Protocol: systematic review of screening and treatment of thyroid dysfunction in asymptomatic, nonpregnant, community-dwelling adults

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Section I. Background and Purpose

Thyroid dysfunction is characterised by an imbalance in TSH, with or without an imbalance in T4 and/or T3 hormone levels. Hypothyroidism occurs when the thyroid fails to produce sufficient amount of T4 and T3, resulting in elevated levels of TSH. Hypothyroidism, both subclinical and overt, can produce symptoms including fatigue, cold intolerance, weight gain, dry skin, hair loss, constipation, depression, irritability, poor concentration, slowed speech and intellectual function, slowed reflexes, muscle cramps, abnormal menstrual cycles, and decreased libido. However, hypothyroidism may also be asymptomatic or nonspecific symptoms may go unrecognized. In rare cases, undiagnosed or untreated/undertreated hypothyroidism can result in myxedema coma.

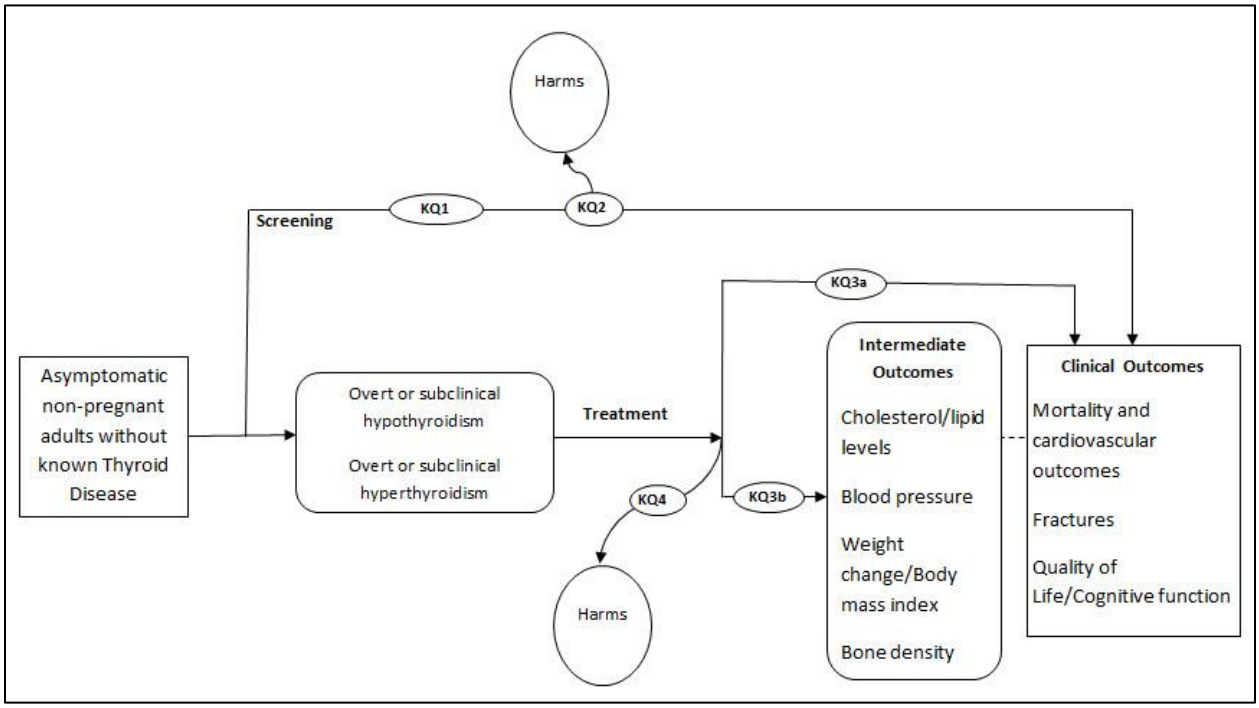
Symptoms of hyperthyroidism include fatigue, heat intolerance, excessive perspiration, weight loss, hyperactivity, nervousness, anxiety, insomnia, breathlessness, muscle weakness, fine tremor, light or absent menstrual periods, hair loss, heart palpitations, increased bowel movements. As with hypothyroidism, both subclinical and overt hyperthyroidism may be asymptomatic or go unrecognized because symptoms can be nonspecific. Although uncommon, undiagnosed or undertreated hyperthyroidism can lead to stroke, seizures, thyrotoxicosis or thyroid storm (symptoms may include fever, delirium, seizures, and coma).

