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## **Subclinical hypothyroidism in community-dwelling older people: consequences and treatment outcomes**

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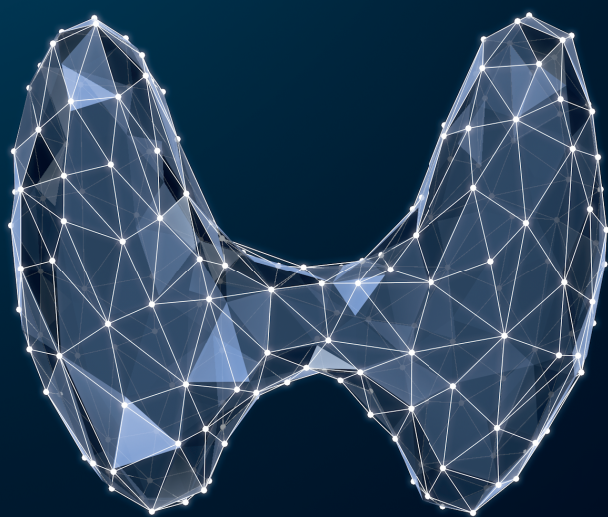
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# Chapter 7

Association between levothyroxine treatment and thyroid-related symptoms among adults aged 80 years and older with subclinical hypothyroidism

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## **Treatment of older adults with subclinical hypothyroidism – reply**

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## ABSTRACT

### Importance

It is unclear whether levothyroxine treatment provides clinically important benefits in adults aged 80 years and older with subclinical hypothyroidism.

### Objective

To determine the association of levothyroxine treatment for subclinical hypothyroidism with thyroid-related quality of life in adults aged 80 years and older.

### Design, Setting, and Participants

Prospectively planned combined analysis of data involving community-dwelling adults aged 80 years and older with subclinical hypothyroidism. Data from a randomised clinical trial were combined with a subgroup of participants aged 80 years and older from a second clinical trial. The trials were conducted between April 2013 and May 2018. Final follow-up was May 4, 2018.

### Exposures

Participants were randomly assigned to receive levothyroxine ( $n = 112$ ; 52 participants from the first trial and 60 from the second trial) or placebo ( $n = 139$ ; 53 participants from the first trial and 86 from the second trial).

### Main Outcomes and Measures

Co-primary outcomes were Thyroid-Related Quality of Life Patient-Reported Outcome (ThyPRO) questionnaire scores for the domains of hypothyroid symptoms and tiredness at 1 year (range, 0-100; higher scores indicate worse quality of life; minimal clinically important difference, 9).

### Results

Of 251 participants (mean age, 85 years; 118 [47%] women), 105 were included from the first clinical trial and 146 were included from the second clinical trial. A total of 212 participants (84%) completed the study. The hypothyroid symptoms score decreased from 21.7 at baseline to 19.3 at 12 months in the levothyroxine group vs from 19.8 at baseline to 17.4 at 12 months in the placebo group (adjusted between-group difference, 1.3 [95% CI, -2.7 to 5.2];  $P = .53$ ). The tiredness score increased from 25.5 at baseline to 28.2 at 12 months in the levothyroxine group vs from 25.1 at baseline to 28.7 at 12 months in the placebo group (adjusted between-group difference, -0.1 [95% CI, -4.5 to 4.3];  $P = .96$ ). At least 1 adverse event occurred in 33 participants (29.5%) in the levothyroxine group (the most common adverse event was cerebrovascular accident, which occurred in 3 participants [2.2%]) and 40



participants (28.8%) in the placebo group (the most common adverse event was pneumonia, which occurred in 4 [3.6%] participants).

## Conclusions and Relevance

In this prospectively planned analysis of data from 2 clinical trials involving adults aged 80 years and older with subclinical hypothyroidism, treatment with levothyroxine, compared with placebo, was not significantly associated with improvement in hypothyroid symptoms or fatigue. These findings do not support routine use of levothyroxine for treatment of subclinical hypothyroidism in adults aged 80 years and older.

## Trial Registration

ClinicalTrials.gov Identifier: NCT01660126; Netherlands Trial Register: NTR3851

## Key Points

### Question

Among adults aged 80 years and older with subclinical hypothyroidism, what is the association between treatment with levothyroxine and thyroid-related symptoms?

### Findings

In this pooled analysis of data from 2 randomised clinical trials that included 251 participants aged 80 years and older, treatment with levothyroxine, compared with placebo, was not significantly associated with improvement in thyroid-related patient-reported quality of life outcome scores (range, 0-100; higher scores indicate worse quality of life; minimal clinically important difference, 9) for hypothyroid symptoms (adjusted between-group difference, 1.3) or tiredness (adjusted between-group difference, 0.1).

### Meaning

These findings do not support routine treatment with levothyroxine for subclinical hypothyroidism in adults aged 80 years and older.

## INTRODUCTION

The prevalence of subclinical hypothyroidism increases with age.[1] Subclinical hypothyroidism is defined by elevated levels of thyrotropin (often referred to as thyroid-stimulating hormone [TSH]) simultaneously with free thyroxine (FT4) within the normal range. Some patients with subclinical hypothyroidism report symptoms such as constipation, mental slowness, fatigue, or depressive symptoms.[2,3] Subclinical hypothyroidism has also been associated with an increased risk of cardiovascular disease.[4]

In a 2017 clinical randomised trial of 737 participants aged 65 years and older, treatment with levothyroxine demonstrated no benefit on the primary outcome of thyroid-specific quality of life.[5] However, individuals aged 80 years and older with subclinical hypothyroidism have been underrepresented in clinical trials[6,7] and outcomes such as quality of life have not been reported for this age group. Because the prevalence of comorbidities and frailty increase with age, it is possible that benefits and harms from managing subclinical hypothyroidism may differ in adults aged 80 years and older compared with younger age groups.[8] The lack of evidence for older patients may have contributed to significant treatment variation by primary care clinicians.[9]

This study combined data from the Institute for Evidence-Based Medicine in Old Age (IEMO) 80-plus thyroid trial[10] and the subgroup of participants in the Thyroid Hormone Replacement for Untreated Older Adults With Subclinical Hypothyroidism Trial (TRUST) aged 80 years and older.[5] The 2 trials examined the effects of managing subclinical hypothyroidism with levothyroxine on quality of life in adults aged 80 years and older.

## METHODS

Both clinical trials were approved by the Central Committee on Research Involving Human Subjects in the Netherlands and by the Bern and Lausanne ethics committees and Swissmedic, the Swiss authority on drugs, in Switzerland. One trial was also approved by the Multicentre Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency in the United Kingdom, with cosponsors the National Health Services Greater Glasgow and Clyde and the University of Glasgow, and by the Clinical Research Ethics Committee, Cork, and the Health Products Regulatory Authority (formerly known as the Irish Medicines Board) in Ireland. Written informed consent was obtained from all participants. The study protocol and statistical analysis plans for each trial have been published.[10,11] The protocol and statistical analysis plan for the combined analyses are available in Supplement 1 and Supplement 2.

## Design

The included studies were randomised, double-blind, placebo-controlled parallel-group trials investigating the effects of levothyroxine treatment for persons with subclinical hypothyroidism aged 80 years and older and aged 65 years and older.[10,11] They were conducted with similar study designs and included a prospectively planned combined analysis of all participants aged 80 years and older. The cohorts are presented and analysed as a single study group throughout this report.

## Study Population

One trial recruited community-dwelling participants aged 80 and older years between May 2014 and May 2017, from sites in the Netherlands and Switzerland,[10] with a final date of follow-up of May 4, 2018. The other trial recruited community-dwelling participants aged 65 years and older from sites in the Netherlands, Switzerland, Ireland, and the United Kingdom between April 2013 and May 2015, with a final date of follow-up of October 31, 2016 [11]; only participants aged 80 years and older from this trial were included in this report. Participants were followed up for a minimum of 12 months and a maximum of 36 months. Information on participant race was collected to evaluate for racial differences in outcomes. Participants selected their race from 8 prespecified options reflecting the most common racial groups in the countries of the study sites.

## Inclusion Criteria

Eligibility criteria for both trials have been published.[10,11] Individuals with persistent subclinical hypothyroidism aged 80 years and older, defined as elevated thyrotropin levels (4.6–19.9 mIU/L), measured on at least 2 occasions between 3 months and 3 years apart, who had FT4 levels within laboratory reference ranges were eligible. Eligible persons were identified from lists of patients with laboratory test results from hospitals and primary care practices. Exclusion criteria included 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.

## Randomization and Blinding

Participants were randomised in a 1:1 ratio using a computer-based program to receive levothyroxine or placebo using randomly permuted blocks in a block size of 4, stratified by site, sex, and starting dose. Randomization was performed separately for each trial. The independent data centre (Robertson Centre for Biostatistics, University of Glasgow, United Kingdom) provided the randomization schedule; the 2 interventions were identically packaged by Mawdsley Brooks & Co (United Kingdom). Participants, general practitioners, and

study personnel were blinded to treatment allocation and thyroid function test results throughout the study.

## **Intervention and Control**

The study medication consisted of levothyroxine sodium tablets and matching placebo tablets taken orally once daily. The levothyroxine group started with 50 µg daily (or 25 µg for participants with body weight < 50 kg or a history of coronary heart disease) and the placebo group started with a matching placebo for 6 to 8 weeks. The dose of levothyroxine was adjusted in 25-µg increments based on thyrotropin levels measured 6 to 8 weeks after starting the intervention, 6 to 8 weeks after each dose adjustment, and at 12- and 24-month follow-up with the goal of attaining a thyrotropin level within the reference range (0.4-4.6 mIU/L) in the levothyroxine group. An identical schedule for adjusting the dose of the placebo was used to achieve an equal number of titrations between the groups to maintain blinding. Laboratory test results were uploaded in the computer system by laboratory personnel not involved in the study, and study medication was prescribed in a blinded fashion using an automated system, according to the algorithm. The participants, investigators, and treating physicians were unaware of the results of thyrotropin measurements throughout the course of the trial and remained blinded for treatment allocation.

