

1 Incidence and determinants of spontaneous normalization of 2 subclinical hypothyroidism in older adults

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15 **Disclosure summary**

16 All authors have declared that they have no conflicts of interest to disclose.

18 **Trial registration:** ClinicalTrials.gov, NCT01660126 and Netherlands Trial Register, NTR3851.

1 **Abstract**

2 **Context.** With age, the prevalence of subclinical hypothyroidism rises. However, incidence and
3 determinants of spontaneous normalization remain largely unknown.

4 **Objective.** To investigate incidence and determinants of spontaneous normalization of thyroid-
5 stimulating hormone (TSH) levels in older adults with subclinical hypothyroidism.

6 **Design.** Pooled data were used from the (i) pre-trial population, and (ii) in-trial placebo group
7 from two randomized, double-blind, placebo-controlled trials (TRUST and IEMO thyroid 80-plus
8 thyroid trial).

9 **Setting.** Community-dwelling 65+ adults with subclinical hypothyroidism from the Netherlands,
10 Switzerland, Ireland, and the United Kingdom.

11 **Participants.** The pre-trial population (N=2335) consisted of older adults with biochemical
12 subclinical hypothyroidism, defined as ≥ 1 elevated TSH measurement (≥ 4.60 mIU/L) and a free
13 thyroxine (fT4) within the laboratory-specific reference range. Individuals with persistent
14 subclinical hypothyroidism, defined as ≥ 2 elevated TSH measurements ≥ 3 months apart, were
15 randomized to levothyroxine/placebo, of which the in-trial placebo group (N=361) was included.

16 **Main Outcome Measures.** Incidence of spontaneous normalization of TSH levels and
17 associations between participant characteristics and normalization.

18 **Results.** In the pre-trial phase, TSH levels normalized in 60.8% of participants in a median
19 follow-up of one year. In the in-trial phase, levels normalized in 39.9% of participants after one
20 year follow-up. Younger age, female sex, lower initial TSH level, higher initial fT4 level, absence
21 of thyroid peroxidase antibodies, and a follow-up measurement in summer were independent
22 determinants for normalization.

23 **Conclusions.** Since TSH levels spontaneously normalized in a large proportion of older adults
24 with subclinical hypothyroidism (also after confirmation by repeat measurement), a third
25 measurement may be recommended before considering treatment.

1 Introduction

2 With increasing age, circulating levels of thyroid stimulating hormone (TSH) generally rise,
3 accompanied by a higher prevalence of subclinical hypothyroidism ^{1,2}. Subclinical
4 hypothyroidism is defined as an elevated TSH level while the serum free thyroxine (fT4)
5 concentration is within the normal range ³. Several randomized controlled trials have shown that
6 treatment of mild subclinical hypothyroidism in older adults does not improve clinical outcomes ⁴⁻
7 ⁹. Therefore, it has been suggested to reevaluate the reference range for TSH in older adults ¹⁰.
8 To this end, we need to further explore the natural course of subclinical hypothyroidism in older
9 adults. Interestingly, several studies in adults have shown that subclinical hypothyroidism can
10 spontaneously normalize ¹¹⁻¹⁸. However, it is not known what the most important determinants
11 are for spontaneous TSH normalization in older adults. Enhanced understanding of the natural
12 history and factors contributing to normalization may help clinical decision making on the follow-
13 up strategy.

14
15 In this longitudinal study, we aimed to investigate the incidence of spontaneous normalization of
16 TSH levels and identify determinants of normalization in a large group of adults aged 65 years
17 and over with (persistent) subclinical hypothyroidism. We combined individual participant level
18 data from two randomized trials investigating the effect of levothyroxine treatment in older adults
19 with subclinical hypothyroidism; TRUST and IEMO trials ^{4,6,19,20}. Because we were interested in
20 spontaneous normalization, we only included the pre-trial screening populations and the in-trial
21 placebo groups of the two clinical trials.