Section II. Review Approach and Scope

Analytic Framework

Figure 1 is an analytic framework that depicts the structure used to address the Key Questions (KQs) for evaluating the benefits and harms of screening for thyroid dysfunction in asymptomatic, non-pregnant adults.

Figure 1: Analytic Framework



Review Questions:

KQ1. Does screening asymptomatic, nonpregnant adults for thyroid dysfunction reduce morbidity or mortality?

KQ2. What are the harms of screening asymptomatic, nonpregnant adults for thyroid dysfunction?

KQ3a. Does treatment of screen-detected overt or subclinical thyroid dysfunction improve morbidity or mortality? KQ3b. Does treatment of screen-detected overt or subclinical thyroid dysfunction improve intermediate outcomes??

KQ3b. Does treatment of screen-detected overt or subclinical thyroid dysfunction improve intermediate outcomes (i.e., serum lipid levels, blood pressure, weight, bone density)?

KQ4: What are the harms of treating screen-detected thyroid dysfunction in asymptomatic, nonpregnant adults?

KQ5. What are asymptomatic, nonpregnant adults ' preferences and values regarding screening for thyroid dysfunction?

KQ6. What is the cost-effectiveness of screening asymptomatic, nonpregnant adults for thyroid dysfunction?

Searches

The current systematic review will both update and expand the 2014 Agency for Healthcare Research and Quality (AHRQ) "Screening for and Treatment of Thyroid Dysfunction: An Evidence Review for the U.S. Preventive Services Task Force." To update the 2014 AHRQ review, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R), Ovid OLDMEDLINE(R), and Cochrane library will be systematically searched between July 1, 2014 to present to identify titles and/or abstracts of English language articles examining the benefits and harms of screening for thyroid dysfunction, as well as the benefits and harms of treatment of screen-detected overt or subclinical thyroid dysfunction. Further information relating to the search strategy can be found in Appendix 1.

To expand the 2014 AHRQ review, we will consider two additional outcomes: thyroid cancer and mortality; both of these outcomes have been added to KQ1 (screening) and KQ3a (treatment).

Two additional key questions have also been added to this review: KQ 5 (asymptomatic, nonpregnant adults' preferences and values regarding screening), and KQ6 (cost-effectiveness of screening). To address the new outcomes and new key questions, MEDLINE and Cochrane library Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R), Ovid OLDMEDLINE(R), and Cochrane library will be systematically searched for titles and/or abstracts of English or French language articles, using an open start date to present. For new key questions, MEDLINE and Cochrane library Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R), Ovid OLDMEDLINE(R), Cochrane library, ProQuest Public Health, EMBASE and Scopus will be systematically searched for titles and/or abstracts of English or French language articles present , using an open search date to present (see Search Strategy in Appendix 1).

Eligibility Criteria

Table 1: Inclusion and Exclusion Criteria for Key Questions

Population	Inclusions: Asymptomatic, nonpregnant, community-dwelling adults with no prior history of thyroid disease or clear symptoms of hypo- or hyperthyroidism who were screened or treated for thyroid dysfunction. Nonpregnant, community dwelling adults with uninvestigated mild, nonspecific symptoms will also be considered. Studies involving nonpregnant, community-dwelling adults with subclinical hypothyroidism that do not clearly describe whether study subjects were symptomatic or not at enrolment will also be considered. Exclusions: Patients with a prior history of thyroid disease or currently diagnosed with hypothyroidism or hyperthyroidism. Hospitalized or recently hospitalized participants, as they may have elevated TSH levels. Patients undergoing treatment with medications that may alter thyroid levels, such as lithium, amiodarone, radiation, and chemotherapy.
Intervention	KQ1, 2, 5, 6: screening for thyroid dysfunction using TSH KQs 3a, 3b, 4 , 5: Treatment of overt thyroid disease, subclinical

