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The Effect of Thyroid Hormone Therapy on Muscle Function, Strength and Mass in Older Adults with Subclinical Hypothyroidism- an Ancillary Study within two Randomized Placebo Controlled Trials

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ABSTRACT

Background: Loss of skeletal muscle function, strength and mass is common in older adults, with important socioeconomic impacts. Subclinical hypothyroidism is common with increasing age and has been associated with reduced muscle strength. Yet, no randomized placebo-controlled trial (RCT) has investigated whether treatment of subclinical hypothyroidism affects muscle function and mass.

Methods: This is an ancillary study within two RCTs conducted among adults aged ≥65 years with persistent subclinical hypothyroidism (thyrotropin (TSH) 4.60-19.99mIU/L, normal free thyroxine). Participants received daily levothyroxine with TSH-guided dose adjustment or placebo and mock titration. Primary outcome was gait speed at final visit (median 18 months). Secondary outcomes were handgrip strength at 1-year follow-up and yearly change in muscle mass.

Results: We included 267 participants from Switzerland and the Netherlands. Mean age was 77.5 years (range 65.1 to 97.1), 129 (48.3%) were women, and their mean baseline TSH was 6.36mIU/L (standard deviation [SD] 1.9). At final visit, mean TSH was 3.8mIU/L (SD 2.3) in the levothyroxine group and 5.1mIU/L (SD 1.8, $p<0.05$) in the placebo group. Compared to placebo, participants in the levothyroxine group had similar gait speed at final visit (adjusted between-group mean difference [MD] 0.01m/s, 95% confidence interval [CI] -0.06 to 0.09), similar handgrip strength at one year (MD -1.22kg, 95%CI -2.60 to 0.15) and similar yearly change in muscle mass (MD -0.15m^2, 95%CI -0.49 to 0.18).

Conclusions: In this ancillary analysis of two RCTs, treatment of subclinical hypothyroidism did not affect muscle function, strength and mass in individuals 65 years and older.

Introduction

Low muscle strength, mass and function, that are all components of a disease called sarcopenia, are common, affecting up to 29% of community-dwelling older adults.[1, 2] Recent revised European consensus guidelines recommended a three step approach to diagnose sarcopenia, with the assessment of muscle strength (e.g. handgrip strength), muscle mass (e.g. measurement by dual-energy x-ray absorptiometry) and muscle function (or physical performance, e.g. gait speed).[3]

The skeletal muscle is a major target of thyroid hormone signalling. In skeletal muscle, the inactive tetraiodothyronine(T4) can be converted to the active triiodothyronine(T3), which can then either leave the cell or directly display its effects via nuclear receptors, promoting muscle development, growth, contractility and thermogenesis.[4] In patients with a deficit in thyroid hormones, muscle complaints are common, affecting up to 80% of the patients.[5-8] Overt hypothyroidism, defined as elevated thyrotropin (TSH) levels and diminished thyroxine (FT4) levels, is also associated with poor gait and falls, and a clear indication for thyroid hormone treatment.[9-11] Subclinical hypothyroidism, defined as elevated TSH levels with FT4 in the reference range, affects up to 10% of the adult population, is more prevalent in women and increases with age.[12] It remains unclear whether subclinical hypothyroidism should be treated, which is reflected in the conflicting opinions in recent guidelines.[12-14] Yet, two large recent trials show no effect of thyroid hormone therapy on multiple outcomes, such as hypothyroid symptom scores,[15, 16] depression,[17] fatigability[18] or atherosclerosis[19], putting treatment of subclinical hypothyroidism in older adults further into question.

A small number of observational studies and two randomized placebo-controlled trials (RCT) have evaluated the association of subclinical hypothyroidism with muscle function, strength and/or mass with measurements recommended by the European consensus guidelines on Sarcopenia[3] and showed conflicting results.[15, 20-24] The two RCTs assessed only muscle strength, one showing no difference and one showing improvement. [15, 24] No previous RCT evaluated muscle mass or function using recommended measurements.[3]

Therefore, in this ancillary study of two large RCTs we aimed to assess the effect of thyroid hormone therapy on muscle function, strength and mass, with gait speed as the primary outcome and handgrip strength, muscle mass and the prevalence of sarcopenia as secondary outcomes.

