

# IEMO 80-plus thyroid trial.

No registrations found.

<b>Ethical review</b>	Positive opinion
<b>Status</b>	Recruiting
<b>Health condition type</b>	-
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON22581

### Source

Nationaal Trial Register

### Brief title

IEMO 80-plus

### Health condition

Subclinical hypothyroidism

Levothyroxin

Older adults

Randomized placebo-controlled trial

Subklinische hypothyreoidie

Levothyroxine

Ouderen

Gerandomiseerd placebo-gecontroleerde trial

## Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum

**Source(s) of monetary or material Support:** ZonMw project no 627001001

## Intervention

## Outcome measures

### Primary outcome

The main study endpoint is change in thyroid-specific quality of life and symptom burden assessed using the hypothyroid symptoms scale score and tiredness symptoms scale score on the thyroid-specific quality of life (ThyPRO) questionnaire at baseline, six to eight weeks and 12 months after recruitment and at the close-out visit are included.

## **Secondary outcome**

1. General quality of life;
2. Handgrip strength;
3. Cognitive function, particularly executive function;
4. Total mortality and cardiovascular mortality;
5. Functional ability (basic Activities of Daily Living (ADL); extended activities of daily living);
6. Gait speed;
7. Depressive symptoms.
8. Fatal and non-fatal cardiovascular events (this will include acute myocardial infarction; stroke; amputations for peripheral vascular disease; revascularisations for atherosclerotic vascular disease, including for acute coronary syndrome and heart failure hospitalisations)

## **Study description**

### **Background summary**

Background of the study:

Subclinical hypothyroidism is a common condition (8-18%) among older men and women. Although by definition subclinical hypothyroidism comprises biochemically mild thyroid hormone deficiency, it is a possible contributor to multiple problems in older age. Thyroid hormone has effects

on numerous physiological systems, including the vascular tree, heart, skeletal muscle and brain. Therefore, thyroxine substitution to overcome thyroid hormone deficiency has the potential to give multisystem benefits to older people with subclinical hypothyroidism. Small studies have reported reduced atherosclerosis and improved heart function with thyroxine replacement, but no large clinical trials have been performed. Therefore the available evidence is limited, leading to major variations in guidelines and clinical practice, with uncertainty regarding the indications for screening and treatment. This is especially the case for the oldest old, because observational studies are conflicting and very few oldest old are included in clinical trials, although they have the highest prevalence of subclinical hypothyroidism and its

potentially related symptoms and diseases.

#### Objective of the study:

1. Does Levothyroxine treatment for subclinical hypothyroidism give multi-modal benefits for the oldest old people with subclinical hypothyroidism?
2. Are benefits seen across a wide range of outcomes, including prevention of cardiovascular disease, and improving health-related quality of life, muscle function and cognition?
3. Are benefits seen in specific subgroups of oldest old people with SCH, including women, and those with mild degrees of subclinical hypothyroidism (TSH 4.6-10 mU/L)?
4. Are any benefits offset by adverse effects, such as atrial fibrillation or heart failure?
5. To store study blood samples in a repository of blood samples from which potential biomarkers and/or genes may be identified that better predict those older people with SCH who are at risk of dying or developing ill-health, including cardiovascular and cerebrovascular disease.

#### Study design:

Randomised double-blind placebo-controlled parallel group trial. The IEMO 80-plus thyroid trial was set up as an independent randomised double-blind placebo-controlled parallel group trial of levothyroxine for oldest old persons with subclinical hypothyroidism. From the outset the study was designed jointly and in parallel with the TRUST trial and both trials share a near identical design and infrastructure including study protocols, standard operating procedures, independent data monitoring and endpoint committees, databases, statisticians and study nurses.

#### Study population:

145 community-dwelling patients aged >80 years with subclinical hypothyroidism, diagnosed on the basis of persistently elevated TSH levels, measured on a minimum of two occasions at least 3 months apart, over 2 years.

#### Intervention:

Oral Levothyroxine 50 µg daily (reduced to 25 mcg daily in subjects < 50 kg body weight or if known coronary heart disease) versus matching placebo.

#### Primary study parameters/outcome of the study:

The main study endpoint is change in thyroid-specific quality of life and symptom burden assessed using the hypothyroid symptoms scale score and tiredness symptoms scale score on the thyroid-specific quality of life (ThyPRO) questionnaire at baseline, six to eight weeks and 12 months after recruitment and at the close-out visit are included.

#### Secondary study parameters/outcome of the study:

1. General quality of life;
2. Handgrip strength;
3. Cognitive function, particularly executive function;
4. Total mortality and cardiovascular mortality;
5. Functional ability (basic Activities of Daily Living (ADL); extended activities of daily living);
6. Gait speed;
7. Haemoglobin;
8. Depressive symptoms ;
9. Fatal and non-fatal cardiovascular events (this will include

acute myocardial infarction; stroke; amputations for peripheral vascular disease; revascularisations for atherosclerotic vascular disease, including for acute coronary syndrome and heart failure hospitalisations).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Adverse events (atrial fibrillation, heart failure and fractures in particular) are likely to occur only in the context of over replacement of Levothyroxine. Our dose titration scheme and study processes of careful monitoring of thyroid function tests are designed to ensure we avoid prolonged periods of thyroid hormone excess. For the group allocated to placebo, there is risk of developing overt clinical hypothyroidism; however, our study processes of careful monitoring of thyroid function tests are designed to avoid this scenario.