	hypothyroidism, and subclinical hyperthyroidism, including hormone replacement therapy, antithyroid medications (i.e., methimazole), and ablation therapy (i.e., radioactive iodine, surgery)
Comparator	KQ 1, 6: No screening KQs 3a, 3b: No treatment
Outcomes	KQs 1, 3a: Clinical outcomes, including cardiovascular outcomes (cardiovascular disease, coronary artery disease, congestive heart failure, atrial fibrillation), thyroid cancer, mortality, fractures, and cognitive function, as well as measures of quality of life. Also, number needed to screen (NNS), number needed to treat (NNT), and number needed to harm (NNH). KQ 2: Psychological effects, harms of workup, overdiagnosis, and overtreatment KQ 3b: Intermediate outcomes, including cholesterol/lipid levels, blood pressure, body mass index/weight change, bone density. KQ 4: Harms of treatment (directly linked) KQ 5: Willingness to be screened and factors considered in the decision to be screened (i.e. what components of screening do patients place more value on when deciding whether to be screened or not (e.g. potential overdiagnosis and overtreatment resulting from screening). If evidence on patient preferences for screening cannot be found, evidence on patient preferences and values, willingness to be treated, and experiences with treatment of overt or subclinical thyroid dysfunction will be considered (i.e. what components of treatment do patients place more value on when deciding whether to accept treatment, which treatments will be considered, what factors are considered in the decision to accept certain types of treatment (e.g. potential complications, adverse effects resulting from treatment), factors that may influence compliance with treatment). KQ 6: Cost-effectiveness analysis outcomes (e.g., resource use, quality adjusted life years [QALY], incremental cost-effective ratio [ICER], incremental cost utility ratio [ICUR], cost-benefit ratio [CBR]) or budget impact analysis outcomes).
Study Design	KQ1, 2, 3, 4: Randomized, controlled trials or controlled observational studies. KQ5: Descriptive studies (surveys, qualitative) and mixed-methods studies. KQ6: RCTs, economic evaluations, and economic modelling studies.
Setting	KQ1, 2, 3, 4, 5, 6: Representative of Primary Care KQ6: Canada, OECD countries
Language	English or French

Study Selection

Records from systematic bibliographic searches will be collated into Distiller SR. Studies will undergo two stages of initial screening for inclusion eligibility.

In the first stage of screening, two reviewers will independently screen all search results by title and abstract for relevance to the research questions using predetermined criteria. Articles with potential relevance for the review will be selected for full text review. Articles irrelevant to the review question will be discarded. If relevance of an article is unclear it will be included in full text screening.

In the second stage of screening, all potentially relevant articles will be retrieved and undergo full text review by two independent reviewers using a priori inclusion eligibility criteria.

At all stages consensus between reviewers will be required for inclusion. Disagreements between reviewers will be resolved by discussion or consulting a third reviewer if consensus cannot be reached. The study selection process will be presented using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Data Extraction

Two independent reviewers will extract data on study characteristics, including: population, intervention(s), comparator, setting, study design, methods, timeframe, outcomes, findings; as well as report characteristics, including language, publication status, publication date. Reviewers will crosscheck and verify the accuracy and completeness of the other's data extraction. Disagreements will be resolved through discussion or consulting a third reviewer for unresolved conflicts. Study authors will be contacted for any missing or incomplete data, if necessary.

Risk of bias (quality) assessment
Quality Assessments:

Two reviewers will independently assess the quality of each included study using the assessment tool that is most appropriate. Quality assessment will involve a two-step process: first we will critically appraise the methodological quality of all studies; next we will assess the strength and quality of the evidence on each outcome of interest. We will use the AMSTAR tool for systematic reviews and meta-analyses, the Cochrane Risk of Bias tool for RCTs, and the Newcastle-Ottawa Scale for Non-Randomized Studies of Interventions. A modified version of the Drummond Checklist will be used to assess disease-progression modelling studies. The quality appraisal of qualitative studies will follow criteria outlines in the Critical Appraisal Skills Programme (CASP) quality assessment tool for qualitative studies checklist: http://media.wix.com/ugd/dded87_29c5b002d99342f788c6ac670e49f274.pdf

The GRADE system will be used to assess the strength and quality of the evidence for all outcomes ranked as 'critical' or 'important' by the CTFPHC working group members and the patient sample.

