# L-thyroxine therapy for older adults with subclinical hypothyroidism and hypothyroid symptoms: secondary analysis of a randomized trial

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# Levothyroxine therapy in older adults with subclinical hypothyroidism and hypothyroid symptoms: secondary analysis of a randomized trial

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# Abstract

**Background:** Levothyroxine does not improve hypothyroid symptoms among adults with subclinical hypothyroidism (SCH). However, those with greater symptoms prior to treatment may still benefit.

**Objective:** To determine whether levothyroxine improves hypothyroid symptoms and tiredness among older adults with SCH and greater symptom burden.

**Design:** Secondary analysis of the randomized, placebo-controlled TRUST trial.

**Setting:** Switzerland, Ireland, the Netherlands, Scotland.

**Participants:** 638 persons ≥65 years with persistent SCH (thyrotropin 4.6-19.9mIU/L for >3months, normal free thyroxine) and complete outcome data.

**Intervention:** Levothyroxine or matching placebo with mock dose-titration.

**Measurements:** One year change in Hypothyroid Symptom and Tiredness scores (range 0-100, higher scores indicate more symptoms) on the Thyroid-Related Quality-of-Life Questionnaire among participants with high symptom burden (baseline Hypothyroid Symptoms score >30 or Tiredness score >40) vs. lower symptom burden.

**Results:** 132 participants had Hypothyroid Symptoms score >30 and 133 had Tiredness score >40. Among the high symptom group, the Hypothyroid Symptoms score improved similarly between those on levothyroxine (mean within-group change -12.3, 95% CI -16.6 to -8.0) and those on placebo (-10.4, 95% CI -15.3 to -5.4) at 1 year; the adjusted between-group difference was -2.0, 95% CI -5.5 to 1.5, p=0.27. Improvement in Tiredness scores were also similar between those on levothyroxine (within-group change -8.9, 95% CI -14.5 to -3.3) and those on placebo (-10.9, 95% CI -16.0 to -5.8), adjusted between-group difference 0.0, 95% CI -4.1 to 4.0, p=0.99. There was no evidence that baseline Hypothyroid Symptom score or Tiredness score modified the effects of levothyroxine vs. placebo (p for interaction=0.20 and 0.82, respectively).

**Limitation:** Post-hoc analysis, small sample size, only examined patients with 1 year outcome data.

**Conclusion:** In older adults with SCH and high symptom burden at baseline, levothyroxine did not improve hypothyroid symptoms or tiredness compared to placebo.

**Trial Registration:** NCT01660126.

**Primary Funding Source:** European Union FP7.

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# Introduction

Subclinical hypothyroidism, defined as elevated thyrotropin in combination with a normal free thyroxine,(1) is common, with a prevalence of up to 20% in older adults.(2) Following current guidelines from endocrine societies,(3, 4) subclinical hypothyroidism is often treated with levothyroxine.(5) This practice may contribute to levothyroxine being the most prescribed drug from 2014 onwards in the US,(5, 6) with more than 15% of Americans older than 61 years taking levothyroxine.(7) A recent large trial among older adults (TRUST trial), followed by a systematic review and meta-analysis of all randomized controlled trials observed no benefit of levothyroxine in patients with subclinical hypothyroidism in terms of symptoms or quality of life.(8, 9)

It has been argued, however, that persons with subclinical hypothyroidism and greater symptoms may still benefit from levothyroxine treatment, because the majority of participants in clinical trials were asymptomatic or had only mild symptoms.(10, 11) This secondary analysis of the TRUST trial,(9) the largest randomized placebo-controlled trial of individuals with subclinical hypothyroidism to date, evaluated whether levothyroxine therapy improved hypothyroid symptoms and tiredness in older individuals with higher symptom burden at baseline.

