INSTITUT NATIONAL D'ASSURANCE MALADIE-INVALIDITÉ
SERVICE DES SOINS DE SANTÉ
Comité d'évaluation des pratiques médicales en matière de médicaments

RIJKSINSTITUUT VOOR ZIEKTE- EN INVALIDITEITSVERZEKERING
DIENST GENEESKUNDIGE VERZORGING
Comité voor de evalutie van de medische praktijk inzake geneesmiddelen

Management of hypothyroidism and the rational use of thyroid hormones

Literature review: full report

Consensus conference
November 24th 2022
Auditorium Lippens (Royal Library)
Brussels

This literature review was performed by BCFI/CBIP.

Researchers
Main researcher:
Natasja Mortier, MD (BCFI/CBIP)

Co-researchers:
Barbara Bosier, PharmD, PHD (BCFI/CBIP)
Griet Goesaert MD (BCFI/CBIP)
Abdelbari Baitar, MSc., PHD (BCFI/CBIP)

Table of contents

1 Abbreviations

ART assisted reproductive technology
BMD: Bone Mineral Densitometry
CI: confidence interval
CO: crossover RCT
CVD: cardiovascular disease
DB: double blind
EQ-5D: EuroQol 5 dimensions
fT4: free T4
HR: hazard ratio
HRQoL: Health Related Quality of Life
ITT: intention-to-treat analysis
MA: meta-analysis
MD: mean difference
MID: minimally important difference
n: number of patients
N: number of studies
NR: not reported
NS: not statistically significant
NT: no statistical test
OL: open label
PG: parallel group
PO: primary outcome
QoL: Quality of life
RPL: recurrent pregnancy loss
SAE: Serious adverse event: Serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity.
SB: single blind
SCH: subclinical hypothyroidism
SD: standard deviation
SS: statistically significant
T4: levothyroxine
TAI thyroid antibodies
Tg-Ab: thyroglobulin antibody
TPO-Ab: thyroid peroxidase antibodies
TSH: thyroid stimulating hormone
VAS: Visual Analogue Scale

2 Methodology

2.1 Introduction

This literature review was conducted in preparation of the consensus conference "**Management of hypothyroidism and the rational use of thyroid hormones"** which will take place on the 24th of November 2022.

2.2 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are:

1. Algemene inleiding: algemeen concept van hypothyroïdie

a. Welke zijn de criteria om de diagnose hypothyroïdie te kunnen stellen?
b. Welke zijn de mogelijke oorzaken van hypothyroïdie?
c. Hoe wordt de diagnose gesteld? Welke zijn essentiële testen/onderzoeken? En welke testen zijn niet noodzakelijk?
d. Welke zijn de farmacotherapeutische mogelijkheden (therapeutische klassen)?
e. Is er een rol weggelegd voor voeding en/of nutritionele supplementen, en zo ja, voor welke?

1. Introduction générale : le concept général d'hypothyroïdie

a. Quels sont les critères diagnostiques de l'hypothyroïdie ?
b. Quelles sont les causes possibles de l'hypothyroïdie ?
c. Comment faire le diagnostic? Quels sont les tests/examens indispensables ? Et lesquels ne sont pas nécessaires ?
d. Quelles sont les options pharmaco-thérapeutiques(classes thérapeutiques) ?
e. L'alimentation et/ou les compléments alimentaires jouent-ils un rôle, et si oui, lequel ?

2. Subklinische hypothyroïdie

a. Welke zijn de criteria om de diagnose subklinische hypothyroïdie te kunnen stellen?
    i. Zijn deze criteria geldig in alle patiëntenpopulaties of zijn er aanpassingen noodzakelijk voor bepaalde patiëntenpopulaties (buiten deze die aan bod komen in 3.a.i. en 4.a.i.)?
    ii. Is er een verschillende TSH-drempelwaarde naargelang leeftijd, geslacht, ethniciteit? Zo ja, welk is deze drempelwaarde?
b. Welke andere testen/onderzoeken kunnen bij deze diagnose zinvol zijn?
c. Wat is het preventief en therapeutisch belang van voeding en nutritionele supplementen?
d. Is er een plaats voor farmacotherapie bij subklinische hypothyroïdie, en zo ja, voor welke?

2. Hypothyroïdie subclinique

a. Quels sont les critères diagnostiques de l'hypothyroïdie subclinique ?

i. Ces critères sont-ils valables pour tous les patients ou faut-il faire des différences pour certaines populations (outre celles discutées aux points 3.a.i. et 4.a.i.) ?
ii. Y a-t-il une variation de la valeur seuil de la TSH selon l' âge, le sexe, l'ethnie ? Si oui, quelle est la valeur seuil ?

b. Quels autres tests/examens peuvent-ils être utiles pour établir ce diagnostic ?
c. Quel intérêt préventif et thérapeutique l'alimentation et les compléments alimentaires offrent-ils ?
d. Y a-t-il une place pour la pharmacothérapie en cas d'hypothyroïdie subclinique, et si oui, laquelle ?

3. Hypothyroïdie en ouderen

a. i. Welke zijn de criteria om de diagnose "subklinische hypothyroïdie" bij ouderen te kunnen stellen?
ii. Welke zijn de criteria om de diagnose "hypothyroïdie" bij ouderen te kunnen stellen?
b. Wanneer moeten ouderen behandeld worden? Welke zijn hiervoor de criteria?
c. Hoe behandelen?
i. Farmacologisch
ii. Niet-farmacologisch
d. Hoe opvolgen?

3. Hypothyroïdie et personnes âgées

a. i. Quels sont les critères diagnostiques de « l'hypothyroïdie subclinique » chez les personnes âgées ?
ii. Quels sont les critères diagnostiques de « l'hypothyroïdie » chez les personnes âgées ?
b. Quand traiter les personnes âgées ? Quels sont les critères ?
c. Comment traiter cette population ?
i. Du point de vue pharmacologique
ii. Du point de vue non-pharmacologique
d. Comment assurer le suivi ?

4. Hypothyroïdie bij zwangeren en vrouwen met fertiliteitsproblemen

a. Zwangerschap
i. 1) Welke zijn de criteria om de diagnose "subklinische hypothyroïdie" bij zwangere vrouwen te kunnen stellen?
2) Welke zijn de criteria om de diagnose "hypothyroïdie" bij zwangere vrouwen te kunnen stellen?
ii. Is een schildklier-screening in deze specifieke populatie aanbevolen?
iii. Hoe behandelen? Is er hierbij een rol weggelegd voor voeding en nutritionele supplementen, en zo ja, voor welke?
iv. Hoe opvolgen?
b. Fertiliteitsproblemen
i. 1) Hoe de link leggen tussen fertiliteit en subklinische hypothyroïdie? Welke testen/onderzoeken zijn hierbij zinvol en welke niet?

2) Hoe de link leggen tussen fertiliteit en hypothyroïdie? Welke testen/onderzoeken zijn zinvol en welke niet?

ii. Is een screening in geval van fertiliteitsproblematiek aanbevolen?

iii. Hoe behandelen? Is er hierbij een rol weggelegd voor voeding en nutritionele supplementen, en zo ja, voor welke?

iv. Hoe opvolgen?

4. Hypothyroïdie chez les femmes enceintes et les femmes ayant des problèmes de fertilité

a. Grossesse

i. 1) Quels sont les critères diagnostiques de « l'hypothyroïdie subclinique » chez la femme enceinte ?

2) Quels sont les critères diagnostiques de « l'hypothyroïdie » chez la femme enceinte ?

ii. Est-il recommandé d'effectuer un dépistage thyroïdien dans cette population particulière ?

iii. Comment traiter cette population ? L'alimentation et les compléments alimentaires ont-ils un rôle à jouer en la matière, et si oui, lequel ?

iv. Comment assurer le suivi ?

b. Problèmes de fertilité

i. 1) Comment établir un lien entre la fertilité et l'hypothyroïdie subclinique ? Quels tests/examens sont utiles et lesquels ne le sont pas ?

2) Comment établir un lien entre la fertilité et l'hypothyroïdie ? Quels tests/examens sont utiles et lesquels ne le sont pas ?

ii. Est il recommandé d'effectuer un dépistage en cas d'infertilité ?

iii. Comment traiter cette population ? L'alimentation et les compléments alimentaires ont-ils un rôle à jouer dans ce cas, et si oui, lequel ?

iv. Comment assurer le suivi ?

5. Hypothyroïdie en lichaamsgewicht

a. Bestaat er een eventueel (oorzakelijk) verband tussen lichaamsgewicht en hypothyroïdie?

b. Treden er veranderingen op in de schildklierfunctie in geval van obesitas (BMI ≥ 30) ?

c. Wat zijn de diagnostische criteria om van een te behandelen hypothyroïdie te spreken bij obese personen?

d. Zin/onzin van de toediening van schildklierhormoon bij obese personen zonder hypothyroïdie?

5. Hypothyroïdie et poids corporel

a. Existe-t-il un lien (de causalité) entre le poids corporel et l'hypothyroïdie ?

b. Y a-t-il des modifications de la fonction thyroïdienne en cas d'obésité (IMC ≥ 30) ?

c. Quels sont les critères diagnostiques d'une hypothyroïdie traitable chez les patients obèses?

d. Utilité/inutilité de l'administration d'hormones thyroïdiennes chez les patients obèses sans hypothyroïdie ?

6. Aanpak op basis van symptomatologie versus biochemische parameters

a. Wat primeert om de behandeling van hypothyroïdie bij te sturen: de symptomatologie of de biochemische parameters? Is er een plaats voor de dosage van vrij T3 versus vrij T4?
b. Wat is, buiten een bewezen hypothyroïdie, het nut van schildklierhormoonbehandeling in volgende klinische entiteiten:
    i. In het kader van de aanpak van 'vermoeidheid'?
    ii. In het kader van anti-aging?
    iii. In het kader van suppressietherapie bij euthyroïde multinodulaire goiter?
c. Is er in de behandeling een plaats voor T3 (Triiodothyronine) versus T4 (Thyroxine) ? Is er plaats voor een combinatiebehandeling bestaande uit T4 en T3?

6. Approche basée sur la symptomatologie versus les paramètres biochimiques

a. Qu'est ce qui prédomine dans l'ajustement du traitement de l'hypothyroïdie : la symptomatologie ou les paramètres biochimiques ? Y a-t-il une place pour le dosage T3 libre versus T4 libre ?
b. Hormis une hypothyroïdie avérée, quel est l'intérêt d'un traitement par hormones thyroïdiennes pour les entités cliniques suivantes :
    i. Lutte contre la « fatigue » ?
    ii. Stratégie anti-âge ?
    iii. Traitement suppressif en cas de goitre multinodulaire euthyroïdien ?
c. Y a-t-il dans le traitement une place pour la T3 (Triiodothyronine) versus T4 (Thyroxine) ? Y a-t-il une place pour un traitement combiné T4 et T3?

7. Opvolging van medicamenteuze behandeling, ongewenste effecten en eventuele drug-drug interacties

a. Hoe - concreet - de medicamenteuze behandeling van hypothyroïdie opvolgen?
    (Hierbij ligt de nadruk op de opvolging in de 1e lijn)
b. Welke zijn mogelijke ongewenste effecten van de medicatie? Hoe ermee omgaan?
c. Kan er zonder problemen worden overgeschakeld van het ene schildklierhormoonpreparaat naar het andere? Dient hierbij een specifieke opvolging ingesteld te worden?
d. Met welke eventuele drug-drug interactie moet er rekening gehouden worden?
    i. Welke geneesmiddelen beïnvloeden de absorptie van schildklierhormonen?
    ii. Welke geneesmiddelen beïnvloeden de leverklaring van schildklierhormonen?
    iii. Welke geneesmiddelen kunnen eventueel leiden tot hypothyroïdie?

7. Surveillance du traitement médicamenteux, des effets indésirables et des éventuelles interactions médicamenteuses

a. Comment suivre - de façon concrète – le traitement médicamenteux d'un patient souffrant d'hypothyroïdie?
    (L'accent est mis ici sur le suivi en 1re ligne)
b. Quels sont les effets indésirables de la médication ? Comment les gérer ?
c. Peut-on passer d'une préparation d'hormones thyroïdiennes à une autre sans problème ? Cela requiert-t-il un suivi spécifique ?
d. Quelles sont les éventuelles interactions médicamenteuses à prendre en compte ?

i. Quels sont les médicaments qui modifient l'absorption des hormones thyroïdiennes?
ii. Quels sont les médicaments qui modifient la clearance hépatique des hormones thyroïdiennes ?
iii. Quels sont les médicaments qui vont entraîner une éventuelle hypothyroïdie?

2.3 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss **selected guidelines**.
  - See 2.3.1 for guideline inclusion criteria.
- To perform a literature review:
  - To search and report relevant **RCTs or systematic reviews/meta-analyses of RCTs** to provide an answer to certain research questions.
  - See 2.3.2 for information on study type inclusion criteria and 2.3.3 for search details.
  - To discuss information from **additional sources** for information on safety, contra-indications, specific subgroups, precautions and monitoring.
- See chapter "**14 Additional safety information from other sources**".

In the table below, we provide an overview of the research task of the literature group per jury question. We also indicate in what chapter the results can be found.

Question 1 – General concept of hypothyroidism
• This question will be answered by an expert-speaker. • Although it was not part of our research task, an overview of recommendations from selected **guidelines** can be found in chapter 5.1 • **RCTs** that evaluate the therapeutic use of nutritional supplements for hypothyroidism are discussed in chapter 6. Details of the studies can be found in the appendix chapter 15.
Question 2 – Subclinical hypothyroidism
• The literature group will discuss the selected **guidelines** in chapter 5.2 • The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs that evaluate the therapeutic use of nutritional supplements for SCH in chapter 6. Details of the studies can be found in the appendix chapter 15. • **Additional safety information** on nutritional supplements can be found in chapter 14. • An expert speaker will provide comments and additional information.
Question 3 – Hypothyroidism and older individuals
• The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.3. • The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs regarding levothyroxine therapy. The results of the literature search can be found in chapter 7 and details in appendix 16 • **Additional safety information** on levothyroxine can be found in chapter 14. • An expert speaker will provide comments and additional information.
Question 3 – Hypothyroidism in pregnant women or women with infertility

• The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.4. • The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs regarding levothyroxine therapy. The results of the literature search can be found in chapter 8 and 9 and details in appendix 17 and 18. • **Additional safety information** on levothyroxine can be found in chapter 14. • An expert speaker will provide comments and additional information.
Question 5 – Hypothyroidism and body weight
• The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.5. • The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs regarding levothyroxine therapy. The results of the literature search can be found in chapter 10 and details in appendix 19. • **Additional safety information** on levothyroxine can be found in chapter 14. • An expert speaker will provide comments and additional information.
Question 6 – Approach based on symptomatology versus biochemical parameters
• The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.6. • The literature group will perform a literature search of **RCTs or systematic reviews/meta-analyses** of RCTs regarding levothyroxine therapy in chronic fatigue syndrome, anti-aging, and euthyroid multinodular goiter. The results of the literature search can be found in chapter 11-13 and details in appendix 20-22. • **Additional safety information** on levothyroxine can be found in chapter 14. • An expert speaker will provide comments and additional information.
Question 7 – Follow-up, adverse effects and drug-drug interactions
• The literature group will discuss the selected **guidelines**. This discussion can be found in chapter 5.7 • **Additional safety information** can be found in chapter 14. • An expert speaker will provide comments and additional information.

2.3.1 Guidelines

Guidelines will be selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2017 onwards are to be selected. Exceptions can be made when only older guidelines regarding a certain topic are available.
- Quality assessment: Only guidelines that report levels of evidence/recommendation are to be selected.
- Systematic review: the guideline needs to be based on a good systematic search and review of the literature.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain “Rigour of development”. More information can be found on http://www.agreetrust.org/. [1]

This table gives an overview of the items assessed in this domain according to the Agree II score.[1]

No.	**Description of the item**
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table: Items assessed by the domain "Rigour of development" in Agree II score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.
In the chapter about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.
The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.
Similarities and discrepancies between guidelines are to be reported.

2.3.2 Study types

We will look at meta-analyses, systematic reviews, RCTs and observational (cohort) studies.
To be included in our review, the selected studies need to meet certain criteria.

Meta-analyses and systematic reviews

- Research question matches research question for this literature review
- Systematic search in multiple databases
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes (that match our selected outcomes)
- Only direct comparisons (no network meta-analyses)

If some of the included studies in a meta-analysis do not match all the inclusion criteria for our Consensus Conference literature review (for example: it may include some studies with a small sample size, or studies with drugs that are not on the Belgian market), this meta-analysis may be included in our review if judged to be sufficiently relevant. In this case, the discrepancies with our inclusion criteria will be discussed clearly.

RCT's

- Research question matches research question for this literature review

- Blinding: unblinded (open-label) studies will not be included
- Minimum number of participants: 40 per study-arm. For studies with multiple treatment arms, we will look at the number of participants in comparisons relevant to our search.
- Phase III trials (no phase II trials)
- Post hoc (subgroup) analyses are excluded.

Other sources for safety, contra-indications, specific subgroups, precautions and monitoring

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI) / Centre Belge d'Information Pharmacothérapeutique (CBIP)
    - *Gecommentarieerd geneesmiddelenrepertorium/ Répertoire Commenté des Médicaments(1)*
    - *Folia Pharmacotherapeutica*
- Martindale: The complete drug reference, 40th edition(2)

Some publications will be excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English
- Unpublished studies

2.3.3 Specific search criteria

2.3.3.1 (Subclinical) hypothyroidism, nutrition

Population	a) Persons with (subclinical) hypothyroidism <u>Exclusion criteria</u> pre-operative supplementation in patients undergoing thyroidectomy
Interventions	iodine, selenium, iron, omega 3, vitamin D Placebo / no treatment
Comparisons	Supplement vs placebo or no treatment
Outcomes	● Mortality ● Quality of life ● Cardiovascular morbidity-ischemic heart disease, heart failure ● Arrhythmia ● CVA ● TSH/T4 (attained values) ● Symptoms (symptom scores) ● Adverse events ○ Total adverse events ○ Severe adverse events ○ osteoporosis, arrhythmia
Study design	RCT No post hoc analyses Minimum treatment period 3M Minimum 40 participants per treatment arm

2.3.3.2 Elderly people

Population	Elderly people (65+) with hypothyroidism Elderly people with subclinical hypothyroidism
Interventions	Levothyroxine (T4) Placebo/no treatment
Comparisons	T4 vs placebo / no treatment Treatment target TSH/fT4 A vs treatment target TSH/fT4 B (when treated with T4)
Outcomes	● Mortality ● Quality of life ● Cardiovascular morbidity-ischemic heart disease, heart failure ● Arrhythmia ● CVA ● TSH/T4 (attained values) ● Symptoms (symptom scores) ● Adverse events ○ Total adverse events ○ Severe adverse events ○ osteoporosis, arrhythmia
Study design	RCT Blinded (for subjective outcomes) No post hoc analyses Minimum treatment period 6 months Minimum 40 participants per treatment arm

2.3.3.3 Pregnancy

Population	Pregnant women with hypothyroidism Pregnant women with subclinical hypothyroidism (definition may include euthyroidism with autoimmunity)
Interventions	Levothyroxine (T4) Placebo/no treatment
Comparisons	T4 vs placebo / no treatment Treatment target TSH/fT4 A vs treatment target TSH/fT4 B (when treated with T4)
Outcomes	● Mortality ● Quality of life ● Obstetric outcomes ● Infant health outcomes ● Adverse events ○ Total adverse events ○ Severe adverse events ○ osteoporosis, arrhythmia
Study design	RCT No post hoc analyses No minimum treatment/ follow-up period Minimum 40 participants per treatment arm

2.3.3.4 Infertility

Population	Women with infertility and hypothyroidism Women with infertility and subclinical hypothyroidism Women with infertility and TPO-antibodies (euthyroid)
Interventions	Levothyroxine (T4) Placebo/no treatment
Comparisons	T4 vs placebo / no treatment Treatment target TSH/fT4 A vs treatment target TSH/fT4 B (when treated with T4)
Outcomes	● Mortality ● Quality of life ● Pregnancy outcomes ● Obstetric outcomes ● Infant health outcomes ● Adverse events ○ Total adverse events ○ Severe adverse events ○ osteoporosis, arrhythmia
Study design	RCT No post hoc analyses No minimum treatment period Minimum 40 participants per treatment arm

2.3.3.5 Obesity

Population	People with obesity and subclinical hypothyroidism People with obesity, without hypothyroidism
Interventions	Levothyroxine (T4) Placebo/no treatment
Comparisons	T4 vs placebo / no treatment
Outcomes	● Weight loss ● Mortality ● Quality of life ● Cardiovascular morbidity-ischemic heart disease, heart failure ● Arrhythmia ● CVA ● Symptoms (symptom scores) ● Adverse events ○ Total adverse events ○ Severe adverse events ○ osteoporosis, arrhythmia
Study design	RCT Blinded No post hoc analyses Minimum 40 participants per treatment arm

2.3.3.6 Fatigue

Population	Chronic fatigue syndrome with or without elevated TSH or other abnormal thyroid function parameter
Interventions	Levothyroxine (T4) Triiodothyronine (T3) Combination therapy of T3 and T4 Placebo/no treatment
Comparisons	Thyroid hormone treatment vs Placebo / no treatment
Outcomes	● Mortality ● Quality of life ● Symptom scores (fatigue) ● Adverse events ○ Total adverse events ○ Severe adverse events ○ osteoporosis, arrhythmia
Study design	RCT Blinded No post hoc analyses Minimum treatment period Minimum 40 participants per treatment arm

2.3.3.7 Anti-aging

Population	No restrictions
Interventions	Levothyroxine (T4) Triiodothyronine (T3) Combination therapy of T3 and T4 Placebo/no treatment
Comparisons	Thyroid hormone treatment vs Placebo / no treatment
Outcomes	● Mortality ● Quality of life ● Symptom scores ● Adverse events ○ Total adverse events ○ Severe adverse events ○ osteoporosis, arrhythmia
Study design	RCT Blinded No post hoc analyses Minimum treatment period Minimum 40 participants per treatment arm

2.3.3.8 Euthyroïd multinodular goiter

Population	Non-toxic multinodular goiter <u>Exclusion criteria</u> Prophylactic use of thyroid hormone to prevent goiter recurrence after surgery
Interventions	Levothyroxine (T4) Placebo/no treatment
Comparisons	T4 vs placebo/ no treatment
Outcomes	● Mortality ● Quality of life ● Size reduction of goiter ● Alleviation of symptoms (globus, dysphonia, dysphagia, dyspnea…) ● Adverse events ○ Total adverse events ○ Severe adverse events ○ osteoporosis, arrhythmia
Study design	RCT Blinded (for subjective outcomes) No post hoc analyses Minimum treatment period Minimum 40 participants per treatment arm

2.4 Search strategy

2.4.1 Principles of systematic search

*Relevant RCTs, meta-analyses and systematic review*s were searched in a stepwise approach.

As a start we have searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library, systematic reviews for included guidelines) that answer some or all of our research questions. One or more systematic reviews were selected as our basic source. From these sources, all references of relevant publications were screened manually.

In a second step, we conducted a systematic search in the Medline (PubMed) electronic database for randomised controlled trials (RCTs), meta-analyses, systematic reviews that were published after the search date of our selected systematic reviews.

Guidelines were searched through the link "evidence-based guidelines" on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to 'guideline search engines', like G-I-N.

2.4.2 Source documents

The following systematic reviews were selected as source documents and starting points to find relevant publications for our literature review:

Topic	Source document
Elderly	NICE 2019(3) Thyroid disease: assessment and management
Euthyroid multinodular goiter	NICE 2019(3) Thyroid disease: assessment and management
Supplements: selenium	NICE 2019(3) Thyroid disease: assessment and management
Supplements: iodine	NICE 2019(3) Thyroid disease: assessment and management

For all these research questions, a search string was developed to search Medline via Pubmed from the research date of the selected source document up until 1st June 2022.
For all other topics no source document was found, and a search of Medline without a starting date was performed.

2.4.3 Search strategy details

The full search strategies can be found in chapter 23.

2.5 Selection procedure

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and

abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.
In - and exclusion criteria of the different types of studies are found in "2.3.3. Specific search criteria" with relevant populations, interventions, endpoints and study criteria.
The selection of the studied drugs and supplements was based on discussions with experts of the organisation committee.
The list of articles excluded after reading of the full text can be found in chapter 24.

2.6 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.
The GRADE system assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table. Items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed.
In assessing the different criteria, we have applied the following rules:
Study design

In this literature review RCT's and observational studies are included. RCTs start out as high quality of evidence (4 points), observational studies start out as low quality of evidence (2 points). Points can be deducted for items that are assessed as having a high risk of bias.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Application in GRADE:

Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.

For example:

> Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
>
> A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group based on the total of available studies, whilst taking into account:

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
- For meta-analyses: Statistical heterogeneity.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

A point can be deducted for imprecision if the 95%-confidence interval crosses both the point of appreciable harm AND the point of appreciable benefit (e.g. RR 95%CI ≤0.5 to ≥1.5).

Additional considerations for observational studies

For observational studies, when no points are deducted for risk of bias in one of the above categories, a point can be added if there is a large magnitude of effect (high odds ratio), if there is evidence of a dose-response gradient or (very rarely) when all plausible confounders or other biases increase our confidence in the estimated effect.

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

2.7 Synopsis of the study results

The complete report contains:

- (Comprehensive) summary of selected guidelines.
- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English).

The synopsis report contains:

- (Brief) summary of selected guidelines.
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions of this report have been discussed and adjusted through discussions between the authors of the literature search.

3 Critical reflections of the literature group

3.1 Scope of the review

The Organizing Committee focused on questions surrounding overt or subclinical hypothyroidism and the use of levothyroxine considering the existing controversies regarding this topic and the many unanswered questions in clinical practice . This lack of clarity is usually due to a lack of sufficient evidence. Given these circumstances, we expected that our literature search would not result in many eligible studies for our analysis which indeed was the case.
When there is a lack of evidence for efficacy, the precautinary principle applies. This is especially true in populations that are more sensitive to adverse effects and interactions, such as the elderly and pregnant women.
In consultation with the Organizing Committee, we determined the specific populations, interventions, comparisons, and outcomes to be reported and for which a search of the literature was to be conducted. The studied populations, interventions and outcomes are discussed here in short. More details on the studied populations, interventions, comparisons and outcomes can be found in 2.3.3. Specific search criteria.

3.1.1 Populations

Most search questions did not concern the general population with (subclinical) hypothyroidism.
The following specific populations were studied:

- elderly individuals
- pregnant women
- women with infertility
- individuals with euthyroid multinodular goiter
- persons with chronic fatigue syndrome
- persons being treated in the context of anti-aging
- individuals with obesity (and euthyroidism)

3.1.2 Interventions

Our report focused mainly on levothyroxine (T4), the only thyroid hormone registered as a drug in Belgium.
However, T3 is sometimes used in practice or requested by patients, and it can be imported by the pharmacist following a written request. Because of this, we also sought evidence on the efficacy and safety of T3 in limited indications (see chapter 5.6.5: guideline recommendations on T3 vs T4; chapter 11: anti-aging; chapter 12: chronic fatigue syndrome; and chapter 13: euthyroid multinodular goiter). The usefulness of this treatment should certainly be questioned, given the lack of evidence on its efficacy and long-term safety.

We also sought evidence on the efficacy and safety of some dietary supplements in the treatment of (subclinical) hypothyroidism.

3.1.3 Outcomes

We focused mainly on hard endpoints. These are endpoints that really matter to the patient, such as mortality, quality of life, symptom burden.
We also reported TSH and T4. Keep in mind that these are not hard endpoints. Normalization of TSH should not be the only goal of treatment.
Quality of life and symptom burden are hard endpoints, but they are subjective and thus more difficult to measure and more susceptible to bias, especially if there was no or incomplete blinding of treatment. To evaluate subjective symptoms and quality of life, studies commonly use symptom scales.
A reliable scale is validated and a Minimally Important Difference (MID) is defined: the smallest difference at which the patient actually notices an improvement.
We also reported adverse effects from the studies. RCTs are not usually designed to detect adverse effects. Some adverse effects do not appear until a considerable time has passed. The study duration is often not long enough to detect them. Some adverse effects are rare and there often are not enough study participants included to detect them.

3.2 General remarks

3.2.1 Non-statistically significant results

A great majority of results in this report were not statistically significant. Does this always mean that there really is no difference between levothyroxine and control for efficacy?
If it concerns a high-quality study and a narrow confidence interval, then it is very likely that there really is no difference for efficacy.
However, it would also be possible that there is a difference in reality, but that the study was not large enough (underpowered) to show it. A wide confidence interval is often a sign of a study underpowered to detect a difference in a certain outcome. The actual difference could lie anywhere within that confidence interval.
In addition, it would be possible that there is in fact a difference, but that the study did not study the correct population, intervention, or outcome, or was designed in a methodologically inadequate way.
We reported a GRADE for each result that provides an estimate of the reliability of the result. It is also important to take this into account for results that are not statistically significant.

3.2.2 Thyroid-antibodies

The role of thyroid antibodies (such as TPO-Ab and Tg-Ab) was examined in this report for the "pregnancy and infertility" topic only.

Some authors suggested that thyroid antibodies might also play a role in other populations. The presence of thyroid antibodies might increase the risk of future hypothyroidism(4). The question is whether there is a subpopulation of individuals with these autoantibodies that would benefit from levothyroxine treatment. However, this has not yet been adequately investigated.

3.3 Remarks on specific chapters

3.3.1 Guidelines

We searched for guidelines, published in the past 5 years, that made recommendations about the treatment of (subclinical) hypothyroidism in different populations. We selected guidelines that stated levels of evidence in their recommendations and that were based on a good systematic search and review.
Exceptions were made for these guidelines that are commonly in use in practice, such as the ATA guideline, which did not meet our selection criteria in all areas but are followed by specialists worldwide, or for guidelines that were published more than 5 years ago if we did not find more recent guidelines for certain topics.
We grouped and compared the recommendations of different guidelines to highlight similarities and differences. However, it was not always clear whether the recommendations applied to the exact same population of patients. For example, the definition of subclinical hypothyroidism was not the same in all guidelines and populations. As a result, it is possible that certain recommendations were compared that are actually referring to (slightly) different populations.
Some guidelines (especially these on thyroid problems in pregnancy and infertility) are quite specialized in nature. We ask that the Jury take into account the tasks of a primary care professional regarding diagnosis, therapy and monitoring.

3.3.2 Nutritional supplements

We found no RCTs on the use of dietary supplements versus placebo or no treatment for the treatment of overt or subclinical hypothyroidism with a follow-up of 6 months or longer.
We therefore included studies with a shorter duration than this stated minimum duration.
We were able to include one RCT evaluating vitamin D in hypothyroidism and one evaluating selenium in subclinical hypothyroidism.
These studies reported only biochemical endpoints and no hard endpoints. As discussed earlier, hard endpoints need to be studied estimate the true clinical impact in patients.

3.3.3 Elderly individuals

We found no RCTs that assessed the efficacy or safety of levothyroxine in the elderly with overt hypothyroidism.

The studies assessed levothyroxine as a treatment for subclinical hypothyroidism as determined by TSH-level.

Outcomes such as depressive symptoms, fatigue and cardiac function were evaluated. These are indeed important clinical endpoints.
However, on average, the study participants did not have a significant symptom burden at baseline.
In practice, one would probably not consider initiating treatment with levothyroxine in these patients with subclinical hypothyroidism diagnosed on the basis of biochemical results alone.
In practice, it is more likely that a patient will present with certain complaints of fatigue or depressive symptoms, upon which subclinical hypothyroidism is diagnosed after investigations.
It would be useful to investigate whether levothyroxine is effective in a population with subclinical hypothyroidism AND with pronounced symptoms (such as depressive symptoms or fatigue). No studies have yet been performed in (older) individuals with greater symptom burden.
One study did analyze cardiovascular endpoints in an older population with a history of cardiovascular disease; however, very broad confidence intervals suggest that the study was underpowered to detect a difference.
Lastly, the studies included very few patients with an initial TSH level higher than 10 mIU/L, so we cannot draw any conclusions about the efficacy or safety of levothyroxine in these patients.
However, it is precisely the patients with a TSH level higher than 10 mIU/L in whom, according to the NICE 2019 guideline, levothyroxine treatment should be considered (regardless of age).

3.3.4 Pregnancy and infertility

We did not find any RCTs evaluating levothyroxine treatment versus no treatment or placebo in pregnant women with overt hypothyroidism, presumably because of ethical reasons.
There were several difficulties in selecting and reporting the trials regarding levothyroxine treatment in pregnant women with subclinical hypothyroidism:

1) **The definition of (subclinical) hypothyroidism in pregnant women is not consistent between different guidelines and studies, and has changed throughout time.**
    - Cut-offs for the diagnosis of subclinical hypothyroidism vary between studies
    - Auto-immunity (TPO-Ab-status) is sometimes used as a criterium for starting levothyroxine treatment, including in euthyroid women with TPO-Ab positivity
2) **Most trials and SRs evaluated levothyroxine in pregnant women with (combinations of) additional distinct characteristics**
    - TSH level
    - TPO-Ab status
    - recurrent pregnancy loss (RPL)
    - infertility, with or without assisted reproduction

    There were no SRs of sufficient quality that grouped all pregnant women with subclinical hypothyroidism. Most SRs agreed that the characteristics described above represented different populations and that levothyroxine might have a different effect in all of them. It is doubtful that the results of these studies can be extrapolated to all pregnant women (or all women with infertility problems).

    In this document, we decided to report two SRs that included populations that most corresponded to the jury questions:

- Pregnant euthyroid women with TPO-Ab-positivity (irrespective of RPL status, natural or assisted reproduction status)
- Pregnant women with subclinical hypothyroidism (irrespective of TPO status, RPL status, natural or assisted reproduction status)

Because of this, there is some overlap with studies included in the chapter about infertility.

3) The treatment differed between studies with respect to:

- Regimen: some studies used a fixed dosage, some a dose according to body weight, while others titrated the dose to achieve a target TSH level.
- Gestational age at initiation of levothyroxine.

Additional difficulties were considerable methodological problems in many of the studies, particularly in the studies of levothyroxine in pregnancy.

3.3.5 Euthyroid multinodular goiter

We did not find RCTs that specifically included participants with a diagnosis of euthyroid multinodular goiter.
We reported a systematic review (Bandeira-Echtler 2014(5)) that included RCTs of levothyroxine for benign thyroid nodules. The RCTs in this systematic review included mostly participants diagnosed with a solitary benign nodule. Most specified that the participants should also be euthyroid. None specified the diagnosis "euthyroid multinodular goiter". However, we elected to report this systematic review as the introduction of the review states the following:
Quote: "*A clinically solitary thyroid nodule is a discrete swelling within an otherwise palpable normal thyroid gland. The overwhelming majority of these nodules are composed of irregularly enlarged follicles containing abundant colloid (benign adenomatous nodules).* ***About half of individuals with clinically apparent solitary nodules are found to have multinodular goitres at surgery*****."**(5)
However, it remains unclear whether the results of this systematic review can be applied to all patients with a diagnosis of euthyroid multinodular goiter.

3.3.6 Chronic fatigue and anti-aging

We found no RCTs that examined the use of levothyroxine, triiodothyronine (T3), or a combination of T4 and T3 in persons with chronic fatigue syndrome or in anti-aging.
Thus, the use of T4 and/or T3 in chronic fatigue syndrome or anti-aging is not supported by any evidence from clinical trials.
The impact of levothyroxine on fatigue in the elderly with subclinical hypothyroidism (i.e., not chronic fatigue syndrome) was also investigated, but it should be noted here that these were individuals with little symptom burden at baseline. We can therefore not draw conclusions on the efficacy of levothyroxine in the elderly with fatigue as a main complaint.

3.3.7 Obesity

We found no RCTs meeting our inclusion criteria that examined the efficacy or safety of levothyroxine in obesity (without overt or subclinical hypothyroidism). The use of levothyroxine to achieve weight reduction is not supported by any evidence from clinical trials.
We cited recommendations from guidelines surrounding the treatment of hypothyroidism with levothyroxine in obese patients .

4 General information on selected guidelines

4.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in the following tables.

4.1.1 Hypothyroidism and subclinical hypothyroidism.

Abbreviation	Guideline
NICE 2019(3)	Thyroid disease: assessment and management; NICE guideline NG145; 2019.
BMJ 2019(6)	Bekkering GE, Agoritsas T, Lytvyn L, et al.; Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline; 2019.
BTA 2016(7)	Okosieme O, Gilbert J, Abraham P, et al.; Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee; 2016.

Table 1: Selected guidelines and their abbreviations as used in this report.

4.1.2 Hypothyroidism and pregnant women and women with fertility problems

Abbreviation	Guideline
ATA 2017(8)	Alexander EK, Pearce EN, Brent GA, et al.; Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum; 2017
ETA 2014(9)	John Lazarus J, Brown RS, Daumerie C, et al.; European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children; 2014
ETA 2021(10)	Poppe K, Bisschop P, Fugazzola L et al., European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction, 2021
ASRM 2015(11)	Subclinical hypothyroidism in the infertile female population: a guideline; Practice Committee of the American Society for Reproductive Medicine; 2015

Table 2: Selected guidelines and their abbreviations as used in this report.

4.1.3 Hypothyroïdism and obesity

Abbreviation	Guideline
ESE 2020(12)	Pasquali R, Casanueva F, Haluzik M, et al. ; European Society of Endocrinology Clinical Practice Guideline: Endocrine work-up in obesity; 2020
NHG 2020(13)	NHG-werkgroep: Van Binsbergen JJ, Langens FNM, Dapper ALM, et al.; NHG-Standaard, Obesitas (M95) ; 2020.
VA/DoD 2020(14)	Department of Veterans Affairs, Department of Defense ; VA/DoD Clinical practice guideline for the management of adult overweight and obesity ; U.S. 2020.

Table 3: Selected guidelines and their abbreviations as used in this report.

4.1.4 Symptomatology: chronic fatigue

Abbreviation	Guideline
NICE Fatigue(15)	Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management; NICE guideline; NG206; 2021
DEGAM 2017(16)	Müdigkeit; S3-Leitlinie; DEGAM, AWMF 053-002; 2017.

Table 4: Selected guidelines and their abbreviations as used in this report.

4.1.5 Symptomatology: suppression therapy in euthyroid multinodular goiter

Abbreviation	Guideline
AACE/ACE/AME 2016(17)	Gharib H, Papini E, Garber JR, et al.; American association of clinical endocrinologist, American college of endocrinology, and associazione medici endocrinologi medical guidelines for clinical practice for the diagnostic and the management of thyroid nodules; 2016 update

Table 5: Selected guidelines and their abbreviations as used in this report.

4.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in the following tables.

NICE 2019		
Grades of recommendation:	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used are worded in the text using the term “offer”, “refer”, “advise” or similar…	There is clear evidence of benefit. We are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective.
	Intervention that could (or could not) be used are worded in the text using the term “consider”	Reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute strength levels to each particular recommendation.	

Table 6: Grades of recommendation and Level of evidence of the NICE 2019 guideline.

BMJ 2019		
Grades of recommendation: According to GRADE	Strong	The desirable effects of the intervention clearly outweigh the undesirable effects, or clearly do not.
	Weak	Evidence suggest that desirable and undesirable effect are closely balanced.
Levels of evidence According to GRADE	High	Further research is very unlikely to change our confidence in the estimate of effect.
	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
	Very Low	Any estimate of effect is uncertain.

Table 7: Grades of recommendation and Level of evidence of the BMJ 2019 guideline.

BTA 2016		
Grades of recommendation: According to GRADE	Strong (1)	The desirable effects of an intervention clearly outweigh the undesirable effects.
	Weak (2)	There is uncertainty about the trade-offs.
	Summary Statement (SS)	Formal clinical recommendation is not feasible because of sparse evidence.
Levels of evidence According to GRADE	High (+++)	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate (++0)	
	Low (+00)	
	Insufficient (000)	
In addition to the statement, we have summarized the relevant recommendations from the ATA 2014(18) and ETA 2012(19) guidelines relating to the diagnosis and management of primary hypothyroidism. The strength of the recommendations and the quality of the evidence supporting these recommendations are included as judged by the authors of the original guidelines.		

Table 8: Grades of recommendation and Level of evidence of the BTA 2016 guideline.

ESE 2020		
Grades of recommendation: According to GRADE	Strong : The recommendations are worded as “recommend”.	The meaning of a strong recommendation can be stated as follows: reasonably informed persons (clinicians, politicians and patients) would want the management in accordance with the recommendation.
	Weak : The recommendations are worded as “suggest”.	For a weak recommendation, most persons would still act in accordance with the guideline, but a substantial number would not.
	Good clinical practice and experience of the panelists were not graded	
Levels of evidence According to GRADE	High (++++)	
	Moderate (+++0)	
	Low (++00)	

	Very low(+000)	

Table 9: Grades of recommendation and Level of evidence of the ESE 2020 guideline.

NHG 2020		
Grades of recommendation:	Strong: expressed in the wording of the recommendation	/
	Weak: expressed in the wording of the recommendation	This often means there is not enough evidence to recommend a specific option and that medical professionals, together with their patient, make a choice from different options.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE) NICE does not explicitly attribute strength levels to each particular recommendation.	

Table 10: Grades of recommendation and Level of evidence of the NHG 2020 guideline.

VA/DoD 2020		
Grades of recommendation: According to GRADE	Strong (for or against) : worded as « we recommend ».	High confidence in the quality of the available scientific evidence, clear difference in magnitude between the benefits and harms of an intervention, similar patient or provider values and preferences, and understood influence of other implications (e.g., resource use, feasibility).
	Weak (for or against): worded as « we suggest ».	If the Work Group has less confidence after the assessment across these domains and believes that additional evidence may change the recommendation, it assigns a “Weak” recommendation.
	Neither for nor against	the Work Group feels there is insufficient evidence to make a recommendation for or against a particular therapy or preventive measure (absence of studies on a particular topic that met evidence review inclusion criteria, studies included in the evidence review report conflicting results, or studies included in the evidence review report inconclusive results regarding the desirable and undesirable outcomes)
	High	**Confidence in the quality of the evidence** reflects the quality of the evidence base and the certainty in that
	Moderate	

Levels of evidence According to GRADE	Low	evidence. This second domain reflects the methodological quality of the studies for each outcome variable. In general, the strength of recommendation follows the level of evidence, but not always, as other domains may increase or decrease the strength.
	Very Low	

Table 11: Grades of recommendation and Level of evidence of the VA/DoD 2020 guideline.

NICE Fatigue		
Grades of recommendation:	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used are worded in the text using the term “offer”, “refer”, “advise” or similar…	There is clear evidence of benefit. We are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective.
	Intervention that could (or could not) be used are worded in the text using the term “consider”	Reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute strength levels to each particular recommendation.	

Table 12: Grades of recommendation and Level of evidence of the NICE Fatigue guideline.

DEGAM 2017		
Grades of recommendation: Depending on the level of evidence and question domain: **T** Therapie – Prävention **K** Kausalität/Ätiologie – Risikofaktoren – Nebenwirkungen von Therapie **P** Prognose **D** Diagnose	A	hohe Empfehlungsstärke
	B	mittlere Empfehlungsstärke
	C	niedrige Empfehlungsstärke

S Symptomevaluation – Differentialdiagnose		
Levels of evidence	Ia	Höchste Stufe, Evidenznachweis durch Metaanalysen oder systematischen Reviews randomisiert kontrollierter Studien
	Ib	Evidenznachweis durch einzelne randomisiert kontrollierte Studien
	II	Evidenznachweis durch Kohortenstudien
	III	Evidenznachweis durch Fall-Kontrollstudien
	IV	Evidenznachweis durch Fallserien
	(V) GCP	Good Clinical Practice; Expertenkonsens

Table 13: Grades of recommendation and Level of evidence of the Degam 2017 guideline.

ASRM 2015		
Grades of recommendation:	A	There is good evidence to support the recommendations, either for or against.
	B	There is fair evidence to support the recommendations, either for or against.
	C	There is insufficient evidence to support the recommendations, either for or against.
Levels of evidence	I	Evidence obtained from at least one properly designed randomized, controlled trial.
	II-1	Level II-1: Evidence obtained from well-designed controlled trials without randomization.

	II-2	Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
	II-3	Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
	III	Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Table 14: Grades of recommendation and Level of evidence of the ASRM 2015 guideline.

ETA 2021		
Grades of recommendation: According to GRADE	Strong (1)	
	Weak or suggestion (2)	
Levels of evidence According to GRADE	High (ØØØØ)	According to GRADE (assessment of risk of bias, directness, consistency and precision of the estimates)
	Moderate (ØØØO)	
	Low (ØØOO)	
	very low (ØOOO)	

Table 15: Grades of recommendation and Level of evidence of the ETA 2021 guideline.

ETA 2014		
Grades of recommendation: using modified GRADE criteria	Strong (S): worded as a recommendation	Strong recommendations are clinically important best practice and should be applied to most patients in most circumstances.
	Weak: (W) : worded as a suggestion.	Weak statements should be considered by the clinician and will be applicable best practice only to certain patients or under certain circumstances.
Levels of evidence	High (level 1)	RCT evidence

using modified GRADE criteria	Moderate (level 2)	intervention short of RCT or large observational studies
	Low (level 3)	case series, case reports, expert opinion

Table 16: Grades of recommendation and Level of evidence of the ETA 2014 guideline.

ATA 2017		
Grades of recommendation:	Strong	For high and moderate quality of evidence: Can apply to most patients in most circumstances without reservation for low quality of action: May change when higher-quality evidence becomes available
	Weak	For high and moderate quality of evidence: Best action may differ based on circumstances or patients' values for low quality of action: Other alternatives may be equally reasonable
	Insufficient	Insufficient evidence to recommend for or against
Levels of evidence According to GRADE	High	RCT without important limitations or overwhelming evidence from observational studies
	Moderate	RCT with important limitations or strong evidence from observational studies
	Low	Observational studies/case studies

Table 17: Grades of recommendation and Level of evidence of the ATA 2017 guideline.

AACE/ACE/AME 2016			
Grades of recommendation:	A	>1 Conclusive level 1 publications demonstrating benefit >> risk	Action recommended for indications reflected by published reports Action based on strong evidence Action can be used with other conventional therapy or as first-line therapy
	B	No conclusive level 1 publication ≥1 Conclusive level 2 publications demonstrating benefit >> risk	Action recommended for indications reflected by the published reports Use if the patient declines or does not respond to conventional therapy; must monitor for adverse effects

			Action based on intermediate evidence Can be recommended as "second-line" therapy
	C	No conclusive level 1 or 2 publications ≥1 Conclusive level 3 publication demonstrating benefit >> risk Or No conclusive risk at all and no benefit at all	Action recommended for indications reflected by the published reports Use when the patient declines or does not respond to conventional therapy, provided there are no important adverse effects; No objection" to recommending their use Or "No objection" to continuing their use Action based on weak evidence
	D	No conclusive level 1, 2, or 3 publication demonstrating benefit >> risk Conclusive level 1, 2, or 3 publication demonstrating risk >> benefit	Not recommended Patient is advised to discontinue use Action not based on any evidence
Levels of evidence	1	Well-controlled, generalizable, randomized trials Adequately powered, well-controlled multicenter trials Large meta-analyses with quality ratings All-or-none evidence	
	2	Randomized controlled trials with limited body of data Well-conducted prospective cohort studies Well-conducted meta-analyses of cohort studies	
	3	Methodologically flawed randomized clinical trials Observational studies Case series or case reports Conflicting evidence, with weight of evidence supporting the recommendation	
	4	Expert consensus Expert opinion based on experience "Theory-driven conclusions" Unproven claims	

Table 18: Grades of recommendation and Level of evidence of the AACE/ACE/AME 2016 guideline.

4.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in the table below. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score (%)
NICE 2019	7	7	7	4	7	7	5	5	**49**	**87,5**
BMJ 2019	5	4	7	5	7	7	5	5	**45**	**80,3**
BTA2016	3	2	3	5	3	5	3	2	**26**	**46,4**
ASRM 2015	4	3	4	2	4	4	3	2	**26**	**46,4**
ETA 2021	2	3	3	4	4	6	4	2	**28**	**50**
ETA 2014	4	3	4	3	4	6	4	2	**30**	**53,5**
ATA 2017	1	2	3	5	4	5	5	5	**30**	**53,5**
ESE 2020	6	6	6	4	5	6	4	2	**39**	**69,4**
NHG 2020	7	4	4	5	6	7	6	3	**42**	**75**
VA/DoD 2020	7	7	5	5	5	7	6	6	**48**	**85,7**
NICE fatigue	7	7	7	4	7	7	5	5	**49**	**87,5**
DEGAM 2017	7	7	7	6	5	7	6	6	**51**	**91**
AACE/ACE/AME 2016	6	2	5	1	5	7	3	3	**32**	**57,1**

Table 19: AGREE score of selected guidelines on item “Rigour of development”, see methodology for a description of the items.

4.4 Included populations – interventions – main outcomes

In the following tables, the populations, interventions and main outcomes considered in the selected guidelines are represented.

NICE 2019	
Population	• Children, young people and adults with thyroid disease. This includes following areas: - Investigation of thyroid dysfunction or thyroid enlargement - Management of non-malignant thyroid enlargement with normal thyroid function - Management of primary hypothyroidism - Management of thyrotoxicosis - Management of subclinical thyroid dysfunction - Information for people with thyroid disease, their families and carers It does not cover: managing thyroid cancer, thyroid disease in pregnancy, screening for congenital hypothyroidism.
Interventions	for hypothyroidism: • Different thyroid function tests () • Levothyroxine [L-T4], liothyronine [L-T3], combination of L-T4 and L-T3, thyroid extracts, and iodine and selenium. It does not covers: dietary and lifestyle interventions.
Outcomes	for hypothyroidism: • Mortality • Quality of life • Number of people receiving treatment • Patient/family/carer experience of care • Healthcare contacts • Symptom scores • Cardiovascular morbidity-ischemic heart disease, heart failure • Arrhythmias • Osteoporosis • Impaired cognitive function • Depression • Growth • TSH suppression • Neurodevelopment

Table 20: Included population, intervention and main outcomes of the NICE 2019 guideline.

BMJ 2019	
Population	• Adults with subclinical hypothyroidism (Elevated levels of thyroid stimulating hormone (TSH) + Normal free T4 (thyroxine) levels . Including patients with no symptoms (diagnosed after screening) and patients with non-specific symptoms. It does not apply to: - women who are trying to become pregnant - those with very high TSH levels (>20 mIU/L) and with normal T4 (thyroxine) levels It may not apply to: - Those with severe symptoms, as - Very young adults (such as ≤30 years old). - Women at risk of unplanned pregnancy. - Patients who already take thyroid hormones
Interventions	• Thyroid hormones
Outcomes	• General quality of life • Thyroid-related symptoms • Fatigue / tiredness • Depressive symptoms • Cognitive function • BMI • Muscle strength • Mortality • Cardiovascular events • Serious adverse events • Side effects

Table 21: Included population, intervention and main outcomes of the BMJ 2019 guideline.

BTA 2016	
Population	• Patients with primary hypothyroidism Not addressed : subgroups such as pregnant women, patients treated for thyroid cancer or secondary hypothyroidism.
Interventions	• Levothyroxine [L-T4] • Liothyronine [L-T3] • Combination of L-T4 and L-T3 • Other therapies
Outcomes	• Diagnosis and management of hypothyroidism • Management of euthyroidism, • Patient satisfaction, • Deleterious effect of L-T4

Table 22: Included population, intervention and main outcomes of the BTA 2016 guideline.

ESE 2020	
Population	• Patients with obesity was defined as BMI ≥30 kg/m$_2$ and/or large waist circumference as expression of abdominal obesity (definition of enlargement based on different criteria used in included articles). The guidelines where not developed with the specific aim to cover rare forms of obesity.
Interventions	/
Outcomes	The present guideline is primarily about the endocrine work-up in obesity, that is, about diagnostic questions.

Table 23: Included population, intervention and main outcomes of the ESE 2020 guideline.

NHG 2020	
Population	• Volwassenen en kinderen vanaf 2 jaar met obesitas. Deze richtlijnen zijn eveneens van toepassing bij volwassenen met overgewicht, indien dit gepaard gaat met een ernstig vergrote buikomvang of met comorbiditeit die met het overgewicht samenhangt. **Buiten de scope:** het opstellen van een cardiovasculair risicoprofiel en screening op diabetes mellitus type 2 bij volwassenen met obesitas en overgewicht
Interventions	• Medicamenteuze bahandeling • Niet-medicamenteuz behandeling
Outcomes	Diagnostiek bij en de behandeling van patiënten met obesitas

Table 24: Included population, intervention and main outcomes of the NHG 2020 guideline.

VA/DoD 2020	
Population	• Adult Overweight and Obesity
Interventions	• Lifestyle Intervention • Pharmacotherapy • Bariatric Procedures

Outcomes	The specialties and clinical areas of interest included: • metabolic/bariatric surgery, • endocrinology, internal medicine, • family medicine, • nutrition, • nursing, • pharmacology, • physical therapy, • psychiatry, • psychology, • rheumatology, • general surgery, • and primary care.

Table 25: Included population, intervention and main outcomes of the VA/DoD 2020 guideline.

NICE Fatigue	
Population	• Everyone with myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome (ME/CFS) regardless of symptom severity.
Interventions	• Pharmacological management, • Dietary management • Lightening • Cognitive behavioral therapy
Outcomes	Assessment, diagnosis, management and reviewing of person with ME/CFS

Table 26: Included population, intervention and main outcomes of the NICE Fatigue guideline.

DEGAM 2017	
Population	• Akute und chronische Müdigkeit“ bei Erwachsenen jeglicher Altersstufe
Interventions	• Allgemeine Therapieprinzipien • Die Therapie eines Eisenmangels ohne manifeste Anämie
Outcomes	Adäquate diagnostische und therapeutische Vorgehen bei Patienten,

Table 27: Included population, intervention and main outcomes of the DEGAM 2017 guideline.

ASRM 2015	
Population	• Female patients with a history of infertility and miscarriage
Interventions	• No treatment

	• Levothyroxine
Outcomes	Risks and benefits of treating subclinical hypothyroidism for patients and obstetrical and neonatal outcomes

Table 28: Included population, intervention and main outcomes of the ASRM 2015 guideline.

ETA 2021	
Population	• Males and females with subfertility. Subfertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse • Women receiving assisted reproductive therapies
Interventions	• Levothyroxine (concerning subfertility)
Outcomes	• Screening and management of subclinical hypothyroidism and hypothyroidism (concerning subfertility)

Table 29: Included population, intervention and main outcomes of the ETA 2021 guideline.

ETA 2014	
Population	• Pregnant women and children with subclinical hypothyroidism. Subclinical hypothyroidism (SCH) in pregnancy is defined by a serum thyroid-stimulating hormone (TSH) concentration higher than the upper limit of the pregnancy-related reference range associated with a normal serum thyroxine [T_4; either total (TT_4) or free (FT_4)] concentration. The serum tri-iodothyronine (T_3) level is normal. It occurs in approximately 2-2.5% of pregnant women [1], although in China the incidence has been reported to be 4.0% [2], in Belgium 6.8% [3] and in Northern Spain as high as 13.7% [4.] This is in contrast to overt hypothyroidism (defined as FT_4 below normal in conjunction with elevated TSH or TSH higher than 10 mU/l irrespective of FT_4 levels) which has a prevalence of around 0.2-0.5% in pregnancy and which will not be considered further in this guideline. In children the prevalence of SCH is less than 2% [5]. When considering SCH, it was agreed that the so-called isolated hypothyroxinaemia as a separate entity should also be included in the discussion. This is normally defined as a serum T_4 concentration (TT_4 or FT_4) as being in the lower 2.5% of the reference range [6]. This definition implies that hypothyroxinaemia is associated with a normal TSH concentration.
Interventions	• Iodine

	• levothyroxine
Outcomes	• Screening and diagnosis of subclinical hypothyroidism • Effects of treatment • Adverse events of treatment

Table 30: Included population, intervention and main outcomes of the ETA 2014 guideline.

ATA 2017	
Population	• Pregnant and breastfeeding woman • Mother • Foetus • Child
Interventions	• Iodine supplementation • levothyroxine
Outcomes	• screening, diagnosis, management and monitoring

Table 31: Included population, intervention and main outcomes of the ATA 2017 guideline.

AACE/ACE/AME 2016	
Population	• Thyroid nodular disease during pregnancy and childhood are also presented herein (not thyroid cancer management
Interventions	For management: • medical treatment (levothyroxine) • surgical treatment • radioiodine therapy
Outcomes	key issues discussed in these guidelines : • US-based categorization of the malignancy risk and indications for US-guided FNA (henceforth, FNA), • cytologic classification of FNA samples, • the roles of immunocytochemistryand molecular testing applied to thyroid FNA, • therapeutic options, • follow-up strategy. Thyroid • nodule management during pregnancy and in children are also addressed.

Table 32: Included population, intervention and main outcomes of the AACE/ACE/AME 2016 guideline.

4.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the following tables.

NICE 2019	
Development group	A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members.
Target audience	• Healthcare professionals • Commissioners and providers • People with thyroid disease, their families and carers

Table 33: Members of the development group and target audience of the NICE 2019 guideline.

BMJ 2019	
Development group	International panel including methodologists, general practitioners, internists, endocrinologists, and patient partners with subclinical hypothyroidism (SCH). Two people with lived experience of subclinical hypothyroidism were members of the panel and participated in the whole process.
Target audience	Clinicians and their patients

Table 34: Members of the development group and target audience of the BMJ 2019 guideline.

BTA 2016	
Development group	Members of the BTA executive committee with expertise in thyroid disease management and research and relevant stakeholder groups.
Target audience	• Primary care practitioners, • Hospital physicians, • Clinical biochemists and endocrinologists involved in caring for patients with hypothyroidism

Table 35: Members of the development group and target audience of the BTA 2016 guideline.

ESE 2020	
Development group	The multidisciplinary team consisted of the following experts, including methodological experts and representative of the European Association of the Study of Obesity (EASO).
Target audience	healthcare providers involved in the care of patients with obesity, which covers a broad range of doctors.

Table 36: Members of the development group and target audience of the ESE 2020 guideline.

NHG 2014	
Development group	Hierin nemen naast huisartsen ook vertegenwoordigers van andere beroepsgroepen zitting. De werkgroep bestaat uit maximaal acht personen. Een wetenschappelijke medewerker en senior wetenschappelijk medewerker van de NHG-afdeling Richtlijnontwikkeling en Wetenschap begeleiden de werkgroep.
Target audience	De NHG-Standaarden geven richtlijnen voor het handelen van de huisarts.

Table 37: Members of the development group and target audience of the NHG 2014 guideline.

