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

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25

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27 **Abstract**

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

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

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

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

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

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

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

40 **Results:** 132 participants had Hypothyroid Symptoms score >30 and 133 had Tiredness score >40. Among the high
41 symptom group, the Hypothyroid Symptoms score improved similarly between those on levothyroxine (mean within-group
42 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-
43 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
44 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),
45 adjusted between-group difference 0.0, 95% CI -4.1 to 4.0, $p=0.99$. There was no evidence that baseline Hypothyroid
46 Symptom score or Tiredness score modified the effects of levothyroxine vs. placebo (p for interaction=0.20 and 0.82,
47 respectively).

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

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

51 **Trial Registration:** NCT01660126.

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

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54 **Introduction**

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

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

67 **Methods**

68 **Study design**

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

74 **Participants**

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

82 Interventions

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

91 High symptom burden groups

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

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

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

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

113

114 Outcome Measures

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

121 Statistical Analysis

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

125 We used linear mixed effects regression with repeated measures to analyze Hypothyroid Symptoms scores collected at
126 baseline, 6-8 week follow-up, and at 1 year. The model assumed no difference between randomized groups at baseline, and
127 allowed for differences between treatment groups (levothyroxine vs. placebo), separately at 6-8 weeks and at 1 year.
128 Different treatment effects were assumed for those with a high symptom burden at baseline (Hypothyroid Symptoms score
129 >30 points) and for those without (Hypothyroid Symptoms score \leq 30). The model was adjusted for the randomization
130 stratification variables (sex, country and starting dose of levothyroxine), and included a random subject effect. Treatment
131 effect estimates at 1 year are reported with 95% confidence intervals and are displayed graphically. A likelihood ratio test
132 comparing this model to one with a common treatment effect at 1 year gave a test of treatment effect heterogeneity
133 according to baseline symptom burden. Similar analyses were done regarding the Tiredness score (cut-off point >40), the
134 EQ-5D Health Utility score (cut-off point <0.75), and handgrip strength (<20kg cut-off point).

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

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

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

144 Role of the Funding Source

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

152 Results

153 Of 2647 persons ≥ 65 years old with subclinical hypothyroidism screened, 1910 were excluded, mainly because subclinical
154 hypothyroidism was not persistent; 737 participants underwent randomization and were assigned to receive either placebo
155 or levothyroxine (see Appendix Figure 1). Ninety-nine participants were excluded from the main analysis; 68 were lost to
156 follow-up, and 31 had their 12 month visit outside the pre-specified visit window (i.e., ± 31 days). Among the 638
157 participants included in this current study, 132 (20.7%) had a baseline Hypothyroid Symptoms score > 30 points and 133
158 (20.8%) had a baseline Tiredness score > 40 . Of note, 56 had both a baseline Hypothyroid Symptoms score > 30 points and a
159 baseline Tiredness score > 40 . Tables 1 and 2 present the baseline characteristics of our sample according to treatment
160 assignment and high symptom burden based on their Hypothyroid Symptom Score and Tiredness Score on the ThyPRO
161 questionnaire. Baseline characteristics were generally similar between the active treatment and the placebo groups except
162 for the distribution of some comorbid conditions and smoking status. Of note, among the 99 participants who were
163 excluded for this secondary analysis, 34 had a Hypothyroid Symptoms score > 30 and 26 a Tiredness score > 40 ,
164 respectively.

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

170 After 1 year, the adjusted between-group difference (levothyroxine vs. placebo) in the Hypothyroid Symptom score was -
171 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
172 participants (Hypothyroid Symptoms score ≤30), the adjusted between-group difference was 0.6, 95%CI -1.6 to 2.7,
173 p=0.62 (Table 3). Furthermore, when baseline Hypothyroid Symptoms scores were dichotomized into >30 points vs. ≤30
174 points, there was no evidence that the effect of levothyroxine treatment differed between those with higher baseline scores
175 compared to those with lower baseline scores (interaction p value =0.20).

