The Journal of Clinical Endocrinology & Metabolism, 2024, **109**, e1167–e1174
https://doi.org/10.1210/clinem/dgad623
Advance access publication 20 October 2023
Clinical Research Article

ENDOCRINE SOCIETY

OXFORD

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

Evie van der Spoel,[1] Nicolien A. van Vliet,[1] Rosalinde K.E. Poortvliet,[2] Robert S. Du Puy,[2] Wendy P.J. den Elzen,[3] Terence J. Quinn,[4] David J. Stott,[4] Naveed Sattar,[5] Patricia M. Kearney,[6] Manuel R. Blum,[7,8] Heba Alwan,[8,9] Nicolas Rodondi,[8,9] Tinh-Hai Collet,[10,11] Rudi G.J. Westendorp,[12,13] Bart E. Ballieux,[14] J. Wouter Jukema,[15,16] Olaf M. Dekkers,[17,18] Jacobijn Gussekloo,[1,2] Simon P. Mooijaart,[1] and Diana van Heemst[1]

With increasing age, circulating levels of TSH generally rise, accompanied by a higher prevalence of subclinical hypothyroidism . Subclinical hypothyroidism is defined as an elevated TSH level while the serum free T4 (fT4) concentration is within the normal range .

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

Therefore, it has been suggested to reevaluate the reference range for TSH in older adults .

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

However, it is not known what the most important determinants are for spontaneous TSH normalization in older adults.

Enhanced understanding of the natural history and factors contributing to normalization may help clinical decision making on the follow-up strategy.

In this longitudinal study, we aimed to investigate the incidence of spontaneous normalization of TSH levels and identify determinants of normalization in 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 .

Materials and Methods

The present study pooled data from 2 randomized, doubleblind, placebo-controlled parallel-group clinical trials investigating the effect of levothyroxine treatment for older adults with subclinical hypothyroidism: the TRUST and the IEMO 80-plus thyroid trial .

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

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

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

Trial protocols were approved by the relevant ethics committees and regulatory authorities in all the countries involved in the trials.

