	Quality	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV	NPV
Atrial fibrillation (subclinical thyrotoxicosis)	3,233 (1 study)	MODERATE[a] due to risk of bias	9% (2% to 20%)	95% (94% to 96%)	2.4%	98.5%
Atrial fibrillation (subclinical or clinical hypothyroidism)	3,233 (1 study)	MODERATE[a] due to risk of bias	5% (3% to 7%)	95% (94% to 96%)	15.5%	83.0%

(a) Risk of bias was assessed using the QUIPS checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias, and downgraded by 2 increments if the majority of studies were rated at very high risk of bias.

See Appendix F: for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.5.3 Health economic modelling

This area was not prioritised for new cost-effectiveness analysis.

1.5.4 Resource costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 11: UK costs of thyroid tests

Tests	Median (a)
TSH	£2.15
TSH+FT4	£4.41
FT3	£3.12
FT4	£2.10

Source: Costs obtained from five different hospitals
(a) Costs quoted include reagent, any consumables and staff pay

Tests	*Unit costs*
Phlebotomy (a)	£3.04

Source: NHS reference cost 2016-17
(a) Currency code DAPS08

1.6 Evidence statements

1.6.1 Clinical evidence statements

Miscarriage

- No clinically important association between spontaneous miscarriage and hypothyroidism or subclinical hypothyroidism (1 study, low and moderate quality respectively)

Depression

- Clinically important association between depression symptoms and hypothyroidism (1 study, low quality)
- No clinically important association between depression symptoms and subclinical hypothyroidism (1 study, low quality)
- Depression had a low PPV for subclinical thyrotoxicosis (1.1%, 1 study, moderate quality), subclinical hypothyroidism (2.9-9.0%, 2 studies, low quality), combined subclinical and clinical hypothyroidism (10.7%, 1 study, high quality) and feeling more depressed had a low PPV for combined subclinical and clinical hypothyroidism (9.1%, 1 study, moderate quality)

Diabetes mellitus

- There was no clinically important association between AIDM and hypothyroidism and hyperthyroidism in women (1 study, high and low quality respectively).
- There was no clinically important association between T2DM and hypothyroidism and hyperthyroidism in women (1 study, moderate quality).
- There was no/ was no clinically important association between AIDM and hypothyroidism and hyperthyroidism in men (1 study, high and moderate quality respectively).
- There was no clinically important association between T2DM and hypothyroidism and hyperthyroidism in men (1 study, moderate quality).
- Diabetes had a low PPV for subclinical thyrotoxicosis (2.4%, 1 study, moderate quality), combined subclinical and clinical hypothyroidism (17.8%, 1 study, moderate quality)
- AIDM had a low PPV for hypothyroidism (16.4%, 1 study, high quality) and hyperthyroidism (5.5%, 1 study, high quality)
- T2DM had a low PPV for hypothyroidism (10.6%, 1 study, high quality) and hyperthyroidism (3.7%, 1 study, high quality).

Anxiety

- Anxiety had a low PPV for subclinical hypothyroidism (3.2%, 1 study, low quality).

Symptoms

- Hoarser voice had a low PPV for combined subclinical and clinical hypothyroidism (7.7%-10.3%, 2 studies, moderate quality).
- Drier skin had a low PPV for combined subclinical and clinical hypothyroidism (10.4% – 10.5%, 2 studies, moderate quality).
- Feeling colder had a low PPV for combined subclinical and clinical hypothyroidism (9.8%-11.5%, 2 studies, moderate quality).
- Feeling more tired had a low PPV for combined subclinical andclinical hypothyroidism (9.9%-10.7%, 2 studies, low quality).
- Puffier eyes had a low PPV for combined subclinical and clinical hypothyroidism (9.7% - 10.8%, 2 studies, moderate quality).
- More muscle cramps had a low PPV for combined subclinical and clinical hypothyroidism (9.8% - 10.9%, 2 studies, moderate quality)
- More constipation had a low PPV for combined subclinical and clinical hypothyroidism (11% - 11.3%, 2 studies, moderate quality).
- Poorer memory had a low PPV for combined subclinical and clinical hypothyroidism (9.6% - 10.9%, 2 studies, moderate quality).

Atrial fibrillation

- Atrial fibrillation had a low PPV for subclinical thyrotoxiscosis (2.4%, 1 study moderate quality) and for combined subclinical and clinical hypothyroidism (15.5%, 1 study, moderate quality).

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee agreed that the critical outcomes for this review were the association between predictors and thyroid dysfunction and their accuracy as predictors (sensitivity, specificity, positive and negative predictive values). There was particular emphasis on positive predictive value as it gave an indication of the number of tests that would be expected to come back negative in people being tested.

1.7.1.2 The quality of the evidence

The quality of the evidence varied from low to high quality. Accuracy data was typically downgraded due to risk of bias in the underlying studies while association data was typically downgraded due to risk of bias and imprecision.

There were many outcomes on the protocol for which no evidence was identified in this review, the committee noted that this was likely due to the restriction on the minimum number of participants in the studies and the need for key confounders to be adjusted for in non-randomised association studies. However they agreed this restriction was appropriate to determine the most accurate and representative evidence.

1.7.2 Benefits and harms

The evidence in the review identified depression symptoms and type 1 (autoimmune) diabetes as being two indicators for testing with a clinically important association with thyroid dysfunction (in both cases the precise outcome was association with hypothyroidism). The committee agreed that for these predictors it was appropriate to test for thyroid dysfunction even in people without other obvious symptoms or indicators of thyroid dysfunction.

The committee noted that no one symptom of thyroid disease was a good predictor for thyroid dysfunction, with positive predictive values varying but generally around 10%. The symptoms of thyroid disease are often non-specific (for example tiredness, cognitive impairment).

The committee discussed the impact of acute illness on thyroid function tests. They were aware that these tests are often ordered in hospital in the context of non-thyroidal acute illness and generally cannot be interpreted as the underlying acute illness can cause derangement of these markers. This review did not identify any evidence on the role of acute illness.

The committee noted that the review did not capture the importance of the interplay between thyroid dysfunction and co-existing conditions. For example, even though atrial fibrillation did not appear to be a good predictor for thyroid dysfunction, the impact of thyroid dysfunction on atrial fibrillation (essentially making the latter untreatable) was so significant that the committee agreed it was still appropriate to test in this context. The committee also noted that testing in the presence of co-existing conditions (for example depression or anxiety) is more important when the co-existing condition has been shown to be refractory to standard treatment options.

The committee discussed whether they could make specific recommendations about the timing of testing and the need for repetition. They agreed that this was beyond the scope of this review but noted that it would vary from indication to indication and be impacted by the management pathways for any co-existing conditions. Where a co-existing condition leads to

regular annual blood tests (for example type-1 diabetes), thyroid testing may be incorporated into that program.

1.7.3 Cost effectiveness and resource use

No relevant published economic evidence was identified. The committee reviewed the unit costs of different thyroid function tests.

Where there is clinical suspicion of thyroid dysfunction, the committee made recommendations to test, as it is more likely to indicate thyroid disease. The committee noted that if too low a threshold was used and people with one symptom, and no clinical suspicion were also referred for testing, this would lead to increased costs with little benefit, and this strategy would unlikely be cost-effective. However, the committee acknowledge that there could be other reasons to justify referral for testing, for example in autoimmune disease, where the clinical evidence showed a high association to thyroid disease, hence high prevalence in this group is more likely to make the strategy cost-effective. In addition, tests should be offered to people with thyroid dysfunction and who have new-onset atrial fibrillation; where there is likely to be significant complications with thyroid disease, rendering it untreatable and therefore early detection can improve quality of life and is likely to be cost-effective. Furthermore, the committee considered testing in people with co-existing conditions that may benefit from treatment as the co-existing condition may not be easily treated with standard treatment options or can result in severe complications if not detected early. The committee noted that these are current practice and therefore unlikely to have substantial resource impact.

On balance, the committee made a recommendation against the current practice of testing for thyroid dysfunction in acute non-thyroid illness and solely because of the presence of type 2 diabetes. It acknowledged that this recommendations is likely to have substantial cost saving and would reduce uncertainty in the interpretation of results. It noted that TFTs are currently being performed as part of routine clinical assessments in some conditions, such as Type 2 diabetes.

