Supplementary Online Content

Mooijaart S, Du Puy RS, Stott DJ, et al. Association between levothyroxine treatment and thyroid-related symptoms among adults aged 80 years and older with subclinical hypothyroidism [published online October 30, 2019. JAMA. doi:10.1001/jama.2019.17274

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplemental materials

Contents

Supplemental table S1. Characteristics of participants aged 80 years and over at baseline for the IEMO 80-plus Thyroid trial and TRUST Thyroid trial participants separately

	Levothyroxine (N=112)			**Placebo (N=139)**	
Characteristic	**IEMO 80-plus (N=52)**	**TRUST 80-plus (N=60)**		**IEMO 80-plus (N=53)**	**TRUST 80-plus (N=86)**
Age (yrs)					
- Mean (SD)	84.5 (3.6)	83.6 (3.1)		85.8 (3.9)	84.5 (3.6)
- Range	80.0 – 97.1	80.2 – 93.0		80.4 – 96.7	80.1 – 93.4
Sex					
- Male	26 (50.0%)	34 (56.7%)		27 (50.9%)	46 (53.5%)
- Female	26 (50.0%)	26 (43.3%)		26 (49.1%)	40 (46.5%)
Self-identified race					
- White	52 (100.0%)	60 (100.0%)		52 (98.1%)	85 (98.8%)
- Asian	0	0		1 (1.9%)	0
- Black	0	0		0	0
- Other[a]	0	0		0	1 (1.2%)
Living independently	49 (94.2%)	57 (95.0%)		50 (94.3%)	79 (91.9%)
Previous medical conditions and clinical descriptors					
Hypertension	27 (51.9%)	33 (55.0%)		24 (45.3%)	39 (45.9%)
Ischemic heart disease	13 (25.0%)	10 (16.7%)		12 (22.6%)	26 (30.2%)
Atrial fibrillation	13 (25.0%)	11 (18.6%)		9 (17.0%)	15 (17.4%)
Osteoporosis	9 (17.3%)	7 (12.1%)		11 (20.8%)	12 (14.0%)
Diabetes mellitus	7 (13.5%)	7 (11.7%)		3 (5.7%)	14 (16.5%)
Current smoking	3 (5.8%)	3 (5.0%)		2 (3.8%)	4 (4.7%)
Concomitant medicines	49 (94.2%)	57 (95.0%)		50 (94.3%)	84 (97.7%)
No. of concomitant medications (IQR)[b]	5.0 (3.0, 7.0)	5.0 (3.0, 7.0)		4.0 (2.0, 6.0)	4.5 (3.0, 7.0)
Mini-mental state examination score (IQR)[c]	29.0 (27.0, 30.0)	28.0 (27.0, 29.0)		28.0 (27.0, 29.0)	29.0 (27.0, 29.0)
Weight <50kg	1 (1.9%)	0 (0.0%)		0 (0.0%)	1 (1.2%)
Laboratory results					
Thyrotropin (mIU/L)[d]					
- Mean (SD)	6.4 (1.7)	6.5 (1.9)		6.2 (1.6)	6.3 (2.0)
- Median (IQR)	5.7 (5.0, 7.2)	5.9 (5.1, 7.1)		5.7 (5.1, 7.0)	5.7 (5.3, 6.5)
- Range	4.6 – 11.5	4.6 – 12.5		4.6 – 12.0	4.6 – 17.6
fT4 (pmol/liter)[e]	14.2 (2.0)	13.6 (2.1)		14.0 (2.5)	13.7 (2.0)
Outcome measures					
ThyPro - Hypothyroid Symptoms score[f]					
- Mean (SD)	21.6 (19.2)	20.1 (19.2)		20.5 (21.3)	19.3 (18.1)
- Median (IQR)	18.8 (6.2, 37.5)	18.8 (6.2, 26.6)		12.5 (6.2, 31.2)	18.8 (6.2, 31.2)
ThyPro - Tiredness score[f]					
- Mean (SD)	24.1 (20.8)	26.4 (21.2)		24.5 (18.5)	26.4 (20.2)
- Median (IQR)	20.1 (7.1, 35.7)	21.4 (12.1, 39.3)		17.9 (10.7, 35.7)	21.4 (11.2, 35.7)
Euroqol-5D[g]	0.772 (0.220)	0.776 (0.226)		0.765 (0.275)	0.835 (0.163)
Euroqol VAS[h]	75.3 (14.3)	74.4 (15.4)		73.1 (11.2)	74.3 (16.1)
Hand-grip strength (kg)[i]	25.4 (10.8)	24.3 (7.2)		26.1 (9.3)	23.3 (10.2)
Letter-digit coding test[j]	20.3 (6.9)	22.6 (7.2)		20.6 (7.4)	21.7 (8.2)