Methods

Study setting

This ancillary study is based on two coordinated, randomized placebo-controlled trials: TRUST (Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism Trial, clinicaltrials.gov registry NCT01660126) and IEMO (Institute for Evidence-Based Medicine in Old Age 80-plus thyroid trial, Netherland Trial Register ID NTR3851), which investigated the effect of levothyroxine treatment in older adults with subclinical hypothyroidism.[15, 16] Both trials had identical study designs and included pre-planned prospective pooled analyses (clinicaltrials.gov registry NCT04354896). The study protocol and main results for both studies have been published.[15, 16, 25, 26] The trials were performed in accordance with the principals of the Declaration of Helsinki and Good Clinical Practice guidelines. We report this ancillary study in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement.[27]

Participants

The TRUST trial recruited community-dwelling adults aged ≥65 years in participating sites in Switzerland, Ireland, Scotland and the Netherlands between April 2013 and May 2015, with a final date of follow up of October 31, 2016.[15, 25] The IEMO trial recruited community-dwelling adults aged ≥80 years at several sites in the Netherlands and Switzerland, between May 2014 and May 2017, with a final date of follow up of May 4, 2018.[16, 26] Switzerland and the Netherlands are both iodine-poor countries, but have used iodine enriched table salt for decades, with sufficient iodine intake in the last surveys. [28, 29] Both trials included participants with persistent subclinical hypothyroidism, defined as elevated TSH levels (≥4.60mIU/L and ≤19.99mIU/L) with normal FT4 in at least two separate blood samples at least three months apart. Participants were identified from clinical laboratory and general practice databases and records. Main exclusion criteria were current prescription of drugs with potential influence on TSH levels, thyroid surgery within 12 months, hospitalization or acute coronary syndrome within 4 weeks, dementia and terminal illness.[15, 16, 25, 26]

Participants were randomly allocated to receive placebo or levothyroxine, participants, study personnel and treating physicians were blinded to allocation.

We only included participants of the IEMO trial and those recruited at Swiss sites of the TRUST trial, as gait speed was not measured at follow-up at other sites.

Gait speed was not part of the initial TRUST protocol but is part of the IEMO protocol,[26] with the IEMO trial starting after the TRUST trial. Of the TRUST sites, Switzerland decided to add gait speed as a measurement at follow-up, as baseline visits had already been completed, for preplanned pooled analyses. The change was approved by the local ethic committees.

Of the 322 TRUST and IEMO participants initially considered for this ancillary study, 55(17.1%) did not have gait speed at the final visit, most commonly due to withdrawal of consent(n=15), death(n=9), logistic(n=7) or patient mobility problems(n=7). 267 participants were analyzed(figure 1). 246(92.1%) had the secondary outcome of baseline and 1-year follow-up handgrip measurement, 128(52%) in the levothyroxine group and 118(48%) in the placebo group. The secondary outcome of muscle mass was a preplanned substudy in the Swiss TRUST sites, with inclusion of all consecutive participants from start of enrolment. Unwillingness to participate was the only exclusion criterion. 138 participants(51.7%) had baseline and follow-up measurements, 68(49.3%) in the levothyroxine group and 70(50.7%) in the placebo group. Reasons for missing values are listed in figure 1.

Intervention

Participants were blinded and randomized in a 1:1 ratio using a randomization sequence by an independent data center (Robertson Centre for Biostatistics, Glasgow, Scotland).[16, 25] They either received 50mcg levothyroxine or matching placebo as a starting dose. Participants weighing <50kg and those with previous cardiovascular disease received 25mcg levothyroxine or matching placebo as a starting dose. The levothyroxine group received medication titrations to a TSH target range of 0.40 to 4.59mIU/L.[30] The placebo group received mock titrations. All titrations were executed by a computer without a physician. The medication was packaged by Mawdsley Brooks & Co (United Kingdom). Participants, physicians and study personnel remained blinded throughout the studies.