## **Study Outcomes**

Primary outcomes and prespecified secondary outcomes were measured at the 12-month follow-up and at the end of the study, defined as the last study visit for each participant. The co-primary study outcomes were the change from baseline to the 12 month follow-up in the hypothyroid symptoms score (4 items) and tiredness score (7 items) from the Thyroid-Related Quality of Life Patient-Reported Outcome (ThyPRO) [12] questionnaire (range, 0-100; higher scores indicate more symptoms; minimal clinically important difference [MCID], 9).[13]

Prespecified secondary outcomes differed between the protocol (Supplement 1), which was finalised in June 2016, and the statistical analysis plan (Supplement 2), which was finalised in May 2018 before the results from the trial of patients aged 80 years and older were known to the investigators. The secondary outcomes were prespecified in the statistical analysis plan (Supplement 2) and include change from baseline to 12 months in thyrotropin levels; general quality of life measured using the EuroQol-5D index (range, -0.59 to 1.00; higher scores indicate a better quality of life; MCID, 0.037-0.069) [14] and the EuroQoL Visual Analogue Scale (range, 0-100; higher scores indicate better quality of life; MICD, 8) [15]; handgrip strength using the Jamar isometric dynamometer (best of 3 measurements in the dominant hand; MCID, 5.0-6.5 kg [16]); weight and body mass index (MCID, 5%-10% change for both [17,18]); waist circumference (MCID, 4 cm [19]); systolic and diastolic blood pressure (MCID, 5 mm Hg [20]), FT4 test results; and incidence of falls.

The statistical analysis plan (Supplement 2) also prespecified end-of-study outcomes, which were measured at the final follow-up visit attended by each participant. The prespecified end-of-study outcomes were all of the secondary outcomes listed above in addition to change from baseline in the hypothyroid symptoms and tiredness scores (assessed with the ThyPRO), Barthel Index [21] activities of daily living score (range, 0-20; higher scores indicate greater ability to perform activities of daily living; MCID, 1.85 [22,23]), Older Americans Resources and Services [24] instrumental activities of daily living score (range, 0-14; higher scores indicate better performance in instrumental activities of daily living; MCID, 1 [25]), executive cognitive function measured with the Letter Digit Coding Test [26] (the number of correct substitutions of digits and letters in a 90-second period; minimum score, 0; higher scores indicate better cognitive function; MCID, 4 or 10% [27]), living situation (living independently or not independently and living alone or not living alone), gait speed (MICD for change, 0.1-0.2 m/s [28]), and ThyPRO-39 questionnaire score. However, the following prespecified outcomes were listed in the statistical analysis plan but were not reported here: FT4 test results, ThyPRO-39 score, gait speed, and falls. Information on gait speed and falls was only available for 1 of the trials.

### Adverse Events

The statistical analysis plan (Supplement 2) prespecified the following outcomes, consisting of adverse events, at the end of the study: combined fatal and nonfatal cardiovascular events (defined as acute myocardial infarction, stroke, amputations for peripheral vascular disease, revascularizations for atherosclerotic vascular disease, acute coronary syndrome, and heart failure hospitalizations), fatal cardiovascular events, and mortality. The following safety outcomes were also prespecified in the statistical analysis plan (Supplement 2): hypothyroidism, atrial fibrillation, heart failure, and fractures. Adverse events were reviewed by a blinded adjudication group of 5 investigators. The hyperthyroid symptom score from the ThyPRO questionnaire [12] was used to assess for overtreatment or the development of hyperthyroidism.

### Sample Size

The sample size was calculated for the primary outcomes of mean change from baseline in the hypothyroid symptoms and tiredness scores at 12 months (pooled data). All sample size calculations were based on statistical power of 0.80 and a 2-sided  $\alpha$  of .05. The 2-sided significance level for each primary outcome was .025. The study was considered positive if this level of significance was achieved for either outcome.

Assuming an SD of 26 for the score change for each primary outcome,[29] 264 participants were required (132 per group) to detect the MCID of 9 on the hypothyroid symptoms and tiredness scores. Assuming a dropout rate of 10% in the first 12 months, the target sample



size was 291 participants in the pooled analysis. Originally, the proposed sample size was 900 participants for the primary outcomes of fatal and nonfatal cardiovascular events and mean change in hypothyroid symptoms and tiredness scores on the ThyPRO questionnaire. Due to recruitment difficulty, protocols were amended and fatal or nonfatal cardiovascular events became prespecified secondary outcomes in the protocols and adverse events in the statistical analysis plan (Supplement 2).[10,11] Investigators were blinded to this process.

## Statistical Methods

Primary outcome and adverse event analyses were performed for participants with data available at the 12-month follow-up. In a preplanned secondary analysis, analyses were repeated for the outcome at the final visit instead of 12 months. Continuous variables measured at baseline and during follow-up were analysed at each time point, comparing change from baseline between the placebo and levothyroxine groups, using mixed-effects models, adjusting for stratification variables and baseline values and including study as a random effect. Outcomes measured at more than 1 follow-up were also analysed using linear mixed-effects regression analysis, including data at all time points up to 12 months and repeated analyses including data at all available time points. Additional sensitivity analyses were performed using mixed-effect models and multiple imputations.[30] Ten imputed data sets were generated, imputing all missing values of the outcome variable at 12-month follow-up from age, sex, baseline thyrotropin level, baseline measurement of the outcome variable and, if available, measurement of the outcome variable at 6- to 8-week follow-up visits.

Total ThyPRO scores per domain containing missing items were scaled to maintain the maximum possible score for analyses. If more than 50% of the items for a score were missing, the score was considered to be missing. Categorical outcomes were analysed using Cox proportional hazards regression analysis in models that contained the randomised treatment allocation and stratification variables as covariates. Adjusted differences were analysed using the Wald test. Corresponding point estimates and 95% CIs for the hazard ratio for treatment were estimated. The assumption of proportionality of hazards was checked, and the assumption was met, using diagnostic plots of the  $\log(-\log(\text{survival}))$  vs  $\log(\text{survival})$  and of the Schoenfeld residuals over time. The 2-sided significance level was .025 for each primary outcome (hypothyroid symptoms and tiredness scores) and .05 for secondary outcomes. Because of the potential for type I error due to multiple comparisons, secondary outcomes should be interpreted as exploratory. All statistical analyses were performed in R, version 3.2.4 (R Development Core Team).

## RESULTS

Of 251 randomised participants aged 80 years and older in the combined analyses, 112 (52 from the first trial and 60 from the second) were randomised to receive levothyroxine and 139 (53 from the first trial and 86 from the second) were randomised to receive the placebo. Results are presented for the combined group of participants in the 2 trials and for each trial separately (Supplemental tables 1, 3, 4, and 5 and Supplemental figures 1 and 2). In one trial, 342 adults aged 80 years and older were screened for eligibility. In the other trial, 2,647 participants aged 65 years and older were screened for eligibility (Figure 1; Supplemental figure 1). The mean (SD) age of participants was 84.6 (3.6) years and 118 (47%) were women. A higher percentage of participants in the placebo group had a history of ischemic heart disease compared with the levothyroxine group (27.3% vs 20.5%) (Table 1). Mean (SD)

**Table 1.** Baseline Characteristics of Participants

Characteristic	No. (%)	
	Levothyroxine (n = 112)	Placebo (n = 139)
Age, mean (SD) [range], y	84.0 (3.3) [80.0-97.1]	85.0 (3.7) [80.1-96.7]
Sex		
Men	60 (53.6)	73 (52.5)
Women	52 (46.4)	66 (47.5)
Self-identified race <sup>a</sup>		
White	112 (100.0)	137 (98.6)
Asian	0	1 (0.7)
Black	0	0
Other	0	1 (0.7)
Living independently	106 (94.6)	129 (92.8)
<b>Previous medical conditions or clinical descriptors</b>		
<b>Hypertension</b>	60 (53.6)	63 (45.7)
Ischemic heart disease	23 (20.5)	38 (27.3)
Atrial fibrillation	24 (21.6)	24 (17.3)
Osteoporosis	16 (14.5)	23 (16.5)
Diabetes mellitus	14 (12.5)	17 (12.3)
Current smoker	6 (5.4)	6 (4.3)
Concomitant medicines	106 (94.6)	134 (96.4)
No. of concomitant medications, median (IQR) <sup>b</sup>	5.0 (3.0-7.0)	4.0 (2.5-7.0)
Mini-Mental State Examination score, median (IQR) <sup>c</sup>	28.0 (27.0-29.5)	28.0 (27.0-29.0)
Weight < 50 kg	1 (0.9)	1 (0.7)
<b>Laboratory results</b>		
Thyrotropin level, mIU/L <sup>d</sup>		
Mean (SD)	6.4 (1.8)	6.3 (1.9)
Median (IQR) [range]	5.8 (5.1-7.2) [4.6-12.5]	5.7 (5.2-6.6) [4.6-17.6]
Free thyroxine, pmol/L <sup>e</sup>	13.8 (2.1)	13.8 (2.2)

**Table 1.** Baseline Characteristics of Participants (*continued*)

Characteristic	No. (%)	
	Levothyroxine (n = 112)	Placebo (n = 139)
<b>Outcome measures</b>		
ThyPRO hypothyroid symptoms score <sup>f</sup>		
Mean (SD)	20.8 (19.1)	19.7 (19.3)
Median (IQR)	18.8 (6.2, 31.2)	12.5 (6.2, 31.2)
ThyPRO tiredness score <sup>f</sup>		
Mean (SD)	25.3 (21.0)	25.7 (19.6)
Median (IQR)	21.4 (9.8-35.7)	18.8 (10.7-35.7)
EuroQoL-5D score <sup>g</sup>	0.774 (0.222)	0.808 (0.215)
EuroQoL VAS score <sup>h</sup>	74.8 (14.8)	73.9 (14.4)
Handgrip strength, kg <sup>i</sup>	24.8 (9.0)	24.3 (9.9)
Letter-digit coding test <sup>j</sup>	21.6 (7.1)	21.3 (7.9)
Blood pressure, mean (SD), mmHg		
Systolic	144.2 (20.4)	145.4 (20.7)
Diastolic	70.8 (11.8)	72.0 (11.9)
Body mass index	27.8 (4.5)	27.4 (3.9)
Waist circumference, cm	99.2 (12.1)	98.0 (11.0)
Barthel index, median (IQR) <sup>k</sup>	20.0 (19.0-20.0)	20.0 (19.0-20.0)
Instrumental activities of daily living score, median(IQR)	14.0 (13.0-14.0)	14.0 (13.0-14.0)

<sup>a</sup> Participants selected their race from prespecified options reflecting the most common race groups in the study site countries.

