In the Name of God

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Incidence and Determinants of Spontaneous Normalization of Subclinical Hypothyroidism in Older Adults

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With **increasing age, TSH generally rise**, accompanied by a higher prevalence of subclinical hypothyroidism.

Several trials have shown that treatment of mild subclinical hypothyroidism in older adults does not improve clinical outcomes.

Reevaluate the reference range for TSH in older adults is necessary.

Several studies in adults have shown that subclinical hypothyroidism can spontaneously normalize.

A large group of adults aged 65 years and older with (persistent) subclinical hypothyroidism.

We combined individual participant level data from 2 randomized trials investigating the effect of levothyroxine treatment in older adults with subclinical hypothyroidism:
the Thyroid Hormone Replacement for Untreated Older Adults With Subclinical Hypothyroidism Trial (**TRUST)** and Institute for Evidence-Based Medicine in Old Age (**IEMO)** trials.

Because we were interested in spontaneous normalization, we only included the pretrial screening populations and the in-trial placebo groups of the 2 clinical trials.

Materials and Methods

Study Design

Data from 2 randomized, doubleblind, placebo-controlled clinical trials (the TRUST and the IEMO)

TRUST participants aged 65 years and older in the Netherlands, Switzerland, Ireland, and the United Kingdom between April 2013 and May 2015.

Participants for the IEMO 80-plus thyroid trial were aged 80 years and older in the Netherlands and Switzerland between May 2014 and May 2017.

Both trials shared a near-identical design and recruitment strategy.

Inclusion of pretrial population:

Participants with biochemical subclinical hypothyroidism, defined as an elevated TSH level (4.60-19.99 mIU/L) and an fT4 level within the laboratory specific reference range, 3 months to 3 years before the trial baseline were invited for a repeated measurement.

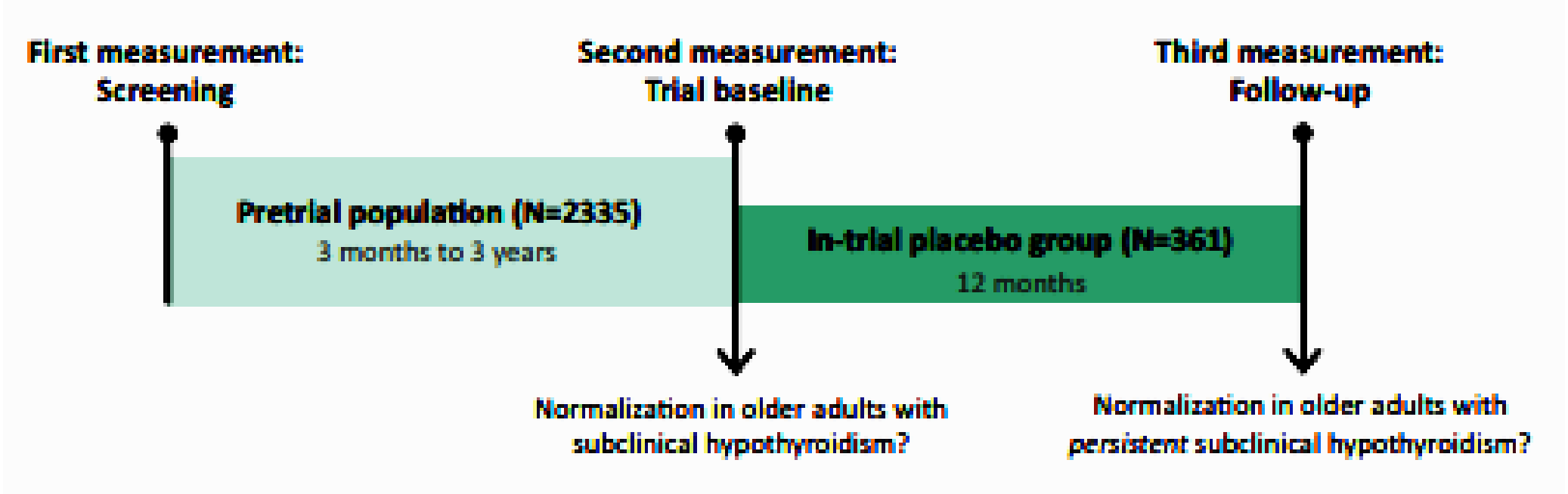
This repeated measurement was taken to assess whether they had persistent subclinical hypothyroidism. Individuals with 2 TSH measurements (the pretrial screening and the trial baseline) were included in the pretrial population.