Blood pressure					
- Systolic (mmHg)	145.8 (21.8)	142.8 (19.1)		153.3 (22.0)	140.5 (18.4)
- Diastolic (mmHg)	72.2 (11.2)	69.5 (12.2)		73.6 (13.2)	71.0 (11.0)
Body mass index (kg/m^2)	27.7 (4.7)	27.8 (4.3)		27.5 (4.1)	27.4 (3.8)
Waist circumference (cm)	98.3 (11.8)	99.9 (12.5)		97.7 (11.9)	98.2 (10.5)
Barthel Index (IQR)[k]	20.0 (19.0, 20.0)	20.0 (19.0, 20.0)		20.0 (19.0, 20.0)	20.0 (19.0, 20.0)
Instrumental Activities of Daily Living (IQR)[l]	14.0 (13.0, 14.0)	14.0 (12.8, 14.0)		14.0 (12.0, 14.0)	14.0 (13.0, 14.0)

Results were reported as mean (standard deviation, SD) or median (inter quartile range, IQR) for continuous variables, and as n (%) for proportions. Abbreviations: fT4, free thyroxine; VAS, Visual Analog Scale.

[a]Participants selected race from 'white', 'asian', 'black' and 5 other pre-specified options reflecting most common race groups in the study site countries

[b]Number of concomitant medications used, both prescribed or over-the-counter available, counted as number of distinct ATC codes excluding emollients and protectives, antiseptics and disinfectants, topical products for joint and muscular pain, nasal preparations, ophthalmologicals or otologicals.

[c]range 0-30, higher scores indicate less cognitive impairment

[d]Inclusion criterium reference range 4.6 - 19.99 mIU/L

[e]Inclusion criterium reference ranges were lab and method specific (all reference ranges within 9 and 26 pmol/L), however repeated within-participant measurements were solely performed using the same method for that individual to exclude any bias due to different assays. SI conversion of fT4 pmol/l to ng/dl, divide by 12.87.

[f]Range 0-100, higher scores represent more symptoms or severity of disease

[g]Range 0.50-1.00, higher scores indicate a better quality of life

[h]Range 0-100, higher scores indicate better health

[i]Higher scores indicate better muscle strength

[j] Number of digits coded within 90 seconds. No upper limit, higher scores indicate better executive cognitive function

[k]Range 0-20, higher scores indicate higher independence in activities of daily living

[l]Range 5-30, higher scores indicate more impairment in instrumental activities of daily living

Supplemental table S2. Characteristics of participants aged 80 years and over at baseline that were included in the primary efficacy analysis