<sup>b</sup> The number of distinct ATC codes, excluding emollients and protectives, antiseptics and disinfectants, topical products for joint and muscular pain, nasal preparations, and local eye and ear medications.

<sup>c</sup> Range, 0-30; 29-30 indicates no cognitive impairment; 25-28, mild cognitive impairment; 19-24, moderate cognitive impairment; less than 19, cognitive impairment.

<sup>d</sup> Inclusion criteria range, 4.6-19.99 mIU/L.

<sup>e</sup> Inclusion criteria ranges were laboratory and method specific (all reference ranges within 9 and 2 pmol/L), however, repeated within-participant measurements were solely performed using the same method for that individual to exclude any bias due to different assays.

<sup>f</sup> Range 0-100; higher scores indicate more symptoms. The mean scores in the general population are 14 for hypothyroid symptoms and 35 for tiredness.

<sup>g</sup> Range 0.50-1.00; higher scores indicate a better quality of life.

<sup>h</sup> Range 0-100; higher scores indicate better health.

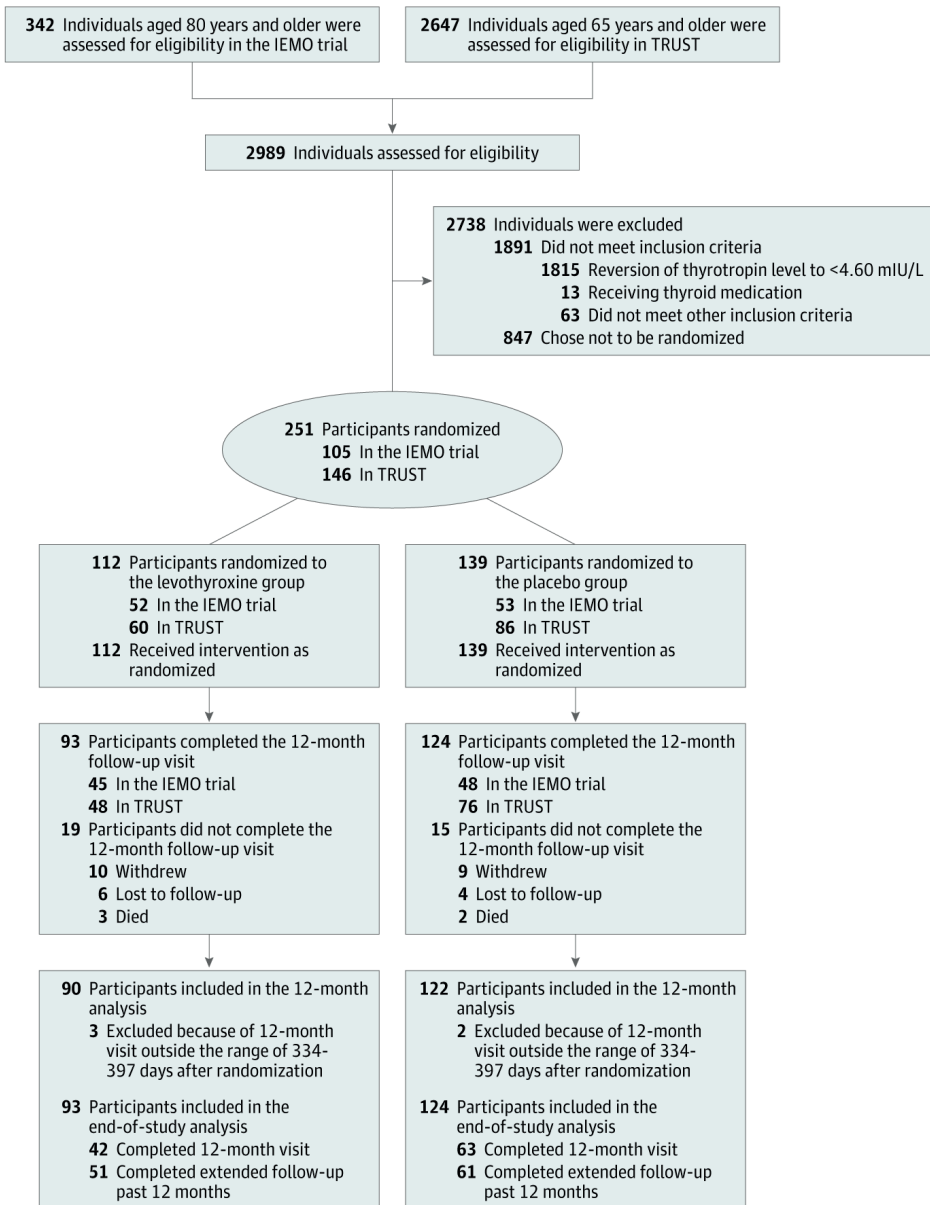
<sup>i</sup> Higher scores indicate better muscle strength; median for women aged at least 80 years, 15.4 kg; median for men older than 80 years, 24.5 kg.

<sup>j</sup> The number of digits coded within 90 seconds; higher scores indicate better executive cognitive function.

<sup>k</sup> Range 0-20; 20 indicates fully independent in activities of daily living and mobility; 15-19, moderately to fully independent; 10-14, needing help but capable of own activities; 5-9, severely dependent; 0-4, totally dependent.

<sup>l</sup> Range 0-14, higher scores indicate better performance in instrumental activities of daily living.

**Abbreviations:** IQR, interquartile range; ThyPRO, Thyroid-Related Quality of Life Patient-Reported Outcome; VAS, visual analogue scale.

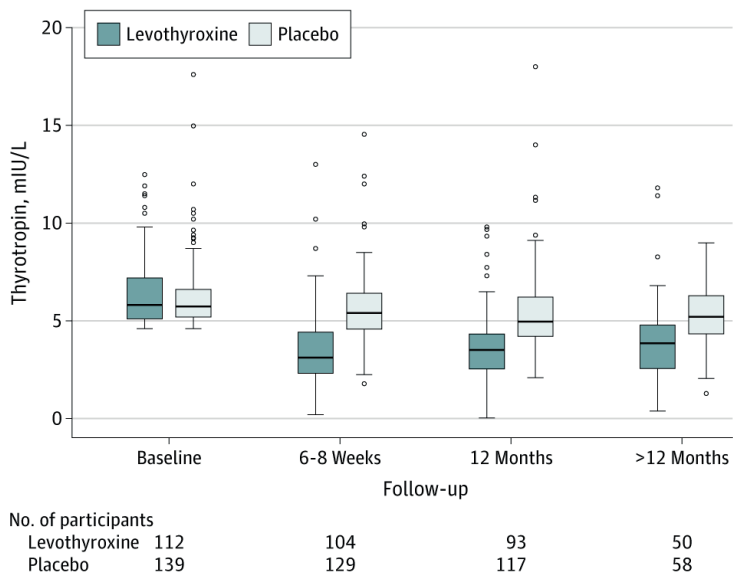


**Figure 1.** Recruitment, randomization, and patient flow of the participants in a study of the association between levothyroxine treatment and thyroid-related symptoms among adults aged 80 years and older with subclinical hypothyroidism

The difference in the number of participants randomised was due to a chance occurrence and, in part, to the failure to stratify randomization by age in the Thyroid Hormone Replacement for Untreated Older Adults With Subclinical Hypothyroidism Trial (TRUST). The 12-month window was defined as between 334 and 397 days after randomization. IEMO indicates Institute for Evidence-Based Medicine in Old Age.

thyrotropin at baseline was 6.3 (1.9) mIU/L in the placebo group vs 6.4 (1.8) mIU/L in the levothyroxine group. No other clinically relevant differences between treatment groups at baseline were observed (Supplemental table 1).

Dropout rates were similar between the groups (10 participants [8.9%] in the levothyroxine group vs 9 [6.5%] in the placebo group). After 12 months, 122 (88%) participants in the placebo group and 90 (80%) in the levothyroxine group had follow-up laboratory measures available (Supplemental table 2). Mean (SD) thyrotropin levels decreased from 6.20 (1.48) mIU/L at baseline to 5.49 (2.21) mIU/L at 12 months in the placebo group and from 6.50 (1.80) mIU/L at baseline to 3.69 (1.81) mIU/L at 12 months in the levothyroxine group (estimated mean between-group difference,  $-1.9$  mIU/L [95% CI,  $-2.49$  to  $-1.45$ ];  $p < 0.001$ ; Figure 2) in regression models. Thyrotropin levels were significantly different between the placebo and levothyroxine groups at all time points during follow-up (all  $p < 0.001$ ), including when the 2 studies were analysed separately (all  $p < 0.01$ ) (Supplemental figure 2).