22
23

1 **Materials and Methods**

2 **Study design**

3 The present study pooled data from two randomized, double-blind, placebo-controlled parallel-
4 group clinical trials investigating the effect of levothyroxine treatment for older adults with
5 subclinical hypothyroidism; the Thyroid Hormone Replacement for Untreated Older Adults With
6 Subclinical Hypothyroidism Trial (TRUST) and the Institute for Evidence-Based Medicine in Old
7 Age (IEMO) 80-plus thyroid trial ^{4,6}. TRUST included community-dwelling participants aged 65
8 years and older in the Netherlands, Switzerland, Ireland, and the United Kingdom recruited
9 between April 2013 and May 2015 ^{4,19}. Participants for the IEMO 80-plus thyroid trial were 80
10 years and older and recruited in the Netherlands and Switzerland between May 2014 and May
11 2017 ^{6,20}. Both trials shared a near identical design and recruitment strategy. Trial protocols
12 were approved by the relevant ethics committees and regulatory authorities in all the countries
13 involved in the trials. The trials were conducted in accordance with the principles of the
14 Declaration of Helsinki and Good Clinical Practice guidelines and participants provided written
15 informed consent. Trial registration: ClinicalTrials.gov, NCT01660126 and Netherlands Trial
16 Register, NTR3851.

18 **Inclusion of study participants**

19 The timeline and the two populations of the present study are presented in Figure 1 (Fig 1).

20 *Inclusion of pre-trial population*

21 Participants were identified from clinical laboratory databases and general practice records.
22 Older adults with biochemical subclinical hypothyroidism, defined as an elevated TSH level
23 (4.60 to 19.99 mIU/L) and an fT4 level within the laboratory-specific reference range, three
24 months to three years before the trial baseline were invited for a repeated measurement. This
25 repeated measurement was taken to assess whether they had persistent subclinical
26 hypothyroidism and were eligible for trial inclusion. Individuals with two TSH measurements (the

1 pre-trial screening and the trial baseline) were included in the pre-trial population. Participants
2 recruited during the screening period in Switzerland were excluded, because for Swiss
3 participants demographic data were only registered centrally for those who were randomized.

4 *Inclusion of in-trial placebo group*

5 Persistent subclinical hypothyroidism was defined as an elevated TSH level (4.60 to 19.99
6 mIU/L) and an fT4 level within the laboratory-specific reference range at both the pre-trial
7 screening (first measurement) and at the trial baseline (second measurement). Participants with
8 persistent subclinical hypothyroidism who fulfilled the inclusion criteria were randomized to
9 receive levothyroxine treatment or placebo in the clinical trials. For the present study, we only
10 included the in-trial participants assigned to placebo treatment with mock titration. TSH
11 normalization was checked at the follow-up visit after 300 to 400 days (third measurement).
12

13 **Thyroid status measurements**

14 For nearly all participants, TSH and fT4 measurements were performed at the same clinical
15 laboratory or general practice where the initial measurement for identification of subclinical
16 hypothyroidism was performed. A subsample (80.1%) of the in-trial placebo group donated
17 blood for biobanking at randomization (a few weeks after the trial baseline), which was stored
18 centrally at -80° Celsius to be analyzed later. In these serum samples, thyroid peroxidase
19 antibodies (anti-TPO) were measured using the Cobas E602 module from Roche, Almere, the
20 Netherlands, performed in a single batch at the Department of Clinical Chemistry and
21 Laboratory Medicine of the Leiden University Medical Center. The threshold for elevated anti-
22 TPO is > 34 kU/L (detection range 10-599.99 kU/L), the coefficient of variation was 11.3% to
23 15.6%.
24
25

1 **Participant characteristics**

2 *Pre-trial population*

3 Determinants of interest were age, sex, TSH level at first measurement, fT4 level at first
4 measurement, and the interval between the first and second measurements (divided into <6
5 months, 6 – 12 months, >12 months). To investigate whether season of follow-up testing has an
6 influence on TSH normalization, the season of the second measurement (divided into
7 meteorological summer (1 June – 31 August), autumn (1 September – 30 November), winter (1
8 December – 28/29 February), and spring (1 March – 31 May)) was assessed as determinant.

9 *In-trial placebo group*

10 Determinants of interest for the in-trial placebo group were age, sex, TSH level at trial baseline,
11 fT4 level at trial baseline, and anti-TPO positivity. As the interval between the trial baseline and
12 follow-up measurements for all participants in the in-trial placebo group was between 300 to 400
13 days, the interval and season of testing were not included as determinants.

14

15 **Statistical analyses**

16 Summary statistics were estimated using median and interquartile range for continuous
17 variables and number and percentage for categorical variables. Logistic regression was
18 performed with TSH normalization as the outcome using the glm function in R. Univariable
19 models were created for the determinants of interest separately and multivariable models were
20 created with all determinants combined. All models were adjusted for country as fixed effect. To
21 visualize the probability of normalization for each unit in TSH level, probability plots were
22 created using logistic regression models with initial TSH level as independent determinant and
23 TSH normalization as outcome, adjusted for country (United Kingdom as reference). For the
24 pre-trial phase, a sensitivity analysis was performed excluding the participants who had both
25 measurements in the same season (N=20%) to investigate the true effect of a follow-up

1 measurement in a certain season compared to another season. Analyses were conducted in R
2 version 4.1.2²¹ and figures were produced using Graphpad and Adobe Illustrator.

