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Association of Thyroid Hormone Therapy With Quality of Life and Thyroid-Related Symptoms in Patients With Subclinical Hypothyroidism
A Systematic Review and Meta-analysis

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Supplemental content

IMPORTANCE The benefit of thyroid hormone therapy for subclinical hypothyroidism is uncertain. New evidence from recent large randomized clinical trials warrants an update of previous meta-analyses.

OBJECTIVE To conduct a meta-analysis of the association of thyroid hormone therapy with quality of life and thyroid-related symptoms in adults with subclinical hypothyroidism.

DATA SOURCES PubMed, EMBASE, ClinicalTrials.gov, Web of Science, Cochrane Library, CENTRAL, Emcare, and Academic Search Premier from inception until July 4, 2018.

STUDY SELECTION Randomized clinical trials that compared thyroid hormone therapy with placebo or no therapy in nonpregnant adults with subclinical hypothyroidism were eligible. Two reviewers independently evaluated eligibility based on titles and abstracts of all retrieved studies. Studies not excluded in this first step were independently assessed for inclusion after full-text evaluation by 2 reviewers.

DATA EXTRACTION AND SYNTHESIS Two independent reviewers extracted data, assessed risk of bias (Cochrane risk-of-bias tool), and evaluated the quality of evidence (GRADE tool). For synthesis, differences in clinical scores were transformed (eg, quality of life) into standardized mean differences (SMDs; positive values indicate benefit of thyroid hormone therapy; 0.2, 0.5, and 0.8 correspond to small, moderate, and large effects, respectively). Random-effects models for meta-analyses were applied.

MAIN OUTCOMES AND MEASURES General quality of life and thyroid-related symptoms after a minimum follow-up of 3 months.

RESULTS Overall, 21 of 3088 initially identified publications met the inclusion criteria, with 2192 adults randomized. After treatment (range, 3-18 months), thyroid hormone therapy was associated with lowering the mean thyrotropin value into the normal reference range compared with placebo (range, 0.5-3.7 mIU/L vs 4.6 to 14.7 mIU/L) but was not associated with benefit regarding general quality of life (n = 796; SMD, −0.11; 95% CI, −0.25 to 0.03; I^2=66.7%) or thyroid-related symptoms (n = 858; SMD, 0.01; 95% CI, −0.12 to 0.14; I^2=0.0%). Overall, risk of bias was low and the quality of evidence assessed with the GRADE tool was judged moderate to high.

CONCLUSIONS AND RELEVANCE Among nonpregnant adults with subclinical hypothyroidism, the use of thyroid hormone therapy was not associated with improvements in general quality of life or thyroid-related symptoms. These findings do not support the routine use of thyroid hormone therapy in adults with subclinical hypothyroidism.

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Subclinical hypothyroidism, defined as elevated thyrotropin in combination with normal-range free thyroxine,[1] is common.[2,3] According to the NHANES III report,[4] an estimated 13 million people have subclinical hypothyroidism in the United States. The prevalence is higher in women and in older people.[2,3] Subclinical hypothyroidism is often treated with thyroid hormones (levothyroxine),[5] particularly when it co-occurs with symptoms potentially attributable to hypothyroidism, such as tiredness, constipation, and unexplained weight gain.[5]

Relatively limited evidence exists from randomized clinical trials (RCTs) to guide therapy of subclinical hypothyroidism. Systematic reviews have been inconclusive and clinical practice guidelines have varied regarding recommendations for managing subclinical hypothyroidism.[6-10] Two large randomized trials of levothyroxine therapy in patients with subclinical hypothyroidism were recently completed.[11,12] This meta-analysis and systematic review incorporated recent trials and evaluated whether thyroid hormone therapy was associated with improved symptoms and other benefits in nonpregnant adults with subclinical hypothyroidism.

Key Points

Question Among patients with subclinical hypothyroidism, is the use of thyroid hormone therapy associated with improvements in general quality of life or thyroid-related symptoms?

Findings In this meta-analysis of 21 randomized clinical trials including 2192 participants with subclinical hypothyroidism, thyroid hormone therapy was not significantly associated with improvements in general quality of life (standardized mean difference, −0.11) or thyroid-related symptoms (standardized mean difference, 0.01).

Meaning These findings do not support the routine use of thyroid hormone therapy in adults with subclinical hypothyroidism.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[13] and published the protocol of this systematic review in the PROSPERO database (identifier: CRD42017055536).

Eligibility Criteria, Literature Search, and Study Selection

We considered randomized trials that included nonpregnant adults with subclinical hypothyroidism. Subclinical hypothyroidism was defined as a thyrotropin level above the reference range in combination with a free thyroxine level within the reference range (according to center-specific reference ranges). The intervention had to consist of thyroid hormone therapy (triiodothyronine, thyroxine, or a combination of both) for at least 1 month, with a minimum follow-up of 3 months. The control group had to receive either placebo or no therapy. To be included, studies had to report quantitative data for at least 1 of the study's primary or secondary outcomes: general quality of life, thyroid-related quality of life/hypothyroid symptoms, depressive symptoms, fatigue/tiredness, cognitive function, pain, muscle strength, blood pressure, body mass index, cardiovascular events (myocardial infarction, stroke, revascularization), mortality, or adverse effects (hyperthyroidism due to overdosing). Data had to be reported with effect estimates and measures of precision (standard deviations or standard errors). The primary outcomes were general quality of life and thyroid-related quality of life/hypothyroid symptoms, whereas depressive symptoms, fatigue/tiredness, cognitive function, pain, muscle strength, blood pressure, body mass index, cardiovascular events, mortality, and adverse effects were secondary outcomes. Studies that included only patients with subclinical hypothyroidism in combination with another specific condition (eg, patients with diabetic nephropathy and subclinical hypothyroidism) were excluded because this type of study population is not representative of most patients with subclinical hypothyroidism. We excluded studies that exclusively enrolled pregnant women or women who wanted to become pregnant. Pseudorandomization (eg, pre-post comparisons) did not qualify for inclusion.