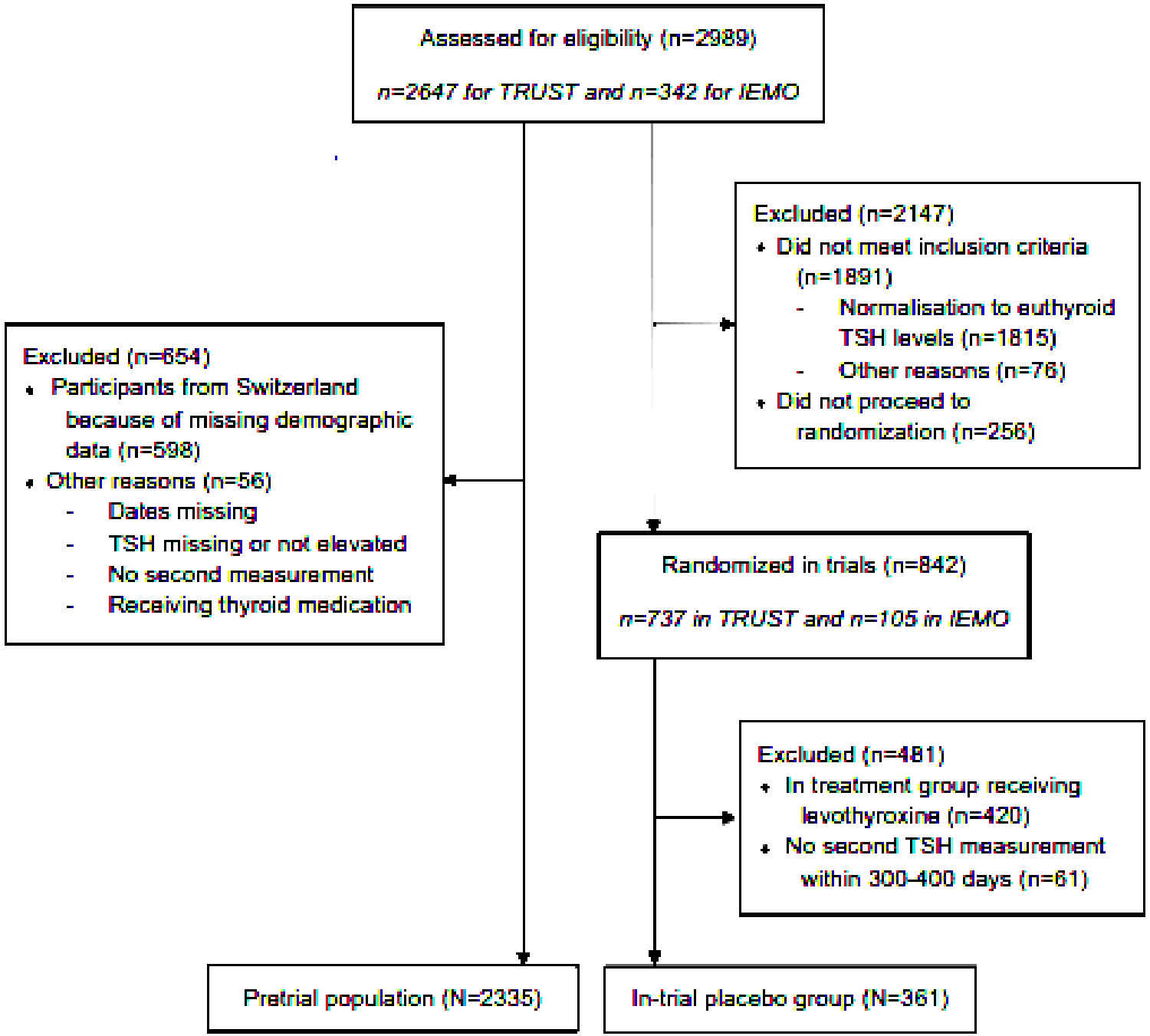
Inclusion of in-trial placebo group:

Persistent subclinical hypothyroidism at both the pretrial screening (first measurement) and at the trial baseline (second measurement).

Participants who fulfilled the inclusion criteria were randomized to receive levothyroxine treatment or placebo in the clinical trials.

For the present study, we only included the in-trial participants assigned to placebo treatment. TSH normalization was checked at the follow-up visit after 300 to 400 days (third measurement).


First measurement:
Screening
Second measurement:
Trial baseline
Third measurement:
Follow-up
Pretrial population (N=2335)
3 months to 3 years
In-trial placebo group (N=361)
12 months
Normalization in older adults with subclinical hypothyroidism?
Normalization in older adults with *persistent* subclinical hypothyroidism?