# Methods

## Study design

As previously reported,(9, 12) TRUST was a randomized, double-blind, parallel-group trial of levothyroxine versus placebo conducted from May 2014 until November 2016.(9) Participants were included from centers in Switzerland, Ireland, the Netherlands and Scotland. Randomization in a 1:1 ratio was performed using randomly permuted blocks with stratification by starting dose, country and sex. The randomization sequence was generated by the independent data center (Robertson Centre for Biostatistics, Glasgow).(12)

## Participants

Participants were identified from clinical laboratory and Primary Care databases and records. Eligible persons were ≥65 years old and presented with persistent subclinical hypothyroidism, defined as an elevated thyrotropin level (4.60 to 19.99 mIU/L), measured at two separate timepoints ranging from 3 months to 3 years apart, in combination with a normal free thyroxine level. Reasons for participant exclusion were: current prescription of levothyroxine, antithyroid drugs, lithium, or amiodarone; thyroid surgery or receiving radioactive iodine in the last 12 months; hospitalization for an elective procedure or a major illness within the previous 4 weeks; acute coronary syndrome within the previous 4 weeks; clinical diagnosis of dementia; or terminal illness.(12)

## Interventions

The study drug provided was either levothyroxine at a starting dose of 50 mcg daily (or 25 mcg in patients weighing <50 kg or with known coronary heart disease, i.e. previous myocardial infarction or symptoms of angina pectoris); or matching placebo. The levothyroxine dose was titrated to result in a thyrotropin level within the reference range of 0.40 to 4.59 mIU/L. Participants in the placebo arm underwent mock titration to ensure blinding and aimed to deliver the same frequency of mock titrations as would be required in the levothyroxine treated group. All dose adjustments (in both levothyroxine and placebo treated groups) were automatically generated through a computer program at the Robertson Centre for Biostatistics in Glasgow (Scotland). In order to adequately blind the study, treating physicians, participants and investigators were unaware of the thyrotropin values during the course of the trial.(12)

## High symptom burden groups

We defined four different high symptom groups based on patient reports on two quality of life measures (which were administered in English, French, German, or Dutch, as appropriate) and their performance on the handgrip test at baseline. We used cut-off points that approximated the most symptomatic quartile of participants in each group, based on baseline symptom scores derived from 638 participants who provided 1 year outcome data.

The Thyroid-Related Quality-of-Life Patient-Reported Outcome measure (ThyPRO) questionnaire is a measurement tool for the assessment of health-related quality of life, with the best clinical validity and reliability in patients with benign thyroid disorders.(13, 14) ThyPRO was developed based on multi-trait scaling and internal consistency analyses.(15) It proved to be a reliable scale with complete convergent validity and almost complete discriminant validity across different clinical and sociodemographic subgroups.(13) We defined two groups of high symptom subjects based on scores on the Hypothyroid Symptoms score (4 items) and Tiredness score (7 items) from the ThyPRO questionnaire; these are scored from 0 to 100, with higher values indicating more hypothyroid symptoms or tiredness, respectively. In the absence of agreed upon cut-off points, we estimated a clinically significant threshold in collaboration with the developer of the ThyPRO questionnaire (Prof. Torquil Watt, co-author) and defined high symptom burden on the ThyPRO questionnaire as Hypothyroid Symptoms score >30 and Tiredness score >40 at baseline, respectively.

Additionally, we used subjects' EQ-5D Health Utility score as assessed by the EuroQoL (EQ) Group 5-Dimension Self-Report Questionnaire (range 0.00 to 1.00) with higher score indicating higher QOL).(9, 16) Subjects with a score of <0.75 for EQ-5D Health Utility were classified as having high symptoms. Handgrip strength was measured with a Jamar isometric dynamometer (best of three measurements in the dominant hand).(17) We determined a threshold of <20kg for handgrip strength as clinically significant threshold for our fourth high symptom burden group. Out of all of the TRUST

measures, we selected EQ-5D and handgrip strength because EQ-5D is the most comprehensive scale for quality of life available within TRUST, and handgrip strength is an objective measure of weakness.

## Outcome Measures

The two main outcomes for this analysis were change in the Hypothyroid Symptoms score and Tiredness score from the Thyroid-Related Quality-of-Life Patient-Reported Outcome measure (ThyPRO) questionnaire assessed after 1 year.(13) The minimal clinically important difference for each score has been estimated as 9 points. Additional outcomes also assessed after 1 year included change in the EQ-5D Health Utility score [minimal clinically important difference of approximately 0.05],(18) and change in handgrip strength measured with a Jamar isometric dynamometer (best of three measurements in the dominant hand; no validated minimal clinically important difference exists).(17)

## Statistical Analysis

For this secondary analysis, we included participants who provided outcome data at 1 year for the two main outcomes. Baseline characteristics were summarized by treatment group separately for participants in the high symptom burden group compared to other participants for each score.