We searched MEDLINE, EMBASE, Web of Science, Cochrane Library, CENTRAL, Emcare, and Academic Search Premier from inception until July 4, 2018, in cooperation with a trained librarian. Search terms were adapted according to the syntax of each specific database, and no language restrictions were applied. We searched trial registries on ClinicalTrials.gov for upcoming and not yet published trials on this research topic and asked authors for the status of the trial if not published yet. We screened references of key articles for additional potentially relevant articles. Details of the search strategy are presented in eAppendix 1 in Supplement 1.

Two researchers (M.S. and M.D.M.) evaluated eligibility independently based on titles and abstracts of all studies retrieved in the electronic search. Studies not excluded in this first step were independently assessed for inclusion after full-text evaluation by 2 reviewers (M.F. and M.S.). We manually screened bibliographies of the included studies as well as guidelines and review articles for additional studies. Discrepancies were resolved by consensus among the study team.

Data Extraction and Risk-of-Bias Assessment

A standard data extraction form was used, adapted from a template suggested by Cochrane (eAppendix 2 in Supplement 1).[14] Two researchers (M.S. and E.M.) independently extracted bibliographic details, funding source, eligibility criteria, information about the study population and setting, study design, risk of bias, intervention/control intervention, and results and independently evaluated the quality of evidence using the GRADE tool.[15] If a study reported more than 1 outcome measure for a specific outcome domain (eg, more than 1 cognition test to assess cognitive function), we chose measures that were most relevant to the largest number of patients, including international usage. This was determined by consensus among the study team. As an example, Parle et al[16] reported 5 different cognition tests. We analyzed results from the Mini-Mental State Examination because it is used worldwide and because it is a more general assessment of cognitive function than more specific alternative tests, such as the Trail Making Test. When a study mentioned an outcome of interest without providing estimates (eg, the study reported no difference in body mass index between the intervention and the control group without providing data on mean differences and standard deviations), we contacted the author for the data. If studies reported results for an outcome at multiple time points during the intervention (eg, body mass index at 6 and 12 months), only the most recent measurement was used in statistical analyses. Data were extracted in duplicate by 2 independent reviewers (M.S. and E.M.) and differences were resolved by consensus.

Statistical Analyses

Study results were presented separately for each outcome with estimates as reported in the original publication and transformed into standardized mean differences (SMDs) when different scales were used for the same outcome domain. We coded SMDs such that positive values indicated benefit of thyroid hormone therapy, with 0.2, 0.5, and 0.8 corresponding to small, moderate and large effects, respectively.[17] In contrast, for body mass index and blood pressure, negative values indicated a benefit of thyroid hormone therapy. For estimations of treatment effects, we used mean values and their standard deviations at the end of treatment in both groups, assuming balanced baseline values due to the randomized designs.

For outcomes on which studies reported treatment effects at different time points, we included only the estimate at the most recent follow-up time point, thereby avoiding counting a study twice in a formal meta-analysis. Overall results were calculated using random-effects models unless fewer than 5 studies were included for a meta-analysis because in that case, the between-study variance could not be estimated reliably, so a fixed-effects analysis was performed. For better clinical interpretation, overall SMDs were also back-transformed to one original scale according to a method proposed by the Cochrane Collaboration[17] for general quality of life, thyroid-related quality of life/hypothyroid symptoms, depressive symptoms, cognitive function, and muscle strength. Heterogeneity was assessed visually with forest plots and quantified with I^2 (low: 0%-40%; moderate: 40%-75%; and high: >75%). If substantial heterogeneity existed and a sufficient number of publications was available (n = 10), we aimed to explore potential sources of heterogeneity in protocol prespecified subgroup analyses (eg, restricting the analysis to high-quality studies). In addition, a post hoc sensitivity analysis was performed with the aim to evaluate heterogeneity after excluding studies showing a statistically significant benefit of placebo treatment. If a sufficient number of publications was available (n = 10), publication bias was assessed via funnel plots (visually) and more formally with the Egger test.[18] Statistical significance testing was 2-sided and $P<.05$ was considered statistically significant. All analyses were conducted with Stata, release 14 (StataCorp).

Results

The systematic literature search retrieved 3086 studies, and 2 additional studies were retrieved after searching references of key articles. After removing 1438 duplicates, 2 reviewers (M.S. and M.D.M.) independently screened 1650 unique articles for potential eligibility based on title and abstract. Forty-nine potentially eligible studies were evaluated in full text independently by 2 reviewers (M.F. and M.S.). Among these, 25 studies did not meet the inclusion criteria. Three additional studies were excluded because of data presentation problems[19-21]; for 2 of these articles, the authors indicated that data were no longer available[19,20]; for one, the author could not be reached[21] (eTable 1 in Supplement 1).