**Figure 2.** Thyrotropin Levels of Participants in a Study of the Association Between Levothyroxine Treatment and Thyroid-Related Symptoms Among Adults Aged 80 Years and Older With Subclinical Hypothyroidism

There was no significant association of levothyroxine treatment with change in the hypothyroid symptoms score at the 12-month follow-up (21.7 at baseline and 19.3 at 12 months in the levothyroxine group vs 19.8 at baseline and 17.4 at 12 months in the placebo group; adjusted between-group difference,  $1.27$  [95% CI,  $-2.69$  to  $5.23$ ];  $P = .53$ ). There was also no significant association in the tiredness score (25.5 at baseline and 28.2 at 12 months in the



**Table 2.** Outcomes at 12 months for participants in a study of the association between levothyroxine treatment and thyroid-related symptoms among adults aged 80 years and older with subclinical hypothyroidism

Outcomes	Mean (SD)				Adjusted Difference (95% CI) <sup>a</sup>	p Value
	Baseline		12 Months			
	Levothyroxine (n = 90)	Placebo (n = 122)	Levothyroxine (n = 90)	Placebo (n = 122)		
<b>Co-primary outcomes</b>						
ThyPRO hypothyroid symptoms score <sup>b</sup>	21.7 (19.5)	19.8 (19.6)	19.3 (18.2)	17.4 (18.1)	1.27 (−2.69 to 5.23)	0.53
ThyPRO tiredness score <sup>b</sup>	25.2 (21.5)	25.1 (19.5)	28.2 (20.0)	28.7 (19.9)	−0.10 (−4.51 to 4.31)	0.96
<b>Prespecified secondary outcomes</b>						
Thyrotropin, mIU/L	6.50 (1.80) (n = 90)	6.20 (1.48) (n = 116)	3.69 (1.81) (n = 90)	5.49 (2.21) (n = 116)	−1.97 (−2.49 to −1.45)	<0.001
EuroQol-5D <sup>c</sup>	0.785 (0.199) (n = 90)	0.811 (0.210) (n = 122)	0.754 (0.268) (n = 90)	0.785 (0.244) (n = 122)	−0.012 (−0.063 to 0.039)	0.64
EuroQol VAS <sup>d</sup>	75.27 (14.59) (n = 90)	73.98 (14.26) (n = 122)	74.16 (13.67) (n = 90)	73.67 (13.58) (n = 122)	−0.42 (−3.57 to 2.72)	0.79
Handgrip strength, kg	25.4 (9.4) (n = 81)	24.7 (10.2) (n = 114)	23.4 (9.7) (n = 81)	23.0 (9.2) (n = 114)	−0.27 (−1.79 to 1.25)	0.73
Blood pressure, mmHg						
Systolic	144.4 (19.4) (n = 90)	146.2 (20.7) (n = 122)	141.3 (19.0) (n = 90)	142.6 (20.7) (n = 122)	−0.42 (−5.23 to 4.39)	0.86
Diastolic	71.3 (11.8) (n = 90)	72.3 (12.3) (n = 122)	68.7 (11.9) (n = 90)	69.6 (12.5) (n = 122)	−0.31 (−3.06 to 2.44)	0.83
Weight	76.5 (13.1) (n = 90)	75.1 (12.3) (n = 121)	76.2 (12.7) (n = 90)	73.9 (12.3) (n = 121)	0.97 (0.11 to 1.82)	0.03
Body mass index	27.7 (4.4) (n = 90)	27.5 (3.9) (n = 121)	27.6 (4.4) (n = 90)	27.1 (3.9) (n = 121)	0.38 (0.08 to 0.68)	0.01
Waist circumference, cm	99.0 (11.6) (n = 90)	98.0 (10.9) (n = 121)	99.0 (11.4) (n = 90)	96.5 (11.7) (n = 121)	1.52 (0.09 to 2.95)	0.04

<sup>a</sup> 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.  
<sup>b</sup> Range 0-100; higher scores indicate more symptoms. The mean scores in the general population are 14 for hypothyroid symptoms and 35 for tiredness.  
<sup>c</sup> Range 0.50-1.00; higher scores indicate a better quality of life.  
<sup>d</sup> Range 0-100; higher scores indicate better health.

**Abbreviations:** ThyPRO, Thyroid-Related Quality of Life Patient-Reported Outcome; VAS, visual analogue scale.

levothyroxine group vs 25.1 at baseline and 28.7 at 12 months in the placebo group; adjusted between-group difference,  $-0.10$  [95% CI,  $-4.51$  to  $4.31$ ];  $P = .96$ ) (Table 2).

Levothyroxine treatment was not significantly associated with changes from baseline to 12 months in general quality of life measured with the EuroQol-5D index (change from 0.785 to 0.754 in the levothyroxine group vs 0.811 to 0.785 in the placebo group; adjusted difference,  $-0.012$  [95% CI,  $-0.063$  to  $0.039$ ]) or physical function as measured by handgrip strength at 12 months (change from 25.4 kg to 23.4 kg in the levothyroxine group vs 24.7 kg to 23.0 kg in the placebo group; adjusted between-group difference,  $-0.27$  kg [95% CI,  $-1.79$  to  $1.25$ ]) (Table 2).

Treatment with levothyroxine was associated with a statistically significant increase in body mass index (between-group difference,  $0.38$  [95% CI,  $0.08$ - $0.68$ ];  $P = .01$ ) and in waist circumference (between-group difference,  $1.52$  cm [95% CI,  $0.09$ - $2.95$ ];  $P = .04$ ) compared with placebo (Table 2).

Data for 17 participants (12%) in the placebo group and 22 (20%) in the levothyroxine group who had incomplete follow-up data were imputed. Sensitivity analyses using repeated measures mixed-effect regression models and imputed data for outcomes at 12 months showed similar results (Supplemental table 4).

For the end-of-study outcomes, the mean follow-up was 17 months. Treatment with levothyroxine was not significantly associated with thyroid-specific or overall quality of life based on the end-of-study outcomes (Table 3). There was no significant association of levothyroxine treatment with activities of daily living measured using the Barthel Index (from 19.3 at baseline to 19.0 at the end of the study in the levothyroxine group vs from 19.4 to 19.1 in the placebo group; adjusted mean difference,  $0.09$  [95% CI,  $-0.33$  to  $0.52$ ]) or in executive cognitive function measured with the Letter Digit Coding Test (mean between-group difference,  $1.24$  [95% CI,  $-0.30$  to  $2.78$ ]) at the end of the study.

During a mean follow-up of 17 months (median follow-up, 13 months), 9 participants (3.6%) died (1 cardiovascular death). Levothyroxine was not associated with increased rates of fatal or nonfatal cardiovascular events (unadjusted hazard ratio,  $0.61$  [95% CI,  $0.24$ - $1.50$ ]; event rate per 100 person-years of 4.2 in the levothyroxine group and 7.64 in the placebo group) or overall mortality (unadjusted hazard ratio,  $1.39$  [95% CI,  $0.37$ - $5.19$ ]; event rate of 2.99 in the levothyroxine group and 2.02 in the placebo group) (Table 4). A total of 73 participants (29%; 33 [29.5%] in the levothyroxine group and 40 [28.8%] in the placebo group) experienced 1 or more serious adverse events. Adverse events included new-onset atrial fibrillation (10 participants [4.5%]), heart failure (9 [4.1%]), and fractures (9 [4.1%]). Hypothyroidism did not occur in any of the participants. In the levothyroxine group, the most common adverse

**Table 3.** End-of-study outcomes for participants in a study of the association between levothyroxine treatment and thyroid-related symptoms among adults aged 80 years and older with subclinical hypothyroidism.

Prespecified Secondary Outcome	Mean (SD)				Adjusted Difference (95% CI) <sup>a</sup>	p Value
	Baseline		End of Study			
	Levothyroxine	Placebo	Levothyroxine	Placebo		
ThyPRO hypothyroid symptoms score <sup>b</sup>	22.2 (19.4) (n = 93)	19.9 (19.5) (n = 124)	19.9 (19.6) (n = 93)	18.2 (19.9) (n = 124)	−0.48 (−6.88 to 5.91)	0.88
ThyPRO Tiredness score <sup>b</sup>	24.9 (21.4) (n = 93)	25.1 (19.4) (n = 124)	29.5 (18.2) (n = 93)	30.2 (23.3) (n = 124)	−0.77 (−7.07 to 5.54)	0.81
EuroQol-5D <sup>b</sup>	0.777 (0.212) (n = 93)	0.812 (0.209) (n = 124)	0.763 (0.228) (n = 93)	0.806 (0.213) (n = 124)	−0.024 (−0.097 to 0.049)	0.52
EuroQol VAS <sup>b</sup>	74.88 (14.68) (n = 93)	73.94 (14.20) (n = 123)	74.10 (11.97) (n = 93)	74.28 (14.32) (n = 123)	−1.60 (−6.16 to 2.96)	0.49
Handgrip strength, kg <sup>b</sup>	24.9 (9.3) (n = 89)	24.1 (10.4) (n = 109)	19.4 (8.0) (n = 89)	21.8 (10.6) (n = 109)	−1.43 (−4.17 to 1.31)	0.31
Letter-digit coding test <sup>b</sup>	22.0 (7.1) (n = 85)	21.9 (7.7) (n = 109)	21.6 (9.2) (n = 85)	20.5 (7.1) (n = 109)	1.24 (−0.30 to 2.78)	0.11
Barthel index <sup>b</sup>	19.3 (1.5) (n = 91)	19.4 (1.2) (n = 117)	19.0 (1.9) (n = 91)	19.1 (2.1) (n = 117)	0.09 (−0.33 to 0.52)	0.66
Instrumental activities of daily living <sup>b</sup>	13.3 (1.3) (n = 91)	13.2 (1.5) (n = 117)	12.4 (2.4) (n = 91)	12.7 (2.3) (n = 117)	−0.40 (−0.92 to 0.13)	0.14

<sup>a</sup> Adjusted difference was estimated in linear mixed-effects regression models predicting change from baseline to end of the study with study site, sex, and intervention as stratification variables and study as random effect.

<sup>b</sup> For scale definitions see Table 1 footnotes.

**Abbreviations:** ThyPRO, Thyroid-Related Quality of Life Patient-Reported Outcome; VAS, visual analogue scale.

**Table 4.** Clinical and adverse events in in a study of the association between levothyroxine treatment and thyroid-related symptoms among adults aged 80 years and older with subclinical hypothyroidism.