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Appendices

Appendix A: Review protocols

Table 12:

ID	Field	Content
I	Review question	Who should be investigated for thyroid disease?
II	Type of review question	Prognostic/diagnostic A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	Identify groups of people (based on risk factors) that have an increased risk of thyroid disease to inform recommendations about who should and who should not be investigated for thyroid disease
IV	Eligibility criteria – population / disease / condition / issue / domain	• People without a previous diagnosis of thyroid disease
V	Eligibility criteria – exposure(s)/ prognostic factor(s)	Any of the following, alone or in combination: • Co-existing conditions: ○ Obstructive sleep apnoea/hypopnea syndrome (OSAHS) ○ Osteoporosis ○ Autoimmune conditions (e.g. T1DM, RA) ○ Arrhythmia ○ T2DM ○ Congenital conditions (e.g. Turners/Downs/DiGeorge) • Symptoms or signs: ○ Dry skin ○ Hoarse voice ○ Cognitive impairment ○ Tremor ○ Palpitations ○ Muscle cramps ○ Weight loss/gain ○ Tiredness ○ Anxiety ○ Low mood/depression ○ Temperature disturbance ○ Abnormal menstrual cycle ○ Breathlessness ○ Bowel habit changes ○ Infertility/recurrent miscarriage ○ Eye symptoms • Other: ○ Family history of thyroid disease

VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Absence of risk factor
VII	Outcomes and prioritisation	Association with hypothyroidism • RR/OR adjusted for confounders • Sensitivity, specificity, PPV, NPV of risk factors Association with hyperthyroidism • RR/OR adjusted for confounders • Sensitivity, specificity, PPV, NPV of risk factors Due to variety of risk factors under investigation, the committee discussed the importance of the magnitude of association on an outcome by outcome basis

VIII	Eligibility criteria – study design	• Cross-sectional studies for accuracy type data
		• Cross-sectional or cohort studies for association type data
		• Including RR/OR only if adjusted for confounders
		  ○ Age
		  ○ Sex
		  ○ BMI
		  ○ Smoking
		• Including studies only where entire population is tested for thyroid disease

IX	Other inclusion exclusion criteria	• Minimum sample size (n>1000), studies with n>500 considered if insufficient evidence for decision making with sample size >1000 • No minimum duration of follow-up for longitudinal data • Excluding case control studies
X	Proposed sensitivity / subgroup analysis, or meta-regression	**Stratifications** • Age – young children (0-4), children and young people (4-18), adults (>18-65), older adults (>65) • Outcome – clinical vs subclinical **Subgroup analyses** • Age subdivisions (18-50, 50-65, 65-80, >85) • Acute illness vs not • Sex
XI	Selection process – duplicate screening / selection / analysis	• A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please see the separate Methods report for this guideline.
XII	Data management (software)	• EndNote was used for reference management, sifting, citations and bibliographies. • Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).
XIII	Information sources – databases and	Medline and Embase

	dates	
XIV	Identify if an update	Not an update
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10074
XVI	Highlight if amendment to previous protocol	Not an amendment
XVII	Search strategy – for one database	For details please see Appendix B:.
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as Appendix D: of the evidence report.
XIX	Data items – define all variables to be collected	For details please see evidence tables in Appendix D: (clinical evidence tables) or H (health economic evidence tables).
XX	Methods for assessing bias at outcome / study level	QUIPS checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee [to add link to history page of the guideline after publication] developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.

XX VII	Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
XX VIII	Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXI X	Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
XX X	PROSPERO registration number	Not registered

Table 13: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see Appendix B: below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[76] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are

	helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2018 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review. [Add cross reference after publication]

B.1 Clinical search literature search strategy

Searches were constructed using the following approach:

- Population AND Prognostic/risk factor terms AND Study filter(s)

Table 14: Database date parameters and filters used

Database	Dates searched	Search filter used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 07 January 2019	Exclusions Observational studies Prognostic studies
Embase (OVID)	1974 – 07 January 2019	Exclusions Observational studies Prognostic studies

1 **Medline (Ovid) search terms**

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Sleep Apnea, Obstructive/
28.	(obstructive adj2 sleep adj2 apnoea).ti,ab.
29.	"hypopnea syndrome".ti,ab.
30.	Osteoporosis/
31.	(osteoporosis or osteopenia or (bone adj (density or mass or loss)) or hepatic osteodystrophy).ti,ab.
32.	exp autoimmune diseases/
33.	exp Diabetes Mellitus, Type 2/
34.	(Type* adj ("2" or "II" or two) adj (diabete* or diabetic*)).ti,ab.
35.	((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).ti,ab.
36.	((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).ti,ab.

37.	((Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).ti,ab.
38.	NIDDM.ti,ab.
39.	Hashimoto Disease/
40.	(Hashimoto* adj3 (disease* or thyroiditis)).ti,ab.
41.	(thyroid* adj3 (chronic lymphocytic or autoimmun*)).ti,ab.
42.	Arthritis, Rheumatoid/
43.	(rheumatoid adj (arthritis or arthrosis)).ti,ab.
44.	(caplan* adj2 syndrome).ti,ab.
45.	(felty* adj2 syndrome).ti,ab.
46.	(rheumatoid adj2 factor).ti,ab.
47.	((inflammatory or idiopathic) adj2 arthritis).ti.
48.	"inflammatory polyarthritis".ti,ab.
49.	exp Multiple Sclerosis/
50.	((multiple or disseminated) adj scleros*).ti,ab.
51.	encephalomyelitis disseminata.ti,ab.
52.	MS.ti.
53.	celiac disease/
54.	(celiac or coeliac or "gluten sensitive enteropathy" or sprue).ti,ab.
55.	Arrhythmias, Cardiac/
56.	atrial fibrillation/
57.	(atrial adj3 fibrillat*).ti,ab.
58.	(auricular adj3 fibrillat*).ti,ab.
59.	(arrythmia* or Afib or a-fib).ti,ab.
60.	palpitation*.ti,ab.
61.	exp Obesity/
62.	exp Overweight/
63.	Weight Loss/
64.	(obesity or obese).ti.
65.	(weight adj (loss or lost or losing or reduc*)).ti,ab.
66.	(weight adj (gain or increase or rise or rising or risen)).ti,ab.
67.	((over adj (weight or eating)) or overweight).ti,ab.
68.	((under adj (weight or eating)) or underweight).ti,ab.
69.	Turner Syndrome/ or Down syndrome/ or DiGeorge Syndrome/
70.	((turner* or down* or digeorge*) adj syndrome).ti,ab.
71.	myxedema/
72.	(myxedema or myxoedema).ti,ab.
73.	((dry* or wax* or itch* or flak* or crack*) adj3 skin).ti,ab.
74.	Hoarseness/
75.	(hoarseness or ((hoarse or harsh or rasp* or strained) adj3 voice)).ti,ab.
76.	cognitive dysfunction/
77.	(cognitive adj (dysfunction* or impairement* or defec*)).ti,ab.
78.	Muscle Cramp/
79.	(muscle adj3 (spasm* or cramp*)).ti,ab.
80.	depression/
81.	Anxiety/

82.	fatigue/
83.	(tiredness or fatigue or anxiet* or anxious or depression or low mood or tearfulness or irritability or nervousness).ti,ab.
84.	(sleep* adj (disturbance* or difficult* or trouble* or disorder* or problem*)).ti,ab.
85.	body temperature regulation/
86.	(temperature adj2 (disturbance or regulat*)).ti,ab.
87.	Thermogenesis/
88.	thermogenes*.ti,ab.
89.	Menstruation Disturbances/
90.	((long* or heav* or more or increas* or abnormal or irregular or cramp* or pain* or disturb*) adj2 (period* or menses or menstruation)).ti,ab.
91.	exp Dyspnea/
92.	((paroxysmal or exertion*) adj3 (dyspnoea or dyspnea)).ti,ab.
93.	(dyspnoea or dyspnea or "shortness of breath" or breathlessness or air hunger).ti,ab.
94.	Diarrhea/
95.	Constipation/
96.	((digestive or bowel or gut or stool) adj3 (change* or problem* increase or slow-down or slowdown or inconsisten* or irregularit*)).ti,ab.
97.	(constipat* or diarrhoea or diarrhea or bloating or gas or cramping or loose stool* or burping or heartburn or flatulence).ti,ab.
98.	abortion, spontaneous/ or abortion, habitual/
99.	(recurrent miscarriage or habitual abortion or spontaneous abortion or recurrent pregnancy loss or RPL or pregnancy loss).ti,ab.
100.	Photophobia/
101.	photophobia.ti,ab.
102.	((eye* or eyelid*) adj2 (bulge or bulging or staring or grittiness or gritty or dry or water* or swollen or swelling or oedema or edema or fullness or red* or blurr* or double vision or ache or pain or difficult* mov* or retraction)).ti,ab.
103.	Genetic predisposition to disease/
104.	((family or familial or genetic) adj2 (disease* or history)).ti,ab.
105.	((autoimmune or auto immune) adj disease*).ti,ab.
106.	or/27-105
107.	Risk/
108.	Risk Assessment/
109.	Risk Factors/
110.	risk*.ti.
111.	risk factor*.ti,ab.
112.	(risk adj3 assess*).ti,ab.
113.	prevalence/
114.	prevalence.ti,ab.
115.	or/107-114
116.	26 and (106 or 115)
117.	prognosis/
118.	(predict* or prognos*).ti,ab.
119.	Logistic models/
120.	Disease progression/
121.	or/117-120

122.	Epidemiologic studies/
123.	Observational study/
124.	exp Cohort studies/
125.	(cohort adj (study or studies or analys* or data)).ti,ab.
126.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
127.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
128.	Controlled Before-After Studies/
129.	Historically Controlled Study/
130.	Interrupted Time Series Analysis/
131.	(before adj2 after adj2 (study or studies or data)).ti,ab.
132.	or/122-131
133.	exp case control study/
134.	case control*.ti,ab.
135.	or/133-134
136.	132 or 135
137.	Cross-sectional studies/
138.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
139.	or/137-138
140.	132 or 139
141.	132 or 135 or 139
142.	116 and (121 or 141)