We used linear mixed effects regression with repeated measures to analyze Hypothyroid Symptoms scores collected at baseline, 6-8 week follow-up, and at 1 year. The model assumed no difference between randomized groups at baseline, and allowed for differences between treatment groups (levothyroxine vs. placebo), separately at 6-8 weeks and at 1 year. Different treatment effects were assumed for those with a high symptom burden at baseline (Hypothyroid Symptoms score >30 points) and for those without (Hypothyroid Symptoms score ≤30). The model was adjusted for the randomization stratification variables (sex, country and starting dose of levothyroxine), and included a random subject effect. Treatment effect estimates at 1 year are reported with 95% confidence intervals and are displayed graphically. A likelihood ratio test comparing this model to one with a common treatment effect at 1 year gave a test of treatment effect heterogeneity according to baseline symptom burden. Similar analyses were done regarding the Tiredness score (cut-off point >40), the EQ-5D Health Utility score (cut-off point <0.75), and handgrip strength (<20kg cut-off point).

Four sensitivity analyses were carried out. First, we compared the treatment effect (levothyroxine vs. placebo) at 1 year in the subgroup of participants who had both a Hypothyroid Symptoms score >30 and a Tiredness score >40. Second, we additionally adjusted the main analyses for comorbid conditions showing baseline differences between the levothyroxine and placebo group i.e. ischemic heart disease, hypertension, diabetes mellitus and smoking. Third, we repeated the main analysis among participants with baseline thyrotropin values 7 to 9.9 mIU/L. Fourth, we repeated the analyses including

data from 31 participants who were previously excluded from the analysis because their visits took place outside of the pre-specified visit window (±31 days at the 12 month follow-up).

All statistical analyses were conducted using R for Windows v3.6.0. Linear mixed effects models were fitted using the lme function from the nlme package. Statistical tests were 2-sided and $p<0.05$ was considered significant.

### Role of the Funding Source

The TRUST trial was predominantly financed through the European Union FP7 program. Merck (Darmstadt, Germany) provided levothyroxine and matching placebo tablets free of charge. The funder, the trial sponsors (NHS Greater Glasgow and Clyde Health Board and University of Glasgow, United Kingdom; University College Cork, Ireland; Leiden University Medical Center, the Netherlands; and University of Bern and Bern University Hospital, Switzerland), and Merck played no role in the design, analysis, or reporting of the trial. The main sponsor (NHS Greater Glasgow and Clyde Health Board) contributed to the writing of the protocol. None of the sponsors were involved in the analysis nor the reporting of the results.

## Results

Of 2647 persons ≥65 years old with subclinical hypothyroidism screened, 1910 were excluded, mainly because subclinical hypothyroidism was not persistent; 737 participants underwent randomization and were assigned to receive either placebo or levothyroxine (see Appendix Figure 1). Ninety-nine participants were excluded from the main analysis; 68 were lost to follow-up, and 31 had their 12 month visit outside the pre-specified visit window (i.e., ±31 days). Among the 638 participants included in this current study, 132 (20.7%) had a baseline Hypothyroid Symptoms score >30 points and 133 (20.8%) had a baseline Tiredness score >40. Of note, 56 had both a baseline Hypothyroid Symptoms score >30 points and a baseline Tiredness score >40. Tables 1 and 2 present the baseline characteristics of our sample according to treatment assignment and high symptom burden based on their Hypothyroid Symptom Score and Tiredness Score on the ThyPRO questionnaire. Baseline characteristics were generally similar between the active treatment and the placebo groups except for the distribution of some comorbid conditions and smoking status. Of note, among the 99 participants who were excluded for this secondary analysis, 34 had a Hypothyroid Symptoms score >30 and 26 a Tiredness score >40, respectively.

Thyrotropin levels at baseline and 1 year follow-up of the four high symptom burden groups are shown separately for the levothyroxine and placebo groups in Appendix Table 1. The proportion of participants with normal thyrotropin concentrations with placebo treatment after 1 year were numerically but not statistically significantly higher for the high symptom burden groups than for the remaining participants [48.4% vs. 39.8%, respectively, for Hypothyroid Symptoms ($p=0.25$) and 46.3% vs. 40.2% for Tiredness ($p=0.40$)].