Outcomes	No. (%)		Event Rate per 100 Person-Years		Estimated Risk Difference (95% CI) <sup>b</sup>
	Levothyroxine (n = 112)	Placebo (n = 139)	Levothyroxine (n = 112)	Placebo (n = 139)	
Prespecified secondary outcomes					
Clinical outcomes					
Fatal or nonfatal cardiovascular event	7 (6.3)	14 (10.1)	4.52	7.64	Hazard ratio, 0.61 (0.24 to 1.50)
Death from any cause	5 (4.5)	4 (2.9)	2.99	2.02	Hazard ratio, 1.39 (0.37 to 5.19)
Adverse events					
Cardiovascular death <sup>c</sup>	0	1 (0.7)	0.00	0.51	
Serious adverse events					
Events	53	61			
Participants with >1 serious adverse event <sup>d</sup>	33 (29.5)	40 (28.8)	−0.01 (−0.04 to 0.01)		
Adverse event of special interest					
New-onset atrial fibrillation	4 (3.6)	6 (4.3)	2.57	3.19	0.00 (−0.02 to 0.03)
Heart failure	3 (2.7)	6 (4.3)	1.90	3.21	0.01 (−0.03 to 0.05)
Fracture	4 (3.6)	5 (3.6)	2.53	2.68	0.00 (−0.04 to 0.03)
Hypothyroidism <sup>e</sup>	0 (0.0)	0 (0.0)			
Withdrawal					
Permanent discontinuation of trial regimen <sup>f</sup>	38 (33.9)	43 (30.9)	27.34	24.84	−0.04 (−0.15 to 0.05)
Withdrawal from follow-up <sup>g</sup>	10 (8.9)	9 (6.5)	5.98	4.56	−0.03 (−0.09 to 0.02)
ThyPRO hyperthyroid symptoms scores <sup>h</sup>	10.9 (11.3)	9.1 (10.8)	9.6 (9.4)	9.3 (10.4)	Adjusted difference, −0.50 (−2.62 to 1.63) <sup>e</sup>

- <sup>a</sup> Adverse events were recorded and reported until the end of the study. Preplanned secondary outcomes effects were estimated using Cox proportional hazard regression models adjusted for sex, dose at randomization, study site and study. Adverse events event rates were estimated using Cox proportional hazard regression models with, where possible, adjustment for study site, study, dose at randomization, sex, and age, presented as risk differences and 95% CIs, obtained through bootstrap resampling in 1000 iterations
- <sup>b</sup> Unless otherwise noted.
- <sup>c</sup> For outcomes with too few events to run regression models, event rates and a log-rank test p value were reported. Serious adverse events were all undesired medical events involving a participant, which are not necessarily associated with the treatment, that are fatal, threaten the life of the participant, make hospital admission or an extension of the admission necessary, cause persistent or significant invalidity or work disability, manifest themselves in a congenital abnormality or malformation, or could, according to the researchers, have developed to a serious undesired medical event but were prevented because of premature interference.
- <sup>d</sup> Analysis adjusted for study site, sex, dose at randomization, and age.
- <sup>e</sup> Defined as thyrotropin level of 20 mIU/L or higher during trial laboratory measurements.
- <sup>f</sup> Analysis adjusted for study site, sex, and dose at randomization.
- <sup>g</sup> 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.
- <sup>h</sup> For scale definitions see Table 1 footnotes.



events were stroke (3 participants [2.2%]), anaemia (2 [1.4%]), and pneumonia (2 [1.4%]). In the placebo group, the most common adverse events were pneumonia (4 participants [3.6%]), cardiac failure (2 [1.8%]), and respiratory failure (2 [1.8%]). At the end of the study, treatment discontinuation occurred in 81 participants (32%) during follow-up, whereas total study withdrawal occurred in 19 (8%) participants. There was no significant difference in treatment discontinuation (38 participants [31%] in the levothyroxine group and 43 [34%] in the placebo) or withdrawal (2 participants [3.8%] in the levothyroxine group and 1 [1.9%] in the placebo group) between the groups.

## DISCUSSION

In this prospective analysis that combined data from 2 trials of community-dwelling adults aged 80 years and older with subclinical hypothyroidism, levothyroxine treatment, compared with placebo, was not associated with improvement in hypothyroid symptoms or fatigue. There was no association of levothyroxine treatment with risk of adverse events or secondary outcomes, except for with body mass index and waist circumference; however, the magnitude of these associations was small and likely due to chance given the large number of comparisons. There were no differences in dropout rates between treatment groups, suggesting that levothyroxine treatment was not associated with adverse effects.

These findings do not support routine use of levothyroxine for managing subclinical hypothyroidism in adults aged 80 years and older. Consistent with results reported in the current trial, European and US guidelines do not recommend routine treatment for individuals aged 80 years and older with subclinical hypothyroidism.[31,32] However, in both guidelines, treatment is recommended for individuals with thyrotropin levels of 10 mIU/L or higher (age is not mentioned), and the European guideline suggests ongoing monitoring of thyroid function in patients older than 80 years with subclinical hypothyroidism. Participants in the current study had only mildly elevated thyrotropin levels and a low symptom burden at baseline, consistent with findings in a population study of older individuals with subclinical hypothyroidism.[1] The findings of the present study are thus relevant to the large group of adults aged 80 years and older with few symptoms in whom elevated thyrotropin levels are identified during a routine evaluation.

A Cochrane review of 11 double-blinded randomised clinical trials that examined the effects of thyroid hormone treatment of subclinical hypothyroidism on various outcomes reported no association of thyroid hormone treatment with clinically relevant outcomes.[7] However, these 11 randomised clinical trials of 350 participants included few older participants and had outcomes that were diverse with respect to length of follow-up and type of outcome

studied, such as lipids, mood, and heart function.[7] Results of the current study were consistent with the overall results of the included trial of adults aged 65 years and older, in which levothyroxine treatment was found to have no beneficial effect on thyroid-related symptoms, generic quality of life, cognitive or physical function, and activities of daily living scores, and there was no increase in adverse events.[5]

## Limitations

This study has several limitations. First, there were no preplanned subgroup analyses of participants with high symptom burden or higher elevated thyrotropin level at baseline. Results may not apply to these participants. Second, antithyroid antibody status, which may identify individuals who have an increased risk of progression to overt hypothyroidism, was not available. Third, the study population was homogeneous with respect to race. Fourth, there were participants who discontinued treatment (32%), which may have biased results. However, numbers of and reasons for discontinuation were similar between treatment groups.

## Conclusions

In this prospectively planned analysis of data from 2 clinical trials involving adults aged 80 years and older with subclinical hypothyroidism, treatment with levothyroxine, compared with placebo, was not significantly associated with improvement in hypothyroid symptoms or fatigue. These findings do not support routine use of levothyroxine for treatment of subclinical hypothyroidism in adults aged 80 years and older.

## Online supplemental material

<https://jamanetwork.com/journals/jama/fullarticle/2753909>

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**Supplemental table S1.** Characteristics of participants aged 80 years and over at baseline for the IEMO 80-plus Thyroid trial and TRUST Thyroid trial participants separately.

Characteristic	Levothyroxine (N=112)		Placebo (N=139)	
	IEMO 80-plus (N=52)	TRUST 80-plus (N=60)	IEMO 80-plus (N=53)	TRUST 80-plus (N=86)
Age (yrs)				
Mean (SD)	84.5 (3.6)	83.6 (3.1)	85.8 (3.9)	84.5 (3.6)
Range	80.0 – 97.1	80.2 – 93.0	80.4 – 96.7	80.1 – 93.4
Sex				
Male	26 (50.0%)	34 (56.7%)	27 (50.9%)	46 (53.5%)
Female	26 (50.0%)	26 (43.3%)	26 (49.1%)	40 (46.5%)
Self-identified race				
White	52 (100.0%)	60 (100.0%)	52 (98.1%)	85 (98.8%)
Asian	0	0	1 (1.9%)	0
Black	0	0	0	0
Other <sup>a</sup>	0	0	0	1 (1.2%)
Living independently	49 (94.2%)	57 (95.0%)	50 (94.3%)	79 (91.9%)
<b>Previous medical conditions and clinical descriptors</b>				
Hypertension	27 (51.9%)	33 (55.0%)	24 (45.3%)	39 (45.9%)
Ischemic heart disease	13 (25.0%)	10 (16.7%)	12 (22.6%)	26 (30.2%)
Atrial fibrillation	13 (25.0%)	11 (18.6%)	9 (17.0%)	15 (17.4%)
Osteoporosis	9 (17.3%)	7 (12.1%)	11 (20.8%)	12 (14.0%)
Diabetes mellitus	7 (13.5%)	7 (11.7%)	3 (5.7%)	14 (16.5%)
Current smoking	3 (5.8%)	3 (5.0%)	2 (3.8%)	4 (4.7%)
Concomitant medicines	49 (94.2%)	57 (95.0%)	50 (94.3%)	84 (97.7%)
No. of concomitant medications (IQR) <sup>b</sup>	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)	4.0 (2.0, 6.0)	4.5 (3.0, 7.0)
Mini-mental state examination score (IQR) <sup>c</sup>	29.0 (27.0, 30.0)	28.0 (27.0, 29.0)	28.0 (27.0, 29.0)	29.0 (27.0, 29.0)
Weight < 50kg	1 (1.9%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
<b>Laboratory results</b>				
Thyrotropin (mIU/L) <sup>d</sup>				
Mean (SD)	6.4 (1.7)	6.5 (1.9)	6.2 (1.6)	6.3 (2.0)
Median (IQR)	5.7 (5.0, 7.2)	5.9 (5.1, 7.1)	5.7 (5.1, 7.0)	5.7 (5.3, 6.5)
Range	4.6 – 11.5	4.6 – 12.5	4.6 – 12.0	4.6 – 17.6
fT4 (pmol/litre) <sup>e</sup>	14.2 (2.0)	13.6 (2.1)	14.0 (2.5)	13.7 (2.0)
<b>Outcome measures</b>				
ThyPro - Hypothyroid Symptoms score <sup>f</sup>				
Mean (SD)	21.6 (19.2)	20.1 (19.2)	20.5 (21.3)	19.3 (18.1)
Median (IQR)	18.8 (6.2, 37.5)	18.8 (6.2, 26.6)	12.5 (6.2, 31.2)	18.8 (6.2, 31.2)



**Supplemental table S1.** Characteristics of participants aged 80 years and over at baseline for the IEMO 80-plus Thyroid trial and TRUST Thyroid trial participants separately. (*continued*)

