# Effects of discontinuation of levothyroxine treatment in older adults: a self-controlled study.

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Primary aim1) To investigate what proportion of levothyroxine users aged 60 years and older can withdraw from levothyroxine treatment successfully, defined as having normal fT4 levels and TSH levels =50% dose reduction b. Substantial dose lowering...

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| **Ethical review** | Approved WMO |
| **Status** | Completed |
| **Health condition type** | Thyroid gland disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON52395

**Source**
ToetsingOnline

**Brief title**
RELEASE

### Condition

- Thyroid gland disorders

**Synonym**
hypothyroidism; underactive thyroid

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** ZonMW HGOG

## Intervention

**Keyword:** Discontinuation, Levothyroxine, Older adults, Self-controlled trial

## Outcome measures

### Primary outcome

The primary outcome is the proportion of participants that withdraw their thyroid medication successfully (defined as normal fT4 levels and TSH levels <10 mU/L) at 52 weeks after start of the discontinuation.

### Secondary outcome

Effects of discontinuing levothyroxine on:

- Thyroid-related quality of life including somatic, psychological and social domains
- General health
- Treatment satisfaction for medication
- Daily functioning

Proportion of levothyroxine users who can achieve a substantial dose lowering of their levothyroxine dose after one year.

Demographic, clincal characteristics and attitudes towards discontinuation of those levothyroxine users aged 60 years and older willing to discontinue levothyroxine treatment and those successfully reducing their dosage.

Characteristics of persons aged 60 years and older that physicians consider safe to withdraw thyroid medication from, and medical reasons not to

discontinue treatment.

Frequency of discontinuation (or stepping-down) levothyroxine treatment by

general practitioners in usual care .

Physicians* experience on the recruitment of patients and the consultations,

Study participants* experience of discontinuation of medication.

# Study description

**Background summary**

Many older persons in the Netherlands use levothyroxine (2015: >215.000 aged 65+), and often have been using levothyroxine for a very long time. Initial indications for treatment are often not well registered, inaccurate or even inappropriate due to changing guidelines. Currently, levothyroxine treatment is indicated for patients with overt hypothyroidism (high Thyroid Stimulating Hormone [TSH], low free Thyroxin [fT4]). For subclinical hypothyroidism (high TSH, normal fT4), the most common thyroid disorder in older people (3-18% aged 65+), guidelines vary. Recently, in the TRUST trial, it was shown that levothyroxine treatment was not clinically beneficial in people aged 65 years and older with subclinical hypothyroidism. Given the high prevalence of levothyroxine use, the ambiguous treatment indications, the lack of evidence for beneficial effects of treatment and the health risks associated with (over)treatment, we hypothesize that discontinuation of levothyroxine is feasible in many older persons without negative consequences.

**Study objective**

Primary aim
1) To investigate what proportion of levothyroxine users aged 60 years and older can withdraw from levothyroxine treatment successfully, defined as having normal fT4 levels and TSH levels <10 mU/L at 52 weeks after start of the discontinuation.

Secondary aims
1) To study the effect of discontinuing levothyroxine on a) thyroid specific quality of life, b) general health and c) treatment satisfaction for

medication, by comparing scores on validated questionnaires before and after stopping in a self-controlled design.
2) To study what proportion of levothyroxine users aged 60 years and older can achieve a substantial dose lowering of their levothyroxine dose after one year.
a. Substantial dose lowering will be defined as >=50% dose reduction
b. Substantial dose lowering will be defined by the participant themselves.
3) To study the demographic, clinical characteristics and attitudes towards discontinuation of those levothyroxine users aged 60 years and older willing to discontinue levothyroxine treatment and those successfully reducing their dosage.
4) To study the characteristics of persons aged 60 years and older that physicians consider safe to withdraw thyroid medication from, and medical reasons not to discontinue treatment.

Through add-on observational studies in Routine Medical Care data including the ELAN data warehouse, we will get insights in how often general practitioners stop levothyroxine treatment (or lower dose) in usual care.

Through add-on qualitative studies, we will get insights in physicians* experience on the recruitment of patients and the consultations, but also participants* experience of discontinuation of medication.

## Study design

A self-controlled study.