1 **Embase (Ovid) search terms**

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/

21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	sleep disordered breathing/
25.	(obstructive adj2 sleep adj2 apnoea).ti,ab.
26.	"hypopnea syndrome".ti,ab.
27.	*osteoporosis/
28.	(osteoporosis or osteopenia or (bone adj (density or mass or loss)) or hepatic osteodystrophy).ti,ab.
29.	exp autoimmune disease/
30.	*non insulin dependent diabetes mellitus/
31.	(Type* adj ("2" or "II" or two) adj (diabete* or diabetic*)).ti,ab.
32.	((Maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).ti,ab.
33.	((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).ti,ab.
34.	((Non insulin* or Noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).ti,ab.
35.	NIDDM.ti,ab.
36.	((autoimmune or auto immune) adj disease*).ti,ab.
37.	*hashimoto disease/
38.	(Hashimoto* adj3 (disease* or thyroiditis)).ti,ab.
39.	(thyroid* adj3 (chronic lymphocytic or autoimmun*)).ti,ab.
40.	*rheumatoid arthritis/
41.	(rheumatoid adj (arthritis or arthrosis)).ti,ab.
42.	(caplan* adj2 syndrome).ti,ab.
43.	(felty* adj2 syndrome).ti,ab.
44.	(rheumatoid adj2 factor).ti,ab.
45.	((inflammatory or idiopathic) adj2 arthritis).ti.
46.	"inflammatory polyarthritis".ti,ab.
47.	*multiple sclerosis/
48.	((multiple or disseminated) adj scleros*).ti,ab.
49.	encephalomyelitis disseminata.ti,ab.
50.	MS.ti.
51.	celiac disease/
52.	(celiac or coeliac or "gluten sensitive enteropathy" or sprue).ti,ab.
53.	heart arrhythmia/
54.	atrial fibrillation/
55.	(atrial adj3 fibrillat*).ti,ab.
56.	(auricular adj3 fibrillat*).ti,ab.
57.	(arrythmia* or Afib or a-fib).ti,ab.
58.	palpitation*.ti,ab.
59.	exp obesity/
60.	*weight reduction/
61.	(obesity or obese).ti.
62.	(weight adj (loss or lost or losing or reduc*)).ti,ab.
63.	(weight adj (gain or increase or rise or rising or risen)).ti,ab.
64.	((over adj (weight or eating)) or overweight).ti,ab.

65.	((under adj (weight or eating)) or underweight).ti,ab.
66.	digeorge syndrome/ or turner dysndrome/ or down syndrome/
67.	((turner* or down* or digeorge*) adj syndrome).ti,ab.
68.	myxedema/
69.	(myxedema or myxoedema).ti,ab.
70.	((dry* or wax* or itch* or flak* or crack*) adj3 skin).ti,ab.
71.	hoarseness/
72.	(hoarseness or ((hoarse or harsh or rasp* or strained) adj3 voice)).ti,ab.
73.	*cognitive defect/
74.	(cognitive adj (dysfunction* or impairement* or defec*)).ti,ab.
75.	muscle cramp/
76.	(muscle adj3 (spasm* or cramp*)).ti,ab.
77.	*depression/
78.	*anxiety/
79.	*fatigue/
80.	(tiredness or fatigue or anxiet* or anxious or depression or low mood or tearfulness or irritability or nervousness).ti,ab.
81.	(sleep* adj (disturbance* or difficult* or trouble* or disorder* or problem*)).ti,ab.
82.	thermoregulation/
83.	(temperature adj2 (disturbance or regulat*)).ti,ab.
84.	*thermogenesis/
85.	thermogenes*.ti,ab.
86.	menstruation disorder/
87.	((long* or heav* or more or increas* or abnormal or irregular or cramp* or pain* or disturb*) adj2 (period* or menses or menstruation)).ti,ab.
88.	*dyspnea/
89.	((paroxysmal or exertion*) adj3 (dyspnoea or dyspnea)).ti,ab.
90.	(dyspnoea or dyspnea or "shortness of breath" or breathlessness or air hunger).ti,ab.
91.	*diarrhea/
92.	constipation/
93.	((digestive or bowel or gut or stool) adj3 (change* or problem* increase or slow-down or slowdown or inconsisten* or irregularit*)).ti,ab.
94.	(constipat* or diarrhoea or diarrhea or bloating or gas or cramping or loose stool* or burping or heartburn).ti,ab.
95.	*spontaneous abortion/
96.	recurrent abortion/
97.	(recurrent miscarriage or habitual abortion or spontaneous abortion or recurrent pregnancy loss or RPL or pregnancy loss).ti,ab.
98.	*photophobia/
99.	photophobia.ti,ab.
100.	((eye* or eyelid*) adj2 (bulge or bulging or staring or grittiness or gritty or dry or water* or swollen or swelling or oedema or edema or fullness or red* or blurr* or double vision or ache or pain or difficult* mov* or retraction)).ti,ab.
101.	exp genetic predisposition/
102.	((family or familial or genetic) adj2 (disease* or history)).ti,ab.
103.	*risk/
104.	risk factor/

105.	*risk assessment/
106.	risk*.ti.
107.	risk factor*.ti,ab.
108.	(risk adj3 assess*).ti,ab.
109.	prevalence/
110.	prevalence.ti,ab.
111.	or/24-102
112.	or/103-110
113.	23 and (111 or 112)
114.	exp prognosis/
115.	prognostic assessment/
116.	(predict* or prognos*).ti,ab.
117.	disease course/
118.	statistical model/
119.	or/114-118
120.	Clinical study/
121.	Observational study/
122.	family study/
123.	longitudinal study/
124.	retrospective study/
125.	prospective study/
126.	cohort analysis/
127.	follow-up/
128.	cohort*.ti,ab.
129.	127 and 128
130.	(cohort adj (study or studies or analys* or data)).ti,ab.
131.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
132.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
133.	(before adj2 after adj2 (study or studies or data)).ti,ab.
134.	or/120-126,129-133
135.	exp case control study/
136.	case control*.ti,ab.
137.	or/135-136
138.	134 or 137
139.	cross-sectional study/
140.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
141.	or/139-140
142.	134 or 141
143.	134 or 137 or 141
144.	113 and (119 or 143)
145.	Limit 144 to English language

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a thyroid disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 15: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 07 January 2019	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	2014 – 07 January 2019	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 07 January 2019 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/

22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	quality-adjusted life years/
55.	sickness impact profile/
56.	(quality adj2 (wellbeing or well being)).ti,ab.
57.	sickness impact profile.ti,ab.
58.	disability adjusted life.ti,ab.
59.	(qal* or qtime* or qwb* or daly*).ti,ab.
60.	(euroqol* or eq5d* or eq 5*).ti,ab.
61.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63.	(hui or hui1 or hui2 or hui3).ti,ab.
64.	(health* year* equivalent* or hye or hyes).ti,ab.
65.	discrete choice*.ti,ab.

66.	rosser.ti,ab.
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
71.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73.	or/54-72
74.	26 and (43 or 53 or 73)

1 **Embase (Ovid) search terms**

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis*.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/

31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	statistical model/
40.	exp economic aspect/
41.	39 and 40
42.	*theoretical model/
43.	*nonbiological model/
44.	stochastic model/
45.	decision theory/
46.	decision tree/
47.	monte carlo method/
48.	(markov* or monte carlo).ti,ab.
49.	econom* model*.ti,ab.
50.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
51.	or/41-50
52.	quality adjusted life year/
53.	"quality of life index"/
54.	short form 12/ or short form 20/ or short form 36/ or short form 8/
55.	sickness impact profile/
56.	(quality adj2 (wellbeing or well being)).ti,ab.
57.	sickness impact profile.ti,ab.
58.	disability adjusted life.ti,ab.
59.	(qal* or qtime* or qwb* or daly*).ti,ab.
60.	(euroqol* or eq5d* or eq 5*).ti,ab.
61.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63.	(hui or hui1 or hui2 or hui3).ti,ab.
64.	(health* year* equivalent* or hye or hyes).ti,ab.
65.	discrete choice*.ti,ab.
66.	rosser.ti,ab.
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.