Characteristic	Levothyroxine (N=112)		Placebo (N=139)	
	IEMO 80-plus (N=52)	TRUST 80-plus (N=60)	IEMO 80-plus (N=53)	TRUST 80-plus (N=86)
ThyPro - Tiredness score <sup>f</sup>				
Mean (SD)	24.1 (20.8)	26.4 (21.2)	24.5 (18.5)	26.4 (20.2)
Median (IQR)	20.1 (7.1, 35.7)	21.4 (12.1, 39.3)	17.9 (10.7, 35.7)	21.4 (11.2, 35.7)
Euroqol-5D <sup>g</sup>	0.772 (0.220)	0.776 (0.226)	0.765 (0.275)	0.835 (0.163)
Euroqol VAS <sup>h</sup>	75.3 (14.3)	74.4 (15.4)	73.1 (11.2)	74.3 (16.1)
Hand-grip strength (kg) <sup>i</sup>	25.4 (10.8)	24.3 (7.2)	26.1 (9.3)	23.3 (10.2)
Letter-digit coding test <sup>j</sup>	20.3 (6.9)	22.6 (7.2)	20.6 (7.4)	21.7 (8.2)
Blood pressure				
Systolic (mmHg)	145.8 (21.8)	142.8 (19.1)	153.3 (22.0)	140.5 (18.4)
Diastolic (mmHg)	72.2 (11.2)	69.5 (12.2)	73.6 (13.2)	71.0 (11.0)
Body mass index (kg/m <sup>2</sup> )	27.7 (4.7)	27.8 (4.3)	27.5 (4.1)	27.4 (3.8)
Waist circumference (cm)	98.3 (11.8)	99.9 (12.5)	97.7 (11.9)	98.2 (10.5)
Barthel Index (IQR) <sup>k</sup>	20.0 (19.0, 20.0)	20.0 (19.0, 20.0)	20.0 (19.0, 20.0)	20.0 (19.0, 20.0)
Instrumental Activities of Daily Living (IQR) <sup>l</sup>	14.0 (13.0, 14.0)	14.0 (12.8, 14.0)	14.0 (12.0, 14.0)	14.0 (13.0, 14.0)

Results were reported as mean (standard deviation, SD) or median (inter quartile range, IQR) for continuous variables, and as n (%) for proportions.

<sup>a</sup> Participants selected race from 'white', 'asian', 'black' and 5 other pre-specified options reflecting most common race groups in the study site countries

<sup>b</sup> Number of concomitant medications used, both prescribed or over-the-counter available, counted as number of distinct ATC codes excluding emollients and protectives, antiseptics and disinfectants, topical products for joint and muscular pain, nasal preparations, ophthalmologicals or otologicals.

<sup>c</sup> range 0-30, higher scores indicate less cognitive impairment

<sup>d</sup> Inclusion criterium reference range 4.6 - 19.99 mIU/L

<sup>e</sup> Inclusion criterium reference ranges were lab and method specific (all reference ranges within 9 and 26 pmol/L), however repeated within-participant measurements were solely performed using the same method for that individual to exclude any bias due to different assays. SI conversion of fT4 pmol/l to ng/dl, divide by 12.87.

<sup>f</sup> Range 0-100, higher scores represent more symptoms or severity of disease

<sup>g</sup> Range 0.50-1.00, higher scores indicate a better quality of life

<sup>h</sup> Range 0-100, higher scores indicate better health

<sup>i</sup> Higher scores indicate better muscle strength

<sup>j</sup> Number of digits coded within 90 seconds. No upper limit, higher scores indicate better executive cognitive function

<sup>k</sup> Range 0-20, higher scores indicate higher independence in activities of daily living

<sup>l</sup> Range 5-30, higher scores indicate more impairment in instrumental activities of daily living

**Abbreviations:** fT4, free thyroxine; VAS, Visual Analog Scale.

**Supplemental table S2.** Characteristics of participants aged 80 years and over at baseline that were included in the primary efficacy analysis.

Characteristic	Total (N=212)	
	Levothyroxine (n=90)	Placebo (n=122)
Age (yrs)		
Mean (SD)	84.1 (3.4)	84.9 (3.7)
Range	80.0 – 97.1	80.1 – 96.7
Sex		
Male	49 (54.4%)	63 (51.6%)
Female	41 (45.6%)	59 (48.4%)
Self-identified race		
White	90 (100.0%)	120 (98.4%)
Asian	0 (0.0%)	1 (0.8%)
Black	0 (0.0%)	0 (0.0%)
Other <sup>a</sup>	0 (0.0%)	1 (0.8%)
Living independently	84.1 (3.4)	84.9 (3.7)
<b>Previous medical conditions and clinical descriptors</b>		
Hypertension	48 (53.3%)	55 (45.5%)
Ischemic heart disease	20 (22.2%)	33 (27.0%)
Atrial fibrillation	15 (16.7%)	22 (18.0%)
Osteoporosis	14 (15.9%)	20 (16.4%)
Diabetes mellitus	11 (12.2%)	15 (12.4%)
Current smoking	5 (5.6%)	5 (4.1%)
Concomitant medicines	84 (93.3%)	117 (93.3%)
No. of concomitant medications (IQR) <sup>b</sup>	5.0 (3.0, 7.0)	4.0 (3.0, 6.8)
Mini-mental state examination score (IQR) <sup>c</sup>	29.0 (27.0, 30.0)	28.0 (27.0, 29.0)
Weight < 50kg	1 (1.1%)	0 (0.0%)
<b>Laboratory results</b>		
Thyrotropin (mIU/L) <sup>d</sup>		
Mean (SD)	6.5 (1.8)	6.2 (1.5)
Median (IQR)	5.8 (5.1, 7.4)	5.7 (5.2, 6.6)
Range	4.6 – 11.9	4.6 – 12.0
ft4 (pmol/litre) <sup>e</sup>	13.8 (2.0)	13.8 (2.1)
<b>Outcome measures</b>		
ThyPro - Hypothyroid Symptoms score <sup>f</sup>		
Mean (SD)	21.7 (19.5)	19.8 (19.6)
Median (IQR)	18.8 (6.2, 35.9)	12.5 (6.2, 31.2)
ThyPro - Tiredness score <sup>f</sup>		
Mean (SD)	25.2 (21.5)	25.1 (19.5)
Median (IQR)	20.1 (7.1, 35.7)	17.9 (10.7, 35.7)

**Supplemental table S2.** Characteristics of participants aged 80 years and over at baseline that were included in the primary efficacy analysis. (*continued*)

Characteristic	Total (N=212)	
	Levothyroxine (n=90)	Placebo (n=122)
Euroqol-5D <sup>a</sup>	0.8 (0.2)	0.8 (0.2)
Euroqol VAS <sup>h</sup>	75.3 (14.6)	74.0 (14.3)
Hand-grip strength (kg) <sup>i</sup>	25.1 (9.4)	24.8 (10.0)
Letter-digit coding test <sup>j</sup>	21.9 (7.1)	21.8 (7.7)
Blood pressure		
Systolic (mmHg)	25.2 (21.5)	25.1 (19.5)
Diastolic (mmHg)	20.1 (7.1, 35.7)	17.9 (10.7, 35.7)
Body mass index (kg/m <sup>2</sup> )	0.8 (0.2)	0.8 (0.2)
Waist circumference (cm)	75.3 (14.6)	74.0 (14.3)
Barthel Index (IQR) <sup>k</sup>	25.1 (9.4)	24.8 (10.0)
Instrumental Activities of Daily Living (IQR) <sup>l</sup>	21.9 (7.1)	21.8 (7.7)

Results were reported as mean (standard deviation, SD) or median (inter quartile range, IQR) for continuous variables, and as n (%) for proportions. Participants selected race from 'white', 'asian', 'black' and 5 other pre-specified options reflecting most common race groups in the study site countries

<sup>a</sup> Number of concomitant medications used, both prescribed or over-the-counter available, counted as number of distinct ATC codes excluding emollients and protectives, antiseptics and disinfectants, topical products for joint and muscular pain, nasal preparations, ophthalmologicals or otologicals.

<sup>b</sup> Range 0-30, higher scores indicate less cognitive impairment

<sup>c</sup> Inclusion criterium reference range 4.6 - 19.99 mIU/L

<sup>d</sup> Inclusion criterium reference ranges were lab and method specific (all reference ranges within 9 and 26 pmol/L), however repeated within-participant measurements were solely performed using the same method for that individual to exclude any bias due to different assays. SI conversion of fT4 pmol/L to ng/dl, divide by 12.87.

<sup>e</sup> Range 0-100, higher scores represent more symptoms or severity of disease

<sup>f</sup> Range 0.50-1.00, higher scores indicate a better quality of life. Average in general population for Hypothyroidism Symptoms score is 14 and for Tiredness score 35.

<sup>g</sup> Range 0-100, higher scores indicate better health, <sup>l</sup> Higher scores indicate better muscle strength

<sup>h</sup> Number of digits coded within 90 seconds. No upper limit, higher scores indicate better executive cognitive function

<sup>i</sup> Range 0-20, higher scores indicate higher independence in activities of daily living

<sup>j</sup> Range 5-30, higher scores indicate more impairment in instrumental activities of daily living. Five means functionally completely independent.