VA/DoD 2020	
Development group	A panel of multidisciplinary experts (working group) and leaders to serve as Champions group. The Lewin Team, including The Lewin Group, Duty First Consulting, ECRI, Sigma Health Consulting, and Anjali Jain Research & Consulting, was contracted by the VA to support the development of this CPG and conduct the evidence review. Has included discussion with a patient focus group
Target audience	…is intended for VA and DoD healthcare practitioners including: physicians, nurse practitioners, physician assistants, social workers, psychologists, dietitians, nurses, pharmacists, physical therapists, kinesiotherapists, and others involved in caring for Service Members or Veterans with overweight or obesity. Additionally, this guideline is intended for those in community practice involved in the care of Service Members or Veterans with overweight or obesity.

Table 38: Members of the development group and target audience of the VA/DoD 2020 guideline.

NICE Fatigue	
Development group	A multidisciplinary guideline committee comprising health professionals and researchers as well as lay members.
Target audience	• Health and social care professionals, including those working or providing input into educational and occupational health services • Commissioners • People with suspected or diagnosed ME/CFS, their families and carers and the public

Table 39: Members of the development group and target audience of the NICE Fatigue guideline.

DEGAM 2017	
Development group	Fachärztin für Allgemeinmedizin, Sportmedizin, Palliativmedizin, Psychotherapeutische Medizin, spezifischer Selbsthilfegruppen/Patientenvertretungen, die Krebsberatungsstelle und Krebs-Selbsthilfekontaktstelle e. V., die Deutsche Gesellschaft für ME/CFS (Herr Musch und Herr Hattesohl),das Bündnis ME/CFS mit der darin beteiligten Organisation: Lost Voices Stiftung (Frau Krüger) sowie der Bundesverband Chronisches Erschöpfungssyndrom ME/CFS/CFIDS Fatigatio e.V. (Frau Klasing)
Target audience	Ärztinnen in der Primärversorgung

Table 40: Members of the development group and target audience of the DEGAM 2017 guideline.

ASRM 2015	
Development group	Task forces develop ASRM **guidelines**. Task forces are comprised of topic experts of varying levels of experience, a past DEEST scholar (if possible), other experts as needed, an international member of ASRM (non-USA based), the task force chair who is a member of the Practice Committee, the Practice Committee chair, a clinical epidemiologist, a guidelines specialist with experience in systematic search strategies and unbiased evaluation of the scientific literature, coordinator for the Practice Committee, the ASRM chief executive officer, and the ASRM chief scientific officer.
Target audience	Physicians

Table 41: Members of the development group and target audience of the ASRM 2015 guideline.

ETA 2021	
Development group	• A chairperson (K.P.) to lead the task force • After agreement of the ETA executive committee, K.P. assembled a team of European clinicians who authored this manuscript. • µMembership on the panel was based on clinical expertise, scholarly approach, representation of endocrinology, and mostly are ETA members.
Target audience	Endocrinologists and gynecologists providing care to subfertile couples with thyroid disorders.

Table 42: Members of the development group and target audience of the ETA 2021 guideline.

ETA 2014	
Development group	Task force for the development of guidelines
Target audience	Not mentioned

Table 43: Members of the development group and target audience of the ETA 2014 guideline.

ATA 2017	
Development group	A task force of specialists with complementary expertise (adult and pediatric endocrinology, obstetrics, maternal-fetal medicine, endocrine surgery, iodine nutrition, and epidemiology) was appointed.
Target audience	Clinicians, patients, researchers, and health policy makers

Table 44: Members of the development group and target audience of the ATA 2017 guideline.

AACE/ACE/AME 2017	
Development group	Representatives of endocrinologists, endocrine surgeons, and thyroid pathologists
Target audience	Health care professionals

Table 45: Members of the development group and target audience of the AACE/ACE/AME 2017 guideline.

5 Recommendations from guidelines

5.1 Overt Hypothyroidism

The literature group was not asked to report recommendations on the diagnosis of hypothyroidism, but some information on the diagnosis that was found in the selected guidelines is reported in the present document for context.

Diagnosing overt hypothyroidism: criteria and tests

Both guidelines (NICE 2019 and BTA 2016) state that the diagnosis of hypothyroidism is based on biochemical evidence of elevated serum TSH together with low free T4.

BTA 2016 adds that primary hypothyroidism should not be diagnosed in individuals with normal serum TSH who otherwise have intact pituitary function. BTA also mentions that the significance of perturbations in serum T3 concentrations within the reference range, or of mildly low serum T3, is unknown.

NICE 2019 further recommends for adults when thyroid dysfunction is suspected but not secondary thyroid dysfunction (pituitary disease), to:

- first measure TSH alone.
  THEN
- if the TSH is above the reference range, measure free FT4 in the same sample
- if the TSH is below the reference range, measure FT4 and FT3 in the same sample.

When hypothyroidism is confirmed, only NICE 2019 recommends to consider measuring TPO-Abs for adults with TSH levels above the reference range, but not to repeat TPO-Abs testing.

When secondary thyroid dysfunction is suspected NICE 2019 recommends to consider measuring both TSH and FT4.

According to NICE 2019, these tests should be repeated (no sooner than 6 weeks from the most recent test) if symptoms worsen or new symptoms develop.

Treating hypothyroidism

Both guidelines agree (NICE 2019 and BTA 2016) that levothyroxine is the recommended treatment of hypothyroidism.

According to NICE 2019 levothyroxine should be considered at:

- a dosage of 1,6 µg/kg/day (rounded to the nearest 25 µg) for adults < 65 with primary hypothyroidism and no history of cardiovascular disease.
- a dosage of 25 to 50 µg/day with titration for adults ≥ 65 and adults with a history of cardiovascular disease.

The BTA 2016 guideline did not mention a specific dosage regimen.

Dietary supplements

BTA 2016 (from ATA) recommends against the use of dietary supplements, nutraceuticals or other over the counter products in euthyroid individuals as well as for hypothyroidism and particularly

warns against the use of pharmacologic doses of iodine because of the risk of thyrotoxicosis and hypothyroidism (intact thyroid glands susceptible to becoming further dysregulated).

NICE 2019 was unable to make recommendations on iodine or selenium supplements because of a lack of evidence.

5.2 Subclinical hypothyroidism

Diagnosing subclinical hypothyroidism: criteria, tests, different patient populations, threshold values

Definition: in all guidelines: elevated serum TSH together with normal free T4.

A normal TSH level reference range is cited in some guidelines:

- ASRM 2015: upper limit of normal range as 4.5–5.0mIU/L.
- ASRM 2015: serum TSH reference range between 0,41 to 6,10 mIU/L
- BTA 2016: serum reference range between 0,4 to 4,0 mIU/L.

Both guidelines state that the evidence in favour of narrowing the serum TSH reference range is not convincing.

TPOAbs:

- NICE 2019 and BTA 2016: the presence of antibodies may suggest an underlying thyroid disease and may influence the likelihood of TSH to return to normal upon treatment.
- NICE 2019 recommends to consider measuring TPOAbs for adults with TSH levels above the reference range, but do not repeat TPOAbs testing.

T3:

- BTA 2016: the significance of perturbations in serum T3 concentrations within the reference range, or of mildly low serum T3, is unknown.

Different patient populations:

- NICE 2019: most studies used 65 years as a cut-off. Therefore NICE 2019 decided to define older adults as over 65 and to make separate recommendations for this group.
- BMJ 2019: their recommendations do not apply to women who are trying to become pregnant or patients with TSH >20 mIU/L and may not apply to patients with severe symptoms or young adults (such as those ≤30 years old).

TSH threshold:

- BTA 2016: spontaneous recovery in subjects with subclinical hypothyroidism is more likely in those with negative antithyroid antibodies, serum TSH levels less than 10 mU/l, and within the first 2 years after diagnosis. TSH distribution progressively shifts towards higher concentration with age.
- BTA 2016 and ASRM 2015: the reference range varies in different ethnic communities, pregnancy and by age.

Pharmacotherapy for subclinical hypothyroidism

NICE 2019 recommends to:

- consider levothyroxine for adults with subclinical hypothyroidism who have a TSH of 10 mIU/l or higher on 2 separate occasions 3 months apart,
- consider a 6-month trial of levothyroxine for adults under 65 with subclinical hypothyroidism who have TSH above the reference range but lower than 10 mIU/l on 2 separate occasions 3 months apart **AND** symptoms of hypothyroidism.
- if symptoms do not improve, re-measure TSH and adjust the dose; if symptoms persist when serum TSH is within the reference range, consider stopping levothyroxine.

On the contrary, BMJ 2019 issues a strong recommendation against thyroid hormones in adults with SCH. Instead, clinicians should monitor the progression or resolution of the thyroid dysfunction in these adults. BMJ 2019 also notes that guidelines generally recommend thyroid hormones for adults with TSH levels above 10 mIU/L. and proposes a summary of current guidance from various organisations.

ASRM 2015 notes that there is no benefit (lipid profile and/or cardiovascular risk) of treatment for a TSH level between 5 and 10 mIU/L and reports that the positive predictive value for hypothyroidism of a TSH between 2.5 and 5 mIU/L is small while there is potential risk (bone loss in women).

If untreated subclinical hypothyroidism or adults having stopped levothyroxine treatment for subclinical hypothyroidism, NICE 2019 recommend to monitor TSH and fT4: once a year (if patients have features suggesting underlying thyroid disease) or once every 2 to 3 years (if patients have no features suggesting underlying thyroid disease). BMJ 2019 also propose regular visits and blood samples to monitor progression or resolution without any specification.

BTA 2016 does not formulate any recommendations or comments concerning management of subclinical hypothyroidism.

Dietary supplements

None of the guidelines formulated specific recommendations concerning the use of dietary supplementations in subclinical hypothyroidism.

5.3 Hypothyroidism in the elderly

Diagnosing subclinical and overt hypothyroidism in the elderly

None of the guidelines formulated specific recommendations concerning criteria for diagnosing subclinical or overt hypothyroidism in the elderly.

Managing hypothyroidism in the elderly

NICE 2019 recommends to consider starting levothyroxine at a dosage of 25 to 50 micrograms per day with titration for adults aged 65 and over and adults with a history of cardiovascular disease.

Managing subclinical hypothyroidism in elderly

Both BMJ 2019 and NICE 2019 do not recommend routine treatment with levothyroxine for subclinical hypothyroidism in older adults.

NICE 2019 states that levothyroxine should be considered for (all) adults with a TSH level of 10 IU/L or more, but not for older adults 65 and above with a TSH above the reference range but lower than 10 mlU/litre.

The BMJ 2019 panel agreed that the possibility of harms contributes towards a strong recommendation against routine levothyroxine treatment. BMJ 2019 also reports that there is high certainty that there is little to no difference in general quality of life, thyroid related symptoms, depressive symptoms, fatigue, cognitive function, muscle strength, and body mass index.

BTA 2016 suggests that in older people, higher serum TSH and lower free T4 concentrations, both within the euthyroid range, are associated with lower risk of multiple adverse events including mortality.

Monitoring hypothyroidism in the elderly

None of the guidelines formulated specific recommendations concerning the follow up of subclinical or overt hypothyroidism in the elderly.

5.4 Hypothyroidism in pregnant women and women with fertility problems

5.4.1 Pregnant women

No specific comments or recommendations were provided in NICE 2019 or BMJ 2019 guidelines regarding pregnancy with the exception of NICE 2019 formulating a general recommendation to inform about how thyroid disease and medicines may affect pregnancy and fertility.

Diagnosing subclinical and overt hypothyroidism : criteria, screening

Criteria

BTA 2016, ATA 2017 and ETA 2014 recommends the determination of population-based trimester-specific reference ranges for serum TSH. Reference range determinations ,through assessment of local population data representative of a health care provider's practice, should only include pregnant women with no known thyroid disease, optimal iodine intake, and negative TPO-Ab status (ATA 2017).

If internal or transferable pregnancy-specific TSH reference ranges are not available,

- BTA 2016 proposes serum TSH reference range:
  - 0.4–2.5 mU/l in the first trimester
  - 0.4–3.0 mU/l in the second and third trimesters
- ATA 2017 proposes upper reference limits of ± 4.0 mU/L
- ETA 2014 proposes upper reference limits of:
  - first trimester, 2.5 mU/l;
  - second trimester, 3.0 mU/l;
  - third trimester, 3.5 mU/l.

Method-specific and trimester specific pregnancy reference ranges should be applied for serum FT4 measurement (ATA 2017, ETA 2014).

Screening

Both ATA 2017 and ETA 2014 mention the beneficial effects of levothyroxine treatment on obstetric outcome but they also report insufficient evidence regarding screening for abnormal TSH concentrations in early pregnancy thus:

- ATA 2017 fails to formulated any recommendation, neither for nor against but recommends testing for serum TSH if any of the following risk factors are present:

1. history of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction
2. Known thyroid antibody positivity or presence of a goiter
3. History of head or neck radiation or prior thyroid surgery
4. Age >30 years
5. Type 1 diabetes or other autoimmune disorders
6. History of pregnancy loss, preterm delivery, or infertility
7. Multiple prior pregnancies (≥2)
8. Family history of autoimmune thyroid disease or thyroid dysfunction
9. Morbid obesity (BMI≥40 kg/m2)
10. Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
11. Residing in an area of known moderate to severe iodine insufficiency

- ETA 2014 does not recommend universal screening for SCH but adds that the majority of the authors (C.D., A.H.-D., J.L., R.N.) recommend universal screening because of the beneficial effects of levothyroxine treatment on unknown overt hypothyroidism, on obstetric outcome and the fact that the targeted approach will miss a large percentage of women with SCH, especially in mildly iodine-deficient women.

ATA 2017 does not recommend universal screening to detect low FT4 concentrations in pregnant women. Rather pregnant women should be verbally screened at the initial prenatal visit for any history of thyroid dysfunction.

ASRM 2015 does not routinely recommended anti-TPO antibody testing but admits that testing might be consider testing if repeated TSH values >2.5 mIU/L or when other risk factors for thyroid disease are present. If anti-TPO antibodies are detected, TSH levels should be checked and treatment should be considered if the TSH level is over 2.5 mIU/L.

Diagnosis

ETA 2014 recommends to measure TSH at the beginning of pregnancy. If TSH is elevated, FT4 and TPOAb should be determined. In the case of elevated TSH and negative TPO-Ab, Tg-Ab should be measured. ATA 2017 recommends to evaluated for TPO-Ab status in pregnant women with TSH concentrations >2.5 mU/L.

TT4 and FT4 assays are both suitable for thyroid function testing in pregnancy (ETA 2014).
TT4 measurement (with a pregnancy-adjusted reference range) is a highly reliable means of estimating hormone concentration during the last part of pregnancy. Accurate estimation of the FT4 concentrations can also be done by calculating a FT4 index (ATA 2017).

Managing hypothyroidism

Overt hypothyroidism

BTA 2016, ATA 2017 and ETA 2014 recommend treatment of overt hypothyroidism preconception and during pregnancy with T4 to achieve the reference range. It is reasonable to target TSH level in the lower half of the trimester-specific reference range (ATA 2017) or below 2.5 mU/L (ATA 2017 and ETA 2014).

Hypothyroid women already treated with levothyroxine before conception

The increase in levothyroxine may vary from 25 to 50%, depending on the etiology of hypothyroidism and pre-pregnancy TSH level (ETA 2014).

ATA 2017 recommends to increase the dose of LT4 by ± 20%–30% (a.e. two additional tablets weekly of the patient's current daily dosage) and urgently notify caregiver for prompt testing and further evaluation..

Overt hypothyroidism following delivery

ATA 2017 recommends to reduce LT4 to the patient's preconception dose. Additional thyroid function testing should be performed at approximately 6 weeks post-partum.

Women in whom LT4 is initiated during pregnancy are candidates for discontinuing LT4, especially when the LT4 dose is ≤ 50 µg/d. If LT4 is discontinued, serum TSH should be evaluated in approximately 6 weeks.

Subclinical hypothyroidism

ETA 2014 generally recommends the treatment with levothyroxine of SCH arising before conception or during gestation.

- LT4 should ensure normalization of maternal serum TSH values within the trimester-specific pregnancy reference range or TSH level <2.5 mU/l for women desiring pregnancy.
- For newly diagnosed patients with SCH in pregnancy, a starting dose of 1,20 µg/kg/day is recommended (ETA 2014).

ARSM 2015 advises to treat when the TSH is >2.5 mIU/L during the first trimester of pregnancy.

ATA 2017 formulates range-specific recommendations:

- LT4 therapy is recommended for
  - TPO-Ab-positive women with a TSH greater than the pregnancy-specific reference range.
  - TPO-Ab-negative women with a TSH greater than 10.0 mU/L.
- LT4 therapy may be considered for
  - TPO-Ab-positive women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy-specific reference range.
  - TPO-Ab-negative women and TPO-Ab-negative women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 mU/L.
- LT4 therapy is not recommended for TPO-Ab-negative women with a normal TSH (TSH within the pregnancy-specific reference range or <4.0 mU/L if unavailable).

Subclinical hypothyroidism following delivery

ETA 2014 recommends to reduce LT4 dose to the preconception dose.

Women diagnosed with SCH during pregnancy with TSH less than 5 mU/l and negative TPO-Ab could stop levothyroxine after delivery and have thyroid function checked 6 weeks after delivery. Women diagnosed with SCH during pregnancy should be re-evaluated 6 months and 1 year after delivery to ascertain the continuing requirement for levothyroxine (ETA 2014).

Other thyroid hormone preparations

BTA 2016 makes specific recommendation against LT4 + LT3 combination therapy in pregnancy. Both ATA 2017 and ETA 2014 do not recommend other thyroid preparations than T4 such as T3 or desiccated thyroid.

Role for dietary supplement?

Iodine

ATA 2017 and ETA 2014 as well as The WHO (as reported in ATA 2017) recommend a daily iodine intake during pregnancy and lactation of 250 µg. This should not exceed 500 µg/d. They both notices that this is usually provided by supplementing with formulas containing 150 µg of iodine/day, ideally starting before conception.

ATA 2017 recommends potassium iodide as iodate form, 3 months in advance of planned pregnancy, and states that strategies may need to be varied based on country of origin.

ATA 2017 particularly warns against dietary supplements such as kelp and some iodine preparations that may contain very large amounts of iodine (several thousand times higher than the daily upper limit).

Institute of Medicine (as reported in ATA 2017) recommends as goals for individual total daily iodine intake (dietary and supplement):

- 150 µg/d for women planning a pregnancy,
- 220 µg/d for pregnant women,
- 290 µg/d for women who are breastfeeding,
- the tolerable upper limit for daily iodine intake is 1100 µg/d in all adults, including pregnant women.

ATA 2017 notices that In Europe many countries, **including Belgium**, the Czech Republic, Denmark, France, Latvia, Norway, Spain, and the United Kingdom, have recorded significant iodine deficiency in their pregnant populations.

In low-resource countries and regions where neither salt iodization nor daily iodine supplements are feasible, a single annual dose of ± 400 mg of iodized oil for pregnant women and women of childbearing age can be used as a temporary measure to protect vulnerable populations. This should not be employed as a long-term strategy or in regions where other options are available (ATA 2017)

ATA 2017 states that there is no need to initiate iodine supplementation in **pregnant women who are being treated for hyperthyroidism** or who are taking LT4.

ETA 2014 also specifies that the effectiveness and side effects of iodine prophylaxis together with or without levothyroxine therapy **in subclinically hypothyroid women** should be assessed.

Selenium

ATA 2017 does not recommende selenium supplementation for the treatment of TPO-Ab-positive women during pregnancy.

Monitoring thyroid hypofunction in pregnant women

ATA 2017 recommends to monitor **women with overt and subclinical hypothyroidism** (treated or untreated) or **those at risk** for hypothyroidism (e.g., patients who are euthyroid but TPO-Ab or TgAb positive, post-hemithyroidectomy, or treated with radioactive iodine) with:

- serum TSH measurement every 4 weeks until mid-gestation
- at least once near 30 weeks gestation.

ETA 2014 recommends to monitor **subclinical hypothyroidism** during pregnancy by:

- checking TSH values every 4–6 weeks during the first trimester
- once during the second and third trimesters

For women with adequately treated hypothyroidism, ATA 2017 does not recommend any other maternal or fetal testing (such as serial fetal ultrasounds, antenatal testing, and/or umbilical blood sampling) beyond measurement of maternal thyroid function unless needed due to other circumstances of pregnancy. An exception to this is women with Graves' disease effectively treated with 131I ablation or surgical resection, who require TSH receptor antibody (TR-Ab) monitoring.

For **hypothyroid women** treated with LT4 who are **planning pregnancy**, ATA 2017 recommends to evaluate serum TSH preconception, and adjust LT4 dose adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L.

5.4.2 Women with fertility problems

Relationship between thyroid hypofunction and fertility problems

Overt hypothyroidism

ETA 2021 suggests that overt hypothyroidism is associated with an increased risk of adverse effects on fertility as well as early and late complications of pregnancy.

Subclinical hypothyroidism

ASRM 2015 reports that there is insufficient evidence that SCH (defined as TSH>2.5 mIU/L with a normal FT4) is associated with infertility. The same is suggested by ETA 2021. ETA 2021 however notices that association with adverse fertility outcomes seems to surface at TSH levels >4.0 mIU/L.

Autoimmunity

According to ASRM 2015 there is good evidence that thyroid autoimmunity is associated with miscarriage and fair evidence that it is associated with infertility. ETA 2021 reports an increased prevalence of thyroid antibodies (TAI) (mainly TPO-Ab) in women with recurrent pregnancy loss and subfertility and associated with lower anti-mullerian hormone (AMH) levels.

Screening for thyroid hypofunction in women with fertility problems

ATA 2017 states that there is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations preconception, with the exception of women planning assisted reproduction or those known to have TPO-Ab positivity.

Both ATA 2017 and ETA 2021 recommend evaluation of serum TSH for all women seeking care for infertility. The same is considered reasonable by ASRM 2015.

ETA 2021 also recommends screening for TPO-Ab and mentions that Tg-Ab can be added systematically according to the local regulatory authority rules. ETA 2021 suggests to screening for increased Tg-Ab in subfertile women with TSH levels >2.5 mIU/L and without increased TPO-Ab levels.

ETA 2021 also recommends screening for serum TSH and autoimmunity in

- women with primary ovarian insufficiency (POI) and diminished ovarian reserve (DOR),
- subfertile women with unexplained subfertility,
- subfertile women in their later reproductive years (i.e., ≥35 years).

ASRM 2015 does not routinely recommend TPO-Ab testing but suggest to consider this if repeated TSH values >2.5 mIU/L or when other risk factors for thyroid disease are present.

ASRM also states that if anti-TPO antibodies are detected, TSH levels should be checked.

Management of thyroid hypofunction

Overt hypothyroidism

ATA 2017 and ETA 2021 agree to recommend LT4 treatment for infertile women with overt hypothyroidism who desire pregnancy.

Subclinical hypothyroidism

ATA 2017 states that there is Insufficient evidence to determine if LT4 therapy improves fertility in subclinically hypothyroid, thyroid autoantibody–negative women who are attempting natural conception (not undergoing assisted reproductive techniques). But recons it could be considered given its ability to prevent progression to more significant hypothyroidism once pregnancy is achieved and the minimal risk carried by low doses (25–50 µg/d).

Rather, ETA 2021 and ARSM 2015 recommend LT4 treatment when TSH values are above 4.0 mIU/L to maintain levels below 2.5 mIU/L.

ASRM 2015 adds that if TSH levels prior pregnancy are between 2.5 and 4 mIU/L, management options include either monitoring levels and treating when TSH >4 mIU/L, or treating with levothyroxine to maintain TSH <2.5 mIU/L.

Autoimmunity

ATA 2017 fails to formulate any recommendations regarding LT4 therapy for nonpregnant, thyroid autoantibody–positive **euthyroid** women who are attempting natural conception (not undergoing ART) as Insufficient evidence exists to determine if it improves fertility.

ETA 2021:

- recommends LT4 treatment in women with TAI and **TSH levels >4.0 mIU/L** to keep TSH levels <2.5 mIU//L.
- suggests LT4 treatment in subfertile women with TAI and **serum TSH >2.5 mIU/L** on a case-by-case basis to allow for optimized ovarian reserve and optimized embryo development.

ARSM 2015 states to consider treatment if T**PO-Ab** are detected **and TSH level is over 2.5 mIU/L**.

Role for dietary supplements

None of the guidelines formulated specific recommendations concerning the use of dietary supplementations for thyroid hypofunction in women with fertility problem.

Monitoring thyroid hypofunction in women with fertility women

None of the guidelines formulated specific recommendations concerning monitoring of thyroid function in women with fertility problems.

5.5 Hypothyroïdism and body weight

Relationship between hypothyroidism and body weight/modification of thyroid function in obesity

No specific recommendations or comments were provided in NICE 2019 and BMJ 2019.

ESE 2020 is a guideline regarding endocrine work up in obesity which has specifically discussed the link between thyroid function and body weight. Other guidelines were more general on obesity and have not reported on this relationship.

ESE 2020 recommends that weight loss in obesity is emphasized as key to restoration of hormonal imbalances.

- Higher prevalence of subclinical hypothyroidism has been shown in obesity
- Obesity is not caused by other endocrine diseases or hormonal disturbances
- For most hormones (TSH, cortisol. testosterone), the proper equilibrium is restored following weight reduction.
- Hypothyroidism contributes to an unfavourable lipid profile, and thus, potentially increases vascular risk.
- Treatment of overt hypothyroidism produces only a modest weight loss (usually of less than 10%), indicating that severe obesity is usually not secondary to hypothyroidism.
- Longitudinal studies suggest that changes in thyroid hormones are side effects of increasing body weight rather than the cause. This suggests that in obesity the increase in serum TSH (in the absence of thyroid autoantibodies) is likely an adaptive response rather

than the primary event.

Screening

ESE 2020 recommends that all patients with obesity are tested for thyroid function, taking into account drugs and dietary supplements that interfere with hormone measurements. Similar advices where formulated by VA/DoD 2020 and NHG 2020.

Hypothyroidism management in patients with obesity

ESE 2020 recommends that overt hypothyroidism (elevated TSH and decreased FT4) is treated in obesity irrespective of antibodies

ESE 2020: for obese patients the same normal hormonal values are applied as for non-obese.

VA/DoD 2020: normalization of the hypothyroid state is associated with small losses of weight (typically less than 1 kg), which are not durable beyond 12 – 24 months.

BTA 2016 (from ATA) considers that there is insufficient evidence of benefit to recommend that treatment with L-T4 be targeted to achieve low-normal serum TSH values or high-normal serum T3 values in patients with hypothyroidism, including those who are overweight.

No specific recommendations or comments were provided in NICE 2019 and BMJ 2019.

Thyroid hormones for obese patients without hypothyroidism

BTA 2016 (from ATA) and ESE 2020 recommend against the treatment of obesity with LT4 or LT3 in euthyroid individuals.

Va/DoD 2020 while not making formal recommendations warns against the risks associated with hyperthyroidism (particularly cardiac, ocular, bone, and neuropsychiatric) and mentions that intentional creation of a hyperthyroid state is highly inadvisable for weight loss.

No specific recommendations or comments were provided in NICE 2019 and BMJ 2019.

5.6 Approach based on symptomatology versus biochemical parameters

5.6.1 Symptomatology or biochemical parameters

Symptomatology and biochemical parameters

Hypothyroidism

NICE 2019 and BTA 2016: the aim is to maintain TSH levels within the reference range when treating primary hypothyroidism. Both recommend to consider optimal wellbeing (through

adjusting the dose of levothyroxine if symptoms persist-NICE 20191) and to avoid overtreatment (iatrogenic thyrotoxicosis).

NICE 2019: TSH level can take up to 6 months to return to the reference range.

BTA 2016 (from ATA) :

- Symptoms alone lack sensitivity and specificity and therefore are not recommended for judging adequacy of replacement in the absence of biochemical assessment. Symptoms should be followed, but considered in the context of serum TSH values, relevant comorbidities and other potential causes.
- Data are lacking on the established instruments used to measure hypothyroid symptoms, regarding their sensitivity and specificity in the 'everyday' clinical setting to recommend their routine clinical use.

BTA 2016 (from ATA) recommends acknowledgement of patients' symptoms and evaluation for alternative causes if patients treated for hypothyroidism but with normal serum TSH values continue to perceive suboptimal health status. They suggest (from ETA) awareness of a chronic disease, presence of associated autoimmune diseases, thyroid autoimmunity per se (independent of thyroid function), and inadequacy of L-T4 treatment to restore physiological T4 and T3 concentrations in serum and tissue as explanations for persistent symptoms.

According to BTA 2016 (from ATA), there is insufficient evidence of benefit to recommend that treatment with L-T4 be targeted to achieve low-normal serum TSH values or high-normal serum T3 values in patients with hypothyroidism.

BTA 2016 (from ATA) does not recommend serum T3 as a therapeutic target in the management of hypothyroidism. The significance of perturbations in serum T3 concentrations within the reference range, or of mildly low serum T3, is unknown.

BTA 2016 (from ATA) does not recommend tissue biomarkers of thyroid hormone action for routine clinical use, outside of the research setting.

Subclinical hypothyroidism

NICE 2019 recommends to monitor symptoms and "If symptoms do not improve after starting levothyroxine, re-measure TSH and if the level remains raised, adjust the dose. If symptoms persist when serum TSH is within the reference range, consider stopping levothyroxine and follow the recommendations on monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment. "

BMJ 2019 recommends against treatment of subclinical hypothyroidism and therefore does not formulate any recommendations or comments concerning evaluation of the treatment.

5.6.2 Fatigue

Fatigue

BTA 2016 (from ATA) recommends against the use of L-T4 treatment in patients who have nonspecific symptoms and normal biochemical indices of thyroid function, as no role exists for use

of L-T4 in this situation. NICE fatigue also recommends to not offer any medicines or supplements to cure chronic fatigue syndrome.

Both NICE fatigue and DEGAM 2017 recommend to perform laboratory test including TSH if chronic fatigue is primarily unexplained.

No specific recommendations or comments were provided from NICE 2019 and BMJ 2019.

5.6.3 Anti-aging

Anti-aging

BTA 2016 (from ATA) recommends against the use of L-T4 treatment in patients who have nonspecific symptoms and normal biochemical indices of thyroid function, as no role exists for use of L-T4 in this situation.

No specific recommendations or comments regarding anti-aging were provided from NICE 2019 and BMJ 2019.

5.6.4 Suppression therapy in euthyroid multinodular goiter

Suppression therapy in euthyroid multinodular goiter

NICE 2019 does not recommend treatment for adults with non-malignant thyroid enlargement, normal thyroid function and mild or no symptoms unless they have breathing difficulty or there is clinical concern, for example, because of marked airway narrowing (NICE 2019).

AACE/ACE/AME 2016 does not recommend LT4 suppressive therapy for benign nodules but **recommends non suppressive LT4 replacement** for young patients with subclinical hypothyroidism and benign nodules. Non-suppressive LT4 treatment or iodine supplementation may be considered for young patients with a small nodular goiter and high-normal TSH levels. Non suppressive LT4 therapy is not recommended for preventing recurrence after lobectomy when serum TSH stays in the normal range.

No specific recommendations or comments were provided from NICE 2019 and BTA 2016.

5.6.5 T3 versus T4

T3 versus T4

NICE 2019 and BTA 2016 (from ATA and ETA) both recommend LT4 as first line treatment of hypothyroidism.

Other thyroid hormone preparations

NICE 2019 recommends to not offer liothyronine (alone or in combination) or natural thyroid extract for primary hypothyroidism, because there is not enough evidence that it offers benefits over levothyroxine monotherapy, and its long-term adverse effects are uncertain.

While not formally formulating recommendations, BTA 2016 reports (from ATA) that there is no convincing evidence to support the routine use of LT3 or thyroid extracts and that there are potential safety concerns. BTA 2016 adds (from ATA) that longer term controlled clinical trials using a longer acting form of L-T3 are needed, before considering the endorsement of synthetic L-T3 therapy for routine clinical use.

<u>L-T4+L-T3 combination therapy</u>

Both BTA 2016 and NICE 2019 recommend to not use L-T4 + L-T3 combination therapy in patients with hypothyroidism. L-T4 + L-T3 is not recommended in pregnancy and in patients with cardiac arrhythmias (BTA 2016, from ATA).

BTA 2016 adds:

- In the case of suspected allergy to an excipient of standard thyroid hormone preparations that cannot be avoided it may be reasonable to consider use of compounded products (from ATA).
- L-T4 + L-T3 could be consider as **an experimental approach** in compliant LT4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range (from ETA). No trial outside a formal clinical trial (from ATA).
- If a trial is given,
  - patients should have unambiguously not benefited from L-T4,
  - it should be reached following an open discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data, with documentation of agreement,
  - it should be supervised by accredited endocrinologists.
- Future research into whether there are subgroups of population being treated for hypothyroidism who might benefit from combination therapy is encouraged (from ATA).
- Many clinicians may not agree that a trial of L-T4/L-T3 combination therapy is warranted, their clinical judgement must be recognized as being valid.
- Preference for L-T4 + L-T3 combination therapy may be influenced by polymorphisms in thyroid hormone pathway genes, specifically in thyroid hormone transporters and deiodinases (from ETA). However, genetic testing is not recommended (from ATA) as a guide to selecting therapy.

BTA 2016 also gives recommendations (from ETA) for administration and monitoring of L-T4 + L-T3 combination therapy:

- Start L-T4+L-T3 at L-T4/L-T3 dose ratio between 13:1 and 20:1 by weight.
- L-T4 can be given once daily, and the daily L-T3 dose should be divided (if possible) in two doses, one before breakfast and the largest one before bed.
- Available combination preparations contain a L-T4/L-T3 dose ratio lower than 13:1, so it is recommended to use separate L-T4 and L-T3 tablets.
- L-T4+L-T3 should be monitored by thyroid function tests L-T4 and L-T3 in blood samples taken before the morning dose, aiming at normal ranges.
- If dose adjustment of L-T4+L-T3 combination therapy is necessary to achieve a normal serum ranges, the dose of L-T3, should be preferably changed.
- Discontinue after 3 months if no improvement.

5.7 Follow-up, adverse effects, and drug-drug interactions

Treatment follow up

NICE 2019 provides a list of information their recommend to give to people with thyroid disease, and their family or careers concerning their pathology and the medication (levothyroxine).

Both NICE 2019 and BTA 2016 recommend TSH monitoring after initiation of L-T4 for primary hypothyroidism until stable level.

- NICE 2019 recommends every 3 months (stable level is 2 similar measurements within the reference range, 3 months apart).
- BTA 2016 recommends intervals of 6–8 weekly until stabilization and then 4–6 monthly without any additional specifications.
-

They both recommend once a year TSH measurement after stabilization.

For adults who continue to have symptoms of hypothyroidism after starting levothyroxine NICE 2019 also recommend to consider measuring FT4 and TSH.

Subclinical hypothyroidism
BMJ 2019 proposes long term regular visits and blood samples to monitor hormone levels without mentioning time intervals.

Adverse effects

BTA 2016 states against deliberate serum TSH suppression with high dose thyroid hormone replacement therapy (serum TSH < 0_1 mU/L) as this carries a risk of adverse effects such as cardiac rhythm disorders including atrial fibrillation, strokes, osteoporosis and fracture. This is especially true in older persons and postmenopausal women.

In the context of subclinical hypothyroidism, for younger person, BMJ 2019 was concerned about possible long term adverse cardiovascular effects and the risk of delayed in diagnosis of another condition such as mood disorder. For older people, BMJ 2019 was concerned about a signal of harm (mortality). BMJ 2019 mentions the risk of overdosage and hyperthyroidism symptoms.

Switch between preparations

According to BTA 2016 brand or named supplier prescribing is not considered necessary for the vast majority of patients on L-T4. This was justified by the recommendations made from The Medicines and Healthcare Products Regulatory Agency ensuring the quality and the consistency of L-T4 tablets on the UK market.

Interactions

No specific recommendations or comments were provided concerning interactions in any guidelines.

6 Summary and conclusions from the literature review. Supplements

6.1 Iodine vs placebo for overt hypothyroidism

A systematic review (NICE 2019(3)) searched for RCTs evaluating iodine supplementation vs placebo in (overt) hypothyroidism.

No RCTs were found.

We did not identify any additional RCT's that met our inclusion criteria.

6.2 Iodine vs placebo for subclinial hypothyroidism

A systematic review (NICE 2019(3)) searched for RCTs evaluating iodine supplementation vs placebo in subclinical hypothyroidism.

No RCTs were found.

We did not identify any additional RCT's that met our inclusion criteria.

6.3 Selenium vs placebo for overt hypothyroidism

A systematic review (NICE 2019(3)) searched for RCTs evaluating selenium supplementation vs placebo in overt hypothyroidism.

No RCTs were found.

We did not identify any additional RCT's that met our inclusion criteria.

6.4 Selenium versus no treatment for subclinical hypothyroidism

Selenium versus no treatment for subclinical hypothyroidism due to Hashimoto's thyroiditis			
Bibliography: Pirola 2016			
Outcomes	**N° of participants (studies)**	**Results**	**Quality of the evidence (GRADE)**

	Follow up		
Participants with restored euthyroidism (TSH ≤ 4,5 mIU/L)	196 (192 analyzed) 1 study 4 months	Selenium: 30/96 (31,3%) No treatment: 3/96 (3,1%) **P<0.0001** **SS** **More participants with restored euthyroidism with selenium**	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 high risk of selective reporting, unclear funding, open label Consistency: NA Directness: -1 single center Imprecision: -1 (small number of events)

From the reference list of a review we found one unblinded RCT(Pirola 2016) that compared selenium supplementation (83 mcg/day) to no treatment in a population of patients with subclinical hypothyroidism due to Hashimoto's thyroiditis. The duration of supplementation was 4 months.

There are some methodological problems that limit our confidence in the estimate of the results: there was a high risk of bias due to selective reporting: there is no mention of adverse effects, no definition of the primary outcome in the text; only a subset of the results of the outcomes TSH/fT4/TPO-Ab were analyzed for selenium versus no treatment. The sponsor for this study was not mentioned. It is not clear whether the open-label nature of this study could have influenced the measurements of the objective outcome.

In a population with **subclinical hypothyroidism due to Hashimoto's thyroiditis**, **selenium supplementation** resulted in **more restored euthyroidism** compared to no treatment.

GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

6.5 Iron vs placebo for overt or subclinical hypothyroidism

We did not identify any RCTs that met our inclusion criteria

6.6 Omega 3 vs placebo for overt or subclinical hypothyroidism

We did not identify any RCTs that met our inclusion criteria

6.7 Vitamin D in hypothyroidism or subclinical hypothyroidism.

There are not a lot of studies about vitamin D in hypothyroidism.

We found some studies that did not meet our inclusion criteria, due to sample size, duration or lack of reporting of relevant endpoints. (See appendix and list of excluded studies). The aim of most of these studies was to assess the effect of vitamin D on TPO-antibodies in auto-immune thyroid disorders.

We were able to find one study that answered our research question and met our inclusion criteria (see below).

Vitamin D versus placebo in hypothyroid patients

Vitamin D 50.000 IU 1x/w versus placebo in hypothyroid patients			
Bibliography: Talaei 2018(20)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
TSH change from baseline (PO)	201 1 study	VIT D −0.4 ± 0.6 µIU/mL Pla +0.1 ± 2.0 µIU/mL P = 0.02 SS in favour of vit D	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear reporting on exclusion, age…, short study duration Consistency: NA Directness: short duration, see Study quality Imprecision: -1 low number of participants
T4 change from baseline (PO)	201 1 study	Vit D +0.2±3.0 µg/dL Pla -0.3±2.7 µg/dL P=0.22 NS	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear reporting, short study duration Consistency: NA Directness: short duration, see Study quality Imprecision: -1 low number of participants
T3 change from baseline (PO)	201 1 study	Vit D 0.01 ± 0.6 µg/dL Pla -0.1 ± 0.5 µg/dL P=0.23 NS	⊕⊕⊖⊖ **LOW** Study quality:-1 unclear reporting, short study duration Consistency: NA Directness: short duration, see Study quality Imprecision: -1 low number of participants
Adverse events	201 1 study	*'No side effects were reported following the consumption of vitamin D supplements in participants throughout the study'*	⊕⊖⊖⊖ VERY **LOW** Study quality:-2 unclear reporting, no short study duration, Consistency: NA Directness: short duration, see Study quality Imprecision: -1 low number of participants

In this RCT, 50.000 IU vitamin D weekly was compared to placebo in 201 Iranian patients with hypothyroidism with stable levothyroxine doses, between 20 and 60 years old.

Trial duration was 12 weeks.
The aim of this study was to evaluate the effect of vitamin D on thyroid function.

There are some methodological problems that limit our confidence in the estimate of the results.

- *This is only 1 small study over a short study duration. Ideally we would like to study a larger group of patients and follow them up for much longer, since hypothyroidism is a chronic disease.*
- *The dose of vitamin D is quite high compared to European Summary of product characteristics.*
- *The study also has quality issues: e.g. no exclusion criteria mentioned, no preplanned safety endpoints to be analysed, no mention of gender of participants and some issues regarding blinding.*

At 12 weeks, there was a statistically significant decrease in TSH in the vitamin D group compared to the placebo group.
There was no statistically significant change in T4 or T3 levels.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

The study authors state that there were no adverse events reported following the consumption of vitamin D throughout the study. However, the authors do not describe how and whether they assessed adverse events in this study.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

7 Summary and conclusions from the literature review. Older adults

7.1 Levothyroxine vs placebo for older adults (65+) with subclinical hypothyroidism

T4 vs placebo for older adults (65+) with subclinical hypothyroidism			
Bibliography: Stott 2017(4); Gencer 2020(21); Gonzalez 2019(22); Stuber 2020(23); Wildisen 2021(24), Zijlstra 2021(25)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Change in the Hypothyroid Symptoms score (PO)* at one year from the ThyPRO (thyroid-specific) questionnaire *range of scale is 0 to 100, with higher scores indicating more symptoms; minimum clinically important difference: 9 points*	737 (1 study) 12 months	Levothyroxine: 16.6±16.9 Placebo: 16.7±17.5 Difference (95% CI): 0.0 (−2.0 to 2.1) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 primary outcome changed Consistency: NA Directness: -1; 98% white population Imprecision: ok
Tiredness score (PO)* at one year from the ThyPRO (thyroid-specific) questionnaire *range of scale is 0 to 100, with higher scores indicating more tiredness; minimum clinically important difference: 9 points*	737 (1 study) 12 months	Levothyroxine: 28.7±20.2 Placebo: 28.6±19.5 Difference (95% CI): 0.4 (−2.1 to 2.9) NS	⨁⨁⨀⨀ **LOW** Study quality: -1 primary outcome changed Consistency: NA Directness: -1; 98% white population Imprecision: ok
Health-related quality of life EQ-5D descriptive score	737 (1 study) 12 months	Levothyroxine: 0.833±0.191 Placebo: 0.853±0.212 Difference (95% CI): -0.025 (−0.050 to 0.000)	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1; 98% white population Imprecision: ok

(non-thyroid-specific questionnaire) range from −0.59 to 1.00, with higher scores indicating better quality of life		P=0.05 NS	
Health-related quality of life EQ-5D VAS score (non-thyroid-specific questionnaire) range from 0 to 100, with higher scores indicating better quality of life	737 (1 study) 12 months	Levothyroxine: 77.3±15.6 Placebo: 77.4±13.7 Difference (95% CI): −1.3 (−3.2 to 0.6) NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1; 98% white population Imprecision: ok
TSH (mIU/L)	737 (1 study) 12 months	Levothyroxine: 3.63±2.11 Placebo: 5.48±2.48 Difference (95% CI): −1.92 (−2.24 to −1.59) **SS** **P <0.001** **Lower TSH with levothyroxine**	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1; 98% white population Imprecision: ok
Hyperthyroid Symptoms score The score on the Hyperthyroid Symptoms scale was recorded as a measure of possible adverse effects (on a scale from 0 to 100, with higher scores indicating more symptoms; minimum clinically important difference has	737 (1 study) 12 months	Levothyroxine: 10.5±10.8 Placebo: 10.3±11.3 Difference (95% CI): 0.6 (−0.7 to 1.3) NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1; 98% white population Imprecision: ok

been estimated as 9 points).			
LVEF (% ±SD) (PO) (systolic function)	217 (185 analysed) (1 study) Median 18,4 months	Levothyroxine: 62,7 ± 7,9 Placebo: 62,5 ±7,4 Difference (95% CI): 0,4 (-1,8 to 2,5) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 dropout, no ITT Consistency: NA Directness: -1; 98% white population Imprecision: ok
E/e' (mean ±SD) (PO) *Ratio between mitral peak velocity of early filling to early diastolic mitral annular velocity* (diastolic function)	217 (185 analysed) (1 study) Median 18,4 months	Levothyroxine: 10,6 ±3,7 Placebo: 10,1 ± 3,3 Difference (95% CI): 0.4 (-0,7 to 1,4) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 dropout, no ITT Consistency: NA Directness: -1; 98% white population Imprecision: ok
All-cause death n (%)	842 (2 studies) Median 17 months	Levothyroxine: 12 (209%) Placebo: 9 (2.1%) HR (95%CI) 1.28 (0.54 – 3.03) NS	⊕⊕⊖⊖ **LOW** Study quality: ok Consistency: ok Directness: -1; 98% white population Imprecision: -1 (wide CI)
Serious adverse event Participants with ≥1 SAE N(%)	217 (185 analysed) (1 study) Median 18,4 months	Levothyroxine: 30/109 (27,5%) Placebo: 35/108 (32,4%) *No statistical analysis*	NA
Serious adverse event Number of events, n	842 (2 studies) Median 17 months	Levothyroxine: 90 (21.4%) Placebo: 116 (27.5%) **HR (95%CI) 0.73 (0.55 – 0.96)** **SS fewer serious adverse events with levothyroxine**	⊕⊕⊕⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1; 98% white population Imprecision: ok
Lumbar spine BMD Changes after one year treatment (%) *105 analysed*	*217 (105 analysed)* (1 study) 12 months	Levothyroxine: 0,8 Placebo: -0,6 Difference (95% CI): 1,4 (-0,1 to 2,9) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 dropout, no ITT Consistency: NA Directness: -1; 98% white population Imprecision: ok
Total hip BMD Changes after one year treatment (%)	217 (196 analysed) (1 study) 12 months	Levothyroxine: -0,5 Placebo: 0,7 Difference (95% CI): -1,3 (-3,1 to 0,6) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 dropout, no ITT Consistency: NA Directness: -1; 98% white population Imprecision: ok

Femoral neck BMD Changes after one year treatment (%) *113 analysed*	*217 (113 analysed)* (1 study) 12 months	Levothyroxine: -0,6 Placebo: -0,4 Difference (95% CI): -0,2(-1,1 to 0,7) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 dropout, no ITT Consistency: NA Directness: -1; 98% white population Imprecision: ok
Fatigability - Physical score (PO) *(The Pittsburgh Fatigability Scale (PFS) physical and mental subscores range from 0 to 50 with higher scores indicating greater fatigability)*	276 (230 analysed) (1 study) 12 months	Levothyroxine: Baseline 14,7 ± 9,3 at 1 year 14,8 ± 9,6 Placebo: Baseline 11,1 ± 9,1 at 1 year 12,4 ± 9,3 Adjusted Between-Group Difference (95% CI): 0,2 (-1,8 to 2,1) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 dropout, no ITT Consistency: NA Directness: -1; 99% white population Imprecision: ok
Fatigability - Mental score (PO) *(The Pittsburgh Fatigability Scale (PFS) physical and mental subscores range from 0 to 50 with higher scores indicating greater fatigability)*	276 (230 analysed) (1 study) 12 months	Levothyroxine: Baseline 7,4 ± 8,0 at 1 year 6,0 ± 7,8 Placebo: Baseline 5,1 ± 6,9 at 1 year 6,0 ± 8,0 Adjusted Between-Group Difference (95% CI): -1,0 (-2,8 to 0,8) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 dropout, no ITT Consistency: NA Directness: -1; 99% white population Imprecision: ok
Change in GDS-15 score *GDS-15, 15-item Geriatric Depression Scale Questionnaire (range, 0-15; higher scores indicate more severe depressive symptoms; minimal clinically important difference, 2 points)*	472 (427 analysed) (1 study) 12 months	Levothyroxine mean (SD) Baseline 1,26 (1,85) At 12 months 1,39 (2,13) Placebo mean (SD) Baseline 0,96 (1,58) At 12 months 1,07 (1,67) Unadjusted mean difference at 12 months (95%CI) 0.32 (−0.05 to 0.68)	⊕⊕⊖⊖ **LOW** Study quality: -1 dropout, no ITT Consistency: NA Directness: -1; 98% white population Imprecision: ok

		NS Adjusted* mean difference at 12 months (95%CI) 0.15 (−0.15 to 0.46) NS **Adjusted for age, sex, GDS-15 score at baseline, levothyroxine dose at baseline, and country.*	
Fatal and non-fatal cardiovascular event	842 (2 studies) Median 17 months	Levothyroxine: 19 (4.5%) Placebo: 25 (5.9%) HR (95%CI) 0.74 (0.41-1.35) NS	⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: ok Directness: -1; 98% white population Imprecision: -1 (wide CI)
New-onset atrial fibrillation	842 (2 studies) 12 months	Levothyroxine: 11 (2.6%) Placebo: 15 (3.6%) HR (95%CI) 0.69 (0.32 – 1.52) NS	⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: ok Directness: -1; 98% white population Imprecision: -1 (wide CI)
New-onset heart failure	842 (2 studies) 12 months	Levothyroxine: 4 (1.0%) Placebo: 9 (2.1%) HR (95%CI) 0.41 (0.13 – 1.35) NS	⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: ok Directness: -1; 98% white population Imprecision: -1 (wide CI)

Stott 2017 (the TRUST-trial) was a double blind RCT that evaluated levothyroxine versus placebo in adults 65 years or older, with subclinical hypothyroidism (defined as TSH 4,60 to 19,99 mIU/L and free thyroxine level within the reference range).

Gencer 2020; Gonzalez 2019; Stuber 2020; Wildisen 2021 were four preplanned substudies in which different outcomes were evaluated within a subpopulation of the Stott 2017 trial.

Zijlstra 2021 was a prespecified pooling of individual results from the TRUST trial, together with the results of IEMO80+ , a trial with an identical protocol to TRUST other than the inclusion of only individuals who were 80 or older.

There were several methodological problems that limit our confidence in the results:

- The primary outcome planned in the protocol of Stott 2017 was changed. (Quote: *"We had initially planned for cardiovascular events and thyroid-specific quality of life to be the two primary outcomes. However, this plan was modified during the trial to thyroid-specific quality of-life scores as the two primary outcomes and cardiovascular events as a secondary outcome when it became apparent that the trial would be underpowered for cardiovascular events owing to delays and difficulties in recruitment.")*.

- The recruited population was very homogenous (98% white) with regard to race, which may not be a true reflection of the real-life population.
- The substudies did not analyze the results by true intention-to-treat. The population that was analyzed (those who completed additional tests on follow-up) may differ from the total included population.

There was **no difference** between levothyroxine and placebo for **change in the Hypothyroid Symptoms score (from the ThyPRO thyroid-specific questionnaire)** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo for **change in Tiredness score (from the ThyPRO thyroid-specific questionnaire)** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

There was **no difference** between levothyroxine and placebo for **change in health-related quality of life** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

I**n older adults (65+) with subclinical hypothyroidism**, **levothyroxine** treatment resulted in **a lower level of TSH** compared with placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **hyperthyroid symptoms (score on the Hyperthyroid Symptoms scale)** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **LVEF (systolic function)** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo for **E'/E (diastolic function)** in **older adults (65+) with subclinical hypothyroidism**.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo for **all-cause death** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **older adults (65+) with subclinical hypothyroidism**, levothyroxine therapy resulted in **fewer serious adverse events** than placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **changes in Lumbar spine, total hip, or femoral neck bone densitometry (BDM)** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo for **Fatigability (physical or mental score of the Pittsburgh Fatigability Scale)** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo for **changes in the Geriatric Depression Scale Questionnaire score (GDS-15)** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo in number of **fatal or non-fatal cardiovascular events** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo of **new-onset atrial fibrillation** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo of **new-onset heart failure** in **older adults (65+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

7.2 Levothyroxine vs placebo for older adults (80+) with subclinical hypothyroidism

T4 vs placebo for older adults (80+) with subclinical hypothyroidism			
Bibliography: Mooijaart 2019(26)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Change in the Hypothyroid Symptoms score (PO)* at one year from the ThyPRO (thyroid-specific) questionnaire *range of scale is 0 to 100, with higher scores indicating more symptoms; minimum clinically important difference: 9 points*	251 (1 study)	Levothyroxine mean (SD) Baseline 21,7 (19,5) At 12 months 19,3 (18,2) Placebo mean (SD) Baseline 19,8 (19,6) At 12 months 17,4 (18,1) Adjusted* difference at 12 months (95%CI) 1,27 (−2,69 to 5,23) NS * *Adjusted difference was estimated in linear regression models predicting change from baseline to 12-month visit (95%*	⨁⨁⨁⊖ **MODERATE** Study quality:ok Consistency: NA Directness: -1 (99% white population) Imprecision: ok

		CI) with study site, sex, and randomization dose as stratification variables and study as random effect.	
Tiredness score (PO)* at one year from the ThyPRO (thyroid-specific) questionnaire *range of scale is 0 to 100, with higher scores indicating more tiredness; minimum clinically important difference: 9 points*	251 (1 study)	Levothyroxine mean (SD) Baseline 25,2 (21,5) At 12 months 28,2 (20,0) Placebo mean (SD) Baseline 25,1 (19,5) At 12 months 28,7 (19,9) Adjusted* difference at 12 months (95%CI) -0,10 (−4,51 to 4,31) NS * *Adjusted difference was estimated in linear regression models predicting change from baseline to 12-month visit (95% CI) with study site, sex, and randomization dose as stratification variables and study as random effect.*	⨁⨁⨁⊖ **MODERATE** Study quality:ok Consistency: NA Directness:-1 (99% white population) Imprecision: ok
TSH (mIU/L)	251 (1 study)	Levothyroxine mean (SD) Baseline 6,50 (1,80) At 12 months 3,69 (1,81) Placebo mean (SD) Baseline 6,20 (1,48) At 12 months 5,49 (2,21) Adjusted* difference at 12 months (95%CI) -1,97 (-2,49 to -1,45) **P<0.001** **SS** **Lower TSH with levothyroxine** * *Adjusted difference was estimated in linear regression models predicting change from baseline to 12-month visit (95% CI) with study site, sex, and*	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (99% white population) Imprecision: ok

		randomization dose as stratification variables and study as random effect.	
Death from any cause	251 (1 study)	Levothyroxine 5/112 (4,5%) Placebo 4/139 (2,9%) Estimated risk difference (95%CI) HR 1,39 (0,37 to 5,19) NS	⨁⨁⨀⨀ **LOW** Study quality:ok Consistency: NA Directness: -1 (99% white population) Imprecision: -1 (broad CI)
Cardiovascular death	251 (1 study)	Levothyroxine 0/112 (0%) Placebo 1/139 (0,7%) *No statistical analysis*	NA
Fatal or nonfatal cardiovascular event	251 (1 study)	Levothyroxine 7/112 (6,3%) Placebo 14/139 (10,1%) Estimated risk difference (95%CI) HR 0,60 (0,24 to 1,50) NS	⨁⨁⨀⨀ **LOW** Study quality: ok Consistency: NA Directness: -1 (99% white population) Imprecision: -1 (broad CI)
Serious adverse events Events (n)	251 (1 study)	Levothyroxine 53 Placebo 61 *No statistical analysis*	NA:
Serious adverse events Participants with >1 serious adverse event	251 (1 study)	Levothyroxine 33/112 (29,5%) Placebo 40/139 (28,8%) Estimated risk difference (95%CI) -0,01 (-0,04 to 0,01) NS	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (99% white population) Imprecision: ok
New-onset atrial fibrillation	251 (1 study)	Levothyroxine 4/112 (3,6%) Placebo 6/139 (4,3%) Estimated risk difference (95%CI) 0,00 (-0,02 to 0,03) NS	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (99% white population) Imprecision: ok
Heart failure	251 (1 study)	Levothyroxine 3/112 (2,7%) Placebo 6/139 (4,3%) Estimated risk difference (95%CI) 0,01 (-0,03 to 0,05) NS	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (99% white population) Imprecision: ok
Fracture	251 (1 study)	Levothyroxine 4/112 (3,6%) Placebo 5/139 (3,6%) Estimated risk difference (95%CI)	⨁⨁⨁⨀ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (99% white population)

		0,00 (-0,04 to 0,03) NS	Imprecision: ok

Mooijaart 2019 was a prospectively planned combined analysis of data from an RCT in elderly people (80y+) with subclinical hypothyroidism, and a subgroup of participants aged 80 years or older from a second RCT (Stott 2017, see above), to evaluate the effect of levothyroxine versus placebo.

Both RCTs employed the same definition of subclinical hypothyroidism (elevated thyrotropin levels (4.6-19.9 mIU/L) and FT4 levels within laboratory reference ranges).

Levothyroxine was started at 50 µg daily (or 25 µg if the body weight was <50 kg or the patient had coronary heart disease) and titrated to a TSH target of 0,40 to 4,59 mIU/L.

There were several methodological problems that limit our confidence in the results:

- The recruited population was very homogenous with regards to race (99% white), which may not be a true reflection of the real-life population.
- 32% of participants discontinued treatment (numbers and reasons for discontinuation were similar between treatment groups), which may have biased results.

There was **no difference** between levothyroxine and placebo for **change in Hypothyroid Symptoms score** (from the ThyPRO thyroid-specific questionnaire) in **older adults (80+) with subclinical hypothyroidism.**
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **change in Tiredness score** (from the ThyPRO thyroid-specific questionnaire**) in older adults (80+) with subclinical hypothyroidism**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

In **older adults (80+) with subclinical hypothyroidism**, levothyroxine therapy resulted in **lower TSH levels** than placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **death from any cause** in **older adults (80+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence

Our confidence that the results of the studies reflect the true effect is low.

There was **insufficient evidence** to assess **cardiovascular death** or **number of serious adverse events** in **older adults (80+) with subclinical hypothyroidism**.

