Association of Thyroid Hormone Therapy with Mortality in Subclinical Hypothyroidism: A Systematic Review and Meta-analysis

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Abstract

Context:

Benefits of thyroid hormone therapy on mortality in adults with subclinical hypothyroidism remain undetermined.

Objective:

To summarize the impact of thyroid hormone therapy on mortality in adults with subclinical hypothyroidism.

Data Sources:

PubMed, Embase, Scopus, Web of Science, and Clinicaltrials.gov from inception until April 25, 2020.

Study Selection:

Studies comparing the effect of thyroid hormone therapy with that of placebo or no therapy in adults with subclinical hypothyroidism on all-cause and/or cardiovascular mortality.

Data Extraction:

Two reviewers independently extracted data and performed quality assessments. Random-effects models for meta-analyses were used.

Data Synthesis:

Five observational studies and two randomized controlled trials with 21,055 adults were included. Overall, thyroid hormone therapy was not significantly associated with all-cause (pooled relative risk [RR] = 0.95, 95% confidence interval [CI]: 0.75–1.22, p = 0.704) or cardiovascular (pooled RR = 0.99, 95% CI: 0.82–1.20, p = 0.946) mortality. Subgroup analyses revealed that in younger adults (aged < 65–70 years), thyroid hormone therapy was significantly associated with a lower all-cause (pooled RR = 0.50, 95% CI: 0.29–0.85, p = 0.011) and cardiovascular (pooled RR = 0.54, 95% CI:

0.37–0.80, p = 0.002) mortality. However, no significant association between thyroid hormone therapy and mortality was observed in older adults (aged ≥ 65–70 years).

Conclusions:

Use of thyroid hormone therapy does not provide protective effects on mortality in older adults with subclinical hypothyroidism. However, thyroid hormone therapy for subclinical hypothyroidism may show benefits on morality in adults aged < 65–70 years.

Keywords: Subclinical hypothyroidism; thyroid hormone therapy; levothyroxine; all-cause mortality; cardiovascular mortality

Introduction

Subclinical hypothyroidism (SH), a biochemical diagnosis, is defined as an elevated serum thyrotropin (TSH) level with a normal free thyroxine level (1). The prevalence of SH is approximately 10% among people living in iodine-sufficient areas, with an increased prevalence observed among women and the elderly (2,3). The fact that TSH levels rise with increasing age (4) may likely lead to an overestimation of the prevalence of SH. Despite the presence of some variations in treatment recommendations across different age and TSH level cutoffs, the consensus is to consider treatment of SH when the TSH level is greater than 10 mIU/L in nonpregnant adults (5-7). The rationale behind treatment in such settings is the potential amelioration of cardiovascular-risk markers, such as myocardial function, lipid profile and vascular function (8-10), and the prevention of progression to overt hypothyroidism (1).

Two landmark randomized controlled trials (RCTs) failed to demonstrate the benefits of levothyroxine treatment in the improvement of hypothyroid symptoms or fatigue among older adults with SH (11,12). A meta-analysis on thyroid hormone therapy (THT) for SH regardless of age was also unable to demonstrate improvements in patients' quality of life and thyroid-related symptoms (13). A recently published meta-analysis showed that SH was not associated with increased all-cause or cardiovascular mortality in older populations (14), whereas another meta-analysis demonstrated that it was associated with higher all-cause mortality and cardiovascular event rates in younger individuals aged < 65 years with a high cardiovascular risk (15).

Despite the ongoing debate surrounding the need for treatment of SH, no meta-analysis has evaluated the effect of THT on mortality in people with the condition. Herein, we conducted a systematic review and meta-analysis to investigate whether THT is associated with a decreased mortality rate in adults with SH.

Methods

Data Sources and Searches

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline (16) in the conduction of this systematic review and meta-analysis. The protocol was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (registration number INPLASY202060086) and PROSPERO (registration number CRD42020182621).

With the help of an experienced informationist, we searched PubMed, Embase, Scopus, Web of Science, and ClinicalTrials.gov for articles that evaluated the treatment effects of THT in patients with SH from inception until April 25, 2020. In brief, we searched for articles using a combination of the following terms: "subclinical hypothyroidism," "thyroxine treatment," and "mortality." Details on the search strategy are presented in the Supplementary Materials file (17). We manually screened the reference lists from the relevant review articles and meta-analyses for additional potentially relevant articles.