71.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73.	or/52-72
74.	24 and (38 or 51 or 73)

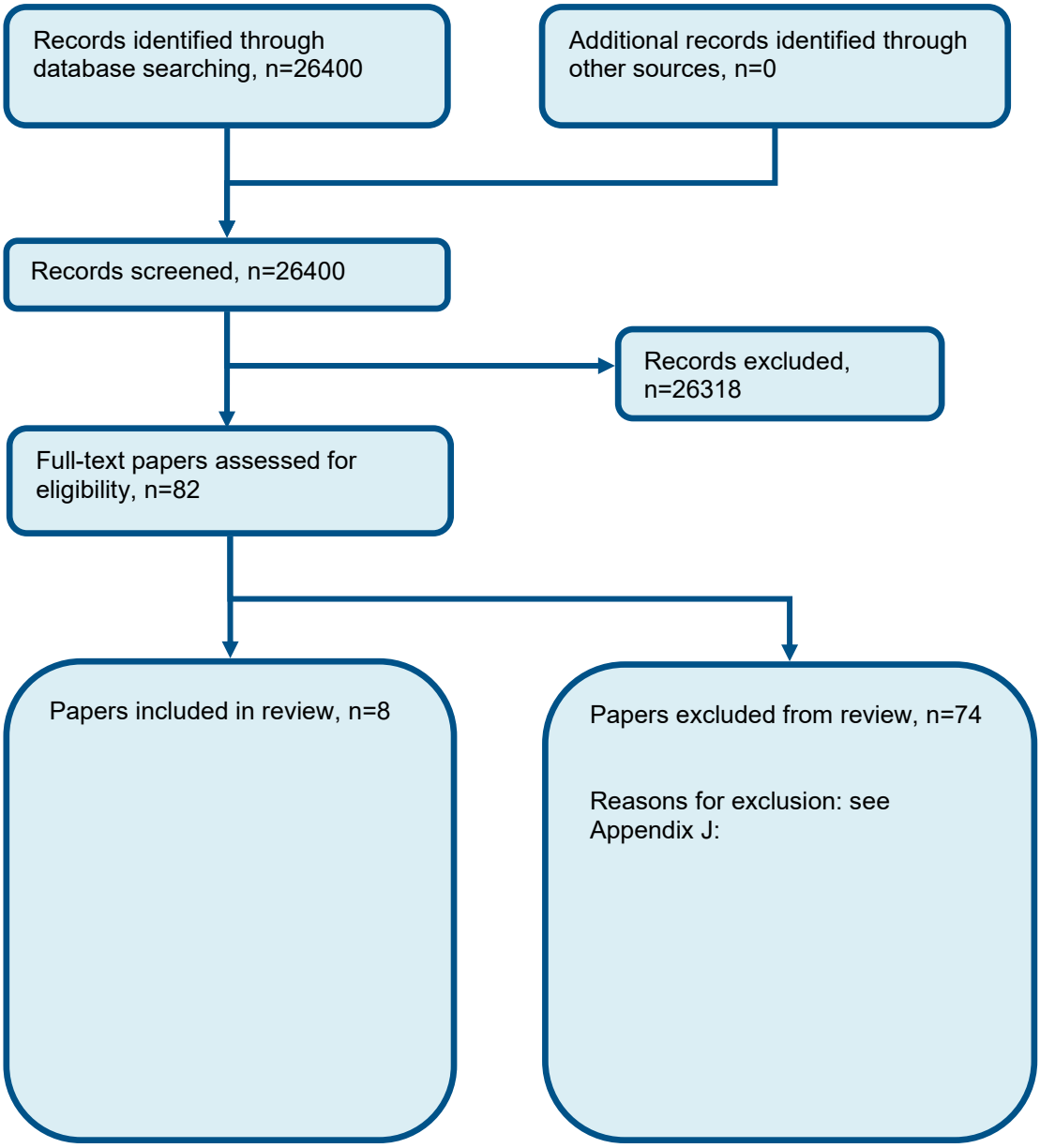
1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Thyroid Diseases EXPLODE ALL TREES
#2.	hyperthyroid*
#3.	hypothyroid*
#4.	thyrotoxicosis*
#5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*))
#6.	#1 OR #2 OR #3 OR #4 or #5

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of who should be tested



1

2

Appendix D: Clinical evidence tables

Reference	Almeida 2011[6]
Study type and analysis	Cross-sectional study
Number of participants and characteristics	n=3932 Depression n=189 (4.8%) SCH n=428 (10.8%) SCT n=31 (1.0%) Inclusion criteria: Age >65 No previous thyroid disease Selection: Randomly selected from electoral register Sample of 41,000 19,352 invited to screening trial (unrelated topic) 12,203 attended screening appointment 5,585 completed assessment 4,249 donated morning blood sample 3,932 with full results meeting inclusion criteria Baseline details: 55% overweight, 20% obese
Prognostic variable	Depression (self-rated by Geriatric Depression Scale, score of 7 or more)
Confounders strategy	Not applicable

Reference	Almeida 2011[6]
Outcomes and effect sizes	Fasting blood sample done in the morning. SCH if TSH >4 mIU/L and fT4 >10pmol/L, SCT TSH <0.4mIU/L and fT4 10-23pmol/L SCT: PPV: 1.1% NPV 99.2% SN: 6% (1% to 21%) SP: 95% (94% to 96%) SCH: PPV: 9.0% NPV 89.0% SN: 4% (2% to 6%) SP: 95% (94% to 96%)
Comments	High risk of bias due to study attrition

Reference	Canaris 2000[20]
Study type and analysis	Cross-sectional study
Number of participants and characteristics	n=25,862 SCH/clinical hypothyroidism prevalence = 9.5% Inclusion criteria: Participants in a Colorado Health fair Selection: 33,661 participants in fair 6,319 excluded as no thyroid survey results

<table>
<tr><th>Reference</th><th>Canaris 2000[20]</th></tr>
<tr><td></td><td>1,480 excluded as no thyroid function tests available

Baseline details:
Median age 56</td></tr>
<tr><td>Prognostic variable</td><td>Thyroid symptoms (new or changed), self-assessed by survey:
Hoarser voice
Drier skin
Feeling colder
More tired
Puffier eyes
More muscle cramps
More constipation
Poorer memory</td></tr>
<tr><td>Confounders strategy</td><td>Not applicable</td></tr>
<tr><td>Outcomes and effect sizes</td><td>Fasting blood sample done in the morning. Euthyroid if TSH 0.3-5.1mIU/L, hypothyroid TSH >5.1mIU/L and T4 <57.9 nmol/L. SCH if TSH >5.1mIU/L and T4 >/= 57.9nmol/L. Accuracy results only provided for combination of clinical and subclinical hypothyroidism
<table>
<tr><th></th><th>SN</th><th>SP</th><th>PPV</th><th>NPV</th></tr>
<tr><td>Hoarser voice</td><td>6% (5% to 6%)</td><td>95% (95% to 95%)</td><td>10.3%</td><td>90.6%</td></tr>
<tr><td>Drier skin</td><td>28% (27% to 30%)</td><td>75% (74% to 75%)</td><td>10.5%</td><td>90.9%</td></tr>
<tr><td>Colder</td><td>15% (13% to 16%)</td><td>88% (88% to 89%)</td><td>11.5%</td><td>90.8%</td></tr>
<tr><td>More tired</td><td>18% (17% to 20%)</td><td>84% (84% to 84%)</td><td>10.7%</td><td>90.8%</td></tr>
<tr><td>Puffier eyes</td><td>11% (10% to 13%)</td><td>90% (90% to 91%)</td><td>10.8%</td><td>90.7%</td></tr>
<tr><td>Muscle cramps</td><td>18% (16% to 19%)</td><td>85% (84% to 85%)</td><td>10.9%</td><td>90.8%</td></tr>
<tr><td>More constipation</td><td>6% (5% to 7%)</td><td>95% (95% to 95%)</td><td>11.3%</td><td>90.6%</td></tr>
<tr><td>Poorer memory</td><td>24% (23% to 26%)</td><td>79% (79% to 80%)</td><td>10.9%</td><td>90.9%</td></tr>
</table></td></tr>
<tr><td>Comments</td><td>Low risk of bias</td></tr>
</table>

Reference	Canaris 2013[21]
Study type and analysis	Cross-sectional study
Number of participants and characteristics	n=794 SCH/clinical hypothyroidism prevalence = 11.5% Inclusion criteria: Volunteers at a Michigan Health fair during Thyroid Awareness week Selection: 858 people volunteered 64 excluded because did not have full results Those with previous thyroid disease excluded from this analysis Baseline details: Mean age 51.9 42% with FMH of thyroid disease
Prognostic variable	Thyroid symptoms (new or changed in last year), self-assessed by survey: Hoarser voice Drier skin Feeling colder More tired Puffier eyes More muscle cramps More constipation Poorer memory
Confounders strategy	Not applicable
Outcomes and effect sizes	Non-fasting blood sample, thyroid status based solely on TSH (no FT4 measurement). TSH >5.5uIU/ml classified as hypothyroid

	SN	SP	PPV	NPV

Reference	Canaris 2013[21]				
	Hoarser voice	6% (5% to 6%)	90% (87% to 92%)	7.7%	88.0%
	Drier skin	30% (20% to 41%)	66% (63% to 70%)	10.4%	87.9%
	Colder	13% (6% to 23%)	84% (81% to 87%)	9.8%	88.1%
	More tired	34% (23% to 45%)	59% (55% to 63%)	9.9%	87.4%
	Puffier eyes	14% (7% to 24%)	82% (79% to 85%)	9.7%	88.1%
	Muscle cramps	18% (10% to 29%)	78% (74% to 81%)	9.8%	88.0%
	More constipation	9% (4% to 18%)	90% (88% to 93%)	11.0%	88.4%
	More depressed	22% (13% to 33%)	71% (67% to 75%)	9.1%	87.5%
	Poorer memory	26% (17% to 37%)	68% (64% to 72%)	9.6%	87.6%
Comments	High risk of bias due to outcome measurement				