After 1 year, the adjusted between-group difference (levothyroxine vs. placebo) in the Hypothyroid Symptom score was -2.0, 95%CI -5.5 to 1.5, p=0.27 among those with Hypothyroid Symptoms score >30 (Table 3). In the remaining 506 participants (Hypothyroid Symptoms score ≤30), the adjusted between-group difference was 0.6, 95%CI -1. 6 to 2.7, p=0.62 (Table 3). Furthermore, when baseline Hypothyroid Symptoms scores were dichotomized into >30 points vs. ≤30 points, there was no evidence that the effect of levothyroxine treatment differed between those with higher baseline scores compared to those with lower baseline scores (interaction p value =0.20).

In the high symptom burden group with Tiredness score >40, after 1 year the adjusted between-group difference in the Tiredness score was 0.0 95%CI -4.1 to 4.0, p=0.99 (Table 3). In the remaining 505 participants (Tiredness score ≤40), the adjusted between-group difference was 0.5, 95%CI -2.0 to 3.0, p=0.69. Furthermore, when baseline Tiredness scores were dichotomized into >40 vs. ≤40, there was no evidence that the effect of levothyroxine treatment differed between those with higher baseline scores compared to those with lower baseline scores (interaction p value =0.81).

**Other Outcomes**

Among the 152 participants who had EQ-5D score <0.75 at baseline, the EQ-5D score didn't change in the levothyroxine group and improved in the placebo group after 1 year (adjusted between group difference -0.093, 95%CI -0.129 to -0.057, p <0.001; Table 3), whereas no difference between levothyroxine and placebo was observed in the ≥0.75 group of EQ-5D (adjusted between group difference -0.002, 95%CI -0.026 to 0.023, p=0.90, interaction p-value <0.001) (Table 3). Furthermore, among the 125 participants with handgrip strength <20kg at baseline, there was no difference between the levothyroxine and the placebo group after 1 year (adjusted between-group difference 0.7, 95%CI -0.8 to 2.2, p=0.33; Table 3) and no difference between levothyroxine and placebo was observed in the rest of participants with ≥20kg of handgrip strength (adjusted between group difference -0.3, 95%CI -1.1 to 0.6, p=0.53, interaction p-value =0.20; Table 3). Overall, there was no indication of levothyroxine benefit compared to placebo (Figure 1).

**Sensitivity analyses**

We performed a number of sensitivity analyses as detailed in Appendix Table 2. First, when comparing the treatment effect (levothyroxine vs. placebo) in the subgroup of participants who had both a Hypothyroid Symptoms score >30 and a Tiredness score >40 (n=56), there was no benefit of levothyroxine. Second, when we additionally adjusted for comorbid conditions showing baseline differences between levothyroxine and the placebo group, i.e. ischemic heart disease, hypertension, diabetes mellitus and smoking, there was no benefit of levothyroxine regarding any of the 4 outcome variables. Third, when the analyses were limited to the 20-29 participants with baseline thyrotropin levels between 7.0 and 9.9 mIU/L results again remained similar for all 4 high symptom burden groups. The number of participants with baseline thyrotropin values ≥10 mIU/L was too small (26 /638 participants) to perform stratified analyses. Fourth, when we included

data from 31 participants previously excluded because the visit took place outside of the pre-specified visit window, the results again remained similar.

## Discussion

In this secondary analysis of the TRUST trial, levothyroxine therapy did not improve measures of hypothyroid symptoms, tiredness, quality of life or handgrip strength to a greater extent than placebo after 1 year of treatment, even among those with high symptom burden at baseline. Of note, quality of life as assessed by EQ-5D Health Utility score appeared to improve to a lesser degree among those treated with levothyroxine than those treated with placebo. However, given the multiple comparisons made, we consider the possibility that this may represent a chance finding.