Outcome measurements

Primary outcome gait speed was assessed in Swiss TRUST participants at the final visit, which occurred 12 to 42 months after baseline(median 18 months), using a 3-meter corridor walk with four consecutive repetitions, the best time was taken.[31] In the IEMO participants, gait speed was assessed at baseline, 1-year follow-up and/or final visit(12 to 42 months after baseline), by a 6-meter corridor walk done at least twice, the best time was taken. Both studies recorded gait speed in meters per second(m/s). Previous studies show high comparability of these tests.[31, 32] We used gait speed at final visit, with a sensitivity analysis using the baseline gait speed where available.

Secondary outcomes

Handgrip strength was assessed in both studies with the Jamar isometric dynamometer.[33] It was measured three times in the dominant hand and the best measurement was recorded. Baseline and 1-year follow-up measurements were used in this study.

Muscle mass was measured as appendicular lean mass(ALM) with dual-energy x-ray absorptiometry(DXA) at only the TRUST study sites, on a General Electric Health Care-Lunar Prodigy(GEHC, Madison, WI, USA) at the Bern study site, and on a GEHC-Lunar iDXA(GEHC, Madison, WI, USA) at the Lausanne site at baseline, 1-year and/or 2-year follow-up. The machines were cross-calibrated at the beginning of the trial, without statistical differences. Daily on-site quality control assessments did not reveal longitudinal changes during the study period. Measured ALM was divided by BMI for the primary analysis and by height^2 in a sensitivity analysis for comparable results.[3, 34]

Sarcopenia was assessed using the cut-offs recommended by the revised European consensus guidelines. Gait speed is recommended to determine physical performance and severity of sarcopenia, with a measurement <0.8m/s indicating severe sarcopenia.[3] The reported minimally clinically important difference ranges from 0.08-0.14m/s.[35, 36] For handgrip strength, the cut-off used was <27kg for men and <16kg for women.[3] The reported minimally clinically important difference ranges from 5 to 6.5kg.[37] The sarcopenia cut-off used for muscle mass(ALM/BMI) was <0.79m^2 for men and <0.51m^2 for women.[38]

Statistical analysis

We used a modified intention-to-treat analysis, as was done for the main trials.[15, 16] We checked model assumptions for all our analyses. For gait speed, we used a mixed-effects regression analysis adjusting for sex, treatment, levothyroxine starting dose, time to final visit and study site, similar to the main publications,[15, 16] using the respective trial(TRUST or IEMO) as a random effect. Handgrip strength was analyzed with the same model, with baseline values as additional adjustment variable. For muscle mass we used the yearly change from the baseline, to the 1-year and/or 2-year measurements. We used linear regression with the same adjustment variables, but without random effect, as only participants of the TRUST study were included. We used logistic regression to estimate the odds of sarcopenia and severe sarcopenia at follow-up for the placebo group vs. the treatment group with the same adjustment variables.

In sensitivity analyses, we adjusted final gait speed for antibody status when available (anti-thyroid peroxidase(TPO) and anti-thyroglobulin(TG) antibodies) and for baseline gait speed, which was only assessed in the IEMO trial. Subgroup analyses for the primary outcome were performed according to age(<75 and ≥75, pre-specified cut-off to evaluate if older participants react differently to treatment), sex and baseline TSH(<7, ≥7 to <10, ≥10mIU/L, as participants with low TSH might benefit less from treatment, and treatment is often recommended in TSH>10mIU/L[13]). We repeated the key analyses for the primary outcome after imputing final gait speed and time to final visit(multiple imputation generating 50 data sets) based on sex, starting dose, study site and study. As 55 IEMO and Swiss TRUST participants were missing gait speed measurements at the final visit, we compared the baseline characteristics of the participants with and without the final measurement. We assessed how the results of missing data might impact the statistical and clinical significance of our primary outcome with low and high gait speed value assumptions for the participants with missing gait speed. Statistical analyses were performed using STATA version 15(StataCorp, College Station, TX) for Windows. Statistical significance was considered for p-values <0.05.