Reference	Cappola 2006[22]
Study type and analysis	Cross-sectional study
Number of participants and characteristics	n=3233 Atrial fibrillation 5.2% Diabetes 14.0% Inclusion criteria: Age >65 No previous thyroid disease or medication that could affect TFTs Non-institutionalised No active treatment for cancer Not wheelchair bound Capable of consenting

Reference	Cappola 2006[22]
	Selection: Randomly selected from medicare register, household members also invited Sample of 5888, no information on numbers screened 3699 samples tested, no information on reason for number not with blood samples 3233 met final inclusion criteria Baseline details: Mean age 72.7 (SD 5.6) 60% female 95% white race Mean BMI 26.2 51% current or former smokers
Prognostic variable	Atrial fibrillation (self-reported or as assessed by baseline ECG) Diabetes (type not specified, based on baseline fasting blood glucose >7mmol/L)
Confounders strategy	Not applicable
Outcomes and effect sizes	Fasting blood sample done in the morning. FT4 only done on those with abnormal TSH, done in 95% of those cases (where serum available). SCT if TSH 0.10-0.44mU/L or less than 0.10 with a normal FT4. SCH if TSH >4.5mU/L and <20mU/L with normal FT4. Overt hypothyroidism if TSH >20mU/L or TSH >4.5mU/L with FT4 below normal (0.7ng/dL). AF: SCT: PPV: 2.4% NPV 98.5% SN: 9% (2% to 20%) SP: 95% (94% to 96%) Hypo/SCH:

Reference	Cappola 2006[22]
	PPV: 15.5% NPV 83.0% SN: 5% (3% to 7%) SP: 95% (94% to 96%) DM: SCT: PPV: 2.4% NPV 98.7% SN: 23% (12% to 38%) SP: 86% (85% to 87%) Hypo/SCH: PPV: 17.8% NPV 83.2% SN: 15% (12% to 18%) SP: 86% (85% to 87%)
Comments	High risk of bias due to study participation, study attrition

Reference	Engum 2005[39]
Study type and analysis	Cross-sectional study
Number of participants and characteristics	n=30,175 Depression: 13.2% Anxiety: 16.7% Thyroid autoimmunity: 3.3%

Reference	Engum 2005[39]
	Inclusion criteria: Aged 40 to 84 HADS and blood test results available from HUNT Selection: 92,100 invited 65,648 responded 30,175 meeting inclusion criteria Baseline details: No other information provided
Prognostic variable	Depression assessed by HADS-D (cut-off 8) Anxiety assessed by HADS-A (cut-off 11)
Confounders strategy	Not applicable
Outcomes and effect sizes	Thyroid autoimmunity: TSH carried out in all women and 50% of men. T4 measured if TSH abnormal. TPOAb measured in all samples with TSH >/= 4.0mU/l (n=1700) and in randomly selected samples from people with normal TSH who answered no to symptom survey (n=745). 995 were TPOAb positive of which 78 had normal thyroid function, 15 had decreased TSH levels, 902 had elevated TSH levels. T4 was normal in 784 individuals, T4 was decreased in 157 individuals. Depression: PPV: 2.9% NPV: 96.6% SN: 12% (10% to 14%) SP: 87% (86% to 87%) Anxiety: PPV: 3.2% NPV: 96.7%

Reference	Engum 2005[39]
	SN: 16% (14% to 19%) SP: 83% (83% to 84%)
Comments	Risk of bias very high due to study participation, attrition and outcome measurement

Reference	Feldthusen 2015[40]
Study type and analysis	Cross-sectional study
Number of participants and characteristics	n=11,254 Spontaneous miscarriage: 21% SCH: 6.7% Hypothyroidism: 9.4% Inclusion criteria: Women aged 20 to 84 (100% of women aged >30 invited) European origin Questionnaire and TFT results available Selection: All women in age range in county invited 45% participated (11,565) Of those 11,254 met inclusion criteria Baseline details: Mean age 56.3 Mean BMI 25.3 16.9% smoker
Prognostic variable	Spontaneous miscarriage (at least one, self-reported)
Confounders	Logistic regression using age, menopause, BMI, smoking, diabetes, antiHTN medication, cholesterol lowering medication,

Reference	Feldthusen 2015[40]
strategy	contraception, income, unemployment, education
Outcomes and effect sizes	Hypothyroidism: TSH> 3.7mU/L, FT4 and FT3 below the reference range SCH: TSH> 3.7mU/L, FT4 and FT3 in the reference range Hypothyroidism: aOR 1.02 (0.89 to 1.22) Subclinical hypothyroidism: aOR 0.96 (0.79 to 1.17)
Comments	High risk of bias for hypothyroidism due to study attrition and outcome measurement, low risk of bias for SCH

Reference	Fleiner 2016[42]
Study type and analysis	Cross-sectional study
Number of participants and characteristics	n = 48,809 T2DM: 3.1% Autoimmune diabetes: 0.5% Hypothyroidism: 6.8% Hyperthyroidism: 3.6% Inclusion criteria: Inhabitants aged 20 and older in HUNT3 Complete blood test and survey data available Selection: All people in age range in county invited 54% of those invited (93,860) participated

Reference	Fleiner 2016[42]
	48,809 available for hypothyroidism results 39,940 available for hyperthyroidism results Baseline details: Median age 53 for no diabetes, 51 for AIDM, 66 for T2DM Median BMI 27 for no diabetes, 28 for AIDM, 31 for T2DM
Prognostic variable	Diabetes (self-reported), classified as AIDM if GADA results available (64%) and supporting or if diagnosed at age 30 or younger
Confounders strategy	Logistic regression using age, smoking, BMI and stratified by gender
Outcomes and effect sizes	Hypothyroidism: TSH> 4.5mU/L, FT4 and FT3 below the reference range Hyperthyroidism: TSH< 0.45mU/L, FT4 and FT3 in the reference range Association data: Hypothyroidism, women, AIDM: 2.15 (1.54 to 2.99) Hypothyroidism, women, T2DM: 1.09 (0.91 to 1.32) Hyperthyroidism, women, AIDM: 0.89 (0.32 to 2.33) Hyperthyroidism, women, T2DM: 1.09 (0.77 to 1.54) Hypothyroidism, men, AIDM: 4.12 (2.49 to 6.80) Hypothyroidism, men, T2DM: 1.15 (0.84 to 1.57) Hyperthyroidism, men, AIDM: 3.79 (1.75 to 8.23) Hyperthyroidism, men, T2DM: 0.79 (0.45 to 1.38) Accuracy data: T2DM as predictor for hypothyroidism: PPV: 10.6%

Reference	Fleiner 2016[42]
	NPV: 93.3% SN: 5% (4% to 6%) SP: 97% (97% to 97%) AIDM as predictor for hypothyroidism: PPV: 16.4% NPV: 93.2% SN: 1% (1% to 2%) SP: 99% (99% to 100%) T2DM as predictor for hyperthyroidism: PPV: 3.7% NPV: 96.3% SN: 3.5% (3% to 5%) SP: 96.6% (96% to 97%) AIDM as predictor for hyperthyroidism: PPV: 5.5% NPV: 96.4% SN: 1% (0% to 1%) SP: 100% (99% to 100%)
Comments	Low risk of bias

Reference	Guimaraes 2009[49]
Study type and analysis	Cross-sectional study
Number of participants	n = 1,249

Reference	Guimaraes 2009[49]
and characteristics	Depression symptoms: 45.7% Hypothyroidism: 1.6% Hyperthyroidism: 8.2% Inclusion criteria: Women in Rio de Janeiro Not pregnant or lactating No hyperthyroidism Selection: 15 households randomly sampled from 100 primary sample units in the city One female resident selected from each household Sample of 1,500 participants 1,298 participants responded After exclusion of those with hyperthyroidism and missing results 1,249 Baseline details: Mean age of 53.6 46.4% white 33.1% overweight
Prognostic variable	Depression symptoms (based on self-assessment with 12 yes/no questionnaire (PRIME-MD))
Confounders strategy	Restricted to women, adjusted for age, race, smoking, BMI
Outcomes and effect sizes	Hypothyroidism: TSH >4mU/L, FT4<0.7ng/dL SCH: TSH >4mU/L, normal FT4 Association data: Hypothyroidism: 8.05 (2.38 to 27.21) SCH: 1.02 (0.60 to 1.74)

Reference	Guimaraes 2009[49]
	Accuracy data: Depressive symptoms as predictor for SCH/hypothyroidism: PPV: 10.7% NPV: 90.8% SN: 50% (40% to 59%) SP: 55% (52% to 58%)
Comments	High risk of bias due to prognostic factor measurement