3

4 **Results**

5 As presented in Figure 2 (Fig 2), a total of 2989 older adults were identified from clinical
6 laboratory databases and general practice records and assessed for eligibility for the TRUST or
7 IEMO trials. Of these, 2335 participants were included in the pre-trial population to investigate
8 the incidence and determinants of spontaneous TSH normalization in older adults with at least
9 one measurement of biochemical subclinical hypothyroidism. For the in-trial placebo group, we
10 included participants who were randomized to placebo in one of the two trials and had a follow-
11 up in-trial TSH measurement in 300 to 400 days. In total, 361 participants were included in the
12 in-trial placebo group to investigate the incidence and determinants of spontaneous TSH
13 normalization in older adults with persistent subclinical hypothyroidism (defined as at least two
14 measurement of elevated TSH levels with normal fT4 levels more than three months apart).

15

16 **Pre-trial population: older adults with biochemical subclinical hypothyroidism (N=2335)**

17 *Characteristics of study population*

18 The median (interquartile range, IQR) age of the pre-trial population was 72.9 (68.0-79.3) years
19 and 60.7% of the participants were female (Table 1). Median (IQR) levels of TSH and fT4 at the
20 first measurement (screening) were 5.40 (4.91-6.31) mIU/L and 13.6 (12.3-15.0) pmol/L,
21 respectively. Most participants had their second measurement (trial baseline) in summer
22 (32.7%) or autumn (31.5%) and were included in The Netherlands (50.3%).

23

24 *Normalization of subclinical hypothyroidism*

25 From a total of 2335 participants, TSH levels normalized in 1419 (60.8%) participants in a
26 median follow-up of 344 (IQR: 207-594) days. Lower age (OR 0.98 (95%CI 0.97 to 0.99),

1 P=0.007), female sex (OR 1.39 (95%CI 1.15 to 1.69), P<0.001), lower screening TSH level (OR
2 0.57 (95%CI 0.52 to 0.62), P<0.001), higher normal screening fT4 level (OR 1.06 (95%CI 1.01
3 to 1.11), P=0.03), and a second measurement in summer (compared to winter: OR 0.59 (95%CI
4 0.44 to 0.79), P<0.001) were independently associated with a higher chance of TSH
5 normalization (Table 2). An interval between measurements of more than 12 months was
6 associated with TSH normalization (OR 1.40 (95%CI 1.07 to 1.82), P=0.01), but this was not
7 statistically significant in the multivariable model (Table 2). When restricted to participants
8 having their second measurement in another season than the first (N=1866), having the second
9 measurement in summer was still independently associated with a higher chance of
10 normalization (compared to winter: OR 0.55 (95%CI 0.39 to 0.78), P<0.001), data not shown).

12 **In-trial placebo group: older adults with persistent subclinical hypothyroidism (N=361)**

13 *Characteristics of study population*

14 The median (IQR) age of the in-trial placebo group was 75.1 (69.6-81.4) years and 51.8% of the
15 participants were female (Table 3). Median (IQR) levels of TSH and fT4 at the trial baseline
16 measurement were 5.75 (5.10-6.86) mIU/L and 13.4 (12.1-14.7) pmol/L, respectively. A quarter
17 (25.3%) of the participants had antibodies to TPO.

19 *Normalization of persistent subclinical hypothyroidism*

20 From a total of 361 participants, in 144 (39.9%) participants TSH levels normalized in a median
21 follow-up of 362 (IQR 345-370) days. Lower age (OR 0.96 (95%CI 0.92 to 1.00), P=0.05),
22 female sex (OR 1.80 (95%CI 1.01 to 3.23), P=0.05), lower trial baseline TSH level (OR 0.52
23 (95%CI 0.38 to 0.67), P<0.001), higher normal trial baseline fT4 levels (OR 1.22 (95%CI 1.05 to
24 1.44), P=0.01), and the absence of TPO antibodies (OR 0.36 (95%CI 0.17 to 0.77), P=0.007)
25 were independently associated with a higher chance of normalization (Table 4).