Study Selection and Outcomes

Studies were included in the systematic review if: (1) the participants were adults (age ≥ 18 years) with a diagnosis of SH, defined as elevated TSH level with free thyroxine level within reference range. (2) the outcome measurements included all-cause mortality and/or cardiovascular-related mortality with sufficient data on the risk estimates comparing patients with and without THT (thyroxine, triiodothyronine, or a combination of both), and (3) the studies were published as original articles. We excluded studies that focused on children, as well as women who were pregnant or seeking fertility treatment because the indications for treatment in these populations differ from those in the general population. Animal studies or those conducted in laboratory settings were excluded, as were review articles, case reports, editorials, or letters to the editor that did not report original

findings. Two reviewers (C.C.P. and B.B.W.) independently evaluated the eligibility of the studies based on their titles and abstracts.

The primary outcome was all-cause mortality. The secondary outcome was cardiovascular mortality, including death caused by ischemic heart disease, advanced heart failure, cardiac arrest, or other circulatory disorders.

Data Extraction and Quality Assessment

Two authors (C.C.P. and B.B.W.) independently extracted data using a standardized data extraction form that included the author or trial names, publication year, study design, geographic location, funding source, mean follow-up duration, study population, number of participants, sex, mean age, definition of SH, grades of SH, risk estimates, and the covariates adjusted for in the multivariable analyses. For observational studies, we extracted adjusted relative risks (RRs) (such as hazard ratios, incidence rate ratios, or risk ratios) and adjusted odds ratios in cohort and case–control studies, with their standard errors. The estimates with most appropriate adjustments for the confounders were utilized, such as those with adjustment for age, sex, and comorbidities. For RCTs, we extracted the RR if it was directly reported; otherwise, we extracted the mortality event and patient numbers for risk ratio calculation. Corresponding authors were further contacted through email if the data were insufficient for analysis.

The quality of the studies was assessed independently by two reviewers (B.B.W. and R.H.C.) using the Newcastle–Ottawa Scale for cohort studies and Cochrane Risk of Bias Tool for RCTs (18,19). Discrepancies in the data extraction and quality assessment were resolved by other reviewers (H.K.H. and C.C.P.) for the achievement of a consensus.

Data Synthesis and Statistical Analysis

We synthesized the RRs that were obtained from both the RCTs and observational studies for the calculation of the pooled RRs in our meta-analysis. The odds ratios reported in case–control studies were also pooled together with RRs in our primary analyses. Between-study heterogeneity was evaluated using I^2 statistics, and was considered low, moderate, and high at I^2 <50%, 50–75%, and >75%, respectively. We calculated the pooled RRs and their 95% confidence intervals (CIs) using the DerSimonian and Laird random-effects model (20). Pre-defined subgroup analyses were conducted for the assessment of the effects of study-level factors on the pooled estimates, according to study design, sample size, age at entry in the study, baseline cardiovascular disease (CVD) risk, SH grade, and type of ratio (RR or odds ratio). We defined the level of CVD risk as high if the study population had the following baseline diseases: coronary, cerebral, or peripheral artery disease, cardiomyopathy, heart failure, atrial fibrillation, venous thromboembolism, diabetes mellitus, or chronic kidney disease (15). SH was classified as: grade 1 (TSH level 5.0–10 mIU/L) and grade 2 (TSH level > 10 mIU/L) (21,22). The subgroup analyses for grades of SH were performed based on studies that specifically defined the grading in the study population. Potential publication bias was assessed by funnel plots and Egger's regression test (23). Sensitivity analyses were conducted by the omission of each study individually for the evaluation of the influence of each study on the overall pooled estimate. Sensitivity analyses that excluded case–control studies reporting odds ratios were further performed to determine whether pooling odds ratios with RRs affected the study results. All statistical tests were two-sided, with the significance level set at $p < 0.05$, and were performed using Stata version 15.1 (StataCorp).