Results

Study Population

267 Swiss TRUST and IEMO participants were analyzed in this ancillary study(figure 1). At baseline, the 267 participants had a mean age of 77.5 years(range 65.1 to 97.1), 129(48.3%) were female, mean TSH was 6.36mIU/L(SD 1.9) and median FT4 was 13.5pmol/l(interquartile range: 12.1-15pmol/l). Mean BMI was 27.4kg/m^2 (SD 4.8). 137 participants(51.3%) were in the levothyroxine group and 130(48.7%) in the placebo group. The final visit occurred 12 to 42 months after baseline(median 18 months). Baseline characteristics were evenly distributed among the treatment groups(table 1). IEMO participants were older than TRUST participants due to differences in the enrollment criteria, and had more comorbidities(supplement table 1). The 55 participants without gait speed at final visit were slightly older(median age 80.5 years vs. 77.8 years, P=0.02), more likely to suffer from heart failure(12.7% vs. 4.1%, P=0.01) and took more medications(median 5 vs. 4, P=0.003) than the participants with available outcome. There were no significant differences regarding sex or treatment allocation(supplement table 2).

Primary outcome

At final visit, the mean TSH was 3.8mIU/L in the levothyroxine group and 5.13mIU/L in the placebo group(P<0.05). Gait speed at final visit did not significantly differ between the treatment groups with an adjusted mean between-group difference (MD) of 0.01m/s (95% confidence interval[CI] -0.06 to 0.09, P=0.72, table 2).

Secondary outcomes

Handgrip strength at 1 year did not significantly differ with an MD of -1.22kg(95 %CI -2.60 to 0.15, P=0.08, table 2). The yearly change in muscle mass, measured by ALM/BMI, did not significantly differ with an MD of -0.15m^2 (95%CI -0.49 to 0.18, P=0.37). The results did not differ when using the measurement ALM/$height^2$.

At baseline and after 1 year, 19.5% and 31.6% of the participants had a handgrip strength consistent with sarcopenia (<27kg for men, <16kg for women).[3] Regarding muscle mass, 18.8% fulfilled sarcopenia criteria at baseline (<0.79m^2 for men, <0.51m^2 for women), and 18.8% at follow-up. Overall, only 6 out of 133(4.5%) participants were classified as sarcopenic at baseline and 8 out of 129(6.2%) at follow-up. At the end of follow-up, 4 of 129(3.1%) were considered having "severe" sarcopenia (additional gait speed <0.8m/s[3]). There were no statistically significant differences in the odds of sarcopenia(odds ratio 2.3, 95% CI 0.3 to 16.6, P=0.39). For severe sarcopenia at follow-up odds ratio was 1.1(95%CI 0.1 to 10.6, P=0.91).

Sensitivity analyses

Subgroup analyses of the primary outcome did not yield significant results when examined by sex, age(<75 years, ≥75 years) and TSH categories(TSH <7, ≥7 and <10, ≥10mIU/L) (supplement table 3). Antibody status was available in 233 participants (87.3%), 46(19.7%) were anti-TPO positive and 51(21.9%) were anti-TG positive. Adjusting for antibodies yielded similar results(MD 0.03m/s, 95% CI -0.05 to 0.11, p=0.44). A sensitivity analysis with adjustment for baseline gait speed where available again yielded similar results with an MD of -0.05m/s (95% CI -0.16 to 0.58, P=0.35). The imputation analysis yielded similar results (MD 0.01m/s, 95% CI -0.06 to 0.09, P=0.72). Imputing a 5-fold slower final gait speed for all participants in the placebo group missing gait speed(n= 31) was required to achieve a statistically significant result(MD 0.077m/s, 95% CI 0.001 to 0.15, P= 0.05; minimally clinically important difference 0.08m/s[36]) but only imputing a 7 times slower gait speed yielded a minimally clinically important difference(0.082m/s, 95% CI 0.005 to 0.16, P= 0.04). Assuming participants in the levothyroxine group missing gait speed(n=24) were 3.7 times faster(=mean gait speed 2.96m/s) yielded a significant result in favor of levothyroxine(0.12m/s, 95% CI 0.00 to 0.24, P= 0.05; supplement table 4).