	Total (N=212)	
Characteristic	**Levothyroxine (n=90)**	**Placebo (n=122)**
Age (yrs)		
- Mean (SD)	84.1 (3.4)	84.9 (3.7)
- Range	80.0 – 97.1	80.1 – 96.7
Sex		
- Male	49 (54.4%)	63 (51.6%)
- Female	41 (45.6%)	59 (48.4%)
Self-identified race		
- White	90 (100.0%)	120 (98.4%)
- Asian	0 (0.0%)	1 (0.8%)
- Black	0 (0.0%)	0 (0.0%)
- Other[a]	0 (0.0%)	1 (0.8%)
Living independently	85 (94.4%)	113 (92.6%)
Previous medical conditions		
and clinical descriptors		
Hypertension	48 (53.3%)	55 (45.5%)
Ischemic heart disease	20 (22.2%)	33 (27.0%)
Atrial fibrillation	15 (16.7%)	22 (18.0%)
Osteoporosis	14 (15.9%)	20 (16.4%)
Diabetes mellitus	11 (12.2%)	15 (12.4%)
Current smoking	5 (5.6%)	5 (4.1%)
Concomitant medicines	84 (93.3%)	117 (93.3%)
No. of concomitant medications (IQR)[b]	5.0 (3.0, 7.0)	4.0 (3.0, 6.8)
Mini-mental state examination score (IQR)[c]	29.0 (27.0, 30.0)	28.0 (27.0, 29.0)
Weight <50kg	1 (1.1%)	0 (0.0%)
Laboratory results		
Thyrotropin (mIU/L)[d]		
- Mean (SD)	6.5 (1.8)	6.2 (1.5)
- Median (IQR)	5.8 (5.1, 7.4)	5.7 (5.2, 6.6)
- Range	4.6 – 11.9	4.6 – 12.0
fT4 (pmol/liter)[e]	13.8 (2.0)	13.8 (2.1)
Outcome measures		
ThyPro - Hypothyroid Symptoms score[f]		
- Mean (SD)	21.7 (19.5)	19.8 (19.6)
- Median (IQR)	18.8 (6.2, 35.9)	12.5 (6.2, 31.2)
ThyPro - Tiredness score[f]		
- Mean (SD)	25.2 (21.5)	25.1 (19.5)
- Median (IQR)	20.1 (7.1, 35.7)	17.9 (10.7, 35.7)
Euroqol-5D[g]	0.8 (0.2)	0.8 (0.2)
Euroqol VAS[h]	75.3 (14.6)	74.0 (14.3)
Hand-grip strength (kg)[i]	25.1 (9.4)	24.8 (10.0)

Letter-digit coding test[j]	21.9 (7.1)	21.8 (7.7)
Blood pressure		
- Systolic (mmHg)	144.4 (19.4)	146.2 (20.7)
- Diastolic (mmHg)	71.3 (11.8)	72.3 (12.3)
Body mass index (kg/m^2)	27.7 (4.4)	27.5 (3.9)
Waist circumference (cm)	99.0 (11.6)	98.0 (10.9)
Barthel Index (IQR)[k]	20.0 (19.0, 20.0)	20.0 (19.0, 20.0)
Instrumental Activities of Daily Living (IQR)[l]	14.0 (13.0, 14.0)	14.0 (13.0, 14.0)

Results were reported as mean (standard deviation, SD) or median (inter quartile range, IQR) for continuous variables, and as n (%) for proportions. Abbreviations: fT4, free thyroxine; VAS, Visual Analog Scale.

[a]Participants selected race from 'white', 'asian', 'black' and 5 other pre-specified options reflecting most common race groups in the study site countries

[b]Number of concomitant medications used, both prescribed or over-the-counter available, counted as number of distinct ATC codes excluding emollients and protectives, antiseptics and disinfectants, topical products for joint and muscular pain, nasal preparations, ophthalmologicals or otologicals.

[c]range 0-30, higher scores indicate less cognitive impairment

[d]Inclusion criterium reference range 4.6 - 19.99 mIU/L

[e]Inclusion criterium reference ranges were lab and method specific (all reference ranges within 9 and 26 pmol/L), however repeated within-participant measurements were solely performed using the same method for that individual to exclude any bias due to different assays. SI conversion of fT4 pmol/l to ng/dl, divide by 12.87.

[f]Range 0-100, higher scores represent more symptoms or severity of disease

[g]Range 0.50-1.00, higher scores indicate a better quality of life. Average in general population for Hhypothyroidism Symptoms score is 14 and for Ttiredness score 35.

gRange 0.50-1.00, higher scores indicate a better quality of life

[h]Range 0-100, higher scores indicate better health

[i]Higher scores indicate better muscle strength

[j]Number of digits coded within 90 seconds. No upper limit, higher scores indicate better executive cognitive function

[k]Range 0-20, higher scores indicate higher independence in activities of daily living

[l]Range 5-30, higher scores indicate more impairment in instrumental activities of daily living. Five means functionally completely independent.