Twenty-one studies met the inclusion criteria[11,12,16,22-39] (eFigure in Supplement 1). Among the 21 studies, a total of 2192 adults were randomized (**Table**). Study sizes ranged from 20 to 737 participants; mean ages ranged from 32 to 74 years; percentages of women ranged from 46% to 100%; and baseline mean thyrotropin values ranged from 4.4 to 12.8 mIU/L. Two studies (99 participants) had a mean baseline thyrotropin level greater than 10 mIU/L.[22,23] Seven studies provided information about hypothyroid symptoms at baseline, and in these studies, the burden of symptoms was mild to moderate (Table).[12,22-27] In the thyroid hormone therapy groups, mean thyrotropin levels at the end of follow-up ranged between 0.5 and 3.7 mIU/L (eTable 2 in Supplement 1), indicating that treatment was associated with normalization of thyrotropin levels. In contrast, mean thyrotropin in the placebo/no intervention groups remained elevated at the end of follow-up, ranging from 4.6 to 14.7 mIU/L (eTable 2). The duration of the intervention (thyroid hormone therapy or placebo/no therapy) ranged from 3 months to 18 months. Three studies compared thyroid hormone therapy with no intervention and the other studies compared thyroid hormone therapy with placebo.[11,28,29] Two studies were supported by industry (Table).[22,30]

Thyroid hormone therapy was not associated with benefit for either of the 2 primary outcomes. Four studies including 796 participants evaluated general quality of life (SMD, −0.11; 95% CI, −0.25 to 0.03; I^2=66.7%) (**Figure 1**).[12,26,27,31] It is estimated that on the Euro Quality of Life 5 Dimensions Questionnaire (range, −0.59 to 1.00; higher scores indicate better quality of life), this SMD would represent a difference of 0.02 (95% CI, −0.01 to 0.05) in favor of placebo. Four studies including 858 participants evaluated thyroid-related quality of life/hypothyroid symptoms (SMD, 0.01; 95% CI, −0.12 to 0.14; I^2=0.0%) (Figure 1).[12,22,31,32] It is estimated that on the ThyPRO hypothyroid symptoms score (range, 0-100; higher scores indicate more hypothyroid symptoms), this SMD would represent a difference of 0.18 (95% CI, −2.10 to 2.45) in favor of levothyroxine. Similarly, thyroid hormone therapy was not

Table. Characteristics of 21 Included Randomized Clinical Trials on Thyroid Hormone Therapy for Subclinical Hypothyroidism in Adults

Source	Country	Funding Source	Definition of Subclinical Hypothyroidism	No. of Participants	Age, Mean (SD), y	Women, No. (%)	Intervention	Control	Planned Follow-up Duration, mo	Outcomes[a]	Hypothyroid Symptoms at Baseline, Intervention vs Control
Stott et al,[12] 2017	The Netherlands, Switzerland, United Kingdom, Ireland	Nonindustry	Thyrotropin 4.6-19.99 mIU/L on 2 occasions and normal free thyroxine	737	74 (6.3)	396 (54)	Levothyroxine	Placebo	≥12[b]	ThyPRO,[40] EQ-5D,[41] Letter-Digit Coding Test,[42] hand-grip strength, blood pressure, BMI, cardiovascular events, mortality, adverse effects[40]	ThyPRO hypothyroid symptom score: 17.5 (SD, 18.8) vs 16.9 (SD, 17.9)
Zhao et al,[11] 2016	China	Nonindustry	Thyrotropin 4.2-10.0 mIU/L and normal free thyroxine on 2 occasions	369	55 (7.6)	270 (73)	Levothyroxine	No intervention	15	Blood pressure, BMI	NR
Najafi et al,[24] 2015	Iran	Nonindustry	Thyrotropin >4.5 mIU/L, normal free thyroxine, and positive TPO-Ab	60	34 (10.0)	51 (85)	Levothyroxine	Placebo	3	BDI[43]	Mean number of hypothyroid symptoms per participant (range, 0-12): 4.8 vs 5.1
Ersoy et al,[29] 2012	Turkey	Not declared	Thyrotropin 5.0-10.0 mIU/L and normal free thyroxine	60	46 (13.1)	58 (97)	Levothyroxine	No intervention	6	Blood pressure, BMI	NR
Aghili et al,[25] 2012	Iran	Nonindustry	Thyrotropin >4.5 mIU/L, normal free thyroxine, and positive TPO-Ab	60	34 (10.8)	51 (85)	Levothyroxine	Placebo	3	Cognitive function (Wechsler memory scale[44])	Mean number of hypothyroid symptoms per participant (range, 0-7): 3.2 vs 3.7
Reuters et al,[31] 2012	Brazil	Not declared	Thyrotropin >4.0 mIU/L and normal free thyroxine on 2 occasions	71	50 (10.9)	62 (87)	Levothyroxine	Placebo	6	Zulewski score,[45] Short Form 36,[46] BDI,[43] quadriceps strength	Zulewski score (only change from baseline reported)
Cabral et al,[28] 2011	Brazil	Not declared	Thyrotropin >4 mIU/L and normal free thyroxine on 2 occasions	32	46 (9.0)	32 (100)	Levothyroxine	No intervention	12	BMI[c]	NR
Parle et al,[16] 2010	United Kingdom	Nonindustry	Thyrotropin >5.5 mIU/L and normal free thyroxine	94	74 (5.8)	57 (61)	Thyroxine	Placebo	12	HADS,[47] cognitive function (MMSE,[48] MEAMS,[49] SCOLP,[50] and Trail Making Test[51])	NR
Nagasaki et al,[36] 2009	Japan	Nonindustry	Increased thyrotropin and normal free triiodothyronine/free thyroxine	95	65 (19.3)	95 (100)	Levothyroxine	Placebo	5	Blood pressure, BMI	NR
Teixeira et al,[30] 2008	Brazil	Industry supported	Thyrotropin >4 mIU/L and normal free thyroxine on ≥2 occasions	60	48 (10.5)	57 (95)	Levothyroxine	Placebo	12	BMI	NR
Razvi et al,[32] 2007	United Kingdom	Nonindustry	Thyrotropin >4 mIU/L and normal free thyroxine on ≥2 occasions	100	54 (12.6)	82 (82)	Levothyroxine	Placebo	3	ThyDQoL,[52] blood pressure, BMI[c]	ThyDQoL (only change from baseline reported)
Jorde et al,[26] 2006	Norway	Nonindustry	Thyrotropin 3.5-10 mIU/L	69	62 (11.9)	32 (46)	Thyroxine	Placebo	12	GHQ-30,[53] BDI,[43] composite cognitive score[26]	Mean number of hypothyroid symptoms per participant (range, 0-19): 4.0 vs 4.0