Appendix E: Forest plots

E.1 Association data

Figure 2: Depression symptoms and hypothyroidism

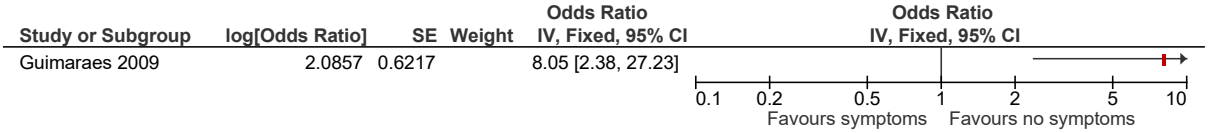


Figure 3: Depression symptoms and subclinical hypothyroidism

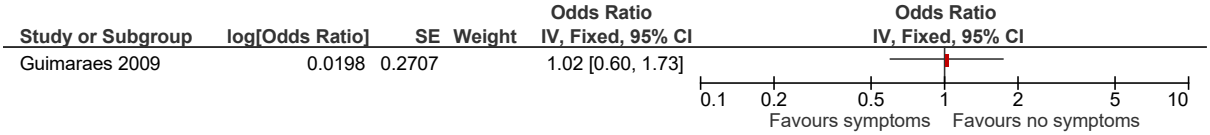


Figure 4: Spontaneous miscarriage and hypothyroidism

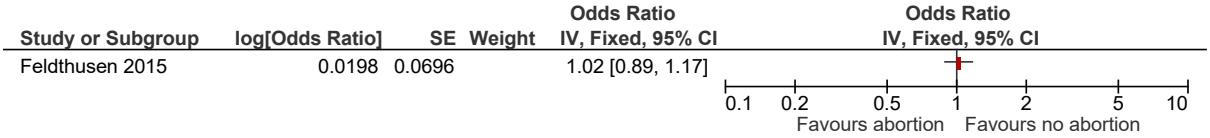


Figure 5: Spontaneous miscarriage and subclinical hypothyroidism

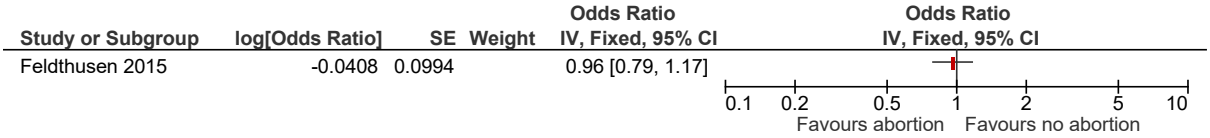


Figure 6: AIDM and hypothyroidism, in women

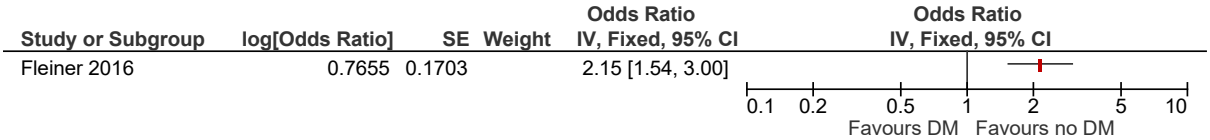
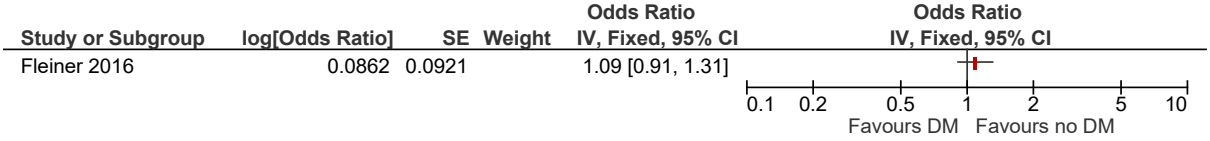
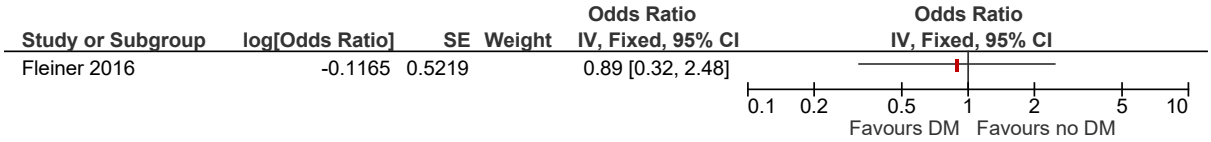


Figure 7: T2DM and hypothyroidism, in women



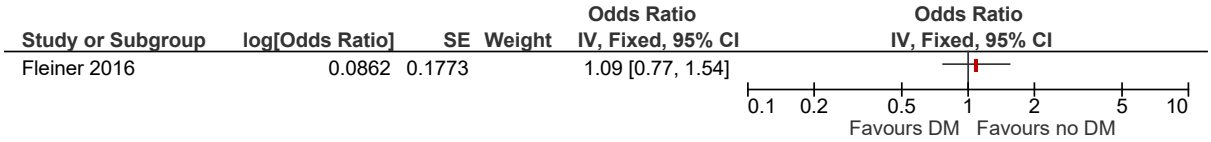
1

Figure 8: AIDM and hyperthyroidism, in women



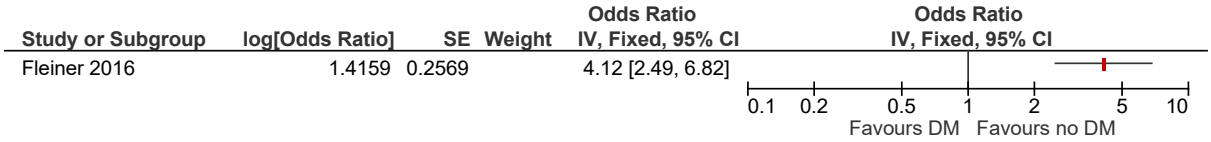
2

Figure 9: T2DM and hyperthyroidism, in women



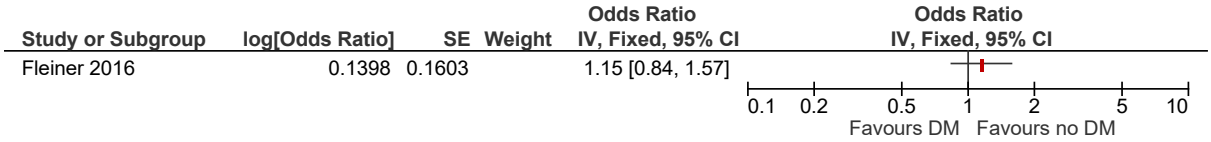
3

Figure 10: AIDM and hypothyroidism, in men



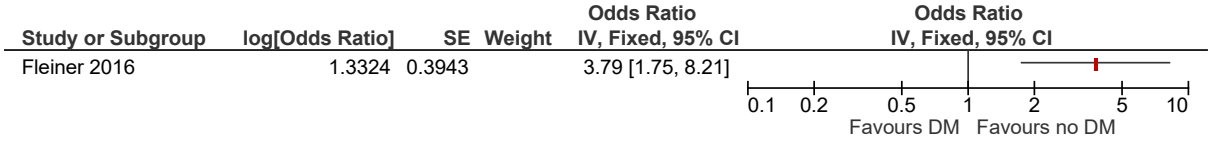
4

Figure 11: T2DM and hypothyroidism, in men



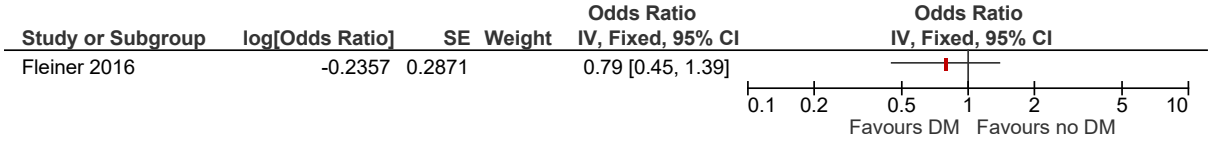
5

Figure 12: AIDM and hyperthyroidism, in men



6

Figure 13: T2DM and hyperthyroidism, in men



E.2 Accuracy data

Figure 14: Depression

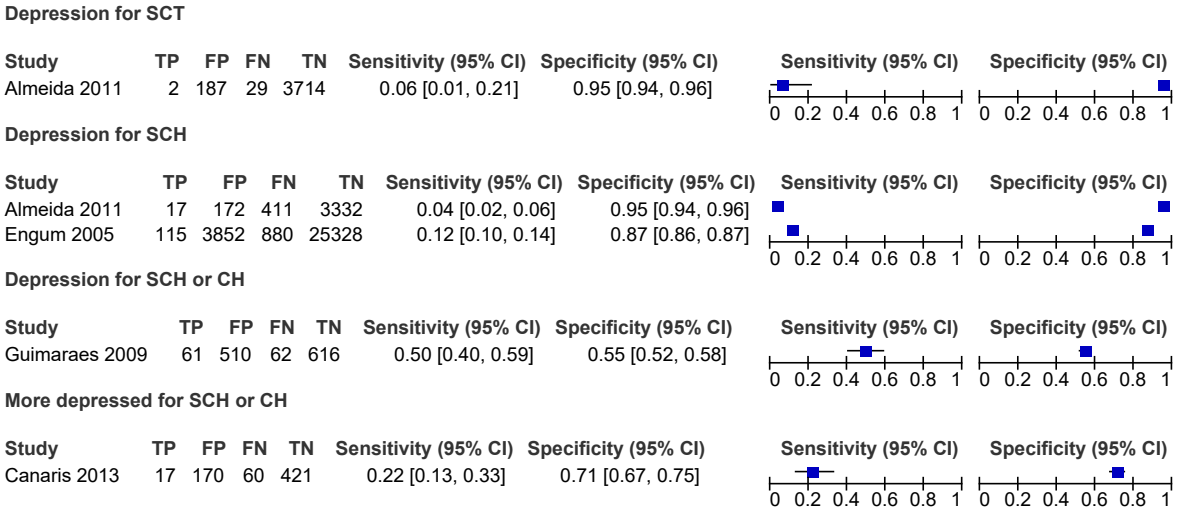


Figure 15: Anxiety

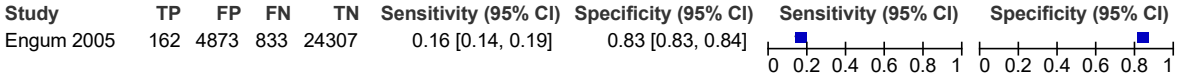
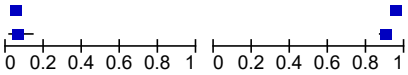