26

1 **TSH level as determinant of normalization of subclinical hypothyroidism**

2 Figure 3 (Fig 3) visualizes that the probability of TSH normalization decreases for each unit in
3 TSH level from 5 to 10 mIU/L in both populations. In the pre-trial population, there was an
4 interaction between TSH screening level and sex ($P=0.004$) showing that the probability of
5 normalization tended to decrease more for men than for women (Fig 3A). As an example, older
6 men with biochemical subclinical hypothyroidism with a screening TSH level of 5 mIU/L have a
7 76.3% (95%CI 70.2% to 82.3%) chance of normalization, while the chance becomes 7.3%
8 (95%CI 2.7% to 11.8%) when having a screening TSH level of 10 mIU/L. For older women, the
9 chance of TSH normalization decreases from 73.3% (95%CI 68.2% to 78.5%) at 5 mIU/L to
10 20.1% (95%CI 12.1% to 28.1%) at 10 mIU/L. Older adults with already two elevated TSH
11 measurements more than three months apart, still have a 64.3% (95%CI 51.6% to 77.1%)
12 chance to normalize when their second (trial baseline) TSH level is 5 mIU/L (Fig 3B). However,
13 when the second (trial baseline) TSH level is 10 mIU/L in older adults with persistent subclinical
14 hypothyroidism, then the chance of normalization is only 5.9% (95%CI 0.0% to 12.0%).

16 **Discussion**

17 In this study we aimed to investigate the incidence and determinants of spontaneous TSH
18 normalization in a large group of adults 65 years and older with (persistent) subclinical
19 hypothyroidism. In 60.8% of the older adults with biochemical subclinical hypothyroidism based
20 on at least one elevated TSH measurement, TSH levels had returned to the normal range
21 without intervention after a median follow-up of one year. Subsequently, TSH levels had still
22 normalized after one year in 39.9% of older adults with persistent subclinical hypothyroidism,
23 defined as at least two elevated TSH measurements more than three months apart. Younger
24 age, female sex, lower initial TSH level, higher normal initial fT4 level, the absence of TPO

1 antibodies, and a second measurement in summer were independent determinants for TSH
2 normalization.

3
4 The large proportions of normalization of TSH levels in older adults with subclinical
5 hypothyroidism after approximately one year in the present study are in line with percentages of
6 35 to 70% during a follow-up of 0.5 to 5 years found in studies in adults aged 55 years and over
7 ^{11-15,17}. In three of those studies, a lower initial TSH levels was found to be the strongest
8 determinant for normalization ^{11,13,15}. A lower initial TSH level as a determinant for TSH
9 normalization can be statistically explained by regression to the mean, but it can also be
10 reasoned that mildly elevated TSH levels normalize easier than higher levels, especially
11 considering normal fluctuations in TSH levels ²². These fluctuations within an individual over
12 time are caused by both internal and external factors, such as pulsatile secretion, the biological
13 clock, illness, and medication use ²²⁻²⁴. The association between high normal fT4 levels and
14 TSH normalization was also found by Díez *et al.* ¹¹, which is expected given the negative
15 feedback of thyroid hormones on TSH secretion. TPO-antibodies generally associate with
16 higher TSH levels ²⁵, which might explain anti-TPO negativity as a determinant for normalization
17 as confirmed by two studies ^{11,15}, but not by others ¹³. Although older women are generally more
18 affected by (subclinical) hypothyroidism and tend to have higher TSH levels than older men ^{26,27},
19 we found in our study that women have a higher probability for normalization than men,
20 especially at a higher TSH level. TSH levels generally rise with age ¹, so older age coincides
21 with higher TSH levels which might explain the association found between older age and a
22 lower chance of TSH normalization. However, in three studies with older adults with subclinical
23 hypothyroidism without known previous thyroid disease, no relation was observed between sex,
24 age and TSH normalization ^{11,13,15}. A second measurement in summer was associated with
25 normalization, which is in line with a study in individuals aged 18-90 years ²⁸. TSH levels are

1 subject to change of season with highest levels in winter ²², which is probably caused by
2 changes in environmental temperature ²⁹.