Supplemental table S3. Outcomes at 12 months and end of study for participants of the IEMO 80-plus Thyroid trial and TRUST Thyroid trial, with subclinical hypothyroidism aged 80 years and over, separately

	Baseline					At 12 months								
	IEMO 80-plus			TRUST 80-plus		IEMO 80-plus					TRUST 80-plus			
	Levothyroxine	Placebo		Levothyroxine	Placebo	Levothyroxine	Placebo	Adjusted difference[a]	p-value		Levothyroxine	Placebo	Adjusted Difference[a]	p-value
Variables	(N=45)	(N=46)		(N=45)	(N=70)	(N=45)	(N=46)	(95% CI)			(N=45)	(N=70)	(95% CI)	
Co-primary outcomes														
ThyPro Hypothyroid Symptoms score[b]	23.1 (19.8)	22.1 (21.7)		20.4 (19.4)	18.2 (18.1)	17.2 (16.7)	16.1 (18.4)	0.69 (-5.43, 6.80)	0.82		21.4 (19.6)	18.3 (18.0)	1.27 (-3.95, 6.49)	0.63
ThyPro Tiredness score[b]	23.7 (21.4)	23.3 (18.9)		26.8 (21.7)	26.3 (19.9)	25.9 (20.7)	26.4 (22.1)	-0.78 (-8.26, 6.70)	0.84		30.6 (19.2)	30.2 (18.3)	-0.66 (-6.20, 4.89)	0.82
Pre-specified secondary outcomes														
Thyrotropin (mIU/L)	6.45 (1.75)	6.28 (1.66)		6.55 (1.87)	6.15 (1.36)	3.76 (1.67)	5.88 (2.66)	-2.23 (-3.07, -1.40)	<0.001		3.61 (1.96)	5.23 (1.84)	-1.75 (-2.45, -1.05)	<0.001
median (IQR)	5.70 (5.20, 7.40)	5.66 (5.08, 7.00)		5.82 (5.11, 7.22)	5.74 (5.35, 6.49)	3.40 (2.90, 4.30)	4.98 (4.52, 6.34)	-	-		3.51 (2.26, 4.40)	4.99 (4.03, 6.18)	-	-
Euroqol-5D[b]	0.774 (0.201)	0.768 (0.261)		0.796 (0.198)	0.838 (0.165)	0.729 (0.296)	0.709 (0.317)	0.019 (-0.082, 0.120)	0.71		0.780 (0.237)	0.834 (0.167)	-0.026 (-0.074, 0.022)	0.28
Euroqol VAS[b]	76.22 (12.89)	73.33 (11.15)		74.31 (16.20)	74.39 (16.01)	74.96 (10.81)	73.60 (12.78)	0.03 (-4.20, 4.27)	0.99		73.36 (16.12)	73.72 (14.16)	-0.68 (-5.49, 4.13)	0.78
Hand-grip strength (kg)[b]	24.8 (11.0)	26.1 (9.8)		26.2 (7.3)	23.9 (10.4)	22.7 (11.0)	23.2 (9.0)	0.40 (-2.16, 2.97)	0.76		24.1 (7.9)	22.9 (9.4)	-0.45 (-2.32, 1.41)	0.63
Blood pressure														
Systolic (mmHg)	146.0 (21.0)	154.7 (22.2)		142.8 (17.7)	140.7 (17.7)	142.6 (20.0)	146.2 (23.3)	0.04 (-8.38, 8.46)	0.99		139.9 (18.1)	140.3 (18.7)	-1.39 (-7.42, 4.65)	0.65
Diastolic (mmHg)	72.3 (11.2)	73.8 (13.5)		70.2 (12.4)	71.4 (11.5)	69.1 (11.8)	70.6 (14.6)	-0.66 (-5.13, 3.81)	0.77		68.3 (12.1)	68.9 (11.0)	-0.41 (-4.06, 3.24)	0.82
Body mass index (kg/m^2)	27.5 (4.9)	27.4 (4.1)		27.8 (3.8)	27.5 (3.8)	27.5 (4.9)	26.8 (3.9)	0.66 (0.21, 1.12)	0.005		27.7 (3.8)	27.3 (3.9)	0.15 (-0.27, 0.58)	0.47
Waist circumference (cm)	99.0 (11.6)	98.0 (10.9)		100.1 (11.0)	98.5 (10.5)	99.0 (11.4)	96.5 (11.7)	1.52 (0.09, 2.96)	0.04		100.7 (10.7)	97.6 (12.0)	1.42 (-0.75, 3.60)	0.2
						At end of study					At end of study			
						Levothyroxine	Placebo	Adjusted difference[a]	p-value		Levothyroxine	Placebo	Adjusted difference[a]	p-value
Letter-digit coding test[b,c]	20.6 (6.7)	21.5 (7.0)		23.6 (7.3)	22.2 (8.1)	19.8 (7.2)	19.6 (6.6)	1.05 (-0.52, 2.62)	0.19		23.5 (10.8)	20.9 (7.5)	1.64 (-1.00, 4.29)	0.22
Barthel index[b,c]	19.5 (1.3)	19.2 (1.5)		19.2 (1.6)	19.6 (0.9)	19.2 (1.5)	18.6 (2.8)	0.31 (-0.38, 0.99)	0.38		18.9 (2.2)	19.3 (1.4)	-0.17 (-0.73, 0.39)	0.54
Instrumental Activities of Daily Living[b,c]	13.4 (0.8)	12.8 (2.0)		13.2 (1.6)	13.5 (1.0)	12.7 (1.7)	12.2 (3.0)	-0.04 (-0.88, 0.80)	0.92		12.1 (2.9)	13.0 (1.7)	-0.64 (-1.37, 0.09)	0.08