Results

Search Results

Through the initial systematic literature search, 3,638 studies were retrieved, and seven additional studies were included from the reference lists of relevant articles. After the exclusion of 1,841 duplicates, 1,804 studies underwent title and abstract screening. Based on the eligibility criteria, 477 potentially eligible studies were retrieved for full-text review. Figure 1 illustrates the article selection process. Notably, two cohort studies, one published by Huang et al. (24) and the other by Lillevang- Johansen et al. (25) were excluded as no data for free T4 to confirm SH were provided. Seven published articles, including 21,055 participants, met all the eligibility criteria and were included in the meta-analysis (11,12,21,22,26-28). Two studies were RCTs, and five were observational studies. All seven included studies used levothyroxine for medical intervention.

Two studies—those by Andersen et al. (2015) (21) and Andersen et al. (2016) (22)—used Denmark's national administrative registers. The study cohort enrolled in the study by Andersen et al. (2015) comprised adult citizens of Copenhagen who underwent thyroid function tests in the primary care setting at the Elective Laboratory of the Capital Region, Copenhagen, during 2000–2009 (21). In the study by Andersen et al. in 2016, the cohort comprised adult citizens of three regions in Denmark (including Copenhagen) with known heart disease undergoing thyroid function tests between 1997 and 2011 (22). Some degree of overlap between the two aforementioned studies may be present, particularly pertaining to people in Copenhagen diagnosed with heart disease from 2000–2009. However, as the majority of people enrolled in those two studies were different, both of them were included in our meta-analysis (21,22). Grossman et al., reported that treatment with levothyroxine was associated with significantly increased mortality (adjusted odds ratio = 1.19, 95% CI = 1.03–1.38) in people with SH (28). However, it is unclear whether the reported odds ratio represented the comparison of the level of mortality risk between the levothyroxine treatment and non-treatment arms, or the increased risk of mortality by the number of months of levothyroxine treatment per year

according to the statements in that study. We used the former definition for our meta-analysis as the corresponding data were more conservative and reasonable.

Table 1 presents detailed data on the characteristics of each article. The results of the quality assessment, using the Cochrane Risk of Bias Tool for RCTs and Newcastle–Ottawa Scale for cohort and case–control studies, are presented in Supplemental Tables S1, S2, and S3, respectively (17). The adjusted covariates in each of the cohort studies are shown in Table S4.

Subclinical Hypothyroidism and All-cause Mortality

Seven studies were included in the analyses of all-cause mortality. Overall, in patients with SH, THT was not significantly associated with all-cause mortality (pooled RR = 0.95, 95% CI: 0.75–1.22, p = 0.704). The between-study heterogeneity was high (I^2 = 75.6%) (Table 2; Figure 2). No evidence of publication bias was found according to Egger's test (p = 0.353), as is also supported by the funnel plot (Supplemental Figure S1) (17). The sensitivity analysis, performed with the omission of one study at a time, demonstrated that the pooled RR was robust, with only minor changes (Supplemental Figure S2) (17).

The pre-specified subgroups, according to study design, sample size, baseline CVD risk, and SH grade demonstrated similar results, showing that THT was not significantly associated with all-cause mortality (Table 2; Supplemental Figures S3-S6) (17). However, in the younger subgroup (aged < 65–70 years), THT was significantly associated with a lower all-cause mortality (pooled RR = 0.50, 95% CI: 0.29–0.85, p = 0.011). An association between THT and all-cause mortality was not observed in the older subgroup (aged ≥ 65–70 years) (pooled RR = 1.08, 95% CI: 0.91–1.28, p = 0.363) (Table 2; Figure 3).

Regarding analyses of subgroups based on the type of ratio, the pooled results from six studies reporting RRs showed no significant association between THT and all-cause mortality, while the only one case–control study (Grossman 2017) reporting odds ratio showed higher all-cause mortality

associated with THT (Table 2; Supplemental Figure S7). We further performed sensitivity analyses that excluded Grossman 2017; the results of the overall analyses and all aforementioned subgroup analyses remained similar, indicating the robustness of our findings (for details, please refer to Supplemental Table S5).

Subclinical Hypothyroidism and Cardiovascular Mortality

Five studies were included in the analyses of cardiovascular mortality. Overall, there was no significant association between THT and cardiovascular mortality in patients with SH (pooled RR = 0.99, 95% CI: 0.82–1.20, p = 0.946), with minimal between-study heterogeneity (I^2 = 0%) (Table 2; Figure 4). No evidence of publication bias was found (Egger's test: p = 0.370), as also shown in the funnel plot (Supplemental Figure S8) (17). The sensitivity analysis in which each study was omitted one at a time also demonstrated robust pooled RRs (Supplemental Figure S9) (17).