Figure 16: Symptoms

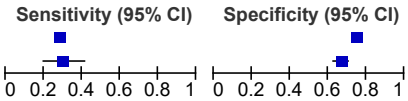
Hoarser voice for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Canaris 2000	135	1171	2315	22241	0.06 [0.05, 0.06]	0.95 [0.95, 0.95]
Canaris 2013	5	62	72	529	0.06 [0.02, 0.15]	0.90 [0.87, 0.92]



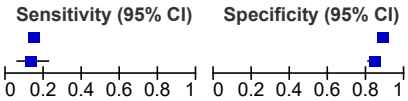
Drier skin for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Canaris 2000	693	5923	1757	17489	0.28 [0.27, 0.30]	0.75 [0.74, 0.75]
Canaris 2013	23	198	54	393	0.30 [0.20, 0.41]	0.66 [0.63, 0.70]



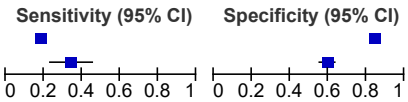
Feeling colder for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Canaris 2000	358	2763	2092	20649	0.15 [0.13, 0.16]	0.88 [0.88, 0.89]
Canaris 2013	10	95	67	496	0.13 [0.06, 0.23]	0.84 [0.81, 0.87]



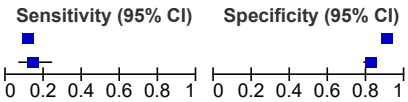
More tired for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Canaris 2000	448	3746	2002	19666	0.18 [0.17, 0.20]	0.84 [0.84, 0.84]
Canaris 2013	26	240	51	351	0.34 [0.23, 0.45]	0.59 [0.55, 0.63]



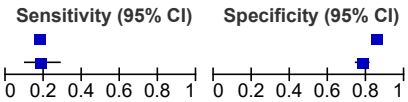
Puffier eyes for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Canaris 2000	277	2294	2173	21118	0.11 [0.10, 0.13]	0.90 [0.90, 0.91]
Canaris 2013	11	106	66	485	0.14 [0.07, 0.24]	0.82 [0.79, 0.85]



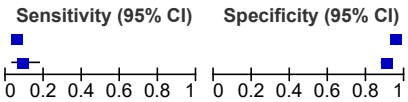
More muscle cramps for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Canaris 2000	431	3535	2019	19877	0.18 [0.16, 0.19]	0.85 [0.84, 0.85]
Canaris 2013	14	131	63	460	0.18 [0.10, 0.29]	0.78 [0.74, 0.81]



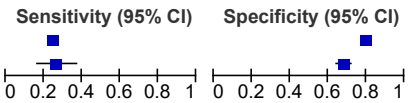
More constipation for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Canaris 2000	149	1171	2301	22241	0.06 [0.05, 0.07]	0.95 [0.95, 0.95]
Canaris 2013	7	57	70	534	0.09 [0.04, 0.18]	0.90 [0.88, 0.93]



Poorer memory for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Canaris 2000	600	4893	1850	18519	0.24 [0.23, 0.26]	0.79 [0.79, 0.80]
Canaris 2013	20	189	57	402	0.26 [0.17, 0.37]	0.68 [0.64, 0.72]

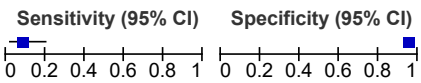


1

Figure 17: Atrial fibrillation

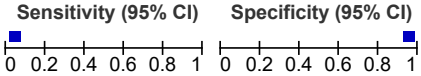
Atrial fibrillation for SCT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cappola 2006	4	163	43	3023	0.09 [0.02, 0.20]	0.95 [0.94, 0.96]



Atrial fibrillation for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cappola 2006	26	141	521	2545	0.05 [0.03, 0.07]	0.95 [0.94, 0.96]

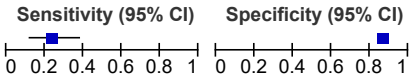


2

Figure 18: Diabetes

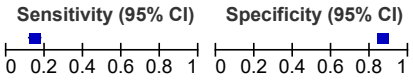
Diabetes for SCT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cappola 2006	11	443	36	2743	0.23 [0.12, 0.38]	0.86 [0.85, 0.87]



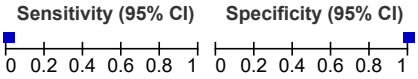
Diabetes for SCH or CH

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cappola 2006	81	373	466	2313	0.15 [0.12, 0.18]	0.86 [0.85, 0.87]



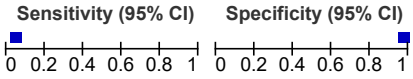
Diabetes (AIDM only) for hypothyroidism

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fleiner 2016	40	204	3282	45283	0.01 [0.01, 0.02]	1.00 [0.99, 1.00]



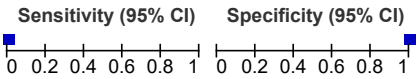
Diabetes (T2DM only) for hypothyroidism

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fleiner 2016	161	1353	3161	44134	0.05 [0.04, 0.06]	0.97 [0.97, 0.97]



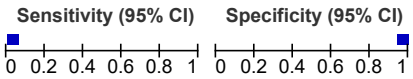
Diabetes (AIDM only) for hyperthyroidism

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fleiner 2016	11	190	1429	38310	0.01 [0.00, 0.01]	1.00 [0.99, 1.00]



Diabetes (T2DM only) for hyperthyroidism

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fleiner 2016	50	1299	1390	37201	0.03 [0.03, 0.05]	0.97 [0.96, 0.97]



Appendix F: GRADE tables

Table 16: Clinical evidence profile: association data for depression symptoms

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	
Depression symptoms and hypothyroidism								
1	Cross-sectional study	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	Adjusted OR: 8.05 (2.38 to 27.23)	LOW
Depression symptoms and subclinical hypothyroidism								
1	Cross-sectional study	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	Adjusted OR: 1.02 (0.60 to 1.73)	LOW

[1] Downgraded by 1 or 2 increments because evidence was at high or very high risk of bias as per QUIPS assessment, see Appendix D: for more information
[2] Downgraded by 1 increment as the 95% CI crosses the null line or subjectively wide confidence intervals, downgraded by 2 increments if the 95% CI crosses the null line and subjectively wide confidence intervals

Table 17: Clinical evidence profile: association data for spontaneous miscarriage

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Pooled effect (95% CI)	

Spontaneous miscarriage and hypothyroidism								
1	Cross-sectional study	serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	Adjusted OR: 1.02 (0.89 to 1.17)	LOW
Spontaneous miscarriage and subclinical hypothyroidism								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	Adjusted OR: 0.96 (0.79 to 1.17)	MODERATE

[1] Downgraded by 1 or 2 increments because evidence was at high or very high risk of bias as per QUIPS assessment, see Appendix D: for more information
[2] Downgraded by 1 increment because the confidence interval crossed the null line