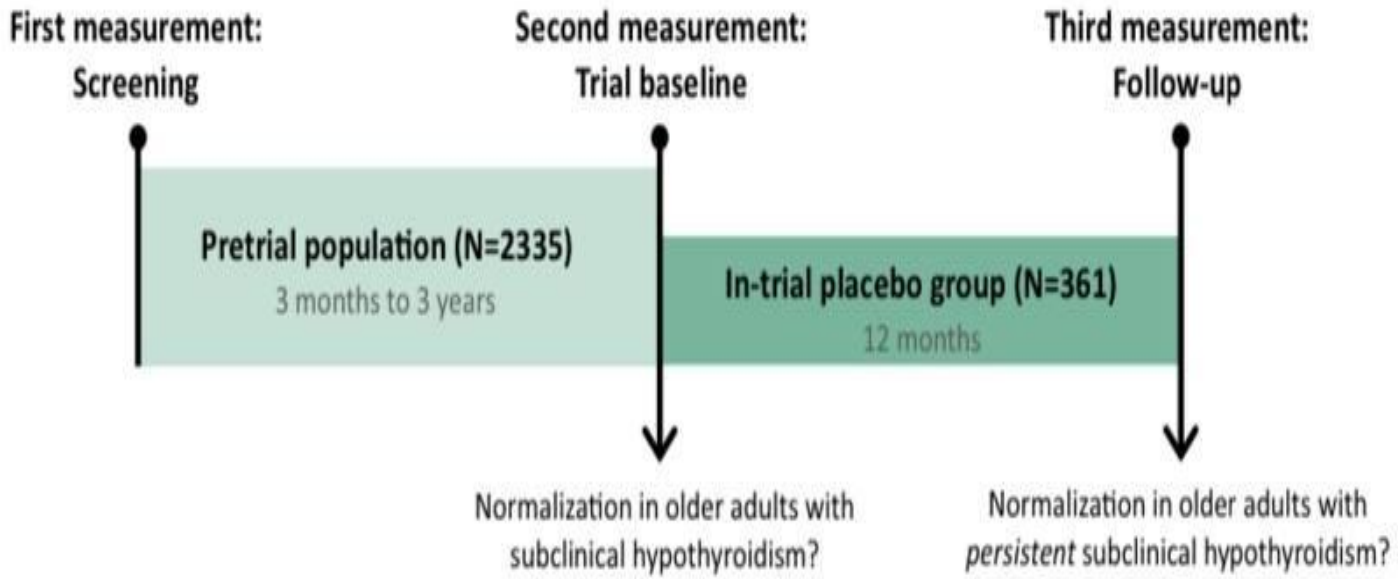

Figure 1. Timeline of the study. The pretrial population consisted of older adults with ≥1 elevated TSH measurement (≥4.60 mIU/L) and an fT4 level within the laboratory-specific reference range, during the previous 3 months to 3 years (screening). The second measurement was at the trial baseline to assess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

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

Individuals with 2 TSH measurements (the pretrial screening and the trial baseline) were included in the pretrial population.

Participants recruited during the screening period in Switzerland were excluded because Swiss demographic data were only registered centrally for those who were randomized.

Participants with persistent subclinical hypothyroidism 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 intrial participants assigned to placebo treatment with mock titration. TSH normalization was checked at the follow-up visit after 300 to 400 days (third measurement).

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.

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.

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 general practice records and assessed for eligibility for the TRUST or IEMO trials. Of these, **2335 participants** were included in the pretrial population to investigate the incidence and determinants of spontaneous TSH normalization in older adults with at least 1 measurement of biochemical subclinical hypothyroidism.

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 (defined as at least 2 measurement of elevated TSH levels with normal fT4 levels more than 3 months apart.