There was **no difference** between levothyroxine and placebo for **fatal and nonfatal cardiovascular events** in **older adults (80+) with subclinical hypothyroidism**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo for **number of participants with at least 1 serious adverse effect** in **older adults (80+) with subclinical hypothyroidism**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **new-onset atrial fibrillation** in **older adults (80+) with subclinical hypothyroidism**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **heart failure** in **older adults (80+) with subclinical hypothyroidism**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **fractures** in **older adults (80+) with subclinical hypothyroidism**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

7.3 Levothyroxine vs placebo for older adults (65+) with subclinical hypothyroidism and with a history of cardiovascular disease

Levothyroxine vs placebo for older adults (65+) with a history of cardiovascular disease			
Bibliography: Zijlstra 2021(25)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**

Fatal and non-fatal cardiovascular event	302 (2 studies) median 17 months	Levothyroxine: 11 (7.3%) Placebo: 14 (9.3%) HR (95%CI) 0.77 (0.35-1.71) NS	⨁⨁⨀⨀ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)
Death from any cause	302 (2 studies) median 17 months	Levothyroxine: 7 (4.6%) Placebo: 4 (2.6%) HR (95%CI) 1.60 (0.46 – 5.53) NS	⨁⨁⨀⨀ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)
Serious adverse event	302 (2 studies) median 17 months	Levothyroxine: 47 (31.1%) Placebo: 56 (37.1%) HR (95%CI) 0.82 (0.55 – 1.20) NS	⨁⨁⨀⨀ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)
New-onset atrial fibrillation	302 (2 studies) 12 months	Levothyroxine: 2 (1.3%) Placebo: 7 (4.6%) HR (95%CI) 0.29 (0.06 – 1.42) NS	⨁⨁⨀⨀ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)
New-onset heart failure	302 (2 studies) 12 months	Levothyroxine: 3 (2.0%) Placebo: 5 (3.3%) HR (95%CI) 0.53 (0.13 – 2.24) NS	⨁⨁⨀⨀ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)

Zijlstra 2021 was a prespecified pooling of individual results from the TRUST trial, together with the results of IEMO80+ , a trial with an identical protocol to TRUST other than the inclusion of only individuals who were 80 or older.

Zijlstra made stratified analyses for patients with or without a history of cardiovascular disease at inclusion.

There were several methodological problems that limit our confidence in the results:

- The recruited population was very homogenous with regard to race (98% white), which may not be a true reflection of the real-life population.
- The results show great imprecision for all outcomes, which suggests that the study was underpowered to detect a difference.

There was **no difference** between levothyroxine and placebo for **fatal and non-fatal cardiovascular events** in **older adults (65+) with subclinical hypothyroidism and a history of cardiovascular disease**.

GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

There was **no difference** between levothyroxine and placebo for **death from any cause** in **older adults (65+) with subclinical hypothyroidism and a history of cardiovascular disease**..
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

There was **no difference** between levothyroxine and placebo for **serious adverse events** in **older adults (65+) with subclinical hypothyroidism and a history of cardiovascular disease**..
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

There was **no difference** between levothyroxine and placebo for **new-onset atrial fibrillation** in **older adults (65+) with subclinical hypothyroidism and a history of cardiovascular disease**..
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

There was **no difference** between levothyroxine and placebo for **new-onset heart failure** in **older adults (65+) with subclinical hypothyroidism and a history of cardiovascular disease**..
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

7.4 Levothyroxine vs placebo for older adults (65+) with subclinical hypothyroidism and without a history of cardiovascular disease

Levothyroxine vs placebo for older adults (65+) with a history of cardiovascular disease			
Bibliography: Zijlstra 2021(25)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Fatal and non-fatal cardiovascular event	540 (2 studies) median 17 months	Levothyroxine: 8 (3.0%) Placebo: 11 (4.1%) HR (95%CI) 0.70 (0.28 -1.74) NS	⨁⨁⨀⨀ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)
Death from any cause	540 (2 studies) median 17 months	Levothyroxine: 5 (1.9%) Placebo: 5 (1.8%) HR (95%CI) 0.97 (0.27 – 3.52) NS	⨁⨁⨀⨀ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)

Serious adverse event	540 (2 studies) median 17 months	Levothyroxine: 43 (16.0%) Placebo: 60 (22.1%) **HR (95%CI) 0.65 (0.44 – 0.97)** **SS fewer serious adverse events with levothyroxine**	⨁⨁⨁⊖ **MODERATE** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: ok
New-onset atrial fibrillation	540 (2 studies) 12 months	Levothyroxine: 9 (3.3%) Placebo: 8 (3.0%) HR (95%CI) 0.97 (0.36 – 2.62) NS	⨁⨁⊖⊖ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)
New-onset heart failure	540 (2 studies) 12 months	Levothyroxine: 1 (0.4%) Placebo: 4 (1.5%) HR (95%CI) 0.28 (0.03 – 2.25) NS	⨁⨁⊖⊖ **LOW** Study quality: Consistency: ok Directness: -1; 98% white population Imprecision: -1 (broad CI)

Zijlstra 2021 was a prespecified pooling of individual results from the TRUST trial, together with the results of IEMO80+ , a trial with an identical protocol to TRUST other than the inclusion of only individuals who were 80 or older.

Zijlstra made stratified analyses for patients with or without a history of cardiovascular disease at inclusion.

There were several methodological problems that limit our confidence in the results:

- The recruited population was very homogenous with regard to race (98% white), which may not be a true reflection of the real-life population.
- The results show great imprecision for all outcomes, which suggests that the study was underpowered to detect a difference.

There was **no difference** between levothyroxine and placebo for **fatal and non-fatal cardiovascular events** in **older adults (65+) with subclinical hypothyroidism without a history of cardiovascular disease**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

There was **no difference** between levothyroxine and placebo for **death from any cause** in **older adults (65+) with subclinical hypothyroidism without a history of cardiovascular disease**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

In **older adults (65+) with subclinical hypothyroidism without a history of cardiovascular disease**, levothyroxine therapy resulted in **fewer serious adverse events** than placebo.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **new-onset atrial fibrillation** in **older adults (65+) with subclinical hypothyroidism without a history of cardiovascular disease**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

There was **no difference** between levothyroxine and placebo for **new-onset heart failure** in **older adults (65+) with subclinical hypothyroidism without a history of cardiovascular disease**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low

8 Summary and conclusions from the literature review. Pregnancy

8.1 Levothyroxine versus placebo or no treatment in pregnant women with subclinical hypothyroidism

Levothyroxine versus placebo or no treatment in pregnant women with subclinical hypothyroidism			
Bibliography: Ding 2021(27) including Nazarpour 2018(28), Casey 2017(29), Nazarpour 2017(30) Additional RCT's: Mir 2022(31), Leng 2022(32) and Costantine 2020(33)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Live birth	227 (1 study) First trimester until delivery, max 1 year	78/112 vs 71/115 p value: 0.210 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (risk of unbalanced treated and control groups and risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Preterm birth	895 (3 studies) 8-20 w gestation until delivery	39/464 vs 58/431 OR: 0.40 (95%CI: 0.15 to 1.11) NS I^2: 65 %	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 (risk of unbalanced treated and control groups and risk of selective data reporting in 2 studies, no ITT in these two studies) Consistency:-1 (heterogeneity in the MA) Directness:-1 (1 medium study in China only include TPO-Ab negative women, 1 small study included women with assisted reproduction) Imprecision:-1 (wide CI and low number of events in the studies)
	80 (1 study) 15-18 w gestation until delivery	4/41 vs 4/39 p value 0.941 NS	
	227 (1 study) First trimester until delivery, max 1 year	2/112 vs 7/115 p value: 0.097 NS	
Pregnancy loss	677 (1 study) 8-20 w gestation until delivery	4/339 vs 7/338 OR: 0.56 (95%CI: 0.16 to 1.95) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 (risk of unbalanced treated and control groups and risk of selective data reporting in 2 studies, no ITT in these two studies) Consistency:-1 (1 study with higher % of events) Directness:-1 (1 medium study in China only include TPO-Ab negative women, 1 small study included women with assisted reproduction) Imprecision:-1 (wide CI and low number of events in the studies)
	80 (1 study) 15-18 w gestation until delivery	3/41 vs 2/39 p value 0.686 NS	
	227 (1 study) First trimester until delivery, max 1 year	24/112 vs 22/115 p value: 0.667 NS	
Gestational hypertension	677 (1 study)	33/339 vs 36/338 OR: 0.90 (95%CI: 0.55 to 1.49)	⨁⊖⊖⊖ **VERY LOW**

	8-20 w gestation until delivery	NS	Study quality:-1 (risk of unbalanced treated and control groups and risk of selective data reporting in 1 study, no ITT in this one) Consistency: ok Directness:-1 (1 medium study in China only include TPO-Ab negative women, 1 small study included women with assisted reproduction) Imprecision:-1 (wide CI and low number of events in the studies)
	227 (1 study) First trimester until delivery, max 1 year	5/112 vs 3/115 p value: 0.448 NS	
Preeclampsia	677 (1 study) 8-20 w gestation until delivery	22/339 vs 20/338 p value: 0.76 NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1 (risk of unbalanced treated and control groups and risk of selective data reporting in 1 study, no ITT in this one) Consistency: -1 (difference in % of events between studies) Directness:-1 (1 medium study in China only include TPO-Ab negative women, 1 small study included women with assisted reproduction) Imprecision:-1 (no CI but low number of events in the studies)
	227 (1 study) First trimester until delivery, max 1 year	1/112 vs 2/115 p value: 0.577 NS	
Gestational diabetes	677 (1 study) 8-20 w gestation until delivery	25/339 vs 22/338 OR: 1.14 (95%CI: 0.63 to 2.07) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1 (risk of unbalanced treated and control groups and risk of selective data reporting in 1 study, no ITT in this one) Consistency: ok Directness:-1 (1 medium study in China only include TPO-Ab negative women, 1 small study included women with assisted reproduction) Imprecision:-1 (wide CI and low number of events in the studies)
	227 (1 study) First trimester until delivery, max 1 year	4/112 vs 7/115 p value: 0.378 NS	
Placental abruption	677 (1 study) 8-20 w gestation until delivery	1/339 vs 5/338 OR: 0.20 (95%CI: 0.02 to 1.70) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1 (risk of unbalanced treated and control groups and risk of selective data reporting in 1 study, no ITT in this one) Consistency: ok Directness:-1 (1 medium study in China only include TPO-Ab negative women, 1 small study included women with assisted reproduction) Imprecision:-1 (wide CI and low number of events in the studies)
	227 (1 study) First trimester until delivery, max 1 year	0/112 vs 1/115 p value: 0.323 NS	
Premature rupture of membrane	677 (1 study) 8-20 w gestation until delivery	33/339 vs 27/338 OR: 1.24 (95%CI: 0.73 to 2.12) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1 (risk of unbalanced treated and control groups and risk of selective data

	80 (1 study) 15-18 w gestation until delivery	3/41 vs 1/39 p value 0.330 NS	reporting in 1 study, no ITT in this one) Consistency: ok Directness:-1 (1 medium study in China only include TPO-Ab negative women, 1 small study included women with assisted reproduction) Imprecision:-1 (wide CI and low number of events in the studies)
	227 (1 study) First trimester until delivery, max 1 year	6/112 vs 1/115 p value: 0.051 NS	
Small for gestational age	677 (1 study) 8-20 w gestation until delivery	33/339 vs 27/338 OR: 1.24 (95%CI: 0.73 to 2.12) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 (risk of unbalanced treated and control groups and risk of selective data reporting in 1 study, no ITT in this one) Consistency: -1 (difference in % of events between studies) Directness:-1 (1 medium study in China only include TPO-Ab negative women) Imprecision:-1 (no CI but low number of events in the studies)
	227 (1 study) First trimester until delivery, max 1 year	1/112 vs 2/115 p value: 0.577 NS	
Macrosomia	227 (1 study) First trimester until delivery, max 1 year	2/112 vs 7/115 p value: 0.546 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (risk of unbalanced treated and control groups and risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Asphyxia neonatorum	227 (1 study) First trimester until delivery, max 1 year	0/112 vs 1/115 p value: 0.323 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (risk of unbalanced treated and control groups and risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Maternal depressive symptom score, third trimester gestation (CES-D scale, from 0 to 60, higher scores indicating greater symptoms of depression)	245 (1 study) 8-20 w gestation, until 1 year post-partum	CES-D score 10 [5, 15] vs 10 [5, 17] p value: 0.46 NS	⨁⨁⊖⊖ **LOW** Study quality:-1 (underpowered, unclear concealment, unclear risk of detection bias, unclear risk of attrition bias) Consistency: NA Directness: ok Imprecision: -1 (no CI but low number of events)
Maternal depressive	245 (1 study)	6 [3, 11] vs 6 [3, 12] p value: 0.79	⨁⨁⊖⊖ **LOW** Study quality:-1 (underpowered, unclear concealment, unclear

symptom score ,1 year post-partum (CES-D scale, from 0 to 60, higher scores indicating greater symptoms of depression)	8-20 w gestation, until 1 year post-partum	NS	risk of detection bias, unclear risk of attrition bias) Consistency: NA Directness: ok Imprecision: -1 (no CI but low number of events)
Percentage of women positive for depression, third trimester gestation (CES-D score ≥ 16)	245 (1 study) 8-20 w gestation, until 1 year post-partum	24.3% vs 30.1% p value: 0.34 NS	⨁⨁⨀⨀ **LOW** Study quality:-1 (underpowered, unclear concealment, unclear risk of detection bias, unclear risk of attrition bias) Consistency: NA Directness: ok Imprecision: -1 (no CI but low number of events)
Percentage of women positive for depression, 1 year post-partum (CES-D score ≥ 16)	245 (1 study) 8-20 w gestation, until 1 year post-partum	9.7% vs 15.8% p value: 0.19 NS	⨁⨁⨀⨀ **LOW** Study quality:-1 (underpowered, unclear concealment, unclear risk of detection bias, unclear risk of attrition bias) Consistency: NA Directness: ok Imprecision: -1 (no CI but low number of events)

SR Ding was a systematic review evaluating pregnancy and neonatal outcomes of levothyroxine versus placebo or no treatment in women diagnosed with subclinical hypothyroidism (defined as TSH more than 4.0mIU/L and less than 10.0mIU/L) in pregnancy.

The review included RCTs or cohort studies. Only the 3 found RCTs were considered in the present synthesis.

One study included in the review was on TPO-Ab negative pregnant women with SCH defined as TSH between 2.5 to 10 mIU/L. One study was on TPO-Ab positive pregnant euthyroid and SCH women. For these two studies, data from women with TSH >4.0 mIU/L were extracted and included in the MA. The third study was on pregnant women with SCH defined as a TSH >4.0 mIU/L, no description of TPO-Ab status was reported for these women, but was supposed to be representative of the population.

Additional RCTs were found:

The Mir RCT evaluated levothyroxine versus no treatment in pregnant women with SCH defined as TSH levels of 2.5–3.9 mIu/L in the first trimester or 3–4.1 mIu/L in the second and third trimesters in an Iranian center. This study included women who conceived naturally, with IVF or with medication. This study included patients in treatment and control groups were unbalanced regarding TSH and % of naturally conceived pregnancies.

The Leng RCT was a Chinese study evaluating levothyroxine versus placebo in TPO-Ab negative SCH pregnant women who conceived naturally. Ongoing pregnancies at the time of outcome

measurement, which could potentially influence other outcomes, were statistically higher in the control group.

The Costantine RCT evaluated levothyroxine versus no treatment in pregnant women with SCH. No information was provided about TPO status. Women reported clinical diagnosis of depression, other psychiatric disorders or anti-depressant medications at baseline were excluded.

There are some methodological problems that limit our confidence in the estimate of the results:

- *The 3 studies included in the MA were of good quality and evaluated with low risk of bias. For the outcome preterm birth we however had to downgrade for heterogeneity between studies included in the MA. There was also a risk of bias due to unclear follow up, unbalanced population and selective data reporting in two RCT.*
- *The MA analysis also included cohort studies that are not included as per our methodology, therefore we reported a subgroup analysis or partial data coming from RCTs only.*
- *GRADE scoring was downgraded for indirectness because of the included population in the Leng RCT and the Mir RCT*
- *We downgraded most of the outcomes for imprecision because wide CI in the data coming from the MA and the low number of events in the Leng and Mir RCTs.*
- *The size of the included RCTs is in general small.*
- *Several confounders that may cause bias have not been systematically reported for treatment and control groups including iodine status, TPO-Ab status, ethnicity, BMI…*
- *These studies differed in terms of SCH range defined for included population, gestational age at diagnosis and initiation of LT4 treatment and LT4 dosage and/or treatment regimen.*
- *In the Costantine RCT, only 82% of planned sample size was achieved, that could prevent detection of an effect.*

There was **no difference** between levothyroxine and placebo or no treatment for **live birth** in **pregnant women with SCH**.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between levothyroxine and placebo or no treatment for **gestational outcomes** (**preterm birth**, **pregnancy loss, gestational hypertension, preeclampsia, gestational diabetes, placental abruption, premature rupture of membrane)** in **pregnant women with SCH**.
GRADE for these different outcomes: VERY LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is very low.

There was **no difference** between levothyroxine and placebo or no treatment for **neonatal outcomes (small for gestational age, macrosomia, asphyxia neonatorum)** in **pregnant women with SCH**.
GRADE for these different outcomes: VERY LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is very low.

There was **no difference** between levothyroxine and placebo **for maternal depressive symptoms and women positive for depression** in **pregnant women with SCH**.
GRADE for these different outcomes: LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is low.

8.2 Levothyroxine versus placebo or no treatment in pregnant women subclinical hypothyroidism and a history of recurrent pregnancy loss

Levothyroxine versus placebo or no treatment in pregnant women subclinical hypothyroidism and a history of recurrent pregnancy loss			
Bibliography: RCT: Leng 2022(32)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Live birth	267 (1 study) First trimester until delivery, max 1 year	92/131 vs 64/136 **p value <.001** **SS in favour of levothyroxine**	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Preterm birth	267 (1 study) First trimester until delivery, max 1 year	11/131 vs 22/136 p value: 0.054 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Pregnancy loss	267 (1 study) First trimester until delivery, max 1 year	28/131 vs 54/136 **p value <.001** **SS in favour of levothyroxine**	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)

Gestational hypertension	267 (1 study) First trimester until delivery, max 1 year	6/131 vs 3/136 p value: 0.283 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Preeclampsia	267 (1 study) First trimester until delivery, max 1 year	Levothyroxine: 0/131 No treatment: 0/136	Insufficient evidence
Gestational diabetes	267 (1 study) First trimester until delivery, max 1 year	8/131 vs 1/136 p value: 0.015 **SS in favour of no treatment**	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Placental abruption	267 (1 study) First trimester until delivery, max 1 year	1/131 vs 1/136 p value: 0.979 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Premature rupture of membrane	267 (1 study) First trimester until delivery, max 1 year	0/131 vs 0/136	Insufficient evidence
Small for gestational age	267 (1 study) First trimester until delivery, max 1 year	8/131 vs 3/136 p value: 0.109 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women)

			Imprecision:-1 (no CI and total number of events < in the studies)
Macrosomia	267 (1 study) First trimester until delivery, max 1 year	0/131 vs 3/136 p value: 0.087 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)
Asphyxia neonatorum	267 (1 study) First trimester until delivery, max 1 year	0/131 vs 2/136 p value: 0.164 NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-2 (unblinded, unclear allocation concealment, risk of unbalanced treated and control groups and unclear risk of selective data reporting, no ITT) Consistency: NA Directness:-2 (study in China only include TPO-Ab negative women) Imprecision:-1 (no CI and total number of events < in the studies)

In this trial, Leng RCT, levothyroxine versus no treatment was evaluated in pregnant women with a history of recurrent pregnancy loss who conceived naturally and were had subclinical hypothyroidism (defined as TSH between 2.5 and 10.0 mIU/L) and were negative for TPO-Ab.

There are some methodological problems that limit our confidence in the estimate of the results:

- *Study was downgraded for risk due to lack of blinding, unclear allocation concealment, risk of unbalanced group due to not pre-specified ongoing pregnancy outcome, unclear follow up, and unclear risk of selective reporting due to missing information concerning lack of SCH top-Ab positive women, lack of ITT.*
- *Study was downgraded for indirectness because it only 2 centers in China and the selected women with SCH were all TPO-Ab negative which is not representative of SCH women population.*
- *No confidence intervals were provided but number of events was low resulting in imprecision.*

In **women with SCH and history of RPL**, **levothyroxine** resulted in **more live birth** compared to no treatment.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **women with SCH and history of RPL**, **levothyroxine** resulted in **lower risk of pregnancy loss** compared to no treatment.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **women with SCH and history of RPL**, **levothyroxine** resulted in **higher risk of gestational diabetes** compared to no treatment.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between **levothyroxine** and no treatment for **other obstetric outcomes (preterm birth, gestational hypertension, placental abruption)** in **women with SCH and history of RPL**.
GRADE for these outcomes: VERY LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is very low.

We have **insufficient data** to compare the risk of **preeclampsia** and **premature rupture of membrane** in **women with SCH and history of RPL**.

There was **no difference** between **levothyroxine** and no treatment for **neonatal outcomes (small for gestational age, macrosomia, asphyxia neonatorum)** in **women with SCH and history of RP**.
GRADE for these outcomes: VERY LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is very low.

8.3 Levothyroxine versus placebo or no treatment in pregnant euthyroid TPO-Ab+ women

Levothyroxine versus placebo or no treatment in pregnant euthyroid TPO-Ab+ women			
Bibliography: Wang 2020(34) including Negro 2005(35), Negro 2006(36), Negro 2016(37), Nazarpour 2017(30), Wang 2017(38), Dhillon-Smith 2019(39) Additional RCT: Leng 2022(32)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Live birth	1626 (3 studies) before and/or throughout pregnancy until delivery	287/813 vs 285/813 RR: 1.00 (95% CI: 0.88 to 1.15) NS I^2: 8%	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: OK Directness:-1 (only included women with infertility and assisted reproduction, included some SCH) Imprecision: ok
	81 (1 study) First trimester until delivery, max 1 year	34/41 vs 35/40 p value: 0.562 NS	

Preterm birth	2179 in total 1354 analysed (live birth or pregnant women) (5 studies) Before and/or throughout pregnancy until 3 days after delivery	69/672 vs 96/682 RR: 0.69 (95% CI: 0.45 to 1.06) NS I^2: 45%	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 (risk of bias, risk of unbalance group, comparison, confounding treatment) Consistency: ok Directness: -1 (women with infertility and assisted reproduction, some SCH) Imprecision: -1 (CI)
	81 (1 study) First trimester until delivery, max 1 year	2/41 vs 6/40 p value: 0.127 NS	
Pregnancy loss	2265 in total 1427 analysed (confirmed pregnancy) (6 studies) before and/or throughout pregnancy until 3 days after delivery	121/708 vs 143/719 RR: 0.87 (95% CI: 0.70 to1.07) NS I^2: 0%	⊕⊕⊖⊖ **LOW** Study quality: -1 (risk of bias, risk of unbalance group, comparison, confounding treatment) Consistency: OK Directness:-1 (women with infertility and assisted reproduction) Imprecision: ok
	81 (1 study) First trimester until delivery, max 1 year	4/41 vs 3/40 p value: 0.718 NS	
Clinical pregnancy	1626 in total 1226 analysed (total or confirmed pregnancy) (3 studies) before and/or throughout pregnancy until delivery	368/606 vs 382/617 RR: 0.98 (95%CI: 0.93 to 1.04) NS I^2: 0%	⊕⊕⊖⊖ **LOW** Study quality: -1 (risk of bias, risk of unbalance group, comparison) Consistency: ok Directness:-1 (only included women with infertility and assisted reproduction, distinct reference group) Imprecision: ok
Ectopic pregnancy	1540 in total 1140 analysed (total or confirmed pregnancy) (2 studies)	3/566 vs 11/574 RR: 0.34 (95%CI: 0.08 to 1.53) NS I^2: 18%	⊕⊖⊖⊖ **VERY LOW** Study quality: -1 (risk of bias, risk of unbalance group, comparison) Consistency: OK Directness: -1 (only included women with infertility and assisted reproduction, distinct reference group) Imprecision: -1 (CI)

Gestational hypertension	81 (1 study) First trimester until delivery, max 1 year	2/41 vs 4/40 p value: 0.379 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: na Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events < in the studies)
Preeclampsia	81 (1 study) First trimester until delivery, max 1 year	Levothyroxine: 0/41 No treatment: 0/40	Insufficient evidence
Gestational diabetes	81 (1 study) First trimester until delivery, max 1 year	2/41 vs 3/40 p value: 0.624, NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: na Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events < in the studies)
Placental abruption	81 (1 study) First trimester until delivery, max 1 year	0/41 vs 0/40	Insufficient evidence
Premature rupture of membrane	81 (1 study) First trimester until delivery, max 1 year	0/41 vs 2/40 p value: 0.147 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: na Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events < in the studies)
Small for gestational age	81 (1 study) First trimester until delivery, max 1 year	2/41 vs 2/40 p value: 0.980 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: na Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events < in the studies)

Macrosomia	81 (1 study) First trimester until delivery, max 1 year	3/41 vs 1/40 p value: 0.317 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: na Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events < in the studies)
Asphyxia neonatorum	81 (1 study) First trimester until delivery, max 1 year	0/41 vs 1/40 p value: 0.308 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: na Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events < in the studies)
Neonatal admission in intensive care unit	1071 in total 493 analysed (total or live birth) (2 studies) before and/or throughout pregnancy until delivery	29/248 vs 36/245 RR: 0.49 (0.08 to 3.07) NS I^2: 83 %	⨁⊖⊖⊖ **VERY LOW** Study quality: OK Consistency: -1 Directness: -1 (mainly women with infertility and assisted reproduction, distinct reference group) Imprecision:-1 (CI and low number of event)
Birth weight	1071 in total 493 analysed (total or live birth) (2 studies) before and/or throughout pregnancy until delivery	Mean difference: -0.02 (95%CI: -0.12 to 0.08) NS I^2: 0%	⨁⨁⨁⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 (mainly women with infertility and assisted reproduction, distinct reference group) Imprecision: ok

SR Wang 2020 was a systematic review evaluating pregnancy and neonatal outcomes of levothyroxine versus placebo or no treatment in women with TPO-autoimmunity. The review include 6 trials among which 3 trials were performed on women with infertility undergoing assisted reproduction. One small study enrolled both euthyroid and SCH women, 4 other studies enrolled euthyroid women based on a maximal TSH threshold superior to 2.5mUI/L. Depending on the considered threshold values women with TSH superior to 2.5mUI/L could be considered SCH.

An additional RCT was found (Leng 2022) evaluating levothyroxine versus no treatment in TPO-Ab positive pregnant women with normal TSH (below 2.5 mIU/L) and natural conception in China.

There are some methodological problems that limit our confidence in the estimate of the results:

- *In 3 studies the use of intention-to-treat was not clear depending on the outcome (sometime analysed among confirmed pregnancy or live birth), analysis in the MA was done on an ITT basis for all outcomes.*
- *One large trial had a low risk of bias, one small trial had an unclear risk, and four trials had a high risk mainly due to the lack of blinding to intervention.*
- *In one medium-sized study with a per protocol analysis, levothyroxine was provided to nearly half of the control group during follow-up, which could indicate confounding of treatment.*
- *One small study was downgraded for risk due to lack of blinding, unclear allocation concealment, unclear follow up, and unclear risk of selective reporting due to missing information concerning lack of SCH TPO-Ab positive women, lack of ITT*
- *Infertile women undergoing assisted reproduction do not correspond to the general population. Depending on the TSH threshold some of the included women have to be considered with SCH.*

There was **no difference** between **levothyroxine** and no placebo or no treatment for **live birth** in **pregnant euthyroid TPO-Ab positive women**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between **levothyroxine** and placebo or no treatment for **pregnancy loss** in **pregnant euthyroid TPO-Ab positive women**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between **levothyroxine** and placebo or no treatment for **clinical ectopic pregnancy** in **pregnant euthyroid TPO-Ab positive women**.
GRADE for these outcomes: LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is low.

There was **no difference** between **levothyroxine** and placebo or no treatment for other **obstetric outcomes** (**preterm birth**, **ectopic pregnancy, gestational hypertension, gestational diabetes, premature rupture of membrane)** in **pregnant euthyroid TPO-Ab positive women**.
GRADE for these outcomes: VERY LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is very low.

We have **insufficient data** to compare the risk of **preeclampsia** and **placental abruption** in **pregnant euthyroid TPO-Ab positive women**.

There was **no difference** between **levothyroxine** and placebo or no treatment for **neonatal outcomes (small for gestational age, macrosomia, asphyxia neonatorum, neonatal admission)** in **pregnant euthyroid TPO-Ab positive women**.
GRADE for these outcomes: VERY LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is very low.

There was **no difference** between **levothyroxine** and placebo or no treatment for **birth weight** in **pregnant euthyroid TPO-Ab positive women**.
GRADE: MODERATE quality of evidence
Our confidence that the results of these studies reflect the true effect is moderate.

8.4 Levothyroxine versus placebo or no treatment in euthyroid TPO-Ab positive pregnant women with recurrent pregnancy loss

Levothyroxine versus placebo or no treatment in euthyroid TPO-Ab positive pregnant women with recurrent pregnancy loss			
Bibliography: RCT's: Leng 2022(32) and Van Dijk 2022(40)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Live birth	83 (1 study) First trimester until delivery, max 1 year	38/42 vs 28/41 p value: 0.012 **SS in favour of levothyroxine**	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, unbalanced group-and follow up, but ITT) Consistency: -1 (different results) Directness: -1 one study in China and one study using normal conception the other both normal and assisted reproduction, different TSH thresholds. Imprecision: -1 (CI and low number of event)
	187 (1 study) Before conception until 28 d post-delivery, maximum 2-year	47/94 vs 45/93 RR (95% CI): 1.03 (0.77 to 1.38) NS	
Preterm birth	83 (1 study) First trimester until delivery, max 1 year	3/42 vs 3/41 p value: 0.976 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -2 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, un balanced group and follow up, no ITT) Consistency: ok Directness: :-1 study in China and one study using normal conception the other both normal and assisted reproduction, different TSH thresholds.
	187 (1 study) Before conception until 28 d post-delivery, maximum 2-year	4/69 vs 3/73 RR (95% CI): 1.41 (0.33 to 6.08) NS	

			Imprecision: -1 (CI and total number of events is low)
Pregnancy loss	83 (1 study) First trimester until delivery, max 1 year	3/42 vs 11/41 p value: 0.017 **SS in favour of levothyroxine**	⊕⊖⊖⊖ **VERY LOW** Study quality: -2 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, unbalanced group and follow up, no ITT) Consistency: -1 (different results) Directness: :-1 study in China and one study using normal conception the other both normal and assisted reproduction, different TSH thresholds. Imprecision: -1 (CI and total number of events is low)
	187 (1 study) Before conception until 28 d post-delivery, maximum 2-year	16/69 vs 24/73 RR (95% CI): 0.71 (0.41 to 1.21) NS	
Pregnancy	187 (1 study) Before conception until 28 d post-delivery, maximum 2-year	69/94 vs 73/93 RR (95% CI): 0.94 (0.81 to 1.12) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1 (unclear risk of selective data reporting, unbalanced group and follow up, no ITT) Consistency: NA Directness: -1 both normal and assisted reproduction, different TSH thresholds. Imprecision: -1 (low number of event)
Ongoing pregnancy at 12 w	187 in total 142 analysed (total pregnancy) (1 study) Before conception until 28 d post-delivery, maximum 2-year	49/69 vs 24/73 RR (95% CI): 1.08 (0.85 to 1.37) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1 (unclear risk of selective data reporting, unbalanced group and follow up, no ITT) Consistency: NA Directness: -1 both normal and assisted reproduction, different TSH thresholds. Imprecision: -1 (low number of event)
Ectopic pregnancy	187 in total 142 analysed (total pregnancy) (1 study) Before conception until 28 d post-delivery, maximum 2-year	2/69 vs 3/73 (4%) RR (95% CI): 0.71 (0.12 to 4.09) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1 (unclear risk of selective data reporting, unbalanced group and follow up, no ITT) Consistency: NA Directness: -1 both normal and assisted reproduction, different TSH thresholds. Imprecision: -1 (low number of event)
Pregnancy of unknown location	187 in total 142 analysed (total pregnancy) (1 study) Before conception until 28 d post-	4/69 vs 1/73 (1%) RR (95% CI): 4.23 (0.48 to 36.93) NS	⊕⊖⊖⊖ **VERY LOW** Study quality:-1 (unclear risk of selective data reporting, unbalanced group and follow up, no ITT) Consistency: NA

	delivery, maximum 2-year		Directness: -1 both normal and assisted reproduction, different TSH thresholds. Imprecision: -1 (low number of event)
Gestational hypertension	83 (1 study) First trimester until delivery, max 1 year	0/42 vs 2/41 p value: 0.147 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: NA Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events low)
Preeclampsia	83 (1 study) First trimester until delivery, max 1 year	Levothyroxine: 0/42 No treatment: 1/41 p value: 0.309, NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: NA Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events low)
Gestational diabetes	83 (1 study) First trimester until delivery, max 1 year	4/42 vs 1/41 p value: 0.175 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: NA Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events low)
Placental abruption	83 (1 study) First trimester until delivery, max 1 year	0/42 vs 0/41	No enough evidence
Premature rupture of membrane	83 (1 study) First trimester until delivery, max 1 year	1/42 vs 0/41 p value: 0.320, NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: NA Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events low)
Small for gestational age	83 (1 study) First trimester until delivery, max 1 year	3/42 vs 0/41 p value: 0.081 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: NA Directness: :-1 (study in China)

			Imprecision: -1 (no CI and total number of events low)
Macrosomia	83 (1 study) First trimester until delivery, max 1 year	0/42 vs 1/41 p value: 0.309 NS	⨁⊖⊖⊖ **VERY LOW** Study quality: -1 (unblinded, unclear allocation concealment, and unclear risk of selective data reporting, no ITT) Consistency: NA Directness: :-1 (study in China) Imprecision: -1 (no CI and total number of events low)
Asphyxia neonatorum	83 (1 study) First trimester until delivery, max 1 year	0/42 vs 0/41	No enough evidence
Survival 28 days of neonatal life	187 in total 142 analysed (total pregnancy) (1 study) Before conception until 28 d post-delivery, maximum 2-year	49/69 vs 45/73 (62%) RR (95% CI): 1.11 (0.87 to 1.41) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 (unclear risk of selective data reporting, unbalanced group and follow up, no ITT) Consistency: NA Directness: -1 both normal and assisted reproduction, different TSH thresholds. Imprecision: -1 (low number of event)
Serious adverse event	187 (1 study) Before conception until 28 d post-delivery, maximum 2-year	7/94 vs 7/93 (8%) RR (95% CI): 1.00 (0.92 to 1.09) NS	⨁⊖⊖⊖ **VERY LOW** Study quality:-1 (unclear risk of selective data reporting, unbalanced group and follow up, no ITT) Consistency: NA Directness: -1 both normal and assisted reproduction, different TSH thresholds. Imprecision: -1 (low number of event)

The Leng 2022 trial evaluated levothyroxine versus no treatment in TPO-Ab positive pregnant women with normal TSH (defined as below 2.5 mIU/L) and recurrent pregnancy loss (RPL).

The Van Dijk 2022 trial evaluated levothyroxine versus placebo in TPO-Ab positive pregnant women with normal TSH and recurrent pregnancy loss. Women trying to conceive both with and without the use of assisted reproductive technology were included. For TSH, the most commonly used reference interval was 0.5–5.0 mIU/L. Depending on the considered threshold values women with TSH superior to 2.5mUI/L could be considered SCH.

The included population in the two studies varied regarding TSH level threshold for euthyroidism status. One of the study also included women using assisted reproduction. The two studies differed regarding gestational age at inclusion, and at starting treatment. Levothyroxine dosage and treatment regimen was different between the two studies.

Other methodological considerations that limit our confidence in the estimate of the results:

- *1 study had unclear allocation concealment and was unblinded,*
- *1 study had a unclear follow up and a risk of unbalanced intervention and control groups, only the primary outcome in this study was reported on an intention-to-treat basis,*
- *2 studies were evaluated to have a risk of selective reporting bias*
- *The study sizes are small which could mean that they are underpowered to detect an effect*

In **TPO-Ab positive euthyroid pregnant women with a history of recurrent pregnancy loss, levothyroxine** resulted in **more live births** compared to no treatment in one study and resulted in **no difference** compared to placebo in another study.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

In **TPO-Ab positive euthyroid pregnant women with a history of recurrent pregnancy loss, levothyroxine** resulted in **fewer pregnancy losses** compared to no treatment in one study and resulted in **no difference** compared to placebo in another study.
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between **levothyroxine** and placebo or no treatment for other **obstetric outcomes** (**preterm birth, pregnancy and ongoing pregnancy, ectopic pregnancy and pregnancy of unknown location, gestational hypertension, preeclampsia, gestational diabetes, premature rupture of membrane)** in **TPO-Ab positive euthyroid pregnant women with a history of recurrent pregnancy loss**.
GRADE for these outcomes: VERY LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is very low.

There was **no difference** between **levothyroxine** and placebo or no treatment for **neonatal outcomes (small for gestational age, macrosomia, survival at 28 d of neonatal age)** in **TPO-Ab positive euthyroid pregnant women with a history of recurrent pregnancy loss**
GRADE for these outcomes: VERY LOW quality of evidence
Our confidence that the results of these studies reflect the true effect is very low.

We have **insufficient data** to compare the risk of **placental abruption and asphyxia neonatorum** in **TPO-Ab positive euthyroid pregnant women with a history of recurrent pregnancy loss.**

There was **no difference** between **levothyroxine** and placebo for **serious adverse events** in **TPO-Ab positive euthyroid pregnant women with a history of recurrent pregnancy loss**
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

9 Summary and conclusions from the literature review. Infertility

9.1 Levothyroxine vs placebo in women with fertility problems and euthyroid auto-immune thyroid disease

Levothyroxine vs placebo in women with fertility problems and euthyroid auto-immune thyroid disease			
Bibliography: SR Akhtar 2019 (41), including Negro 2005(35) and Wang 2017(38); Dhillon-Smith 2019(39)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Live birth rate	686 (2 studies)	Levothyroxine 111/343 No levothyroxine 107/343 RR: 1,04 (95%CI 0,83 to 1,29) NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 (different doses/treatment targets of intervention) Imprecision: ok
	952 (1 study)	Levothyroxine: 176/470 (37,4%) Placebo: 178/470 (37,9%) RR 0,97 (95%CI 0,83 to 1,14) NS	
Miscarriage	686 (2 studies)	Levothyroxine 19/343 No levothyroxine 23/343 RR: 0,83 (95%CI 0,47 to 1,46) NS	⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: ok Directness: -1 (different doses/treatment targets of intervention) Imprecision: -1 (broad confidence interval)
	952 (1 study)	Levothyroxine: 75/266 (28,2%) Placebo: 81/274 (29,6%) RR 0,95 (95%CI 0,73 to 1,23) NS	
Clinical pregnancy rate	686 (2 studies)	Levothyroxine 131/343 No levothyroxine 134/343 RR: 0,98 (95%CI 0,81 to 1,18) NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: ok Directness: -1 (different doses/treatment targets of intervention) Imprecision: ok
	952		

	(1 study)	Levothyroxine: 266/470 (56,6%) Placebo: 274/470 (58,3%) RR 0,97 (95%CI 0,88 to 1,07) NS	
Birth weight (g)	375 (1 study)	Levothyroxine: 3226±660 Placebo: 3262±668 MD −35 (95%CI −168 to 97) NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (intervention single dose – not to target) Imprecision: ok
Apgar score at 1 minute median (IQR)	375 (1 study)	Levothyroxine: 9 (9-9) Placebo: 9(8-9) MD 0.1 (95%CI −0.2 to 0.4) NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (intervention single dose – not to target) Imprecision: ok
Apgar score at 5 minutes median (IQR)	375 (1 study)	Levothyroxine: 9 (9-10) Placebo: 9(9-10) MD 0.0 (95%CI −0.2 to 0.2) NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (intervention single dose – not to target) Imprecision: ok
Serious adverse events Total number of participants experiencing a SAE (either maternal or neonatal)	952 (1 study)	Levothyroxine: 28/470 (6%) Placebo: 18/470 (4%) p-value 0.14 NS	⨁⨁⨁⊖ **MODERATE** Study quality: ok Consistency: NA Directness: -1 (intervention single dose – not to target) Imprecision: ok

SR Ahktar was a Cochrane systematic review evaluating the effect of levothyroxine versus placebo or no treatment in women undergoing assisted reproduction treatment, with a history of subfertility and with subclinical hypothyroidism or with euthyroid autoimmune thyroid disease.

The review found 2 RCTs that reported pregnancy and infant outcomes in euthyroid women with autoimmune thyroid disease. Levothyroxine was given either in a dose according to weight in one study and titrated according to TSH level in another study.

This Cochrane reported outcomes in a population of women with subclinical hypothyroidism with or without anti-TPO antibodies. However, these results were based on 1 RCT with 32 participants per treatment arm. We therefore excluded these analyses on the basis of the insufficient sample size.

An additional RCT (Dhillon-Smith 2019) was found. This RCT evaluated levothyroxine versus placebo in women who had a history of miscarriage or infertility, were euthyroid and TPO-antibody-positivity, and were trying to conceive either naturally or through assisted conception. In this study, a daily dose of 50 µg levothyroxine was compared to placebo.

There was **no difference** between levothyroxine and placebo for **live birth rate** in **women with fertility problems and euthyroid auto-immune thyroid disease**.

GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **miscarriage** in **women with fertility problems and euthyroid auto-immune thyroid disease**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

There was **no difference** between levothyroxine and placebo for **clinical pregnancy rate** in **women with fertility problems and euthyroid auto-immune thyroid disease**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **birth weight, Apgar score (at 1 and 5 minutes)** of the infant born to **women with fertility problems and euthyroid auto-immune thyroid disease**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

There was **no difference** between levothyroxine and placebo for **serious adverse events** in **women (or their infants) with fertility problems and euthyroid auto-immune thyroid disease**.
GRADE: MODERATE quality of evidence
Our confidence that the results of the studies reflect the true effect is moderate.

9.2 Levothyroxine versus placebo for subfertile women with euthyroid autoimmune thyroid disease and subclinical hypothyroidism

Levothyroxine versus placebo for subfertile women with euthyroid autoimmune thyroid disease and subclinical hypothyroidism			
Bibliography: Dhillon-Smith 2019(39)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Live birth after at least 34 weeks **TSH at baseline >2,5 mIU/L**	288 (1 study)	Levothyroxine: 55/145 (37,9%) Placebo: 58/143 (40,6%) RR 0,91 (95%CI 0,69 to 1,20) NS	⨁⨁⊖⊖ **LOW** Study quality: ok Consistency: ok Directness: -1 (subpopulation; treatment dose) Imprecision: -1 (broad CI)

An RCT (Dhillon-Smith 2019) evaluated levothyroxine versus placebo in women who had a history of miscarriage or infertility, were euthyroid and had TPO-antibody-positivity, and were trying to conceive either naturally or through assisted conception.

In this RCT a prespecified subanalysis of women with TSH **>2,5 mIU/L** was made.

There was **no difference** between levothyroxine and placebo for **live birth after at least 34 weeks** in **women with fertility problems and euthyroid auto-immune thyroid disease and TSH>2,5 mIU/L**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

10 Summary and conclusions from the literature review. Obesity

10.1 Levothyroxine vs placebo for obesity

A systematic review (Kaptein 2009(42)) searched for RCTs or prospective observational studies evaluating T4 or T3 vs placebo in adult obese subjects.

No RCTs that met our inclusion criteria were found.

We did not identify any additional RCT's that met our inclusion criteria.

11 Summary and conclusions from the literature review. Anti-aging

11.1 Levothyroxine vs placebo for anti-aging

We did not identify any RCTs that met our inclusion criteria

12 Summary and conclusions from the literature review. Chronic fatigue syndrome

12.1 Levothyroxine vs placebo for chronic fatigue syndrome

We did not identify any RCTs that met our inclusion criteria

13 Summary and conclusions from the literature review. Euthyroid multinodular goiter

13.1 Levothyroxine vs placebo or no treatment for euthyroid multinodular goiter

Levothyroxine vs placebo or no treatment for euthyroid multinodular goiter			
Bibliography: Bandeira-Echtler 2014(5)			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Nodule volume reduction ≥50%	958 (10 studies) 6 months-2years	Levothyroxine 80/489 Control 46/469 RR 1,57 (95%CI 1,04 to 2,38) **SS** **More nodule volume reduction with levothyroxine**	⨁⨁⨀⨀ **LOW** Study quality: -1 (small studies, risk of incomplete outcome data and selective reporting) Consistency: ok Directness: -1 (solitary nodule) Imprecision: ok
Adverse events: participants without signs of hyperthyroidism	270 (3 studies) 12-18 months	*No meta-analysis performed because of considerable heterogeneity* Papini 1993: Levothyroxine 27/51 Control 47/50 **RR 0,56 (95%CI 0,43 to 0,74)** **SS** **More signs of hyperthyroidism with levothyroxine** La Rosa 1995: Levothyroxine 23/23 Control 23/23 RR 1 (95%CI 0,92 to 1,09) NS Wemeau 2002 : Levothyroxine 53/64 Control 53/59 RR 0,92 (95%CI 0,8 to 1,06) NS	⨁⨀⨀⨀ **VERY LOW** Study quality: -1 (small studies, high risk of bias for subjective outcomes, unclear risk of incomplete outcome data) Consistency: -1 (heterogeneity) Directness: -1 (solitary nodule) Imprecision: ok

Adverse events: participants without nodule volume increase > 50%	551 (3 studies) 12 months	Levothyroxine 193/278 Control 174/273 RR 1,1 (95%CI 0,99 to 1,22) NS	⊕⊕⊖⊖ **LOW** Study quality: -1 (small studies, high risk of incomplete outcome data and selective reporting in largest study) Consistency: ok Directness: -1 (solitary nodule) Imprecision: ok

This Cochrane systematic review and meta-analysis by Bandeira-Echtler searched for all RCTs of levothyroxine, percutaneous injection sclerotherapy (PEI), interstitial laser photocoagulation (LP), ultrasound-guided radiofrequency ablation therapy (RF), high-intensity focused ultrasound ablation therapy (HIFU) or ultrasound-guided microwave ablation therapy (MW) therapy in participants with an established diagnosis of benign thyroid nodules.

There are a number of methodological problems that limit our confidence in the estimate of the results: many of the included studies were very small in size (<40 participants per study arm), which could mean that they were underpowered to detect adverse events; high risk of bias for subjective outcomes (as the assessors were only blinded for the ultrasound), and an unclear to high risk of incomplete outcome data or selective reporting in the larger trials)

An additional uncertainty is the diagnosis of euthyroid multinodular goiter. The RCTs in this systematic review included mostly participants with a solitary benign nodule. Most specified that the participants should also be euthyroid. None specified the diagnosis "euthyroid multinodular goiter". However, we elected to report this systematic review as the introduction states the following:

Quote: *"A clinically solitary thyroid nodule is a discrete swelling within an otherwise palpable normal thyroid gland. The overwhelming majority of these nodules are composed of irregularly enlarged follicles containing abundant colloid (benign adenomatous nodules). About half of individuals with clinically apparent solitary nodules are found to have multinodular goitres at surgery."*

In **patients with euthyroid multinodular goiter**, levothyroxine resulted in **more nodule volume reduction** compared to placebo.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

In **patients with euthyroid multinodular goiter**, the risk of **symptoms of hyperthyroidism** with **levothyroxine** versus placebo is **unclear and conflicting.**
GRADE: VERY LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is very low.

There was **no difference** between levothyroxine and placebo for **participants without a nodule volume increase of more than 50%** in **patients with euthyroid multinodular goiter**.
GRADE: LOW quality of evidence
Our confidence that the results of the studies reflect the true effect is low.

14 Additional safety information from other sources

Regarding thyroid hormones, in Belgium only levothyroxine-based drugs are registered on the market. However, it is possible to prescribe liothyronine or a combination of liothyronine and levothyroxine. These drugs are available in other countries and can be easily imported by the pharmacists using a written request. The generic term "thyroid hormones" has been used unless otherwise specified in our source documents. Regarding iodine and selenium, there are no registered drugs on the Belgian market, but there are many food supplements for iodine or selenium supplementation. That is why the additional safety information for liothyronine, iodine and selenium have been added in this document.

14.1 Thyroid hormones

14.1.1 Contraindications of levothyroxine

- Untreated hyperthyroidism (1)

14.1.2 Adverse effects of levothyroxine

Levothyroxine is a drug with a narrow therapeutic-toxic range (43).

- Symptoms of hyperthyroidism, especially in case of too high doses or too rapid increase of the dose: agitation, anxiety, insomnia, weight loss (43), tremors (44), hypertension, palpitations and cardiac arrhythmias (43), tachycardia, anginal pain, headache, muscle weakness and cramps, heat intolerance, sweating, flushing(2), heat stroke (43), fever, menstrual irregularities, diarrhoea, and vomiting (2). These adverse reactions usually disappear after dosage reduction or temporary withdrawal of treatment (2).

- Rarely: decrease in bone density with prolonged treatment in postmenopausal women (43).

  Hyperthyroidism is a known risk factor for osteoporosis and theoretically thyroid hormone therapy may also be a risk factor. A review of over 3000 patients from 63 studies summarised the available evidence : It was stressed that current findings were complex and confusing and poor methodological quality made comparison of results difficult. It was concluded that neither dose of levothyroxine nor duration of therapy had any relationship with bone mineral density. (2)

  For <u>postmenopausal women,</u> particularly those with a history of hyperthyroidism, the review recommended monitoring of thyroid hormone levels to avoid clinical hyperthyroidism, and screening for risk factors of osteoporosis; if warranted, bone densitometry, and appropriate management of any decline in BMD, should be used. A retrospective case-control study[2] found a significant association between current levothyroxine use and increased risk of fracture in people over 70 years of age, with a strong dose-response relationship. An increased risk remained in those who had stopped levothyroxine therapy within the previous 6 months. (2)

- Elevations in liver function tests have been reported(2).
- Hypersensitivity reactions can occur(2).
- Thyroid storm has occasionally been reported after massive or chronic intoxication(2).
- Convulsions, cardiac arrhythmias, heart failure, coma, and death have occurred(2).
- Thyroid hormones may occasionally precipitate or exacerbate a pre-existing myasthenic syndrome(2).

14.1.3 Adverse effects of liothyronine

See levothyroxine (according to martindale).

14.1.4 Interactions of thyroid hormones

- Decreased T4 absorption when combined with iron, calcium, antacids, soy products, and anion exchange resins; a 3-4 hour interval between doses is indicated(43).
- Decreased T4 absorption (related to changes in gastric pH) with chronic PPI therapy(43).
- Thyroid hormones enhance the effects of oral anticoagulants(2). Increased effect of vitamin K antagonists by accelerated degradation of coagulation factors(43).
- Decreased plasma T4 concentrations when treated with barbiturates, carbamazepine, phenytoin, estrogens (oral), rifampin or viral protease inhibitors(43).
  Enzyme induction enhances thyroid hormone metabolism resulting in reduced serum concentrations of thyroid hormones (2).
- Androgens reduce the concentration of binding globulin, which may result in clinical hyperthyroidism when administered to postmenopausal women on levothyroxine replacement therapy(2).
- Amiodarone may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine with a rise in the concentration of inactive reverse tri-iodothyronine(2).
- Some drugs such as lithium act directly on the thyroid gland and inhibit the release of thyroid hormones leading to clinical hypothyroidism(2).
- The effects of levothyroxine in hypothyroid patients may be decreased by use with sertraline, and the dose of levothyroxine may need to be increased(2).
- Propranolol may inhibit the de-iodination of thyroxine to tri-iodothyronine resulting in a decreased concentration of tri-iodothyronine and a rise in the concentration of inactive reverse tri-iodothyronine(2).
- Hypothyroidism and decreased control of hypothyroidism have been reported with concomitant use of orlistat and levothyroxine. This may be due to decreased absorption of iodine salts and/or levothyroxine. It may be necessary to adjust the dose of levothyroxine or to take the two drugs at different times of the day (45). Licensed product information in the United States recommends monitoring patients for changes in thyroid function if they are taking both levothyroxine and orlistat; at least a 4-hour interval is indicated between administration of the two drugs(2).

14.1.5 Special precautions regarding thyroid hormones

- Thyroid hormones should be used with extreme caution in patients with cardiovascular disorders including angina, heart failure, myocardial infarction, and hypertension(2): thyroid hormones increase the heart rate and oxygen consumption of the myocardium(43). Lower initial doses, smaller increments, and longer intervals between increases should be used as necessary. An ECG performed before starting treatment with levothyroxine may help to distinguish underlying myocardial ischaemia from changes induced by hypothyroidism(2).
- Levothyroxine should also be introduced very gradually in elderly patients and those with long-standing hypothyroidism (1, 2) to avoid any sudden increase in metabolic demands(2).
- Levothyroxine should not be given to patients with adrenal insufficiency without adequate corticosteroid cover otherwise the thyroid replacement therapy might precipitate an acute adrenal crisis. Prompt diagnosis and replacement of corticosteroids can prevent the development of a potentially fatal crisis. It has been pointed out that a raised concentration of thyroid-stimulating-hormone alone may not necessarily imply hypothyroidism in patients with chronic adrenocortical insufficiency. Even confirmed hypothyroidism in these patients may not be permanent. (2)
- Care is also required when levothyroxine is given to patients with diabetes mellitus or diabetes insipidus(2).
- Thyroid hormones may affect the seizure threshold and care is needed when levothyroxine is given to patients with epilepsy(2).

14.1.6 Thyroid hormones in pregnancy and lactation

- From the beginning of pregnancy, an increase in the dose of levothyroxine is recommended for women with hypothyroidism (increased need for thyroid hormone during pregnancy; risk to mother and child if underdosed). Regular monitoring of thyroid function is recommended.(43)
- Most authorities consider that thyroid hormones do not readily cross the placenta. Placental transfer has been reported, but in amounts so limited that a mother with physiological concentrations of thyroxine and tri-iodothyronine would not provide normal thyroid hormone concentrations to a fetus with congenital hypothyroidism. (2)
- A systematic review and meta-analysis indicated that the presence of thyroid autoantibodies in women with normal thyroid function was strongly associated with an increased risk of miscarriage and preterm birth. There was some evidence suggesting that low-dose levothyroxine treatment during pregnancy might reduce these risks, but further studies were needed. (2)
- Minimal amounts of thyroid hormones are distributed into breast milk. The last available guidance from the American Academy of Pediatrics noted that no effects had been seen in breast-fed infants whose mothers were taking levothyroxine and as such considered its use to be usually compatible with breast feeding. (2)

- Although levothyroxine in breast milk will be insufficient to treat any hypothyroidism in the suckling newborn, it has been suggested that it may mask detection of any hypothyroidism in such a neonate.[2] However, the BNF considers that the amounts involved are too small to affect tests for neonatal hypothyroidism. (2)

14.1.7 Thyroid hormone overdose

Symptoms of thyrotoxicosis can occur within the first 6 hours after ingestion of liothyronine but can be delayed for 2 to 5 days after levothyroxine, due to the time taken for metabolic conversion to liothyronine.

- Symptoms of thyrotoxicosis that have been reported include: fever, arrhythmias, tachycardia, increased blood pressure, confusion, agitation, neurological complications, and coma.

(2)

Levothyroxine overdosage requires an extended follow-up period as symptoms may be delayed for up to 6 days due to the gradual peripheral conversion of levothyroxine to tri-iodothyronine; glucocorticoids may be given to inhibit this conversion. (2)

- Treatment of overdose:
  - is usually symptomatic and supportive.
  - Propranolol may be useful in controlling the symptoms of sympathetic overactivity.
  - The UK National Poisons Information Service states that the benefit of gastric decontamination in acute overdosage of levothyroxine is uncertain. Oral activated charcoal may be considered for an adult or child presenting within 1 hour of ingestion of doses over 100 micrograms/kg.
  - Diuresis and haemodialysis do not enhance elimination because thyroid hormones are highly protein bound. It has also been concluded that plasmapheresis and haemoperfusion provide no significant clinical benefit. (2)

14.1.8 Thyroid hormone misuse

- Thyroid drugs have been tried in the treatment of obesity in euthyroid patients, but they produce only temporary weight loss, mainly of lean body-mass, and can produce serious adverse effects, especially cardiac complications. Hypothyroidism has also been reported when these drugs were withdrawn from previously euthyroid patients being treated for simple obesity.
- Levothyroxine appears to have been abused by some athletes to promote weight loss; liothyronine has been abused similarly. (2)

14.1.9 Administration of thyroid hormones

- The peak therapeutic effect of regular oral levothyroxine may not be achieved for several weeks and there is a slow response to changes in dosage. Similarly, effects may persist for several weeks after withdrawal.
- Levothyroxine is given as the sodium salt in a single daily dose. Its absorption can be irregular and it is probably best taken on an empty stomach, usually before breakfast.
- In hypothyroidism an initial oral dose of 50 to 100 micrograms of levothyroxine sodium daily may be increased by 25 to 50 micrograms at intervals of about 3 to 4 weeks until the thyroid

deficiency is corrected and a maintenance dose is established. The maintenance dose is usually between 100 and 200 micrograms daily.

- In patients over 50 years, in those with cardiac disease, or in those with severe hypothyroidism of long standing, treatment should be introduced more gradually: an initial dose of 12.5 to 50 micrograms daily increased by increments of 12.5 to 25 micrograms at intervals ranging from about 2 to 8 weeks may be appropriate, to usual maintenance doses between 50 and 200 micrograms daily.
- Although levothyroxine is usually taken in the morning on an empty stomach for hypothyroidism, a controlled study found improved thyroid hormone concentrations when the dose was given at night. No significant changes in patients' plasma lipid concentrations or quality of life were seen.