(continued)

Table. Characteristics of 21 Included Randomized Clinical Trials on Thyroid Hormone Therapy for Subclinical Hypothyroidism in Adults (continued)

Source	Country	Funding Source	Definition of Subclinical Hypothyroidism	No. of Participants	Age, Mean (SD), y	Women, No. (%)	Intervention	Control	Planned Follow-up Duration, mo	Outcomes[a]	Hypothyroid Symptoms at Baseline, Intervention vs Control
Iqbal et al,[37] 2006	Norway	Nonindustry	Thyrotropin 3.5-10 mIU/L on 2 occasions and normal free triiodothyronine/free thyroxine	64	64 (12.2)	31 (48)	Thyroxine	Placebo	12	BMI	NR
Caraccio et al,[38] 2005	Italy	Nonindustry	Thyrotropin >3.6 mIU/L and normal free triiodothyronine	23	32 (9.6)	21 (91)	Levothyroxine	Placebo	6	BMI	NR
Yazici et al,[35] 2004	Turkey	Not declared	Increased thyrotropin and normal free triiodothyronine/free thyroxine	45	40 (7.9)	38 (84)	Levothyroxine	Placebo	12	Blood pressure, BMI	NR
Monzani et al,[34] 2004	Italy	Not declared	Thyrotropin >3.6 mIU/L	45	37 (11.0)	37 (82)	Levothyroxine	Placebo	6	Blood pressure, BMI	NR
Kong et al,[27] 2002	United Kingdom	Not declared	Thyrotropin 5-10 mIU/L and normal free thyroxine	40	50 (15.2)	40 (100)	Thyroxine	Placebo	6	GHQ-30,[53] HADS,[47] BMI	Overall, 33/40 (83%) reported fatigue and 32/40 (80%) reported weight gain
Caraccio et al,[39] 2002	Italy	Nonindustry	Thyrotropin >3.6 mIU/L on 2 occasions and positive TPO-Ab	49	35 (9.1)	42 (86)	Levothyroxine	Placebo	6	BMI	NR
Monzani et al,[33] 2001	Italy	Not declared	Thyrotropin >3.6 mIU/L for >1 y and normal free thyroxine	20	32 (12.1)	18 (90)	Levothyroxine	Placebo	6	Blood pressure, BMI	NR
Meier et al,[22] 2001	Switzerland	Nonindustry and industry supported[d]	Thyrotropin >5 mIU/L on 2 consecutive blood tests and normal free thyroxine	66	57 (10.6)	66 (100)	Levothyroxine	Placebo	12	Billewicz score[54,e]	Billewicz score: −25.7 (SD, 5.2) vs −28.3 (SD, 14.1)
Cooper et al,[23] 1984	United States	Nonindustry	Increased thyrotropin and normal free triiodothyronine/free thyroxine	33	54 (10.1)	32 (97)	Levothyroxine	Placebo	12	BMI	Mean number of hypothyroid symptoms per participant (range, 0-6): 2.1 vs 2.4

Abbreviations: BDI, Beck Depression Inventory; BMI, body mass index; EQ-5D, Euro Quality of Life 5 Dimensions Questionnaire; GHQ-30, General Health Questionnaire (30 items); HADS, Hospital Anxiety and Depression Scale; MEAMS, Middlesex Elderly Assessment of Mental State; MMSE, Mini Mental State Examination; NR, not reported; SCOLP, Speed and Capacity of Language Processing Test; ThyDQoL, 18-Item Underactive Thyroid-Dependent Quality of Life; ThyPRO, Thyroid-Related Quality-of-Life Patient-Reported Outcome Measure (hypothyroid score: 4 items; range, 0-100; higher scores indicate more hypothyroid symptoms; tiredness score: 7 items); TPO-Ab, thyroid peroxidase antibody.

[a] Only outcomes relevant to this systematic review are listed; ie, outcomes that were included in the study protocol and published in the PROSPERO database.

[b] The Letter-Digit Coding Test outcome was available after 18 months of levothyroxine or placebo intervention; the other outcomes after 12 months.

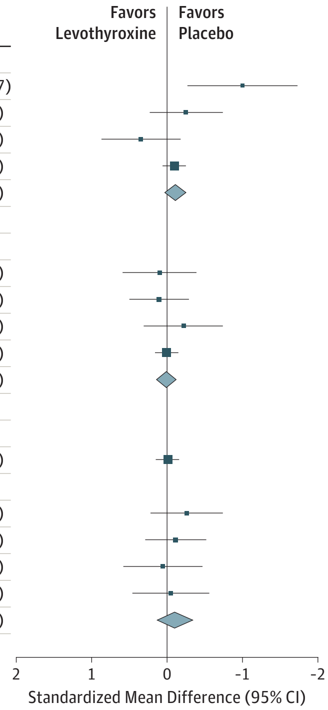
[c] Data obtained through direct communication with author.