Statistical analysis:

The participants of the present project will be included in a pre-planned combined analysis with the international TRUST consortium, of which the LUMC is the Dutch member (protocol number P12.203), who includes a total number of 738 participants over the age of 65 years. The present project adds 145 80-plus year old participants to perform an adequately powered sub-group analysis in the over eighties age group. The main analysis will be the association between thyroid specific quality of life and treatment in the combined study population of IEMO and the 80-plus participants of TRUST. Treatment effects will be assessed using analysis of covariance (ANCOVA) adjusting for gender and baseline levels of the same variable. To assess for associations with cardiovascular events, time to first event Cox regression analysis are used stratified by gender in models containing the randomised treatment allocation as a covariate (intention-to-treat). Tests of treatment effect will be based on the Wald test and corresponding point estimates and 95% confidence intervals for the hazard ratio for treatment will be calculated. The assumption of proportionality of hazards will be tested. Additional end points relevant to older people will be assessed for the present study alone and in combination with the 80-plus participants in TRUST.

## Study objective

1. Does Levothyroxine treatment for subclinical hypothyroidism give multi-modal benefits for the oldest old people with subclinical hypothyroidism?
2. Are benefits seen across a wide range of outcomes, including prevention of cardiovascular disease, and improving health-related quality of life, muscle function and cognition?
3. Are benefits seen in specific subgroups of oldest old people with subclinical hypothyroidism, including women, and those with mild degrees of subclinical hypothyroidism (TSH 4.6-10 mU/L)?
4. Are any benefits offset by adverse effects, such as atrial fibrillation or heart failure?
5. To store study blood samples in a repository of blood samples from which potential biomarkers and/or genes may be identified that better predict those older people with SCH who are at risk of dying or developing ill-health, including cardiovascular and cerebrovascular disease.

## Study design

The primary outcome will be assessed at baseline, six to eight weeks and 12 months after recruitment and eventually at 24 and 36 months.

## Intervention

Oral Levothyroxine 50 µg daily (reduced to 25 mcg daily in subjects < 50 kg body weight or if known coronary heart disease) versus matching placebo. The intervention will have a maximum of 3 years.

## Contacts

### Public

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## Eligibility criteria

### Inclusion criteria

Community-dwelling patients aged >80 years with SCH.

SCH is defined as persistently elevated TSH levels ( $>4.6$  and  $\leq 19.9$  mU/L) and free thyroxine (fT4) in reference range measured on a minimum of two occasions at least 3 months apart.

### Exclusion criteria

1. Subjects currently on Levothyroxine or antithyroid medication (e.g. Carbimazole, methimazole, propylthiouracil, potassium percholate), amiodarone or lithium;
2. Recent thyroid surgery or radio-iodine therapy (within 12 months);
3. Grade IV NYHA heart failure;
4. Prior clinical diagnosis of dementia;
5. Recent hospitalisation for major illness (within 4 weeks);
6. Recent acute coronary syndrome, including myocardial infarction or unstable angina (within 4 weeks);
7. Acute myocarditis or acute pancarditis;
8. Untreated adrenal insufficiency;
9. Terminal illness;
10. Patients known to have rare hereditary problem of galactose intolerance;

11. Subjects who are participating in ongoing RCTs of therapeutic interventions (including clinical trials of investigational medicinal products [CTIMPs]);
12. Plan to move out of the region in which the trial is being conducted within the next 2 years (proposed minimum follow-up period).

## Study design

### Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

### Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	13-05-2014
Enrollment:	145
Type:	Anticipated

### IPD sharing statement

**Plan to share IPD:** Undecided

## Ethics review

Positive opinion	
Date:	12-02-2013
Application type:	First submission

## Study registrations



## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

Register	ID
NTR-new	NL3681
NTR-old	NTR3851
Other	EudraCT : 2012-004160-22
ISRCTN	ISRCTN wordt niet meer aangevraagd.

## Study results

### Summary results

#### Trial Results

Mooijaart SP, Du Puy RS, Stott DJ, Kearney PM, Rodondi N, Westendorp RGJ, den Elzen WPJ, Postmus I, Poortvliet RKE, van Heemst D, van Munster BC, Peeters RP, Ford I, Kean S, Messow CM, Blum MR, Collet TH, Watt T, Dekkers OM, Jukema JW, Smit JWA, Langhorne P, Gussekloo J. Association Between Levothyroxine Treatment and Thyroid-Related Symptoms Among Adults Aged 80 Years and Older With Subclinical Hypothyroidism. JAMA. 2019 Oct 30;1-11. doi: 10.1001/jama.2019.17274. [Epub ahead of print] PubMed PMID: 31664429; PubMed Central PMCID: PMC6822162.

#### Methods paper

Du Puy RS, Postmus I, Stott DJ, Blum MR, Poortvliet RKE, Den Elzen WPJ, Peeters RP, van Munster BC, Wolffenbuttel BHR, Westendorp RGJ, Kearney PM, Ford I, Kean S, Messow CM, Watt T, Jukema JW, Dekkers OM, Smit JWA, Rodondi N, Gussekloo J, Mooijaart SP. 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 Sep 19;18(1):67. doi: 10.1186/s12902-018-0285-8. PubMed PMID: 30231866; PubMed Central PMCID: PMC6146605.