Assessed for eligibility (n=2989)
n=2647 for TRUST and n=342 for IEMO
Excluded (n=2147)
Did not meet inclusion criteria (n=1891)
Normalisation to euthyroid TSH levels (n=1815)
Other reasons (n=76)
Did not proceed to randomization (n=256)
Excluded (n=654)
Participants from Switzerland because of missing demographic data (n=598)
Other reasons (n=56)
Dates missing
TSH missing or not elevated
No second measurement
Receiving thyroid medication
Randomized in trials (n=842)
n=737 in TRUST and n=105 in IEMO
Excluded (n=481)
In treatment group receiving levothyroxine (n=420)
No second TSH measurement within 300–400 days (n=61)
Pretrial population (N=2335)
In-trial placebo group (N=361)

TSH and fT4 measurements were performed at the same clinical laboratory.

A subsample (80.1%) of the in-trial placebo group donated blood for biobanking at randomization (a few weeks after the trial baseline), which was stored centrally at −80° C to be analyzed later. In these serum samples, thyroid peroxidase antibodies (anti-TPO) were measured. The threshold for elevated anti-TPO is > 34 kU/L (detection range, 10-599.99 kU/L).

Participant Characteristics:

Pretrial population:

Determinants of interest were age, sex, TSH level at first measurement, fT4 level at first measurement, and the interval between the first and second measurements (divided into <6 months, 6-12 months, >12 months).

To investigate whether season of follow-up testing has an influence on TSH normalization, the season of the second measurement (divided into meteorological summer [1 June-31 August], autumn [1 September-30 November], winter [1 December-28/29 February], and spring [1 March-31 May]) was assessed as a determinant.

In-trial placebo:

group Determinants of interest for the in-trial placebo group were age, sex, TSH level at trial baseline, fT4 level at trial baseline, and anti-TPO positivity.

Because the interval between the trial baseline and follow-up measurements for all participants in the in-trial placebo group was between 300 to 400 days, the interval and season of testing were not included as determinants.

Statistical Analyses:

Summary statistics were estimated using median and interquartile range for continuous variables and number and percentage for categorical variables.

Logistic regression was performed with TSH normalization as the outcome using the glm function in R. Univariable models were created for the determinants of interest separately and multivariable models were created with all determinants combined.

All models were adjusted for country as fixed effect.

To visualize the probability of normalization for each unit in TSH level, probability plots were created using logistic regression models with initial TSH level as independent determinant and TSH normalization as outcome, adjusted for country (United Kingdom as reference).

For the pretrial phase, a sensitivity analysis was performed excluding the participants who had both measurements in the same season (N = 20%) to investigate the true effect of a follow-up measurement in a certain season compared to another season.

Results:

A total of 2989 older adults were identified from clinical laboratory databases and assessed for eligibility for the TRUST or IEMO trials. 2335 participants were included in the pretrial.

For the in-trial placebo group, we included participants who were randomized to placebo and had a follow-up in-trial TSH measurement in 300 to 400 days.

In total, 361 participants were included in the in-trial placebo group to investigate the incidence and determinants of spontaneous TSH normalization in older adults with persistent subclinical hypothyroidism.

Pretrial Population:

Older Adults With Subclinical Hypothyroidism (N = 2335) Characteristics of study population The median (interquartile range[IQR]) age of the pretrial population was 72.9 (68.0-79.3) years and 60.7% of the participants were female.
Median (IQR) levels of TSH and fT4 at the first measurement (screening) were 5.40 (4.91-6.31) mIU/L and 13.6 (12.3-15.0) pmol/L, respectively.
Most participants had their second measurement (trial baseline) in summer (32.7%) or autumn (31.5%) and were included in The Netherlands (50.3%) cohort.
TSH levels normalized in 1419 (60.8%) participants in a median follow-up of 344 (IQR, 207-594) days.

Table 1. Characteristics of older adults with subclinical hypothyroidism

Characteristic	Pretrial population (N = 2335)
Age, y	72.9 (68.0-79.3)
Age ≥80 y, 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)[a]	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 mo, n (%)	465 (19.9)
6-12 mo, n (%)	778 (33.3)
>12 mo, 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)

Values shown are median (interquartile range) unless indicated otherwise.
Abbreviation: fT4, free T4.
[a]First fT4 measurement was missing for n = 10.