3
4 The present study is a large, multicenter study in which adults aged 65 years and over, enriched
5 for adults aged 80+, with mild subclinical hypothyroidism were included. Strengths of this study
6 are that changes in TSH levels were observed over a long follow-up time ranging from three
7 months to four years, without intervention. Another strength of this study is that we compared
8 TSH normalization after at least one elevated TSH measurement and after at least two elevated
9 TSH measurements. Measurements follow real-world practice as all thyroid measurements
10 were performed in routine clinical care, thus preventing potential degradation of TSH by long-
11 term sample storage and/or freeze/thaw cycles. Although biochemical assays differed between
12 clinical centers, baseline and follow-up measurements were performed in the same clinical
13 centers for nearly all participants. Unfortunately, time of blood sampling was not recorded.
14 Selection bias could play a role in the pre-trial screening population, since individuals who
15 became overt hypothyroid or started with thyroid medication for other reasons were not enrolled
16 in the study. Therefore, we were not able to investigate the incidence and determinants of the
17 progression of subclinical hypothyroidism to overt hypothyroidism in the pre-trial screening
18 population. Almost all older subjects had mild subclinical hypothyroidism (TSH < 10 mIU/L) in
19 our study, which limits the generalizability to higher TSH levels. With age, the TSH distribution
20 shift towards a higher level, and the 97.5th percentile of the TSH distribution was shown to be
21 7.5 mU/liter in subjects aged 80 years and older ³⁰.

22
23 In this study, we have demonstrated that in a large proportion of older adults with mild
24 subclinical hypothyroidism, TSH levels spontaneously normalized in a median follow-up of one
25 year, even after two consecutive measurements (\geq three months apart) of elevated TSH levels.
26 These results have clinical relevance. Current guidelines recommend that a single

1 measurement of elevated serum TSH, with fT4 within reference range, should be confirmed by
2 a repeat measurement of both serum TSH and fT4, along with thyroid peroxidase antibodies,
3 after a 2- to 3-month interval ³¹. However, international guidelines differ in their
4 recommendations on the TSH threshold at which treatment of subclinical hypothyroidism should
5 be considered in older adults ³². Once levothyroxine treatment is initiated, it is often continued
6 lifelong ³³. Based on the observation that with age, the TSH distribution shifts towards a higher
7 level, it has been proposed to extend the upper limit of the TSH reference to 7 mU/L for people
8 aged 80 years or older ³⁴. Although increasing the upper reference limit will likely reduce
9 unnecessary levothyroxine prescribing for older people, instead of a binary approach, our
10 results support applying more continuous age-related reference ranges, that may be modified
11 by other factors such as sex and season. Moreover, based on the high incidence of
12 spontaneous normalization of TSH levels in a large proportion of older adults with subclinical
13 hypothyroidism (also after confirmation by repeat measurement), a third measurement may be
14 recommended before considering initiation of treatment. Based on such an approach, the
15 frequency of the diagnosis subclinical hypothyroidism can likely be reduced in older adults. This
16 could potentially contribute to a reduction in health care costs, treatment burden, and risk of
17 overtreatment. These results may also have implications for follow-up studies. Levothyroxine is
18 among the most frequently prescribed drugs. Although general practitioner prescription
19 practices vary widely between countries ³⁵, many older adults have initiated levothyroxine
20 treatment based on a mildly elevated TSH. Moreover, in clinical practice, treatment has often
21 been started after a single measurement of TSH ³³. A recent meta-analysis indicated that
22 deprescribing levothyroxine could be successful for carefully selected patients although the
23 quality of available evidence was considered low ³⁶. This underscores the need for future high-
24 quality studies to assess the effects of safely withholding levothyroxine treatment in older adults
25 who initiated levothyroxine treatment based on a diagnosis of mild subclinical hypothyroidism on
26 relevant patient outcomes ³⁶.

1 **Author contributions**

2 All authors have contributed substantially to the conception or design of the work, or the
3 acquisition, analysis or interpretation of data; drafting the work or revising it critically for
4 important intellectual content; and final approval of the version published.

6 **Data availability**

7 Restrictions apply to the availability of some or all data generated or analyzed during this study
8 to preserve patient confidentiality or because they were used under license. The corresponding
9 author will on request detail the restrictions and any conditions under which access to some
10 data may be provided.