  The recommendation that levothyroxine be taken on an empty stomach has also been questioned; in particular, on the grounds that it may cause problems with adherence in infants and children. US expert bodies have suggested that consistent administration with regard to timing and meals is more important than the presence or absence of food (although giving it with iron or calcium should be avoided). In addition, soya-based infant formulas may impair absorption of levothyroxine, and frequent testing may be needed, particularly when there are changes in formula.
- Levothyroxine sodium may be given by intravenous injection. It has also been given intramuscularly. In myxoedema (hypothyroid) coma a dose of 300 to 500 micrograms by intravenous injection may be given initially. Further doses of 50 to 100 micrograms may be given daily until the patient is clinically stable and can tolerate oral doses. (2)

14.2 Iodine and iodides

14.2.1 Adverse effects

- Adverse effects include metallic taste, increased salivation, burning or painful mouth; there may be coryza-like symptoms, and swelling and inflammation of the throat and salivary glands. Eyes may be irritated and swollen and there may be increased lachrymation. Pulmonary oedema, dyspnoea, and bronchospasm may develop. Skin reactions include mild acneform eruptions or, more rarely, severe eruptions (iododerma).
- Other reported effects include depression, insomnia, impotence, headache, and gastrointestinal disturbances. corrosive effects on the gastrointestinal tract; vomiting, abdominal pain, and bloody diarrhoea can occur.
- Iodine and iodides have variable effects on the thyroid and can produce hyperthyroidism (the Iod-Basedow or Jod-Basedow phenomenon) as well as goitre and hypothyroidism. The latter have also occurred in infants born to mothers who had taken iodides during pregnancy. Iodide may be isolated by the body from a variety of sources, including an iodine-rich diet, or some disinfectants and drugs containing iodine (amiodarone).
- Although iodine is required for the production of thyroid hormones, excessive quantities can cause hyperthyroidism, or even paradoxical goitre and hypothyroidism.
- Hypersensitivity reactions to iodides may include urticaria, angioedema, cutaneous haemorrhage or purpuras, fever, arthralgia, lymphadenopathy, and eosinophilia.
- Large doses or prolonged use of iodides may lead to a range of adverse effects, often called `iodism', some of which resemble hypersensitivity reactions.
- Systemic toxicity may lead to hypotension, tachycardia, fever, headache, delirium, metabolic acidosis, and renal impairment. Circulatory failure due to shock, pulmonary oedema,

aspiration pneumonia, or asphyxiation can occur. Fatalities have been reported. Oesophageal stricture is a possible complication if the patient survives the acute stage.

- Retinal toxicity has been seen with overdose of potassium iodate.
- The normal daily requirement ranges from 100 to 300 micrograms. Quantities of 500 micrograms to 1 mg daily probably have no untoward effects on thyroid function in most cases.

14.2.2 Interactions

- The effects of iodine and iodides on the thyroid may be altered by other compounds including amiodarone and lithium (2).
- Hypothyroidism and decreased control of hypothyroidism have been reported with concomitant use of orlistat and levothyroxine. This may be due to decreased absorption of iodine salts and/or levothyroxine. It may be necessary to adjust the dose of levothyroxine or to take the two drugs at different times of the day. (45)

14.2.3 Special precautions

- Caution is necessary if preparations containing iodine or iodides are taken for long periods, and such preparations should not be taken regularly during pregnancy except when iodine supplementation is required.
- Caution is also required when giving iodine or iodides to children.
- Patients over the age of 45 years or with nodular goitres are especially susceptible to hyperthyroidism when given iodine supplementation. Reduced doses should therefore be used and supplementation with iodised oil may not be appropriate. (2)

14.2.4 Pregnancy and lactation

- Iodine is concentrated by the mammary gland into breast milk to ensure an adequate supply to the breast-fed infant. Since this is dependent on the maternal dietary intake, WHO recommends a daily iodine intake of 200 micrograms for lactating women.
- The BNFC considers treatment with iodine or iodides to be a contra-indication to breast feeding. However, the last available guidance from the American Academy of Pediatrics considered that such treatment was usually compatible with breast feeding although it was noted that goitre or effects on thyroid function had been reported. (2)

14.2.5 Administration

- For the prophylaxis and treatment of iodine deficiency it may be given as potassium iodide, potassium iodate, or as iodised oil. Sodium iodide has also been used.

- In the UK the reference nutrient intake (RNI) for adults is 140 micrograms (1.1 micromoles) of iodine daily and in the USA the recommended dietary allowance (RDA) is 150 micrograms daily.
- The International Council for Control of Iodine Deficiency Disorders, UNICEF, and WHO recommend the following daily iodine intakes:
    - 90 micrograms for infants and children up to 59 months of age
    - 120 micrograms for children in their 6th to 12th year
    - 150 micrograms for adolescents and adults
    - 200 to 250 micrograms for pregnant and lactating women.
- Iodine or iodides may suppress neonatal thyroid function and it is generally recommended that iodine compounds should be avoided during pregnancy. However, where it is essential to prevent neonatal goitre and cretinism, iodine supplementation should not be withheld from pregnant women.
- Iodine supplementation has been found to be effective in preventing brain-damage in the fetus provided it is given to the mother in the first or second trimester; treatment later in pregnancy was not effective in improving neurological status, although some developmental improvement was seen and hypothyroidism will be corrected.
- WHO has stated that in areas where iodine deficiency disorders are moderate to severe, iodised oil given either before or at any stage of gestation is beneficial. The following doses are recommended[9] during pregnancy and for one year postpartum:
    - 480 mg intramuscularly once yearly, or
    - 300 to 480 mg orally once yearly, or
    - 100 to 300 mg orally every 6 months
    - Non-pregnant fertile women may be given:
    - 480 mg intramuscularly once yearly, or
    - 400 to 960 mg orally once yearly, or
    - 200 to 480 mg orally every 6 months

    (2)

14.3 Selenium

14.3.1 Adverse effects

- Acute overdose: gastrointestinal disorders, muscle spasms. (43) Characteristic symptoms of selenium toxicity are garlicky or sour breath odour, vomiting and gastrointestinal disturbances, restlessness, hypersalivation, muscle spasms, haemolysis, liver necrosis, cerebral and pulmonary oedema, coma, and death. (2)
- Chronic overdose: skin and phanera damage (43) such as nail and hair loss and dermatitis (2), peripheral neuropathy (43), toxic effects on endocrine function, hepatotoxicity, gastrointestinal disturbances, and dermatological effects such as nail and hair loss and dermatitis (2). There has been some suggestion also of neurotoxicity, and a possible increased risk of amyotrophic lateral sclerosis(2).

14.3.2 Special precautions

- Serum selenium levels should be monitored regularly (43).

14.4 Vitamine D

14.4.1 Contraindications

- Hypercalcemia, metastatic calcification(43).

14.4.2 Adverse effects

- Gastrointestinal disorders, constipation, sensation of thirst, polyuria, stupor and tissue calcifications in case of intoxication(43).

14.4.3 Special precautions

- Vitamin D should be used with caution in infants, who may have increased sensitivity to hypercalcaemia, and patients with renal impairment or calculi, or heart disease, who might be at increased risk of organ damage if hypercalcaemia occurred (2).
- Monitoring of blood calcium levels is recommended if treatment is given at doses greater than 800 IU of vitamin D per day, or if calcitriol, calcifediol or alfacalcidol is used. At conventional prophylactic doses, such monitoring is not necessary (43).
- Similar monitoring is recommended in infants if they are breast-fed by mothers receiving pharmacological doses of vitamin D(2).
- Plasma phosphate concentrations should be controlled during vitamin D therapy to reduce the risk of ectopic calcification(2).

14.4.4 Interactions

- Increased risk of hypercalcemia when combining vitamin D with calcium (1) (2), thiazide diuretics or phosphate (2).
- The use of some anti-epileptic drugs (e.g. carbamazepine, phenobarbital, phenytoin, and primidone(2)) increases the need for vitamin D, whose degradation they accelerate (43).
- Rifampicin and isoniazid may reduce the effectiveness of vitamin D (2).
- Corticosteroids may counteract the effect of vitamin D (2).
- Ketoconazole may inhibit the metabolism of paricalcitol and these drugs should be used with caution together. Care should be taken when using paricalcitol with other potent inhibitors of the cytochrome P450 isoenzyme CYP3A4(2).

14.4.5 Overdosage

- Excessive intake of vitamin D leads to the development of hyperphosphataemia or hypercalcaemia (2) with muscle weakness, apathy, headache, anorexia, nausea and vomiting, bone pain, ectopic calcification, proteinuria, hypertension, and cardiac arrhythmias (1) (2). Associated effects of hypercalcaemia include hypercalciuria, ectopic calcification, and renal and cardiovascular damage. Chronic hypercalcaemia can lead to generalised vascular calcification, nephrocalcinosis, and rapid deterioration of renal function (1) (2).
- Symptoms of overdosage include: anorexia, lassitude, nausea, vomiting, constipation or diarrhoea, polyuria, nocturia, sweating, headache, thirst, somnolence, and vertigo. Interindividual tolerance to vitamin D varies considerably; infants and children are generally more susceptible to its toxic effects. The vitamin should be withdrawn if toxicity occurs. It has been stated that vitamin D dietary supplementation may be detrimental in persons already receiving an adequate intake through diet and exposure to sunlight, since the difference between therapeutic and toxic concentrations is relatively small (2).
- The most potent forms of vitamin D, such as alfacalcidol and calcitriol, might reasonably be expected to pose a greater risk of toxicity; however, their effects are reversed rapidly on withdrawal (2).

14.4.6 Pregnancy and lactation

- Reports noted increased requirements for vitamin D preparations during pregnancy for the treatment of hypoparathyroidism. The dose needed tended to increase during the second half of pregnancy.
- Hypercalcaemia during pregnancy may produce congenital disorders in the offspring, and neonatal hypoparathyroidism. However, the risks to the fetus of untreated maternal hypoparathyroidism are considered greater than the risks of hypercalcaemia due to vitamin D therapy.
- Vitamin D is distributed into breast milk, and its concentration appears to correlate with the amount of vitamin D in the serum of exclusively breast-fed infants.The American Academy of Pediatrics considers the use of vitamin D to be usually compatible with breast feeding, although they and others recommend that the infant be closely monitored for hypercalcaemia or clinical manifestations of vitamin D toxicity if the mother is taking pharmacological doses of vitamin D. (2)

14.5 Iron

14.5.1 Contraindications

- Hemochromatosis, iron overload, repeated blood transfusions (43).
- Iron dextran (i.v.): severe hepatic insufficiency, hepatitis (43).

14.5.2 Adverse effects

14.5.2.1 Oral administration

- Digestive disorders (43), gastrointestinal irritations and abdominal pain with nausea and vomiting. These irritant adverse effects are usually related to the amount of elemental iron taken rather than the type of preparation (2).
- Diarrhea or constipation, blackening of stools (43).
- Liquid oral preparations and effervescent tablets: also reversible staining of the teeth (it is preferable to drink them with a straw) (43).

14.5.2.2 Intravenous administration

- Especially with iron-dextran complex: hypotension (especially with rapid intravenous administration) to shock; generalized hypersensitivity reactions to severe anaphylaxis, with an increased risk in patients with allergic conditions such as asthma or eczema, and in patients with immune or inflammatory conditions.(43)
- Intramuscular administration: pain and brownish discoloration, sometimes irreversible, of the skin at the injection site(43).
- Overdose can lead to severe intoxication, especially in children(43).

14.5.3 Interactions

- Iron salts are not well absorbed orally, and food may further impair their absorption (2).
- Decreased absorption of, among others, bisphosphonates, levodopa, levothyroxine, quinolones and tetracyclines when iron is used concurrently (43).
- Decreased iron absorption when taking antacids, calcium salts (43), magnesium, mineral supplements (2), tetracyclines, quinolones, dairy products, coffee or tea (43).
- Zinc salts may also decrease the absorption of iron (2).
- An interval of at least 2 to 3 hours is recommended between taking iron and other medications (43).
- The response to iron may be delayed in patients receiving systemic chloramphenicol (2).
- Some agents, such as ascorbic acid and citric acid, may actually increase the absorption of iron (2).

14.5.4 Special precautions

- It is not advisable to administer iron without knowing the cause of the iron deficiency.
- Administering iron during or after a meal reduces gastrointestinal distress but also reduces absorption.
- The sodium content of effervescent preparations (tablets, powders, granules) may be a problem in patients on a strict salt-restricted diet.
- Oral preparations may aggravate digestive disorders in patients with inflammatory bowel disease.
- Intravenous Administration: Test dose administration is not predictive of an anaphylactic reaction. During and after intravenous administration, the patient should be monitored and resuscitation equipment should be available. (43)
- Iron compounds should not be given to patients receiving repeated blood transfusions (2).
- Oral and parenteral iron therapy should not be used together (2).

14.5.5 Overdosage

Acute iron overdosage can be divided into four stages.

- first phase, up to 6 hours after oral ingestion: gastrointestinal toxicity, notably vomiting and diarrhoea. Other effects may include cardiovascular disorders such as hypotension, metabolic changes including acidosis and hyperglycaemia, and CNS depression ranging from lethargy to coma. Patients with only mild to moderate poisoning do not generally progress past this first phase.
- second phase, which is not always seen, 6 to 24 hours after ingestion: is characterised by a temporary remission or clinical stabilisation.
- third phase, 12 to 48 hours after ingestion: gastrointestinal toxicity recurs together with shock, metabolic acidosis, severe lethargy or coma, hepatic necrosis and jaundice, hypoglycaemia, coagulation disorders, oliguria or renal failure, and possible myocardial dysfunction.
- fourth phase may occur several weeks after ingestion and is characterised by gastrointestinal obstruction and possibly late hepatic damage.

Relatively small amounts of iron may produce symptoms of toxicity. It has been stated that more than the equivalent of 20 mg/kg of iron could lead to some symptoms of toxicity and that toxicity is likely with doses containing more than the equivalent of about 60 mg/kg of iron; the equivalent of 200 to 250 mg/kg iron is considered potentially fatal.Serum-iron concentrations have also been used as an indication of the severity of overdosage. (2)

Overdosage in pregnancy: Limited data on the treatment of iron overdose in pregnancy from the UK National Teratology Information Service, suggested that treatment with desferrioxamine should not be withheld if clinically indicated. Most pregnancies had a normal outcome. A literature review of iron overdose in pregnant women found that women with peak serum-iron concentrations greater than or equal to 4 micrograms/mL were more frequently symptomatic, but that there was no relationship between peak iron level and frequency of spontaneous abortion, preterm delivery, congenital anomalies, or perinatal or maternal death. However, women with stage 3 iron toxicity, defined as those manifesting with hepatic, renal, or cardiac failure, were more likely to spontaneously abort, deliver preterm, or die. (2)

14.6 Omega-3 fatty acids

14.6.1 Adverse effects

- Dyspepsia and other gastrointestinal disorders (43) including nausea, eructation, vomiting, abdominal distension, diarrhoea, and constipation(2).
- Moderate elevation of liver enzymes(43).
- Rare: rash, urticaria, bleeding(43).

14.6.2 Interactions

- The effect of vitamin K antagonists can be enhanced when used simultaneously with high doses of omega-3 fatty acids (43).

14.6.3 Special precautions

- Preparations vary widely in concentration and purity. Some preparations contain significant amounts of vitamins A and D and long-term use could cause toxicity.
- There is a theoretical possibility of vitamin E deficiency with long-term use, although many preparations contain vitamin E as an antoxidant.
- Concern has been expressed over the high calorific value and cholesterol content of some preparations.
- Omega-3 fatty acids have antithrombotic activity and should be given with caution to patients with haemorrhagic disorders or to those receiving anticoagulants or other drugs affecting coagulation.
- Hepatic function should be monitored in patients with hepatic impairment, particularly if receiving high doses.
- Caution may also be required in asthmatic patients sensitive to aspirin since omega-3 fatty acids may affect prostaglandin synthesis. (2)

15 Appendix. Evidence tables. Supplements

15.1 Iodine versus placebo for (overt) hypothyroidism

Meta-analysis: NICE 2019(3)

Inclusion criteria: People with primary hypothyroidism; interventions T3, T4, combination T3 and T4, natural thyroid extract, **iodine supplementation**, selenium supplementation, placebo; RCTs only, minimum treatment duration of 3 months
Search strategy: Medline (OVID), Embase (OVID) and The Cochrane Library (Wiley) were searched from conception up to January 2019.
Assessment of quality of included trials: yes
Other methodological remarks: 9 RCTs were identified. No studies comparing iodine vs placebo for hypothyroidism were identified.

15.2 Iodine versus placebo for subclinical hypothyroidism

Meta-analysis: NICE 2019(3)

Inclusion criteria: People diagnosed with subclinical hypothyroidism (TSH greater than upper limit of context specific reference range, T3/T4 within reference range); interventions T3, T4, combination T3 and T4, natural thyroid extract, **iodine supplementation**, selenium supplementation, placebo; RCTs only, minimum treatment duration of 3 months
Search strategy: Medline (OVID), Embase (OVID) and The Cochrane Library (Wiley) were searched from conception up to January 2019.
Assessment of quality of included trials: yes
Other methodological remarks: 6 RCTs were identified. No relevant clinical trials comparing iodine supplementation with any other intervention or placebo were identified.

15.3 Selenium versus placebo for (overt) hypothyroidism

Meta-analysis: NICE 2019(3)

Inclusion criteria: People with primary hypothyroidism; interventions T3, T4, combination T3 and T4, natural thyroid extract, iodine supplementation, **selenium supplementation**, placebo; RCTs only, minimum treatment duration of 3 months
Search strategy: Medline (OVID), Embase (OVID) and The Cochrane Library (Wiley) were searched from conception up to January 2019.
Assessment of quality of included trials: yes
Other methodological remarks: 9 RCTs were identified. No studies comparing selenium supplementation vs placebo for hypothyroidism were identified.

15.4 Selenium versus placebo for subclinical hypothyroidism

Meta-analysis: NICE 2019(3)

Inclusion criteria: People diagnosed with subclinical hypothyroidism (TSH greater than upper limit of context specific reference range, T3/T4 within reference range); interventions T3, T4, combination T3 and T4, natural thyroid extract, iodine supplementation, **selenium supplementation**, placebo; RCTs only, minimum treatment duration of 3 months
Search strategy: Medline (OVID), Embase (OVID) and The Cochrane Library (Wiley) were searched from conception up to January 2019.
Assessment of quality of included trials: yes
Other methodological remarks: 6 RCTs were identified. No relevant clinical trials comparing selenium supplementation with any other intervention or placebo were identified.

Selenium versus no treatment for subclinical hypothyroidism due to Hashimoto's thyroiditis

Study details	n/Population	Comparison	Outcomes		Methodological
Pirola 2016(46) Design: RCT (OL; PG) Duration of follow-up: 4 months	n= 196 Mean age (years): 6,32,2 (Selenium); 33,1 (No treatment) Mean TSH (mIU/L): 6,11 (Selenium); 6,31 (No treatment) Mean fT4 (pg/mL) 10,6 (Selenium); 10,4 (No treatment) <u>Inclusion</u> 18–65 years old, mild subclinical hypothyroidism (TSH 4,0 – 10,0 mIU/L) due to Hashimoto's thyroiditis (presence	Oral selenomethionine 83 mcg/day Vs No treatment	Efficacy		RANDO: Adequate ALLOCATION CONC: No BLINDING : Participants: no Personnel: no Assessors: no Remarks on blinding method: Open-label FOLLOW-UP: Drop-out and Exclusions: 2% • Described: yes • Balanced across groups: yes ITT: No SELECTIVE REPORTING: high risk of bias (no mention of adverse effects; no definition of primary
			Participants with restored euthyroidism	Selenium: 30/96 (31,3%) No treatment: 3/96 (3,1%) **P<0.0001** **SS** **More participants with restored euthyroidism with selenium**	
			Safety		
			/	/	

	of detectable TPOAb serum levels + presence of ultrasound features), and no previous treatment *Subclinical hypothyroidism defined as:* Subclinical hypothyroidism (SCH) is biochemically defined as an elevated serum concentration of thyroidstimulating hormone (TSH) with normal concentration of free thyroxine (FT4) levels occurring simultaneously <u>Exclusion</u> Pregnant women, those who wanted to become pregnant and				outcome; no reporting/analysis of mean TSH/fT4/TPOAb of supplemented participants versus control patients) Sponsor: not reported (unclear risk of bias)

	patients that had to start levothyroxine treatment in accordance with recent guidelines				

15.5 Vitamin D versus placebo in hypothyroid patients

Study details	n/Population	Comparison	Outcomes		Methodological
Ref Talaei 2018(20) Design: RCT (DB) (PG)	n= 201 hypothyroid patients no reporting of gender of participants Mean age: Vit D 36.8 +/- 11 Pla 38.2 +/-12 Mean TSH:	50,000 IU vitamin D 1x/w Vs Placebo 1x/w For 12 weeks	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear description BLINDING : Described as 'double blind' Participants: unclear Personnel: unclear Investigators: unclear Remarks on blinding method:
			TSH change from baseline (PO)	VIT D −0.4 ± 0.6 µIU/mL Pla +0.1 ± 2.0 µIU/mL P = 0.02 SS in favour of vit D	
			T4 change from baseline (PO)	Vit D +0.2±3.0 µg/dL Pla -0.3±2.7 µg/dL P=0.22 NS	

Duration of follow-up: 12 weeks Location endocrinology service of Arak University of Medical Sciences (AUMS) (Iran)	Vit D 2.6±1.4 (mIU/L) Pla2.7±1.3 (mIU/L) Mean T4: VIT D 8.5±2.3 (µg/dL) Pla 8.7±2.3 (µg/dL) <u>Inclusion</u> Patients aged 20–60 years old were stable for more than one year on their levothyroxine dose and thyroid-stimulating hormone (TSH) level was at 0.5–5 mIU/L without need to change the levothyroxine dose <u>Exclusion</u> Not defined (19 excluded before randomization for not		T3 change from baseline (PO)	Vit D 0.01 ± 0.6 µg/dL Pla -0.1 ± 0.5 µg/dL P=0.23 NS	*"Randomization assignment was conducted using computer-generated random numbers as blindness by a trained midwife at clinic."* Vit D and placebos provided by different companies FOLLOW-UP: Lost-to follow-up: 0% Drop-out and Exclusions: 0% "100% of tablets taken in both groups" (reliable?) ITT: Yes SELECTIVE REPORTING: no evidence of selective reporting Other remarks: no prespecified safety endpoints defined, no description of male/female patients, no exclusion criteria defined
			Safety		
				'no side effects were reported following the consumption of vitamin D supplements in participants throughout the study'	

	meeting inclusion criteria, 9 excluded for not living in Arak) 58% of the patients were vitamin D deficient as described when vitamin D is less than 20 ng/ml.				Sponsor: no

16 Appendix. Evidence tables. Elderly people

16.1 Levothyroxine versus placebo for (overt) hypothyroidism in an elderly population

Meta-analysis: NICE 2019(3)

Inclusion criteria: People with primary hypothyroidism; interventions T3, T4, combination T3 and T4, natural thyroid extract, iodine supplementation, selenium supplementation, placebo; RCTs only, minimum treatment duration of 3 months
Search strategy: Medline (OVID), Embase (OVID) and The Cochrane Library (Wiley) were searched from conception up to January 2019.
Assessment of quality of included trials: yes
Other methodological remarks: 9 RCTs were identified. All included studies were in the adult (18-65) age stratum. No studies comparing T4 vs placebo for hypothyroidism in an elderly population were identified.

16.2 Levothyroxine versus placebo for subclinical hypothyroidism in an elderly population

Meta-analysis: NICE 2019(3)

Inclusion criteria: People diagnosed with subclinical hypothyroidism (TSH greater than upper limit of context specific reference range, T3/T4 within reference range); interventions T3, T4, combination T3 and T4, natural thyroid extract, iodine supplementation, selenium supplementation, placebo; RCTs only, minimum treatment duration of 3 months
Search strategy: Medline (OVID), Embase (OVID) and The Cochrane Library (Wiley) were searched from conception up to January 2019.
Assessment of quality of included trials: yes
Other methodological remarks: 6 RCTs were identified. All compared T4 to placebo. Five included studies were in the adult (18-65) age stratum, whereas one study was in the older adult (>65) stratum. Therefore we will report this RCT separately: see Stott 2017(4)

Levothyroxine vs placebo in older adults with subclinical hypothyroidism

Study details	n/Population	Comparison	Outcomes		Methodological
Stott 2017(4) Design: RCT (DB, PG) Duration of follow-up: 12 months With extended follow-up: median follow-up for all participants was 17,3 months (placebo) and 18 months (levothyroxine)	n= 737 Mean age: 74,4 years Mean TSH: 6.40±2.01 mIU/ L Mean T4: 13.3 – 13.4 pmol/L <u>Inclusion</u> Adults 65 years of age or older *Subclinical hypothyroidism defined as:* persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter, measured on at	Levothyroxine (at a starting dose of 50 µg daily, or 25 µg if the body weight was <50 kg or the patient had coronary heart disease, with dose adjustment according to the thyrotropin level; aimed to result in a thyrotropin level within the reference range (0.40 to 4.59 mIU per liter)) Vs Placebo	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All dose adjustments were generated and executed by means of computer without the intervention of a physician. FOLLOW-UP (at 12 months): Drop-out and Exclusions: 9,2% • Described: yes • Balanced across groups: yes ITT: ITT population defined as participants with data on the outcome of interest (modified ITT)
			Change in the Hypothyroid Symptoms score (PO)* at one year from the ThyPRO (thyroid-specific) questionnaire *range of scale is 0 to 100, with higher scores indicating more symptoms; minimum clinically important difference: 9 points*	Levothyroxine: 16.6±16.9 Placebo: 16.7±17.5 Difference (95% CI): 0.0 (−2.0 to 2.1) NS	
			Tiredness score (PO)* at one year from the ThyPRO (thyroid-specific) questionnaire *range of scale is 0 to 100, with higher scores indicating more*	Levothyroxine: 28.7±20.2 Placebo: 28.6±19.5 Difference (95% CI): 0.4 (−2.1 to 2.9) NS	

	least two occasions that were 3 months to 3 years apart; free thyroxine level within the reference range) <u>Exclusion</u> current prescription of levothyroxine, antithyroid drugs, amiodarone, or lithium; thyroid surgery or receipt of radioactive iodine within the previous 12 months; dementia; hospitalization for a major illness; elective surgery within previous 4 weeks; an acute coronary heart syndrome within the previous 4 weeks); and terminal illness	(with mock adjustment)	*tiredness; minimum clinically important difference: 9 points*		SELECTIVE REPORTING: no Other important methodological remarks: *Primary outcome was changed during trial: "We had initially planned for cardiovascular events and thyroid-specific quality of life to be the two primary outcomes. However, this plan was modified during the trial to thyroid-specific quality of-life scores as the two primary outcomes and cardiovascular events as a secondary outcome when it became apparent that the trial would be underpowered for cardiovascular events owing to delays and difficulties in recruitment." Sponsor: Academic or government funding (European Union FP7)
			TSH (mIU/L)	Levothyroxine: 3.63±2.11 Placebo: 5.48±2.48 Difference (95% CI): −1.92 (−2.24 to −1.59) SS P <0.001	
			Health-related quality of life EQ-5D descriptive score (non-thyroid-specific questionnaire) range from −0.59 to 1.00, with higher scores indicating better quality of life	Levothyroxine: 28.7±20.2 Placebo: 28.6±19.5 Difference (95% CI): 0.4 (−2.1 to 2.9) NS	
			Health-related quality of life	Levothyroxine: 77.3±15.6 Placebo: 77.4±13.7 Difference (95% CI): −1.3 (−3.2 to 0.6) NS	

			EQ-5D VAS score (non-thyroid-specific questionnaire) range from 0 to 100, with higher scores indicating better quality of life		
			Safety		
			Hyperthyroid Symptoms score The score on the Hyperthyroid Symptoms scale was recorded as a measure of possible adverse effects (on a scale from 0 to 100, with higher scores indicating more symptoms; minimum clinically important difference has been estimated as 9 points).	Levothyroxine: 0.833±0.212 Placebo: 0.853±0.191 Difference (95% CI): −0.025 (−0.050 to 0.000) P=0.05 NS	

Study details	n/Population	Comparison	Outcomes		Methodological
Gencer 2020(21) Design: RCT (DB, PG) Planned substudy nested within the TRUST trial (Stott 2017(4))	n= 217 (185 analysed) Mean age: 74,4 years (T4); 73,8 y (placebo) Mean TSH (mIU/L): 6,26 (T4); 6,47 (placebo) Mean fT4 (pmol/L): 13,6 (T4); 13,7 (placebo) <u>Inclusion</u> Adults 65 years of age or older	Levothyroxine (at a starting dose of 50 µg daily, or 25 µg if the body weight was <50 kg or the patient had coronary heart disease, with dose adjustment according to the thyrotropin level; aimed to result in a thyrotropin level within the reference range	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All dose adjustments were generated and executed by means of computer without the intervention of a physician. FOLLOW-UP: Drop-out and Exclusions: 14,7% • Described: yes
			LVEF (% ±SD) (PO) (systolic function)	Levothyroxine: 62,7 ± 7,9 Placebo: 62,5 ±7,4 Difference (95% CI): 0,4 (-1,8 to 2,5) NS	
			E/e' (mean ±SD) (PO) *Ratio between mitral peak velocity of early filling to early diastolic mitral annular velocity* (diastolic function)	Levothyroxine: 10,6 ±3,7 Placebo: 10,1 ± 3,3 Difference (95% CI): 0.4 (-0,7 to 1,4) NS	
			Safety		
			All-cause death n (%)	Levothyroxine: 4/109 (3,7%) Placebo: 1/108 (0,9%) *No statistical analysis*	

Duration of follow-up: median 18,4 months	*Subclinical hypothyroidism defined as:* persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter, measured on at least two occasions that were 3 months to 3 years apart; free thyroxine level within the reference range) <u>Exclusion</u> current prescription of levothyroxine, antithyroid drugs, amiodarone, or lithium; thyroid surgery or receipt of radioactive iodine within the previous 12 months; dementia; hospitalization for a	(0,40 to 4,59 mIU per liter)) Vs Placebo (with mock adjustment)			• Balanced across groups: yes ITT: ITT population defined as population of participants randomized with echocardiography data (modified ITT) SELECTIVE REPORTING: post hoc analyses not shown but described and available online Sponsor: This study was supported grants of the Swiss National Science Foundation to NR (SNSF 320030-150025 and 320030-172676), and investigator-driven grants of the Velux Stiftung (974a, to NR) and of the Swiss Heart Foundation (to NR)
			Serious adverse event Participants with ≥1 SAE N(%)	Levothyroxine: 30/109 (27,5%) Placebo: 35/108 (32,4%) *No statistical analysis*	
			Serious adverse event Number of events, n	Levothyroxine: 54 Placebo: 67 *No statistical analysis*	

	major illness; elective surgery within previous 4 weeks; an acute coronary heart syndrome within the previous 4 weeks); severe heart failure (NYHA stage IV);and terminal illness				

Study details	n/Population	Comparison	Outcomes		Methodological
Gonzalez Rodriguez 2020(22) Design: RCT, PG DB Planned substudy nested within the TRUST trial	n= 217 (196 analysed) Mean age: 74,3 years Mean TSH(mIU/ L): 6,3 (T4); 6,5 (placebo) Mean T4 (pmol/L): 13,5 (T4) ; 13,7 (placebo)	Levothyroxine (at a starting dose of 50 µg daily, or 25 µg if the body weight was <50 kg or the patient had coronary heart disease, with dose adjustment according to the	Safety		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All dose adjustments were generated and executed by
			Lumbar spine BMD Changes after one year treatment (%) *105 analysed*	Levothyroxine: 0,8 Placebo: -0,6 Difference (95% CI): 1,4 (-0,1 to 2,9) NS	
			Total hip BMD Changes after one year treatment (%)	Levothyroxine: -0,5 Placebo: 0,7 Difference (95% CI): -1,3 (-3,1 to 0,6) NS	

(Stott 2017(4)) Duration of follow-up: 12 months	<u>Inclusion</u> Adults 65 years of age or older *Subclinical hypothyroidism defined as:* persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter, measured on at least two occasions that were 3 months to 3 years apart; free thyroxine level within the reference range) <u>Exclusion</u> current prescription of levothyroxine, antithyroid drugs, amiodarone, or lithium; thyroid surgery or receipt of	thyrotropin level; aimed to result in a thyrotropin level within the reference range (0.40 to 4.59 mIU per liter)) Vs Placebo (with mock adjustment)	Femoral neck BMD Changes after one year treatment (%) *113 analysed*	Levothyroxine: -0,6 Placebo: -0,4 Difference (95% CI): -0,2(-1,1 to 0,7) NS	means of computer without the intervention of a physician. FOLLOW-UP: Drop-out and Exclusions: 9,7% • Described: yes • Balanced across groups: unclear ITT: No; only participants who underwent DXA scans were analysed SELECTIVE REPORTING: no Sponsor: supported by grants from the Swiss National Science Foundation (PZ00P3-167826).

	radioactive iodine within the previous 12 months; dementia; hospitalization for a major illness; elective surgery within previous 4 weeks; an acute coronary heart syndrome within the previous 4 weeks); and terminal illness				

Study details	n/Population	Comparison	Outcomes		Methodological
Stuber 2020(23) Design: RCT (DB, PG) Planned substudy nested within the TRUST trial (Stott 2017(4))	n= 276 (230 analysed) Mean age (y): 73,9 (T4); 73,5 (placebo) Mean TSH (mIU/ L): 6,12 (T4); 6,31 (placebo) Mean fT4 (pmol/L): 13,7 (T4); 13,5 (placebo)	Levothyroxine (at a starting dose of 50 µg daily, or 25 µg if the body weight was <50 kg or the patient had coronary heart disease, with dose adjustment according to the thyrotropin level; aimed to	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All dose adjustments were generated and executed by means of computer without the intervention of a physician.
			Fatigability - Physical score (PO) *(The Pittsburgh Fatigability Scale (PFS) physical and mental subscores range from 0 to 50 with higher scores indicating greater fatigability)*	Levothyroxine: Baseline 14,7 ± 9,3 at 1 year 14,8 ± 9,6 Placebo: Baseline 11,1 ± 9,1 at 1 year 12,4 ± 9,3 Adjusted Between-Group Difference (95% CI): 0,2 (-1,8 to 2,1) NS	

Duration of follow-up: 12 months	<u>Inclusion</u> Adults 65 years of age or older *Subclinical hypothyroidism defined as:* persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter, measured on at least two occasions that were 3 months to 3 years apart; free thyroxine level within the reference range) <u>Exclusion</u> current prescription of levothyroxine, antithyroid drugs, amiodarone, or lithium; thyroid surgery or receipt of	result in a thyrotropin level within the reference range (0.40 to 4.59 mIU per liter)) Vs Placebo (with mock adjustment)	Fatigability - Mental score (PO) *(The Pittsburgh Fatigability Scale (PFS) physical and mental subscores range from 0 to 50 with higher scores indicating greater fatigability)*	Levothyroxine: Baseline 7,4 ± 8,0 at 1 year 6,0 ± 7,8 Placebo: Baseline 5,1 ± 6,9 at 1 year 6,0 ± 8,0 Adjusted Between-Group Difference (95% CI): -1,0 (-2,8 to 0,8) NS	FOLLOW-UP: Drop-out and Exclusions: 16,7% • Described: yes • Balanced across groups: yes ITT: Modified ITT population defined all participants with outcome of interest, and not more than three missing answers in the PFS. SELECTIVE REPORTING: no Sponsor: grant from the Swiss National Science Foundation (SNSF 320030-172676 to N.R.).

	radioactive iodine within the previous 12 months; dementia; hospitalization for a major illness; elective surgery within previous 4 weeks; an acute coronary heart syndrome within the previous 4 weeks); and terminal illness			

Study details	n/Population	Comparison	Outcomes		Methodological
Wildisen 2021(24) Design: RCT (DB, PG) Planned substudy nested within the TRUST trial (Stott 2017(4))	n= 472 (427 analysed) Mean age: 74,0 years (T4); 75,0 y (placebo) Mean TSH (mIU/L): 6,57 (T4); 6,55 (placebo) Mean fT4 (pmol/L): 13,7 (T4); 13,6 (placebo)	Levothyroxine (at a starting dose of 50 µg daily, or 25 µg if the body weight was <50 kg or the patient had coronary heart disease, with dose adjustment according to the thyrotropin level; aimed to	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All dose adjustments were generated and executed by means of computer without the intervention of a physician.
			Change in GDS-15 score *GDS-15, 15-item Geriatric Depression Scale Questionnaire (range, 0-15; higher scores indicate more severe depressive symptoms; minimal clinically important difference, 2 points)*	Levothyroxine mean (SD) Baseline 1,26 (1,85) At 12 months 1,39 (2,13) Placebo mean (SD) Baseline 0,96 (1,58) At 12 months 1,07 (1,67) Unadjusted mean difference at 12 months (95%CI) 0.32 (−0.05 to 0.68)	

Duration of follow-up: 12 months	<u>Inclusion</u> Adults 65 years of age or older *Subclinical hypothyroidism defined as:* persisting subclinical hypothyroidism (thyrotropin level, 4.60 to 19.99 mIU per liter, measured on at least two occasions that were 3 months to 3	result in a thyrotropin level within the reference range (0,40 to 4,59 mIU per liter)) Vs Placebo (with mock adjustment)		NS Adjusted* mean difference at 12 months (95%CI) 0.15 (−0.15 to 0.46) NS **Adjusted for age, sex, GDS-15 score at baseline, levothyroxine dose at baseline, and country.*	FOLLOW-UP: Drop-out and Exclusions: 9,5% • Described: yes • Balanced across groups: yes ITT: Modified ITT population defined as population of participants having depressive symptoms outcomes SELECTIVE REPORTING: no

	years apart; free thyroxine level within the reference range) <u>Exclusion</u> current prescription of levothyroxine, antithyroid drugs, amiodarone, or lithium; thyroid surgery or receipt of radioactive iodine within the previous 12 months; dementia; hospitalization for a major illness; elective surgery within previous 4 weeks; an acute coronary heart syndrome within the previous 4 weeks); severe heart failure (NYHA stage IV);and terminal illness			Sponsor: This ancillary study on depressive symptoms was funded by the Swiss National Science Foundation (SNSF 320030-172676 to Dr Rodondi).

Study details	n/Population	Comparison	Outcomes		Methodological
Zijlstra 2021(25) Design: Prespecified combined analysis of 2 RCTs (DB, PG) (TRUST and IEMO80+) Duration of follow-up: Minimum of 12 months; maximum of 36 months Median 17 months follow-up	n= 842 Median age(y): 75,0 y History of CVD: 35,9% Mean TSH(mIU/L): 6,38±5,7 <u>Inclusion</u> *Subclinical hypothyroidism defined as: elevated thyrotropin levels (4.6-19.9 mIU/L) and FT4 levels within laboratory reference ranges* Individuals with persistent (measured on at least 2 occasions	Levothyroxine (at a starting dose of 50 µg daily, or 25 µg if the body weight was <50 kg or the patient had coronary heart disease, with dose adjustment according to the thyrotropin level; aimed to result in a thyrotropin level within the reference range (0.40 to 4.59 mIU per liter)) Vs Placebo	Efficacy		ANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All dose adjustments were generated and executed by means of computer without the intervention of a physician FOLLOW-UP: Drop-out and Exclusions:13,2% • Described: yes • Balanced across groups: yes ITT: Modified ITT defined as participants with data on the outcome of interest SELECTIVE REPORTING: no
			Fatal and non-fatal cardiovascular event (*all-cause and cardiovascular mortality, cardiovascular events and cardiovascular side effects;* *Cardiovascular events defined as fatal and non-fatal cardiovascular events, including myocardial infarction, stroke, amputations for peripheral vascular disease, revascularisations for atherosclerotic vascular disease and heart failure hospitalisations)*	*Total population (n=842)* Levothyroxine: 19 (4.5%) Placebo: 25 (5.9%) HR (95%CI) 0.74 (0.41-1.35) NS *History of CVD (n= 302)* Levothyroxine: 11 (7.3%) Placebo: 14 (9.3%) HR (95%CI) 0.77 (0.35-1.71) NS *No history of CVD (n=540)* Levothyroxine: 8 (3.0%) Placebo: 11 (4.1%) HR (95%CI) 0.70 (0.28 -1.74) NS	

	between 3 months and 3 years apart) subclinical hypothyroidism aged 65 years and older in TRUST trial, and 80 years and older in IEMO80+ trial <u>Exclusion</u> use of levothyroxine, antithyroid medication, amiodarone, or lithium; recent thyroid surgery or radioiodine therapy; New York Heart Association class IV heart failure; clinical diagnosis of dementia; recent hospitalization for major illness; recent acute coronary syndrome, acute myocarditis, or pancarditis; and terminal illness.	(with mock adjustment)	Death from any cause	*Total population (n=842)* Levothyroxine: 12 (209%) Placebo: 9 (2.1%) HR (95%CI) 1.28 (0.54 – 3.03) NS *History of CVD (n= 302)* Levothyroxine: 7 (4.6%) Placebo: 4 (2.6%) HR (95%CI) 1.60 (0.46 – 5.53) NS *No history of CVD (n=540)* Levothyroxine: 5 (1.9%) Placebo: 5 (1.8%) HR (95%CI) 0.97 (0.27 – 3.52) NS	Other important methodological remarks Prospectively planned combined analysis of data from a randomized clinical trial (IEMO80+) of participants aged 80 or older were combined with participants aged 65 years and older from a second clinical trial (TRUST). Stratified analyses were executed for patients with or without a history of cardiovascular disease at inclusion. Sponsor: The IEMO trial was supported by research grant (627001001) from ZonMw under the ZonMw programme Evidence-based Medicine in Old age and by grants from the Swiss National Science Foundation (SNSF 320030-150025 and 320030-172676 to Dr Rodondi).

			TSH (mIU/L)	*History of CVD (n= 302)* Levothyroxine (baseline) 6.2±0.1 Placebo (baseline) 6.2±0.2 Levothyroxine (at 12 months) 3.8±0.2 Placebo (at 12 months) 5.5±0.2 **Difference (95%CI) -1.63 (-2.17 to -1.11)** **SS lower TSH with levothyroxine** *No history of CVD (n=540)* Levothyroxine (baseline) 6.5±0.1 Placebo (baseline) 6.4±0.1 Levothyroxine (at 12 months) 3.5±0.1 Placebo (at 12 months) 5.6±0.2 **Difference (95%CI) -2.12 (-2.49 to -1.76)** **SS lower TSH with levothyroxine**	Funding of the TRUST trial was reported earlier.
			Safety		
			Serious adverse event	*Total population (n=842)* Levothyroxine: 90 (21.4%)	

				Placebo: 116 (27.5%) **HR (95%CI) 0.73 (0.55 – 0.96)** **SS fewer serious adverse events with levothyroxine** *History of CVD (n= 302)* Levothyroxine: 47 (31.1%) Placebo: 56 (37.1%) HR (95%CI) 0.82 (0.55 – 1.20) NS *No history of CVD (n=540)* Levothyroxine: 43 (16.0%) Placebo: 60 (22.1%) **HR (95%CI) 0.65 (0.44 – 0.97)** **SS fewer serious adverse events with levothyroxine**	
			New-onset atrial fibrillation	*Total population (n=842)* Levothyroxine: 11 (2.6%) Placebo: 15 (3.6%)	

				HR (95%CI) 0.69 (0.32 – 1.52) NS *History History of CVD (n= 302)* *CVD* Levothyroxine: 2 (1.3%) Placebo: 7 (4.6%) HR (95%CI) 0.29 (0.06 – 1.42) NS *No history of CVD (n=540)* Levothyroxine: 9 (3.3%) Placebo: 8 (3.0%) HR (95%CI) 0.97 (0.36 – 2.62) NS	

			New-onset heart failure	*Total population (n=842)* Levothyroxine: 4 (1.0%) Placebo: 9 (2.1%) HR (95%CI) 0.41 (0.13 – 1.35) NS *History of CVD (n= 302)* Levothyroxine: 3 (2.0%) Placebo: 5 (3.3%) HR (95%CI) 0.53 (0.13 – 2.24) NS *No history of CVD (n=540)* Levothyroxine: 1 (0.4%) Placebo: 4 (1.5%) HR (95%CI) 0.28 (0.03 – 2.25) NS	

16.3 Levothyroxine vs placebo in elderly people (80+) with subclinical hypothyroidism

Study details	n/Population	Comparison	Outcomes		Methodological
Mooijaart 2019(26) Design: RCT (DB, PG) Duration of follow-up: 12 months	n= 251 Mean age(y): 84,0 (T4); 85,0 (placebo) Mean TSH(mIU/L): 6,4 (T4) ; 6,3 (placebo) Mean fT4 (pmol/L): 13,8 (T4) ; 13,8 (placebo) <u>Inclusion</u> *Subclinical hypothyroidism defined as: elevated thyrotropin levels (4.6-19.9 mIU/L) and FT4 levels within*	Levothyroxine (at a starting dose of 50 µg daily, or 25 µg if the body weight was <50 kg or the patient had coronary heart disease, with dose adjustment according to the thyrotropin level; aimed to result in a thyrotropin level within the reference range (0.40 to 4.59 mIU per liter)) Vs	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes Remarks on blinding method: All dose adjustments were generated and executed by means of computer without the intervention of a physician FOLLOW-UP: Drop-out and Exclusions:13,5% • Described: yes • Balanced across groups: yes ITT: For the primary outcome: participants with data available at the 12-month follow-up.
			Change in the Hypothyroid Symptoms score (PO)* at one year from the ThyPRO (thyroid-specific) questionnaire *range of scale is 0 to 100, with higher scores indicating more symptoms; minimum clinically important difference: 9 points*	Levothyroxine mean (SD) Baseline 21,7 (19,5) At 12 months 19,3 (18,2) Placebo mean (SD) Baseline 19,8 (19,6) At 12 months 17,4 (18,1) Adjusted* difference at 12 months (95%CI) 1,27 (−2,69 to 5,23) NS * *Adjusted difference was estimated in linear regression models predicting change from baseline to 12-month visit (95% CI) with study site, sex, and randomization dose as stratification variables and study as random effect.*
			Tiredness score (PO)* at one year	Levothyroxine mean (SD)	

	laboratory reference ranges Individuals with persistent (measured on at least 2 occasions between 3 months and 3 years apart) subclinical hypothyroidism aged 80 years and older <u>Exclusion</u> use of levothyroxine, antithyroid medication, amiodarone, or lithium; recent thyroid surgery or radioiodine therapy; New York Heart Association class IV heart failure; clinical diagnosis of dementia; recent hospitalization for major illness; recent acute coronary syndrome, acute	Placebo (with mock adjustment)	from the ThyPRO (thyroid-specific) questionnaire *range of scale is 0 to 100, with higher scores indicating more tiredness; minimum clinically important difference: 9 points*	Baseline 25,2 (21,5) At 12 months 28,2 (20,0) Placebo mean (SD) Baseline 25,1 (19,5) At 12 months 28,7 (19,9) Adjusted* difference at 12 months (95%CI) -0,10 (−4,51 to 4,31) NS * *Adjusted difference was estimated in linear regression models predicting change from baseline to 12-month visit (95% CI) with study site, sex, and randomization dose as stratification variables and study as random effect.*	SELECTIVE REPORTING: no Other important methodological remarks Prospectively planned combined analysis of data Data from a randomized clinical trial were combined with a subgroup of participants aged 80 years and older from a second clinical trial (TRUST). Sponsor: The IEMO trial was supported by research grant (627001001) from ZonMw under the ZonMw programme Evidence-based Medicine in Old age and by grants from the Swiss National Science Foundation (SNSF 320030-150025 and 320030-172676 to Dr Rodondi).
			TSH (mIU/L)	Levothyroxine mean (SD) Baseline 6,50 (1,80) At 12 months 3,69 (1,81) Placebo mean (SD) Baseline 6,20 (1,48)	

	myocarditis, or pancarditis; and terminal illness.			At 12 months 5,49 (2,21) Adjusted* difference at 12 months (95%CI) -1,97 (-2,49 to -1,45) P<0.001 SS * *Adjusted difference was estimated in linear regression models predicting change from baseline to 12-month visit (95% CI) with study site, sex, and randomization dose as stratification variables and study as random effect.*	Funding of the TRUST trial was reported earlier.
			Safety		
			Death from any cause	Levothyroxine 5/112 (4,5%) Placebo 4/139 (2,9%) Estimated risk difference (95%CI) HR 1,39 (0,37 to 5,19) NS	
			Cardiovascular death	Levothyroxine 0/112 (0%) Placebo 1/139 (0,7%) *No statistical analysis*	

			Fatal or nonfatal cardiovascular event	Levothyroxine 7/112 (6,3%) Placebo 14/139 (10,1%) Estimated risk difference (95%CI) HR 0,60 (0,24 to 1,50) NS	
			Serious adverse events Events (n)	Levothyroxine 53 Placebo 61 *No statistical analysis*	
			Serious adverse events Participants with >1 serious adverse event	Levothyroxine 33/112 (29,5%) Placebo 40/139 (28,8%) Estimated risk difference (95%CI) -0,01 (-0,04 to 0,01) NS	
			New-onset atrial fibrillation	Levothyroxine 4/112 (3,6%) Placebo 6/139 (4,3%) Estimated risk difference (95%CI) 0,00 (-0,02 to 0,03) NS	
			Heart failure	Levothyroxine 3/112 (2,7%) Placebo 6/139 (4,3%) Estimated risk difference (95%CI) 0,01 (-0,03 to 0,05) NS	

			Fracture	Levothyroxine 4/112 (3,6%) Placebo 5/139 (3,6%) Estimated risk difference (95%CI) 0,00 (-0,04 to 0,03) NS	

17 Appendix. Evidence tables. Pregnancy

17.1 Levothyroxine versus placebo or no treatment in pregnant women with SCH

Meta-analysis: Ding 2021(27), Frontiers in Endocrinology, Pregnancy and Neonatal Outcomes With Levothyroxine Treatment in Women With Subclinical Hypothyroidism Based on New Diagnostic Criteria: A Systematic Review and Meta-Analysis.

Inclusion criteria: relevant RCTs or cohort studies were sought for possible inclusion. Studies were eligible if they compared pregnancy outcomes between those with LT4 supplementation and placebo or no treatment; they included women diagnosed with SCH in pregnancy (based on the new 2017 ATA criteria: TSH level above the upper limit of pregnancy-specific reference range or (if unavailable) more than 4.0 mIU/L and less than 10.0 mIU/L) and they reported data on maternal and/or neonatal outcomes.

Excluded: case series or case-control studies; study that did not provide standard design methods, such as inappropriate grouping or irrelevant diagnostic criteria; studies with a lack of sufficient data on outcomes of interest.

Search strategy: Studies published from inception to January 2020 without language restrictions. The databases that were searched included PubMed, Embase, Web of Science, Cochrane Controlled Trials Register and CNKI (China National Knowledge Infrastructure). The search strategy targeted human studies. We also reviewed the relevant studies in references by conducting manual searches when necessary.

Assessment of quality of included trials: yes, Jadad/Cochrane risk of bias tool. Publication bias was not assessed due to the limited number of publications.

Other methodological remarks:
A fixed effects model was used when $I^2 < 50\%$, otherwise, the random effects model was used.

Subgroup analyses was performed to further analyze the effects of LT4 supplementation on pregnancy outcomes based on the TPO-Ab status of the study participants (positive or negative) and study design (RCT or cohort study).**We reported pooled results of RCTs only**. We didn't perform the subgroup analysis on pregnancy loss and gestational hypertension just due
to the limited number of included studies.

Ref	Comparison	N/n	Outcomes	Result
		Obstetric outcomes		
Ding 2021(27) Design: MA Search date: (01-2020)	Levothyroxine Vs Placebo or no treatment	Subgroup analysis for RCT N= 3 n= 895 (Nazarpour 2018, Casey 2017, Nazarpour 2017)	Preterm birth or delivery	39/464 vs 58/431 OR: 0.40 (95%CI: 0.15 to 1.11) NS I^2: 65 %
		N= 4 including 3 cohort studies 1 RCT n= 677 (Casey 2017)	Pregnancy loss (miscarriage, fetal death and stillbirth)	3 cohort studies included in the MA, not considered according to the methodology of this report. RCT alone: 4/339 vs 7/338 OR: 0.56 (95%CI: 0.16 to 1.95) NS
		N= 4 including 3 cohort studies 1 RCT n= 677 (Casey 2017)	Gestational hypertension	3 cohort studies included in the MA, not considered according to the methodology of this report. RCT alone: 33/339 vs 36/338 OR: 0.90 (95%CI: 0.55 to 1.49) NS
		N= 1 (RCT study) n= 677 (Casey 2017)	Preeclampsia	22/339 vs 20/338 p value: 0.76 NS

		N= 4 including 3 cohort studies 1 RCT n= 677 (Casey 2017)	Gestational diabetes	3 cohort studies included in the MA, not considered according to the methodology of this report. RCT alone: 25/339 vs 22/338 OR: 1.14 (95%CI: 0.63 to 2.07) NS
		N= 3 including 2 cohort studies 1 RCT n= 677 (Casey 2017)	Placental abruption	2 cohort studies included in the MA, not considered according to the methodology of this report. RCT alone: 1/339 vs 5/338 OR: 0.20 (95%CI: 0.02 to 1.70) NS
		Neonatal outcomes		
			Fetal growth restriction	No RCT found
		N= 3 including 2 cohort studies 1 RCT: n= 677 (Casey 2017)	Small for gestational age	2 cohort studies included in the MA, not considered according to the methodology of this report. RCT alone: 33/339 vs 27/338 OR: 1.24 (95%CI: 0.73 to 2.12) NS
			Other neonatal complications: low birth weight low Apgar score fetal distress, neonatal intensive care admission, neonatal death congenital malformation	No data provided

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Nazarpour 2018(28) SB RCT	366 in total 147 included in the Ding 2021 MA with TSH >4.0 mIU/L	SCH-TPOAb negative pregnant women from Iran. SCH was defined as a normal FT4I (1 to 4.5) despite an elevated TSH level (2.5 to 10 mIU/L); TPOAb level >50 IU/mL was considered TPOAb positivity. Data extracted for SCH defined as TSH >4.0 mIU/L -TPOAb negative pregnant women Levothyroxine: W 87 Control: W 60 Excluded: twin pregnancies or overt thyroid dysfunction	Until delivery	Levothyroxine 1 µg/kg/d, 4 to 8 days after the first prenatal visit, throughout pregnancy Gestational age at LT4 initiation: 11.4±4 weeks Vs No treatment	ALLOCATION CONC: Adequate/Low risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Inadequate/Hight risk of bias BLINDING (assessors): Adequate/Low risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias DATA SELECTION (reporting): Adequate/Low risk of bias ITT: yes FUNDING: Research Institute for Endocrine Sciences
Casey 2017(29) RCT	677	Women with singleton pregnancy before 20 weeks of gestation with SCH. SCH defined as a TSH > 4.0 mIU/L and a normal free T4 level (0.86 to 1.90 ng/dl ; 11 to 24 pmol/L) Mean gestational age 16.7 weeks at inclusion	Until children age: 5y	Levothyroxine 100 µg /day, dose adjusted to attain thyrotropin level between 0.1 and 2.5 mU per liter, with a maximum daily dose of 200 µg, with sham adjustments for placebo Gestational age at LT4 initiation: 8-20 weeks	ALLOCATION CONC: Unclear/Unclear risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Adequate/Low risk of bias BLINDING (assessors): Adequate/Low risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias

		Levothyroxine: W 339 Ethnic group black 27, hispanic 195, white 109, other 8 Placebo: W 338 Ethnic group black 25, Hispanic 185 , white 117 , other 11 Excluded: Women found to have overt hypothyroidism or hyperthyroidism.		Vs Placebo	DATA SELECTION (reporting): Adequate/Low risk of bias ITT: yes FUNDING: Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke.
Nazarpour 2017(30) SB-RCT	131 in total (used in Wang 2020 MA) 72 included in the Ding 2021 MA with TSH >4.0 mIU/L	TPO-Ab positive (≥ 50 IU/mL), pregnant, euthyroid/subclinical hypothyroid women from Iran Included thyroid function: TSH 0.1–10 mIU/L and FT4: 1–4.5 Levothyroxine: W 65, mean age 26.6 years, median TSH 3.7 mIU/L Control: W 66, mean age 27.7 years, median TSH 3.2 mIU/L Excluded: twin pregnancies, hyperthyroidism or overt hypothyroidism and TPOAb negative subclinical hypothyroid women. For Ding 2021: pregnant, subclinical hypothyroid women with SCH defined as TSH > 4.0 mIU/L -TPO-Ab positive pregnant women	Until delivery	Levothyroxine 0.5 µg/kg/d for TSH < 1.0 mIU/L, 0.75 µg/kg/d for TSH 1.0–2.0 mIU/L, 1 µg/kg/d for TSH > 2.0 mIU/L or TPO-Ab exceeding 1,500 IU/mL, throughout pregnancy Vs No treatment gestational age at LT4 initiation: 10.8±4 weeks (reported for the population used in Ding 2021)	As reported in Wang 2020 ALLOCATION CONC: Unclear/Unclear risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Inadequate/Hight risk of bias BLINDING (assessors): Adequate/Low risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias DATA SELECTION (reporting): Adequate/ Low risk of bias ITT: yes FUNDING: did not receive any specific grant

		Levothyroxine: W 38 Control: W 34			

Remarks: In the present report, according to our methodology, we only considered the subgroup analysis using RCT studies for this MA, as well as reported data of individual RCT's. In this MA, when all studies were considered (N=6, including cohort studies) authors found evidence of beneficial effects of LT4 supplementation on the risk of pregnancy loss and preterm birth in women with SCH. The quality of the three retrospective cohort studies was evaluated as high by the authors while issues about confounding factors of these studies have been raised.

The population included in Nazarpour 2017 and Nazarpour 2018 does not correspond to the definition of SCH given in the present MA. Therefore only the results for women population having TSH value > 4 mIU/L were used in this MA.

Both TPO-Ab positive and negative women have been included in the different studies, but in the RCTs, the TPOAb status had been balanced between the intervention and
control group.

The gestational age at initiation of LT4 treatment and the LT4 dosage (some studies using fixed dosages, while others titrated dose to achieve a target TSH level) varied across studies.

The quality of the three RCTs was evaluated as high, with one Jadad score assessed as 5 (Nazarpour 2018) and the other two as 4 (Casey 2017, Nazarpour 2017). The
high quality of RCT was based on their randomization schemes, the use of randomization hiding, participant blinding, and low levels of loss to follow-up.