176 In the high symptom burden group with Tiredness score >40, after 1 year the adjusted between-group difference in the
177 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
178 adjusted between-group difference was 0.5, 95%CI -2.0 to 3.0, p=0.69. Furthermore, when baseline Tiredness scores were
179 dichotomized into >40 vs. ≤40, there was no evidence that the effect of levothyroxine treatment differed between those
180 with higher baseline scores compared to those with lower baseline scores (interaction p value =0.81).

181 **Other Outcomes**

182 Among the 152 participants who had EQ-5D score <0.75 at baseline, the EQ-5D score didn't change in the levothyroxine
183 group and improved in the placebo group after 1 year (adjusted between group difference -0.093, 95%CI -0.129 to -0.057, p
184 <0.001; Table 3), whereas no difference between levothyroxine and placebo was observed in the ≥0.75 group of EQ-5D
185 (adjusted between group difference -0.002, 95%CI -0.026 to 0.023, p=0.90, interaction p-value <0.001) (Table 3).

186 Furthermore, among the 125 participants with handgrip strength <20kg at baseline, there was no difference between the
187 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
188 3) and no difference between levothyroxine and placebo was observed in the rest of participants with ≥20kg of handgrip
189 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,
190 there was no indication of levothyroxine benefit compared to placebo (Figure 1).

191 **Sensitivity analyses**

192 We performed a number of sensitivity analyses as detailed in Appendix Table 2. First, when comparing the treatment effect
193 (levothyroxine vs. placebo) in the subgroup of participants who had both a Hypothyroid Symptoms score >30 and a
194 Tiredness score >40 (n=56), there was no benefit of levothyroxine. Second, when we additionally adjusted for comorbid
195 conditions showing baseline differences between levothyroxine and the placebo group, i.e. ischemic heart disease,
196 hypertension, diabetes mellitus and smoking, there was no benefit of levothyroxine regarding any of the 4 outcome
197 variables. Third, when the analyses were limited to the 20-29 participants with baseline thyrotropin levels between 7.0 and
198 9.9 mIU/L results again remained similar for all 4 high symptom burden groups. The number of participants with baseline
199 thyrotropin values ≥10 mIU/L was too small (26 /638 participants) to perform stratified analyses. Fourth, when we included

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

202 **Discussion**

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

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

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

234 Our analyses did have several limitations. First, this secondary analysis was not pre-specified in the original trial protocol.
235 Second, the mean thyrotropin level in the levothyroxine group after 1 year of therapy was approximately 3.6 mIU/L across
236 all 4 outcome groups measured in our secondary analysis. It is possible that more aggressive levothyroxine therapy leading
237 to lower thyrotropin levels would confer benefit. Third, TPO antibody levels were not available and we could not determine
238 if antibody status affects response to levothyroxine treatment. Fourth, the TRUST trial may not generalize to certain
239 subgroups. For example, TRUST did not specifically recruit individuals with subclinical hypothyroidism reporting explicit
240 hypothyroid symptoms and/or tiredness and cannot exclude the possibility that a rare subgroup with greater symptoms
241 would benefit from levothyroxine therapy. Within our subgroups with high symptom burden at baseline, only 5/132
242 participants with Hypothyroid Symptoms >30 score and 8/133 participants with Tiredness >40 score had a thyrotropin level
243 ≥ 10 mIU/L; numbers which are too low to allow for further statistical analyses. Only older adults (≥ 65 years) were
244 included. Finally, 68 participants with potentially informative data were lost to follow-up.

245 **Conclusion**

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

251 **Acknowledgements**

252 **Registration**

253 TRUST is registered at ClinicalTrials.gov (NCT01660126).
254

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263

264 **Protocol**

265 The trial protocol was published previously(12) and is available together with the full text TRUST manuscript online at

266 NEJM.org.(9) The relevant ethics committees and regulatory authorities from all trial center countries approved the

267 protocol. Written informed consent was signed by all participants. The trial was conducted in accordance with the

268 principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The Robertson Centre for Biostatistics at

269 the University of Glasgow was the trial data and biostatistics center.

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