Abbreviations: VAS, Visual Analog Scale. Scores were presented as means (standard deviation, SD).

[a]Adjusted difference was estimated in linear regression models predicting change from baseline to 12-month visit (95% CI) with study site, sex and randomization dose as stratification variables and study as random effect.

[b]For scale definitions see Supplemental table 1 footnotes.

[c]Repeat Barthel index, Letter-digit coding test and Instrumental Activities of Daily Living measurements were performed at final visit (i.e. at 12, 24 or 36 months depending on follow-up time), these measurements were included in the estimations.

Supplemental table S4. Sensitivity analysis of outcomes at 12 months for participants with subclinical hypothyroidism aged 80 years and over

	Imputed data				
Variables	**Levothyroxine**	**Placebo**		**Adjusted difference[a]**	**p-value**
Co-primary outcomes					
ThyPRO Hypothyroid Symptoms score[b]	22 (19.6%)	17 (12.2%)		1.79 (-1.60, 5.18)	0.30
ThyPRO Tiredness score[b]	22 (19.6%)	17 (12.2%)		0.84 (-2.99, 4.68)	0.66
Pre-specified secondary outcomes					
Thyrotropin (mIU/L)	22 (19.6%)	23 (16.5%)		-1.74 (-2.18, -1.30)	<0.001
EuroQol-5D[b]	22 (19.6%)	17 (12.2%)		-0.01 (-0.05, 0.03)	0.67
EuroQol VAS[b]	22 (19.6%)	17 (12.2%)		-0.39 (-3.09, 2.30)	0.77
Hand-grip strength (kg)[b]	23 (22.1%)	20 (14.9%)		0.07 (-1.33, 1.19)	0.92
Blood pressure					
Systolic (mmHg)	22 (19.6%)	17 (12.2%)		-0.37 (-4.46, 3.73)	0.86
Diastolic (mmHg)	22 (19.6%)	17 (12.2%)		-0.17 (-2.52, 2.17)	0.89
Weight	21 (18.9%)	18 (12.9%)		0.85 (0.12, 1.57)	0.022
Body mass index (kg/m^2)	21 (18.9%)	18 (12.9%)		0.33 (0.07, 0.59)	0.012
Waist circumference (cm)	22 (19.6%)	18 (12.9%)		1.29 (0.08, 2.50)	0.037

Abbreviations: VAS, Visual Analog Scale. Scores were presented as means (SD).