Table 18: Clinical evidence profile: association data for diabetes mellitus

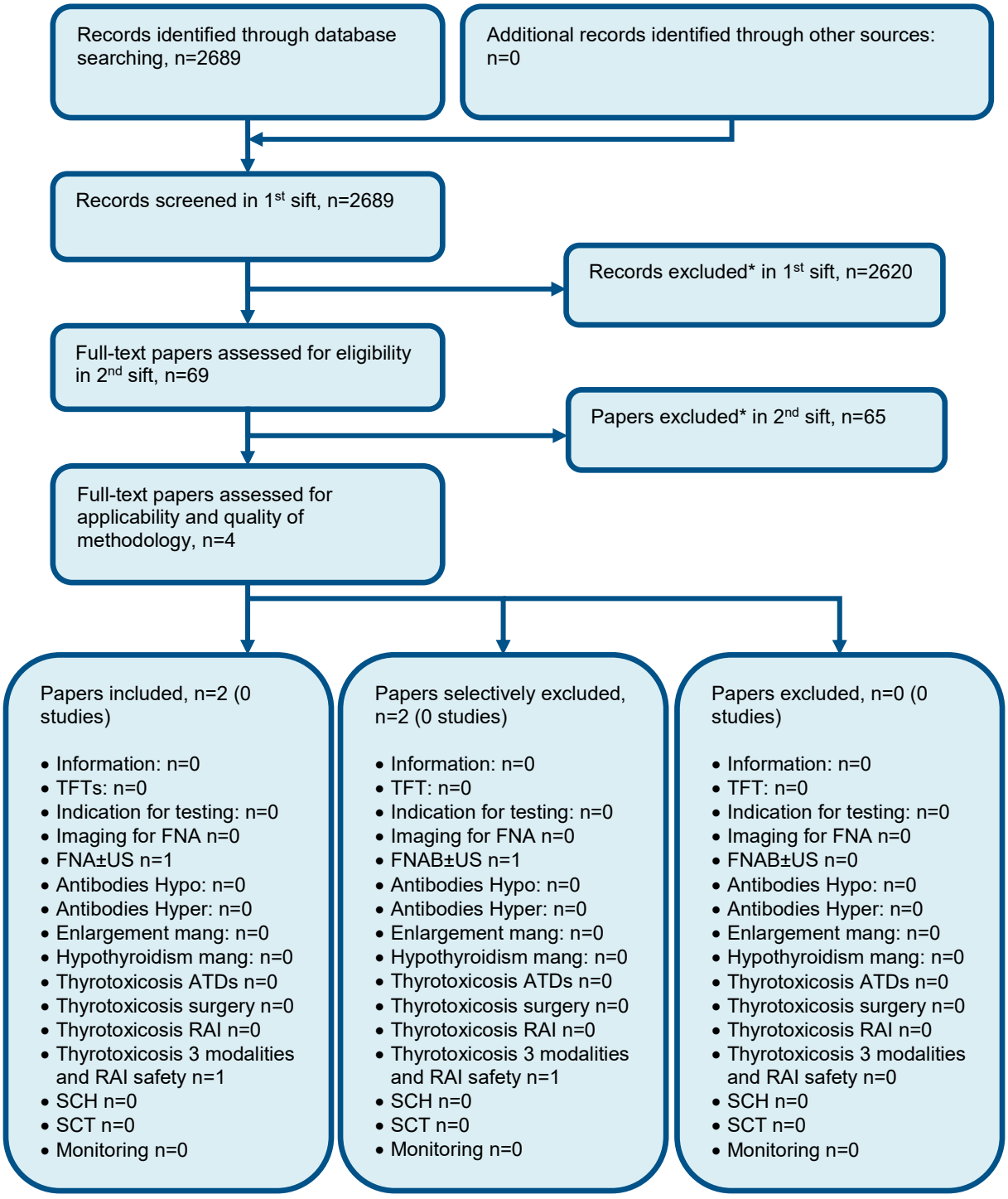
Quality assessment							Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Pooled effect (95% CI)**	
AIDM and hypothyroidism, in women								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted OR: 2.15 (1.54 to 3.00)	HIGH
T2DM and hypothyroidism, in women								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	Adjusted OR: 1.09 (0.91 to 1.31)	MODERATE
AIDM and hyperthyroidism, in women								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious imprecision[1]	none	Adjusted OR: 0.89 (0.32 to 2.48)	LOW
T2DM and hyperthyroidism, in women								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	Adjusted OR: 1.09 (0.77 to 1.54)	MODERATE

AIDM and hypothyroidism, in men								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted OR: 4.12 (2.49 to 6.82)	HIGH
T2DM and hypothyroidism, in men								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	Adjusted OR: 1.15 (0.84 to 1.57)	MODERATE
AIDM and hyperthyroidism, in men								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	Adjusted OR: 3.79 (1.75 to 8.21)	MODERATE
T2DM and hyperthyroidism, in men								
1	Cross-sectional study	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	Adjusted OR: 0.79 (0.45 to 1.39)	MODERATE

[1] Downgraded by 1 increment as the 95% CI crosses the null line or subjectively wide confidence intervals, downgraded by 2 increments if the 95% CI crosses the null line and subjectively wide confidence intervals

Appendix G: Health economic evidence selection

Figure 19: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
TFT; thyroid function test, FNA; fine-needle aspiration, US; ultrasound, RAI; radioactive iodine, ATDs; antithyroid drugs, Mang; management, SCH; Subclinical hypothyroidism, SCT; Subclinical thyrotoxicosis.

1

Appendix H: Health economic evidence tables

None

Appendix I: Health economic analysis

None

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 19: Studies excluded from the clinical review

Reference	Reason for exclusion
Aarflot 1996[1]	No usable outcomes
Ahn 2014[2]	No usable outcomes
Aho 1983[3]	No usable outcomes
Al-Awadhi 2008[4]	Inadequate adjustment for key confounders
Alexander 2016[5]	Whole population not tested for thyroid disease
Alshamrani 2017[7]	Whole population not tested for thyroid disease
Aminorroaya 2009[8]	No usable outcomes
Amouzegar 2017[9]	No usable outcomes
Assa 2017[10]	No usable outcomes
Asvold 2009[12]	No usable outcomes
Asvold 2012[11]	No usable outcomes
Baldwin 1978[13]	No usable outcomes
Bates 1993[14]	No usable outcomes
Bensenor 2011[15]	No usable outcomes
Boekholdt 2010[16]	No usable outcomes
Borkar 2017[17]	Whole population not tested for thyroid disease
Brandt 2013[18]	Whole population not tested for thyroid disease
Brandt 2014[19]	Whole population not tested for thyroid disease
Carle 2011[25]	Whole population not tested for thyroid disease
Carle 2014[24]	No usable outcomes
Carle 2016[23]	No usable outcomes
Ceresini 2009[27]	No usable outcomes
Ceresini 2013[26]	No usable outcomes
Cho 2016[28]	Inappropriate population
Chogle 2013[29]	No usable outcomes
Chu 2011[30]	Whole population not tested for thyroid disease
Collerton 2010[31]	No usable outcomes
Delshad 2012[32]	No usable outcomes
Denzer 2013[33]	No usable outcomes
Diamanti 2011[34]	Incorrect study design
Eaton 2007[36]	Whole population not tested for thyroid disease
Eaton 2010[35]	Whole population not tested for thyroid disease
Edwards 2004[37]	No usable outcomes

Reference	Reason for exclusion
Elfstrom 2008[38]	Whole population not tested for thyroid disease
Flatau 2000[41]	Whole population not tested for thyroid disease
Fontes 2016[43]	Inappropriate population
Forman-Hoffman 2006[44]	No usable outcomes
Garcia-Garcia 2016[45]	No usable outcomes
Garin 2014[46]	No usable outcomes
Garin 2014[47]	No usable outcomes
Grabe 2005[48]	No usable outcomes
Ingordo 2011[50]	Whole population not tested for thyroid disease
Ishay 2009[51]	Incorrect population
Jeong 2017[52]	No usable outcomes
Kakigi 2015[53]	No usable outcomes
Kang 2010[54]	Whole population not tested for thyroid disease
Kang 2010[55]	Whole population not tested for thyroid disease
Kasagi 2009[56]	No usable outcomes
Kim 2014[57]	No usable outcomes
Kim 2015[59]	Whole population not tested for thyroid disease
Kim 2016[58]	No usable outcomes
Klaver 2013[60]	No usable outcomes
Knudsen 1999[61]	No usable outcomes
Lejeune 1993[62]	Incorrect population
Lepoutre 2012[63]	No usable outcomes
Li 2016[64]	Incorrect population
Liu 2014[65]	Incorrect population
Londono 2013[66]	Less than 1000 participants
Magyari 2014[67]	Whole population not tested for thyroid disease
Mannisto 2009[68]	No usable outcomes
Marrie 2015[69]	SR, not matching PICO
Medici 2014[70]	No usable outcomes
Mickelson 1999[71]	No comparison group
Muller 1997[72]	No usable outcomes
Nagai 2015[73]	Whole population not tested for thyroid disease
Nair 2018[74]	Less than 1000 participants
Nanchen 2012[75]	Incorrect population
Nazarpour 2016[77]	Incorrect population
Negro 2010[78]	Incorrect population
Negro 2011[79]	No usable outcomes
Negro 2016[80]	No usable outcomes
Ning 2017[81]	SR, not matching PICO
Okamura 1987[82]	No usable outcomes
Ong 2014[83]	No usable outcomes
Plowden 2015[84]	Abstract only
Plowden 2016[85]	Abstract only
Priyatharshini 2014[86]	Whole population not tested for thyroid disease
Radaideh 2004[87]	Insufficient information on population

Reference	Reason for exclusion
Robles-Osorio 2014[88]	Less than 1000 participants
Ryu 2015[89]	No usable outcomes
Shun 2014[90]	SR, not matching PICO
Sieiro Netto 2004[91]	Incorrect population
Sinaii 2002[92]	Whole population not tested for thyroid disease
Spaans 2017[93]	Whole population not tested for thyroid disease
Strieder 2003[94]	No usable outcomes
Sundbeck 1991[95]	No usable outcomes
Szlejf 2018[96]	No usable outcomes
Tamez-Perez 2012[97]	Whole population not tested for thyroid disease
Thomsen 2005[98]	No usable outcomes
Ueckermann 2013[99]	Incorrect population
Unnikrishnan 2013[100]	No usable outcomes
Wadhwa 2016[101]	Abstract only

J.2 Excluded health economic studies

None