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1 **Table 1. Characteristics of older adults with subclinical hypothyroidism**

Characteristic	Pre-trial population (N=2335)
Age, years	72.9 (68.0-79.3)
Age ≥ 80 years, n (%)	535 (22.9)
Female, n (%)	1418 (60.7)
TSH, mIU/L	
First measurement (screening)	5.40 (4.91-6.31)
> 7 mIU/L, n (%)	368 (15.8)
> 10 mIU/L, n (%)	57 (2.4)
Second measurement (trial baseline)	4.02 (3.01-5.42)
fT4, pmol/L	
First measurement (screening)*	13.6 (12.3-15.0)
Second measurement (trial baseline)	13.0 (12.0-14.6)
Interval between first and second measurements	344 (207-594)
<6 months, n (%)	465 (19.9)
6 to 12 months, n (%)	778 (33.3)
>12 months, n (%)	1092 (46.8)
Season of second measurement (trial baseline), n (%)	
Summer	764 (32.7)
Autumn	735 (31.5)
Winter	318 (13.6)
Spring	518 (22.2)
Country, n (%)	
United Kingdom	494 (21.2)
Ireland	667 (28.6)
The Netherlands	1174 (50.3)

2
3 Values shown are median (interquartile range) unless indicated otherwise. *First fT4 measurement was
4 missing for n=10.

5

6

Table 2. Association between TSH normalization and characteristics in older adults with subclinical hypothyroidism from the pre-trial population (N=2335)

Characteristic	Univariable model		Multivariable model	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per year)	0.98 (0.97 to 0.99)	<0.001	0.98 (0.97 to 0.99)	0.007
Female sex	1.39 (1.16 to 1.66)	<0.001	1.39 (1.15 to 1.69)	<0.001
TSH level (per unit mIU/L)	0.56 (0.52 to 0.61)	<0.001	0.57 (0.52 to 0.62)	<0.001
fT4 level (per unit pmol/L)	1.08 (1.04 to 1.13)	<0.001	1.06 (1.01 to 1.11)	0.03
Interval between measurements				
<6 months	1 (reference)		1 (reference)	
6 to 12 months	1.05 (0.81 to 1.35)	0.73	1.02 (0.78 to 1.34)	0.87
>12 months	1.40 (1.07 to 1.82)	0.01	1.30 (0.97 to 1.72)	0.07
Season second measurement				
Summer	1 (reference)		1 (reference)	
Autumn	0.74 (0.59 to 0.93)	0.008	0.72 (0.57 to 0.92)	0.008
Winter	0.62 (0.47 to 0.82)	<0.001	0.59 (0.44 to 0.79)	<0.001
Spring	0.73 (0.57 to 0.92)	0.009	0.73 (0.56 to 0.95)	0.02

Odds ratios (OR) with 95% confidence intervals (95% CI) resulting from logistic regression analyses. Univariable models were created for each characteristic separately and multivariable models were created with all characteristics combined.

All analyses were adjusted for country.

1 **Table 3. Characteristics of older adults with persistent subclinical hypothyroidism**

Characteristic	In-trial placebo group (N=361)
Age, years	75.1 (69.6-81.4)
Age ≥ 80 years, n (%)	113 (31.3)
Female, n (%)	187 (51.8)
TSH, mIU/L	
First measurement (screening)	5.84 (5.20-7.17)
Second measurement (trial baseline)	5.75 (5.10-6.86)
> 7 mIU/L, n (%)	77 (21.3)
> 10 mIU/L, n (%)	16 (4.4)
Third measurement (follow-up)	4.91 (3.96-6.49)
fT4 at second measurement (trial baseline), pmol/L	13.4 (12.1-14.7)
Anti-TPO positive, n (%)*	73 (25.3)
Interval between second and third measurements	362 (345-370)
Country, n (%)	
United Kingdom	64 (17.8)
Ireland	50 (13.9)
The Netherlands	149 (41.3)
Switzerland	98 (27.1)

2
3 Values shown are median (interquartile range) unless indicated otherwise. *Information on TPO
4 antibodies was missing for n=72.

5

6 **Table 4. Association between TSH normalization and characteristics in older adults with**
 7 **persistent subclinical hypothyroidism from the in-trial placebo group (N=361)**

Characteristic	Univariable model		Multivariable model	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per year)	0.99 (0.96 to 1.02)	0.59	0.96 (0.92 to 1.00)	0.05
Female sex	1.23 (0.79 to 1.92)	0.36	1.80 (1.01 to 3.23)	0.05
TSH level at trial baseline (per unit mIU/L)	0.51 (0.40 to 0.63)	<0.001	0.52 (0.38 to 0.67)	<0.001
fT4 level at trial baseline (per unit pmol/L)	1.32 (1.17 to 1.50)	<0.001	1.22 (1.05 to 1.44)	0.01
Anti-TPO positivity*	0.38 (0.19 to 0.72)	0.004	0.36 (0.17 to 0.77)	0.007

8
 9 Odds ratios (OR) with 95% confidence intervals (95% CI) resulting from logistic regression analyses.
 10 Univariable models were created for each characteristic separately and multivariable models were
 11 created with all characteristics combined. All analyses were adjusted for country. *Information on TPO
 12 antibodies was missing for n=72.