[d] This work was supported by the Swiss Research Foundation and by unconditional research grants from Henning Berlin, Sandoz Research, and Roche Research Foundations.

[e] Billewicz score ranges from −47 to 67; higher scores indicate worse hypothyroid symptoms.

Figure 1. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Quality-of-Life and Mood-Related Outcomes

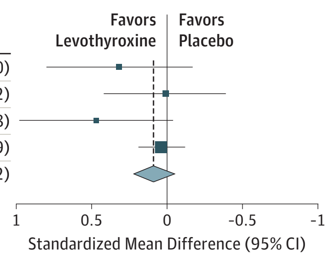
Source	Quality of Life/Mood Scale	No. of Participants Levothyroxine	No. of Participants Placebo	Standardized Mean Difference (95% CI)	Weight, %
General quality of life					
Kong et al,[27] 2002	General Health Questionnaire at 6 mo	20	14	-1.00 (-1.73 to -0.27)	3.70
Jorde et al,[26] 2006	General Health Questionnaire at 12 mo	35	32	-0.25 (-0.74 to 0.23)	8.42
Reuters et al,[31] 2012	Short Form 36 at 6 mo	32	25	0.35 (-0.18 to 0.87)	7.02
Stott et al,[12] 2017	EQ-5D at 12 mo	318	320	-0.10 (-0.25 to 0.06)	80.86
Subtotal				-0.11 (-0.25 to 0.03)	100.00
Overall effect: I^2=66.7%; *P*=.03					
Thyroid-related symptoms					
Meier et al,[22] 2001	Billewicz score at 12 mo	31	32	0.10 (-0.39 to 0.59)	7.34
Razvi et al,[32] 2007	ThyD QoL at 3 mo	100	100	0.11 (-0.29 to 0.50)	11.66
Reuters et al,[31] 2012	Zulewski score at 6 mo	32	25	-0.22 (-0.74 to 0.31)	6.52
Stott et al,[12] 2017	ThyPRO hyperthyroid score at 12 mo	318	320	0.01 (-0.15 to 0.16)	74.48
Subtotal				0.01 (-0.12 to 0.14)	100.00
Overall effect: I^2=0.0%; *P*=.79					
Fatigue and tiredness					
Stott et al,[12] 2017	ThyPRO tiredness score at 12 mo	318	320	-0.01 (-0.16 to 0.15)	100.00
Depressive symptoms					
Jorde et al,[26] 2006	Beck Depression Inventory at 12 mo	35	32	-0.26 (-0.74 to 0.22)	24.09
Parle et al,[16] 2010	HADS at 12 mo	52	42	-0.11 (-0.52 to 0.29)	33.72
Reuters et al,[31] 2012	Beck Depression Inventory at 6 mo	32	25	0.06 (-0.47 to 0.58)	20.39
Najafi et al,[24] 2015	Beck Depression Inventory at 3 mo	30	30	-0.05 (-0.56 to 0.46)	21.80
Subtotal				-0.10 (-0.34 to 0.13)	100.00
Overall effect: I^2=0.0%; *P*=.84					



BDI indicates Beck Depression Inventory; EQ-5D, Euro Quality of Life 5 Dimensions Questionnaire; HADS, Hospital Anxiety and Depression Scale; ThyDQoL, 18-Item Underactive Thyroid-Dependent Quality of Life; ThyPRO, Thyroid-Related Quality-of-Life Patient-Reported Outcome Measure. Mean values of the quality-of-life and mood-related outcome scales per study group are shown in eTable 2 in Supplement 1. Weights are derived from a fixed-effects meta-analysis of standardized mean differences. Sizes of data markers indicate weight of studies. All effect sizes are standardized. Standardized mean differences of 0.2, 0.5, and 0.8 correspond to small, moderate, and large clinical effects, respectively.[55] See Table for descriptions of outcome scales. Numbers differ between participants randomized and participants with available outcome data in the studies by Kong et al,[27] Jorde et al,[26] Reuters et al,[31] Stott et al,[12] and Meier et al[22] (see Table and eTable 2). The study by Razvi et al[32] is a crossover study that included 100 participants.

Figure 2. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Cognitive Function

Source	Cognition Function Scale	No. of Participants Levothyroxine	No. of Participants Placebo	Standardized Mean Difference (95% CI)	Weight, %
Jorde et al,[26] 2006	Composite cognitive score at 12 mo	35	32	0.32 (-0.17 to 0.80)	7.72
Parle et al,[16] 2010	MMSE score at 12 mo	52	42	0.01 (-0.39 to 0.42)	10.87
Aghili et al,[25] 2012	Wechsler memory score at 3 mo	30	30	0.47 (-0.04 to 0.98)	6.82
Stott et al,[12] 2017	Letter-Digit Coding Test score at 18 mo	318	320	0.04 (-0.12 to 0.19)	74.59
Overall effect: I^2=14.7%; *P*=.32				0.09 (-0.05 to 0.22)	100.00