Lower age, female sex, lower screening TSH level, higher normal screening fT4 level, and a second measurement in summer (compared with winter: were independently associated with a higher chance of TSH normalization.

In the pretrial population, there was an interaction between TSH and sex showing normalization tended to decrease for men.

An interval between measurements of more than 12 months was associated with TSH normalization, but this was not statistically significant in the multivariable model.

When restricted to participants having their second measurement in another season than the first (N = 1866), having the second measurement in summer was still independently associated with a higher chance of normalization (compared with winter).

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

Characteristic	Univariable model		Multivariable model	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (per year)	.98 (.97-.99)	<.001	.98 (.97-.99)	.007
Female sex	1.39 (1.16-1.66)	<.001	1.39 (1.15-1.69)	<.001
TSH level (per unit mIU/L)	.56 (.52-.61)	<.001	.57 (.52-.62)	<.001
fT4 level (per unit pmol/L)	1.08 (1.04-1.13)	<.001	1.06 (1.01-1.11)	.03
Interval between measurements				
<6 mo	1 (reference)		1 (reference)	
6-12 mo	1.05 (.81-1.35)	.73	1.02 (.78-1.34)	.87
>12 mo	1.40 (1.07-1.82)	.01	1.30 (.97-1.72)	.07
Season second measurement				
Summer	1 (reference)		1 (reference)	
Autumn	.74 (.59-.93)	.008	.72 (.57-.92)	.008
Winter	.62 (.47-.82)	<.001	.59 (.44-.79)	<.001
Spring	.73 (.57-.92)	.009	.73 (.56-.95)	.02

Odds ratios (OR) with 95% CIs 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.
Abbreviation: OR, odds ratio.

In-trial Placebo Group:

Older Adults With Persistent Subclinical Hypothyroidism (N = 361) Characteristics of study population The median (IQR) age of the in-trial placebo group was 75.1 (69.6-81.4) years and 51.8% of the participants were female. Median (IQR) levels of TSH and fT4 at the trial baseline measurement were 5.75 (5.10-6.86) mIU/L and 13.4 (12.1-14.7) pmol/L, respectively.

One quarter (25.3%) of the participants had antibodies to TPO. Normalization of persistent subclinical hypothyroidism From a total of 361 participants, in 144 (39.9%) participants, TSH levels normalized in a median follow-up of 362 (IQR, 345-370) days.

Table 3. Characteristics of older adults with persistent subclinical hypothyroidism

Characteristic	In-trial placebo group (N = 361)
Age, y	75.1 (69.6-81.4)
Age ≥ 80 y, 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 (%)[a]	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)

Values shown are median (interquartile range) unless indicated otherwise.
Abbreviations: fT4, free T4; anti-TPO, thyroid peroxidase antibodies.
[a]Information on TPO antibodies was missing for n = 72.

Lower age, female sex, lower trial baseline TSH level, higher normal trial baseline fT4 levels, and the absence of TPO antibodies were independently associated with a higher chance of normalization.

TSH normalization decreases for each unit in TSH level from 5 to 10 mIU/L in both populations.

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

Characteristic	Univariable model		Multivariable model	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (per year)	.99 (.96-1.02)	.59	.96 (.92-1.00)	.05
Female sex	1.23 (.79-1.92)	.36	1.80 (1.01-3.23)	.05
TSH level at trial baseline (per unit mIU/L)	.51 (.40-.63)	<.001	.52 (.38-.67)	<.001
fT4 level at trial baseline (per unit pmol/L)	1.32 (1.17-1.50)	<.001	1.22 (1.05-1.44)	.01
Anti-TPO positivity[x]	.38 (.19-.72)	.004	.36 (.17-.77)	.007

Odds ratios (OR) with 95% CIs 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. [x]Information on TPO antibodies was missing for n = 72.
Abbreviation: anti-TPO, thyroid peroxidase antibodies.

As an example, older men with subclinical hypothyroidism with a screening TSH level of 5 mIU/L have a 76.3% chance of normalization, whereas the chance becomes 7.3% when having a screening TSH level of 10 mIU/L.

For older women, the chance of TSH normalization decreases from 73.3% at 5 mIU/L to 20.1% at 10 mIU/L.

Older adults who already had 2 elevated TSH measurements more than 3 months apart still have a 64.3% chance to normalize when their second (trial baseline) TSH level is 5 mIU/L.

When the second (trial baseline) TSH level is 10 mIU/L in older adults with persistent subclinical hypothyroidism, then the chance of normalization is only 5.9%.