Strategy for data synthesis
Each study design will be analyzed separately (i.e., data from RCTs and observational studies will not be quantitatively pooled). The methodological, clinical and statistical heterogeneity will be assessed within

the GRADE domains (i.e., directness across studies, risk of bias, and consistency). We will do a sensitivity analysis based on risk of bias rating (high, unclear, low) for primary outcomes of interest. Number-needed-to-screen (NNS), number-needed-to-treat (NNT), and number-needed-to-harm (NNH) will be calculated based on Cochrane's recommended method.

As appropriate, meta-analysis of pooled data for outcomes of interest will be undertaken using The Cochrane Review Manager software version 5.3. Randomized and non-randomized study designs will be analyzed separately. Analyses of dichotomous outcomes such as frequency of harms will be summarized using relative risks (RRs) and 95% confidence intervals (CIs), and analyses of continuous outcomes will be summarized using differences in means and 95% CIs. When different scales are used, analyses of continuous outcomes will be summarized as standardised mean differences (SMD) with 95% CIs.

If meta-analysis cannot be performed, data will be summarized and presented in narrative and tabular form.

GRADE CERQual will be used to assess the confidence and certainty in evidence from qualitative studies, including assessment of methodological limitations, relevance, coherence and adequacy of data for outcomes of interest. To address heterogeneity of qualitative studies, methodological, clinical and reporting differences will be documented and used to inform analysis.

Qualitative data will be aggregated by outcome, condition, and type of intervention, as well as, analyzed thematically. If possible and appropriate, qualitative analysis will document any apparent convergent or divergent patterns associated with variables such as sex, age, ethnicity, location (rural/urban), education, income, setting and general health status. Findings from qualitative data will be reported narratively and in tabular form.

A narrative synthesis of the evidence on cost-effectiveness will be conducted. Data will be grouped in tables by study design, patient characteristics, or screening method. Modelling analyses will not be performed.

Analysis of subgroups or subsets

For outcomes of benefits of screening and benefits of treatment, further sub-group and sensitivity analyses will be conducted where possible to evaluate statistical stability and effect on statistical heterogeneity. The Cochran's Q (a=0.05) will be employed to detect statistical heterogeneity and the I-squared statistic will be used to quantify the magnitude of statistical heterogeneity between studies.

Where possible and appropriate, qualitative analysis will identify apparent correspondences or differences in findings based on variables, such as age, ethnicity, location (rural/urban), education, income, setting However, given that sample sizes for qualitative studies tend to be small, subpopulation analysis may not be possible or appropriate.

Staged analysis of the cost effective studies, will include analysing the data available from RCTs and subsequently moving to economic data available through observational or evaluation studies if required.

Appendix 1. Search Strategies

Screening

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to Present
Search Strategy:

#	Searches	Results
1	thyroid diseases/ or hyperthyroidism/ or hypothyroidism/	56956
2	(thyroid and disease$).mp.	59439
3	(hypothyroid$ or hyperthyroid$).mp.	62752
4	or/1-3	107026
5	Mass Screening/	87664
6	4 and 5	1033
7	Pregnancy/	737886
8	(pediatric$ or newborn or neonat$ or child$ or infan$).mp.	2728030
9	6 not (7 or 8)	366
10	limit 9 to (abstracts and english language and humans)	189
11	(201407$ or 201408$ or 201409$ or 201410$ or 201411$ or 201412$ or 2015*).dc,ed.	2053154
12	10 and 11	13
13	remove duplicates from 12	10

Database(s): **COCHRANE LIBRARY**
Search Strategy as searched in http://onlinelibrary.wiley.com/cochranelibrary/search/:

#	Searches	Results

1	[Thyroid Diseases] explode all	1696
2	(thyroid and disease$) all text	1852
3	(hypothyroid$ or hyperthyroid$) all text	366
4	#1 or #2 or #3	2927
5	[Mass Screening]	4450
6	screen$ all text	34043
7	#5 or #6	34043
8	#4 and #7	471
9	#4 and #7 Limit=Online Publication Date from Jul 2014 to Nov 2015	104

Treatment

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to Present
Search Strategy:

#	Searches	Results
1	Thyroid Diseases/	14992
2	Hyperthyroidism/	24972
3	Hypothyroidism/	24859
4	(hyperthyroid$ or hypothyroid$).ti.	23233
5	(thyroid deficien* or thyroid insufficien* or thyroid failure).mp.	820
6	or/1-5	60666
7	exp Antithyroid Agents/	13266
8	(anti-thyroid or methimazole or propylthiouracil or radioiodine or radioactive iodine).ti,ab.	17515
9	exp Thyronines/	24963
10	exp Thyroxine/	45092
11	(t3 or t4 or thyroxine or levothyroxine or triiodothyronine or liothyronine or thyrolar or liotrix).ti,ab.	78993
12	or/7-11	115020
13	6 and 12	22598
14	6 and pc.fs.	1698
15	6 and dt.fs.	10454
16	6 and th.fs.	4925

17	or/14-16	15913
18	13 or 17	29616
19	Pregnancy/	737886
20	(child$ or pediatric$ or infan$ or newborn or neonat$ or toddler).mp.	2728114
21	grave's.ti.	7068
22	18 not (19 or 20 or 21)	21592
23	limit 22 to (abstracts and english language and humans)	7117
24	limit 23 to (clinical trial, all or comparative study or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews)	1337
25	(201407$ or 201408$ or 201409$ or 201410$ or 201411$ or 201412$ or 2015*).dc,ed.	2053154
26	24 and 25	94
27	remove duplicates from 26	83

Database(s): **COCHRANE LIBRARY**
Search Strategy as searched in http://onlinelibrary.wiley.com/cochranelibrary/search/:

#	**Searches**	**Results**
1	[Thyroid Diseases]	181
2	[Hyperthyroidism]	265
3	[Hypothyroidism]	311
4	(hyperthyroid$ or hypothyroid$):ti	17
5	("thyroid deficien*" or "thyroid insufficien*" or "thyroid failure")	20

	all text	
6	#1 or #2 or #3 or #4 or #5	723
7	[Antithyroid Agents] explode all	170
8	(anti-thyroid or methimazole or propylthiouracil or radioiodine or "radioactive iodine"):ti,ab	537
9	[Thyronines] explode all	532
10	[Thyroxine] explode all	964
11	(t3 or t4 or thyroxine or levothyroxine or triiodothyronine or liothyronine or thyrolar or liotrix):ti,ab	4402
12	#7 or #8 or #9 or #10 or #11	4982
13	#6 and #12	445
14	[Pregnancy]	63
15	(child$ or pediatric$ or infan$ or newborn or neonat$ or toddler) all text	113085
16	grave's:ti	5
17	#13 not (#14 or #15 or #16)	384
18	#13 not (#14 or #15 or #16) Limit=Online Publication Date from Jul 2014 to Nov 2015	0

All Key Questions

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to Present
Search Strategy:

#	Searches	Results
1	Thyroid Diseases/	14992
2	Hyperthyroidism/	24972
3	Hypothyroidism/	24859
4	(hyperthyroid$ or hypothyroid$).ti.	23233
5	(thyroid deficien* or thyroid insufficien* or thyroid failure).mp.	820
6	or/1-5	60666
7	exp Antithyroid Agents/	13266
8	exp Thyronines/	24963
9	exp Thyroxine/	45092
10	(t3 or t4 or thyroxine or levothyroxine or triiodothyronine or liothyronine or thyrolar or liotrix).ti,ab.	78993
11	or/7-10	104336
12	6 and 11	20398
13	12 not (pregnan$ or pediatric$ or newborn or neonat$ or child$ or infan$).ti.	18306
14	limit 13 to systematic reviews	124
15	(201407$ or 201408$ or 201409$ or 201410$ or 201411$ or 201412$ or 2015*).dc,ed.	2053154
16	14 and 15	18

17	remove duplicates from 16	16

Database(s): **COCHRANE LIBRARY**
Search Strategy as searched in http://onlinelibrary.wiley.com/cochranelibrary/search/:

#	Searches	Results
1	(thyroid or hypothyroid$ or hyperthyroid$) :ti	1697
2	pregnan$.ti	8
3	#1 not #2 Reviews	19
4	#1 not #2 Limit=Online Publication Date from Jul 2014 to Nov 2015	2