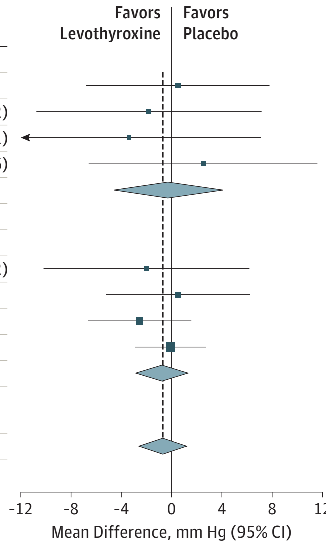


MMSE indicates Mini Mental State Examination. Mean values of the cognition scale per study group are shown in eTable 2 in Supplement 1. Weights are derived from a fixed-effects meta-analysis of standardized mean differences. Sizes of data markers indicate weight of studies. Dashed vertical line represents overall mean effect. All effect sizes are standardized. Standardized mean differences of 0.2, 0.5, and 0.8 correspond to small, moderate, and large clinical effects, respectively.[55] See Table for descriptions of outcome scales. Numbers differ between participants randomized and participants with available outcome data in the studies by Jorde et al[26] and Stott et al[12] (see Table and eTable 2).

associated with benefit regarding the secondary outcomes. For depressive symptoms (4 studies; 278 participants), the SMD was −0.10 (95% CI, −0.34 to 0.13; I^2=0.0%) (Figure 1)[16,24,26,31]; on the Hospital Anxiety and Depression Scale (range, 0-21; higher scores indicate worse depressive symptoms), this SMD would represent a difference of 0.28 (95% CI, −0.36 to 0.95) in favor of placebo. For cognitive function (4 studies; 859 participants), the SMD was 0.09 (95% CI, −0.05 to 0.22; I^2=14.7%) (**Figure 2**)[12,16,25,26]; on the Letter-Digit Coding Test (range, 0 or higher [no upper limit]; higher scores indicate better cognitive function), this SMD would represent a difference of 1.01 (95% CI, −0.56 to 2.46) in favor of levothyroxine. For muscle

Figure 3. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Systolic Blood Pressure

Source	No. of Participants		Systolic Blood Pressure, mm Hg (95% CI)		Mean Difference, mm Hg (95% CI)	Weight, %
	Levothyroxine	Placebo	Levothyroxine	Placebo		
After 3-6 mo of treatment						
Monzani et al,[33] 2001	10	10	117.3 (104.0-130.6)	116.8 (98.0-135.6)	0.5 (-6.8 to 7.8)	6.68
Razvi et al,[32] 2007	100	100	132.8 (88.1-177.5)	134.6 (89.7-179.5)	-1.8 (-10.8 to 7.2)	4.42
Nagasaki et al,[36] 2009	48	47	128.8 (77.6-180.0)	132.2 (81.0-183.4)	-3.4 (-13.9 to 7.1)	3.22
Ersoy et al,[29] 2012	30	30	131.7 (96.6-166.8)	129.2 (94.1-164.3)	2.5 (-6.6 to 11.6)	4.33
Subtotal					-0.3 (-4.6 to 4.1)	18.65
Overall effect: I^2 = 0.0%; *P* = .84						
After 12 mo of treatment						
Monzani et al,[34] 2004	23	22	112.0 (82.6-141.4)	114.0 (88.5-139.5)	-2.0 (-10.2 to 6.2)	5.29
Yazici et al,[35] 2004	23	22	123.6 (104.4-142.8)	123.1 (103.9-142.3)	0.5 (-5.2 to 6.2)	10.82
Zhao et al,[11] 2016	210	159	136.0 (96.6-175.5)	138.6 (99.7-177.4)	-2.5 (-6.6 to 1.6)	21.02
Stott et al,[12] 2017	318	320	138.3 (101.6-175.0)	138.4 (103.5-173.3)	-0.1 (-2.9 to 2.7)	44.22
Subtotal					-0.8 (-2.9 to 1.3)	81.35
Overall effect: I^2 = 0.0%; *P* = .75 Heterogeneity between groups: *P* = .83						
Overall					-0.7 (-2.6 to 1.2)	100.00
Overall effect: I^2 = 0.0%; *P* = .95						



Weights are derived from a fixed-effects meta-analysis of differences in blood pressure. Sizes of data markers indicate weight of studies. Dashed vertical line represents overall mean effect. Numbers differ between participants randomized and participants with available outcome data in the study by Stott et al[12] (see Table and eTable 2 in Supplement 1). The study by Razvi et al[32] is a crossover study that included 100 participants.

strength (2 studies; 695 participants), the SMD was 0.1 (95% CI, −0.1 to 0.2; I^2=0.0%) (eTable 4 in Supplement 1)[12,31]; in handgrip strength, this SMD would represent a difference of 1.12 kg (95% CI, −1.12 to 2.24 kg) in favor of levothyroxine. Systolic blood pressure (8 studies; 1372 participants) was −0.7 mm Hg (95% CI, −2.6 to 1.2 mm Hg; I^2=0.0%) (**Figure 3**).[11,12,29,32-36] Body mass index (calculated as weight in kilograms divided by height in meters squared) (15 studies; 1633 participants) was 0.2 (95% CI, −0.4 to 0.8; I^2=45.5%) (**Figure 4**).[11,12,23,27-30,32-39] Only the TRUST trial (the largest included study, with 737 participants randomized) evaluated fatigue/tiredness, cardiovascular events, mortality, and adverse effects.[12] No beneficial or harmful association between thyroid hormone therapy and these outcomes was reported (Figure 1 and eTables 2 and 4 in Supplement 1). No study included pain as an outcome. Detailed results are summarized in eTables 2 and 4. Subgroup analyses were not performed because the number of studies for a single outcome was too small and/or there was low to moderate heterogeneity such that no exploration was indicated. The meta-analyses for general quality of life and body mass index showed moderate heterogeneity (I^2=66.7% and I^2=45.5%, respectively). Therefore, post hoc sensitivity analyses were performed excluding studies showing a statistically significant benefit of placebo.[23,27,30] Results remained similar, but heterogeneity was lower (for general quality of life, SMD, −0.08 [95% CI, −0.22 to 0.06; I^2=34.7%]; for body mass index, −0.2 [95% CI, −0.6 to 0.2; I^2=1.6%]). We did not formally assess publication bias. Based on the negative results, there was no indication that positive studies were published while negative studies remained unpublished.