13

14 **Figure Legends**

15

16 **Fig 1. Timeline of the study**

17 The pre-trial population consisted of older adults with ≥ 1 elevated TSH measurement (≥ 4.60
18 mIU/L) and a fT4 level within the laboratory-specific reference range, during the previous 3
19 months to 3 years (screening). The second measurement was at the trial baseline to assess
20 whether they had persistent subclinical hypothyroidism or had normalized their TSH levels. The
21 in-trial placebo group consisted of older adults with ≥ 2 elevated TSH measurements, both at the
22 screening and trial baseline, receiving placebo in the clinical trials. After 12 months, at the (third)
23 follow-up measurement, it was determined whether the in-trial placebo group had normalized
24 their TSH levels.

25

26 **Fig 2. Flow diagram of study populations**

27

28 **Fig 3. Probability of TSH normalization (95% CI) based on initial TSH level in older adults** 29 **with (persistent) subclinical hypothyroidism**

30 (A) Probability of normalization stratified for sex in the pre-trial population (N=2335) which
31 includes older adults with subclinical hypothyroidism. (B) Probability of normalization in the in-
32 trial placebo group (N=361) which includes older adults with persistent subclinical
33 hypothyroidism, defined as having at least two measurements of elevated TSH levels ≥ 3
34 months apart.