Search strategy history

Topic #1: Thyroid Dysfunction Screening – Patient preference and values

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to Present
Search Strategy:

#	Searches	Results
1	exp Thyroid Diseases/co, di, pc, px, us [Complications, Diagnosis, Prevention & Control, Psychology, Ultrasonography]	46427
2	Thyroid Function Tests/	12816
3	(hyperthyroid* or hypothyroid* or hyperthyroxinemia or thyrotoxicos*).mp.	65770
4	(thyroid adj3 (dysfunct* or dysgenes* or disorder* or deficien* or abnormal* or disease*)).mp.	32213

5	or/1-4	110441
6	*patient satisfaction/ or *patient preference/	24923
7	*Patient Compliance/px, sn [Psychology, Statistics & Numerical Data]	5863
8	exp *Attitude to Health/	163483
9	(patient adj3 (prefer* or value* or attitude or compliance or satisf* or response*)).mp.	156146
10	or/6-9	269496
11	*Mass Screening/	46190
12	(thyroid adj10 (screen* or test*)).mp.	23313
13	or/11-12	69282
14	5 and 10 and 13	80
15	(pregnan* or infant or newborn).mp.	1812523
16	14 not 15	69
17	limit 16 to (english or french)	63
18	remove duplicates from 17	59

Database(s): **Embase** 1974 to 2015 November 18
Search Strategy:

#	Searches	Results
1	exp thyroid disease/co, di, pc [Complication, Diagnosis, Prevention]	46926
2	exp thyroid function test/	12910
3	(hyperthyroid* or hypothyroid* or hyperthyroxinemia or thyrotoxicos*).mp.	93108
4	(thyroid adj3 (dysfunct* or dysgenes* or disorder* or deficien* or abnormal* or disease*)).mp.	42097
5	or/1-4	145628
6	exp *patient satisfaction/	17277
7	exp *patient preference/	2105
8	*patient compliance/ or *mental compliance/	19244
9	exp *attitude to health/	44522
10	(patient adj3 (prefer* or value* or attitude or compliance or satisf* or response*)).mp.	293063
11	or/6-10	333969
12	*mass screening/	22705
13	(thyroid adj10 (screen* or test*)).mp.	27732
14	or/12-13	50340
15	5 and 11 and 14	188
16	(pregnan* or infant or newborn).mp.	1728649
17	15 not 16	149

18	limit 17 to (english or french)	146
19	remove duplicates from 18	145

Database(s): **ProQuest Public Health**
Search Strategy:

Set#	Searched for	Databases	Results
S1	(mesh.Exact("Thyroid Diseases") OR mesh.Exact("Thyroid Function Tests") OR ALL(hyperthyroid* OR hypothyroid* OR hyperthyroxinemia OR thyrotoxicos*) OR ALL(thyroid NEAR/3 (dysfunct* OR dysgenes* OR disorder* OR deficien* OR abnormal* OR disease*))) AND (mesh.Exact("Patient Preference" OR "Patient Satisfaction" OR "Attitude to Health" OR "Patient Compliance") OR (patient NEAR/3 (prefer* OR value* OR attitude OR compliance OR satisf* OR response*))) AND (mesh.Exact("Mass Screening") OR ALL(thyroid NEAR/10 (screen* OR test*))) NOT ALL(pregnan* OR infant OR newborn) AND PEER(yes)	ProQuest Public Health	55

Database(s): **Scopus**
Search Strategy:

(TITLE-ABS(thyroid w/3 (dysfunct* OR dysgenes* OR disorder* OR deficien* OR abnormal* OR disease* OR screen* OR test*)) OR TITLE-ABS(hyperthyroid* OR hypothyroid* OR hyperthyroxinemia OR thyrotoxicos*)) AND ALL(inciden* OR "new* diagnosis") AND TITLE-ABS-KEY(patient w/3 (prefer* or value* or attitude or compliance or satisf* or response*)) AND TITLE(screen* OR test*) AND NOT (TITLE-ABS-KEY(pregnan* OR infant OR newborn)) AND (LANGUAGE(English OR French)) AND (LIMIT-TO(DOCTYPE,"ar") OR LIMIT-TO(DOCTYPE,"re")) 19 Results