The subgroup analyses according to study design, sample size, and SH grade showed a similar insignificant association between THT and cardiovascular mortality (Table 2; Supplemental Figures S10-S12) (17). Of note, similar to the results of all-cause mortality, the younger subgroup (aged < 65–70 years) had a significant association between THT and lower cardiovascular mortality (pooled RR = 0.54, 95% CI: 0.37–0.80, p = 0.002). No association between THT and cardiovascular mortality was found in the older subgroup (aged ≥ 65–70 years) (pooled RR = 1.05, 95% CI: 0.87–1.27, p = 0.611) (Table 2; Figure 5).

Discussion

In this systematic review and meta-analysis, comprising seven studies with 21,055 participants, no overall benefit of THT on mortality was demonstrated in patients with SH. However, subgroup analyses demonstrated that in younger adults with SH (aged < 65–70 years), THT was associated with a significant 50% decrease and 46% decrease in all-cause mortality and cardiovascular mortality, respectively. Such benefits were not seen in older adults with SH (aged ≥ 65–70 years). Our results provide further insight on whether THT is beneficial for SH. To the best of our knowledge, this is the

first systematic review and meta-analysis to address the manner in which treatment for SH is associated with mortality in adults.

Several recent large-scale meta-analyses (14,15,29) have shown conflicting results on the association between SH and mortality in the general and older populations; however, few studies have focused on mortality outcomes in patients treated for SH. Nonetheless, both the American Thyroid Association (30) and European Thyroid Association (6) do not recommend the initiation of treatment for SH if the TSH level is 10 mIU/L or lower, unless the symptoms are suggestive of hypothyroidism. A recent clinical practice guideline (5) recommended against the initiation of treatment for SH in adults owing to the absence of clinically relevant benefits, in terms of quality of life or thyroid-related symptoms, as supported by a previous meta-analysis (13).

Younger population (aged < 65–70 years)

Despite the attempts to achieve a euthyroid state with SH treatment in clinical practice, it remains unclear whether THT can yield mortality benefits in patients with SH. In the present meta-analysis, although no mortality benefit of THT was observed in the overall analysis, an approximate 50% decreased risk in both all-cause and cardiovascular mortality in the younger age group was observed. Even though only two cohort studies demonstrated a lower cardiovascular risk that contributed to the benefit shown in the younger age group, both trials demonstrated concordant results.

SH affects several cardiovascular risk factors, including lipid profile, diastolic hypertension, endothelium-dependent vasodilatation, arterial thickness and stiffness, and left ventricular systolic and diastolic function (1,31). Hence, it was proposed that untreated SH may increase the risk of adverse cardiovascular outcomes owing to its adverse effects on cardiovascular and metabolic parameters (1). A recent meta-analysis of the general population showed that compared with euthyroidism, SH was related to an increase in both all-cause mortality and cardiovascular mortality (29).

Regarding THT for treating SH, improved cardiac function and vascular endothelial function were observed in several small interventional trials (31). However, there was no significant decrease in systolic blood pressure reported in a recent meta-analysis for those patients treated versus not treated for SH (13). In another systematic review, among several cardiovascular markers, including total cholesterol, low-density lipoprotein, high-density lipoprotein and triglycerides, only total cholesterol level significantly improved with THT for SH (32). Specifically, THT was shown to effectively decrease the total cholesterol level in individuals with grade 1 SH in an RCT (33). Despite the lack of robust evidence indicating THT induces significant improvements in surrogate cardiovascular parameters in patients with SH, its potential benefit of reducing all-cause and cardiovascular mortality in the younger population is an important finding to guide clinical treatment decision making.

Older population (aged ≥ 65–70 years)

A recent meta-analysis targeting the older population (aged ≥ 60 years) suggested that compared with euthyroidism, SH was not significantly associated with either an increased all-cause mortality or cardiovascular mortality (14). In our meta-analysis, THT was not significantly associated with all-cause or cardiovascular mortality in older individuals with SH. It has been shown that the degree of improvement in cardiovascular parameters weakens with increasing age (34,35). Additionally, the U.S. Preventive Services Task Force found that the treatment benefits of THT on lipid-related parameters were not statistically significant, and that the level of clinical significance was uncertain (36). There is a lack of overwhelming evidence demonstrating that THT is linked to lower rates of cardiovascular events and/or mortality in elderly patients (37).