[a]Adjusted difference was estimated in repeated linear mixed regression models predicting change from baseline to 12-month visit (95% CI) with study site, sex and randomization dose as stratification variables and study as random effect using data imputed from ten imputed data sets, imputing all missing values of the outcome variable at 12-month follow-up from age, sex, baseline thyrotropin, baseline measurement of the outcome variable and, if available, measurement of the outcome variable at 6-8-week follow-up visit.

[b]For scale definitions see Supplemental table 1 footnotes.

Supplemental table S5. Clinical and adverse events for the IEMO 80-plus Thyroid trial and TRUST Thyroid trial separately

	IEMO 80-plus						TRUST 80-plus					
	Number of events (%)			Event rates (/100 person years)		p-value	Number of events (%)			Event rates (/100 person years)		p-value
Variables	**Levothyroxine (n=52)**	**Placebo (n=53)**		**Levothyroxine (n=52)**	**Placebo (n=53)**		**Levothyroxine (n=60)**	**Placebo (n=86)**		**Levothyroxine (n=60)**	**Placebo (n=86)**	
Pre-specified secondary outcomes												
Clinical outcomes												
- Fatal or nonfatal cardiovascular event	1 (1.9%)	5 (9.4%)		1.5	7.53	0.11	6 (10.0%)	9 (10.5%)		6.82	7.71	0.92
- Death from any cause	2 (3.8%)	4 (7.5%)		2.85	5.86	0.42	3 (5.0%)	0 (0.0%)		3.08	0	0.06
Adverse events												
- Cardiovascular death	0 (0.0%)	1 (1.9%)		0	1.46	0.32	0	0			-	
Serious adverse events												
- Events	15	17					38	44				
- Patients with >1 serious adverse event[a]	12 (23.1%)	13 (24.5%)		0.86 (0.34, 2.22)		0.76	21 (35.0%)	27 (31.4%)			1.29 (0.60, 2.76)	0.51
Adverse event of special interest												
- New-onset atrial fibrillation	0 (0.0%)	2 (3.8%)		0	3.07	0.12	4 (6.7%)	4 (4.7%)		4.54	3.26	0.64
- Heart failure	1 (1.9%)	3 (5.7%)		1.5	4.53	0.32	2 (3.3%)	3 (3.5%)		2.19	2.48	0.98
- Fracture	1 (1.9%)	3 (5.7%)		1.48	4.65	0.3	3 (5.0%)	2 (2.3%)		3.3	1.64	0.54
- Hypothyroidism[b]	0 (0.0%)	0 (0.0%)										
Withdrawal												
- Permanent discontinuation of trial regimen	16 (30.8%)	18 (34.0%)		28.27	30.9	0.86	22 (36.7%)	25 (29.1%)		26.68	21.77	0.43
- Withdrawal from follow-up[c]	2 (3.8%)	1 (1.9%)		2.85	1.47	0.56	8 (13.3%)	8 (9.3%)		8.23	6.19	0.43
	Baseline (mean, SD)			At 12 months (mean, SD)			Baseline (mean, SD)			At 12 months (mean, SD)		
	Levothyroxine	Placebo		Levothyroxine	Placebo	p-value	Levothyroxine	Placebo		Levothyroxine	Placebo	p-value
ThyPro Hyperthyroid Symptoms scores[d]	11.4 (13.8)	7.2 (8.6)		7.8 (9.8)	9.1 (9.9)	0.06	10.4 (8.2)	10.4 (11.9)		11.4 (8.8)	9.5 (10.7)	0.31

Pre-planned secondary outcomes effects were estimated using cox-proportional hazard regression models adjusted for sex, dose at randomization and study site. Adverse events were estimated using cox-proportional hazard regression models with, where possible, adjustment for study site, dose at randomization, sex and age, presented as event rates and p-values.