Discussion:

Older adults with subclinical hypothyroidism based on at least 1 elevated TSH, 60.8% TSH had returned to the normal range without intervention after a median follow-up of 1 year.

Subsequently, TSH levels had still normalized after 1 year in 39.9% of older adults with persistent subclinical hypothyroidism, defined as at least 2 elevated TSH measurements more than 3 months apart.

Younger age, female sex, lower initial TSH level, higher normal initial fT4 level, the absence of TPO antibodies, and a second measurement in summer were independent determinants for TSH normalization.

The large proportions of normalization of TSH levels in older adults with subclinical hypothyroidism after approximately 1 year in the present study are in line with percentage of 35% to 70% during a follow-up of 0.5 to 5 years.

In some studies in adults aged 55 years and older, a lower initial TSH levels was found to be the strongest determinant for normalization. But it can also be reasoned that mildly elevated TSH levels normalize easier than higher levels, especially considering **normal fluctuations** in TSH levels.

These fluctuations within an individual over time are caused by both internal and external factors, such as pulsatile secretion, the biological clock, illness, and medication use.

The association between high normal fT4 levels and TSH normalization was also found by Díez and Iglesias, and was expected given the **negative feedback** of thyroid hormones on TSH secretion.

TPO antibodies generally associate with higher TSH levels, which might explain anti-TPO negativity as a determinant for normalization as confirmed by some studies, but not by all.

Although older women are generally more affected by (subclinical) hypothyroidism and tend to have higher TSH than older men.

in our study that women have a higher probability for normalization than men, especially at a higher TSH level.

TSH levels generally rise with age, which might explain between older age and a lower chance of TSH normalization.