The administration of thyroid hormone may not be beneficial in older adults. First, the application of age-adjusted TSH reference ranges in clinical practice (38) is advocated, as SH is a laboratory test-defined disease. A shift toward higher TSH levels with increasing age has been observed (4), indicating an age-related population shift rather than a true increase in the

hypothyroidism incidence rate in older people. Second, levothyroxine has a narrow therapeutic window, and higher rates of overtreatment have been observed in elderly people (1). In a previous study, approximately 40–50% of elderly patients taking levothyroxine had a TSH level lower than 0.45 mIU/L (39). In our meta-analysis, six of the seven included studies provided valuable data for the older age group. The finding of no association between THT and mortality in older SH individuals was compatible with results in the existing literature.

Grading of Subclinical Hypothyroidism

A previous meta-analysis revealed that compared with the euthyroid general population, a significant increase in cardiovascular mortality, but not all-cause mortality, was observed in those with grade 1 SH with TSH 7.0–9.9 mIU/L, and grade 2 SH (TSH ≥ 10.0 mIU/L) (40). According to a recent comprehensive review, levothyroxine was recommended for grade 1 SH when TSH was between 7.0 to 9.9 mIU/L if the patient's age is < 65 years, and for grade 2 SH regardless of age, for the prevention of progression to overt hypothyroidism and to help reduce the rates of cardiovascular events and cardiovascular mortality (1). The recommendation was established based on the association observed between SH and increased rates of the above-mentioned outcomes, and not based on evidence stating that treatment could reduce the occurrence rates of those outcomes (1).

In our present meta-analysis, which compared SH patients with and without treatment and focused on mortality risk, only the studies by Andersen et al., in 2015 and 2016 included subgroup analyses for grades 1 and 2 SH (21,22). No significant difference in all-cause or cardiovascular mortality was shown between each grade when treatment was provided. As the results were based on only two observational studies conducted in the same country—Denmark, further studies are warranted to validate this finding and determine whether it can be extrapolated to other populations.

Clinical Implications

Our study's results have the potential to guide clinicians in the prescription of THT for SH. The overall results are aligned with the current consensus that recommends not routinely treating patients with SH (5). However, based on the results of our subgroup analyses, the initiation of treatment for SH in younger adults may provide a protective effect, given the significant risk reduction in all-cause and cardiovascular mortality. This updated evidence provides important clinical insights and reassures clinicians that treating patients aged < 65–70 years is not harmful but beneficial in decreasing mortality risk. As older populations with SH do not show increased mortality (14) and THT is associated with neither a symptomatic (13) nor a mortality benefit, given the increased treatment burden (41), healthcare professionals should consider not prescribing THT to older patients aged ≥ 65–70 years with SH. However, recommendations are not conclusive for the different severities of SH, given the insignificant results in the subgroup analysis for grade 1 versus grade 2 SH.

The median TSH level at the initiation of THT dropped from 8.7 to 7.9 mIU/L between 2001 and 2009, and older individuals were found to have higher odds of starting thyroid hormone treatment with a TSH level of 10.0 mIU/L or lower (41). Unlike younger adults, older people represent a heterogeneous population as they may present with a wide range of disabilities and comorbidities. Individualized treatment for people aged 65–70 years or older should be implemented, as overtreatment could result in iatrogenic thyrotoxicosis and adverse effects such as atrial fibrillation, osteoporosis and fracture (1,42). The elimination of unnecessary treatment will help to mitigate the burden of polypharmacy many elderly individuals face.

Limitations

This meta-analysis has several limitations. First, the study size was small because of the limited number of published articles focusing on the mortality effects associated with thyroid hormone treatment for SH. Despite the promising risk reduction in mortality in the younger age group treated with THT, we should interpret these results cautiously as only two studies were included in this subgroup analysis. Second, the included RCTs had much shorter median duration of follow-up compared with observational studies and may be underpowered to detect the incidence of all-cause or cardiovascular mortality. However, the requirement of prohibitively large samples sizes of people with SH makes the performance of such randomized trials with mortality as the primary endpoint difficult. Third, as most included studies were conducted in Europe, the homogeneity of the study populations and geographic locations may prohibit the generalization of the results to the general population across different geographic locations and ethnicities.