The overall quality of the 21 included studies was good, with only 9 of 126 items judged to be at high risk of bias (eTable 3 in Supplement 1); 2 trials had low risk of bias for all criteria,[12,22] including the largest and most recent trial,[12] and only 1 trial, the second largest and second most recent, had a high risk of bias in 3 of 6 domains.[11] Accordingly, the quality of evidence assessed with the GRADE tool was high regarding the main outcomes of general quality of life and thyroid-related symptoms, as well as regarding muscle strength, blood pressure, and body mass index (eTable 4 in Supplement 1). The quality of evidence was moderate for depressive symptoms, fatigue/tiredness, cognitive function, and adverse effects, whereas it was low for cardiovascular events and mortality (eTable 4).

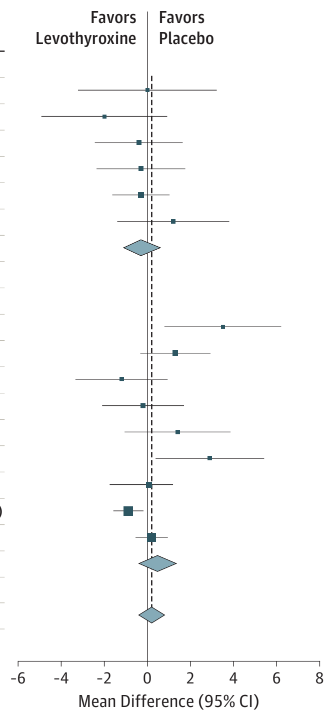
Discussion

In this systematic review and meta-analysis of RCTs in nonpregnant adults with subclinical hypothyroidism, thyroid hormone therapy was not associated with benefit regarding general quality of life, thyroid-related symptoms, depressive symptoms, fatigue/tiredness, cognitive function, muscle strength, blood pressure, or body mass index.

Compared with prior systematic reviews and meta-analyses published between 2007[8] and 2015,[9] this meta-analysis included 2 recent randomized trials, which were the largest trials published to date on this topic.[11,12] Overall, the quality of evidence reported herein was moderate to high. Quality of evidence was high regarding the primary outcomes of this review (general quality of life and thyroid-related symptoms). Results of this review consistently demonstrated no association of thyroid replacement therapy with improved outcomes, including a relatively large number of diverse outcomes. Most outcomes, except cardiovascular events and mortality, had narrow confidence intervals. In addition, this meta-analysis focused on patient-centered outcomes such as quality of life and

Figure 4. Randomized Clinical Trials of Levothyroxine Therapy in Subclinical Hypothyroidism Outcomes on Body Mass Index

Source	No. of Participants: Levothyroxine	No. of Participants: Placebo	Body Mass Index (95% CI): Levothyroxine	Body Mass Index (95% CI): Placebo	Mean Difference (95% CI)	Weight, %
After 3-6 mo of treatment						
Monzani et al,[33] 2001	10	10	23.1 (13.9-32.3)	23.1 (18.8-27.4)	0.0 (-3.2 to 3.2)	2.98
Kong et al,[27] 2002	20	14	25.4 (19.1-31.7)	27.4 (17.8-37.0)	-2.0 (-4.9 to 0.9)	3.48
Caraccio et al,[38] 2005	12	11	22.3 (16.4-28.2)	22.7 (19.0-26.4)	-0.4 (-2.4 to 1.6)	5.95
Razvi et al,[32] 2007	100	100	28.1 (17.9-38.3)	28.4 (18.0-38.8)	-0.3 (-2.4 to 1.8)	5.86
Nagasaki et al,[36] 2009	48	47	21.8 (15.5-28.1)	22.1 (15.4-28.8)	-0.3 (-1.6 to 1.0)	9.63
Ersoy et al,[29] 2012	30	30	30.1 (18.3-41.9)	28.9 (20.7-37.1)	1.2 (-1.4 to 3.8)	4.13
Subtotal					-0.3 (-1.1 to 0.6)	32.02
Overall effect: I^2 = 0.0%; *P* = .76						
After 12 mo of treatment						
Cooper et al,[23] 1984	17	16	28.1 (22.9-33.3)	24.6 (15.0 -34.2)	3.5 (0.8 to 6.2)	3.93
Caraccio et al,[39] 2002	24	25	24.1 (18.0-30.2)	22.8 (17.5-28.1)	1.3 (−0.3 to 2.9)	7.81
Monzani et al,[34] 2004	23	22	23.7 (16.8-30.6)	24.9 (17.5-32.3)	-1.2 (-3.3 to 0.9)	5.56
Yazici et al,[35] 2004	23	22	22.8 (16.1-29.5)	23.0 (16.9-29.1)	-0.2 (-2.1 to 1.7)	6.50
Iqbal et al,[37] 2006	32	32	28.4 (17.0-39.8)	27.0 (19.0-35.0)	1.4 (-1.1 to 3.9)	4.55
Teixeira et al,[30] 2008	11	15	27.4 (21.1-33.7)	24.5 (18.0-31.0)	2.9 (0.4 to 5.4)	4.38
Cabral et al,[28] 2011	14	18	25.8 (21.3-30.2)	25.7 (19.8-31.6)	0.1 (-1.7 to 1.9)	6.83
Zhao et al,[11] 2016	210	159	25.8 (19.6-32.0)	26.7 (19.7-33.6)	-0.9 (-1.6 to -0.2)	14.43
Stott et al,[12] 2017	318	320	27.9 (17.9-37.9)	27.7 (18.7-36.7)	0.2 (-0.6 to 1.0)	13.99
Subtotal					0.5 (-0.4 to 1.3)	67.98
Overall effect: I^2 = 64.9%; *P* = .004						
Overall					0.2 (-0.4 to 0.8)	100.00
Overall effect: I^2 = 45.5%; *P* = .03						