Author's conclusions: "*this study is the first meta-analysis that shows that LT4 supplementation is associated with a decreased risk of pregnancy loss, preterm birth, and gestational hypertension in women with SCH based on the new 2017 ATA diagnostic criteria. Considering the limited number of available studies included in this meta-analysis and the inevitable heterogeneity, the findings cannot be generalized to patients diagnosed with SCH based on other criteria. The results of the present meta-analysis support the recommendation that LT4 should be administered in pregnant women with SCH and TSH > 4.0mIU/L to reduce the risk of pregnancy loss, preterm birth and gestational hypertension.*"

Additional RCTs:

Levothyroxine versus placebo for depressive symptoms in women with SCH during pregnancy

Study details	n/Population	Comparison	Outcomes		Methodological
Costantine 2020(33) Design: RCT (DB) Duration of follow-up: From 8-20 w gestation, until 1 year post-partum	n= 245 (124 vs 121) Mean age: 27.8 ± 5.6 vs 8.0 ± 6.2 Ethnic group Black 10 vs 9 Hispanic 66 vs 56 White 45 vs 54 Other 3 vs 2 Mean TSH: 4.7 (4.3, 5.9) vs 4.8 (4.2, 5.6) Mean T4: 1.01 (0.95, 1.09) vs 1.03 (0.95, 1.12) <u>Inclusion</u> singleton pregnant women presented for prenatal care between 8 and 20 weeks of gestation and diagnosed with subclinical hypothyroidism	Thyroxine therapy, until delivery Vs Placebo	Efficacy		RANDO: Unclear, no description ALLOCATION CONC: Unclear, no description BLINDING : Participants: yes (DB) Personnel: yes Assessors: Unclear Neonatal data were collected prospectively by study personnel blinded to maternal treatment assignment, and outcomes were carefully ascertained FOLLOW-UP: 110/ 124 vs 110/121 Drop-out and Exclusions: • Described: partially • Balanced across groups: yes ITT: no Baseline score n= 244, third trimester score n= 210 and one year post-partum score n= 213
			Maternal depressive symptom score (CES-D scale, range from 0 to 60, with higher scores indicating greater symptoms of depression) (PO)	Baseline CES-D score 10 [5, 16] vs 9 [4, 15] p value 0.31 NS Third trimester CES-D score 10 [5, 15] vs 10 [5, 17] p value: 0.46 NS	
			1 year post-partum maternal depressive symptom score (CES-D scale, range from 0 to 60, with higher scores indicating greater symptoms of depression) (SO)	6 [3, 11] vs 6 [3, 12] p value: 0.79 NS	
			Percentage of women positive for depression (CES-D score ≥ 16) at the third trimester (SO)	26 (24.3%) vs 31 (30.1%) OR 0.75 (95% CI: 0.41 to 1.37) p value: 0.34 NS	
			Percentage of women positive for depression (CES-D score ≥ 16) 1 year post-partum (SO)	10 (9.7%) vs 16 (15.8%) OR 0.57 (95% CI: 0.25 to 1.3) p value: 0.19 NS	

	SCH: probably defined (like in the parent study)TSH> 4.00 mUI/L and fT4 between 0.86 to 1.90 ng/dl (11 to 24 pmol/L) <u>Exclusion</u> overt thyroid disease, diabetes, autoimmune disease, and those diagnosed with depression or receiving anti-depressant medications				SELECTIVE REPORTING: probably no, registered protocol Unpowered assay due to small sample size. Sponsor: grants from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke.

Remarks:
Most of the women did not have elevated depressive symptoms at baseline. Those with reported clinical diagnosis of depression, other psychiatric disorders, and those receiving anti-depressant medications were excluded. Authors also excluded women who were on antidepressant medications in the postpartum (no significant difference between group).

This study in underpowered and only achieved 82% of planned sample size.

Conclusion from authors: "*We found that at least one quarter of pregnant women with subclinical hypothyroidism screened positive for depression and that antenatal thyroxine treatment was not associated with improved depressive symptoms during pregnancy"*

Levothyroxine versus no treatment in pregnant women with subclinical hypothyroidism

Study details	n/Population	Comparison	Outcomes		Methodological
Mir 2022(31) Design: RCT Duration of follow-up: Inclusion (15 vs 18 w gestation) until 36 w gestation	n= 80 (41 vs 39) Mean age: 28.79 Mean TSH: 3.4 ± 30 mIu/L vs 2.3 ± 36 mIu/L, considered statistically significant (p < 0.0001) Mean T4: 10 ± 2.5 vs 10 ± 2.4 Mean free T4: 1.7 ± 3.1 vs 1.5 ± 2.01 TPO-Ab positivity: 6 vs 9 The control group had a higher percentage of normal pregnancies compared to the intervention group (p = 0.023). <u>Inclusion</u> pregnant women with	Levothyroxine at least 50 μg/day Vs No treatment	Efficacy **Obstetric outcomes** Pregnancy loss Preterm delivery Premature rupture of membrane	Levothyroxine: 3/41 (7.32 %) No treatment:2/39 (5.13%) p value 0.686, NS Levothyroxine: 4/41 No treatment:4/39 p value 0.941, NS Levothyroxine: 3/41 No treatment:1/39 p value 0.330, NS	RANDO: Unclear/unclear risk of bias ALLOCATION CONC: Unclear/unclear risk of bias BLINDING : Participants: no Personnel: no Assessors: no Randomly assigned into two groups, no blinding information FOLLOW-UP: No description for drop out, loss to follow up. 106 women were evaluated, 80 met the inclusion criteria and were randomly assigned into two groups • Described: no • Balanced across groups: unclear ITT: no : Pregnant women who could not complete the follow-up period or did not use levothyroxine properly were excluded. SELECTIVE REPORTING: unclear, no information about predefined protocol.

	TSH levels of 2.5–3.9 mIu/L in the first trimester or 3–4.1 mIu/L in the second and third trimesters, normal thyroid size without any nodules on examination, no history of thyroid surgery or previous administration of radioactive iodine or concomitant nonthyroid disease, and the presence of singleton pregnancy. Including IVF and other cases with medication. Anti-TPO Ab levels of more than 34 IU were defined as a positive test. <u>Exclusion</u> those who developed another disease during pregnancy or had to take thyroid-metabolizing drugs such as corticosteroids and betablockers, were excluded from the study.				Sponsor: not mentioned

Remarks

The treatment and control groups were unbalanced with a statistically significant higher basal TSH level in treatment group, and the control group had a higher percentage of normal pregnancies compared to the intervention group.

The TSH threshold values for definition of SCH and inclusion are narrowed: 2.5–3.9 mIu/L in the first trimester or 3–4.1 mIu/L in the second and third trimesters.

No confidence interval provided but low number of events.

Levothyroxine versus no treatment in pregnant with subclinical hypothyroidism and a history of recurrent pregnancy loss

Study details	n/Population	Comparison	Outcomes		Methodological
Leng 2022(32) Design: RCT (SB) Duration of follow-up: from the first day of diagnosis (<12 weeks of gestation) until delivery or miscarriage. With maximum delay of 1 year	n= 267 (131 vs 136) Mean age: 29.52 ± 3.75 vs 29.58 ± 3.51 Mean TSH: 3.32 ± 0.78 vs 3.37 ± 0.84 In china <u>Inclusion</u> pregnant women negative for TPOAb, having a TSH concentrations between 2.5 µIU/mL and 10.0 µIU/mL in the first trimester, having RPL diagnosis (two or more	Levothyroxine 50 µg orodispersible tablets. Vs No treatment	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear : "randomization was performed in blocks of four, using a computer generated list". But no description about How was the allocation. BLINDING : Participants: no Personnel: yes Assessors: no Only the attending health care provider who did not engage in any phase of the study was informed of the subgroup allocation; the physicians involved in the study were blinded to it.
			Live birth (after 28 w gestation)	Levothyroxine: 92/131 No treatment: 64/136 **p value <.001, SS more live births with levothyroxine**	
			Obstetric outcomes		
			Pregnancy loss (before 28 w gestation)	Levothyroxine: 28/131 No treatment:54/136 **p value <.001, SS more pregnancy loss with no treatment**	
			Ongoing pregnancy	Levothyroxine: 11/131 No treatment: 18/136 p value: 0.204, NS	
			Preterm birth (birth between 28-37 w)	Levothyroxine: 11/131 No treatment: 22/136 p value: 0.054, NS	

after recruitment without pregnancy	consecutive or nonconsecutive pregnancy losses; age between 18 and 39 years at randomization, natural conception. Subclinical hypothyroidism was diagnosed in women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 µIU/mL, and FT4 level in the normal range (0.59–1.25 ng/dL). Women with TPOAb levels > 9 IU/mL were considered TPOAb positive. Pregnant women with baseline TSH levels of 0.1–2.5 µIU/mL, FT4 levels of 0.59–1.25 ng/dL, and TPOAb levels of < 9IU/mL were considered euthyroid. <u>Exclusion</u>		Placental abruption (after 20 w gestation)	Levothyroxine: 1/131 No treatment: 1/136 p value: 0.979, NS	FOLLOW-UP: Unclear: lost to follow-up (n = 178), but this was before randomization. Lost to follow up and exclusion reported in general but not for the different groups. • Described: no • Balanced across groups: unclear ITT: No: For the present analysis, we excluded women lost to follow-up. SELECTIVE REPORTING: Unclear, registered protocol-china, why no SCH TPO+ women? Sponsor: grants from National Natural Science Foundation of China and Suzhou Health Project for Critical Diseases.
			Gestational diabetes mellitus	Levothyroxine: 8/131 No treatment: 1/136 **p value: 0.015, SS more gestational diabetes with levothyroxine**	
			Gestational hypertension (systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg), no proteinuria	Levothyroxine: 6/131 No treatment: 3/136 p value: 0.283, NS	
			Preeclampsia	Levothyroxine: 0/131 No treatment: 0/136	
			Premature rupture of membrane	Levothyroxine: 0/131 No treatment: 0/136	
			Neonatal outcomes		
			Small for gestational age birth (with a weight below the 10th percentile for the corresponding gestational age.)	Levothyroxine: 8/131 No treatment: 3/136 p value: 0.109, NS	
			Macrosomia (birth weight > 4000 g.)	Levothyroxine: 0/131 No treatment: 3/136 p value: 0.087, NS	
			Asphyxia neonatorum (1-min Apgar score <7)	Levothyroxine: 0/131 No treatment: 2/136 p value: 0.164, NS	

	Women with hyperthyroidism, overt hypothyroidism, abnormal parental karyotype, or uterine cavity abnormalities, and those were twin pregnancy, inability to conceive naturally (as confirmed by urinary pregnancy tests) within 1 year of recruitment or before the end of the randomization period of the trial, whichever was earlier; antiphospholipid syndrome, other recognized thrombophilic conditions, or uterine cavity abnormalities; abnormal parental karyotype; other identifiable causes of RPL, such as diabetes or systemic lupus erythematosus; and any contraindications to L-T4 use.				

Levothyroxine versus no treatment in pregnant women with subclinical hypothyroidism without a history of recurrent pregnancy loss

Study details	n/Population	Comparison	Outcomes		Methodological
Leng 2022(32) Design: RCT (SB) Duration of follow-up: From the first day of diagnosis (<12 weeks of gestation) until delivery or miscarriage. With maximum delay of 1 year after recruitment	n= 227 (112 vs 115) Mean age: 28.62 ± 3.52 vs 28.53 ± 3.64 Mean TSH: 3.74 ± 1.28 vs 3.73 ± 1.24 In china <u>Inclusion</u> Normal pregnant women negative for TPO-Ab and with TSH concentrations between 2.5 µIU/mL and below 10.0 µIU/mL in the first trimester, with age between 18 and 39 years at randomization and natural conception. Subclinical	Levothyroxine 50 µg orodispersible tablets. Vs No treatment	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear : "randomization was performed in blocks of four, using a computer generated list". But no description about How was the allocation. BLINDING : Participants: no Personnel: yes Assessors: no Only the attending health care provider who did not engage in any phase of the study was informed of the subgroup allocation; the physicians involved in the study were blinded to it. FOLLOW-UP: Unclear: lost to follow-up (n = 178), but this was before randomization. Lost to follow up and exclusion reported in general but not for the different groups.
			Live birth (after 28 w gestation)	Levothyroxine: 78/112 No treatment: 71/115 p value: 0.210, NS	
			Obstetric outcomes		
			Pregnancy loss (before 28 w gestation)	Levothyroxine: 24/112 No treatment: 22/115 p value: 0.667, NS	
			Ongoing pregnancy	Levothyroxine: 10/112 No treatment: 22/115 **p value: 0.027, SS more ongoing pregnancy with no treatment**	
			Preterm birth (birth between 28-37 w)	Levothyroxine: 2/112 No treatment: 7/115 p value: 0.097, NS	
			Placental abruption (after 20 w gestation)	Levothyroxine: 0/112 No treatment: 1/115 p value: 0.323, NS	
			Gestational diabetes mellitus	Levothyroxine: 4/112 No treatment: 7/115 p value: 0.378, NS	
			Gestational hypertension (systolic blood pressure > 140 mmHg and/or diastolic	Levothyroxine: 5/112 No treatment: 3/115 p value: 0.448, NS	

without pregnancy	hypothyroidism was diagnosed in women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 µIU/mL, and FT4 level in the normal range (0.59–1.25 ng/dL). Women with TPOAb levels >9 IU/mL were considered TPOAb positive. Pregnant women with baseline TSH levels of 0.1–2.5 µIU/mL, FT4 levels of 0.59–1.25 ng/dL, and TPOAb levels of < 9 IU/mL were considered euthyroid. <u>Exclusion</u> Women with hyperthyroidism, overt hypothyroidism, abnormal parental karyotype, or uterine		blood pressure > 90 mmHg, no proteinuria)		• Described: no • Balanced across groups: unclear ITT: No : For the present analysis, we excluded women lost to follow up SELECTIVE REPORTING: Unclear, registered protocol-china, why no SCH TPO-Ab positive women? Sponsor: grants from National Natural Science Foundation of China and Suzhou Health Project for Critical Diseases.
			Preeclampsia	Levothyroxine: 1/112 No treatment: 2/115 p value: 0.577, NS	
			Premature rupture of membrane	Levothyroxine: 6/112 No treatment: 1/115 p value: 0.051, NS	
			Neonatal outcomes		
			Small for gestational age birth (with a weight below the 10th percentile for the corresponding gestational age)	Levothyroxine: 1/112 No treatment: 2/115 p value: 0.577, NS	
			Macrosomia (birth weight > 4000 g)	Levothyroxine: 2/112 No treatment: 7/115 p value: 0.546, NS	
			Asphyxia neonatorum (1-min Apgar score <7)	Levothyroxine: 0/112 No treatment: 1/115 p value: 0.323, NS	

	cavity abnormalities, and those were twin pregnancy, inability to conceive naturally (as confirmed by urinary pregnancy tests) within 1 year of recruitment or before the end of the randomization period of the trial, whichever was earlier; antiphospholipid syndrome, other recognized thrombophilic conditions, or uterine cavity abnormalities; abnormal parental karyotype; other identifiable causes of RPL, such as diabetes or systemic lupus erythematosus; and any contraindications to L-T4 use.				

17.2 Levothyroxine versus placebo or no treatment for pregnancy outcomes in women with TPO autoimmunity without overt thyroid dysfunction

Meta-analysis: Wang 2020(34), Fertility and Sterility, Effect of levothyroxine on pregnancy outcomes in women with thyroid autoimmunity: a systematic review with meta-analysis of randomized controlled trials.

Inclusion criteria: Population: women with thyroid autoimmunity (defined as the presence of TPO antibody, that is, TPOantibody and/or thyroglobulin - antibody) without overt thyroid dysfunction (no selection for participants with thyroid dysfunction) "We enrolled trials that included data presenting pregnancy outcomes with good comparability in terms of gestational age."
Study design: randomized controlled trials.

Excluded: case reports, case series, and observational studies.

Search strategy: "We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to July 30, 2019, without any language restrictions. We also checked the authors' files and forward and backward citations of retrieved studies for further relevant studies. We searched trial registries on the World Health Organization International Trials Registry Platform for ongoing studies or the availability of completed studies with reported results."

Assessment of quality of included trials: yes, GRADE/Cochrane Collaboration risk-of bias tool

Other methodological remarks:
As reported by authors: analysis done on an ITT basis for all outcomes
Random effect model was used. Subgroup analyses where performed for live birth and did not detect any beneficial effect in any specific subgroups by the following variables: maternal age, baseline TSH concentration, baseline TPO antibody concentration, body mass index, use of assisted conception, or previous miscarriage.

Ref	Comparison	N/n	Outcomes	Result
Wang 2020(34) Design: MA Search date:	Levothyroxine Vs Placebo or no treatment	N= 3 n= 1626 (Negro 2005, Wang 2017, Dhillon-Smith 2019	Live birth (after 24 weeks of gestation) (PO)	287/813 (35.3%) vs 285/813 (35.0%) Absolute difference (per 1000): 0(−42 to 53) RR: 1.00 (95% CI: 0.88 to 1.15) NS I^2: 8%

(07-2019)		**Obstetric outcomes (SO)**		
		N= 6 n= 2265 in total 1427 analysed (confirmed pregnancy) (Negro 2005, Negro 2006, Negro 2016, Nazarpour 2017, Wang 2017, Dhillon-Smith 2019)	Miscarriage (absence of fetal heartbeat on ultrasonography or spontaneous loss of pregnancy before 24 weeks of gestation)	121/708 (17.1%) vs 143/719 (19.9%) Absolute difference (per 1000): -26 (−60 to 14) RR: 0.87 (95% CI: 0.70 to1.07) NS I^2: 0%
		N= 5 n= 2179 in total 1354 analysed (live birth or pregnant women) (Negro 2006, Negro 2016, Nazarpour 2017, Wang 2017, Dhillon-Smith 2019)	Preterm birth (live neonate deliveries before 37 weeks of gestation)	69/672 (10.2%) vs 96/682 (14%) Absolute difference (per 1000): -44 (−77 to 8) RR: 0.69 (95% CI: 0.45 to 1.06) NS I^2: 45%

		N= 3 n= 1626 in total 1226 analysed (total or confirmed pregnancy) (Negro 2005, Wang 2017, Dhillon-Smith 2019)	Clinical pregnancy (intrauterine pregnancy diagnosed by the presence of a gestational sac on ultrasound scan)	368/606 vs 382/617 Absolute difference (per 1000): -12 (-43 to 25) RR: 0.98 (95%CI: 0.93 to 1.04) NS I^2: 0%
		N= 2 n= 1540 in total 1140 analysed (total or confirmed pregnancy) (Wang 2017, Dhillon-Smith 2019)	Ectopic pregnancy (defined as an embryo implanted outside the uterine cavity)	3/566 vs 11/574 Absolute difference (per 1000): -13 (-18 to 10) RR: 0.34 (95%CI: 0.08 to 1.53) NS I^2: 18%
		Neonatal outcomes (SO)		
		N= 2 n= 1071 in total 493 analysed (total or live birth) (Nazarpour 2017, Dhillon-Smith 2019)	Neonatal admission in intensive care unit	29/248 vs 36/245 Absolute difference (per 1000): -75 (−135 to 304) RR: 0.49 (0.08 to 3.07) NS I^2: 83 %
		N= 2	Birth weight	Mean difference: -0.02 (95%CI: -0.12 to 0.08)

		n= 1071 in total 493 analysed (total or live birth) (Nazarpour 2017, Dhillon-Smith 2019)		NS I^2: 0%

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as judged by Wang 2020)
Negro 2005(35) RCT	86	TPO-Ab positive (>100 IU/mL) infertile women undergoing assisted reproduction technologies (IVF/ICSI) Included thyroid function: TSH 0.27–4.2 mIU/L and FT4 12–33.5 pmol/L Levothyroxine: W 43, mean age 29.2 years, median TSH 1.9 mIU/L Placebo: W 43, mean age 30.1 years, median TSH 1.7 mIU/L	1 month before assisted reproduction technologies, throughout pregnancy	Levothyroxine 1 µg/kg/d, 1 month before and throughout pregnancy Vs Placebo	ALLOCATION CONC: Adequate/Low risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Adequate/Low risk of bias BLINDING (assessors): Adequate/Low risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias DATA SELECTION (reporting): Unclear/Unclear risk of bias OTHER: Unclear risk of bias ITT: unclear: Miscarriage is reported in pregnant women

					only and not in all included women FUNDING: not reported
Negro 2006(36) RCT	115	TPO-Ab positive (>100 IU/mL) Caucasian pregnant women Included thyroid function: TSH 0.27–4.2 mIU/L and FT4 12–33.5 pmol/L Levothyroxine: W 57, mean age 30 years, median TSH 1.6 mIU/L Control: W 58, mean age 30 years, median TSH 1.7 mIU/L	Until 3 days after delivery	Levothyroxine 0.5 µg/kg/d for TSH < 1.0 mIU/L, 0.75 µg/kg/d for TSH 1.0–2.0 mIU/L, 1 µg/kg/d for TSH > 2.0 mIU/L or TPO-Ab exceeding 1,500 IU/mL, throughout pregnancy Vs No treatment	ALLOCATION CONC: Adequate/Low risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Inadequate/High risk of bias BLINDING (assessors): Unclear/Unclear risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias DATA SELECTION (reporting): Unclear/Unclear risk of bias ITT: yes, FUNDING: not mentioned
Negro 2016(37) RCT	393	TPO-Ab positive (≥16 IU/mL) pregnant euthyroid women in Southern Italy Included thyroid function: TSH 0.50-2.5 mIU/L Levothyroxine: W 198, mean age 28.9 years, median TSH 1.42 mIU/L Control: W 195, mean age 29.9 years, median TSH 1.37 mIU/L	Until delivery	Levothyroxine 0.5 µg/kg/d for TSH 0.5–1.5 mIU/L, 1.0 µg/kg/d for TSH 1.5–2.5 mIU/L In the second trimester, if the TSH > 3.0 or < 0.5 mIU/L, LT4 was increased or decreased by 12.5 µg/kg/d respectively. Vs No treatment In the control group, levothyroxine was given when	ALLOCATION CONC: Adequate/Low risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Inadequate/High risk of bias BLINDING (assessors): Unclear/Unclear risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias DATA SELECTION (reporting): Unclear/Unclear risk of bias ITT: no A total of 413 agreed to participate and were

				TSH > 3.0 mIU/L in the second trimester, throughout pregnancy	randomized to group A (n 207) or group B (n 206). Nine women were lost to follow-up, from group A, 11 women, from group B, and 3 women from group C, resulting in 198 women in group A, 195 women in group B, and 197 women in group C. FUNDING: not mentioned
Nazarpour 2017(30)SB-RCT	131 in total (used in Wang 2020 MA) 72 included in the Ding 2021 MA with TSH >4.0 mIU/L	TPO-Ab positive (≥50 IU/mL), pregnant, euthyroid/subclinical hypothyroid women from Iran. Included thyroid function: TSH 0.1–10 mIU/L and FT4I 1–4.5 Levothyroxine: W 65, mean age 26.6 years, median TSH 3.7 mIU/L Control: W 66, mean age 27.7 years, median TSH 3.2 mIU/L Excluded: twin pregnancies, hyperthyroidism or overt hypothyroidism and TPOAb negative subclinical hypothyroid women For Ding 2021: pregnant, subclinical hypothyroid women with SCH defined as TSH >4.0 mIU/L -TPOAb positive pregnant women Levothyroxine: W 38 Control: W 34	Until delivery	Levothyroxine 0.5 μg/kg/d for TSH < 1.0 mIU/L, 0.75 μg/kg/d for TSH 1.0–2.0 mIU/L, 1 μg/kg/d for TSH > 2.0 mIU/L or TPO-Ab exceeding 1,500 IU/mL, throughout pregnancy Vs No treatment gestational age at LT4 initiation: 10.8±4 weeks (reported for the population used in Ding 2021)	ALLOCATION CONC: Unclear/Unclear risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Inadequate/Hight risk of bias BLINDING (assessors): Adequate/Low risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias DATA SELECTION (reporting): Adequate/ Low risk of bias ITT: yes FUNDING: did not receive any specific grant

Wang 2017(38) RCT	600	TPO-Ab positive (≥60 IU/mL), infertile, euthyroid women in China treated for infertility (first or second fresh in vitro fertilization and embryo transfer) Normal included thyroid function: TSH 0.50-4.78 mIU/L Levothyroxine: W 300, mean age 31.3 years, median TSH 2.94 mIU/L Control: W 300, mean age 31.7 years, median TSH 2.12 mIU/L Excluded: Women taking a thyroid hormone or antithyroid medication or who had undergone thyroid surgery or radioiodine	Until delivery	Levothyroxine 25 µg/ d for TSH < 2.5 mIU/L, 50 µg/ d for TSH ≥ 2.5 mIU/mL dose was titrated to keep the TSH level within 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester, and 0.3–3.0 mIU/L in the third trimester, 2–4 w before the controlled ovarian hyperstimulation and throughout pregnancy Vs No treatment	ALLOCATION CONC: Adequate/Low risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Inadequate/High risk of bias BLINDING (assessors): Inadequate/High risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias DATA SELECTION (reporting): Adequate/Low risk of bias ITT: unclear: miscarriage rate was calculated among women who became pregnant and not total include women. Preterm births were calculated only among the number of live births FUNDING: National Key Technology R&D Program and the Chinese National 973 Program, both from the Ministry of Science and Technology of China.
Dhillon-Smith 2019(39) RCT	940	TPO-Ab positive (thresholds varied in centers), infertile/miscarriage, trying to conceive (either naturally or through assisted conception) euthyroid women in the United Kingdom	Until delivery	Levothyroxine 50 µg/d, before and throughout pregnancy Vs Placebo	ALLOCATION CONC: Adequate/Low risk of bias RANDO: Adequate/Low risk of bias BLINDING (participants/personnel): Adequate/Low risk of bias

		Included thyroid function: TSH 0.44-3.63 mIU/L and FT4 10.0-21.0 pmol/L Levothyroxine: W 470, mean age 32.5 years, median TSH 2.10 mIU/L Placebo: W 470, mean age 32.7 years, median TSH 2.01 mIU/L			BLINDING (assessors): Adequate/Low risk of bias FOLLOW-UP (attrition): Adequate/Low risk of bias DATA SELECTION (reporting): Adequate/Low risk of bias ITT: unclear: yes for the primary outcome (live birth). For maternal pregnancy outcomes, the analysis population consisted of all women who had a confirmed pregnancy. Neonatal outcomes are expressed among women with live births. FUNDING: Supported by the United Kingdom NIHR efficacy and mechanism evaluation program

Remarks:

Women in 3 trials Negro 2005, Wang 2017 and Dhillon-Smith 2019 had a history of infertility and underwent assisted reproduction technologies. In these studies, intervention was started before conception. For these 3 studies, the "live birth" outcome was analysed in ITT and the population consisted of all participants who underwent randomization. However for the obstetric outcomes the analysed population consisted of all women who had a confirmed pregnancy or live birth. For Dhillon-Smith 2019, neonatal outcomes were reported among women with live births.

Data for live birth and clinical pregnancy only included these 3 studies and data on ectopic pregnancy only included Wang 2017 and Dhillon-Smith 2019. Thus a large part of the data about levothyroxine in pregnancy comes from a population of women undergoing assisted reproductive techniques.

One trial, Nazarpour 2017, enrolled euthyroid or subclinical women, with normal and mildly increased TSH (upper TSH limit of 10 mUI/L, median TSH in LT4 group of 3.7 mIU/L). As commented by the authors of the systematic review, the other trials enrolled women with normal thyroid function determined by TSH and thyroxine levels. However 4 studies, Negro 2005, Negro 2006, Wang 2017 and Dhillon-Smith 2019 included women with a upper TSH limit superior to the 2.5mIU/L first trimester limit proposed in some guidelines (BTA 2016 and ETA 2014).

One study, Negro 2016, only included euthyroid women using a TSH upper limit of 2.5 mIU/L (median TSH in LT4 group of 1.42 mIU/L). **In Negro 2016, levothyroxine was given in the control group**, when TSH > 3.0 mIU/L in the second or third trimester; dosages were maintained throughout gestation, these women were included in the per protocol analysis of the data.
A total of 49% (81/166) of women in group B (untreated) required levothyroxine therapy as per protocol with 19/166 (11.4%) beginning levothyroxine in the second trimester and 62/147 (42%) beginning in the third trimester.

In Wang 2017, the baseline characteristics were comparable between treated and control groups except for their serum TSH levels.

One trial, Dhillon-Smith 2019, had a low risk of bias, one trial, Negro 2005, had an unclear risk, and four trials Negro 2006, Negro 2016, Nazarpour 2017, Wang 2017 had a high risk. The main bias was due to the lack of blinding to intervention.

Author's conclusions: "*High to moderate-quality evidence showed that in women with thyroid autoimmunity, the use of levothyroxine was not associated with any beneficial effect on pregnancy outcomes, as determined by live birth or miscarriage rates, and neonatal outcomes. This new evidence should lead us to reconsider current recommendations."*

Additional RCTs:

Levothyroxine versus no treatment in TPO-Ab positive pregnant women without a history of recurrent pregnancy loss

Study details	n/Population	Comparison	Outcomes		Methodological
Leng 2022(32)	n= 81 (41 vs 40)	Levothyroxine	Efficacy		RANDO:
			Live birth (after 28 w	Levothyroxine: 34/41	Adequate
Design:	Mean age:		gestation)	No treatment: 35/40	ALLOCATION CONC:

RCT (SB) Duration of follow-up: From the first day of diagnosis (<12 weeks of gestation) until delivery or miscarriage. With maximum delay of 1 year after recruitment without pregnancy	28.64 ± 3.02 vs 28.40 ± 2.57 Mean TSH: 1.21 ± 0.72 vs 1.34 ± 0.71 In china <u>Inclusion</u> Normal pregnant women positive for TPOAb with normal TSH reference range in the first trimester, with age between 18 and 39 years at randomization and natural conception. Subclinical hypothyroidism was diagnosed in women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 µIU/mL, and FT4 level in the normal range (0.59–1.25 ng/dL).	50 µg orodispersible tablets. Vs No treatment		p value: 0.562, NS	Unclear : "randomization was performed in blocks of four, using a computer generated list". But no description about How was the allocation. BLINDING : Participants: no Personnel: yes Assessors: no Only the attending health care provider who did not engage in any phase of the study was informed of the subgroup allocation; the physicians involved in the study were blinded to it. FOLLOW-UP: Unclear: lost to follow-up (n = 178), but this was before randomization. Lost to follow up and exclusion reported in general but not for the different groups. • Described: no • Balanced across groups: unclear ITT: No : For the present analysis, we excluded women lost to follow-up SELECTIVE REPORTING:
			Obstetric outcomes		
			Pregnancy losses (before 28 w gestation)	Levothyroxine: 4/41 No treatment: 3/40 p value: 0.718, NS	
			Ongoing pregnancy	Levothyroxine: 3/41 No treatment: 2/40 p value: 0.665, NS	
			Preterm birth (birth between 28-37 w)	Levothyroxine: 2/41 No treatment: 6/40 p value: 0.127, NS	
			Placental abruption (after 20 week gestation)	Levothyroxine: 0/41 No treatment: 0/40	
			Gestational diabetes mellitus	Levothyroxine: 2/41 No treatment: 3/40 p value: 0.624, NS	
			Gestational hypertension (systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, no proteinuria)	Levothyroxine: 2/41 No treatment: 4/40 p value: 0.379, NS	
			Preeclampsia	Levothyroxine: 0/41 No treatment: 0/40	
			Premature rupture of membrane	Levothyroxine: 0/41 No treatment: 2/40 p value: 0.147, NS	
			Neonatal outcomes		
			Small for gestational age birth (with a weight below the 10th percentile for the	Levothyroxine: 2/41 No treatment: 2/40 p value: 0.980, NS	

	Women with TPOAb levels >9 IU/mL were Considered TPOAb positive. Pregnant women with baseline TSH levels of 0.1–2.5 µIU/mL, FT4 levels of 0.59–1.25 ng/dL, and TPOAb levels of < 9 IU/mL were considered euthyroid. <u>Exclusion</u> Women with hyperthyroidism, overt hypothyroidism, abnormal parental karyotype, or uterine cavity abnormalities, and those were twin pregnancy, inability to conceive naturally (as confirmed by urinary pregnancy tests) within 1 year of recruitment or before the end of the randomization period of the trial, whichever was earlier; antiphospholipid syndrome, other		corresponding gestational age)		Unclear, registered protocol-china, why no SCH TPO+ women? Sponsor: grants from National Natural Science Foundation of China and Suzhou Health Project for Critical Diseases.
			Macrosomia (birth weight > 4000 g)	Levothyroxine: 3/41 No treatment: 1/40 p value: 0.317, NS	
			Asphyxia neonatorum (1-min Apgar score <7)	Levothyroxine: 0/41 No treatment: 1/40 p value: 0.308, NS	

	recognized thrombophilic conditions, or uterine cavity abnormalities; abnormal parental karyotype; other identifiable causes of RPL, such as diabetes or systemic lupus erythematosus; and any contraindications to L-T4 use.				

Remarks

This was a randomized clinical trial in which a 2151 population of pregnant women (875 normal pregnant women, 861 pregnant women with a history of recurrent pregnancy loss(RPL)) was screened for thyroid dysfunction. Population was divided in pregnant women who were negative for TPO-Ab and had SCH in the first trimester (227) women who were positive for TPO-Ab and euthyroid (81), RPL women who were negative for TPO-Ab and have SCH (267) and RPL women who were positive for TPO-Ab and euthyroid (83). While exclusion criteria have been reported, nothing is reported about women with SCH and positive TPO-Ab.

Ongoing pregnancy outcome was not prespecified. While no information was provided about the definition of this outcome, this might represent ongoing pregnancies at the time that outcomes were being measured. Disbalance in this outcome between intervention and control groups, as in the group of pregnant with SCH without recurrent pregnancy loss could impact other outcomes as data is not yet available on the upcoming births.

Author conclusions: "*Treatment with L-T4 decreased the risk of pregnancy loss and increased the live birth rate in RPL pregnant women who were positive for TPO-Ab or subclinical hypothyroidism. The replacement therapy with L-T4 was not beneficial in average pregnant women with TPO-Ab or SCH.*"

Levothyroxine versus no treatment in TPO Ab positive pregnant women and with a history of recurrent pregnancy loss

Study details	n/Population	Comparison	Outcomes		Methodological
Leng 2022(32) Design: RCT (SB) Duration of follow-up: From the first day of diagnosis (<12 weeks of gestation) until delivery or miscarriage. With maximum delay of 1 year after recruitment without pregnancy	n= 83 (42 vs 41) Mean age: 28.72 ± 3.74 vs 29.64 ± 3.98 Mean TSH: 1.46 ± 0.72 vs 1.23 ± 0.74 In china <u>Inclusion</u> Pregnant women positive for TPOAb with a normal TSH reference range in the first trimester (0.1–2.5 µIU/mL), having RPL diagnosis (two or more consecutive or nonconsecutive pregnancy losses), age between 18 and 39 years at randomization, natural conception. Subclinical	Levothyroxine 50 µg orodispersible tablets. Vs No treatment	Efficacy		RANDO: Adequate ALLOCATION CONC: Unclear : "randomization was performed in blocks of four, using a computer generated list". But no description about How was the allocation. BLINDING : Participants: no Personnel: yes Assessors: no Only the attending health care provider who did not engage in any phase of the study was informed of the subgroup allocation; the physicians involved in the study were blinded to it. FOLLOW-UP: Unclear: lost to follow-up (n = 178), but this was before randomization. Lost to follow up and exclusion reported in general but not for the different groups. • Described: no • Balanced across groups: unclear
			Live birth (after 28 w gestation)	Levothyroxine: 38/42 No treatment: 28/41 **p value: 0.012, SS more live births with levothyroxine**	
			Obstetric outcomes		
			Pregnancy loss (before 28 w gestation)	Levothyroxine: 3/42 No treatment: 11/41 **p value: 0.017, SS more pregnancy loss with no treatment**	
			Ongoing pregnancy	Levothyroxine: 1/42 No treatment: 2/41 p value: 0.542, NS	
			Preterm birth (birth between 28-37 w)	Levothyroxine: 3/42 No treatment: 3/41 p value: 0.976, NS	
			Placental abruption (after 20 w gestation)	Levothyroxine: 0/42 No treatment: 0/41	
			Gestational diabetes mellitus	Levothyroxine: 4/42 No treatment: 1/41 p value: 0.175, NS	
			Gestational hypertension (systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, no proteinuria)	Levothyroxine: 0/42 No treatment: 2/41 p value: 0.147, NS	

	hypothyroidism was diagnosed in women with TSH concentrations greater than the pregnancy-specific reference range and below 10.0 µIU/mL, and FT4 level in the normal range (0.59–1.25 ng/dL). Women with TPOAb levels > 9 IU/mL were considered TPOAb positive. Pregnant women with baseline TSH levels of 0.1–2.5 µIU/mL, FT4 levels of 0.59–1.25 ng/dL, and TPOAb levels of < 9 IU/mL were considered euthyroid. <u>Exclusion</u> Women diagnosed with hyperthyroidism, overt hypothyroidism, abnormal parental karyotype, or uterine cavity abnormalities, twin pregnancy,		Preeclampsia	Levothyroxine: 0/42 No treatment: 1/41 p value: 0.309, NS	ITT: No : For the present analysis, we excluded women lost to follow-up Sponsor: grants from National Natural Science Foundation of China and Suzhou Health Project for Critical Diseases.
			Premature rupture of membrane	Levothyroxine: 1/42 No treatment: 0/41 p value: 0.320, NS	
			Neonatal outcomes		
			Small for gestational age birth (with a weight below the 10th percentile for the corresponding gestational age.)	Levothyroxine: 3/42 No treatment: 0/41 p value: 0.081, NS	
			Macrosomia (birth weight > 4000 g)	Levothyroxine: 0/42 No treatment: 1/41 p value: 0.309, NS	
			Asphyxia neonatorum (1-min Apgar score < 7)	Levothyroxine: 0/42 No treatment: 0/41	

	inability to conceive naturally within 1 year of recruitment or before the end of the randomization period of the trial, whichever was earlier; antiphospholipid syndrome, other recognized thrombophilic conditions, or uterine cavity abnormalities; abnormal parental karyotype; other identifiable causes of RPL such as diabetes or systemic lupus erythematosus; and any contraindications to L-T4 use.				

Levothyroxine versus placebo in euthyroid TPO positive women with recurrent miscarriage

Study details	n/Population	Comparison	Outcomes		Methodological
Ref	n= 187	Levothyroxine	Efficacy		RANDO:
Van Dijk 2022 (40)	(94 vs 93)	If TSH <1·0 mU/L: 0·5 µg/kg	Live Birth (after 24 w gestation) (PO)	Levothyroxine: 47/94 (50%) Placebo: 45/93 (48%) RR (95% CI): 1.03 (0.77 to 1.38) NS	Adequate/Low risk of bias ALLOCATION CONC: Adequate/Low risk of bias BLINDING : Participants: yes
	Mean age:	if TSH between			
Design:	34,9 (4.2) vs 33.7 (4.7)	1·0–2·5 mU/L:			
DB-RCT		0·75 µg/kg	**Obstetric outcomes**		

Duration of follow-up: before conception until 28 d post-delivery or 2-year use of medication without pregnancy	Mean TSH: 2.10 (1.40 - 3.11) vs 2.00 (1.36 – 2.70) TPO-Ab 225 (99 – 566) vs 178 (96 – 662) From 15 hospitals. 13 hospitals were in the Netherlands, 1 in Belgium, 1 in Denmark. <u>Inclusion</u> Women 18-42 with two or more pregnancy losses (before 20 weeks gestation) having TSH concentration within the centres' reference range and positive for TPO-Ab (according to institutional reference range). Women trying to conceive both with and without the use of assisted reproductive technology were included.	if TSH > 2·5 mU/L: 1·0 µg/kg, before conception and until delivery Vs Placebo	Pregnancy (SO)	Levothyroxine: 69/94 (73%) Placebo: 73/93 (78%) RR (95% CI): 0.94 (0.81 to 1.12) NS	Personnel: yes Assessors: yes FOLLOW-UP: 69/94 and 64/93 in total yes 9% of the 93 control women developed subclinical hypothyroidism during the study period and discontinued. In the levothyroxine group, 1% of the 94 women developed subclinical hypothyroidism Described: yes Balanced across groups not for development of SCH ITT: Yes for primary outcome. For secondary outcomes: a preplanned per-protocol analysis of women that completed the study was done. For secondary outcomes, crude and adjusted risk ratios were calculated. SELECTIVE REPORTING: Unclear reported outcomes not all the predefined one but all not significant Sponsor: Dutch Organization for Health Research and Development and a Fonds NutsOhra, Dutch Patient
			Pregnancy loss at < 20 w (SO)	Levothyroxine: 16/69 (68%) Placebo: 24/73 (33%) RR (95% CI): 0.71 (0.41 to 1.21) NS	
			Ongoing pregnancy at 12 w n= 142 analysed (total pregnancy)(SO)	Levothyroxine: 49/69 (68%) Placebo: 24/73 (63%) RR (95% CI): 1.08 (0.85 to 1.37) NS	
			Ectopic pregnancy n= 142 analysed (total pregnancy)(SO)	Levothyroxine: 2/69 (3%) Placebo: 3/73 (4%) RR (95% CI): 0.71 (0.12 to 4.09) NS	
			Pregnancy of unknown location n= 142 analysed (total pregnancy) (SO)	Levothyroxine: 4/69 (6%) Placebo: 1/73 (1%) RR (95% CI): 4.23 (0.48 to 36.93) NS	
			Preterm birth (< 37 w) n= 142 analysed (total pregnancy) (SO)	Levothyroxine: 4/69 (6%) Placebo: 3/73 (4%) RR (95% CI): 1.41 (0.33 to 6.08) NS	
			Neonatal outcomes		
			Survival 28 days of neonatal life n= 142 analysed (total pregnancy)(SO)	Levothyroxine: 49/69 (68%) Placebo: 45/73 (62%) RR (95% CI): 1.11 (0.87 to 1.41) NS	
			Safety		
			Serious adverse event (SO)	Levothyroxine: 7/94 (7%)	

	For TSH, the most commonly used reference interval is 0.5–5.0 mIU/L. Most commonly used cut-off levels for TPO antibodies are 60 kIU/L or 100 kIU/L. <u>Exclusion</u> antiphospholipid syndrome (lupus anticoagulant, anticardiolipin IgG or IgM antibodies, or β2-Glycoprotein-I IgG or IgM antibodies), other autoimmune diseases, thyroid disease, or contraindications for levothyroxine use. Pregnancy loss did not include the loss of a biochemical pregnancy (ie, pregnancy confirmed through elevated human chorionic gonadotropin concentrations, but not on ultrasound examination).			Placebo: 7/93 (8%) RR (95% CI): 1.00 (0.92 to 1.09) NS	Organization of Thyroid Disorders, the Jan Dekkerstichting and Dr Ludgardine Bouwmanstichting, personal donation via the Dutch Patient Organization of Thyroid Disorders.

Remarks:

The study size of this study is low which could mean that this study is underpowered. Detection of a difference of 5% in live birth rate would require inclusion of more than 3000 women. However recruitment to this type of trial is extremely difficult due to the relative rarity of women with recurrent pregnancy loss who are TPO-Ab positive with normal thyroid function tests.

Women trying to conceive both with and without the use of assisted reproductive technology were included.

According to the authors in most centers women with normal TSH concentration was determined a reference interval of 0.5–5.0 mIU/L. The upper limit is superior to the 2.5mIU/L first trimester limit proposed in some guidelines (BTA 2016 and ETA 2014). Therefore depending on the considered thresholds to define SCH, some SCH women have been included in this study.

There might be some discrepancies between intervention and control groups regarding baseline TPO-Ab values.

Exclusion due to development of SCH could differ between intervention and control groups that might result in unbalanced groups

The use of different assays for TPO-Ab and TSH concentrations in various centers is a potential limitation of our study but it can be regarded as a reflection of daily practice.

SO at the exception of pregnancy rate and serious adverse event were reported among total pregnancies and not total participants.

Author's conclusion: "*no significant differences in live birth rate, no evidence of a difference in any of the secondary outcomes. On the basis of our findings, we do not advise routine use of levothyroxine in women with recurrent pregnancy loss who have normal thyroid function and are positive for TPO-Ab"*

18 Appendix. Evidence tables. Infertility

18.1 Levothyroxine versus placebo for subfertile women with euthyroid autoimmune thyroid disease

Meta-analysis: Akhtar 2019(41) "Levothyroxine versus placebo for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism"

Inclusion criteria: women undergoing assisted reproduction treatment, meaning both in vitro fertilisation and intracytoplasmic sperm injection, with a **history of subfertility** and with **subclinical hypothyroidism or with euthyroid autoimmune thyroid disease**. RCTs compared thyroxine (levothyroxine) with either placebo or
no treatment.

subclinical hypothyroidism is defined as: biochemical evidence of thyroid hormone deficiency in women with few or no apparent symptoms. It is diagnosed by an elevated TSH concentration with a normal concentration of FT4.

Euthyroid autoimmune thyroid disease is defined as: normal TSH and FT4 concentrations with the presence of thyroid autoantibodies.

Exclusion criteria: women with a previously known clinical hypothyroidism or already taking thyroxine or tri-iodothyronine; women having stimulated and unstimulated intrauterine insemination (IUI) or natural conception.

Search strategy: Cochrane Gynaecology and Fertility (CGF) Group specialised register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL and two trials registers were searched from inception to 8 April 2019.

Assessment of quality of included trials: yes

Other methodological remarks: :

-Author downgraded GRADE two levels for imprecision (broad confidence intervals); we do not use the same criteria for downgrading because of broad confidence intervals.
-1 RCT (Dhillon-Smith 2019) was excluded from this Cochrane review because it included women with spontaneous conception. As this was not an exclusion criterium in our review, we will report Dhillon-Smith 2019 separately.

Ref	Comparison	N/n	Outcomes	Result
Akhtar 2019 Design: SR + MA Search date: (april 2019)	Levothyroxine vs placebo or no treatment	N= 2 n= 686 (Negro 2005, Wang 2017)	Live birth rate – in euthyroid women with anti-TPO antibodies	Levothyroxine 111/343 No levothyroxine 107/343 RR: 1,04 (95%CI 0,83 to 1,29) NS
		N= 2 n= 686 (Negro 2005, Wang 2017)	Miscarriage – in euthyroid women with anti-TPO antibodies	Levothyroxine 19/343 No levothyroxine 23/343 RR: 0,83 (95%CI 0,47 to 1,46) NS
		N= 2 n= 686 (Negro 2005, Wang 2017)	Clinical pregnancy rate – in euthyroid women with anti-TPO antibodies	Levothyroxine 131/343 No levothyroxine 134/343 RR: 0,98 (95%CI 0,81 to 1,18) NS
		N= 1 n= 300 (Wang 2017)	Adverse events including maternal pregnancy complications, foetal complications and adverse effects of thyroxine	1 RCT reported 21/300 preterm births in the experimental group and 19/300 preterm births in the control group in women diagnosed with positive anti-TPO antibodies. None of the RCTs reported on other adverse events.

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology as assessed by Akhtar 2019
Negro 2005(35) RCT	72	Inclusion criteria: infertile women, anti-TPO positive, undergoing ART. Exclusion criteria: women with overt thyroid dysfunction.	unclear	Experimental: 1 month before ART, levothyroxine 1 mg/kg/day and continued it throughout pregnancy. (Note from Cochrane: likely dose was 1 µg/kg/day.) Control: placebo.	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA Low risk SELECTIVE REPORTING Unclear risk (no reporting on adverse effects) OTHER BIAS Unclear risk (discrepancy between results in text vs tables)
Wang 2017(38) RCT	600	Inclusion criteria: women undergoing ART, aged 23–40 years, body mass index < 35. Exclusion criteria: women taking a thyroid hormone or antithyroid medication or who had undergone thyroid surgery or radioiodine treatment were excluded from the trial. Women were not eligible if they	Unclear (until “after birth”)	Experimental: levothyroxine replacement started 2–4 weeks before the controlled ovarian hyperstimulation and continued through the end of pregnancy. Either a 25-µg/d or 50-µg/d dose of levothyroxine was given at initiation and was titrated according to the level of thyroid-stimulating hormone during pregnancy.	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (no detailed information) BLINDING OF PARTICIPANTS AND PERSONNEL Low risk BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA

		had ≥ 2 spontaneous miscarriages; known diabetes mellitus or other endocrinological or metabolic diseases; tested positive for the anticardiolipin antibody, antinuclear antibody or lupus anticoagulants; serum alanine aminotransferase and aspartate aminotransferase levels > 2 times the upper limit of normal; serum creatinine concentration > 1.47 mg/dL (130 µmol/L); or were taking adjuvant treatments, such as anticoagulants, glucocorticoids or other relevant treatments.		Control: no levothyroxine, but otherwise same care.	Low risk SELECTIVE REPORTING Unclear risk (no reporting on adverse effects) OTHER BIAS Low risk

Remarks: This Cochrane reported also outcomes in a population of women with subclinical hypothyroidism with or without anti-TPO antibodies. However, these results were based on 1 RCT with 32 participants per treatment arm. We therefore excluded these analyses on the basis of the insufficient sample size.

Author's conclusions: *"We could draw no clear conclusions in this systematic review due to the very low to low quality of the evidence reported."*

Additional RCT:

Levothyroxine vs placebo in women with infertility and TPO-Ab-positivity

Study details	n/Population	Comparison	Outcomes		Methodological
Dhillon-Smith 2019(39) Design: RCT (DB, PG) Duration of follow-up: Women were followed up every 3 months while trying to conceive,	n= 952 Mean age: 32,5 (T4) – 32,7y (pla) TSH: 30,8% > 2,5 mIU/L Mean fT4: 14,5 (T4)-14,6 (pla) pmol/L <u>Inclusion</u> Women were eligible for enrollment in the trial if they were 16 to 40 years of age, had a history of miscarriage or infertility, and were trying to conceive in	Levothyroxine 50 µg daily Vs placebo (initiated before conception and continued until the end of pregnancy)	Efficacy		RANDO: Adequate ALLOCATION CONC: Adequate BLINDING : Participants: yes Personnel: yes Assessors: yes FOLLOW-UP: Drop-out and Exclusions: 1,3 % • Described: yes • Balanced across groups: yes ITT: Yes (“Outcomes in all women who underwent randomization (pregnant and nonpregnant) were included in the trial intention-to-treat analysis.”)
			Live birth at ≥34 weeks (PO)	Levothyroxine: 176/470 (37,4%) Placebo: 178/470 (37,9%) RR 0,97 (95%CI 0,83 to 1,14) NS	
			Pregnancy at ≤12 months after enrollment	Levothyroxine: 266/470 (56,6%) Placebo: 274/470 (58,3%) RR 0,97 (95%CI 0,88 to 1,07) NS	
			Miscarriage (before 24 weeks)	Levothyroxine: 75/266 (28,2%) Placebo: 81/274 (29,6%) RR 0,95 (95%CI 0,73 to 1,23) NS	
			Live birth at <34 weeks	Levothyroxine: 10/266 (3,8%) Placebo: 10/274 (3,6%) RR 1,02 (95%CI 0,43 to 2,42) NS	
			Live birth at ≥34 weeks	Levothyroxine: 176/266 (66,2%) Placebo: 178/274 (65,0%) RR 1,02 (95%CI 0,90 to 1,15)	

and, once pregnant, were seen each trimester: 6–8 weeks, 16–18 weeks and 28 weeks	the subsequent 12 months (either naturally or through assisted conception). Women who were found to have normal thyroid function and thyroid peroxidase antibody positivity were then invited to take part in the trial. *Definitions:* *Euthyroidism was defined as a thyrotropin level of 0.44 to 3.63 mIU per liter and a free thyroxine (T4) level of 10.0 to 21.0 pmol per liter as measured with one of these specified analyzers: Abbott ARCHITECT (Fisher Scientific); Elecsys, Modular, or Cobas (Roche); and ADVIA Centaur (Siemens [Bayer]). The*			NS	SELECTIVE REPORTING: no Sponsor: This report presents independent research commissioned by the National Institute for Health Research (NIHR).
			Birth weight (g) (375 infants)	Levothyroxine: 3226±660 Placebo: 3262±668 MD −35 (95%CI −168 to 97) NS	
			Apgar score at 1 minute median (IQR) (375 infants)	Levothyroxine: 9 (9-9) Placebo: 9(8-9) MD 0.1 (95%CI −0.2 to 0.4) NS	
			Apgar score at 5 minutes median (IQR) (375 infants)	Levothyroxine: 9 (9-10) Placebo: 9(9-10) MD 0.0 (95%CI −0.2 to 0.2) NS	
			Prespecified subgroup analysis		
			Live birth after at least 34 weeks TSH at baseline >2,5 mIU/L	Levothyroxine: 55/145 (37,9%) Placebo: 58/143 (40,6%) RR 0,91 (95%CI 0,69 to 1,20) NS	

	euthyroid reference range covered the second and third quartiles of all accepted assays. Thyroid peroxidase antibody positivity was defined according to individual hospital laboratory thresholds <u>Exclusion</u> Women were excluded if they were receiving treatment for a thyroid disorder, had cardiac disease, or were receiving amiodarone or lithium				
			Safety		
			Serious adverse events Total number of participants experiencing a SAE (either maternal or neonatal)	Levothyroxine: 28/470 (6%) Placebo: 18/470 (4%) p-value 0.14 NS	

19 Appendix. Evidence tables. Obesity

19.1 Levothyroxine vs placebo for obesity

Meta-analysis: Kaptein 2009(42)
Thyroid Hormone Therapy for Obesity and Nonthyroidal illnesses: A systematic Review

Inclusion criteria: Randomized controlled trials (RCTs) or prospective observational studies comparing T3 and/or T4 therapy, administered for 24 h or longer, to placebo therapy. Populations included euthyroid adult obese subjects during caloric deprivation (<1000 kcal/d) and euthyroid adult patients with acute or chronic nonthyroidal illnesses.

Search strategy: MEDLINE (from 1950), EMBASE (from 1980), and Cochrane Central Register of Controlled Trials were searched from inception to December 2008.

Assessment of quality of included trials: yes

Other methodological remarks:/

Remarks: This systematic review did not identify any studies that met our inclusion criteria.

Author's conclusions: *"Available data are inconclusive regarding effectiveness of thyroid hormone therapy in treating obesity or nonthyroidal illnesses, whereas data support that such therapy induces subclinical hyperthyroidism."*

20 Appendix. Evidence tables. Chronic fatigue

No SRs or RCTs that met our inclusion criteria were found.

21 Appendix. Evidence tables. Anti-aging

No SRs or RCTs that met our inclusion criteria were found.

22 Appendix. Evidence tables. Euthyroid multinodular goiter

22.1 Levothyroxine vs placebo or no treatment for euthyroid multinodular goiter

Meta-analysis: Bandeira-Echtler 2014(5)
Levothyroxine or minimally invasive therapies for benign thyroid nodules

Inclusion criteria: RCTs of levothyroxine, percutaneous injection sclerotherapy (PEI), interstitial laser photocoagulation (LP), ultrasound-guided radiofrequency ablation therapy (RF), high-intensity focused ultrasound ablation therapy (HIFU) or ultrasound-guided microwave ablation therapy (MW) therapy in participants with an established diagnosis of benign thyroid nodules.

Exclusion criteria: trials investigating the prevention of recurrence of thyroid disease after surgery, irradiation or treatment with radioiodine.

Search strategy: The Cochrane Library, MEDLINE, EMBASE and LILACS were searched up to April 2014.

Assessment of quality of included trials: yes

Ref	Comparison	N/n	Outcomes	Result
Bandeira-Echtler 2014(4) Design: SR+ MA Search date: April 2014	Levothyroxine Vs Control (placebo or no treatment)	N= 10 n= 958 (Gharib 1987, Reverter 1992, Papini 1993, La Rosa 1995, Zelmanowitz 1998, Boguszewski 1998, Wemeau	Nodule volume reduction ≥50%	Levothyroxine 80/489 Control 46/469 **RR 1,57 (95%CI 1,04 to 2,38)** **SS** **More nodule volume reduction ≥50% with levothyroxine**

		2002, Larijani 2005, Grussendorf 2011, Bayani 2012)		
		N= 3 n= 270 (Papini 1993, La Rosa 1995, Wemeau 2002)	Adverse events: participants without signs of hyperthyroidism	*No meta-analysis performed because of considerable heterogeneity* Papini 1993: Levothyroxine 27/51 Control 47/50 **RR 0,56 (95%CI 0,43 to 0,74)** **SS** **More participants with signs of hyperthyroidism with levothyroxine** La Rosa 1995: Levothyroxine 23/23 Control 23/23 RR 1 (95%CI 0,92 to 1,09) NS Wemeau 2002 : Levothyroxine 53/64 Control 53/59 RR 0,92 (95%CI 0,8 to 1,06) NS

		N= 3 n= 551 (Papini 1993, Zelmanovitz 1998, Grussendorf 2011)	Adverse events: participants without nodule volume increase > 50%	Levothyroxine 193/278 Control 174/273 RR 1,1 (95%CI 0,99 to 1,22) NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (as assessed by Bandeira- Echtler)
Bayani 2012(47)	40	participants with single palpable thyroid nodule with confirmed tumour benignity based on FNAB; to ensure existence of single nodule, sonography was performed age<60y TSH in normal limits (0.5 to 4.5 mU/L)	6 months	LT4 at an initial dose of 50 µg/day, levothyroxine dose was adapted according to TSH serum levels after 6 weeks of suppressive treatment in order to maintain TSH levels at less than 0.5 mU/L Vs No intervention	RCT did not meet our inclusion criteria (sample size)
Boguszewski 1998(48)	48	solitary thyroid nodule	12 months	Levothyroxine (200 or 250mcg/day) Versus placebo	RCT did not meet our inclusion criteria (sample size)

Gharib 1987(49)	53	colloid solitary thyroid nodule confirmed by biopsy	6 months	Levothyroxine Vs placebo	RCT did not meet our inclusion criteria (sample size)
Grussendorf 2011(50)	405	White; age 18 to 65 years; TSH normal (0.6 to 3.0 mU/L), TN normal size or enlarged thyroid; at least one TN solid (cyst component ≤ 20%), TN ≥ 1 cm, for TN > 1 cm, diagnosis according to guidelines for diagnostic standards of thyroid disorders to exclude malignancy	12 months	Levothyroxine (titrated to a TSH target range of 0.2-0.8 mU/liter.) Levothyroxine (titrated to a TSH target range of 0.2-0.8 mU/liter.) + iodine Vs Iodine Vs placebo	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Low risk BLINDING OF PARTICIPANTS AND PERSONNEL Low risk for objective outcomes High risk for subjective outcomes (possibility of unblinding) BLINDING OF OUTCOME ASSESSMENT Low risk INCOMPLETE OUTCOME DATA High risk (33% dropouts or missing data, reasons not explained) SELECTIVE REPORTING High risk (serious adverse (n=38) mentioned in methods; but not specified in which treatment groups they occurred) OTHER BIAS Unclear risk (study supported by Sanofi-Aventis)
La Rosa 1995(51)	45	solitary solid cold thyroid nodules found to be benign at cytologic examination	12 months	suppressive levothyroxine (thyroid-stimulating hormone level, <0.3 mU/L), vs	RCT did not meet our inclusion criteria (sample size)

				low-dose potassium iodide (2 mg every 2 weeks) vs no treatment	
Larijani 2005(52)	58	single palpable thyroid nodule on physical examination and cytology consistent with benign nature of the nodule on fine needle aspiration biopsy <60 yrs	2 years	Levothyroxine (until complete TSH suppression (<0,1 mIU/L) Vs placebo	RCT did not meet our inclusion criteria (sample size)
Papini 1993(53)	101	single thyroid nodule diagnosed by an endocrinologist with expertise in thyroid disease; normal serum thyroid hormones and TSH concentrations	12 months	Levothyroxine (initial dose 50 µg before breakfast and increased by 25 to 50 µg weekly to the full dose, which was thereafter adjusted to induce TSH suppression) vs placebo	RANDOM SEQUENCE GENERATION Unclear risk (no detailed information) ALLOCATION CONCEALMENT Unclear risk (no detailed information) BLINDING OF PARTICIPANTS AND PERSONNEL Low risk for objective outcomes High risk for subjective outcomes (study design could have introduced bias) BLINDING OF OUTCOME ASSESSMENT Low risk for objective outcomes High risk for subjective outcomes (study design could have introduced bias) INCOMPLETE OUTCOME DATA

					Unclear risk (reasons for dropouts not explained) SELECTIVE REPORTING Low risk OTHER BIAS Low risk
Reverter 1992(54)	40	solitary thyroid nodule on palpation, cold on sclntlgraphy and cytologically benign	Mean 10,6 months	Levothyroxine (titrated to achieve TSH suppression) Vs No treatment	RCT did not meet our inclusion criteria (sample size)
Wemeau 2002(55)	123	single palpable nodule; benign (FNAB); nodule identified < 1 year before begin of study; age from 18 to 55 years	18 months	Levothyroxine (titrated until TSH < 0.3 mU/L) Vs placebo	RANDOM SEQUENCE GENERATION Low risk ALLOCATION CONCEALMENT Unclear risk (no detailed information) BLINDING OF PARTICIPANTS AND PERSONNEL Low risk BLINDING OF OUTCOME ASSESSMENT Low risk for objective outcomes High risk for subjective outcomes (outcomes assessors blinded for ultrasound only) INCOMPLETE OUTCOME DATA Unclear risk (disparate attrition rates; however, analyses were performed on an intention-to-treat basis) SELECTIVE REPORTING Low risk

					OTHER BIAS Unclear risk (commercial funding (Merck-Lipha Santé France)
Zelmanovitz 1998(56)	45	presence of a single thyroid nodule (at ultrasonography), hypofunctioning (at scintigraphy), and benign cytological findings	12 months	Levothyroxine (titrated to obtain a serum TSH less than 0.3 mIU/mL or a TSH) Vs placebo	RCT did not meet our inclusion criteria (sample size)

Author's conclusions:

"No study evaluated all-cause mortality, health-related quality of life or provided systematic data on the development of thyroid cancer. Longest follow-up was five years and median follow-up was 12 months. Nodule volume reductions were achieved by PEI, LP and RF, and to a lesser extent, by LT4. However, the clinical relevance of this outcome measure is doubtful. PEI, LP and RF led to improvements in pressure symptoms and cosmetic complaints. Adverse events such as light-to-moderate periprocedural pain were seen aNer PEI, LP and RF. Future studies should focus on patient-important outcome measures, especially health-related quality of life, and compare minimally invasive procedures with surgery. RCTs with follow-up periods of several years and good-quality observational studies are needed to provide evidence on the development of thyroid cancer, all-cause mortality and long-term adverse events."