Conclusions

In this systematic review and meta-analysis comprising 21,055 participants, we found that the use of THT was not associated with all-cause and cardiovascular mortality overall and in older patients with SH. However, subgroup analyses suggested that THT may have beneficial effects on both all-cause and cardiovascular mortality among younger individuals with SH. These findings may support the use of THT in adults aged < 65–70 years with SH. Further high-quality prospective studies are warranted to validate the findings and determine causality.

Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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Figure legends

Figure 1:

Flow diagram of the literature search and article selection.

Figure 2:

Forest plot of the relative risk of all-cause mortality associated with thyroid hormone therapy in patients with subclinical hypothyroidism.

Figure 3:

Forest plot of the relative risk of all-cause mortality associated with thyroid hormone therapy in subgroups according to a younger or older age.

Figure 4:

Forest plot of the relative risk of cardiovascular mortality associated with thyroid hormone therapy in patients with subclinical hypothyroidism.

Figure 5:

Forest plot of the relative risk of cardiovascular mortality associated with thyroid hormone therapy in subgroups according to a younger or older age.

Table 1. Characteristics of the seven included studies focusing on thyroid hormone therapy for subclinical hypothyroidism in adults

Author/ Trial name	Year	Study design	Country	Funding Source	Participants (database)	Study size (n)	Mean age (year)	Female, No. (%)	Intervention	Control	Median Follow-up, (year)	Definition of SH
Razvi[26]	2010	Retrospective cohort	UK	Not declared	Whickham Survey	97	49.9	76.3	Levothyroxine	Untreated	20†	TSH 6.0 - 15.0 mIU/L and normal total T4 (46 - 174 nmol/L)
Razvi[27]	2012	Retrospective cohort	UK	Non industrial	GPRD	4735	64.1	85.1	Levothyroxine	Untreated	7.6	TSH 5.01 - 10/0 mIU/L and normal FT4 (0.7 - 1.0 ng/dL)
Andersen[21]	2015	Retrospective cohort	Denmark	Non industrial	Five Danish registers*	12212	55.2	83.4	Levothyroxine	Untreated	5	TSH > 5.0 mIU/L and FT4 9 - 22 pmol/L Grade I: TSH 5.0 – 10 mIU/L Grade II: TSH > 10 mIU/L
Andersen[22]	2016	Retrospective cohort	Denmark	Non industrial	Five Danish registers*	1192	73.6	79.8	Levothyroxine	Untreated	5.6	TSH > 5.0 mIU/L and FT4 9 - 22 pmol/L Grade I: TSH 5.0 – 10 mIU/L Grade II: TSH > 10 mIU/L
Grossman[28]	2017	Case-control	Israel	None	CHMO	1977	84.0 (median)	76.7	Death (case)	Alive	5‡	TSH 4.2 - 10 mIU/L and normal FT4 (10 - 20 pmol/L)

TRUST[11]	2017	RCT	UK, Ireland, the Netherlands and Switzerland	Both nonindustrial and industrial	Communities	737	74.4	53.7	Levothyroxine	Placebo	1.5	TSH 4.60 - 19.99 mIU/L and normal FT4
IEMO 80+[12]	2019	RCT	the Netherlands and Switzerland	Both nonindustrial and industrial	Communities	105	85.2	49.5	Levothyroxine	Placebo	1.4†	TSH 4.60 - 19.99 mIU/L and normal FT4

Abbreviations: SH, subclinical hypothyroidism; FT4, free thyroxine; TSH, thyroid stimulating hormone; RCT, randomized controlled trial; GPRD, General Practitioner Research Database; CHMO, Clalit Health Medical Organization database

*Five Danish registers: 1. The Danish National Patient Register, 2. The Civil Registration system, 3. The Danish Register of Causes of Death, 4. The Danish Register of Medicinal Product Statistics, 5. The Danish registers on personal income and transfer payments