## Intervention

Stepwise levothyroxine treatment discontinuation. Levothyroxine at a dose of <= 150 microgram per day will be tapered by the treating physician according to a predetermined schedule while thyroid function is monitored after every step down. Treatment with levothyroxine is ended when a levothyroxine dose of < 25 microgram per day is reached and thyroid function still falls within the standard.

## Study burden and risks

In the run-in period participants enter the study with pre-baseline measurements in which treatment with levothyroxine is continued per usual care with unadjusted daily routine. The pre-baseline measurements are a set of questionnaires and a standard thyroid function laboratory test in a venous blood sample. During the discontinuation phase the participant will start lowering the dose of levothyroxine guided by their own physician according to the study-protocol. Laboratory tests for thyroid function will be assessed accordingly. During final assessment at 12 months, questionnaires and a thyroid function measurement will be collected.

The added burden for the participant consists of completing questionnaires and a few extra thyroid function laboratory tests to control the effects of discontinuation on thyroid function. These laboratory tests are routinely done in patients using levothyroxine at least once a year.

In summary the extent of the burden of participation consist of:
- visits to the laboratory for venous blood sampling to determine thyroid function (up to 9 visits)
- filling out various questionnaires (3 - 8) at 5 or 6 time points
- consultation with the treating physician (up to 9 times)
- collecting a new dosage of levothyroxine from the pharmacist (up to 5 times)

Abnormal thyroid function might arise during discontinuation of levothyroxine due to a deficiency of thyroid hormone. Symptoms related to hypothyroidim may occur, including fatigue, cold intolerance, dry skin, constipation, weight gain, muscle ache, change in cognitive functioning and change of mood. Participants will be required to stop lowering the dose of their levothyroxine treatment when a TSH level >= 10 mU/L or low fT4 levels (below normal range) is identified during any of the laboratory control visits and is confirmed in a re-visit. The treating physician will treat the patient according to the standard guideline.

Safety of the participants will be monitored by an independent Data Safety and Monitoring Board and judged according to pre-defined termination rules. Participants* own physician is responsible for monitoring the clinical safety of the participant (usual care).

This study will not interfere with standard care, diagnostics and treatment.

## Contacts

**Public**
Leids Universitair Medisch Centrum

Hippocratespad 21
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Community dwelling patients and nursing home patients aged 60 and over using levothyroxine continuously for a minimum of 1 year at a stable dose.

## Exclusion criteria

- Last measurement of TSH (thyroid stimulating hormone) >=10 mU/L during levothyroxine treatment
- A history of thyroidectomy, radioactive iodine treatment, neck irradiation, congenital hypothyroidism or secondary hypothyroidism
- Concurrent amiodarone or lithium use
- Concurrent use of liothyronine, thiamazole, carbimazole or propylthiouracil.
- Patients using a dose of more than 150 mcg levothyroxine per day
- Diagnosis of heart failure NYHA grade IV
- Diagnosis of dementia
- Incapacitated adults
- Life-expectancy of less than 6 months
- Participation in ongoing trials of therapeutic interventions
- Persons that plan to move out of the region in which the study is being conducted in the next months

# Study design

## Design

**Study type:** Observational invasive

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Prevention |

## Recruitment

NL

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| Recruitment status: | Completed |
| Start date (anticipated): | 13-02-2020 |
| Enrollment: | 415 |
| Type: | Actual |

# Ethics review

Approved WMO

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|---|---|
| Date: | 19-08-2019 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

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|---|---|
| Date: | 26-11-2019 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 12-12-2019 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 23-01-2020 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 04-03-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 17-07-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

| | |
|---|---|
| Approved WMO Date: | 14-08-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 27-11-2020 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 04-06-2021 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 11-10-2021 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 11-11-2021 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
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|---|---|
| Approved WMO Date: | 29-12-2021 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 26-01-2022 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 05-04-2022 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 25-04-2022 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden) |
| | metc-ldd@lumc.nl |

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|---|---|
| Approved WMO Date: | 30-09-2022 |

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|---|---|
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

# Study registrations

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

No registrations found.

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

ID: 24126
Source: NTR
Title:

## In other registers

| Register | ID |
|---|---|
| CCMO | NL69753.058.19 |
| Other | NL7978 (Nederlands Trial Register) |