Discussion

Among adults aged ≥65 years with subclinical hypothyroidism, treatment with levothyroxine during a median of 18 months did not lead to a change in muscle function, muscle strength or mass, as assessed by gait speed, handgrip strength and appendicular lean mass in DXA, compared to placebo. The results did not differ according to sex, age groups, TSH levels or antibody status.

Based on a recent systematic review of RCTs on treatment of subclinical hypothyroidism,[39] only two placebo-controlled trials examined the effect of levothyroxine on muscle strength. In the main TRUST article,[15] it was already shown that handgrip strength did not change with thyroid hormone therapy in older adults ≥65 years with subclinical hypothyroidism[15]. However, handgrip strength was not analyzed before in the older IEMO population, and both trials did not report on gait speed or muscle mass. Another study that looked at the effect of levothyroxine on muscle strength did not use measurements as defined by the revised European consensus guidelines,[3] and showed a statistically significant increase in inspiratory muscle strength(+11.5cmH2O ± 17.2, P=0.04) but not in quadriceps muscle strength(+5.3kgf ± 11.2, P=0.11) in the levothyroxine group, but the authors did not compare levothyroxine to placebo.[24] The study was further limited by a small sample size(N=52), short follow-up(6 months) and 28.8% of the participants did not complete the study. The study included middle-aged(mean age=51±10 years), predominantly female participants.

Subclinical hypothyroidism is more common in older adults and women and associations with adverse outcomes might be different in older individuals.[40, 41] Observational studies examining subclinical hypothyroidism and physical performance, muscle strength and/or mass using measurements as recommended by the European consensus guidelines[3] showed conflicting results.[20-22] One prospective study conducted among 2290 community-dwelling adults aged 70-79 years reported a similar decline in gait speed in euthyroid participants compared to mild(TSH ≥4.5 to <7mIU/L) to moderate(TSH ≥7 to ≤20mIU/L and normal FT4) subclinical hypothyroidism over two years.[20] A cross-sectional study performed in Korea in individuals aged ≥65 years found an association between subclinical hypothyroidism(TSH >4.1mIU/L and normal FT4) and low muscle mass in women, but not in men, with a very small number of women with subclinical hypothyroidism(n=40).[21] They found no difference in muscle strength. Another cross-sectional study in Brazilian women aged ≥65years found an association between high TSH and low muscle mass(OR 1.08 per 1mIU/L increase, P=0.02), without stratification for subclinical hypothyroidism.[22] In our study, low muscle mass or strength was not more prevalent in women, and levothyroxine treatment did not have an effect in men or women.

The TRUST and IEMO trials have a coordinated parallel design and a combined analysis was pre-planned. By combining them, we have analyzed the pooled results of the largest RCTs assessing the impact of treating subclinical hypothyroidism on all components of sarcopenia: muscle mass, strength and function. Additional strengths are that muscle mass was measured by DXA, both men and women were included and the age range was wide(65-97 years).