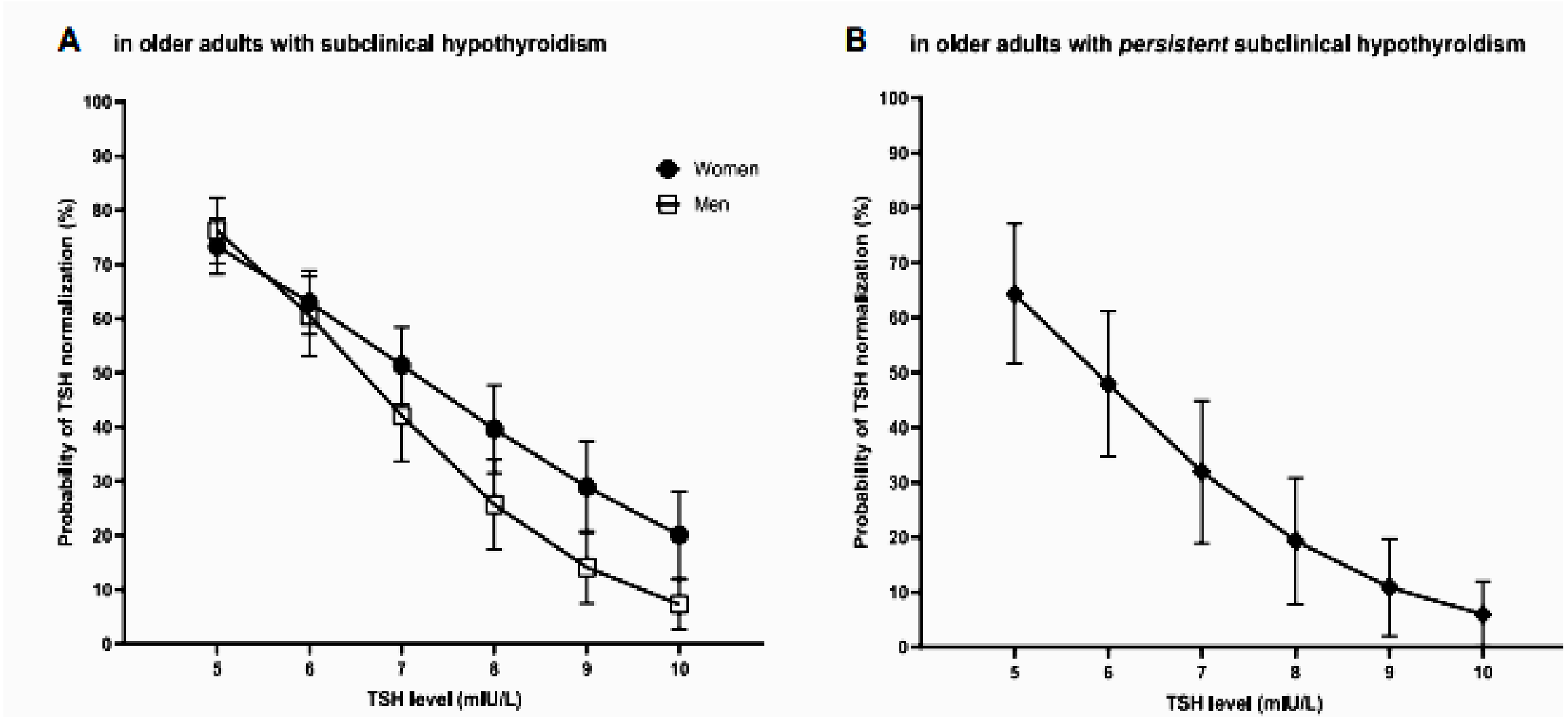


Figure 3. Probability of TSH normalization (95% CI) based on initial TSH level in older adults with (persistent) subclinical hypothyroidism. (A) Probability of normalization stratified for sex in the pretrial population (N = 2335), which includes older adults with subclinical hypothyroidism. (B) Probability of normalization in the in-trial placebo group (N = 361), which includes older adults with persistent subclinical hypothyroidism, defined as having at least 2 measurements of elevated TSH levels ≥3 months apart.

However, in 3 studies with older adults with subclinical hypothyroidism without known previous thyroid disease, no relation was observed between sex, age, and TSH normalization.

A second measurement in summer was associated with increase normalization. TSH levels highest levels in winter, which is probably caused by changes in environmental temperature.

The present study is a large, multicenter study. Strengths of this study are that changes in TSH levels were observed over a long follow-up time ranging from 3 months to 4 years, without intervention and we compared TSH normalization after at least 1 elevated TSH measurement and after at least 2 elevated TSH measurements.

Measurements follow real-world practice because were performed in routine clinical care, thus preventing potential degradation of TSH by long term sample storage and/or freeze/thaw cycles.
Although biochemical assays were performed in the same clinical centers for nearly all participants.

Unfortunately, time of blood sampling was not recorded.

Selection bias could play a role in the pretrial screening population because individuals who became overt hypothyroid or started with thyroid medication for other reasons were not enrolled in the study.

We were not able to investigate the incidence of the progression to overt hypothyroidism in the pretrial screening population. Almost all older subjects had mild subclinical hypothyroidism (TSH < 10 mIU/ L) in our study.

In this study, we have demonstrated that in a large proportion of older adults with mild subclinical hypothyroidism, TSH levels spontaneously normalized in a median follow-up of 1 year, even after 2 consecutive measurements (≥3 months apart) of elevated TSH levels. These results have clinical relevance.

Current guidelines recommend that a single measurement of elevated serum TSH, with fT4 within reference range, should be confirmed by a repeat measurement of both serum TSH and fT4, along with thyroid peroxidase antibodies, after a 2- to 3-month interval.

With age, the TSH distribution shift toward a higher level, and the 97.5th percentile of the TSH distribution was shown to be 7.5 mU/L in subjects aged 80 years and older.

International guidelines differ in their recommendations on the TSH threshold at which treatment of subclinical hypothyroidism should be considered in older adults.

Once levothyroxine treatment is initiated, it is often continued lifelong.
Based on the observation that with age, the TSH distribution shifts toward a higher level, it has been proposed to extend the upper limit of the TSH reference to 7 mU/L for people aged 80 years or older.

Although increasing the upper reference limit will likely reduce unnecessary levothyroxine prescribing for older people, our results support applying more continuous age-related reference ranges, which may be modified by other factors such as sex and season.

Moreover, based on the high incidence of spontaneous normalization of TSH, a third measurement may be recommended before initiation of treatment. The frequency of the diagnosis subclinical hypothyroidism can be reduced in older adults.

This could contribute to a reduction in health care costs, treatment burden, and risk of overtreatment.

Levothyroxine is among the most frequently prescribed drugs. Although general practitioner prescription practices vary widely between countries, many older adults have initiated levothyroxine treatment based on a mildly elevated TSH.
Moreover, in clinical practice, treatment has often been started after a single measurement of TSH.

A recent meta-analysis indicated that deprescribing levothyroxine could be successful for carefully selected patients, although the quality of available evidence was considered low.

This underscores the need for future high-quality studies to assess the effects of safely withholding levothyroxine treatment in older adults who initiated levothyroxine treatment based on a diagnosis of mild subclinical hypothyroidism on relevant patient outcomes.

THANKS FOR YOUR ATTENTION