†Mean

‡Study period (2012-2016) used in the case-control study

Table 2. Subgroup analyses of pooled relative risks of all-cause and cardiovascular mortality associated with thyroid hormone treatment versus non-treatment

	All-cause mortality				Cardiovascular mortality			
Subgroups	**No. of studies**	**Pooled RR (95% CI)**	**p-value**	**I^2 (%)**	**No. of studies**	**Pooled RR (95% CI)**	**p-value**	**I^2 (%)**
Overall	7	0.95 (0.75–1.22)	0.704	75.6	5	0.99 (0.82–1.20)	0.946	0.0
Study design								
Observational study	5	0.94 (0.73–1.21)	0.608	82.3	3	0.99 (0.82–1.20)	0.938	0.0
Randomized controlled trial	2	1.15 (0.33–4.05)	0.830	42.5	2	1.10 (0.16–7.75)	0.924	0.0
Sample size								
N < 1000	3	0.63 (0.16–2.50)	0.510	69.3	3	0.71 (0.16–3.25)	0.658	0.0
N ≥ 1000	4	0.99 (0.78–1.25)	0.918	82.5	2	1.00 (0.83–1.21)	0.990	0.0
Age at entry*								
< 65–70 years	2	0.50 (0.29–0.85)	0.011	50.7	2	0.54 (0.37–0.80)	0.002	0.0
≥ 65–70 years	6	1.08 (0.91–1.28)	0.363	52.2	4	1.05 (0.87–1.27)	0.611	0.0
Baseline CVD risk								
Low CVD risk	6	0.89 (0.66–1.21)	0.467	78.9	5	0.99 (0.82–1.20)	0.946	0.0
High CVD risk	1	1.17 (0.90–1.52)	0.240	NA	0	NA	NA	NA
Grading of SH								
Grade 1 (TSH <10)	2	1.07 (0.91–1.27)	0.399	0.0	1	1.15 (0.88–1.51)	0.310	NA
Grade 2 (TSH ≥10)	2	1.07 (0.87–1.33)	0.518	0.0	1	0.94 (0.66–1.34)	0.732	NA
Type of ratio†								
Relative risk	6	0.87 (0.62–1.22)	0.423	74.6	5	0.99 (0.82–1.20)	0.946	0.0
Odds ratio	1	1.19 (1.03–1.38)	0.020	NA	0	NA	NA	NA

*Razvi 2012 divided SH patients into subgroups: those younger and older than 70 years and reported outcomes respectively; other studies used 65 years as the cut value of age subgroups. Thus, the subgroups of younger and older SH patients here are assigned as < 65–70 and ≥ 65–70 years, respectively.

†Only Grossman 2017 reported odds ratio; the other studies reported relative risk.

Abbreviations: RR, relative risk; CI, confidence interval; CVD, cardiovascular disease; SH, subclinical hypothyroidism; TSH, thyroid stimulating hormone; NA, not applicable