Our study has several limitations. First, changes in gait speed and muscle mass were not part of the aims of the original studies and added when the TRUST trial already started, thus the primary outcome of gait speed was not assessed in all sites at baseline. However, we observed similar results in a sensitivity analysis including only participants with available baseline gait speed. Second, gait speed assessment at the final visit was not available for 17% of the potentially eligible study population. However, using multiple imputation for the missing gait speed, we were able to show that only improbable assumptions would have led to a clinically and statistically significant difference between the levothyroxine and placebo group. Third, only performed in 138 Swiss TRUST participants had muscle mass measured by DXA. While this is the largest RCT on subclinical hypothyroidism and muscle mass to date, it might still be underpowered to evaluate changes in muscle mass. Fourth, the results may not be generalizable to persons with a TSH>10mIU/L, as only 13 participants had a TSH ≥10mIU/L in this analysis. Fifth, the mean TSH in the levothyroxine group at the final visit was 3.8mIU/L, and we do not know if achieving lower TSH values, as recommended by some experts,[14] would result in a change of the examined components of sarcopenia. Sixth, although we only included participants with persistent subclinical hypothyroidism, and mean TSH at final visit was 5.1mIU/L in the placebo group and thus still consistent with subclinical hypothyroidism, still some participants had physiologically elevated TSH levels without autoimmune disease.[12] However, adjusting for antibody status did not change the results of this study or the outcomes of the TRUST and IEMO trials.[42] Seventh, we did not measure fT3. But the value is not needed for the diagnosis of subclinical hypothyroidism.[12] Eighth, the population was predominantly Caucasian and the results might not be generalizable to other ethnicities. Finally, while this was the longest RCT on subclinical hypothyroidism, the follow-up of 12 to 42 months might have been too short to assess more long-term effects.

In summary, in this ancillary analysis of two placebo-controlled RCTs, treatment of subclinical hypothyroidism did not affect muscle function, strength and mass in individuals ≥65 years.