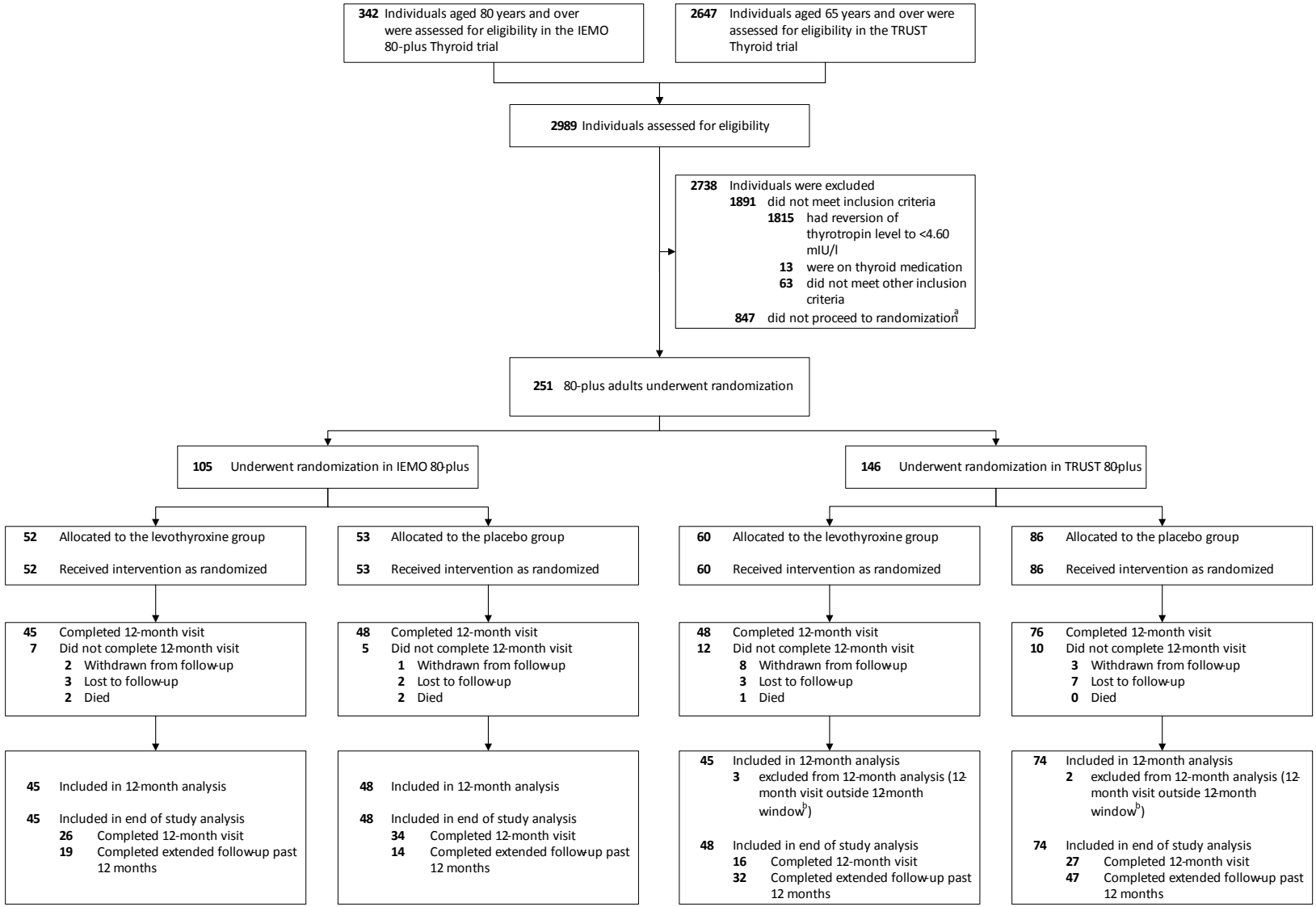
[a]For outcomes with too few events to run regression models, odds ratio (95% CI) and p-value were reported. Serious adverse events were all undesired medical events involving a participant, which are not necessarily associated with the treatment, that are: fatal, threaten the life of the subject, make hospital admission or an extension of the admission necessary, cause persistent or significant invalidity or work disability, manifest themselves in a congenital abnormality or malformation or could, according to the researchers, have developed to a serious undesired medical event, but were however prevented due to premature interference.