Weights are derived from a random-effects meta-analysis of differences in body mass index (calculated as weight in kilograms divided by height in meters squared). Sizes of data markers indicate weight of studies. Dashed vertical line represents overall mean effect. Numbers differ between participants randomized and participants with available outcome data in the studies by Kong et al,[27] Teixeira et al,[30] and Stott et al[12] (see Table and eTable 2 in Supplement 1). The study by Razvi et al[32] is a crossover study that included 100 participants.

fatigue, which are the most common symptoms that prompt therapy in general practice.[56]

Although current guidelines are at first sight cautious with treatment recommendations, more than 90% of persons with subclinical hypothyroidism and a thyrotropin level of less than 10 mIU/L would actually qualify for treatment.[6,10,57] However, results of this meta-analysis are not consistent with these guideline recommendations. In addition to absence of an association of thyroid hormone therapy with improved outcomes, thyroid hormone therapy is associated with adverse effects when overtreatment occurs.[5,58,59]

Limitations

This study has several limitations. First, the RCTs included in this meta-analysis used different questionnaires and/or tests for a given outcome in combination with different treatment durations (eg, 4 different cognitive tests in the 4 studies examining cognitive function, with treatment durations ranging from 3 to 18 months). However, little heterogeneity across the study results was observed except for general quality of life and body mass index. For these outcomes, heterogeneity resulted from 3 studies that showed a statistically significant benefit of placebo.[23,27,30] After excluding these studies in post hoc sensitivity analyses, thyroid hormone therapy remained unassociated with benefit for general quality of life and body mass index, and heterogeneity was lower. Therefore, it seems unlikely that this meta-analysis missed a potential beneficial association between thyroid hormone therapy and any outcome analyzed due to inappropriate pooling of overly heterogeneous studies.

Second, only 1 RCT reported on major adverse cardiovascular events. Therefore, definitive evidence is lacking regarding the association of therapy for subclinical hypothyroidism with reduced cardiovascular event rates.[12] Third, RCTs that reported results only qualitatively were excluded from analyses. Fourth, mean thyrotropin values at baseline were less than 7.0 mIU/L in 11 of 21 included RCTs, and only 2 RCTs examined participants with a mean baseline thyrotropin level higher than 10 mIU/L.[22,23] Therefore, the current findings may not be generalizable to people with subclinical hypothyroidism and a thyrotropin level higher than 10 mIU/L. Fifth, the highest mean age in the included studies was 74 years.[12,16] Therefore, these results may not be generalizable to people older than 80 years. Sixth, only 7 of 21 trials (33%) reported hypothyroid symptoms at baseline, and the burden of symptoms was mild to moderate in these trials. The other 14 trials did not describe symptoms at baseline. It is possible that the subgroup of people with subclinical hypothyroidism and a high burden of symptoms would still benefit from treatment. Seventh, patients with subclinical hypothyroidism and "severe" symptoms of hypothyroidism may be underrepresented in clinical trials because they may be treated immediately with levothyroxine and not included in clinical trials.[60] Therefore, results reported herein may not be generalizable to patients with subclinical hypothyroidism who have severe symptoms. Eighth, 2 RCTs (n = 831) included participants with a mean age older than 65 years.[12,16] Their mean thyrotropin level at baseline was between 6.0 and 7.0 mIU/L. Given the possibility that the upper thyrotropin reference limit may increase with age,[61] the 2 studies may have included older individuals with mildly elevated thyrotropin levels who do not represent subclinical hypothyroidism, although current international guidelines do not use different thyrotropin levels according to age to define subclinical hypothyroidism.[6,10,62] However, this phenomenon may have biased the results toward the null. Ninth, it is possible that thyroid hormone therapy is associated with benefit regarding outcomes that were not examined in this meta-analysis (eg, carotid intima-media thickness, various lipid fractions). Tenth, it is possible that treatment of subclinical hypothyroidism may be beneficial in study populations not included in these analyses (eg, patients with subclinical hypothyroidism and renal impairment). Eleventh, the largest RCT to date[12] contributed substantially to the results of this meta-analysis because of the large sample size relative to the other trials (737 of 2192 participants [33.6%]). However, the mean age of participants in the largest trial was 74 years, while the mean age of participants in the studies included herein ranged from 32 to 74 years.

Conclusions

Among nonpregnant adults with subclinical hypothyroidism, the use of thyroid hormone therapy was not associated with improvements in general quality of life or thyroid-related symptoms. These findings do not support the routine use of thyroid hormone therapy in adults with subclinical hypothyroidism.

ARTICLE INFORMATION

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