Tables and Figures

Figure 1: Flow chart of gait speed, grip strength and muscle mass measurement

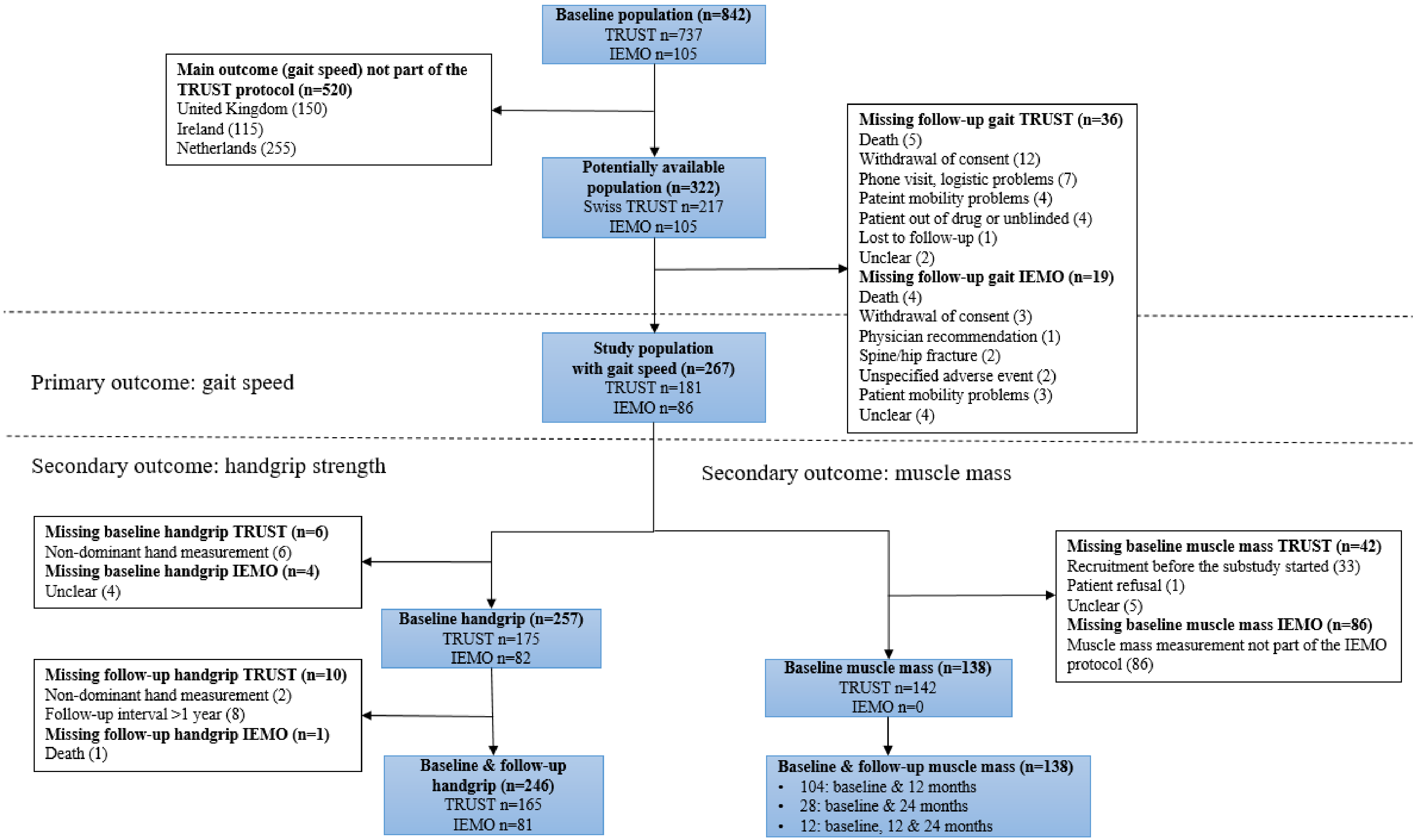
Baseline population (n=842)
TRUST n=737
IEMO n=105
Main outcome (gait speed) not part of the TRUST protocol (n=520)
United Kingdom (150)
Ireland (115)
Netherlands (255)
Potentially available population (n=322)
Swiss TRUST n=217
IEMO n=105
Missing follow-up gait TRUST (n=36)
Death (5)
Withdrawal of consent (12)
Phone visit, logistic problems (7)
Pateint mobility problems (4)
Patient out of drug or unblinded (4)
Lost to follow-up (1)
Unclear (2)
Missing follow-up gait IEMO (n=19)
Death (4)
Withdrawal of consent (3)
Physician recommendation (1)
Spine/hip fracture (2)
Unspecified adverse event (2)
Patient mobility problems (3)
Unclear (4)
Primary outcome: gait speed
Study population with gait speed (n=267)
TRUST n=181
IEMO n=86
Secondary outcome: handgrip strength
Secondary outcome: muscle mass
Missing baseline handgrip TRUST (n=6)
Non-dominant hand measurement (6)
Missing baseline handgrip IEMO (n=4)
Unclear (4)
Baseline handgrip (n=257)
TRUST n=175
IEMO n=82
Missing follow-up handgrip TRUST (n=10)
Non-dominant hand measurement (2)
Follow-up interval >1 year (8)
Missing follow-up handgrip IEMO (n=1)
Death (1)
Baseline & follow-up handgrip (n=246)
TRUST n=165
IEMO n=81
Missing baseline muscle mass TRUST (n=42)
Recruitment before the substudy started (33)
Patient refusal (1)
Unclear (5)
Missing baseline muscle mass IEMO (n=86)
Muscle mass measurement not part of the IEMO protocol (86)
Baseline muscle mass (n=138)
TRUST n=142
IEMO n=0
Baseline & follow-up muscle mass (n=138)
• 104: baseline & 12 months
• 28: baseline & 24 months
• 12: baseline, 12 & 24 months

Table 1: Baseline characteristics of TRUST and IEMO participants with gait speed measured at the final visit