35

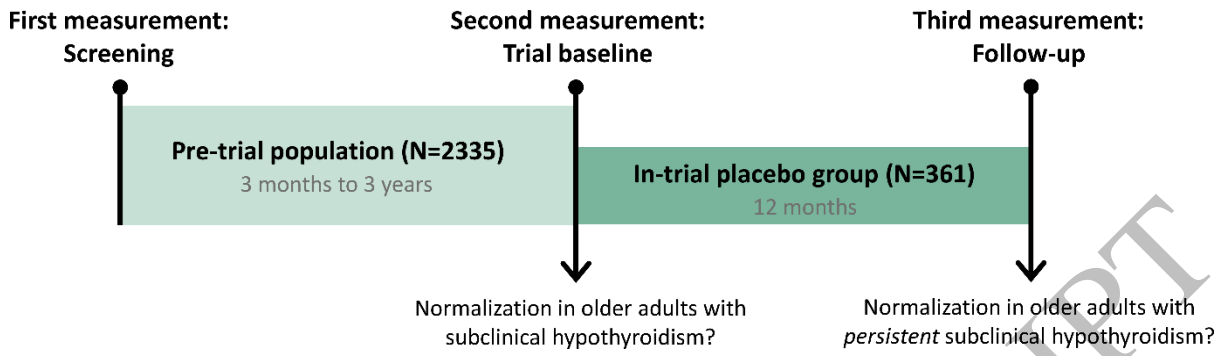


Figure 1
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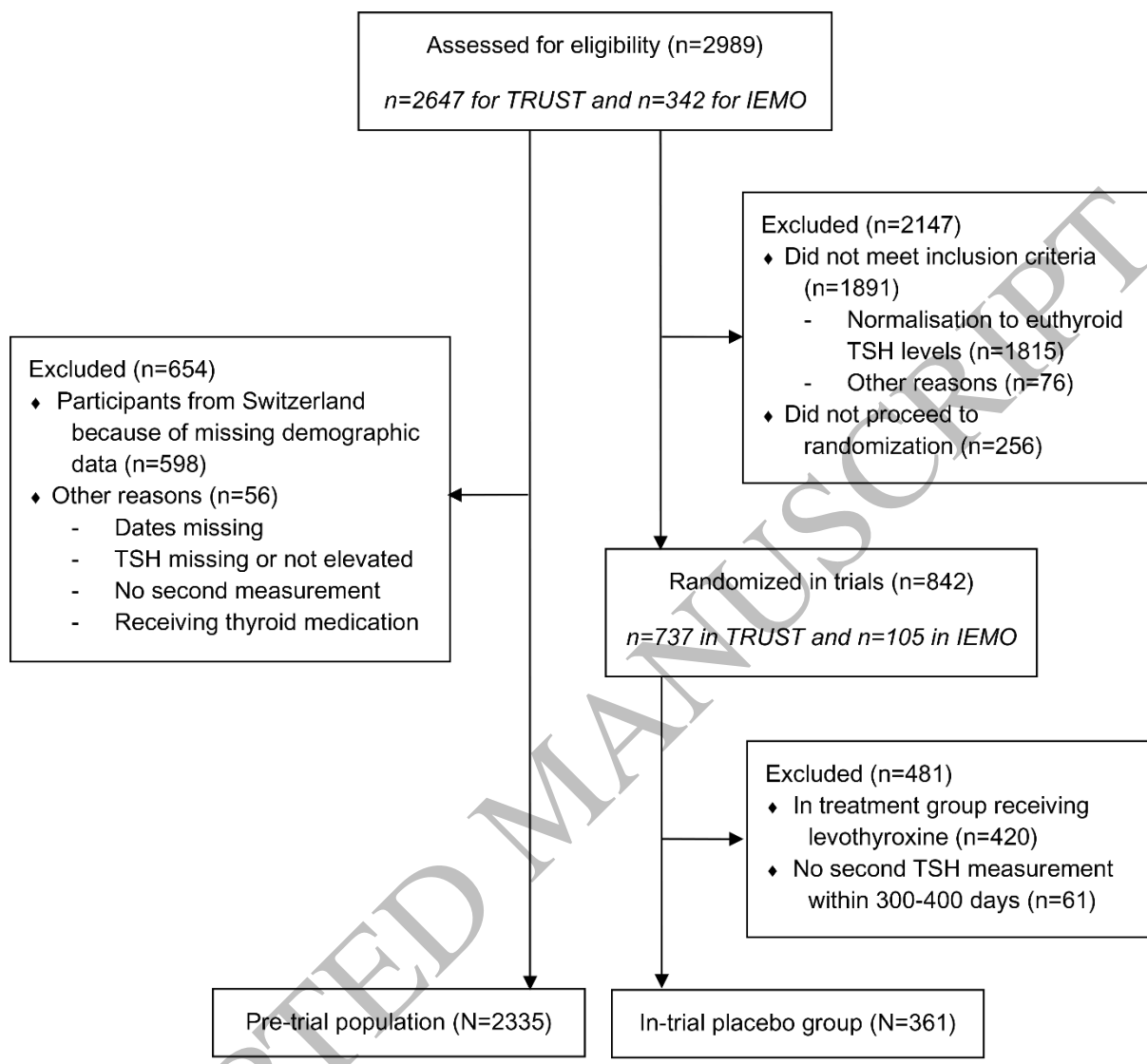
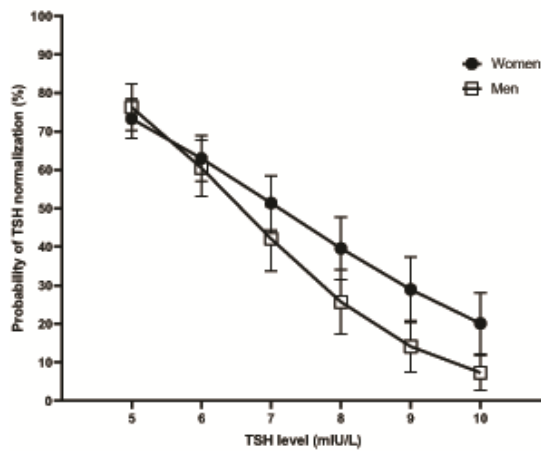


Figure 2. Flow diagram of study populations

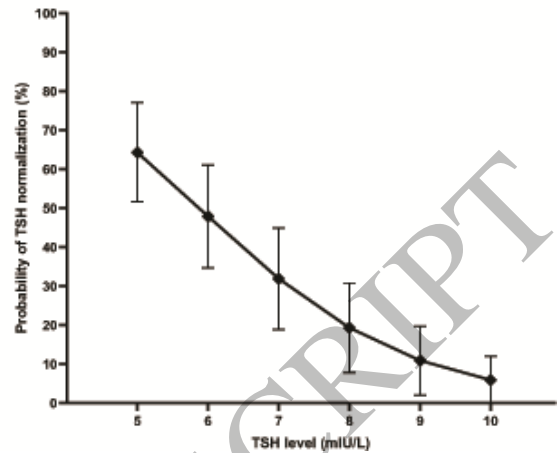
Figure 2
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A) in older adults with subclinical hypothyroidism



B) in older adults with persistent subclinical hypothyroidism



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Figure 3
159x64 mm (x DPI)

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