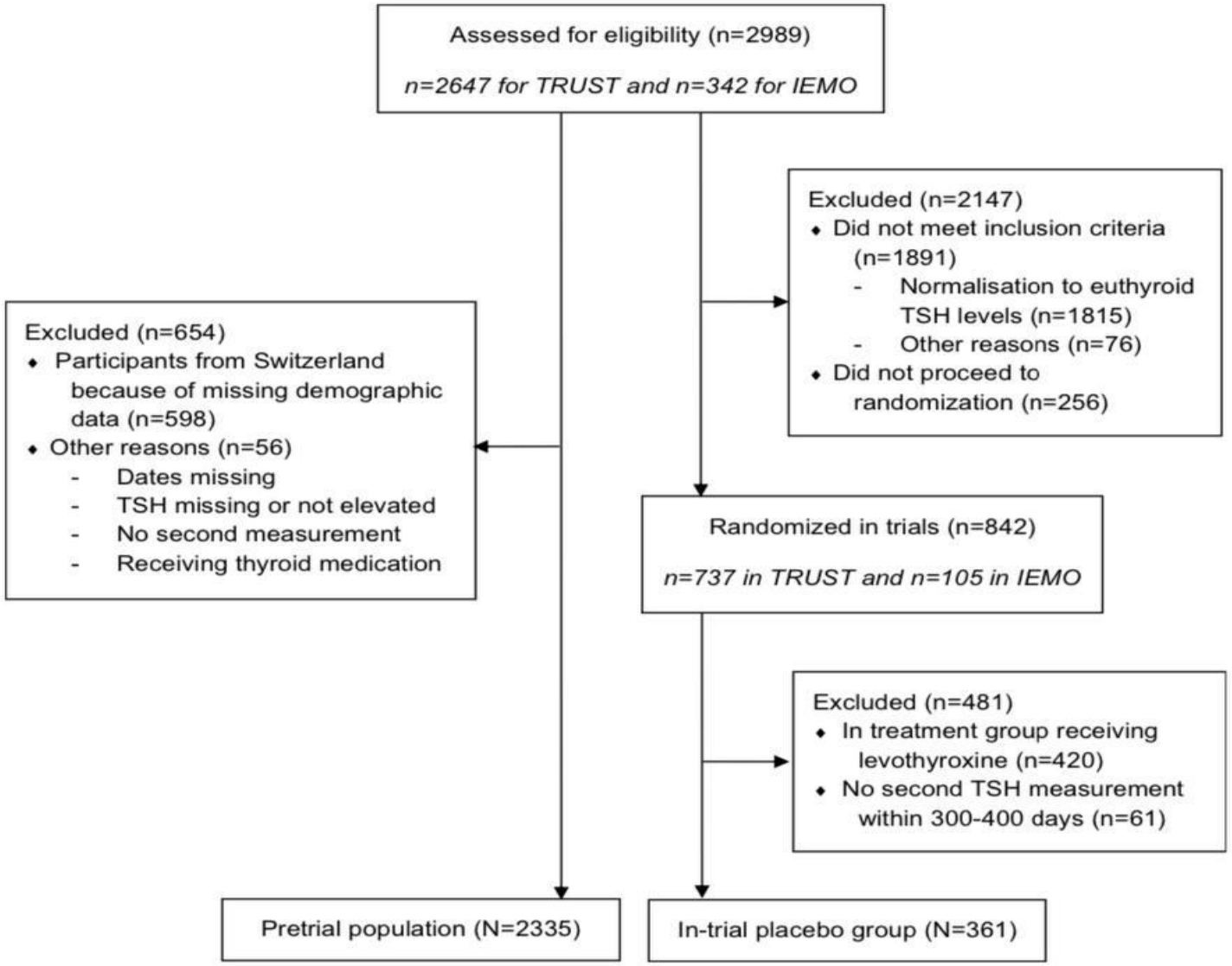

Figure 2. Flow diagram of study populations.

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 (Table 1). 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.

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.

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.

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: OR, 0.55 [95% CI, .39-.78], P < .001), data not shown.

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.

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. Lower age (OR, 0.96 [95% CI, .92-1.00], P = .05), female sex (OR, 1.80 [95% CI, 1.01-3.23], P = .05), lower trial baseline TSH level (OR, 0.52 [95% CI, .38-.67], P < .001), higher normal trial baseline fT4 levels (OR, 1.22 [95% CI, 1.05-1.44], P = .01), and the absence of TPO antibodies (OR, 0.36 [95% CI, .17-.77], P = .007) were independently associated with a higher chance of normalization .

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[×]	.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. [×]Information on TPO antibodies was missing for n = 72.
Abbreviation: anti-TPO, thyroid peroxidase antibodies.

visualizes that the probability of TSH normalization decreases for each unit in TSH level from 5 to 10 mIU/L in both populations. In the pretrial population, there was an interaction between TSH screening level and sex (P = .004) showing that the probability of normalization tended to decrease more for men than for women.