Characteristics	Placebo (n=130)	Levothyroxine (n=137)
Age (years)		
median (p25-p75)	78.7 (70.7-83.7)	76.8 (72.0-83.2)
range	65.2-91.8	65.4-97.1
Female sex – n (%)	63 (48.5)	66 (48.2)
Caucasian ethnicity – n (%)	127 (97.7)	136 (99.3)
Body mass index (kg/m2) - mean±SD	27.1±4.5	27.7±5.0
Standard housing - n (%)*	126 (96.9)	133 (97.1)
Walking with aid – n (%)	9 (6.9)	16 (11.7)
Barthel index - median (p25-p75)†	20 (19-20)	20 (20-20)
History of falls – n (%)	17 (13.1)	18 (13.1)
Comorbidities – n (%)		
Ischemic heart disease (angina pectoris & myocardial infarction)	15 (11.5)	21 (15.3)
Heart failure	7 (5.4)	4 (2.9)
Atrial fibrillation	17 (13.1)	21 (15.3)
Stroke	7 (5.4)	4 (2.9)
Hypertension	58 (44.6)	72 (52.6)
Diabetes mellitus	9 (6.9)	19 (13.9)
Osteoporosis	22 (16.9)	22 (16.1)
Peripheral vascular disease	5 (3.8)	9 (6.6)
Epilepsy	1 (0.8)	5 (3.6)
Current smoking	11 (8.4)	10 (7.3)
Alcohol consumption (units/week) – median (p25- p75)	3 (0-9)	2 (0-9)
No. of concomitant medication - median (p25-p75)	3 (2-6)	4 (3-6)
Laboratory results		
TSH (mIU/L)		
median (p25-p75)	5.73 (5.12-7.0)	5.73 (5.11-7.0)
range	4.6-17.0	4.6-16.76
Free T4 (pmol/l) - median (p25-p75)	13.6 (12.1-15.0)	13.5 (12.1-15.0)
Levothyroxine starting dose of 25ug – n (%)	18 (13.8)	23 (16.8)

* Standard housing was defined as non-sheltered community accommodation. By contrast, sheltered housing is purpose built grouped housing for older persons, often with an on-site manager or warden.

† The Barthel Index is on a scale from 0 to 20, with higher scores indicating more functional independence in the domains of personal care and mobility.

Abbreviations: p25/p75: percentiles at 25/75%; SD: standard deviation; No.: number.

Table 2: Placebo vs. levothyroxine in gait speed, handgrip strength and muscle mass in subclinical hypothyroidism

Variables	Placebo mean±sd	Levothyroxine mean±sd	Difference[¥] (95% CI)	P-value
Primary Outcome				
Gait speed at final visit - m/s[*]	0.83±0.32 (n=130)	0.84±0.30 (n=137)	0.01 (-0.06 to 0.09)	0.72
Secondary Outcomes				
Handgrip strength at 1-year follow-up – kg[†]	26.57±11.55 (n=118)	24.96±11.21 (n=128)	-1.22 (-2.60 to 0.15)	0.08
Muscle mass yearly change – m^2[§]	-0.03±0.87 (n=70)	-0.19±1.13 (n=68)	-0.15 (-0.49 to 0.18)	0.37

[*] Gait speed at final visit (12 to 42 months), using a mixed model with adjustment for sex, starting levothyroxine dose, time to final visit, study site, including study as a random effect. The minimally clinically important difference is 0.08m/s. Severe sarcopenia cut-off according to the European consensus guidelines is 0.8m/s.

[†] Handgrip strength at one-year follow-up, using a mixed model with adjustment for sex, baseline handgrip strength, starting levothyroxine dose, study site, including study as a random effect. The minimally clinically important difference is 5kg. Sarcopenia cut-off according to the European consensus guidelines is <27kg for men, <16kg for women.

[§]Yearly change in muscle mass assessed by appendicular lean mass (ALM) divided by body mass index (BMI), using a linear regression model due to only on study having the outcome, adjusted for sex, starting levothyroxine dose and site. Baseline muscle mass (ALM/BMI) was $0.78m^2$±0.17 in the placebo group and $0.75m^2$±0.17 in the levothyroxine group. The minimally clinically important difference is unclear. Sarcopenia cut-off is $<0.79m^2$ for men, $<0.51m^2$ for women.

[¥]Adjusted between group difference is reported, negative numbers favor placebo.

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