[b]Defined as thyrotropin level of 20 mIU/L or higher during trial laboratory measurements

[c]Analysis adjusted for study site, sex, and dose at randomization.

[d]For scale definitions see Supplemental table 1 footnotes. Scores were presented as means (standard deviation, SD)

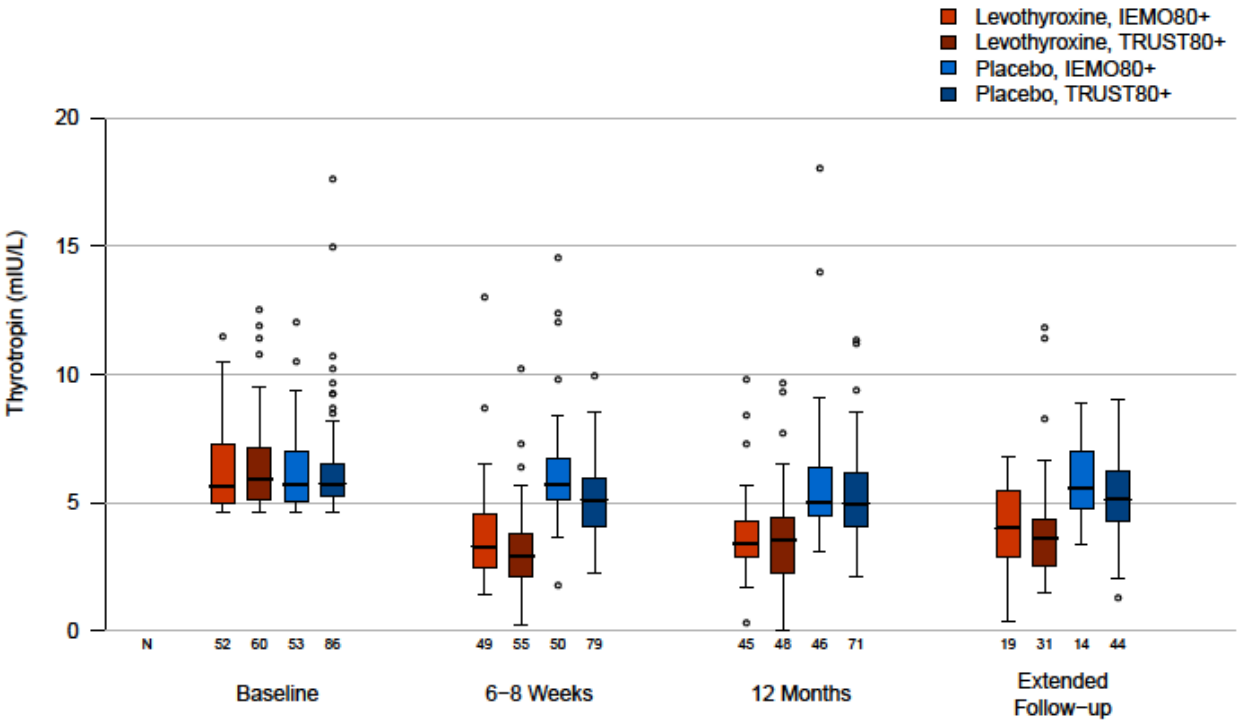
Figure S1. Recruitment, randomization, and patient flow of the participants age 80 years and over in the TRUST and IEMO thyroid trials separately.



[a]These participants completed the screening phase and met the inclusion criteria, yet did not proceed to randomization. For example participant opted not to participate due to developments in the private sphere or after consultation with children.

[b]12-month window was between 334 and 397 days after randomization

Figure S2. Thyrotropin levels in the levothyroxine and placebo group during the studies



Abbreviations: N, number of participants with available thyrotropin measurements. Tukey boxplots depicting medians, quartiles, the lowest and upper datum still within 1.5 IQR of the corresponding quartile and outliers.