Despite the lack of evidence from randomized clinical trials,(8) many believe that levothyroxine therapy benefits those with subclinical hypothyroidism and symptoms attributable to hypothyroidism. This may be one reason why symptomatic patients are under-represented in previous trials of subclinical hypothyroidism.(10) In the absence of evidence from randomized clinical trials specifically designed to examine persons with subclinical hypothyroidism and high symptom burden, the next best approach is to further analyze existing trial data. As shown in these analyses, our results do not support the hypothesis that the subgroup of adults with subclinical hypothyroidism and high symptom burden before treatment benefit from levothyroxine therapy. In this context, three aspects need special emphasis: First, participants who were above the clinically meaningful threshold for the Hypothyroid Symptoms score and the Tiredness score, respectively, in our study had substantially higher symptom scores compared to the general population(19) (Hypothyroid Symptoms score: 45 vs. 14 (SD 16) points; Tiredness score: 57 vs. 35 (SD 21) points). Moreover, our high Hypothyroid Symptoms subgroup also had a much higher mean Hypothyroid Symptoms score compared to a previous trial of 78 participants with subclinical (n=66) and overt (n=12) hypothyroidism(19) (45 vs. 27 points); and a comparable Tiredness score (57 vs. 58 points). This indicates that participants in our study with high symptom burden were truly symptomatic. Second, our results with their corresponding 95% confidence intervals for the two main outcomes (Hypothyroid Symptoms and Tiredness) are not consistent with a beneficial effect that approaches the minimal clinically important difference of 9 points. Third, our high symptom subgroups treated with levothyroxine demonstrated comparable improvements in terms of Hypothyroid Symptoms scores and Tiredness scores to that of the placebo group. This may be due to regression to the mean, the natural history of subclinical hypothyroidism, or the placebo effect, and may explain why many individuals with symptomatic subclinical hypothyroidism as well as their treating physicians are convinced that levothyroxine is beneficial. Of note, 47% of participants in the main high symptom burden groups had normalization of serum thyrotropin concentrations with placebo treatment after 1 year, a finding described in other studies,(20, 21) but in the high symptom group at 1 year thyrotropin remained significantly different between levothyroxine (mean thyrotropin =3.5 mIU/L) and placebo group (mean thyrotropin =5.3 mIU/L). Interestingly, there were more women in the high symptom burden group than in the rest

of participants. It is possible that in general non-specific symptoms like fatigue, sensitivity to cold or dry skin are more commonly perceived and/or reported by elderly women than elderly men. For example, low energy was more common in women than men aged >65 years (22% vs 12%) in a study by Cheng et al.(22)

Our analyses did have several limitations. First, this secondary analysis was not pre-specified in the original trial protocol. Second, the mean thyrotropin level in the levothyroxine group after 1 year of therapy was approximately 3.6 mIU/L across all 4 outcome groups measured in our secondary analysis. It is possible that more aggressive levothyroxine therapy leading to lower thyrotropin levels would confer benefit. Third, TPO antibody levels were not available and we could not determine if antibody status affects response to levothyroxine treatment. Fourth, the TRUST trial may not generalize to certain subgroups. For example, TRUST did not specifically recruit individuals with subclinical hypothyroidism reporting explicit hypothyroid symptoms and/or tiredness and cannot exclude the possibility that a rare subgroup with greater symptoms would benefit from levothyroxine therapy. Within our subgroups with high symptom burden at baseline, only 5/132 participants with Hypothyroid Symptoms >30 score and 8/133 participants with Tiredness >40 score had a thyrotropin level ≥10 mIU/L; numbers which are too low to allow for further statistical analyses. Only older adults (≥65 years) were included. Finally, 68 participants with potentially informative data were lost to follow-up.

## Conclusion

In this secondary analysis of the TRUST trial, levothyroxine therapy as compared to placebo was not associated with an improvement in hypothyroid symptoms or tiredness in older adults with persistent subclinical hypothyroidism and high symptom burden at baseline. In the absence of another RCT specifically designed for persons with subclinical hypothyroidism and high symptom burden, these results do not support routine levothyroxine therapy among older individuals with subclinical hypothyroidism, including those with greater hypothyroid symptoms and tiredness.

## Acknowledgements

**Registration**

TRUST is registered at ClinicalTrials.gov (NCT01660126).

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reporting of the trial. Dr. T-H Collet's research is supported by a grant from the Swiss National Science Foundation (PZ00P3-167826).

## Protocol

The trial protocol was published previously(12) and is available together with the full text TRUST manuscript online at NEJM.org.(9) The relevant ethics committees and regulatory authorities from all trial center countries approved the protocol. Written informed consent was signed by all participants. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Robertson Centre for Biostatistics at the University of Glasgow was the trial data and biostatistics center.

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