23 Appendix. Recommendations from guidelines – details

23.1 Overt Hypothyroidism

23.1.1 NICE 2019

23.1.1.1 Screening for thyroid dysfunction

Consider tests for thyroid dysfunction for adults, children and young people if there is a clinical suspicion of thyroid disease, but bear in mind that 1 symptom alone may not be indicative of thyroid disease.

They agreed, based on evidence and their experience, that most single common symptoms alone are not predictive of thyroid dysfunction. The decision to test should be based on an overall clinical suspicion, taking into account the nature and severity of symptoms, clinical signs and coexisting conditions.

Offer tests for thyroid dysfunction to adults, children and young people with:
type 1 diabetes or other autoimmune diseases, or new-onset atrial fibrillation.

The evidence showed that type 1 diabetes, an autoimmune disease, is associated with thyroid dysfunction.

There was little evidence on thyroid disease in people with atrial fibrillation. However, the committee agreed that the potential importance of thyroid disease and its impact on the treatment of atrial fibrillation is sufficient to justify testing.

Consider tests for thyroid dysfunction for adults, children and young people with depression or unexplained anxiety.

Limited evidence showed that depression can be associated with thyroid dysfunction. The committee agreed that, in their experience, this can also apply to anxiety.

Be aware that in menopausal women symptoms of thyroid dysfunction may be mistaken for menopause.

Do not test for thyroid dysfunction during an acute illness unless you suspect the acute illness is due to thyroid dysfunction, because the acute illness may affect the test results.

Do not offer testing for thyroid dysfunction solely because an adult, child or young person has type 2 diabetes.

Evidence showed that type 2 diabetes is not associated with thyroid dysfunction.

23.1.1.2 Diagnosing hypothyroidism

When thyroid dysfunction in suspected:

Consider measuring thyroid-stimulating hormone (TSH) alone for adults when secondary thyroid dysfunction (pituitary disease) is not suspected. Then:

- **if the TSH is above the reference range, measure free thyroxine (FT4) in the same sample**
- **if the TSH is below the reference range, measure FT4 and free tri-iodothyronine (FT3) in the same sample.** *(Recommendation 1.2.8.)*

Consider measuring both TSH and FT4 for:

- **adults when secondary thyroid dysfunction (pituitary disease) is suspected.** *(Recommendatioin 1.2.9.)*

Consider repeating the tests for thyroid dysfunction in recommendations 1.2.8 or 1.2.9 if symptoms worsen or new symptoms develop (but no sooner than 6 weeks from the most recent test).

No evidence was identified on which tests should be used when thyroid dysfunction is suspected so the committee used their experience to develop the recommendations.

- The committee agreed that in general TSH alone is an appropriate first test for people in whom thyroid dysfunction is suspected. Subsequent tests (cascading) are only needed if TSH is abnormal.
- This approach reduces unnecessary testing compared with simultaneous TSH, FT4 and FT3 testing for all people.
- However, tests should be done in a way to minimise potential delays and the need for additional appointments, for example, by laboratories keeping original samples and performing subsequent tests on the same samples.

For people with confirmed hypothyroidism

Consider measuring thyroid peroxidase antibodies (TPOAbs) for adults with TSH levels above the reference range, but do not repeat TPOAbs testing.

No evidence was identified on the use of antibodies to investigate hypothyroidism so the committee used their experience to develop the recommendations.

- They agreed that testing for TPOAbs may be useful in the early investigation of the underlying cause of hypothyroidism.
- However, for adults there was no role for remeasuring TPOAbs because changes in levels are unlikely to guide treatment decisions.

23.1.1.3 Managing primary hypothyroidism

Offer levothyroxine as first-line treatment for adults, children and young people with primary hypothyroidism.

Consider starting levothyroxine at a dosage of 1,6 micrograms per kilogram of body weight per day (rounded to the nearest 25 micrograms) for adults under 65 with primary hypothyroidism and no history of cardiovascular disease.

Consider starting levothyroxine at a dosage of 25 to 50 micrograms per day with titration for adults aged 65 and over and adults with a history of cardiovascular disease.

There was a clinically important benefit of high-starting levothyroxine dose compared to titrated dose in four quality of life domains (social functioning, role limits due to emotional wellbeing, role limits due to physical functioning and pain) but no difference in four different quality of life domains. There was an absence of cardiac events associated with both dosing strategies.Some evidence showed that a high starting dose of levothyroxine produced more rapid improvements in quality of life than a lower starting dose followed by titration. The committee agreed that this was also their experience and therefore recommended a high starting dose (1.6 micrograms per kilogram body weight per day) in adults unless contraindicated (adults over 65 or with a history of cardiovascular disease).

23.1.1.4 Dietary supplements

The committee were unable to make recommendations on iodine or selenium supplements because of a lack of evidence.

23.1.2 BMJ 2019

BMJ 2019 is a guideline on the treatment of subclinical hypothyroidism, no specific recommendations or comments were provided regarding overt hypothyroidism.

23.1.3 BTA 2016

23.1.3.1 Diagnosing thyroid dysfunction

The diagnosis of primary hypothyroidism is based on clinical features of hypothyroidism supported by biochemical evidence that is elevated serum TSH together with low free T4 (overt hypothyroidism) or normal free T4 (subclinical hypothyroidism). Primary hypothyroidism should not be diagnosed in individuals with normal serum TSH who otherwise have intact pituitary function. (BTA, 1/++0)

The significance of perturbations in serum T3 concentrations within the reference range, or of mildly low serum T3, is unknown (reported from ATA, Summary Statement where formal clinical recommendation is not feasible because of sparse evidence)

23.1.3.2 Managing primary hypothyroidism

L-T4 is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favourable side effect profile, ease of administration, good intestinal absorption, long serum half-life and low cost. (reported from ATA, 1/++0)

23.1.3.3 Dietary supplements

Recommend against the use of dietary supplements, nutraceuticals or other over the counter products either in euthyroid individuals or as a means of treating hypothyroidism. Particularly caution against the use of pharmacologic doses of iodine because of the risk of thyrotoxicosis and hypothyroidism in those with intact thyroid glands susceptible to becoming further dysregulated because of underlying thyroid pathology (reported from ATA, 1/+00)

23.2 Subclinical hypothyroidism

23.2.1 NICE 2019

23.2.1.1 Diagnosing subclinical hypothyroidism

For people with confirmed subclinical hypothyroidism:

Consider measuring TPOAbs for adults with TSH levels above the reference range, but do not repeat TPOAbs testing.

The committee highlighted that the presence of antibodies may also influence the likelihood of TSH to return to normal. Within this context, the committee agreed on the importance of considering factors including antibody status and previous thyroid surgery that may suggest an underlying thyroid disease when it comes to the decision of whether or not to offer treatment for subclinical hypothyroidism.

23.2.1.2 Managing subclinical hypothyroidism

When discussing whether or not to start treatment for subclinical hypothyroidism, take into account features that might suggest underlying thyroid disease, such as symptoms of hypothyroidism, previous radioactive iodine treatment or thyroid surgery, or raised levels of thyroid autoantibodies.

The committee agreed that as most studies used 65 years as a cut-off it was appropriate to define older adults as over 65 and make separate recommendations for this group.

Consider levothyroxine for adults with subclinical hypothyroidism who have a TSH of 10 mIU/litre or higher on 2 separate occasions 3 months apart. Follow the recommendations in section on follow-up and monitoring of hypothyroidism.

Consider a 6-month trial of levothyroxine for adults under 65 with subclinical hypothyroidism who have:

- **TSH above the reference range but lower than 10 mIU/litre on 2 separate occasions 3 months apart,**

AND

- **symptoms of hypothyroidism.**

If symptoms do not improve after starting levothyroxine, re-measure TSH and if the level remains raised, adjust the dose. If symptoms persist when serum TSH is within the reference range, consider stopping levothyroxine and follow the recommendations on monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment.

The committee noted that a TSH level of 5 to 10 mIU/litre might return to the reference range without treatment in around half of people, whereas a TSH level above 10 mIU/litre is less likely to do so and is more often associated with symptoms. They therefore agreed that levothyroxine should be considered for all adults with a TSH level of 10 mIU/litre or more because this may improve symptoms and may have long-term benefits including on cardiovascular outcomes. For people with a TSH level lower than 10 mIU/litre, the committee agreed based on their experience that treatment was less likely to have a benefit but that the balance of risks to benefits was most favourable for adults under the age of 65.

The committee noted that for people over 65 there was less likely to be an improvement in symptoms and the potential for harms from suppressing TSH (such as atrial fibrillation) is greater.

The committee agreed that the trial of levothyroxine treatment should be stopped if symptoms persist with TSH levels within the reference range, as they are likely to be due to causes other than hypothyroidism.It was raised that an overreliance on TSH levels in decision making about treatment that is most often the case in clinical practice may be problematic, and that other factors, including patients' symptomatology are to influence their need for treatment. The committee felt that a trial period of treatment of 6 months would be appropriate for symptomatic patients with TSH lower than the 10 mIU/litre cut-off. The importance of making recommendations for both providing but also stopping treatment, in cases where no apparent benefit in symptoms is achieved was emphasised. There was agreement that whether or not TSH returns to normal is a factor indicating the success of treatment but that symptoms are also important.

23.2.1.3 Monitoring untreated subclinical hypothyroidism

For adults with untreated subclinical hypothyroidism or adults who have stopped levothyroxine treatment for subclinical hypothyroidism, consider measuring TSH and FT4:

- **once a year if they have features suggesting underlying thyroid disease, such as previous thyroid surgery or raised levels of thyroid autoantibodies,**

OR

- **once every 2 to 3 years if they have no features suggesting underlying thyroid disease.**

23.2.2 BMJ 2019

23.2.2.1 Managing subclinical hypothyroidism

Thyroid hormones should not be routinely offered to adults with SCH (strong recommendation).

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

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

For younger people (such as <65):

There was no important benefit shown in younger groups. However, the panel's certainty in the estimates was slightly lower. The same is true for harms. However, the panel was concerned about the burden of lifelong treatment and the limited evidence about possible long term harms of thyroid hormones (such as adverse cardiovascular effects). In addition, patients may experience a delay in diagnosis of another condition (such as mood disorder).

Taking a pill and attending periodic testing on an ongoing or lifelong basis is burdensome.

The panel concluded that almost all adults with SCH would not benefit from treatment with thyroid hormones. Other factors in the strong recommendation include the burden of lifelong management and uncertainty on potential harms.

Instead, clinicians should monitor the progression or resolution of the thyroid dysfunction in these adults.

Guidelines generally recommend thyroid hormones for adults with TSH levels above 10 mIU/L. For those with lower TSH levels, most guidelines recommend treatment only when people are younger,

symptomatic, or have other indications for prescribing (such as cardiovascular disease or antibodies to thyroid peroxidase). Table 1 summarises current guidance from various organisations.

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

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

23.2.2.2 Monitoring untreated subclinical hypothyroidism

Regular visits and blood samples to monitor progression or resolution

23.2.3 BTA 2016

23.2.3.1 Diagnosing subclinical hypothyroidism

The diagnosis of primary hypothyroidism is based on clinical features of hypothyroidism supported by biochemical evidence that is elevated serum TSH together with low free T4 (overt hypothyroidism) or normal free T4 (subclinical hypothyroidism). Primary hypothyroidism should not be diagnosed in individuals with normal serum TSH who otherwise have intact pituitary function. (BTA, 1/++0)

The evidence in favour of narrowing the serum TSH reference range is not convincing and cannot justify the large increase in the number of healthy people that would require investigation. (BTA, 1/++0)

For serum TSH, the reference population shows a log normal distribution and has a diurnal variation with the reference range in thyroid disease free individuals typically cited as between 0,4 and 4,0 mU/l.8 The reference range varies in different ethnic communities, pregnancy and by age.
It has been reported that serum TSH distribution progressively shifts towards higher concentration with age.

The significance of perturbations in serum T3 concentrations within the reference range, or of mildly low serum T3, is unknown (reported from ATA, Summary Statement where formal clinical recommendation is not feasible because of sparse evidence)

A significant proportion of healthy subjects in the community have asymptomatic chronic autoimmune thyroiditis and a significant proportion have subclinical hypothyroidism. Spontaneous recovery has been described in subjects with subclinical hypothyroidism. It is more likely in those with negative antithyroid antibodies and serum TSH levels less than 10 mU/l, and within the first 2 years after diagnosis. The higher the serum TSH value, the greater the likelihood of development of overt hypothyroidism in subjects with chronic autoimmune thyroiditis.

23.2.4 ASRM 2015

ASRM 2015 is a specific guideline on subclinical hypothyroidism in infertile female population but information on thresholds to consider to define subclinical hypothyroidism in general as well on the management in general population were found and are reported in this document.

23.2.4.1 Diagnosing subclinical hypothyroidism

Normative data for TSH have been established by the National Health and Nutrition Examination Survey (NHANES III) population. The data from this examination suggest a median serum level for TSH of 1.50 mIU/L with the corresponding 2.5 and 97.5 percentiles of 0.41 and 6.10, respectively, for a disease-free population.

However, according to the National Academy of Clinical Biochemistry (NACB), 95% of individuals without evidence of thyroid disease have a TSH level <2.5 mIU/L, and the normal reference range is skewed to the right. Therefore, the NACB suggests that a TSH level of 2.5 mIU/L should be the upper limit of normal for all patients. However, if the upper limit of normal was lowered to 2.5 mIU/L, an additional 11.8%–14.2% of the United States population, 22–28 million individuals, would be diagnosed with hypothyroidism. This compares with 2.3%–4.3% (4.6–8.6 million) people being diagnosed according to the classic definition (TSH >5 mIU/L).

Given the absence of demonstrable benefit of treatment, the low positive predictive value and the increased health-care costs of identification and treatment, population screening, and/or lowering the upper limit of normal reference for TSH are not supported.

Given the lack of evidence for treatment of nonpregnant individuals using these cutoffs, the Endocrine Society guidelines do not support changing the cutoff outside of pregnancy.

The recommendation from the Endocrine Society is the following: The reference range of a given laboratory should determine the upper limit of normal for a third generation TSH assay. The normal TSH reference range changes with age. If an age-based upper limit of normal for a third generation TSH assay is not available in an iodine sufficient area, an upper limit of normal of 4.12 mIU/L should be considered.

Summary: Subclinical hypothyroidism is defined as a TSH level greater than the upper limit of normal range (4.5–5.0mIU/L) with normal FT4 levels.

23.2.4.2 Managing subclinical hypothyroidism

Despite the findings that TSH levels are skewed in the general population, current evidence does not support treating nonpregnant women for subtle thyroid abnormalities (TSH <5 mIU/L).

There is no benefit (with respect to lipid profile and/or cardiovascular risk) of treatment for a TSH level between 5 and 10 mIU/L. Thus, any potential benefit of treatment for individuals with TSH <5mIU/L is questioned. While there is potential risk of overtreatment, particularly for women who could suffer bone loss, this study further suggests that the positive predictive value for hypothyroidism of a TSH between 2.5 and 5 mIU/L is small.

23.3 Hypothyroidism in the elderly

23.3.1 NICE 2019

23.3.1.1 Managing primary hypothyroidism

Consider starting levothyroxine at a dosage of 25 to 50 micrograms per day with titration for adults aged 65 and over and adults with a history of cardiovascular disease.

The committee agreed that this was also their experience and therefore recommended a high starting dose (1,6 micrograms per kilogram body weight per day) in adults unless contraindicated (adults over 65 or with a history of cardiovascular disease).

Although evidence about dosing was very limited, the committee agreed that adults over 65 years are more likely to have cardiovascular comorbidities. Most studies of hypothyroidism and subclinical

hypothyroidism use 65 as a cut-off when defining older adults. The committee agreed to recommend a lower starting dose with titration for people over 65.

23.3.1.2 Managing subclinical hypothyroidism

The committee did not recommend treatment with levothyroxine for older adults, when the TSH was above the reference range but lower than 10 mIU/litre, which is in line with current practice.

The committee noted that for people over 65 there was less likely to be an improvement in symptoms and the potential for harms from suppressing TSH (such as atrial fibrillation) is greater.

23.3.2 BMJ 2019

Thyroid hormones should not be routinely offered to adults with SCH (strong recommendation according to GRADE).

For older people (≥65 years):

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

Nonetheless, the panel agreed that the possibility of harms contributes towards the strong recommendation.

23.3.3 BTA 2016

Although epidemiological studies have shown an association between subclinical hypothyroidism and coronary heart disease in younger people (<65 years) or those with high TSH (>10 mU/l), recent evidence suggests that in older people, higher serum TSH and lower free T4 concentrations within the euthyroid range are associated with lower risk of multiple adverse events including mortality.

23.4 Hypothyroidism in pregnant women and women with fertility problems

23.4.1 Pregnant women

23.4.1.1 NICE 2019

Provide people with thyroid disease, and their family or carers if appropriate, with written and verbal information on:

- **…**
- **how thyroid disease and medicines may affect pregnancy and fertility.**

23.4.1.2 BMJ 2019

BMJ 2019 is a guideline on the treatment of subclinical hypothyroidism, no specific recommendations or comments were provided regarding pregnant women.

23.4.1.3 BTA 2016

The serum TSH reference range in pregnancy is 0.4–2.5 mU/l in the first trimester and 0.4–3.0 mU/l in the second and third trimesters or should be based on the trimester-specific reference range for the population if available. These reference ranges should be achieved where possible with appropriate doses of L-T4 preconception and most importantly in the first trimester (BTA, 1/++0).

L-T4/L-T3 combination therapy is not recommended in pregnancy (BTA, 1/+00).

23.4.1.4 ATA 2017

ATA 2017 is a general guideline on thyroid disease during pregnancy including thyrotoxicosis. Only the information concerning hypothyroidism have been reported.

23.4.1.4.1 Screening for thyroid hypofunction

There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations in early pregnancy. (No recommendation, insufficient evidence)

Universal screening to detect low FT4 concentrations in pregnant women is not recommended. (Weak recommendation, moderate-quality evidence)

All pregnant women should be verbally screened at the initial prenatal visit for any history of thyroid dysfunction, and prior or current use of either thyroid hormone (LT4) or antithyroid medications (MMI, CM, or PTU). (Strong recommendation, high-quality evidence)

All patients seeking pregnancy, or newly pregnant, should undergo clinical evaluation. If any of the following risk factors are identified, testing for serum TSH is recommended:
1. history of hypothyroidism/hyperthyroidism or current symptoms/signs of thyroid dysfunction
2. Known thyroid antibody positivity or presence of a goiter
3. History of head or neck radiation or prior thyroid surgery
4. Age >30 years

5. Type 1 diabetes or other autoimmune disorders
6. History of pregnancy loss, preterm delivery, or infertility
7. Multiple prior pregnancies (≥2)
8. Family history of autoimmune thyroid disease or thyroid dysfunction
9. Morbid obesity (BMI ≥40 kg/m2)
10. Use of amiodarone or lithium, or recent administration of iodinated radiologic contrast
11. Residing in an area of known moderate to severe iodine insufficiency
(Strong recommendation, moderate-quality evidence)

For universal screening to be recommended, any index condition must be prevalent, associated with adverse health outcomes, and treatable. Furthermore, effective therapy must exist but also be practical and effectively deliverable. Finally, screening must be cost effective.

Thus, the most notable impact of a universal screening mandate for thyroid dysfunction would be the identification of the large proportion of patients with subclinical hypothyroidism (mild elevations in serum TSH with normal thyroid hormone levels).

Thyroid status can be accurately assessed with currently available blood tests, including TSH, TT4/FT4, and TPOAb. These tests are relatively inexpensive and widely available. Thus, the principal complexity surrounding the screening question relates to the evidence for treatment effectiveness, especially in the population of pregnant women with subclinical hypothyroidism.

Studies strongly suggest an increase in pregnancy loss risk associated with elevated maternal TSH concentrations, especially when elevated TPOAb are detected. Similarly, thyroid dysfunction is a prevalent condition that can be diagnosed with readily available and inexpensive tests. However, the effectiveness of LT4 therapy has not yet been conclusively demonstrated.

Importantly, many have argued that screening for thyroid dysfunction must occur very early in pregnancy (e.g., 4–7 weeks of gestation) to maximize potential benefits of LT4 treatment upon pregnancy loss rates and possibly neurocognitive development. The largest prospective screening studies thus far have provided data most translatable to typical pregnancy care currently provided worldwide, with initial evaluation between 10 and 15 weeks of gestation. This is important to consider because the feasibility of any screening earlier in gestation is unclear.

Therefore, while acknowledging an impressive amount of retrospective data associating thyroid dysfunction with pregnancy harm, the above uncertainties preclude the task force from recommending for or against a universal screening mandate.

In coming to this conclusion, the task force noted that the majority of patients identified through any universal screening process have TSH concentrations between 2.5 and 5.0 mU/L—a population in whom a treatment benefit is not well established. Furthermore, such a strategy could have detrimental effects, labeling many patients with a biochemical abnormality, and in many cases leading to initiation of possibly inappropriate long-term treatment.

One task force member (CD) dissented from this recommendation, feeling that universal testing for maternal TSH and anti-TPO antibodies soon after pregnancy confirmation is warranted given the existing support for the obstetrical benefits of treatment, with minimal risk of harm with appropriate monitoring.

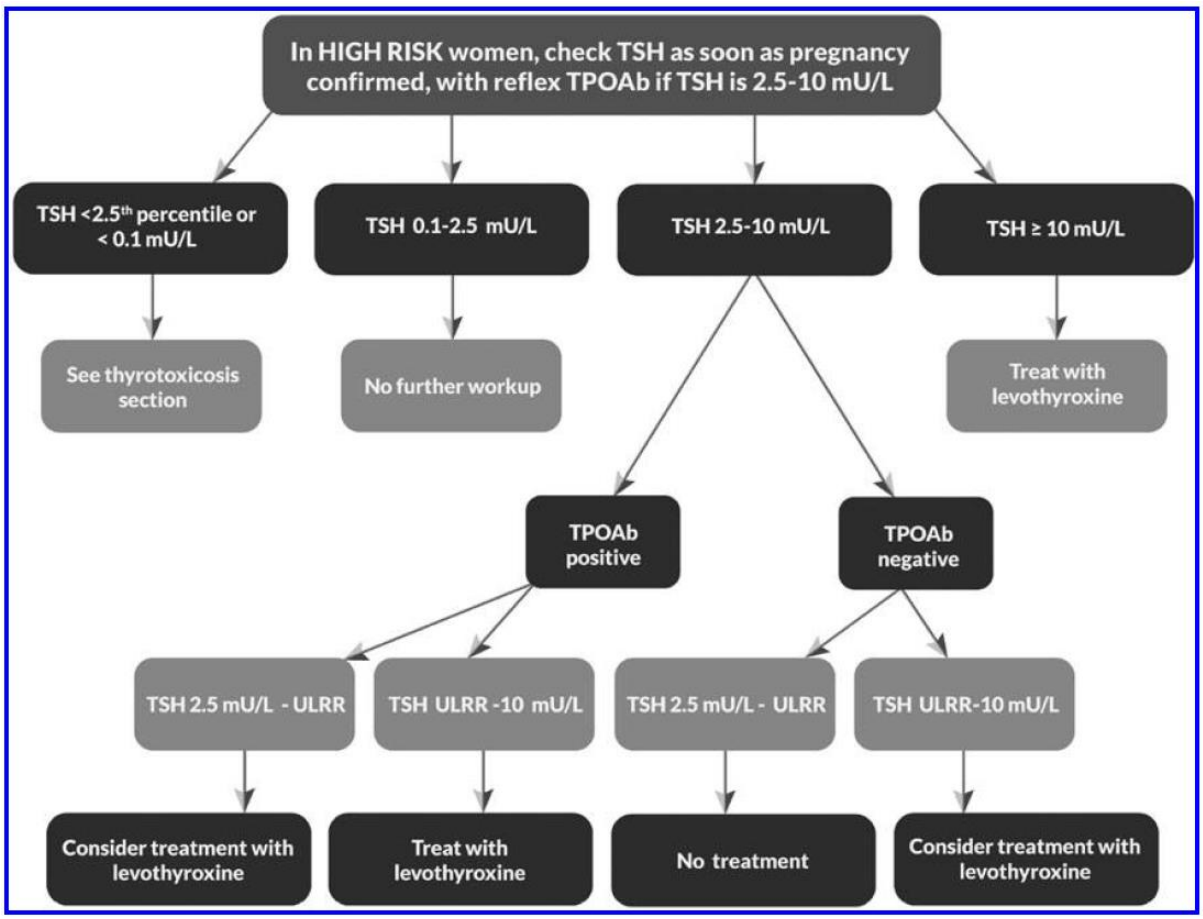

FIG. 1. Testing for thyroid dysfunction in pregnancy. ULRR, upper limit of the reference range.

23.4.1.4.2 Diagnosing thyroid hypofunction

When possible, population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a health care provider's practice. Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake, and negative TPOAb status. (Strong recommendation, moderate-quality evidence)

Following conception, circulating thyroxine binding globulin (TBG) and total T4 (TT4) concentrations increase by week 7 of gestation and reach a peak by approximately week 16 of gestation. These concentrations then remain high until delivery.

In the first trimester, maternal hCG directly stimulates the TSH receptor, increasing thyroid hormone production and resulting in a subsequent reduction in serum TSH concentration. Therefore, during pregnancy, women have lower serum TSH concentrations than before pregnancy, and a TSH below the nonpregnant lower limit of 0.4 mU/L is observed in as many as 15% of healthy women during the first trimester of pregnancy.

Automated immunoassays for FT4, which are employed in most clinical laboratories, are complicated in pregnant women by the increase in TBG and decrease in albumin concentrations. Other methods of direct measurement, such as measurement by equilibrium dialysis, ultrafiltration, or liquid chromatography/tandem mass spectrometry (LC/MS/MS) are less influenced by the pregnancy associated changes in serum proteins but are significantly more expensive and less widely available.

Serum TSH reference range determinations should take into account iodine intake, TPO positivity, and according to some studies, body mass index (BMI).

Although the downward shift in TSH reference ranges is seen in essentially all populations, the extent of this reduction varies significantly between different racial and ethnic groups. Significant geographic and ethnic diversity exist in TSH concentrations during pregnancy, as shown in Table 4

TABLE 4. REFERENCE RANGES FOR THYROTROPIN AND FREE THYROXINE DURING EARLY PREGNANCY WORLDWIDE

Author, country (reference) (analyzing method)	N	Gestation (week)	TSH, mU/L			FT4, pmol/L (ng/dL)			Population characteristics		
			Median	2.5th–97.5th	Median	2.5th–97.5th	(Median, 2.5th–97.5th)	Iodine insufficiency	Mean BMI	Ethnicities
Bestwick *et al.*, Italy (24) (AutoDELFIA)	5505	<16	1.07	0.04–3.19	9.3	7.4–12.2	(0.73, 0.58–0.95)	Moderate-mild [a]	[a]	NR
Bestwick *et al.*, UK (24) (Advia Centaur)	16,334	<16	1.11	0.06–3.50	13.9	10.9–17.9	(1.08, 0.85–1.40)	Moderate-mild [a]	[a]	NR
Bocos-Terraz *et al.*, Spain (264) (Architect)	481	<14	0.94	0.41–2.63	13.9	10.8–17.8	(1.08, 0.84–1.38)	Mild	NR	Caucasian (93%)
Gilbert *et al.*, Australia (271)[b]	1817	9–13	0.74	0.02–2.15	13.5	10.4–17.8	(1.05, 0.81–1.39)	Borderline	NR	Australian
Lambert-Messerlian *et al.*, USA (270)[c] (Immulite 2000)	8351	T1	1.00	0.12–3.37	14.2	10.4–17.8	(1.10, 0.81–1.38)	Mild	NR	Caucasian (67%) and Hispanic (23%),[d]
	8415	T2	1.19	0.35–3.35	13.0	9.3–16.2	(1.01, 0.72–1.26)			
La'ulu *et al.*, USA (139,265)[e]	2172	10–13	0.94	0.02–2.69	14.7	11.4–18.6	(1.15, 0.89–1.45)	Mild	NR	Hispanic (37%), Caucasian (29%), African American (27%), Asian (8%)
	2683	14–20	1.14	0.15–3.11	12.0	9.3–15.2	(0.94, 0.73–1.19)			
Li *et al.*, China (17) (Cobas Elesys 601)	640	7–12	1.47	0.10–4.34	15.8	12.3–20.9	(1.23, 0.96–1.63)	Proven sufficient[f]	NR	Chinese (presumed)
Männistö *et al.*, Finland (266) (Architect i2000)	4333	T1	1.11	0.08–3.54	15.3	11.7–22.8	(1.12, 0.86–1.58)	Sufficient	22.4	Finnish (presumed)
	747	T2	1.37	0.11–4.24	14.6	11.2–23.4	(1.13, 0.87–1.82)			
Medici *et al.*, the Netherlands (267) (Vitros ECI)	5186	8–18	1.30	0.03–4.04	14.7	10.4–22.0	(1.15, 0.81–1.72)	Proven sufficient[f]	24.5	Dutch (52%), Surinamese/Antillean (12%), Turkish (8%), Moroccan (6%)
Pearce *et al.*, USA (142) (Advia Centaur)	585	<14	1.1	0.04–3.60	2.1[h]	1.5–2.9[g]	—	Borderline	NR	White (77%) and African American (10%)
Quinn *et al.*, Russia (272) (Abbott AxSYM)	380	T1	1.66	0.09–4.67	—	—	—	Moderate	NR	Russian (presumed)
	549	T2	2.00	0.20–4.68	—	—	—			
Springer *et al.*, Czech Republic (268)[h] (ADVIA Centaur)	4337	9–11	1.21	0.06–3.67	—	—	—	Mild	NR	Caucasian (99%)
Stricker *et al.*, Switzerland (262) (Architect i2000SR)	575	6–12	0.95	0.07–2.82	13.9	10.5–18.5	(1.08, 0.82–1.44)	Sufficient	NR	Swiss (presumed)
	528	T2	1.02	0.20–2.79	12.2	9.5–15.7	(0.95, 0.74–1.22)			
Vaidya *et al.*, UK (Modular E 170) (274)	1089	<12	1.08	0.14–3.19	14.6	10.7–19.4	(1.12, 0.83–1.59)	Mild-moderate	NR	Caucasian (91) and South Asian (4)

Studies were selected according to the following criteria: $N \geq 500$, exclusion of thyroid peroxidase antibody (TPOAb)-positive women and availability of data from the manuscript or via personal communication. Iodine status was estimated based on references from article, WHO iodine status reports or from the Vitamin and Mineral Nutrition Information System (VMNIS).

[a] Weight reported (Bestwick *et al.* median weight 59 kg in Italian and 67 kg in UK population).

[b] Reported FT4 level is a mean.

[c] Limits are 5th and 98th percentiles for TSH and 2nd and 95th percentiles for FT4.

[d] Based on reports of the total FASTER population.

[e] FT4 determined in normal-range TSH only.

[f] Based on iodine measurements in study population.

[g] Free T4 index (reference range 1.0–4.0).

[h] High hCG levels excluded.

TSH, thyrotropin; FT4, free thyroxine; NR, not reported; T1, first trimester; T2, second trimester.

A reduction in the lower TSH reference range is observed during pregnancy in almost all studies. In a small percentage of women, TSH can be undetectable (<0.01 mU/L), and yet still represent a normal pregnancy. In addressing the clinical importance of a reduced serum TSH during pregnancy, it is important to note that subclinical hyperthyroidism has not been associated with adverse pregnancy outcomes.

The task force recognizes the limited availability of trimester specific reference ranges calculated for most ethnic and racial populations with adequate iodine intake who are free of thyroid autoantibodies. Nonetheless, to provide guidance to all patients and clinicians, the panel recommends use of the following trimester-specific ranges and cutoffs when local assessments are not available.

- In the first trimester, the lower reference range of TSH can be reduced by approximately 0.4 mU/L, while the upper reference range is reduced by approximately 0.5mU/L. For the typical patient in early pregnancy, this corresponds to a TSH upper reference limit of 4.0mU/L. This reference limit should generally be applied beginning with the late first trimester, weeks 7–12, with a gradual return towards the nonpregnant range in the second and third trimesters.

The accuracy of serum FT4 measurement by the indirect analog immunoassays is influenced by pregnancy and also varies significantly by manufacturer. If measured in pregnant women, assay method-specific and trimester specific pregnancy reference ranges should be applied. (Strong recommendation, moderate-quality evidence)

In lieu of measuring FT4, TT4 measurement (with a pregnancy-adjusted reference range) is a highly reliable means of estimating hormone concentration during the last part of pregnancy. Accurate estimation of the FT4 concentrations can also be done by calculating a FT4 index. (Strong recommendation, moderate-quality evidence)

Current uncertainty around FT4 estimates in pregnancy has led some to question the wisdom of relying on any FT4 immunoassays during pregnancy. In contrast, measurement of TT4 and the calculated FT4 index do show the expected inverse relationship with serum TSH.

Changes are predictable, with an increase in TT4 concentration from weeks 7–16 of gestation, ultimately reaching ± 50% above the prepregnancy level. This level is then sustained through pregnancy. Therefore, a clinically acceptable upper range determination can be calculated by shifting the nonpregnant limit 50% higher. However, this limit can only be used after week 16 of pregnancy. If a T4 measurement is required before that time (i.e., weeks 7–16 of pregnancy), a calculation can be made for the upper reference range based on increasing the nonpregnant upper reference limit by 5% per week, beginning with week 7.

In the setting of pregnancy, maternal hypothyroidism is defined as a TSH concentration elevated beyond the upper limit of the pregnancy-specific reference range. (Strong recommendation, high-quality evidence)

The pregnancy-specific TSH reference range should be defined as follows:

- **When available, population- and trimester-specific reference ranges for serum TSH during pregnancy should be defined by a provider's institute or laboratory and should represent the typical population for whom care is provided. Reference ranges should be defined in healthy TPOAb-negative pregnant women with optimal iodine intake and without thyroid illness. (Strong recommendation, high-quality evidence)**
- **When this goal is not feasible, pregnancy-specific TSH reference ranges obtained from similar patient populations and performed using similar TSH assays should be substituted (Table 4) (Strong recommendation, high-quality evidence)**
- **If internal or transferable pregnancy-specific TSH reference ranges are not available, an upper reference limit of ± 4.0 mU/L may be used. For most assays, this limit represents a reduction in the nonpregnant TSH upper reference limit of ± 0.5 mU/L. (Strong recommendation, moderate-quality evidence)**

In the 2011 ATA guidelines, the upper reference limit for serum TSH concentration during pregnancy was defined as 2.5 mU/L in the first trimester, and 3.0 mU/L in the second and third trimesters. Since that publication, additional much larger cohorts have published center-specific and trimester-specific pregnancy reference ranges. However, these data also demonstrate important influences of BMI, geography, and ethnicity upon ‘‘normalcy’’ of TSH concentrations in pregnant women.

In summary, substantial variation exists between populations, with many recent investigations confirming a more liberal upper TSH reference range in healthy pregnant women with no thyroid disease.

Equally important, recent studies have also demonstrated an important additive influence of TPOAb positivity upon maternal thyroid status. Increasingly, there appears to be a greater risk for adverse events in women who are TPOAb positive compared to those who are TPOAb negative, even when thyroid function is identical.

As a consequence, it is difficult to precisely define a universal TSH cutoff above which LT4 therapy should be initiated for all pregnant women. Rather, decisions about LT4 treatment must be based upon both measurement of thyroid function and TPOAb status.

Because substantial differences exist in the upper reference limit for TSH between different populations, each practitioner and hospital should ideally seek to determine their own trimester specific reference ranges, obtained from analysis of healthy, TPOAb-negative, and iodine-sufficient women. However, the task force recognizes that this goal is frequently not feasible.

Pregnant women with TSH concentrations >2.5 mU/L should be evaluated for TPOAb status.

Presently, most studies investigating subclinical hypothyroidism suggest an association with adverse obstetrical outcomes that is linear because greater degrees of TSH elevation are associated with increased risks to the pregnancy. Such adverse outcomes also appear to be influenced by concomitant antithyroid autoimmunity. Exemplifying this, a large prospective study of 3315 women demonstrated the additive effect of anti-TPO positivity to the degree of TSH elevation. In anti-TPO–positive women the risk of pregnancy loss increased significantly beyond a TSH concentration >2.5mU/L (OR 4.95 for TSH 2.5–5.2),with an even greater increase when TSH was >5.2mU/L (OR 9.56 for TSH 5.2–10mU/L), whereas in anti-TPO–negative women, significant increases in risk of pregnancy loss was identified only when TSH concentrations exceeded 5.2mU/L (OR 3.4 for TSH 5.2–10).

23.4.1.4.3 Managing overt hypothyroidism

Treatment of overt hypothyroidism is recommended during pregnancy. (Strong recommendation, moderate-quality evidence)

Overt maternal hypothyroidism has consistently been shown to be associated with an increased risk of adverse pregnancy complications as well as detrimental effects upon fetal neurocognitive

development. Specific adverse outcomes associated with overt maternal hypothyroidism include increased risks of premature birth, low birth weight, pregnancy loss, and lower offspring IQ.

A recent retrospective study of more than 1000 pregnant women on chronic LT4 replacement, showed that the risk of pregnancy loss increased proportionally to the degree of TSH elevation, with no increased risk associated with TSH normalization.

Nonetheless, available data confirm the benefits of treating severe hypothyroidism during pregnancy.

The recommended treatment of maternal hypothyroidism is administration of oral LT4. Other thyroid preparations such as T3 or desiccated thyroid should not be used in pregnancy. (Strong recommendation, low-quality evidence)

The ratio of T4 to T3 in desiccated thyroid preparations is 4.2:1, which is significantly lower than the 14:1 ratio of secretion by the human thyroid gland. This relative excess of T3 leads to supraphysiologic maternal levels of T3 and relatively low levels of T4. Patients using either desiccated thyroid or a treatment regimen combining T3 and T4 are likely at risk for having insufficient transfer of maternal T4 to the fetal brain.

It is notable that the majority of fetal T3 present in the CNS during pregnancy is derived from maternal T4 actively transported into this space. The fetal CNS is relatively impermeable to T3, which therefore argues against use of exogenous T3 during pregnancy.

For these reasons, the task force feels that any T3-containing preparation should be avoided for the treatment of maternal hypothyroidism during pregnancy.

In parallel to the treatment of hypothyroidism in a general population, it is reasonable to target a TSH in the lower half of the trimester-specific reference range. When this is not available, it is reasonable to target maternal TSH concentrations below 2.5 mU/L. (Weak recommendation, moderate-quality evidence)

Hypothyroid patients receiving LT4 treatment with a suspected or confirmed pregnancy (e.g., positive home pregnancy test) should independently increase their dose of LT4 by ± 20%–30% and urgently notify their caregiver for prompt testing and further evaluation. One means of accomplishing this is to administer two additional tablets weekly of the patient's current daily LT4 dosage. (Strong recommendation, high-quality evidence)

Clinical studies have confirmed that the increased requirement for thyroxine (or exogenous LT4) occurs as early as 4–6 weeks of pregnancy. Such requirements gradually increase through 16–20 weeks of pregnancy and plateau thereafter until the time of delivery. These data provide the basis for recommending adjustments of LT4 dosage when affected women become pregnant and also for the timing of follow-up intervals for TSH in treated patients.

Dosage augmentation should occur as soon as possible when a missed menstruation or suspected pregnancy occurs, and this should be discussed with every patient in the prepregnancy setting. Confirmatory biochemical testing should also occur simultaneously.

Following delivery

Following delivery, LT4 should be reduced to the patient's preconception dose. Additional thyroid function testing should be performed at approximately 6 weeks post-partum. (Strong recommendation, moderate-quality evidence)

Some women in whom LT4 is initiated during pregnancy may not require LT4 post-partum. Such women are candidates for discontinuing LT4, especially when the LT4 dose is ≤ 50 μg/d. The decision to discontinue LT4, if desired, should be made by the patient and their caregiver. If LT4 is discontinued, serum TSH should be evaluated in approximately 6 weeks. (Weak recommendation, moderate-quality evidence)

23.4.1.4.4 Managing subclinical hypothyroidism

Subclinical hypothyroidism in pregnancy should be approached as follows:
(a) LT4 therapy is recommended for

- **TPOAb-positive women with a TSH greater than the pregnancy-specific reference range (Strong recommendation, moderate-quality evidence)**
- **TPOAb-negative women with a TSH greater than 10.0 mU/L. (Strong recommendation, low-quality evidence)**

(b) LT4 therapy may be considered for

- **TPOAb-positive women with TSH concentrations >2.5 mU/L and below the upper limit of the pregnancy-specific reference range. (Weak recommendation, moderate-quality evidence)**
- **TPOAb-negative women and TPOAb-negative women with TSH concentrations greater than the pregnancyspecific reference range and below 10.0 mU/L. (Weak recommendation, low-quality evidence)**

(c) LT4 therapy is not recommended for

- **TPOAb-negative women with a normal TSH (TSH within the pregnancy-specific reference range or <4.0 mU/L if unavailable). (Strong recommendation, high-quality evidenc)**

Subclinical hypothyroidism is variably associated with an increased risk of adverse pregnancy outcomes in most, but not all studies, partly because separate studies use differing cutoffs to define an elevated TSH concentration. These include adverse effects on pregnancy outcome (i.e., pregnancy loss), adverse perinatal outcomes (i.e., premature delivery, hypertensive disorders), and adverse neurocognitive outcomes (IQ) in offspring.

Together, despite some differences in study design, biochemical cutoffs applied and slightly differing endpoints, the above studies overall indicate an increasing risk of pregnancy-specific complications, most notably pregnancy loss and preterm delivery, in relation to elevated maternal TSH concentrations. Importantly, however, this effect is exacerbated by the presence of elevated TPOAb,

such that any additive risk is apparent in TPOAb-positive women when TSH exceeds 2.5 mU/L. However, in TPOAb-negative women similar adverse risk is not consistently apparent until maternal TSH exceeds 5–10 mU/L.

Taken together, these prospective results provide insufficient evidence to conclude that treatment of subclinical hypothyroidism is associated with improved neurocognitive outcomes in offspring.

However, despite the limitations of available interventional trials of LT4 therapy in this subclinically hypothyroid group, the data taken in aggregate appear to suggest a benefit of treatment, especially as it applies to reducing miscarriage in TPOAb-positive women. Therefore, it seems reasonable to recommend or consider LT4 treatment for specific subgroups of pregnant women with subclinical hypothyroidism. The strength of such recommendations, however, should differ depending on TPOAb status, as will the strength of evidence supporting treatment for each subgroup. This recommendation also necessitates that any pregnant women with an elevated TSH concentration must also be evaluated for TPOAb status. In making the recommendation, the task force acknowledges the very low risk inherent in initiating low-dose LT4 treatment. A dose of only 50 lg/d is typically required for effective treatment of subclinically hypothyroid women.

23.4.1.4.5 Monitoring hypothyroidism and subclinical hypothyroidism

Women with overt and subclinical hypothyroidism (treated or untreated) or those at risk for hypothyroidism (e.g., patients who are euthyroid but TPOAb or TgAb positive, post-hemithyroidectomy, or treated with radioactive iodine) should be monitored with a serum TSH measurement approximately every 4 weeks until midgestation and at least once near 30 weeks gestation. (Strong recommendation, high-quality evidence)

In women who are TPOAb positive, both overt and subclinical hypothyroidism may occur because of a lack of ability of the thyroid to augment production when needed during pregnancy.

In summary, euthyroid patients who are antithyroid Ab positive, post-hemithyroidectomy, or treated with radioactive iodine have an increased propensity for the development of hypothyroidism in gestation and should be monitored regularly.

Based on findings extrapolated from investigations of treated hypothyroid women from early pregnancy onwards, it is reasonable to evaluate these women for TSH elevation approximately every 4 weeks during pregnancy. Serial testing is preferably continued through midpregnancy because the increased T4 demand continues throughout the first half of gestation.

Treated hypothyroid women of reproductive age should be counseled regarding the likelihood of increased demand for LT4 during pregnancy. Such women should also be counseled to contact their caregiver immediately upon a confirmed or suspected pregnancy. (Strong recommendation, high-quality evidence)

Between 50% and 85% of LT4-treated hypothyroid women need to increase exogenous LT4 dosing during pregnancy.

In hypothyroid women treated with LT4 who are planning pregnancy, serum TSH should be evaluated preconception, and LT4 dose adjusted to achieve a TSH value between the lower reference limit and 2.5 mU/L. (Strong recommendation, moderate-quality evidence)

The preconception level of TSH as well as other factors can also influence the rapidity and extent of LT4 augmentation necessary to maintain a euthyroid state during pregnancy.

Different cutoff values for preconception TSH, ranging from <1.2 to <2.5 mU/L have been advocated. In one study, only 17% of women with TSH <1.2 mU/L had to increase LT4 dose later during pregnancy. Given this, it is recommended that all treated hypothyroid women (currently receiving LT4) optimize thyroid parameters preconception. A maternal serum TSH concentration <2.5 mU/L is a reasonable goal for such women.

In the care of women with adequately treated hypothyroidism, no other maternal or fetal testing (such as serial fetal ultrasounds, antenatal testing, and/or umbilical blood sampling) is recommended beyond measurement of maternal thyroid function unless needed due to other circumstances of pregnancy. An exception to this is women with GD effectively treated with 131I ablation or surgical resection, who require TSH receptor antibody (TRAb) monitoring. (Strong recommendation, moderate-quality evidence)

For recommendation concerning adjustment of preconception LT4 dose in treated hypothyroid women during pregnancy see section on hypothyroidism management

23.4.1.4.6 Euthyroid women with positive thyroid antibodies

Euthyroid pregnant women who are TPOAb or TgAb positive should have measurement of serum TSH concentration performed at time of pregnancy confirmation and every 4 weeks through mid-pregnancy. (Strong recommendation, high-quality evidence.)

Anti-TPO or anti-Tg thyroid autoantibodies are present in 2% to 17% of unselected pregnant women. The prevalence of antibodies varies with ethnicity.

Dietary iodine intake may also be associated with anti-thyroid Ab positivity during pregnancy.

While the task force acknowledges that testing for thyroid autoimmunity using only TPOAb would likely miss a small proportion of women with isolated Tg antibodies, we note that the vastmajority of studies investigating thyroid autoimmunity and clinical outcomes used only TPOAb measurements. For this reason, the task force recommends assessment of TPOAb when testing for the presence of thyroid autoimmunity.

In women with thyroid autoimmunity, hypothyroidism may occur because of the stress of pregnancy because the ability of the thyroid to augment hormone production is compromised.

The authors found that in TPOAb-positive euthyroid women, TSH levels increased as gestation progressed, from a mean of 1.7mU/L (12th week) to 3.5mU/L (term), with 19% of women having a supranormal TSH value at delivery. Because the risk of TSH elevation is increased in this population, increased surveillance of euthyroid thyroid Ab–positive women should occur.

Intravenous immunoglobulin treatment of euthyroid women with a history of recurrent pregnancy loss is not recommended. (Weak recommendation, low-quality evidence)

Endocrine disorders have been previously recognized as risk factors for spontaneous pregnancy loss. Thyroid dysfunction has similarly been associated with increased pregnancy loss (161) Although a clear association has been demonstrated between thyroid antibodies and spontaneous pregnancy loss, it does not prove causality and the underlying mechanisms for such an association remain unclear.

Insufficient evidence exists to conclusively determine whether LT4 therapy decreases pregnancy loss risk in TPOAb-positive euthyroid women who are newly pregnant. However, administration of LT4 to TPOAb-positive euthyroid pregnant women with a prior history of loss may be considered given its potential benefits in comparison with its minimal risk. In such cases, 25–50 lg of LT4 is a typical starting dose. (Weak recommendation, low-quality evidence)

In contrast, LT4 administration in low dosage (25–50 lg/d) is safe. Therefore, its use among patients with recurrent pregnancy loss may be reasonably considered in the setting of early gestation, especially when no other known cause of prior pregnancy loss has been identified.

Insufficient evidence exists to recommend for or against treating euthyroid pregnant women who are thyroid autoantibody positive with LT4 to prevent preterm delivery. (No recommendation, insufficient evidence)

The relationship between thyroid autoantibodies and preterm delivery has been investigated with mixed results…. Together, these data suggest that thyroid autoantibody positivity is associated with increased risk for preterm delivery. In contrast to association studies, interventional studies of LT4 therapy for the prevention of preterm delivery are sparse. Therefore, at present, there are

Insufficient data from which to draw any conclusion regarding the utility of LT4 administration for the purpose of reducing preterm delivery.

23.4.1.4.7 Role of dietary supplements

Iodine and pregnancy

All pregnant women should ingest approximately 250 µg iodine daily. To achieve a total of 250 µg iodine ingestion daily, strategies may need to be varied based on country of origin. (Strong recommendation, high-quality evidence)

In most regions, including the United States, women who are planning pregnancy or currently pregnant, should supplement their diet with a daily oral supplement that contains 150 µg of iodine in the form of potassium iodide. This is optimally started 3months in advance of planned pregnancy. (Strong recommendation, moderate-quality evidence)

Severe iodine deficiency in pregnant women has been associated with increased rates of pregnancy loss, stillbirth, and increased perinatal and infant mortality.
Specifically, maternal and fetal iodine deficiency in pregnancy have adverse effects on the cognitive function of offspring. Iodine deficiency is the leading cause of preventable intellectual deficits worldwide.

Universal salt iodization is the most cost-effective way of delivering iodine and improving maternal and infant heath.

In Europe many countries, including Belgium, the Czech Republic, Denmark, France, Latvia, Norway, Spain, and the United Kingdom, have recorded significant iodine deficiency in their pregnant populations.
Institute of Medicine recommended dietary allowances to be used as goals for individual total daily iodine intake (dietary and supplement) are:

- 150 µg/d for women planning a pregnancy,
- 220 µg/d for pregnant women,
- and 290 µg/d for women who are breastfeeding.

The WHO recommends 250 µg/d for pregnant and lactating women.

In low-resource countries and regions where neither salt iodization nor daily iodine supplements are feasible, a single annual dose of ± 400 mg of iodized oil for pregnant women and women of childbearing age can be used as a temporary measure to protect vulnerable populations. This should not be employed as a long-term strategy or in regions where other options are available. (Weak recommendation, moderate-quality evidence)

There is no need to initiate iodine supplementation in pregnant women who are being treated for hyperthyroidism or who are taking LT4. (Weak recommendation, low-quality evidence)

Women consuming levothyroxine (LT4) regularly do not require supplemental iodine because the substrate is no longer needed for hormone formation.

Excessive doses of iodine exposure during pregnancy should be avoided, except in preparation for the surgical treatment of GD. Clinicians should carefully weigh the risks and benefits when ordering medications or diagnostic tests that will result in high iodine exposure. (Strong recommendation, moderate-quality evidence)

Some individuals do not appropriately escape from the acute Wolff–Chaikoff effect, making them susceptible to hypothyroidism in the setting of high iodine intake. The fetus may be particularly susceptible, since the ability to escape from the acute Wolff–Chaikoff effect does not fully mature until about week 36 of gestation.

Concern exists that some populations may be exposed to excess iodine, possibly resulting in a high prevalence of thyroid dysfunction, an increased rate of hyperthyrotrophinemia, and an increased rate of hyperthyroid newborns. In addition, iodine-induced hypothyroidism has been reported in infants exposed to excess iodine from radiocontrast agents.

It should be recognized that even low-dose iodine supplementation may trigger thyroid autoimmunity in a small proportion of women.

Sustained iodine intake from diet and dietary supplements exceeding 500 µg daily should be avoided during pregnancy due to concerns about the potential for fetal thyroid dysfunction. (Strong recommendation, moderate-quality evidence)

The U.S. Institute of Medicine has defined the tolerable upper limit for daily iodine intake as 1100 µg/d in all adults, including pregnant women and the WHO has stated that daily iodine intake >500 µg may be excessive in pregnancy. Recent population data support theWHO threshold.

In addition, some dietary supplements such as kelp and some iodine preparations may contain very large amounts of iodine (several thousand times higher than the daily upper limit) and should not be taken. Ingestion of iodine and kelp supplements containing in excess of 500 µg/d is not recommended in pregnancy or lactation.

Median UICs can be used to assess the iodine status of populations, but single spot or 24-hour UICs are not a valid marker for the iodine nutritional status of individual patients. (Strong recommendation, high-quality evidence)

However, in areas of even mild to moderate iodine deficiency, total-body iodine stores, as reflected by urinary iodine values, decline gradually from the first to the third trimester of pregnancy.

Because there is substantial diurnal and day-to-day variation in urinary iodine excretion, urinary iodine concentrations (UICs) cannot be used to identify particular individuals with iodine deficiency. Therefore, iodine levels are a population rather than individual marker and outside unusual settings urinary iodide testing is not beneficial for individual use.

<u>Euthyroid women with positive thyroid antibodies and selenium</u>

Selenium supplementation is not recommended for the treatment of TPOAb-positive women during pregnancy. (Weak recommendation, moderate-quality evidence)

Some studies evaluating nonpregnant women have shown that selenium can diminish TPOAb concentrations. However, this reduction has not been observed in all studies.

Euthyroid TPOAb positive pregnant women randomized to treatment with 200 µg/d selenium not only had a significant decrease in the frequency of postpartum thyroid dysfunction ($p < 0.01$) but also had lower TPOAb concentrations during pregnancy compared to those in the untreated group. Importantly, this trial did not measure urinary iodine, a potential confounder because iodine status may influence the thyroidal effects of selenium.

However, in another recent randomized clinical trial performed in mildly iodine-deficient British pregnant women, treatment with 60 µg of selenium daily did not affect TPO concentrations or TPOAb positivity.

Thus, conflicting data regarding selenium supplementation make any generalized recommendation unreliable, especially to regions with different intakes of iodine, selenium, or both.

In addition, patients treated with selenium could be at higher risk for developing type 2 diabetes mellitus.

*23.4.1.5 **ETA 2014***

23.4.1.5.1 Screening for thyroid hypofunction

Despite the beneficial effects of levothyroxine treatment on obstetric outcome and the fact that the previously recommended targeted approach to screening thyroid function will miss a large percentage of women with thyroid dysfunction, we do not recommend universal screening for SCH because of the lack of grade 1 evidence. (2S)

Note: although there are still no well-controlled studies to justify universal screening, the majority of the authors (C.D., A.H.-D., J.L., R.N.) recommend universal screening because of the beneficial effects of levothyroxine treatment on unknown overt hypothyroidism, on obstetric outcome and the fact that the targeted approach will miss a large percentage of women with SCH, especially in mildly iodine-deficient women. (2W)

The universal screening of asymptomatic pregnant women for hypothyroidism in the first trimester is controversial. Because of insufficient evidence, and because the criteria for universal screening are not all satisfactory, most professional societies essentially from iodine sufficient countries recommend targeted case finding rather than universal screening.

All current recommendations support a targeted screening strategy, but such a strategy may miss at least from 33 to 81% of women with hypothyroidism. Therefore some endocrinologists have argued for universal screening for thyroid dysfunction in pregnant women or those planning to become pregnant.

To date there is limited evidence that levothyroxine treatment of pregnant women with SCH, isolated hypothyroxinaemia or thyroid autoimmunity is beneficial. Therefore, there is ongoing debate regarding the need for universal screening for thyroid dysfunction during pregnancy.

Efforts are still required to provide more high-quality evidence to justify screening.