**Abbreviations:** fT4, free thyroxine; VAS, Visual Analogue Scale.

**Supplemental table S3.** Outcomes at 12 months and end of study for participants of the IEMO 80-plus Thyroid trial and TRUST Thyroid trial, with subclinical hypothyroidism aged 80 years and over, separately

Variables	Baseline					
	IEMO 80-plus		TRUST 80-plus		IEMO 80-plus	
	Levo-thyroxine	Placebo	Levo-thyroxine	Placebo	Levo-thyroxine	Placebo
	(N=45)	(N=46)	(N=45)	(N=70)	(N=45)	(N=46)
<b>Co-primary outcomes</b>						
ThyPro Hypothyroid Symptoms score <sup>b</sup>	23.1 (19.8)	22.1 (21.7)	20.4 (19.4)	18.2 (18.1)	17.2 (16.7)	16.1 (18.4)
ThyPro Tiredness score <sup>b</sup>	23.7 (21.4)	23.3 (18.9)	26.8 (21.7)	26.3 (19.9)	25.9 (20.7)	26.4 (22.1)
<b>Pre-specified secondary outcomes</b>						
Thyrotropin (mIU/L)	6.45 (1.75)	6.28 (1.66)	6.55 (1.87)	6.15 (1.36)	3.76 (1.67)	5.88 (2.66)
median (IQR)	5.70 (5.20, 7.40)	5.66 (5.08, 7.00)	5.82 (5.11, 7.22)	5.74 (5.35, 6.49)	3.40 (2.90, 4.30)	4.98 (4.52, 6.34)
Euroqol-5D <sup>b</sup>	0.774 (0.201)	0.768 (0.261)	0.796 (0.198)	0.838 (0.165)	0.729 (0.296)	0.709 (0.317)
Euroqol VAS <sup>b</sup>	76.22 (12.89)	73.33 (11.15)	74.31 (16.20)	74.39 (16.01)	74.96 (10.81)	73.60 (12.78)
Hand-grip strength (kg) <sup>b</sup>	24.8 (11.0)	26.1 (9.8)	26.2 (7.3)	23.9 (10.4)	22.7 (11.0)	23.2 (9.0)
Blood pressure						
Systolic (mmHg)	146.0 (21.0)	154.7 (22.2)	142.8 (17.7)	140.7 (17.7)	142.6 (20.0)	146.2 (23.3)
Diastolic (mmHg)	72.3 (11.2)	73.8 (13.5)	70.2 (12.4)	71.4 (11.5)	69.1 (11.8)	70.6 (14.6)
Body mass index (kg/m <sup>2</sup> )	27.5 (4.9)	27.4 (4.1)	27.8 (3.8)	27.5 (3.8)	27.5 (4.9)	26.8 (3.9)
Waist circumference (cm)	99.0 (11.6)	98.0 (10.9)	100.1 (11.0)	98.5 (10.5)	99.0 (11.4)	96.5 (11.7)
<b>At end of study</b>						
					Levo-thyroxine	Placebo
Letter-digit coding test <sup>b,c</sup>	20.6 (6.7)	21.5 (7.0)	23.6 (7.3)	22.2 (8.1)	19.8 (7.2)	19.6 (6.6)
Barthel index <sup>b,c</sup>	19.5 (1.3)	19.2 (1.5)	19.2 (1.6)	19.6 (0.9)	19.2 (1.5)	18.6 (2.8)
Instrumental Activities of Daily Living <sup>b,c</sup>	13.4 (0.8)	12.8 (2.0)	13.2 (1.6)	13.5 (1.0)	12.7 (1.7)	12.2 (3.0)

<sup>a</sup> 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.

<sup>b</sup> For scale definitions see Supplemental table 1 footnotes.

<sup>c</sup> Repeat Barthel index, Letter-digit coding test and Instrumental Activities of Daily Living measurements were performed at final visit (i.e. at 12, 24 or 36 months depending on follow-up time), these measurements were included in the estimations.

**Abbreviations:** VAS, Visual Analog Scale. Scores were presented as means (standard deviation, SD).

At 12 months						
IEMO 80-plus		TRUST 80-plus				
Adjusted difference <sup>a</sup>	p-value	Levo-thyroxine	Placebo	Adjusted Difference <sup>a</sup>	p-value	
(95% CI)		(N=45)	(N=70)	(95% CI)		
0.69 (-5.43, 6.80)	0.82	21.4 (19.6)	18.3 (18.0)	1.27 (-3.95, 6.49)	0.63	
-0.78 (-8.26, 6.70)	0.84	30.6 (19.2)	30.2 (18.3)	-0.66 (-6.20, 4.89)	0.82	
-2.23 (-3.07, -1.40)	<0.001	3.61 (1.96)	5.23 (1.84)	-1.75 (-2.45, -1.05)	<0.001	
-	-	3.51 (2.26, 4.40)	4.99 (4.03, 6.18)	-	-	
0.019 (-0.082, 0.120)	0.71	0.780 (0.237)	0.834 (0.167)	-0.026 (-0.074, 0.022)	0.28	
0.03 (-4.20, 4.27)	0.99	73.36 (16.12)	73.72 (14.16)	-0.68 (-5.49, 4.13)	0.78	
0.40 (-2.16, 2.97)	0.76	24.1 (7.9)	22.9 (9.4)	-0.45 (-2.32, 1.41)	0.63	
0.04 (-8.38, 8.46)	0.99	139.9 (18.1)	140.3 (18.7)	-1.39 (-7.42, 4.65)	0.65	
-0.66 (-5.13, 3.81)	0.77	68.3 (12.1)	68.9 (11.0)	-0.41 (-4.06, 3.24)	0.82	
0.66 (0.21, 1.12)	0.005	27.7 (3.8)	27.3 (3.9)	0.15 (-0.27, 0.58)	0.47	
1.52 (0.09, 2.96)	0.04	100.7 (10.7)	97.6 (12.0)	1.42 (-0.75, 3.60)	0.2	
At end of study		At end of study				
Adjusted difference <sup>a</sup>	p-value	Levo-thyroxine	Placebo	Adjusted - difference <sup>a</sup>	p-value	
1.05 (-0.52, 2.62)	0.19	23.5 (10.8)	20.9 (7.5)	1.64 (-1.00, 4.29)	0.22	
0.31 (-0.38, 0.99)	0.38	18.9 (2.2)	19.3 (1.4)	-0.17 (-0.73, 0.39)	0.54	
-0.04 (-0.88, 0.80)	0.92	12.1 (2.9)	13.0 (1.7)	-0.64 (-1.37, 0.09)	0.08	

**Supplemental table S4.** Sensitivity analysis of outcomes at 12 months for participants with subclinical hypothyroidism aged 80 years and over.

Variables	Imputed data		Adjusted difference <sup>a</sup>	p-value
	Levothyroxine	Placebo		
Co-primary outcomes				
ThyPRO Hypothyroid Symptoms score <sup>b</sup>	22 (19.6%)	17 (12.2%)	1.79 (-1.60, 5.18)	0.30
ThyPRO Tiredness score <sup>b</sup>	22 (19.6%)	17 (12.2%)	0.84 (-2.99, 4.68)	0.66
Pre-specified secondary outcomes				
Thyrotropin (mIU/L)	22 (19.6%)	23 (16.5%)	-1.74 (-2.18, -1.30)	< 0.001
EuroQol-5D <sup>b</sup>	22 (19.6%)	17 (12.2%)	-0.01 (-0.05, 0.03)	0.67
EuroQol VAS <sup>b</sup>	22 (19.6%)	17 (12.2%)	-0.39 (-3.09, 2.30)	0.77
Hand-grip strength (kg) <sup>b</sup>	23 (22.1%)	20 (14.9%)	0.07 (-1.33, 1.19)	0.92
Blood pressure				
Systolic (mmHg)	22 (19.6%)	17 (12.2%)	-0.37 (-4.46, 3.73)	0.86
Diastolic (mmHg)	22 (19.6%)	17 (12.2%)	-0.17 (-2.52, 2.17)	0.89
Weight	21 (18.9%)	18 (12.9%)	0.85 (0.12, 1.57)	0.022
Body mass index (kg/m <sup>2</sup> )	21 (18.9%)	18 (12.9%)	0.33 (0.07, 0.59)	0.012
Waist circumference (cm)	22 (19.6%)	18 (12.9%)	1.29 (0.08, 2.50)	0.037

<sup>a</sup> Adjusted difference was estimated in repeated linear mixed 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 using data imputed from ten imputed data sets, imputing all missing values of the outcome variable at 12-month follow-up from age, sex, baseline thyrotropin, baseline measurement of the outcome variable and, if available, measurement of the outcome variable at 6-8-week follow-up visit.

<sup>b</sup> For scale definitions see Supplemental table 1 footnotes.

**Abbreviations:** VAS, Visual Analog Scale. Scores were presented as means (SD).

**Supplemental table S5.** Clinical and adverse events for the IEMO 80-plus Thyroid trial and TRUST Thyroid trial separately

Variables	IEMO 80-plus				TRUST 80-plus			
	Number of events (%)		Event rates (/100 person years)		Number of events (%)		Event rates (/100 person years)	
	Levothyroxine (n=52)	Placebo (n=53)	Levothyroxine (n=52)	Placebo (n=53)	Levothyroxine (n=60)	Placebo (n=86)	Levothyroxine (n=60)	Placebo (n=86)
<b>Pre-specified secondary outcomes</b>								
Clinical outcomes								
Fatal or nonfatal cardiovascular event	1 (1.9%)	5 (9.4%)	1.5	7.53	6 (10.0%)	9 (10.5%)	6.82	7.71
Death from any cause	2 (3.8%)	4 (7.5%)	2.85	5.86	3 (5.0%)	0 (0.0%)	3.08	0
<b>Adverse events</b>								
Cardiovascular death	0 (0.0%)	1 (1.9%)	0	1.46	0	0	-	-
Serious adverse events								
Events	15	17			38	44		
Patients with >1 serious adverse event <sup>a</sup>	12 (23.1%)	13 (24.5%)	0.86 (0.34, 2.22)		21 (35.0%)	27 (31.4%)	1.29 (0.60, 2.76)	0.51
Adverse event of special interest								
New-onset atrial fibrillation	0 (0.0%)	2 (3.8%)	0	3.07	4 (6.7%)	4 (4.7%)	4.54	3.26
Heart failure	1 (1.9%)	3 (5.7%)	1.5	4.53	2 (3.3%)	3 (3.5%)	2.19	2.48
Fracture	1 (1.9%)	3 (5.7%)	1.48	4.65	3 (5.0%)	2 (2.3%)	3.3	1.64
Hypothyroidism <sup>b</sup>	0 (0.0%)	0 (0.0%)						
Withdrawal								
Permanent discontinuation of trial regimen	16 (30.8%)	18 (34.0%)	28.27	30.9	22 (36.7%)	25 (29.1%)	26.68	21.77
Withdrawal from follow-up <sup>c</sup>	2 (3.8%)	1 (1.9%)	2.85	1.47	8 (13.3%)	8 (9.3%)	8.23	6.19

**Supplemental table S5.** Clinical and adverse events for the IEMO 80-plus Thyroid trial and TRUST Thyroid trial separately (*continued*)

Variables	IEMO 80-plus				TRUST 80-plus			
	Number of events (%)		Event rates (/100 person years)		Number of events (%)		Event rates (/100 person years)	
	Levothyroxine (n=52)	Placebo (n=53)	Levothyroxine (n=52)	Placebo (n=53)	Levothyroxine (n=60)	Placebo (n=86)	Levothyroxine (n=60)	Placebo (n=86)
	p-value		p-value		p-value		p-value	
	Baseline (mean, SD)		At 12 months (mean, SD)		Baseline (mean, SD)		At 12 months (mean, SD)	
	Levothyroxine	Placebo	Levothyroxine	Placebo	Levothyroxine	Placebo	Levothyroxine	Placebo
ThyPro Hyperthyroid Symptoms scores <sup>d</sup>	11.4 (13.8)	7.2 (8.6)	7.8 (9.8)	9.1 (9.9)	10.4 (8.2)	10.4 (11.9)	11.4 (8.8)	9.5 (10.7)
	p-value		p-value		p-value		p-value	
	0.06		0.06		0.31		0.31	

Pre-planned secondary outcomes effects were estimated using cox-proportional hazard regression models adjusted for sex, dose at randomization and study site. Adverse events were estimated using

cox-proportional hazard regression models with, where possible, adjustment for study site, dose at randomization, sex and age, presented as event rates and p-values.