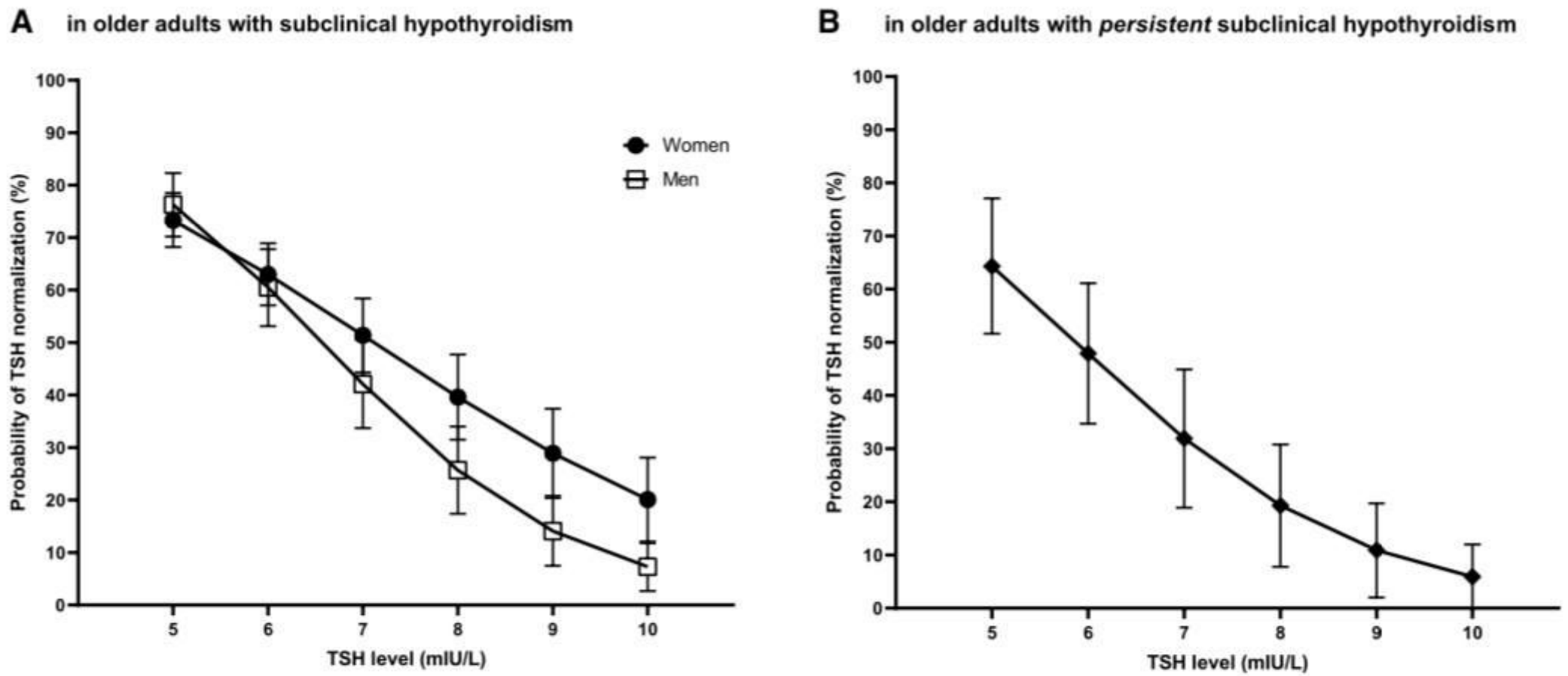

Figure 3. Probability of TSH normalization (95% CI) based on initial TSH level in older adults with (persistent) subclinical hypothyroidism. (A) Probability of normalization stratified for sex in the pretrial population (N = 2335), which includes older adults with subclinical hypothyroidism. (B) Probability 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.

As an example, older men with biochemical subclinical hypothyroidism with a screening TSH level of 5 mIU/L have a 76.3% (95% CI, 70.2-82.3) chance of normalization, whereas the chance becomes 7.3% (95% CI, 2.7-11.8) when having a screening TSH level of 10 mIU/L. For older women, the chance of TSH normalization decreases from 73.3% (95% CI, 68.2-78.5) at 5 mIU/L to 20.1% (95% CI, 12.1-28.1) at 10 mIU/L.

However, 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% (95% CI, .0-12.0).

Discussion

In 60.8% of the older adults with biochemical subclinical hypothyroidism based on at least 1 elevated TSH measurement, TSH levels 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.

In those studies, a lower initial TSH levels was found to be the strongest determinant for normalization .

A lower initial TSH level as a determinant for TSH normalization can be statistically explained by regression to the mean, 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.

TPO antibodies generally associate with higher TSH levels .

which might explain anti-TPO negativity as a determinant for normalization as confirmed by 2 studies , but not by others

Although older women are generally more affected by (subclinical) hypothyroidism and tend to have higher TSH levels than older men , we found 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 , so older age coincides with higher TSH levels, which might explain the association found between older age and a lower chance of TSH normalization.

Howover,with older adults with subclinical hypothyroidism without known previous thyroid disease, no relation was observed between sex, age, and TSH normalization. TSH levels are subject to **change of season with highest levels in winter** , which is probably caused by changes in environmental temperature.

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.

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 .

Moreover, based on the high incidence of spontaneous normalization of TSH levels in a large proportion of older adults with subclinical hypothyroidism (also after confirmation by repeat measurement), a third measurement may be recommended before considering initiation of treatment. Based on such an approach, the frequency of the diagnosis subclinical hypothyroidism can likely be reduced in older adults. This could potentially contribute to a reduction in health care costs, treatment burden, and risk of overtreatment.


Thank you