23.4.1.5.2 Diagnosing thyroid hypofunction

Trimester-specific reference ranges for TSH and T4 (total or free) should be established in each antenatal hospital setting. Local variations may occur. (2S)

If TSH trimester-specific reference ranges are not available in that laboratory, the following reference range upper limits are recommended: first trimester, 2.5 mU/l; second trimester, 3.0 mU/l; third trimester, 3.5 mU/l. (2W)

The reference interval of thyroid function tests in pregnant women differs from that of the general population and among trimesters in the same patient. As the median TSH level is lower in the first trimester of pregnancy when compared with the non-pregnant reference range, the implementation of trimester-specific reference ranges is recommended in order to avoid misclassification of thyroid dysfunction during pregnancy. On the base of published studies, mostly from western countries, either the guidelines sponsored by the American Thyroid Association or by the American Endocrine Society suggested the following reference range: first trimester, 0.1 to 2.5 mU/l; second trimester, 0.2 to 3.0 mU/l; third trimester, 0.3 to 3.0–3.5 mU/l. It is a matter of discussion whether these reference ranges should be used worldwide.

TT4 and FT4 assays are both suitable for thyroid function testing in pregnancy. (2S)

TSH should be measured at the beginning of pregnancy if screening is performed. If TSH is elevated, FT4 and TPOAb should be determined. This will enable SCH or overt hypothyroidism to be diagnosed, in addition to identifying patients with isolated hypothyroxinaemia as well as central hypothyroidism. (1S)

In the case of elevated TSH and negative TPOAb, TgAb should be measured. Thyroid ultrasound may be performed to evaluate hypo-echogenicity or an inhomogeneous echo pattern. (2S)

Other than the increase mentioned above in human chorionic gonadotrophin and the downward shift of TSH, pregnancy is also characterized by an increased iodine renal clearance, increased serum T4 -binding globulin, and inner-ring deiodination of T3 and T4 by the placenta.

These metabolic changes may also influence the T4 concentration that appears to be increased during the first trimester and relatively decreased during the second and the third trimesters. Given the uncertainty in FT 4 measurement during pregnancy, alternative strategies have also been suggested. The first is that the non-pregnant TT4 range (5–12 µg/dl or 50–150 nmol/l) can be adapted by multiplying this range by 1.5-fold.

…the current guideline underlines the importance of ethnic variation in trimester-specific reference ranges for TSH and FT4.

In developing countries the most frequent cause of hypothyroidism is represented by severe iodine deficiency, while in developed countries it is by chronic autoimmune thyroiditis (CAT).

Thyroid auto-antibodies are detected in about 50% of pregnant women with SCH and in more than 80% with overt hypothyroidism. Hence in patients with SCH the measurement of thyroid peroxidase antibodies (TPOAb) is recommended to establish if the woman has thyroid autoimmunity.

After the first trimester the test for thyroid antibodies may be negative due to the immune suppression seen in pregnancy; in the presence of elevated TSH values and negative thyroid antibodies, thyroid ultrasonography may be helpful in detecting abnormal thyroid texture and subsequent diagnosis.

…the current guideline… recognizes the utility of testing TgAb to ascertain autoimmunity as the aetiology of SCH in pregnancy.

23.4.1.5.3 Managing hypothyroidism

Women with SCH and those with overt hypothyroidism desiring pregnancy should take levothyroxine in a dose to ensure a TSH level of <2.5 mU/l. (2S)

In hypothyroid women already treated with levothyroxine before conception, the amount of increase in levothyroxine may vary from 25 to 50%, depending on the aetiology of hypothyroidism and prepregnancy TSH level. (1S)

23.4.1.5.4 Managing subclinical hypothyroidism

Further studies are required to determine the precise effects of SCH on obstetric outcome in addition to their effects on childhood neuro-intellectual development. (2S)

Current data indicate an increase in pregnancy loss, gestational diabetes, gestational hypertension, pre-eclampsia and preterm delivery in women with SCH in pregnancy.

The association between SCH in pregnancy and impaired neuropsychological development of the offspring is inconsistent.

SCH arising before conception or during gestation should be treated with levothyroxine. (2S)

The debate about substitution therapy in SCH is still open both for non-pregnant and pregnant patients. The background of this debate relates to association studies which show detrimental effects of SCH on the course of pregnancy and on the IQ of children born from hypothyroid mothers. Since

results on cognitive testing of children <3 years of age do not predict future development, long-term data are needed.

A randomized control trial has shown that levothyroxine treatment decreased the occurrence of adverse events in the mother and fetus in women who were TPOAb+ and who had a circulating baseline TSH level >2.5 mU/l during the first trimester of pregnancy. A recent prospective study from Belgium found the same reduction in miscarriage rate when treating TPOAb+ women with TSH >1 mU/l with 50 µg of levothyroxine.

To date, only 1 single prospective RCT has assessed the effect of levothyroxine therapy for mild maternal thyroid failure during pregnancy on offspring IQ. At the age of 3, children of women treated with levothyroxine (started at a median gestational age of 13 weeks) had IQ tests which did not differ from the children of untreated women.

Levothyroxine treatment of SCH would appear to have the potential benefits which outweigh the potential risks.

Meanwhile it is reasonable practice to maintain TSH values in women planning pregnancy below 2.5 mU/l, especially in those with positive TPOAb; newly diagnosed patients should be treated in order to normalize maternal serum TSH values within the trimester-specific pregnancy reference range.

Despite the pivotal role of T4 in the neurodevelopment of the fetus, there is no demonstrable effect of maternal levothyroxine treatment on child neurodevelopment in relation to maternal SCH or maternal hypothyroxinaemia (normal TSH values with FT4 below the 5th centile).

The recommended treatment of maternal hypothyroidism is administration of oral levothyroxine. The use of levothyroxine-T3 combinations or desiccated thyroid is not recommended. (1S)

It is strongly recommended not to use other thyroid preparations such as T3 or desiccated thyroid, which cause lowering of serum T4 levels In patients with morning sickness, the administration of levothyroxine late at night may be a valid option.

The goal of levothyroxine treatment is to normalize maternal serum TSH values within the trimester-specific pregnancy reference range. (1S)

In newly diagnosed patients with SCH in pregnancy, a starting dose of 1.20 µg/kg/day is advised. (2S)

When hypothyroidism is newly discovered during pregnancy, a study suggests initiating the treatment with the following levothyroxine doses: 1.20 µg/kg/day for SCH with TSH ≤ 4.2 mU/l, 1.42 µg/kg/day with TSH >4.2–10 and 2.33 µg/kg/day for overt hypothyroidism.

Euthyroid women with positive thyroid antibodies

The question as to whether levothyroxine therapy is indicated for euthyroid women with positive thyroid antibodies is beyond the scope of this guideline.

Women desiring pregnancy

Women with SCH and those with overt hypothyroidism desiring pregnancy should take levothyroxine in a dose to ensure a TSH level of <2.5 mU/l. (2S)

Following delivery

Following delivery the levothyroxine dose should be reduced to the preconception dose. Women diagnosed with SCH during pregnancy with TSH less than 5 mU/l and negative TPOAb could stop levothyroxine after delivery and have thyroid function checked 6 weeks after delivery. (2S)

Women diagnosed with SCH during pregnancy should be re-evaluated 6 months and 1 year after delivery to ascertain the continuing requirement for levothyroxine. (2S)

…suggesting that the majority of cases of SCH in pregnancy are transient and recover after pregnancy. Women with TPOAb and TSH greater than 5 mU/l in pregnancy were more likely to have persistently elevated TSH.

23.4.1.5.5 Monitoring subclinical hypothyroidism

TSH values should be checked every 4–6 weeks during the first trimester and once during the second and third trimesters, and the levothyroxine dose should be adjusted as necessary to reduce TSH to <2.5 mU/l or within the trimester-specific reference range. (2S)

23.4.1.5.6 Role of dietary supplements

The daily iodine intake during pregnancy and lactation should be at least 250 µg and should not exceed 500 µg. (1S)

A sufficient iodine intake is usually provided by supplementing euthyroid pregnant and lactating women with formulas containing 150 µg of iodine/day, ideally before conception. (1S)

In pregnancy there is about a 50% increase in iodine requirement to achieve a dietary intake of 250 µg/day. In chronically iodine-deficient pregnant women, depleted iodine thyroid stores are not able to compensate for increased demands; if deficiency is not corrected, it may result in goitre formation and maternal hypothyroidism.

The contribution of iodine deficiency to the incidence of SCH and isolated hypothyroxinaemia is variable, depending at least on the degree of iodine deficiency and the incidence of thyroid antibodies.

An elevated body mass index (BMI) increases the risk of isolated hypothyroxinaemia in iodine-deficient first trimester women, and the high prevalence of thyroid disorders including SCH in pregnancy in Belgium has been noted.

Iodine supplementation during pregnancy (iodized salt vs. iodine supplements) may not influence postnatal child development, although supplementation in areas of mild iodine deficiency may also be beneficial.

According to the WHO, pregnant and lactating women should be provided with 250 µg iodine daily. This may be achieved by administering iodine supplements containing 150–250 µg of iodine in the form of potassium iodide often as prenatal and pregnancy vitamin supplements. Adequate iodine intake during pregnancy (250 µg of iodine daily) should be preferably achieved before conception. In countries with successful salt iodization programmes, pregnancy-desiring women should be additionally supplemented with 50 µg of iodine. The daily intake of iodine should not exceed 500 µg.

The effectiveness and side effects of iodine prophylaxis together with or without levothyroxine therapy in subclinically hypothyroid women should be assessed. (3S)

Iodine prophylaxis in subclinically hypothyroid pregnant women has not been studied.

Whether iodine administration will prevent SCH in iodine-deficient women is not clear. The data on TSH levels and iodine nutrition in pregnancy are conflicting.

23.4.1.6 ETA 2021

ETA 2021 is a guideline on thyroid disorders prior to and during assisted reproduction, supposing women with fertility problems. No specific recommendations or comments were provided regarding pregnancy.

23.4.1.7 ASRM 2015

ASRM 2015 is a specific guideline on subclinical hypothyroidism in infertile female population but comment and recommendation were also given concerning outcome of subclinical hypothyroidism during pregnancy. There are reported in this section.

23.4.1.7.1 Diagnosing thyroid hypofunction

While thyroid antibody testing is not routinely recommended, one might consider testing anti-thyroperoxidase (TPO) antibodies for repeated TSH values >2.5 mIU/L or when other risk factors for thyroid disease are present. (Grade C)

If anti-TPO antibodies are detected, TSH levels should be checked and treatment should be considered if the TSH level is over 2.5 mIU/L. (Grade B)

The Endocrine Society does not recommend universal screening of healthy women before pregnancy. However, their guideline could not reach agreement with regard to screening recommendations for all newly pregnant women.

The AACE does not recommend universal screening for patients who are pregnant or planning pregnancy, including assisted reproduction patients.

The American College of Obstetricians and Gynecologists does not recommend routine screening for hypothyroidism in pregnancy. However, screening women at high risk (family or personal history of thyroid disease, physical findings or symptoms suggestive of goiter or hypothyroidism, type 1 diabetes mellitus, infertility, history of miscarriage or preterm delivery, or personal history of autoimmune disorders) is advised.

Additional testing may be advised in the face of prior head or neck irradiation, history of infertility, or recurrent miscarriage or preterm delivery.

There is good evidence against recommending universal screening of thyroid function before or during pregnancy. Screening is not recommended beyond those women with clinical evidence suggesting ovulatory abnormality and those identified as ‘‘high risk’’as described previously.

It has been recommended that the normal range of TSH for pregnancy be modified. This is because human chorionic gonadotropin (hCG) can bind to the TSH receptor and influence TSH values.

Accordingly, the Endocrine Society recommends the following: The reference range of TSH in pregnancy is to be dependent on the trimester: 2.5 is the recommended upper limit of normal in the first trimester, 3 in the second and 3.5 in the third.

The normal reference range for TSH changes in pregnancy. The upper limit of normal in most laboratories is 4 mIU/L for nonpregnant women and 2.5 mIU/L in the first trimester of pregnancy.

23.4.1.7.2 Managing subclinical hypothyroidism

During the first trimester of pregnancy it is advisable to treat when the TSH is >2.5 mIU/L. (Grade B)

There is fair evidence that SCH during pregnancy is associated with adverse obstetric outcomes in pregnant patients with TSH outside of the normal reference range in pregnancy. However, there are no data to evaluate whether pre-pregnancy TSH levels between 2.5 and 4 mIU/L are associated with adverse obstetric outcomes.

There is good evidence that overt hypothyroidism and fair evidence that SCH diagnosed in pregnancy are associated with adverse neurodevelopmental outcomes. However, there is no evidence that prepregnancy TSH levels between 2.5 and 4 mIU/L are associated with adverse developmental outcomes.

There is good evidence that levothyroxine treatment in women with SCH defined as TSH >4.0 mIU/L is associated with improvement in pregnancy and miscarriage rates. There is insufficient evidence that levothyroxine therapy in women with TSH levels between 2.5 and 4 mIU/L is associated with improvement in pregnancy and miscarriage rates.

There is fair evidence based on the only randomized clinical trial that levothyroxine treatment for SCH (defined as TSH outside the normal pregnancy range) does not improve developmental outcomes.

There are limited data on whether TSH values >2.5 mIU/L and less than the upper range of normal during pregnancy are associated with adverse pregnancy outcomes. Therefore, treating SCH when the TSH is between 2.5 mIU/L and the upper range of normal prior to pregnancy remains controversial. However, given that there appears to be benefit in some subgroups and minimal risk, it is reasonable to treat even though the evidence is weak. Alternatively, it is reasonable to monitor levels and treat above nonpregnant and pregnancy ranges.

There is fair evidence that treatment of SCH when TSH levels are >4.0 mIU/L is associated with improved pregnancy rates and decreased miscarriage rates.

There is fair evidence that SCH when TSH levels are >4 mIU/L during pregnancy is associated with adverse developmental outcomes; however, treatment did not improve developmental outcomes in the only randomized trial.

If anti-TPO antibodies are detected, TSH levels should be checked and treatment should be considered if the TSH level is over 2.5 mIU/L. (Grade B)

There is good evidence that thyroid autoimmunity is associated with miscarriage and fair evidence that it is associated with infertility. Levothyroxine treatment may improve pregnancy outcomes in women with positive thyroid antibodies, especially if the TSH level is over 2.5 mIU/L.

23.4.2 Women with fertility problems

23.4.2.1 NICE 2019

Provide people with thyroid disease, and their family or carers if appropriate, with written and verbal information on:

- **…**
- **how thyroid disease and medicines may affect pregnancy and fertility.**

23.4.2.2 BMJ 2019

BMJ 2019 is a guideline on the treatment of subclinical hypothyroidism, no specific recommendations or comments were provided regarding infertility.

23.4.2.3 BTA 2016

BTA 2016 is a general guideline on hypothyroidism, no specific recommendations or comments were provided regarding infertility.

23.4.2.4 ATA 2017

ATA 2017 is a general guideline on thyroid disease during pregnancy including thyrotoxicosis. Several sections from this guidelines also considered infertility. Comments and recommendation regarding thyroid disease during infertility are reported in this chapter: the impact of thyroid illness upon infertility and assisted reproduction and screening for thyroid dysfunction before or during pregnancy. Only the information concerning hypothyroidism have been reported.

23.4.2.4.1 Screening for thyroid dysfunction

There is insufficient evidence to recommend for or against universal screening for abnormal TSH concentrations preconception, with the exception of women planning assisted reproduction or those known to have TPOAb positivity. (No recommendation, insufficient evidence)

While screening women for thyroid disease preconception may also prove beneficial, there are currently no data to support such an approach, and the process of testing such a high volume of women, the majority of whom will not become pregnant, seems impractical.

Universal screening for TPOAb in early pregnancy or possibly preconception may also prove an attractive alternative, but it warrants further investigation. The high prevalence of anti-TPO positivity (up to 17% in reproductive age women), the extensive findings demonstrating increased risks in the anti-TPOAb-positive population, and the fact that this test would also identify women at risk for developing hypothyroidism during gestation (20%) and PPT (30–50%), make this test an attractive theoretical consideration. However, no data support this testing algorithm at present.

Evaluation of serum TSH concentration is recommended for all women seeking care for infertility. (Weak recommendation, moderate-quality evidence)

23.4.2.4.2 Managing hypothyroidism

LT4 treatment is recommended for infertile women with overt hypothyroidism who desire pregnancy. (Strong recommendation, moderate-quality evidence)

Thus, despite imperfect data, the majority of evidence appears to support an association between overt thyroid dysfunction and an increased risk of infertility. Thyroid dysfunction is also reversible, and treatment is generally safe and may exert a positive effect on fertility. Therefore, it is reasonable to treat overt thyroid dysfunction in infertile women, with the goal of normalizing thyroid function.

23.4.2.4.3 Managing subclinical hypothyroidism

Insufficient evidence exist to determine if LT4 therapy improves fertility in subclinically hypothyroid, thyroid autoantibody–negative women who are attempting natural conception (not undergoing ART). However, administration of LT4 may be considered in this setting given its ability to prevent progression to more significant hypothyroidism once pregnancy is achieved. Furthermore, low dose LT4 therapy (25–50 µg/d) carries minimal risk. (Weak recommendation, low-quality evidence)

Different definitions of subclinical hypothyroidism have been used in different studies examining this question, and results have been inconsistent. Importantly, whether or not LT4 treatment increases the likelihood of conception in subclinically hypothyroid women not undergoing ART has not been studied in controlled trials. Thus, insufficient data exist for recommending for or against routineLT4 therapy in subclinically hypothyroid, thyroid autoantibody–negative infertile women who are attempting conception but not undergoing ART.

23.4.2.4.4 Euthyroid women with positive thyroid antibodies

A recent study from Belgium in women seeking fertility treatment showed that both TPOAb and TgAb were present in 8% of women, while 5% demonstrated isolated Tg antibodies and 4% demonstrated isolated TPOAb concentrations. Those women with isolated TgAb positivity had a significantly higher serum TSH than women without thyroid autoimmunity.

Insufficient evidence exists to determine if LT4 therapy improves fertility in nonpregnant, thyroid autoantibody–positive euthyroid women who are attempting natural conception (not undergoing ART). Therefore, no recommendation can be made for LT4 therapy in this setting. (No recommendation, insufficient evidence)

Limited evidence suggests that women with female-factor infertility are more likely to be TPOAb positive than age matched women who are not infertile, even if euthyroid.

23.4.2.5 ETA 2014

ETA 2014 is a guideline on the management of subclinical hypothyroidism in pregnancy. No specific recommendations or comments were provided regarding infertility.

23.4.2.6 ETA 2021

ETA 2021 is a guideline on thyroid disorders prior to and during assisted reproduction, supposing women with fertility problems. Only the specific recommendations and comments concerning subfertility are reported in this document, assisted reproduction not being considered for primary.

23.4.2.6.1 Link between fertility and thyroid hypofunction

Subfertility is a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse.

In women of reproductive age, both thyroid dysfunction and TAI are prevalent and have separately been associated with various reproductive difficulties.

Hypothyroidism prevalence varies from 2 to 4% and is largely attributed to TAI. SCH is more prevalent amounting for as high as 10% in women of fertile age.

Overt hypothyroidism

In OH…Indeed, menstrual aberrations are reported in 25–60% of the cases compared to 10% in euthyroid women. Overall, data suggest that OH is associated with an increased risk of adverse effects on fertility as well as early and late complications of pregnancy.

Scarce evidence exists on the impact of thyroid function on the FRs. Cramer et al. describe significant associations between higher TSH levels (>3.9 mIU/L) and fertilisation failure in 509 IVF patients, a relationship that remains intact when controlled for confounders. In a meta-analysis by Velkeniers et al., it was shown that LT4 treatment improved the FRs in women with TSH levels >4.0 mIU/L.

Subclinical hypothyroidism

Whether the prevalence of SCH is higher in subfertile women remains uncertain. Similarly, any detrimental impact of SCH on fertility is yet to be established. Different cutoffs used to define the upper limit of normal TSH concentration and a lack of well-designed prospective studies have led to contradictory conclusions.

…based on these studies, association with adverse fertility outcomes seems to surface at TSH levels >4.0 mIU/L.

Thyroid autoimmunity

Overall, TAI is characterized by increased levels of TPOAb and associated with high(er) TSH concentrations. Although a higher prevalence of elevated TgAb levels has been reported in women

with subfertility, their significance remains uncertain. Research examining TAI prevalence in subfertile women or any association between TAI and fertility outcomes is therefore largely based on the presence of increased TPOAb levels alone.

A meta-analysis pooling 4 studies found that thyroid antibodies are associated with unexplained subfertility in euthyroid patients (OR 1.5, 95% CI: 1.1–2.0).

On the one hand, a TH-dependent effect may occur as the risk of (subclinical) hypothyroidism in women with TAI is increased, especially during pregnancy. …On the other hand, it has also been speculated that the presence of TAI reflects a general immune imbalance that could lead to failure of implantation, and in a recent study, it was shown that TPO is expressed at gene and protein levels in the endometrium and placenta and may explain the higher frequency of miscarriage and infertility in patients with TAI.

An increased prevalence of TAI (mainly TPOAb) is reported in women with recurrent pregnancy loss and subfertility and associated with lower AMH levels.

In the meta-analysis, TAI was not associated with the NOR, and these data were confirmed in a recent study.

23.4.2.6.2 Screening for thyroid dysfunction

We recommend that all women seeking medical advice for subfertility should be screened for serum TSH and TPOAb. TgAb can be added systematically according to the local regulatory authority rules (1ØØØO).

We suggest that subfertile women with TSH levels >2.5 mIU/L and without increased TPOAb levels (according to the local reference range) should be screened for the presence of increased TgAb levels if not yet done at initial workup (2ØØOO).

We recommend screening women with POI and DOR for thyroid dysfunction (serum TSH) and autoimmunity (1, ØØØO).

In a prospective study in women suffering from POI, conducted at the National Institutes of Health in the USA, Hashimoto's thyroiditis was encountered in 37% of POI women with Turner syndrome (45XO) and in 15% of POI patients with 46,XX karyotype, a prevalence that significantly exceeded that in the female US population (i.e., 5.8%, $p < 0.001$; RR 3.0, 95% CI: 2.3–3.7). The European Society of Human Reproduction and Embryology recommends screening for TAI in all women diagnosed with spontaneous POI. Consequently, since women with POI/DOR have a higher prevalence of TAI, they might also have a higher prevalence of SCH.

Although thyroid disease appears to negatively affect the ovarian reserve in subsets of women with (unexplained) infertility and advanced reproductive age, a Belgian study in 4,894 young women with

and without fertility problems could not demonstrate an impact of TAI and hypothyroidism on AMH levels. Another large cross-sectional study in Chinese subfertility patients supports the concept that TAI may be related to idiopathic DOR: 1,044 women were grouped to low, normal, and high ovarian reserve categories according to age-adjusted AMH levels. Women with DOR demonstrated higher percentages of TPOAb (23.3%) when compared to counterparts with normal (14.6%) and high ovarian reserve (10.4%; *p* = 0.014).

We recommend screening subfertile women with unexplained subfertility or in their later reproductive years (i.e., ≥35 years) for thyroid dysfunction (serum TSH) and autoimmunity (1, ØØØO).

23.4.2.6.3 Managing hypothyroidism

We recommend LT4 treatment should be started promptly in case of overt thyroid dysfunction (1,ØØØO).

If treated with LT4, hormonal changes are usually reversed, restoring a normal menstrual pattern and potentially improving fertility.

We suggest LT4 treatment in subfertile women with TAI and serum TSH >2.5 mIU/L on a case-by-case basis to allow for optimized ovarian reserve (2, ØØOO).

However, there seems to be no benefit of LT4 treatment before conception on pregnancy outcomes in euthyroid women with TAI facing subfertility or recurrent miscarriage.

Only limited research was undertaken to answer the question whether LT4 supplementation exerts beneficial effects on functional ovarian reserve.

We recommend LT4 treatment when TSH values are above 4.0 mIU/L or ULRR (1,ØØOO).

Among subfertile women with TAI, a meta-analysis of 3 RCTs, including 2 studies that used TSH levels >4.0 mIU/L to define SCH, found a beneficial effect of LT4 on pregnancy after ART.

We recommend LT4 treatment in women with TAI and TSH levels >4.0 mIU/L/ULRR to keep TSH levels <2.5 mIU//L (1, ØOOO).

We suggest LT4 treatment in subfertile women with TAI and TSH levels >2.5 mIU/L on a case-by-case basis to allow for optimized embryo development (2,ØOOO).

23.4.2.7 ASRM 2015

23.4.2.7.1 Link between fertility and subclinical hypothyroidism

There is insufficient evidence that SCH (defined as TSH>2.5 mIU/L with a normal FT4) is associated with infertility.

The data assessing the effect of SCH on fertility are limited due to varied definitions of SCH (different TSH cutoffs) and lack of adequate control groups. Overall, the incidence of SCH is similar in infertile women and the general female population, although the mean TSH level may be slightly higher in a population of infertile women compared with controls.

There is good evidence that thyroid autoimmunity is associated with miscarriage and fair evidence that it is associated with infertility.

23.4.2.7.2 Screening for thyroid dysfunction

Currently available data support that it is reasonable to test TSH in infertile women attempting pregnancy. (Grade B)

While thyroid antibody testing is not routinely recommended, one might consider testing anti-thyroperoxidase (TPO) antibodies for repeated TSH values >2.5 mIU/L or when other risk factors for thyroid disease are present. (Grade C)

If anti-TPO antibodies are detected, TSH levels should be checked and treatment should be considered if the TSH level is over 2.5 mIU/L. (Grade B)

23.4.2.7.3 Diagnosing and managing thyroid dysfunction

Currently available data support that it is reasonable to test TSH in infertile women attempting pregnancy. If TSH concentrations are over the nonpregnant lab reference range (typically >4 mIU/L), patients should be treated with levothyroxine to maintain levels below 2.5 mIU/L. (Grade B)

Given the limited data, if TSH levels prior to pregnancy are between 2.5 and 4 mIU/L, management options include either monitoring levels and treating when TSH >4 mIU/L, or treating with levothyroxine to maintain TSH <2.5 mIU/L. (Grade C)

It is controversial whether or not to use first-trimester pregnancy thresholds for upper limit of TSH (i.e., >2.5 mIU/L) to diagnose and treat SCH in women attempting pregnancy.

Because the reference range of TSH changes when a woman becomes pregnant, some advocate using pregnancy thresholds for the treatment of women attempting conception in order to minimize the potential risks associated with SCH in pregnancy. This strategy has been controversial, since data are difficult to interpret. Their validity is hindered by a variety of methodological limitations, including the lack of proper controls, recall bias, and failure to control for confounders (i.e., age,

medical conditions) that are known to influence reproductive outcomes. Most importantly, the studies use different TSH cutoffs to define subclinical hypothyroidism.

If anti-TPO antibodies are detected, TSH levels should be checked and treatment should be considered if the TSH level is over 2.5 mIU/L. (Grade B)

23.5 Hypothyroïdism and body weight

23.5.1 NICE 2019

No specific recommendations or comments were provided

23.5.2 BMJ 2019

No specific recommendations or comments were provided

23.5.3 BTA 2016

23.5.3.1 Management of hypothyroidism in overweight patients

There is insufficient evidence of benefit to recommend that treatment with L-T4 be targeted to achieve low-normal serum TSH values or high-normal serum T3 values in patients with hypothyroidism, including those who are overweight, or those who have depression, dyslipidaemia, or who are athyreotic.(ATA, 1/++0)

23.5.3.2 Thyroid hormones in overweight patients without hypothyroidism

Recommend against the treatment of obesity with L-T4 in euthyroid individuals, due to a lack of treatment efficacy for this condition. (ATA, 1/++0)

Recommend against the treatment of obesity with synthetic L-T3 due to a lack of controlled data proving treatment efficacy for this indication. (ATA, 1/+00)

23.5.4 ESE 2020

ESE 2020 is a complete guideline on endocrine work-up in obesity, providing recommendations well beyond hypothyroidism and obesity. Only comments and recommendations regarding hypothyroidism (overt and subclinical) are reported in this document.

23.5.4.1 Link between body weight and hypothyroidism

We recommend that not all patients with obesity are routinely referred to an endocrinologist.

In most cases, despite obesity being a condition of endocrine and metabolic imbalance, obesity is not caused by other endocrine diseases or hormonal disturbances. The endocrinologist should be consulted in case of clear suspicion of an endocrine disease (e.g. endogenous hypercortisolism, hypogonadism in males or androgen excess in women).

We recommend that weight loss in obesity is emphasized as key to restoration of hormonal imbalances.

For most hormones (TSH, cortisol. testosterone), the proper equilibrium is usually restored following weight reduction, irrespective of therapeutic strategy (see following chapters for details).

We recommend that all patients with obesity are tested for thyroid function. (+++0)

Thyroid function is commonly assessed, independently of obesity, because hypothyroidism is one of the most common endocrine diseases. Screening of the general population is mostly not recommended, although some populations at risk, have been identified; interestingly, obesity is not among these conditions, but the usefulness to test TSH in obesity was recently suggested.

A higher prevalence of subclinical hypothyroidism in obesity has been shown. However, despite weight gain being a frequent complaint in hypothyroidism, it is usually of limited extent.

In line, treatment of overt hypothyroidism produces only a modest weight loss (usually of less than 10%), indicating that severe obesity is usually not secondary to hypothyroidism.

No study directly assessed the benefits and harms of screening versus no screening in obese populations. However, if 'true' hypothyroidism is present, it potentiates the risk of obesity to develop cardiovascular risk factors and features of metabolic syndrome. Hypothyroidism contributes to an unfavorable lipid profile, and thus, potentially increases vascular risk.

Finally, untreated hypothyroidism could blight the attempts at loosing body weight

However, some longitudinal studies suggest that changes in thyroid hormones are side effects of increasing body weight (BW) rather than the cause. Furthermore, abnormal thyroid function usually improves after weight loss obtained by calorie restriction or by bariatric surgery. This suggests that in obesity the increase in serum TSH (in the absence of thyroid autoantibodies) is likely an adaptive response rather than the primary event.

We recommend taking into account drugs and dietary supplements that interfere with hormone measurements as part of the hormonal evaluation in obesity.

Beside general drugs used to manage obesity complications, several dietary supplements are commonly taken by patients with obesity, with the aim of facilitating weight loss or well-being, controlling glucose metabolism or preventing cardiovascular events. Some of these exogenous

substances may interfere with the regulation of various hormonal axes as well as with hormonal assays.

23.5.4.2 Diagnosing hypothyroidism

We recommend that testing for hypothyroidism is based on TSH; if TSH is elevated, free T4 and antibodies (anti-TPO) should be measured. (++00)

According to American guidelines, TSH is the best screening test for thyroid dysfunction for the vast majority of clinical situations, in which normal TSH is enough to rule out primary hypothyroidism. Central hypothyroidism, with low-to-normal TSH concentrations and a disproportionately low concentration of fT4, is rare representing less than 1% of cases of hypothyroidism.

In patients with increased TSH, thyroid peroxidase (TPO) antibodies can predict progression to overt disease, with TPO antibodies levels >500 IU/mL indicating an increased risk to progress. Thus, assessment of TPO antibodies is recommended in case of subclinical hypothyroidism.

Although there is discussion about the value of thyroglobulin antibodies, especially in the context of obesity, the evidence is currently too weak to recommend testing for thyroglobulin antibodies; in individual cases, thyroglobulin testing can be considered.

We do not recommend the routine measurement of FT3 in patients with elevated TSH.

There are very few data on the incidence of non-thyroidal illness in the obese population but one publication suggested that inflammation may increase non-thyroidal illness in obesity.

In contrast, FT3 has been described to be higher in obesity than in lean people, this being mainly related to the nutritional status. This shows that the interpretation of FT3 in obesity is not straightforward.

We suggest that for obese patients the same normal hormonal values are applied as for non-obese. (+000)

However, no compelling evidence has been provided that using specific reference values for the obese population would help to identify patients with thyroid dysfunction who need treatment.

23.5.4.3 Management of hypothyroidism in overweight patients

We recommend that overt hypothyroidism (elevated TSH and decreased FT4) is treated in obesity irrespective of antibodies. (++00)

Although the issue is still controversial, treatment with levothyroxine substitution should be considered in case of overt hypothyroidism, or in mild hypothyroidism with TSH >10 mIU/L, in line with current guidelines.

In obesity, treatment of hypothyroidism is followed by a mild increase in resting energy expenditure but only a modest weight loss is achieved, mainly determined by excretion of excess body water.

The target of TSH is the same as in the general population and should not be adjusted with the aim at reducing BMI.

The l-thyroxine dose is usually to be reduced after weight loss achieved by bariatric surgery.

23.5.4.4 Thyroid hormones in overweight patients without hypothyroidism

We recommend against the use of thyroid hormones to treat obesity in case of normal thyroid function. (++00)

Thyroid hormone preparations and their derivatives have been extensively employed in the past century as anti-obesity drugs (the first clinical reports on the weight-lowering effect of sheep-derived thyroid extracts date from the 1890s) and sometimes are still inappropriately prescribed, despite specific recommendations against their use in euthyroid obese subjects.

Several studies have been performed to investigate the ability of thyroid hormone or their analogues to favour weight loss, without producing adverse effects due to iatrogenic thyrotoxicosis. Overall, these studies have demonstrated only minor effects in terms of efficacy, while increased urinary nitrogen excretion has been observed, indicating loss of fat-free tissue beside the occurrence of adverse effects on bone metabolism and affective status.

Furthermore, excessive thyroid hormone in patients with obesity already at risk for cardiovascular disease may facilitate the onset of cardiac arrhythmia, heart failure or ischemic events.

Apart from decreasing body weight, thyroid hormone also improves hepatic lipid metabolism, which was also used as an argument for use in obesity. The development of TRβ-selective agonist supposed to improve metabolic parameters without affecting heart rate did not have a conclusive outcome and the combined peptides that deliver FT3 specifically in the liver are not yet developed.

We recommend that hyperthyrotropinaemia (elevated TSH and normal FT4) should not be treated in obesity with the aim at reducing body weight (++00).

We suggest that for the decision to treat or not to treat hyperthyrotropinaemia, TSH level, thyroid antibodies, and age should be taken into account.

We suggest against the use of routine ultrasound of the thyroid gland irrespective of thyroid function.

23.5.5 NHG 2020

NHG 2020 is a general guideline on obesity. Only comments and recommendations regarding hypothyroidism and obesity (overt or subclinical) have been reported in this document.

23.5.5.1 Link between body weight and hypothyroidism

Besteed aandacht aan: symptomen van onderliggende oorzaken, bijvoorbeeld chronische ziekte(n) met bewegingsbeperking, hypothyreoïdie (voor symptomen, zie NHG-Standaard Schildklieraandoeningen), polycysteusovariumsyndroom (hirsutisme, irregulaire menses, acne), neurologische afwijkingen, verminderde visus of gezichtsveldbeperking (ruimte-innemend proces hypothalamus)

Volwassenen Raadpleeg NHG-Standaard Cardiovasculair risicomanagement of NHG-Standaard Diabetes mellitus type 2 voor de indicaties voor het opstellen van het cardiovasculaire risicoprofiel en het screenen op diabetes. Bij het vermoeden van hypothyreoïdie (overgewicht met 1 ander kenmerk behorend bij hypothyreoïdie), zie NHG-Standaard Schildklieraandoeningen voor het aanvullend onderzoek.

23.5.5.2 Management of obesity

Medicamenteuze therapie wordt bij volwassenen en kinderen ontraden.

This section concerns general drug management of obesity (that mainly included orlistat) and did not mention anything specific about thyroid hormones.

23.5.6 VA/DoD 2020

VA/DoD 2020 is a general guideline on obesity. Only comments and recommendations regarding hypothyroidism and obesity (overt or subclinical) have been reported in this document.

23.5.6.1 Link between body weight and hypothyroidism

Sidebar 3: Assessment of Patients with Overweight or Obesity
• Assess for presence of obesogenic medications (see Sidebar 2 on pharmacotherapy) • Consider assessing waist circumference for patients with a BMI of 25 – 29.9 kg/m^2 (see Standards of Care) • Assess for common overweight and obesity-associated conditions (see Sidebar 1) • Assess for secondary causes of overweight or obesity if physical exam and history warrant, including but not limited to: depression, binge eating disorder, hypothyroidism, hypercortisolism (Cushing's disease or syndrome), traumatic brain injury, brain tumor, cranial irradiation, hypogonadism, menopause, acromegaly • Assess the potential benefit of starting pharmacotherapy and/or bariatric procedure • Assess conditions for which weight loss may not be beneficial (e.g., sarcopenia, active carcinoma, some eating disorders)

Abbreviations: BMI: body mass index; CPG: Clinical Practice Guideline; kg: kilograms; m: meters

23.5.6.2 Thyroid hormones in overweight patients with and without hypothyroidism

Several drugs have been used off-label as a long-term treatment for weight loss. Below is a list and brief discussion of some of these medications.

Thyroid Hormones
Several small studies have evaluated the association between weight loss and the use of levothyroxine and liothyronine replacement in hypothyroid patients. Normalization of the hypothyroid state is associated with small losses of weight (typically less than 1 kg), which are not durable beyond 12 – 24 months.

Normalization of the hyperthyroid state is associated with a weight gain of approximately 7 kg.

Treatment of euthyroid patients to hyperthyroid levels has not been reported outside of control groups in early phase clinical trials. The risks associated with hyperthyroidism – particularly cardiac, ocular, bone, and neuropsychiatric – make intentional creation of a hyperthyroid state highly inadvisable for weight loss. Hyperthyroidism (e.g., Grave's disease) is a condition that requires treatment to avoid negative health consequences. Iatrogenic hyperthyroidism accrues significant harm.

23.6 Approach based on symptomatology versus biochemical parameters

23.6.1 Symptomatology or biochemical parameters

23.6.1.1 NICE 2019

Primary hypothyroidism
Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing, but avoid using doses that cause TSH suppression or thyrotoxicosis.

Evidence showed no clinically important benefits of maintaining TSH levels in the lower rather than higher end of the TSH reference range. Given the need for additional medication to achieve a TSH level in the lower end of the reference range, with the potential for adverse effects and increased cost, the committee concluded that as a starting point TSH levels could be maintained at any point within the reference range. Nevertheless, the committee acknowledged that some people may still have troublesome symptoms even with TSH levels in the reference range. Therefore, they recommended adjusting the dose of levothyroxine if symptoms persist to achieve optimal wellbeing for individual patients. The committee also agreed that it was important not to use doses high enough to cause TSH suppression or thyrotoxicosis

Be aware that the TSH level can take up to 6 months to return to the reference range for people who had a very high TSH level before starting treatment with levothyroxine or a prolonged period of untreated hypothyroidism. Take this into account when adjusting the dose of levothyroxine.

Subclinical hypothyroidism

If symptoms do not improve after starting levothyroxine, re-measure TSH and if the level remains raised, adjust the dose. If symptoms persist when serum TSH is within the reference range, consider stopping levothyroxine and follow the recommendations on monitoring untreated subclinical hypothyroidism and monitoring after stopping treatment.

23.6.1.2 BMJ 2019

No specific recommendations or comments were provided.

23.6.1.3 BTA 2016

Synthetic L-T4 remains the treatment of choice in hypothyroidism with the aim of therapy being to restore physical and psychological well-being while maintaining normal laboratory reference range serum TSH levels. (BTA, 1/++0)

The adverse effects of thyroid hormone deficiency include detrimental effects on the serum lipid profile and progression of cardiovascular disease. We recommend that patients with overt hypothyroidism be treated with doses of L-T4 that are adequate to normalize serum TSH, in order to reduce to eliminate these undesirable effects.(reported from ATA, 1/++0)

L-T4 replacement therapy has three main goals. These are :

(i) to provide resolution of patients' symptoms and hypothyroid signs, including biological and physiological markers of hypothyroidism,

(ii) to achieve normalization of serum TSH with improvement in thyroid hormone concentrations and,

(iii) to avoid overtreatment(iatrogenic thyrotoxicosis), especially in the elderly.

(ATA, 1/++0)

Although it may be helpful to follow changes in clinical symptoms longitudinally in patients treated for hypothyroidism, symptoms alone lack sensitivity and specificity and therefore are not recommended for judging adequacy of replacement in the absence of biochemical assessment. Therefore, symptoms should be followed, but considered in the context of serum TSH values, relevant comorbidities and other potential causes. (ATA, 1/+00)

In L-T4-treated hypothyroid patients with normal serum TSH values, psychological distress, impaired wellbeing and cognitive disturbances occur more often than in controls. (ETA, 1/+00)

In some cases, a retrospective review of the original diagnosis of hypothyroidism may be necessary. Symptom and lifestyle management support should be provided and further dose adjustments may be required (BTA, 1/+00).

It is acknowledged that a proportion of individuals on L-T4 are not satisfied with therapy and have persistent symptoms despite a normal serum TSH. Such symptoms should be given due consideration and patients should be thoroughly evaluated for other potentially modifiable conditions.

Box 1. Some possible causes of persistent symptoms in euthyroid patients on L-T4

Endocrine/autoimmune	Nutritional	Lifestyle
Diabetes mellitus	Vitamin B12 deficiency	Stressful life events
Adrenal insufficiency	Folate deficiency	Poor sleep pattern
Hypopituitarism	Vitamin D deficiency	Work-related exhaustion
Coeliac disease	Iron deficiency	Alcohol excess
Pernicious anaemia	Metabolic	Others
Haematological	Obesity	Obstructive sleep apnoea
Anaemia	Hypercalcaemia	Viral and postviral syndromes
Multiple myeloma	Electrolyte imbalance	Chronic fatigue syndrome
End-organ damage	Drugs	Carbon monoxide poisoning
Chronic kidney disease	Beta-blockers	Depression and anxiety
Chronic liver disease	Statins	Polymyalgia rheumatica
Congestive cardiac failure	Opiates	Fibromyalgia

A key feature of both guidelines is the acknowledgement of the subset of L-T4-treated patients who suffer persistent symptoms despite adequate biochemical thyroid status.

A minority of patients with hypothyroidism, but normal serum TSH values, may perceive a suboptimal health status of unclear aetiology. Acknowledgement of the patients' symptoms and evaluation for alternative causes is recommended in such cases. Future research into whether there are subgroups of the population being treated for hypothyroidism who might benefit from combination therapy should be encouraged. (ATA, 2/+00)

Data suggest that 5–10% of L-T4-treated hypothyroid patients with normal serum TSH have persistent symptoms which can be related to the disease and L-T4 therapy. (ETA, 2/+00)

Suggested explanations for persistent symptoms in L-T4-treated hypothyroid patients despite normalization of serum TSH, include awareness of a chronic disease, presence of associated autoimmune diseases, thyroid autoimmunity per se (independent of thyroid function), and inadequacy of L-T4 treatment to restore physiological T4 and T3 concentrations in serum and tissue. (ETA, 2/+00)

Of the established instruments used to measure hypothyroid symptoms, data are lacking regarding their sensitivity and specificity in the 'everyday' clinical setting to recommend their routine clinical use. Further studies are needed to determine whether and how to combine general psychological screening instruments, hypothyroidism-specific tools, and laboratory assessment of thyroid function to measure the impact of L-T4 replacement therapy on psychological well-being, treatment satisfaction and preference in clinical practice. A combination of general instruments,

combined with hypothyroidism-specific tools, may be the most effective way to examine psychological well-being in the L-T4-treated population in the research setting. (ATA, 1/++0)

Clinical ethical principles in L-T4 treatment for hypothyroidism revolve around two core ethical principles in medicine: the principles of beneficence and nonmaleficence, which guide the risk/benefit analysis in clinical practice, and protect clinicians from deviating from practice to satisfy inappropriate patient demands. Additional ethical obligations revolve around the professional virtues of competence and intellectual honesty. (ATA, Ungraded)

There should be recognition that there are not enough data to resolve clinical disagreement amongst thyroid experts (called 'clinical equipoise') regarding treatment for hypothyroidism. Clinical equipoise is disturbed only by the results of well-designed randomized controlled trials that have the statistical power to settle the question of efficacy between monotherapy and combination therapy, or other forms of therapy. (ATA, Ungraded)

Serum T3 should not be used as a therapeutic target in the management of hypothyroidism as the value of this approach is unproven. (BTA, 1/+00)

Patients with hypothyroidism treated with L-T4 to achieve normal serum TSH values may have serum T3 concentrations that are at the lower end of the reference range, or even below the reference range. The clinical significance of this is unknown. (ATA, Summary statement where formal clinical recommendation is not feasible because of sparse evidence.)

The significance of perturbations in serum T3 concentrations within the reference range, or of mildly low serum T3, is unknown. (ATA, Summary statement where formal clinical recommendation is not feasible because of sparse evidence.)

There is insufficient evidence of benefit to recommend that treatment with L-T4 be targeted to achieve low-normal serum TSH values or high-normal serum T3 values in patients with hypothyroidism, including those who are overweight, or those who have depression, dyslipidaemia, or who are athyreotic. (ATA, 1/++0)

Tissue biomarkers of thyroid hormone action are not recommended for routine clinical use, outside of the research setting, as these parameters are not sensitive, specific, readily available or standardized. (ATA, 2/+00)

There are specific instances in which there appears to be discordance between the thyroid status of the pituitary gland, as reflected by the serum TSH, and the thyroid status of other tissues as indicated by various biomarkers. The clinical significance of this is not known. (ATA, Summary statement where formal clinical recommendation is not feasible because of sparse evidence)

23.6.2 Fatigue

23.6.2.1 NICE 2019

No specific recommendations or comments were provided.

23.6.2.2 BMJ 2019

No specific recommendations or comments were provided.

23.6.2.3 BTA 2016

While not specifically concerning chronic fatigue symptoms, BTA mentioned the following :

Strongly recommend against the use of L-T4 treatment in patients who have nonspecific symptoms and normal biochemical indices of thyroid function, as no role exists for use of L-T4 in this situation. (ATA 1/+++)

23.6.2.4 NICE fatigue

This guideline covers diagnosing and managing myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome (ME/CFS) in children, young people and adults.

This guidelines includes recommendations on diagnosis, assessment and care planning, safeguarding, access to care and managing ME/CFS and its symptoms. Only recommendations concerning thyroid function and or thyroid disturbance treatment where reported in the present document.

If ME/CFS is suspected, carry out:

- **a medical assessment (including symptoms and history, comorbidities, overall physical and mental health)**
- **a physical examination**
- **an assessment of the impact of symptoms on psychological and social wellbeing**
- **investigations to exclude other diagnoses, for example (but not limited to):**
  - **urinalysis for protein, blood and glucose**
  - **full blood count**
  - **urea and electrolytes**
  - **liver function**
  - **thyroid function**
  - **erythrocyte sedimentation rate or plasma viscosity**
  - **C-reactive protein**
  - **calcium and phosphate**
  - **HbA1c**
  - **serum ferritin**
  - **coeliac screening**

- **creatine kinase.**

Managing ME/CFS and coexisting conditions
Do not offer any medicines or supplements to cure ME/CFS.

For recommendations on multimorbidity, thyroid disease and irritable bowel syndrome in adults, refer to the:
- NICE guideline on multimorbidity
- NICE guideline on thyroid disease *Recommendations from this guideline have been included in the present document. No specific recommendation have been found concerning ME/CFS.*
- NICE guideline on irritable bowel syndrome in adults.

23.6.2.5 DEGAM 2017

DEGAM 2017 is a general guideline on fatigue, only comments and recommendations regarding hypothyroidism have been mentioned in this document.

Bei primär ungeklärter Müdigkeit sollten folgende Laboruntersuchungen durchgeführt werden Blut-Glucose, Blutbild, Blutsenkung/CRP, Transaminasen oder g-GT, TSH. (Empfehlungsgrad B Level of evidence D II)

In den oben und im Evidenzbericht dargestellten symptomevaluierenden Studien wurden vereinzelt Schilddrüsenfunktionsstörungen und diabetische Stoffwechsellagen festgestellt; allerdings ist wegen der Seltenheit eine präzise Angabe der zu erwartenden Häufigkeit kaum möglich. Bezüglich subklinischer Hypothyreose ist die Behandlungsschwelle und ein Behandlungsnutzen unklar.

Bei einer seit mehr als vier Wochen bestehenden Müdigkeit ohne Hinweis auf spezifische Ursachen halten wir aufgrund der oben beschriebenen möglichen Ursachen und Therapieeffekte folgende Tests für sinnvoll:
- TSH (level of evidence S I),
- Blut-Glucose, ggf. weitere Diabetes-Diagnostik (level of evidence S I),
- Blutbild (level of evidence S III), BSG (alternativ CRP),
- Transaminasen (level of evidence S II) oder
- g-GT (level of evidence D IV).

Pathologische Laborwerte werden vorschnell als ausreichende Erklärung akzeptiert.

In einer Studie von über Müdigkeit klagenden Patientinnenh wurden vier Fälle als subklinische Hypothyreosen diagnostiziert. Von diesen konnten drei bis zur Normalisierung des TSH substituiert und nachuntersucht werden; bei ihnen hatte sich die Müdigkeit jedoch nicht gebessert! Es handelte sich also um das zufällige Zusammentreffen von zwei häufigen Zuständen (Müdigkeit und subklinische Hypothyreose). Konsequenz: kritische Evaluation von subjektivem Befinden und auffälligen Befunden im Längsverlauf, zurückhaltender Einsatz von Laboruntersuchungen und sonstiger weiterführender Diagnostik.

Je mehr Laboruntersuchungen veranlasst werden, desto höher ist die Wahrscheinlichkeit für eine Abweichung von der Norm aus rein statistischen Gründen, ohne dass eine diagnostische Relevanz gegeben wäre. Eine um 4 Wochen aufgeschobene Blutuntersuchung mit einem be schränkten Testset (Hb, BSG, Glucose, TSH) vermeidet falsch positive Tests und hatte in einer vergleichenden Untersuchung keine negativen Auswirkungen auf die Patienten gegenüber sofortiger Erfassung dieser und weiterer 13 Tests.

23.6.3 Anti-aging

23.6.3.1 NICE 2019

No specific recommendations or comments were provided.

23.6.3.2 BMJ 2019

No specific recommendations or comments were provided.

23.6.3.3 BTA 2016

While not specifically concerning the off-label use and anti-aging agent, BTA mentioned the following:

Strongly recommend against the use of L-T4 treatment in patients who have nonspecific symptoms and normal biochemical indices of thyroid function, as no role exists for use of L-T4 in this situation. (ATA 1/+++)

23.6.4 Suppression therapy in euthyroid multinodular goiter

23.6.4.1 NICE 2019

Provide people with thyroid enlargement, and their family or carers if appropriate, with written and verbal information on:

- **the causes of thyroid enlargement, including the fact that goitre and nodules are common and are usually not cancerous**
- **red flag symptoms to look out for (for example, shortness of breath, rapid growth of nodules, hoarse voice, swallowing difficulties)**

- **treatment options.**

Managing non-malignant thyroid enlargement and follow up

Do not offer treatment to adults with non-malignant thyroid enlargement, normal thyroid function and mild or no symptoms unless:

- **they have breathing difficulty**
  or
- **there is clinical concern, for example, because of marked airway narrowing.**

In general, the committee agreed that surgery would be appropriate for nodules or enlargement causing symptoms, if there has been no response with other options or if there is true compression of nearby organs (for example, tracheal narrowing).

For adults with normal thyroid function and a non-cystic nodule or multinodular or diffuse goitre, consider the following if they have compressive symptoms relating to thyroid enlargement:

- **surgery, particularly if there is marked airway narrowing**
  or
- **radioactive iodine ablation, if there is demonstrable radionuclide uptake,**
  or
- **percutaneous thermal ablation (see the NICE interventional procedures guidance on ultrasound-guided percutaneous radiofrequency ablation for benign thyroid nodules).**

The evidence showed no clinically important effect of levothyroxine on non-cystic nodules and a benefit of radiofrequency ablation and laser ablation. There was no evidence identified on radioactive iodine ablation although the committee noted that it is very commonly used in the UK for diffuse goitres that are causing symptoms, particularly if there is demonstrable radionuclide uptake. The committee also noted that the more recently developed techniques for percutaneous thermal ablation (for example, high-intensity focused ultrasound and microwave ablation) may be appropriate for some people but are not widely available. They made a research recommendation on percutaneous thermal ablation to inform future practice. The committee agreed not to recommend the use of levothyroxine due to the evidence suggesting no clinically important benefit for most outcomes and their awareness of adverse effects (for example, TSH suppression and increasing cardiovascular risk).

23.6.4.2 BMJ 2019

No specific recommendations or comments were provided.

23.6.4.3 BTA 2016

No specific recommendations or comments were provided.

23.6.5 AACE/ACE/AME 2016

Medical treatment for benign nodules :
Levothyroxine (LT4) suppressive therapy is not recommended [BEL 1, GRADE A].

In geographic areas with mild iodine deficiency, iodine supplementation and/or TSH non-suppressive LT4 treatment may be considered for young patients with a small nodular goiter and high-normal TSH levels [BEL 2, GRADE B].

Nonsuppressive LT4 replacement is recommended for young patients with subclinical hypothyroidism due to autoimmune thyroiditis [BEL 2, GRADE A].

A clinically significant (>50%) decrease in nodule volume is reported with LT4 therapy only in a minority of patients [EL 1], especially in small nodules with colloid features at FNA and in iodine-deficient regions [EL 2]. In the same areas, this favorable effect appears more convincing with the concomitant administration of iodine supplements [EL 1].

Long-term TSH suppression may prevent an increase in the size of a thyroid nodule and of the thyroid gland itself [EL 1], but nodule regrowth occurs after cessation of therapy; thus, commitment to long-term therapy seems inevitable.

Moreover, sustained subclinical hyperthyroidism is associated with a decrease in bone density in postmenopausal females [EL 1] and an increase in major osteoporotic fractures [EL 2].

The risk of atrial fibrillation is higher in elderly patients with suppressed TSH levels [EL 2], and overall morbidity appears increased [EL 2], as is the mortality rate [EL 2]. So, a large proportion of patients are ineligible for LT4 therapy [EL 3].

It has recently been reported that lower serum TSH levels, induced by both thyroid autonomy and LT4 treatment, are associated with a reduced risk of clinically detectable thyroid cancer [EL 3]. These studies are not prospective, and their value in practice remains to be determined.

Based on the above information, LT4 treatment in patients with nodular thyroid disease is discouraged. It may be considered in association with iodine supplementation only in young patients who live in iodine-deficient geographic areas who have small nodular goiters with no evidence of functional autonomy. An appropriate LT4 substitution therapy should be considered in patients with nodular goiter and subclinical hypothyroidism.

LT4 therapy is not recommended for preventing recurrence after lobectomy when serum TSH stays in the normal range [BEL 2, GRADE A].

TSH-suppressive therapy with LT4 is reported as not useful for prevention of goiter recurrence after lobectomy in patients with normal TSH levels by most ([EL 2] and [EL 4]) even if not all prospective studies [EL 2].

23.6.6 T3 versus T4

23.6.6.1 NICE 2019

Offer levothyroxine as first-line treatment for adults, children and young people with primary hypothyroidism.

Do not routinely offer liothyronine for primary hypothyroidism, either alone or in combination with levothyroxine, because there is not enough evidence that it offers benefits over levothyroxine monotherapy, and its long-term adverse effects are uncertain.

Do not offer natural thyroid extract for primary hypothyroidism because there is not enough evidence that it offers benefits over levothyroxine, and its long-term adverse effects are uncertain. Natural thyroid extract does not have a UK marketing authorisation so its safety is uncertain.

Potential treatments are levothyroxine, usually prescribed to everyone, liothyronine, which is sometimes prescribed when levothyroxine fails, and natural thyroid extracts (which is currently unlicensed for use in the UK).

Overall the evidence from 7 randomised controlled trials suggested that combination treatment with levothyroxine and liothyronine did not offer any important health benefits compared with levothyroxine monotherapy and was significantly more expensive.

However, the committee noted that some of the trials did show some small benefits in specific quality of life domains and anecdotal evidence from some committee members suggested beneficial effects of combination treatment with levothyroxine and liothyronine in small subgroups of patients. The committee were aware that some people reported still feeling unwell with levothyroxine monotherapy and agreed that in this group adding liothyronine could potentially have greater benefit than in the general population with hypothyroidism, although there are no trials in this population.

Some evidence suggested that combination therapy with levothyroxine and liothyronine could be harmful because it may suppress the production of TSH and its long-term adverse effects are uncertain.

Overall, the committee agreed that the evidence was generally suggestive of combined therapy having no important effect on quality of life and the small and contradictory benefits and harms in subdomains of quality of life were more likely to reflect the low quality of the underlying evidence.

The committee agreed that the evidence for natural thyroid extracts showed no benefit over levothyroxine. The committee also noted that the proportion of T3 to T4 is higher in natural thyroid extracts than produced in the human body and the adverse effects are uncertain.

23.6.6.2 BMJ 2019

No specific recommendations or comments were provided.

23.6.6.3 BTA 2016

L-T4 monotherapy remains the standard treatment of hypothyroidism. (ETA, 1/+++)

L-T4 is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism, long-term experience of its benefits, favourable side effect profile, ease of administration, good intestinal absorption, long serum half-life and low cost. (ATA, 1/++0)

L-T4+L-T3 combination therapy

L-T4/L-T3 combination therapy in patients with hypothyroidism should not be used routinely, as there is insufficient evidence to show that combination therapy is superior to L-T4 monotherapy. (BTA, 1/++0)

Clinicians have an ethical responsibility to adhere to the highest professional standards of good medical practice rooted in sound evidence. This includes not prescribing potentially harmful therapies without proven advantages over existing treatments.

Insufficient evidence that L-T4 + L-T3 combination therapy is superior to L-T4 monotherapy. (ETA, 1/++0)

There is no consistently strong evidence of superiority of combination therapy over monotherapy with L-T4. Therefore, we recommend against the routine use of combination treatment with L-T4 and L-T3 as a form of thyroid replacement therapy in patients with primary hypothyroidism, based on conflicting results of benefits from randomized controlled trials comparing this therapy to L-T4 therapy alone and a paucity of long-term outcome data. (ATA, 2/++0)

Recommend against the routine use of compounded thyroid hormones due to concerns about safety and potency and due to the lack of data proving superiority to standard thyroid hormone preparations. However, in the case of suspected allergy to an excipient of standard thyroid hormone preparations that cannot be avoided with a change in brand or dose formulation,

including a trial of L-T4 gel capsules, it may be reasonable to consider use of compounded products, although a controlled study of this approach has not been published. (ATA, 1/+00)

Both guidelines strongly recommend that L-T4 remains the therapy of choice in hypothyroidism and do not support the routine use of L-T4/L-T3 combination therapy due to insufficient evidence from controlled trials, lack of long-term L-T3 safety data, and unavailability of L-T3 formulations that mirror natural physiology.