Topic #2: Thyroid Dysfunction Screening – Cost-effectiveness and/or resources

Database(s): **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE(R) and Ovid OLDMEDLINE(R)** 1946 to Present
Search Strategy:

#	Searches	Results
1	exp Thyroid Diseases/co, di, pc [Complications, Diagnosis, Prevention & Control]	43574
2	Thyroid Function Tests/	12816
3	(hyperthyroid* or hypothyroid* or hyperthyroxinemia or thyrotoxicos*).mp.	65770
4	(thyroid adj3 (dysfunct* or dysgenes* or disorder* or deficien* or abnormal* or disease*)).mp.	32213
5	or/1-4	108887
6	*Mass Screening/	46190
7	(thyroid adj10 (screen* or test*)).mp.	23313
8	or/6-7	69282
9	exp *"Costs and Cost Analysis"/ec, mt, sn [Economics, Methods, Statistics & Numerical Data]	11738
10	(cost adj3 (effective* or benefi* or analysis)).ti,ab.	108048
11	Quality-Adjusted Life Years/	8164
12	*Health Resources/ec, sn, sd, ut [Economics, Statistics & Numerical Data, Supply & Distribution, Utilization]	3107
13	or/9-12	123101
14	5 and 8 and 13	158

15	(pregnan* or infant or newborn).mp.	1812523
16	14 not 15	115
17	limit 16 to (english or french)	110
18	remove duplicates from 17	108

Database(s): **Embase** 1974 to 2015 November 18
Search Strategy:

#	Searches	Results
1	exp thyroid disease/co, di, pc [Complication, Diagnosis, Prevention]	46926
2	exp thyroid function test/	12910
3	(hyperthyroid* or hypothyroid* or hyperthyroxinemia or thyrotoxicos*).mp.	93108
4	(thyroid adj3 (dysfunct* or dysgenes* or disorder* or deficien* or abnormal* or disease*)).mp.	42097
5	or/1-4	145628
6	*mass screening/	22705
7	(thyroid adj10 (screen* or test*)).mp.	27732
8	or/6-7	50340
9	exp *"cost benefit analysis"/	8479
10	exp *"cost effectiveness analysis"/	17416
11	(cost adj3 (effective* or benefi* or analysis)).ti,ab.	144600
12	*quality adjusted life year/	936
13	or/9-12	151445
14	5 and 8 and 13	239
15	(pregnan* or infant or newborn).mp.	1728649
16	14 not 15	183
17	limit 16 to (english or french)	172
18	remove duplicates from 17	169

Database(s): **ProQuest Public Health**
Search Strategy:

Set#	Searched for	Databases	Results
S2	(mesh.Exact("Thyroid Diseases") OR mesh.Exact("Thyroid Function Tests") OR ALL(hyperthyroid* OR hypothyroid* OR hyperthyroxinemia OR thyrotoxicos*) OR ALL(thyroid NEAR/3 (dysfunct* OR dysgenes* OR disorder* OR deficien* OR abnormal* OR disease*))) AND (MJMESH.EXACT("Costs and Cost Analysis") OR MJMESH.EXACT("Health Resources") OR MJMESH.EXACT("Quality-Adjusted Life Years") OR ALL(cost NEAR/10 (effective* OR benefi* OR analysis))) AND (mesh.Exact("Mass Screening") OR ALL(thyroid NEAR/10 (screen* OR test*))) NOT ALL(pregnan* OR infant OR newborn)	ProQuest Public Health	9

Database(s): **Scopus**
Search Strategy:

(TITLE-ABS(thyroid w/3 (dysfunct* OR dysgenes* OR disorder* OR deficien* OR abnormal* OR disease* OR screen* OR test*)) OR TITLE-ABS(hyperthyroid* OR hypothyroid* OR hyperthyroxinemia OR thyrotoxicos*)) AND TITLE-ABS-KEY(cost w/3 (effective* or benefi* or analysis)) AND TITLE(screen* OR test*) AND NOT (TITLE-ABS-KEY(pregnan* OR infant OR newborn)) AND (LANGUAGE(English OR French)) AND (LIMIT-TO(DOCTYPE,"ar") OR LIMIT-TO(DOCTYPE,"re") OR LIMIT-TO(DOCTYPE,"sh")) 78 Results