- <sup>a</sup> For outcomes with too few events to run regression models, odds ratio (95% CI) and p-value were reported. Serious adverse events were all undesired medical events involving a participant, which are not necessarily associated with the treatment, that are: fatal, threaten the life of the subject, make hospital admission or an extension of the admission necessary, cause persistent or significant invalidity or work disability, manifest themselves in a congenital abnormality or
- <sup>b</sup> malformation or could, according to the researchers, have developed to a serious undesired medical event, but were however prevented due to premature interference.
- <sup>c</sup> Defined as thyrotropin level of 20 mIU/L or higher during trial laboratory measurements
- <sup>d</sup> Analysis adjusted for study site, sex, and dose at randomization.
- <sup>e</sup> For scale definitions see Supplemental table 1 footnotes. Scores were presented as means (standard deviation, SD)
- <sup>f</sup>

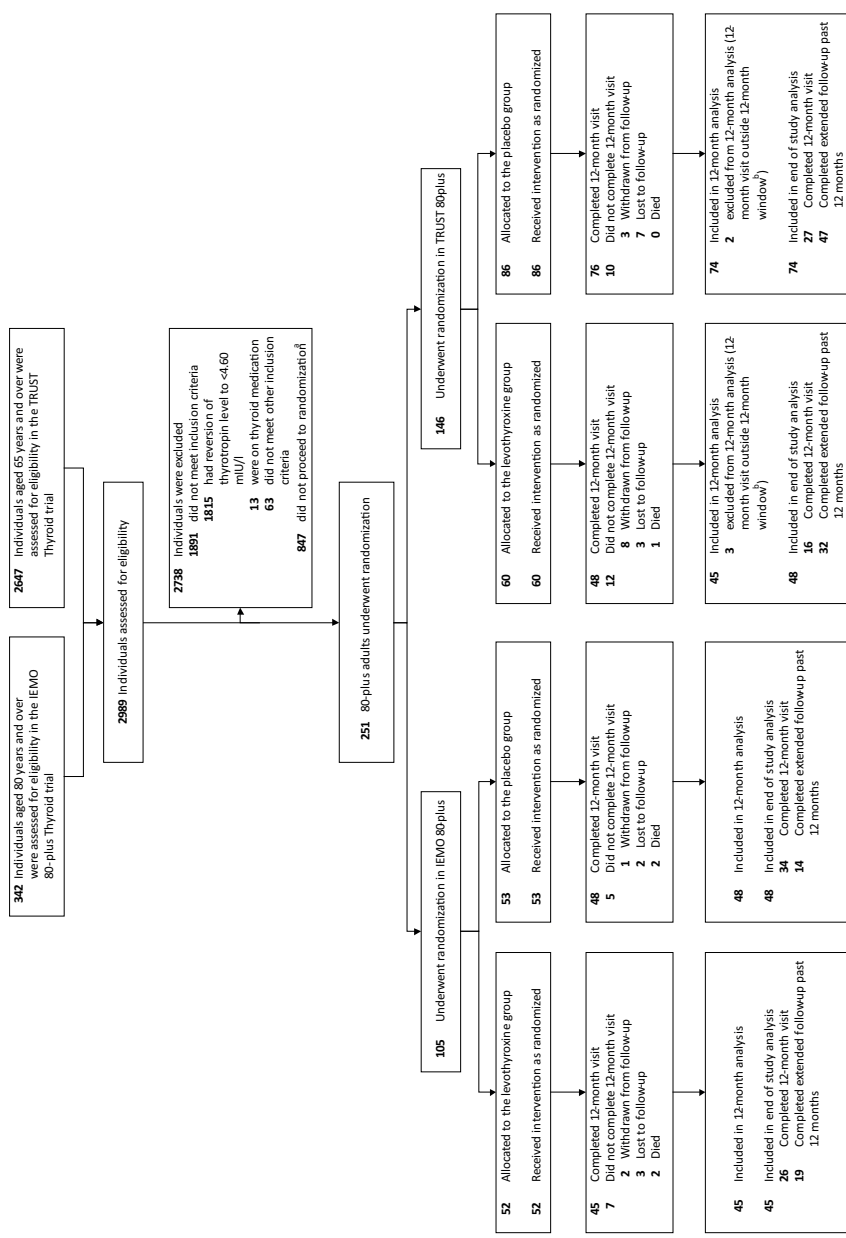


## IN REPLY

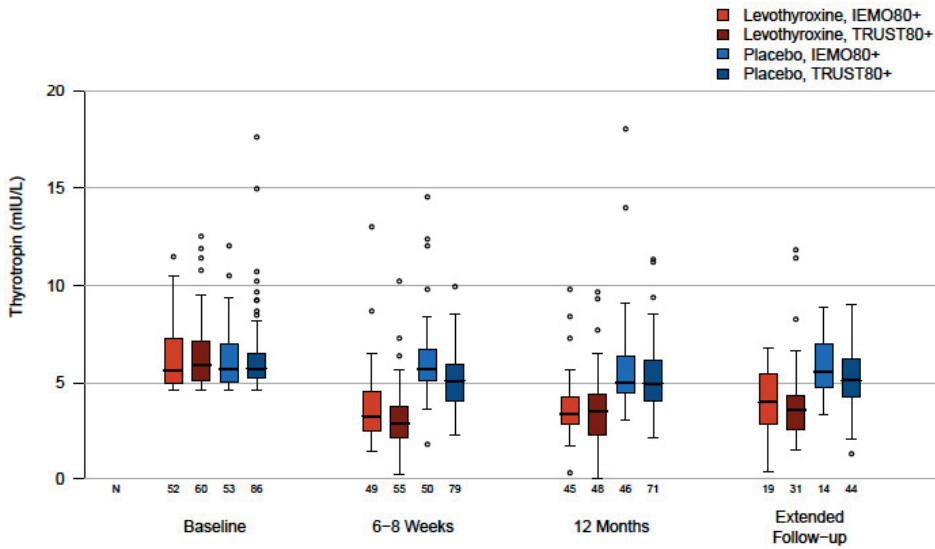
The population distribution of thyrotropin across the human life span has been reported in multiple studies with ambiguous results: both increase and decrease with increasing age have been reported. These inconsistencies may reflect differences in iodine intake across cohorts or age categories and underscore that population distributions alone are unfit to determine reference ranges. Other observational studies of subclinical hypothyroidism, including the NHANES study mentioned by Dr Hershman as well as an individual patient data meta-analysis by Rodondi et al,[1] showed no association of subclinical hypothyroidism with mortality and cardiovascular events in individuals aged 80 years and older. However, because these data have all been observational, they are not suitable to definitely establish or rule out causality. Therefore, until now, existing studies have not justified age-specific reference ranges and guidelines currently do not support them.[2,3]

In our study of 2 randomised clinical trials,[4] we included 251 individuals aged 80 years and older with persistently elevated thyrotropin levels higher than 4.5 mIU/L, according to generally accepted clinical guidelines. We observed no beneficial effects of supplementation, which is in agreement with the overall Thyroid Hormone Replacement for Untreated Older Adults With Subclinical Hypothyroidism Trial (TRUST) of 737 individuals aged 65 years and older,[5] of whom our study included only the 146 individuals aged 80 years and older. Furthermore, in subgroup analyses of TRUST, such as comparing individuals with a thyrotropin level below or above 7 mIU/L, the estimates were similar. These findings provide the highest level of evidence to date regarding thyroid hormone supplementation in older patients with subclinical hypothyroidism.

The definition of reference range and the limit for treatment are separate. We agree that there seems to be no treatment indication for patients aged 80 years and older with elevated thyrotropin levels and normal free thyroxine levels. In an Editorial accompanying our study, Cappola [6] suggested that the upper limit of the reference range for thyrotropin in individuals aged 80 years and older should be changed to 7 mIU/L. Although this is an arbitrary value, it removes the majority of older individuals with elevated thyrotropin from having an indication for supplementation, justified by our experimental evidence.



**Supplemental figure 1.** Recruitment, randomization, and patient flow of the participants age 80 years and over in the TRUST and IEMO thyroid trials separately. <sup>a</sup> These participants completed the screening phase and met the inclusion criteria, yet did not proceed to randomization. For example, participant opted not to participate due to developments in the private sphere or after consultation with children. <sup>b</sup> 12-month window was between 334 and 397 days after randomization



**Supplemental figure 2.** Thyrotropin levels in the levothyroxine and placebo group during the studies. Abbreviations: N, number of participants with available thyrotropin measurements. Tukey boxplots depicting medians, quartiles, the lowest and upper datum still within 1.5 IQR of the corresponding quartile and outliers.

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