Consider L-T4 and L-T3 as an experimental approach in compliant LT4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range, provided they have previously been given support to deal with the chronic nature of their disease and associated autoimmune diseases have been ruled out. (ETA, 2/+00)

L-T4 and L-T3 are not recommended in pregnancy and in patients with cardiac arrhythmias. (ETA, 2/+00)

For patients with primary hypothyroidism who feel unwell on L-T4 therapy alone (in the absence of an allergy to L-T4 constituents or an abnormal serum TSH), there is currently insufficient evidence to support the routine use of a trial of a combination of L-T4 and L-T3 therapy outside a formal clinical trial or N of 1 trial, due to uncertainty in long-term risk benefit ratio of the treatment and uncertainty as to the optimal definition of a successful trial to guide clinical decision-making. (ATA,000)

If a decision is made to embark on a trial of L-T4/L-T3 combination therapy in patients who have unambiguously not benefited from L-T4, then this should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data. Such patients should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion of the risks and potential adverse consequences. Many clinicians may not agree that a trial of L-T4/LT3 combination therapy is warranted in these circumstances and their clinical judgement must be recognized as being valid given the current understanding of the science and evidence of the treatments. (BTA, 2/+00).

However, while both guidelines agree that a trial of L-T3 may occasionally be indicated in such patients, there are significant differences between the guidelines in the implementation of such a trial.

- The ETA would consider a carefully monitored experimental trial of L-T3 if symptoms persist after comorbid conditions have been excluded. Such a trial should be conducted under specialist supervision, be reassessed after a period of 3 months and preferably include objective evaluations of response with standardized quality of life tools.
- The ATA goes further by insisting that any such trial must be rigorously implemented, either as part of a clinical trial or N of 1 trial, with formal ethical and governance approvals. In addition, the ATA highlights the ethical and legal obligations inherent on clinicians managing hypothyroidism including the responsibility to avoid potentially harmful therapies without

proven advantage over existing therapies. The authors further assert that the balance of clinical evidence on the benefits of combination therapy over L-T4 monotherapy would demand that further randomized controlled trials are indicated.

The 2011 RCP statement concluded that L-T3 'should be reserved for use by accredited endocrinologists in individual patients' but did not specifically address management strategies for L-T4-treated patients with persistent symptoms after nonthyroid causes are excluded. Thus, the current ETA and ATA guidelines can be seen as an addition rather than a departure from this position.

Limited data suggest that psychological well-being and preference for L-T4 and L-T3 combination therapy may be influenced by polymorphisms in thyroid hormone pathway genes, specifically in thyroid hormone transporters and deiodinases. (ETA, 2/+00)

Currently, genetic testing is not recommended as a guide to selecting therapy for 3 reasons:

(i) Although there are data suggesting that specific polymorphisms of the type 2 deiodinase gene might be associated with therapeutic response to combination synthetic L-T3 and L-T4 therapy, controlled confirmatory studies are needed.

(ii) Currently, genetic testing for these specific deiodinase polymorphisms is only available in the research setting.

(iii) The small effect of the type 2 deiodinase gene variants identified so far that do affect thyroid hormone concentrations suggests that other factors (e.g. yet unidentified genetic variants) may play a far greater role in determining an individual patient's thyroid hormone concentrations.

(ATA, 1/++0)

Administration **and monitoring of L-T4+L-T3 combination therapy**

Start L-T4+L-T3 at L-T4/L-T3 dose ratio between 13:1 and 20:1 by weight. (ETA, 2/+00)

L-T4 can be given once daily, and the daily L-T3 dose should be divided (if possible) in two doses, one before breakfast and the largest one before bed. (ETA, 2/+00)

Available combination preparations contain a L-T4/L-T3 dose ratio lower than 13:1, so it is recommended to use separate L-T4 and L-T3 tablets. (ETA, 1/+00)

L-T4+L-T3 should be monitored by thyroid function tests L-T4 and L-T3 in blood samples taken before the morning dose, aiming at normal serum TSH, free T4, free T3 and free T4/free T3 ratio. (ETA, 1/++0)

If dose adjustment of L-T4+L-T3 combination therapy is necessary to achieve a normal serum TSH, free T4, free T3 and free T4/free T3 ratio, the dose of one component, preferably L-T3, should be changed. (ETA, 2/+00)

Discontinue L-T4 and L-T3 if no improvement after 3 months. (ETA, 2/++0)

L-T4 and L-T3 therapy should be supervised by accredited internists or endocrinologists. (ETA, 2/++0)

Other thyroid hormone preparations

There is no convincing evidence to support routine use of thyroid extracts, L-T3 monotherapy, compounded thyroid hormones, iodine containing preparations, dietary supplementation and over the counter preparations in the management of hypothyroidism. (ATA, 1/+00).

Although there is preliminary evidence from a short-duration study that some patients may prefer treatment with extracts, high-quality controlled long-term outcome data are lacking to document superiority of this treatment compared to L-T4 therapy. Furthermore, there are potential safety concerns related to the use of thyroid extracts, such as the presence of supraphysiological serum T3 levels and a paucity of long-term safety outcome data. (ATA, 1/++0)

Although short-term outcome data in hypothyroid patients suggest that thrice daily synthetic L-T3 may be associated with beneficial effects on parameters such as weight and lipids, longer term controlled clinical trials using a longer acting form of L-T3 are needed, before considering the endorsement of synthetic L-T3 therapy for routine clinical use. (ATA, 1/++0)

Recommend against the use of dietary supplements, nutraceuticals or other over the counter products either in euthyroid individuals or as a means of treating hypothyroidism. Particularly caution against the use of pharmacologic doses of iodine because of the risk of thyrotoxicosis and hypothyroidism in those with intact thyroid glands susceptible to becoming further dysregulated because of underlying thyroid pathology. (ATA, 1/+00)

23.7 Follow-up, adverse effects, and drug-drug interactions

23.7.1 NICE 2019

23.7.1.1 Treatment follow up

Explain to people with thyroid disease who need treatment, and their family or carers if appropriate, that:

- **Thyroid disease usually responds well to treatment.**
- **The goal of treatment is to alleviate symptoms and align thyroid function tests within or close to the reference range.**
- **People may feel well even when their thyroid function tests are outside the reference range.**
- **Even when there are no symptoms, treatment may be advised to reduce the risk of long-term complications.**

- **Even when thyroid function tests are within the reference range, changes to treatment may improve symptoms for some people.**
- **Symptoms may lag behind treatment changes for several weeks to months.**
- **Day-to-day changes in unexplained symptoms are unlikely to be due to underlying thyroid disease because the body has a large reservoir of thyroxine.**

Provide people with thyroid disease, and their family or carers if appropriate, with written and verbal information on:

- **their underlying condition, including the role and function of the thyroid gland and what the thyroid function tests mean**
- **risks of over- and under-treatment**
- **their medicines**
- **need for and frequency of monitoring**
- **when to seek advice from a healthcare professional.**

Provide people with hypothyroidism, and their family or carers if appropriate, with written and verbal information on:

- **possible drug interactions of thyroid hormone replacements, including interactions with over-the-counter medicines**
- **how and when to take levothyroxine.**

For adults who are taking levothyroxine for primary hypothyroidism, consider measuring TSH every 3 months until the level has stabilised (2 similar measurements within the reference range 3 months apart), and then once a year.

Consider measuring FT4 as well as TSH for adults who continue to have symptoms of hypothyroidism after starting levothyroxine.

23.7.2 BMJ 2019

No specific recommendations or comments were provided regarding overt hypothyroidism however despite this guideline recommends against thyroid hormone for subclinical hypothyroidism, the committee made the following practical issues in case of levothyroxine treatment for subclinical hypothyroidism.

23.7.2.1 Treatment follow up

Long term regular visits and blood samples to monitor hormone levels

23.7.2.2 Adverse effects

Overdosage can lead to hyperthyroidism symptoms (decrease in bone mineral density, atrial fibrillation and other symptoms of drug induced hyperthyroidism)

For younger people (<65 years) : The panel was concerned about the burden of lifelong treatment and the limited evidence about possible long term harms of thyroid hormones (such as adverse cardiovascular effects). In addition, patients may experience a delay in diagnosis of another condition (such as mood disorder).

For older people (≥65 years) : The panel were concerned about a signal of harm in those treated. There were between five fewer and 62 more deaths per year in the treatment group (this is the 95% confidence interval). This interval includes the possibility of benefit (5 fewer deaths) as well as harm (62 more deaths). Additionally, these deaths were evaluated in only one trial with a two year follow-up.

23.7.3 BTA 2016

23.7.3.1 Treatment follow up

After initiation of therapy, TSH should be monitored 6–8 weekly and the dose of L-T4 should be adjusted until a stable TSH is achieved, after which TSH can be checked 4–6 monthly, and then annually. (BTA, 1/+00)

23.7.3.2 Adverse effects

Although fine tuning of serum TSH levels within the reference range may be indicated for individual patients, deliberate serum TSH suppression with high dose thyroid hormone replacement therapy (serum TSH <0_1 mU/L) should be avoided where possible as this carries a risk of adverse effects such as cardiac rhythm disorders including atrial fibrillation, strokes, osteoporosis and fracture. (BTA, 1/++0)

As an exception, patients with a history of thyroid cancer may require deliberate suppression of serum TSH if there is a significant risk of recurrence.

The deleterious health effects of iatrogenic thyrotoxicosis include atrial fibrillation and osteoporosis. Because of these effects, we recommend avoiding thyroid hormone excess and subnormal serum TSH values, particularly serum TSH values below 0,1 mU/L, especially in older persons and postmenopausal women.(ATA, 1/++0)

23.7.3.3 Switch between preparations

For the vast majority of patients on L-T4, brand or named supplier prescribing is not considered necessary (BTA, 2/+00).

The Medicines and Healthcare Products Regulatory Agency (MHRA) have recently made recommendations to ensure the quality and consistency of L-T4 tablets that are on the UK market.

Rarely, patients may require a specific brand of L-T4 to be prescribed due to intolerance of generic preparations.

However, in the case of suspected allergy to an excipient of standard thyroid hormone preparations that cannot be avoided with a change in brand or dose formulation, including a trial of L-T4 gel capsules, it may be reasonable to consider use of compounded products, although a controlled study of this approach has not been published.

24 Appendix. Search strategy

24.1 Supplements

24.1.1 Intervention: iodine and selenium

(("Iodine"[Mesh] OR (iodine [tiab] AND supplement*[tiab]))
OR ("Selenium"[Mesh] OR (selenium[tiab] AND supplement*[tiab])))
AND
(("Hypothyroidism"[Mesh] OR "Thyroid Diseases"[Mesh] OR Hypothyroid*[tiab])
OR (Thyroid*[tiab] AND (dysfunction*[tiab] OR disease*[tiab] OR condition*[tiab] OR disorder*[tiab])))
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("2018/12/12"[Date - Entry] : "3000"[Date - Entry])

24.1.2 Intervention: iron, omega-3 fatty acids, vitamin D

(("Iron"[Mesh] OR (iron[tiab] AND supplement*[tiab]))
OR ("Fatty Acids, Omega-3"[Mesh] OR (omega[tiab] AND supplement*[tiab]))
OR ("Vitamin D"[Mesh] OR vitamin D[tiab] OR cholecalciferol*[tiab] OR ergocalciferol[tiab]))
AND
(("Hypothyroidism"[Mesh] OR "Thyroid Diseases"[Mesh] OR Hypothyroid*[tiab])
OR (Thyroid*[tiab] AND (dysfunction*[tiab] OR disease*[tiab] OR condition*[tiab] OR disorder*[tiab])))
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

24.2 Elderly people

("Hypothyroidism"[Mesh] OR "Thyroid Diseases"[Mesh] OR Hypothyroid*[tiab]) OR
(Thyroid*[tiab] AND (dysfunction*[tiab] OR disease*[tiab] OR condition*[tiab] OR disorder*[tiab]))
AND
("Aged"[Mesh] OR Elderly[tiab] OR geriatr*[tiab] OR old*[tiab])
AND
("Thyroxine"[Mesh] OR thyroxine[tiab] or levothyroxine[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])
AND
("2018/12/12"[Date – Entry] : "2022/06/01"[Date – Entry])

24.3 Pregnancy

("Hypothyroidism"[Mesh] OR "Thyroid Diseases"[Mesh] OR Hypothyroid*[tiab] OR
(Thyroid*[tiab] AND (dysfunction*[tiab] OR disease*[tiab] OR condition*[tiab] OR disorder*[tiab] OR autoimmunity[tiab] OR thyroid peroxidase*[tiab] OR TPO[tiab] OR antibod*[tiab])))
AND
("Pregnant Women"[Mesh] OR pregnan*[tiab] OR gravid*[tiab])
AND
("Thyroxine"[Mesh] OR thyroxine[tiab] or levothyroxine[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

24.4 Infertility

("Hypothyroidism"[Mesh] OR "Thyroid Diseases"[Mesh] OR Hypothyroid*[tiab] OR
(Thyroid*[tiab] AND (dysfunction*[tiab] OR disease*[tiab] OR condition*[tiab] OR disorder*[tiab] OR autoimmunity[tiab] OR thyroid peroxidase antibod*[tiab] OR TPO*[tiab])))
AND
("Infertility"[Mesh] OR Subfertil*[tiab] OR "Reproductive Techniques, Assisted"[Mesh] OR Infertile*[tiab] OR assisted reprod*[tiab] OR assisted concept*[tiab])
AND
("Thyroxine"[Mesh] OR thyroxine[tiab] or levothyroxine[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

24.5 Obesity

("Obesity"[Mesh] OR obes*[tiab])
AND
("Thyroxine"[Mesh] OR thyroxine[tiab] or levothyroxine[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

24.6 Chronic fatigue syndrome

("Fatigue Syndrome, Chronic"[Mesh] OR Myalgic Encephalomyelitis[tiab] OR (tired*[tiab] OR fatigue*[tiab]) AND chronic*[tiab])

AND
("Thyroxine"[Mesh] OR thyroxine[tiab] or levothyroxine[tiab] OR "Triiodothyronine"[Mesh] OR liothyronine[tiab] or triiodothyronine[tiab] or tri-iodothyronine[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

24.7 Anti-aging

("Thyroxine"[Mesh] OR thyroxine[tiab] or levothyroxine[tiab])
OR
("Triiodothyronine"[Mesh] OR liothyronine[tiab] or triiodothyronine[tiab] or tri-iodothyronine[tiab])
AND
("Geroscience"[Mesh] OR "Aging"[Mesh] OR "Longevity"[Mesh] OR life span[tiab] OR health span[tiab] OR pro-longevity[tiab] OR "Off-Label Use"[Mesh])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

24.8 Euthyroid multinodular goiter

((((Thyroid*[tiab]) AND (swell*[tiab] OR enlarge*[tiab] OR nodule*[tiab]))
OR
("Goiter"[Mesh] OR Goiter*[tiab] OR goiter*[tiab]))
AND
(Non-malignan*[tiab] OR nonmalignant*[tiab] OR benign[tiab]))
AND
("Thyroxine"[Mesh] OR thyroxine[tiab] or levothyroxine[tiab] OR "Triiodothyronine"[Mesh] OR liothyronine[tiab] or triiodothyronine[tiab] or tri-iodothyronine[tiab])
AND
(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo OR systematic[sb] OR medline[TIAB])

25 Appendix. Excluded articles

25.1 Supplements

1. Pezeshki B, Ahmadi A, Karimi A. The Effect of Vitamin D Replacement on Patient with Subclinical Hypothyroidism: A Pilot Randomized Clinical Trial. Galen Med J 2020;9:e1592.**n; sample size**
2. Mahmoudi L, Mobasseri M, Ostadrahimi A, et al. Effect of Selenium-Enriched Yeast Supplementation on Serum Thyroid-Stimulating Hormone and Anti-Thyroid Peroxidase Antibody Levels in Subclinical Hypothyroidism: Randomized Controlled Trial. Adv Biomed Res 2021;10:33.**n; sample size**
3. Anaraki PV, Aminorroaya A, Amini M, et al. Effects of Vitamin D deficiency treatment on metabolic markers in Hashimoto thyroiditis patients. J Res Med Sci 2017;22:5.**n; sample size**
4. Santos JAR, Christoforou A, Trieu K, et al. Iodine fortification of foods and condiments, other than salt, for preventing iodine deficiency disorders. Cochrane Database Syst Rev 2019;2:Cd010734.**n; prevention**
5. Biswas K, McLay J, Campbell FM. Selenium Supplementation in Pregnancy-Maternal and Newborn Outcomes. J Nutr Metab 2022;2022:4715965.**n; prevention**
6. Zavros A, Giannaki CD, Aphamis G, et al. The Effects of Zinc and Selenium Supplementation on Body Composition and Thyroid Function in Individuals with Overweight or Obesity: A Systematic Review. J Diet Suppl 2022:1-29.**n; population; only included RCT zinc intervention**
7. Wang S, Wu Y, Zuo Z, et al. The effect of vitamin D supplementation on thyroid autoantibody levels in the treatment of autoimmune thyroiditis: a systematic review and a meta-analysis. Endocrine 2018;59:499-505.**n; population, outcome**
8. Hu Y, Feng W, Chen H, et al. Effect of selenium on thyroid autoimmunity and regulatory T cells in patients with Hashimoto's thyroiditis: A prospective randomized-controlled trial. Clin Transl Sci 2021;14:1390-402.**n; population includes euthyroid, no subanalysis**
9. Knutsen KV, Madar AA, Brekke M, et al. Effect of Vitamin D on Thyroid Autoimmunity: A Randomized, Double-Blind, Controlled Trial Among Ethnic Minorities. J Endocr Soc 2017;1:470-9.**n; population healthy subjects**
10. Simsek Y, Cakır I, Yetmis M, et al. Effects of Vitamin D treatment on thyroid autoimmunity. J Res Med Sci 2016;21:85.**n; population both hypo and hyperthyroid**
11. Duntas LH. Selenium and at-risk pregnancy: challenges and controversies. Thyroid Res 2020;13:16.**n; population (not explicitly hypothyroid or subclinical hypothyroidism)**
12. Candido AC, Azevedo FM, Machamba AAL, et al. Implications of iodine deficiency by gestational trimester: a systematic review. Arch Endocrinol Metab 2021;64:507-13.**n; population**
13. Chaudhary S, Dutta D, Kumar M, et al. Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: An open-labeled randomized controlled trial. Indian J Endocrinol Metab 2016;20:391-8.**n; outcomes**
14. Zhang J, Chen Y, Li H, et al. Effects of vitamin D on thyroid autoimmunity markers in Hashimoto's thyroiditis: systematic review and meta-analysis. J Int Med Res 2021;49:3000605211060675.**n; outcome**
15. Taheriniya S, Arab A, Hadi A, et al. Vitamin D and thyroid disorders: a systematic review and Meta-analysis of observational studies. BMC Endocr Disord 2021;21:171.**n; observational data only**
16. Wang J, Lv S, Chen G, et al. Meta-analysis of the association between vitamin D and autoimmune thyroid disease. Nutrients 2015;7:2485-98.**n; no intervention**
17. Hess SY. The impact of common micronutrient deficiencies on iodine and thyroid metabolism: the evidence from human studies. Best Pract Res Clin Endocrinol Metab 2010;24:117-32.**n; narrative review**
18. Jiang H, Chen X, Qian X, et al. Effects of vitamin D treatment on thyroid function and autoimmunity markers in patients with Hashimoto's thyroiditis-A meta-analysis of randomized controlled trials. J Clin Pharm Ther 2022;47:767-75.**n; mixing RCT and non-randomised cohort**
19. Zuo Y, Li Y, Gu X, et al. The correlation between selenium levels and autoimmune thyroid disease: a systematic review and meta-analysis. Ann Palliat Med 2021;10:4398-408.**n; different SR selected**
20. Qiu Y, Xing Z, Xiang Q, et al. Insufficient evidence to support the clinical efficacy of selenium supplementation for patients with chronic autoimmune thyroiditis. Endocrine 2021;73:384-97.**n; different SR selected**
21. Ravanbod M, Asadipooya K, Kalantarhormozi M, et al. Treatment of iron-deficiency anemia in patients with subclinical hypothyroidism. Am J Med 2013;126:420-4.**n, sample size**

22. Mantovani G, Isidori AM, Moretti C, et al. Selenium supplementation in the management of thyroid autoimmunity during pregnancy: results of the "SERENA study", a randomized, double-blind, placebo-controlled trial. Endocrine 2019;66:542-50.**n, sample size**
23. Nazeri P, Shariat M, Azizi F. Effects of iodine supplementation during pregnancy on pregnant women and their offspring: a systematic review and meta-analysis of trials over the past 3 decades. Eur J Endocrinol 2021;184:91-106.**n, prevention**
24. Zimmermann MB, Zeder C, Chaouki N, et al. Addition of microencapsulated iron to iodized salt improves the efficacy of iodine in goitrous, iron-deficient children: a randomized, double-blind, controlled trial. Eur J Endocrinol 2002;147:747-53.**n, population**
25. Krysiak R, Kowalcze K, Okopień B. Selenomethionine potentiates the impact of vitamin D on thyroid autoimmunity in euthyroid women with Hashimoto's thyroiditis and low vitamin D status. Pharmacol Rep 2019;71:367-73.**n, population**
26. Zimmermann MB, Wegmueller R, Zeder C, et al. Dual fortification of salt with iodine and micronized ferric pyrophosphate: a randomized, double-blind, controlled trial. Am J Clin Nutr 2004;80:952-9.**n, outcome**
27. Zimmermann MB, Wegmueller R, Zeder C, et al. Triple fortification of salt with microcapsules of iodine, iron, and vitamin A. Am J Clin Nutr 2004;80:1283-90.**n, outcome**
28. Asibey-Berko E, Zlotkin SH, Yeung GS, et al. Dual fortification of salt with iron and iodine in women and children in rural Ghana. East Afr Med J 2007;84:473-80.**n, outcome**
29. Andersson M, Thankachan P, Muthayya S, et al. Dual fortification of salt with iodine and iron: a randomized, double-blind, controlled trial of micronized ferric pyrophosphate and encapsulated ferrous fumarate in southern India. Am J Clin Nutr 2008;88:1378-87.**n, outcome**
30. Wan S, Jin B, Ren B, et al. The Relationship between High Iodine Consumption and Levels of Autoimmune Thyroiditis-Related Biomarkers in a Chinese Population: a Meta-Analysis. Biol Trace Elem Res 2020;196:410-8.**n, only observational data**
31. Muscogiuri G, Tirabassi G, Bizzaro G, et al. Vitamin D and thyroid disease: to D or not to D? Eur J Clin Nutr 2015;69:291-6.**n, narrative review**
32. Köhrle J. Selenium and the thyroid. Curr Opin Endocrinol Diabetes Obes 2013;20:441-8.**n, narrative review**
33. Zimmermann MB. Iron status influences the efficacy of iodine prophylaxis in goitrous children in Côte d'Ivoire. Int J Vitam Nutr Res 2002;72:19-25.**n, intervention**
34. Hess SY, Zimmermann MB, Adou P, et al. Treatment of iron deficiency in goitrous children improves the efficacy of iodized salt in Côte d'Ivoire. Am J Clin Nutr 2002;75:743-8.**n, intervention**
35. Grussendorf M. [Therapy of euthyroid iron deficiency goiter. Effectiveness of a combination of L-thyroxine and 150 micrograms iodine in comparison with mono-L-thyroxine]. Med Klin (Munich) 1996;91:489-93.**n, comparison**

25.2 Elderly people

1. Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. Bmj 2019;365:l2006.**n; not an SR**
2. Biondi B, Cappola AR. Subclinical hypothyroidism in older individuals. Lancet Diabetes Endocrinol 2022;10:129-41.**n; narrative review**
3. Blum MR, Gencer B, Adam L, et al. Impact of Thyroid Hormone Therapy on Atherosclerosis in the Elderly With Subclinical Hypothyroidism: A Randomized Trial. J Clin Endocrinol Metab 2018;103:2988-97.**n; outcome**
4. Borzì AM, Biondi A, Basile F, et al. Diagnosis and treatment of hypothyroidism in old people : A new old challenge. Wien Klin Wochenschr 2020;132:161-7.**n; not an SR**
5. Chen Y, Tai HY. Levothyroxine in the treatment of overt or subclinical hypothyroidism: a systematic review and meta-analysis. Endocr J 2020;67:719-32.**n; age population**
6. Chrysant SG. The current debate over treatment of subclinical hypothyroidism to prevent cardiovascular complications. Int J Clin Pract 2020;74:e13499.**n; not an SR**
7. de Montmollin M, Feller M, Beglinger S, et al. L-Thyroxine Therapy for Older Adults With Subclinical Hypothyroidism and Hypothyroid Symptoms: Secondary Analysis of a Randomized Trial. Ann Intern Med 2020;172:709-16.**n; post hoc analysis**

8. Du Puy RS, Poortvliet RKE, Mooijaart SP, et al. No Effect of Levothyroxine on Hemoglobin in Older Adults With Subclinical Hypothyroidism: Pooled Results From 2 Randomized Controlled Trials. J Clin Endocrinol Metab 2022;107:e2339-e47.**n; outcome**
9. Du Puy RS, Postmus I, Stott DJ, et al. Study protocol: a randomised controlled trial on the clinical effects of levothyroxine treatment for subclinical hypothyroidism in people aged 80 years and over. BMC Endocr Disord 2018;18:67.**n; is protocol**
10. Effraimidis G, Watt T, Feldt-Rasmussen U. Levothyroxine Therapy in Elderly Patients With Hypothyroidism. Front Endocrinol (Lausanne) 2021;12:641560.**n; not an SR**
11. Floriani C, Gencer B, Collet TH, et al. Subclinical thyroid dysfunction and cardiovascular diseases: 2016 update. Eur Heart J 2018;39:503-7.**n; observational data only**
12. Gietka-Czernel M, Hubalewska-Dydejczyk A, Kos-Kudła B, et al. Expert opinion on liquid L-thyroxine usage in hypothyroid patients and new liquid thyroxine formulation - Tirosint SOL [Opinia ekspertów dotycząca stosowania płynnej postaci lewotyroksyny oraz nowego preparatu Tirosint SOL u chorych na niedoczynność tarczycy]. Endokrynol Pol 2020;71:441-65.**n; intervention**
13. Leng O, Razvi S. Hypothyroidism in the older population. Thyroid Res 2019;12:2.**n; not an SR**
14. Loh HH, Lim LL, Yee A, et al. Association between subclinical hypothyroidism and depression: an updated systematic review and meta-analysis. BMC Psychiatry 2019;19:12.**n; intervention**
15. Panday P, Arcia Franchini AP, Iskander B, et al. Subclinical Hypothyroidism in Geriatric Population and Its Association With Heart Failure. Cureus 2021;13:e14296.**n; intervention**
16. Razvi S, Ryan V, Ingoe L, et al. Age-Related Serum Thyroid-Stimulating Hormone Reference Range in Older Patients Treated with Levothyroxine: A Randomized Controlled Feasibility Trial (SORTED 1). Eur Thyroid J 2020;9:40-8.**n; sample size**
17. Ross DS. Treating hypothyroidism is not always easy: When to treat subclinical hypothyroidism, TSH goals in the elderly, and alternatives to levothyroxine monotherapy. J Intern Med 2022;291:128-40.**n; not an SR**
18. Samuels MH, Kolobova I, Niederhausen M, et al. Effects of Altering Levothyroxine (L-T4) Doses on Quality of Life, Mood, and Cognition in L-T4 Treated Subjects. J Clin Endocrinol Metab 2018;103:1997-2008.**n; population**
19. von Werder A, von Werder K. [Substitution with thyroid hormones in the elderly : Goals and risks]. Internist (Berl) 2018;59:1114-8.**n; not an SR**
20. Zhao T, Chen BM, Zhao XM, et al. Subclinical hypothyroidism and depression: a meta-analysis. Transl Psychiatry 2018;8:239.**n; RCTs not analysed separately**

25.3 Pregnancy

1. Abdel Rahman AH, Aly Abbassy H, Abbassy AA. Improved in vitro fertilization outcomes after treatment of subclinical hypothyroidism in infertile women. Endocr Pract 2010;16:792-7.**n; population**
2. Akhtar MA, Agrawal R, Brown J, et al. Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. Cochrane Database Syst Rev 2019;6:Cd011009.**n, population**
3. Alcázar Lázaro V, López Del Val T, García Lacalle C, et al. Slightly elevated thyrotropin levels in pregnancy in our clinical practice. Endocrinol Diabetes Nutr (Engl Ed) 2019;66:620-7.**n, language, unclear methodology**
4. Bein M, Yu OHY, Grandi SM, et al. Levothyroxine and the risk of adverse pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. BMC Endocr Disord 2021;21:34.**n; different SR selected**
5. Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. Bmj 2019;365:l2006.**n, population**
6. Chan S, Boelaert K. Optimal management of hypothyroidism, hypothyroxinaemia and euthyroid TPO antibody positivity preconception and in pregnancy. Clin Endocrinol (Oxf) 2015;82:313-26.**n, narrative review**
7. Delitala AP, Capobianco G, Cherchi PL, et al. Thyroid function and thyroid disorders during pregnancy: a review and care pathway. Arch Gynecol Obstet 2019;299:327-38.**n; not an SR**
8. Dhillon-Smith RK, Middleton LJ, Sunner KK, et al. Efficacy and Mechanism Evaluation. Levothyroxine to increase live births in euthyroid women with thyroid antibodies trying to conceive: the TABLET RCT 2019.**n; population**

9. Di Girolamo R, Liberati M, Silvi C, et al. Levothyroxine Supplementation in Euthyroid Pregnant Women With Positive Autoantibodies: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne) 2022;13:759064.**n; RCTs not analysed separately**
10. Dong AC, Morgan J, Kane M, et al. Subclinical hypothyroidism and thyroid autoimmunity in recurrent pregnancy loss: a systematic review and meta-analysis. Fertil Steril 2020;113:587-600.e1.**n; population too restrictive**
11. Dong AC, Stagnaro-Green A. Differences in Diagnostic Criteria Mask the True Prevalence of Thyroid Disease in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid 2019;29:278-89.**n, not a research question**
12. Eligar V, Taylor PN, Okosieme OE, et al. Thyroxine replacement: a clinical endocrinologist's viewpoint. Ann Clin Biochem 2016;53:421-33.**n; not an SR**
13. Fatourechi V. Subclinical hypothyroidism: how should it be managed? Treat Endocrinol 2002;1:211-6.**n, narrative review**
14. Geng X, Chen Y, Wang W, et al. Systematic review and meta-analysis of the efficacy and pregnancy outcomes of levothyroxine sodium tablet administration in pregnant women complicated with hypothyroidism. Ann Palliat Med 2022;11:1441-52.**n; methodological problems (observational studies included despite only RCTs in inclusion criteria)**
15. Gietka-Czernel M, Glinicki P. Subclinical hypothyroidism in pregnancy: controversies on diagnosis and treatment. Pol Arch Intern Med 2021;131:266-75.**n, narrative review**
16. Glueck CJ, Streicher P. Cardiovascular and medical ramifications of treatment of subclinical hypothyroidism. Curr Atheroscler Rep 2003;5:73-7.**n, narrative review**
17. Hales C, Taylor PN, Channon S, et al. Controlled Antenatal Thyroid Screening II: Effect of Treating Maternal Suboptimal Thyroid Function on Child Behavior. J Clin Endocrinol Metab 2020;105.**n; outcome**
18. Han L, Ma Y, Liang Z, et al. Laboratory characteristics analysis of the efficacy of levothyroxine on subclinical hypothyroidism during pregnancy: a single-center retrospective study. Bioengineered 2021;12:4183-90.**n, study type**
19. Han Y, Wang J, Wang X, et al. Relationship Between Subclinical Hypothyroidism in Pregnancy and Hypertensive Disorder of Pregnancy: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne) 2022;13:823710.**n, intervention**
20. Jonklaas J. Optimal Thyroid Hormone Replacement. Endocr Rev 2022;43:366-404.**n, narrative review**
21. Kominiarek MA, Smid MC, Mele L, et al. Child Neurodevelopmental Outcomes by Prepregnancy Body Mass Index and Gestational Weight Gain. Obstet Gynecol 2018;132:1386-93.**n, outcomes**
22. Korevaar TIM, Medici M, Visser TJ, et al. Thyroid disease in pregnancy: new insights in diagnosis and clinical management. Nat Rev Endocrinol 2017;13:610-22.**n, narrative review**
23. Kroopnick JM, Kim CS. Overview of Hypothyroidism in Pregnancy. Semin Reprod Med 2016;34:323-30.**n; not an SR**
24. Lau L, Benham JL, Lemieux P, et al. Impact of levothyroxine in women with positive thyroid antibodies on pregnancy outcomes: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2021;11:e043751.**n; population includes preconception**
25. Li J, Shen J, Qin L. Effects of Levothyroxine on Pregnancy Outcomes in Women With Thyroid Dysfunction: A Meta-analysis of Randomized Controlled Trials. Altern Ther Health Med 2017;23:49-58.**n; population**
26. Ma L, Qi H, Chai X, et al. The effects of screening and intervention of subclinical hypothyroidism on pregnancy outcomes: a prospective multicenter single-blind, randomized, controlled study of thyroid function screening test during pregnancy. J Matern Fetal Neonatal Med 2016;29:1391-4.**n; screening intervention**
27. Mallawa Kankanamalage O, Zhou Q, Li X. Understanding the Pathogenesis of Gestational Hypothyroidism. Front Endocrinol (Lausanne) 2021;12:653407.**n; narrative review**
28. Maraka S, Ospina NM, O'Keeffe DT, et al. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. Thyroid 2016;26:580-90.**n; no RCTs included**
29. Myneni R, Chawla HV, Grewal AS, et al. Thyroxine Replacement for Subfertile Females With Subclinical Hypothyroidism and Autoimmune Thyroiditis: A Systematic Review. Cureus 2021;13:e16872.**n, population**
30. Nazarpour S, Ramezani Tehrani F, Amiri M, et al. Levothyroxine treatment and pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. Arch Gynecol Obstet 2019;300:805-19.**n; RCTs not analysed separately**
31. Nazarpour S, Ramezani Tehrani F, Sajedi F, et al. Evaluation of the impact of levothyroxine treatment on the psychomotor developmental status of three-year-old children born to mothers with mild thyroid

impairment; Tehran Thyroid and pregnancy study: study protocol for a randomized clinical trial. Trials 2019;20:86.**n; protocol**
32. Nazarpour S, Ramezani Tehrani F, Simbar M, et al. Thyroid autoantibodies and the effect on pregnancy outcomes. J Obstet Gynaecol 2016;36:3-9.**n; study type**
33. Negro R. Levothyroxine before conception in women with thyroid antibodies: a step forward in the management of thyroid disease in pregnancy. Thyroid Res 2019;12:5.**n; publication type**
34. Negro R. Outcomes in Pregnant Patients with Subclinical Hypothyroidism and Thyroid Autoimmunity: A Critical Appraisal of Recent Randomized Controlled Trials. Endocr Metab Immune Disord Drug Targets 2021;21:1387-91.**n; limited search date**
35. Negro R, Mangieri T, Coppola L, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. Hum Reprod 2005;20:1529-33.**n; population**
36. Okosieme OE, Agrawal M, Usman D, et al. Method-dependent variation in TSH and FT4 reference intervals in pregnancy: A systematic review. Ann Clin Biochem 2021;58:537-46.**n, subject**
37. Palatnik A, Mele L, Casey BM, et al. Association between Hypertensive Disorders of Pregnancy and Long-Term Neurodevelopmental Outcomes in the Offspring. Am J Perinatol 2021;39:921-9.**n, not a research question**
38. Plowden TC, Schisterman EF, Sjaarda LA, et al. Thyroid-stimulating hormone, anti-thyroid antibodies, and pregnancy outcomes. Am J Obstet Gynecol 2017;217:697.e1-.e7.**n, study type**
39. Poppe K, Velkeniers B, Glinoer D. Thyroid disease and female reproduction. Clin Endocrinol (Oxf) 2007;66:309-21.**n, narrative review**
40. Rao M, Zeng Z, Zhao S, et al. Effect of levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism and thyroid autoimmuneity undergoing in vitro fertilization/intracytoplasmic sperm injection: an updated meta-analysis of randomized controlled trials. Reprod Biol Endocrinol 2018;16:92.**n; population**
41. Rao M, Zeng Z, Zhou F, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. Hum Reprod Update 2019;25:344-61.**n; different SR selected**
42. Shinohara DR, Santos TDS, de Carvalho HC, et al. Pregnancy Complications Associated With Maternal Hypothyroidism: A Systematic Review. Obstet Gynecol Surv 2018;73:219-30.**n; limited search date**
43. Spencer L, Bubner T, Bain E, et al. Screening and subsequent management for thyroid dysfunction pre-pregnancy and during pregnancy for improving maternal and infant health. Cochrane Database Syst Rev 2015:Cd011263.**n; intervention**
44. Sun X, Hou N, Wang H, et al. A Meta-Analysis of Pregnancy Outcomes With Levothyroxine Treatment in Euthyroid Women With Thyroid Autoimmunity. J Clin Endocrinol Metab 2020;105.**n; RCTs not separately analysed**
45. Thompson W, Russell G, Baragwanath G, et al. Maternal thyroid hormone insufficiency during pregnancy and risk of neurodevelopmental disorders in offspring: A systematic review and meta-analysis. Clin Endocrinol (Oxf) 2018;88:575-84.**n; hypothyroxinemia included in analysis**
46. Unuane D, Velkeniers B. Impact of thyroid disease on fertility and assisted conception. Best Pract Res Clin Endocrinol Metab 2020;34:101378.**n, population**
47. Varner MW, Mele L, Casey BM, et al. Thyroid function in neonates of women with subclinical hypothyroidism or hypothyroxinemia. J Perinatol 2018;38:1490-5.**n; outcome**
48. Wang JW, Liao XX, Li T. Thyroid Autoimmunity in Adverse Fertility and Pregnancy Outcomes: Timing of Assisted Reproductive Technology in AITD Women. J Transl Int Med 2021;9:76-83.**n, population**
49. Yamamoto JM, Benham JL, Nerenberg KA, et al. Impact of levothyroxine therapy on obstetric, neonatal and childhood outcomes in women with subclinical hypothyroidism diagnosed in pregnancy: a systematic review and meta-analysis of randomised controlled trials. BMJ Open 2018;8:e022837.**n; different SR selected**
50. Yassa L, Marqusee E, Fawcett R, et al. Thyroid hormone early adjustment in pregnancy (the THERAPY) trial. J Clin Endocrinol Metab 2010;95:3234-41.**n, sample size**
51. Yuan N, Wang L, Li Z, et al. Thyroid Diseases During Pregnancy: Bibliometric Analysis of Scientific Publications. Endocr Metab Immune Disord Drug Targets 2022;22:247-58.**n; subject**
52. Zhao L, Jiang G, Tian X, et al. Initiation timing effect of levothyroxine treatment on subclinical hypothyroidism in pregnancy. Gynecol Endocrinol 2018;34:845-8.**n; sample size**

25.4 Infertility

1. Li J, Shen J, Qin L. Effects of Levothyroxine on Pregnancy Outcomes in Women With Thyroid Dysfunction: A Meta-analysis of Randomized Controlled Trials. Altern Ther Health Med 2017;23:49-58.**n; different review selected**
2. Medenica S, Nedeljkovic O, Radojevic N, et al. Thyroid dysfunction and thyroid autoimmunity in euthyroid women in achieving fertility. Eur Rev Med Pharmacol Sci 2015;19:977-87.**n; different review selected**
3. Negro R. Outcomes in Pregnant Patients with Subclinical Hypothyroidism and Thyroid Autoimmunity: A Critical Appraisal of Recent Randomized Controlled Trials. Endocr Metab Immune Disord Drug Targets 2021;21:1387-91.**n; population**
4. Negro R, Stagnaro-Green A. Clinical aspects of hyperthyroidism, hypothyroidism, and thyroid screening in pregnancy. Endocr Pract 2014;20:597-607.**n; narrative review**
5. Rao M, Zeng Z, Zhao S, et al. Effect of levothyroxine supplementation on pregnancy outcomes in women with subclinical hypothyroidism and thyroid autoimmuneity undergoing in vitro fertilization/intracytoplasmic sperm injection: an updated meta-analysis of randomized controlled trials. Reprod Biol Endocrinol 2018;16:92.**n; different review selected**
6. Rao M, Zeng Z, Zhou F, et al. Effect of levothyroxine supplementation on pregnancy loss and preterm birth in women with subclinical hypothyroidism and thyroid autoimmunity: a systematic review and meta-analysis. Hum Reprod Update 2019;25:344-61.**n; population**
7. Unuane D, Velkeniers B. Impact of thyroid disease on fertility and assisted conception. Best Pract Res Clin Endocrinol Metab 2020;34:101378.**n, narrative review**
8. Velkeniers B, Van Meerhaeghe A, Poppe K, et al. Levothyroxine treatment and pregnancy outcome in women with subclinical hypothyroidism undergoing assisted reproduction technologies: systematic review and meta-analysis of RCTs. Hum Reprod Update 2013;19:251-8.**n; different review selected**
9. Wang X, Zhang Y, Tan H, et al. Effect of levothyroxine on pregnancy outcomes in women with thyroid autoimmunity: a systematic review with meta-analysis of randomized controlled trials. Fertil Steril 2020;114:1306-14.**n; population**

25.5 Obesity

1. Abdelbaki TN, Elkeleny MR, Sharaan MA, et al. Impact of Laparoscopic Sleeve Gastrectomy on Obese Patients with Subclinical Hypothyroidism. J Laparoendosc Adv Surg Tech A 2020;30:236-40.**n; intervention**
2. Azran C, Hanhan-Shamshoum N, Irshied T, et al. Hypothyroidism and levothyroxine therapy following bariatric surgery: a systematic review, meta-analysis, network meta-analysis, and meta-regression. Surg Obes Relat Dis 2021;17:1206-17.**n; subject**
3. Bray GA, Glennon JA, Ruedi B, et al. Triiodothyronine and mercurial diuretics. Effects on excretion of a water load and on plasma free fatty acids in obese patients. Am J Clin Nutr 1969;22:1420-2.**n; intervention**
4. Bray GA, Melvin KE, Chopra IJ. Effect of triiodothyronine on some metabolic responses of obese patients. Am J Clin Nutr 1973;26:715-21.**n; intervention**
5. Gwinup G, Poucher R. A controlled study of thyroid analogs in the therapy of obesity. Am J Med Sci 1967;254:416-20.**n; sample size**
6. Herter-Aeberli I, Cherkaoui M, El Ansari N, et al. Iodine Supplementation Decreases Hypercholesterolemia in Iodine-Deficient, Overweight Women: A Randomized Controlled Trial. J Nutr 2015;145:2067-75.**n; intervention**
7. Hollingsworth DR, Amatruda TT, Jr., Scheig R. Quantitative and qualitative effects of L-triiodothyronine in massive obesity. Metabolism 1970;19:934-45.**n; intervention**
8. Moore R, Grant AM, Howard AN, et al. Treatment of obesity with triiodothyronine and a very-low-calorie liquid formula diet. Lancet 1980;1:223-6.**n; intervention**
9. Ostrowska L, Gier D, Zyśk B. The Influence of Reducing Diets on Changes in Thyroid Parameters in Women Suffering from Obesity and Hashimoto's Disease. Nutrients 2021;13.**n; intervention**

10. Pasquali R, Baraldi G, Biso P, et al. Effect of 'physiological' doses of triiodothyronine replacement on the hormonal and metabolic adaptation to short-term semistarvation and to low-calorie diet in obese patients. Clin Endocrinol (Oxf) 1984;21:357-67.**n; intervention**
11. Wilke H, Frahm H. [Influence of low-caloric-diet and d-triiodothyronine on serum lipids and body weight (author's transl)]. Med Klin 1974;69:1986-9.**n; intervention**

25.6 Anti-aging

1. Duntas LH. Thyroid Function in Aging: A Discerning Approach. Rejuvenation Res 2018;21:22-8.**n; population**

25.7 Euthyroid multinodular goiter

1. Brauer VF, Paschke R. [Pathophysiologic basis for prevention and pharmacotherapy of benign cold thyroid nodules]. Dtsch Med Wochenschr 2003;128:2324-8.**n, narrative review**
2. Castro MR, Caraballo PJ, Morris JC. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: a meta-analysis. J Clin Endocrinol Metab 2002;87:4154-9.**n; more recent review selected**
3. Cesareo R, Iozzino M, Isgrò MA, et al. Short term effects of levothyroxine treatment in thyroid multinodular disease. Endocr J 2010;57:803-9.**n; sample size**
4. Chen F, Tian G, Kong D, et al. Radiofrequency ablation for treatment of benign thyroid nodules: A PRISMA-compliant systematic review and meta-analysis of outcomes. Medicine (Baltimore) 2016;95:e4659.**n; intervention**
5. Cheung PS, Lee JM, Boey JH. Thyroxine suppressive therapy of benign solitary thyroid nodules: a prospective randomized study. World J Surg 1989;13:818-21; discussion 22.**n; sample size**
6. Cooper DS. Clinical review 66: Thyroxine suppression therapy for benign nodular disease. J Clin Endocrinol Metab 1995;80:331-4.**n, narrative review**
7. Costante G, Crocetti U, Schifino E, et al. Slow growth of benign thyroid nodules after menopause: no need for long-term thyroxine suppressive therapy in post-menopausal women. J Endocrinol Invest 2004;27:31-6.**n; single nodule**
8. Csako G, Byrd D, Wesley RA, et al. Assessing the effects of thyroid suppression on benign solitary thyroid nodules. A model for using quantitative research synthesis. Medicine (Baltimore) 2000;79:9-26.**n; more recent review selected**
9. Gharib H, Mazzaferri EL. Thyroxine suppressive therapy in patients with nodular thyroid disease. Ann Intern Med 1998;128:386-94.**n; more recent review selected**
10. Koc M, Ersoz HO, Akpinar I, et al. Effect of low- and high-dose levothyroxine on thyroid nodule volume: a crossover placebo-controlled trial. Clin Endocrinol (Oxf) 2002;57:621-8.**n; sample size**
11. Larijani B, Gharibdoost F, Pajouhi M, et al. Effects of levothyroxine suppressive therapy on bone mineral density in premenopausal women. J Clin Pharm Ther 2004;29:1-5.**n; study type**
12. Lima N, Knobel M, Cavaliere H, et al. Levothyroxine suppressive therapy is partially effective in treating patients with benign, solid thyroid nodules and multinodular goiters. Thyroid 1997;7:691-7.**n; sample size**
13. Mandel SJ, Brent GA, Larsen PR. Levothyroxine therapy in patients with thyroid disease. Ann Intern Med 1993;119:492-502.**n; more recent review selected**
14. Razack MS, Shimaoka K, Sako K, et al. Suppressive therapy of thyroid nodules in patients with previous radiotherapy to the head and neck. Am J Surg 1988;156:290-3.**n; population**
15. Richter B, Neises G, Clar C. Pharmacotherapy for thyroid nodules. A systematic review and meta-analysis. Endocrinol Metab Clin North Am 2002;31:699-722.**n; more recent review selected**
16. Sdano MT, Falciglia M, Welge JA, et al. Efficacy of thyroid hormone suppression for benign thyroid nodules: meta-analysis of randomized trials. Otolaryngol Head Neck Surg 2005;133:391-6.**n; more recent SR selected**
17. Wémeau JL, Cousty C, Vlaeminck V. [Suppressive hormone therapy for thyroid nodules. Prospective evaluation. Preliminary results]. Ann Endocrinol (Paris) 2000;61:119-24.**n; preliminary results**

18. Zhu Y, Huang J, Yue R, et al. Clinical Efficacy of Chinese and Western Medicine in the Treatment of Benign Thyroid Nodules: A Meta-Analysis. Contrast Media Mol Imaging 2022;2022:3108485.**n; comparison**

26 References

1. BCFI. Gecommentarieerd geneesmiddelenrepertorium. https://wwwbcfibe/nl/chapters [last accessed: 01/06/2022].
2. Brayfield A. Martindale: The Complete Drug Reference (40th ed.). London: Pharmaceutical Press; 2020.
3. NICE. Thyroid disease: assessment and management. NICE Guideline 2019.
4. Stott DJ, Rodondi N, Kearney PM, Ford I, Westendorp RGJ, Mooijaart SP, et al. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. The New England journal of medicine 2017;376: 2534-44.
5. Bandeira-Echtler E, Bergerhoff K, Richter B. Levothyroxine or minimally invasive therapies for benign thyroid nodules. The Cochrane database of systematic reviews 2014;2014: Cd004098.
6. Bekkering GE, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365: l2006.
7. Okosieme O, Gilbert J, Abraham P, Boelaert K, Dayan C, Gurnell M, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clinical endocrinology 2016;84: 799-808.
8. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid 2017;27: 315-89.
9. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. European thyroid journal 2014;3: 76-94.
10. Poppe K, Bisschop P, Fugazzola L, Minziori G, Unuane D, Weghofer A. 2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction. European thyroid journal 2021;9: 281-95.
11. Medicine PCotASfR. Subclinical hypothyroidism in the infertile female population: a guideline. Fertility and sterility 2015;104: 545-53.
12. Pasquali R, Casanueva F, Haluzik M, van Hulsteijn L, Ledoux S, Monteiro MP, et al. European Society of Endocrinology Clinical Practice Guideline: Endocrine work-up in obesity. European journal of endocrinology 2020;182: G1-g32.
13. Van Binsbergen JJ, Langens FNM, Dapper ALM, al e. Obesitas (M95). NHG 2020.
14. Group TMoAOaOW. VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF ADULT OVERWEIGHT AND OBESITY. Department of Veterans Affairs, Department of Defense 2020.
15. NICE. Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management. NICE Guideline 2021.
16. DEGAM. Müdigkeit. AWMF online 2017.
17. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedus L, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules - 2016 Update Appendix. Endocrine Practice 2016;22: 1-60.
18. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid 2014;24: 1670-751.
19. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. European thyroid journal 2012;1: 55-71.
20. Talaei A, Ghorbani F, Asemi Z. The Effects of Vitamin D Supplementation on Thyroid Function in Hypothyroid Patients: A Randomized, Double-blind, Placebo-controlled Trial. Indian journal of endocrinology and metabolism 2018;22: 584-8.

21. Gencer B, Moutzouri E, Blum MR, Feller M, Collet TH, Delgiovane C, et al. The Impact of Levothyroxine on Cardiac Function in Older Adults With Mild Subclinical Hypothyroidism: A Randomized Clinical Trial. The American journal of medicine 2020;133: 848-56.e5.
22. Gonzalez Rodriguez E, Stuber M, Del Giovane C, Feller M, Collet TH, Löwe AL, et al. Skeletal Effects of Levothyroxine for Subclinical Hypothyroidism in Older Adults: A TRUST Randomized Trial Nested Study. The Journal of clinical endocrinology and metabolism 2020;105.
23. Stuber MJ, Moutzouri E, Feller M, Del Giovane C, Bauer DC, Blum MR, et al. Effect of Thyroid Hormone Therapy on Fatigability in Older Adults With Subclinical Hypothyroidism: A Nested Study Within a Randomized Placebo-Controlled Trial. The journals of gerontology Series A, Biological sciences and medical sciences 2020;75: e89-e94.
24. Wildisen L, Feller M, Del Giovane C, Moutzouri E, Du Puy RS, Mooijaart SP, et al. Effect of Levothyroxine Therapy on the Development of Depressive Symptoms in Older Adults With Subclinical Hypothyroidism: An Ancillary Study of a Randomized Clinical Trial. JAMA network open 2021;4: e2036645.
25. Zijlstra LE, Jukema JW, Westendorp RGJ, Du Puy RS, Poortvliet RKE, Kearney PM, et al. Levothyroxine Treatment and Cardiovascular Outcomes in Older People With Subclinical Hypothyroidism: Pooled Individual Results of Two Randomised Controlled Trials. Frontiers in endocrinology 2021;12: 674841.
26. Mooijaart SP, Du Puy RS, Stott DJ, Kearney PM, Rodondi N, Westendorp RGJ, et al. Association Between Levothyroxine Treatment and Thyroid-Related Symptoms Among Adults Aged 80 Years and Older With Subclinical Hypothyroidism. Jama 2019;322: 1977-86.
27. Ding Z, Liu Y, Maraka S, Abdelouahab N, Huang HF, Fraser WD, et al. Pregnancy and Neonatal Outcomes With Levothyroxine Treatment in Women With Subclinical Hypothyroidism Based on New Diagnostic Criteria: A Systematic Review and Meta-Analysis. Frontiers in endocrinology 2021;12: 797423.
28. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Minooee S, Rahmati M, et al. Effects of Levothyroxine on Pregnant Women With Subclinical Hypothyroidism, Negative for Thyroid Peroxidase Antibodies. The Journal of clinical endocrinology and metabolism 2018;103: 926-35.
29. Casey BM, Thom EA, Peaceman AM, Varner MW, Sorokin Y, Hirtz DG, et al. Treatment of Subclinical Hypothyroidism or Hypothyroxinemia in Pregnancy. The New England journal of medicine 2017;376: 815-25.
30. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Azizi F. Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. European journal of endocrinology 2017;176: 253-65.
31. Mir F, Chiti H, Mazloomzadeh S. Short-Term Adverse Pregnancy Outcomes in Women with Subclinical Hypothyroidism: A Comparative Approach of Iranian and American Guidelines. Journal of thyroid research 2022;2022: 9315250.
32. Leng T, Li X, Zhang H. Levothyroxine treatment for subclinical hypothyroidism improves the rate of live births in pregnant women with recurrent pregnancy loss: a randomized clinical trial. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 2022;38: 488-94.
33. Costantine MM, Smith K, Thom EA, Casey BM, Peaceman AM, Varner MW, et al. Effect of Thyroxine Therapy on Depressive Symptoms Among Women With Subclinical Hypothyroidism. Obstetrics and gynecology 2020;135: 812-20.
34. Wang X, Zhang Y, Tan H, Bai Y, Zhou L, Fang F, et al. Effect of levothyroxine on pregnancy outcomes in women with thyroid autoimmunity: a systematic review with meta-analysis of randomized controlled trials. Fertility and sterility 2020;114: 1306-14.
35. Negro R, Mangieri T, Coppola L, Presicce G, Casavola EC, Gismondi R, et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. Human reproduction (Oxford, England) 2005;20: 1529-33.

36. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. The Journal of clinical endocrinology and metabolism 2006;91: 2587-91.
37. Negro R, Schwartz A, Stagnaro-Green A. Impact of Levothyroxine in Miscarriage and Preterm Delivery Rates in First Trimester Thyroid Antibody-Positive Women With TSH Less Than 2.5 mIU/L. The Journal of clinical endocrinology and metabolism 2016;101: 3685-90.
38. Wang H, Gao H, Chi H, Zeng L, Xiao W, Wang Y, et al. Effect of Levothyroxine on Miscarriage Among Women With Normal Thyroid Function and Thyroid Autoimmunity Undergoing In Vitro Fertilization and Embryo Transfer: A Randomized Clinical Trial. Jama 2017;318: 2190-8.
39. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al. Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception. The New England journal of medicine 2019;380: 1316-25.
40. van Dijk MM, Vissenberg R, Fliers E, van der Post JAM, van der Hoorn MP, de Weerd S, et al. Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The lancet Diabetes & endocrinology 2022;10: 322-9.
41. Akhtar MA, Agrawal R, Brown J, Sajjad Y, Craciunas L. Thyroxine replacement for subfertile women with euthyroid autoimmune thyroid disease or subclinical hypothyroidism. The Cochrane database of systematic reviews 2019;6: Cd011009.
42. Kaptein EM, Beale E, Chan LS. Thyroid hormone therapy for obesity and nonthyroidal illnesses: a systematic review. The Journal of clinical endocrinology and metabolism 2009;94: 3663-75.
43. BCFI. Hitteslag en maligne hyperthermie door geneesmiddelen. Folia Pharmacotherapeutica 2022.
44. BCFI. Tremor van medicamenteuze oorsprong. Folia Pharmacotherapeutica 2018.
45. BCFI. Geneesmiddelenbewaking: ongewenste effecten van orlistat. Folia Pharmacotherapeutica 2010.
46. Pirola I, Gandossi E, Agosti B, Delbarba A, Cappelli C. Selenium supplementation could restore euthyroidism in subclinical hypothyroid patients with autoimmune thyroiditis. Endokrynologia Polska 2016;67: 567-71.
47. Bayani M, Amani M, Moazezi Z. Efficacy of levothyroxine on benign thyroid nodule. Caspian journal of internal medicine 2012;3: 359-62.
48. Boguszewski CL, Pedrazzini M, Hans G. Assessment of levothyroxine suppressive therapy in patients with solitary thyroid nodules: a double-blind, placebo-controlled, clinical trial. Arquivos Brasileiros de Endocrinologia e Metabologia 1998;42: 214-21.
49. Gharib H, James EM, Charboneau JW, Naessens JM, Offord KP, Gorman CA. Suppressive therapy with levothyroxine for solitary thyroid nodules. A double-blind controlled clinical study. The New England journal of medicine 1987;317: 70-5.
50. Grussendorf M, Reiners C, Paschke R, Wegscheider K. Reduction of thyroid nodule volume by levothyroxine and iodine alone and in combination: a randomized, placebo-controlled trial. The Journal of clinical endocrinology and metabolism 2011;96: 2786-95.
51. La Rosa GL, Lupo L, Giuffrida D, Gullo D, Vigneri R, Belfiore A. Levothyroxine and Potassium Iodide Are Both Effective in Treating Benign Solitary Solid Cold Nodules of the Thyroid. Annals of internal medicine 1995;122: 1-8.
52. Larijani B, Pajouhi M, Bastanhagh MH, Sadjadi A, Aghakhani S, Zare F, et al. Role of levothyroxine suppressive therapy for benign cold nodules of thyroid: a randomized, double-blind, placebo-controlled clinical trial. Therapy 2005;2: 883-8.
53. Papini E, Bacci V, Panunzi C, Pacella CM, Fabbrini R, Bizzarri G, et al. A prospective randomized trial of levothyroxine suppressive therapy for solitary thyroid nodules. Clinical endocrinology 1993;38: 507-13.
54. Reverter JL, Lucas A, Salinas I, Audí L, Foz M, Sanmartí A. Suppressive therapy with levothyroxine for solitary thyroid nodules. Clinical endocrinology 1992;36: 25-8.

55. Wémeau JL, Caron P, Schvartz C, Schlienger JL, Orgiazzi J, Cousty C, et al. Effects of thyroid-stimulating hormone suppression with levothyroxine in reducing the volume of solitary thyroid nodules and improving extranodular nonpalpable changes: a randomized, double-blind, placebo-controlled trial by the French Thyroid Research Group. The Journal of clinical endocrinology and metabolism 2002;87: 4928-34.
56. Zelmanovitz F, Genro S, Gross JL. Suppressive therapy with levothyroxine for solitary thyroid nodules: a double-blind controlled clinical study and cumulative meta-analyses. The Journal of clinical endocrinology and metabolism 1998;83: 3881-5.