Figure 1

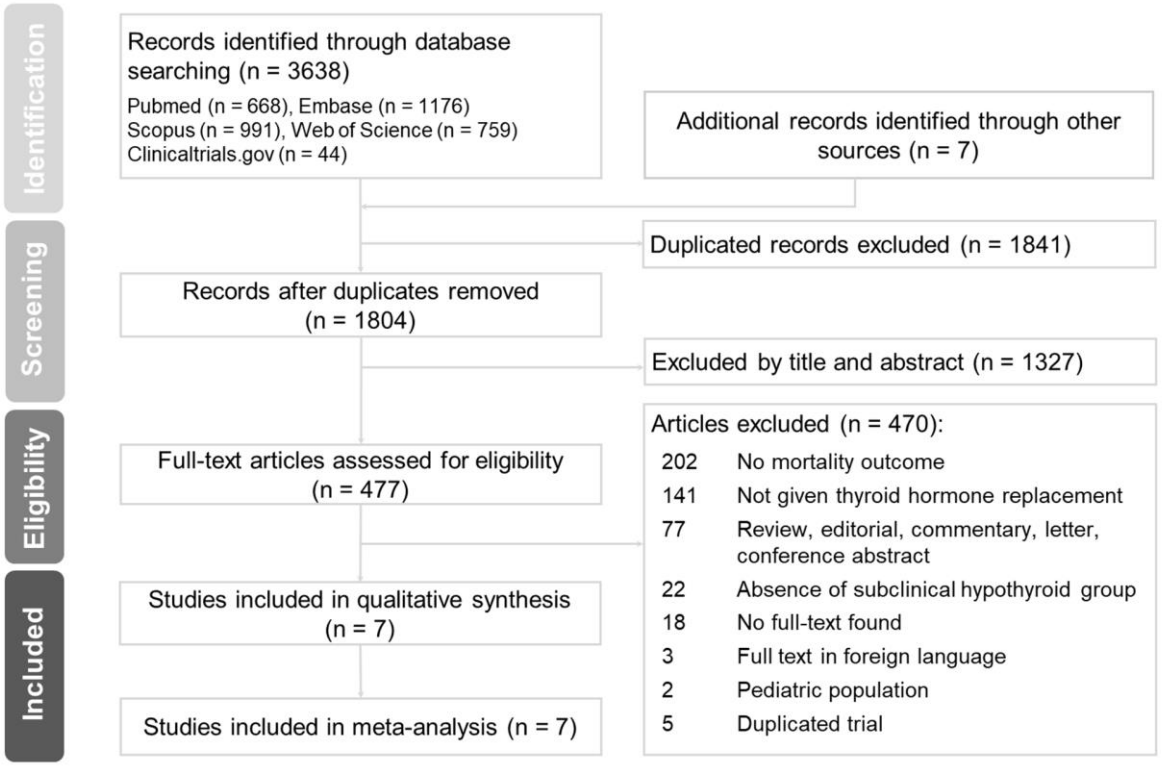
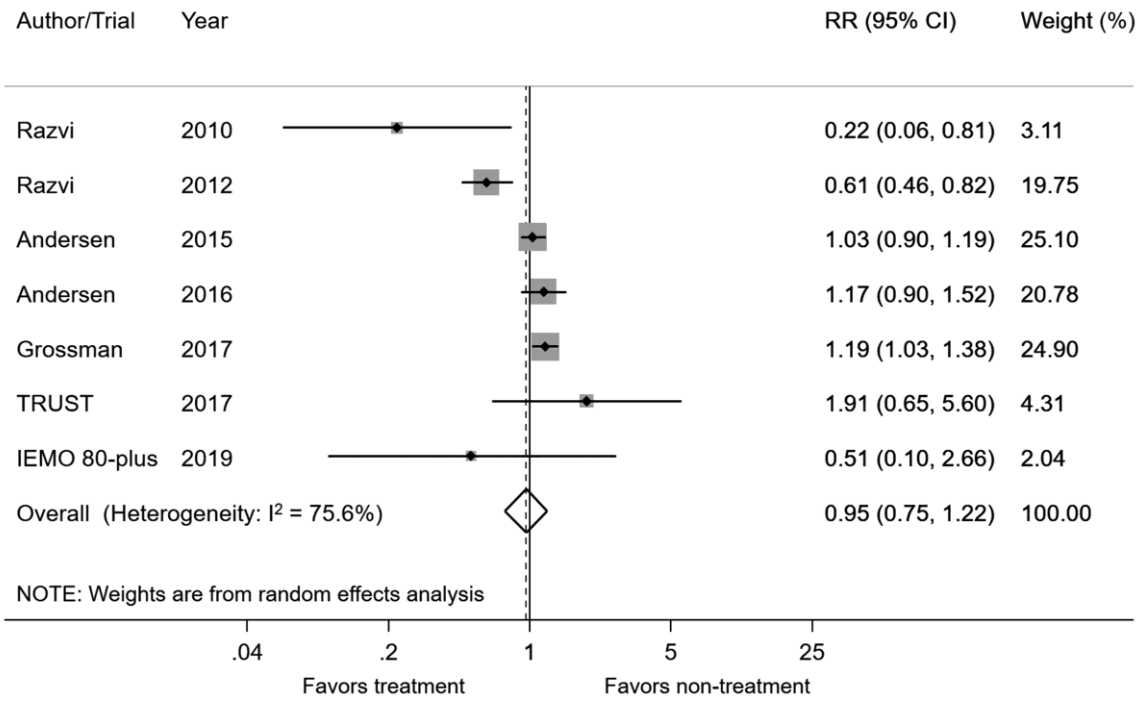


Figure 2



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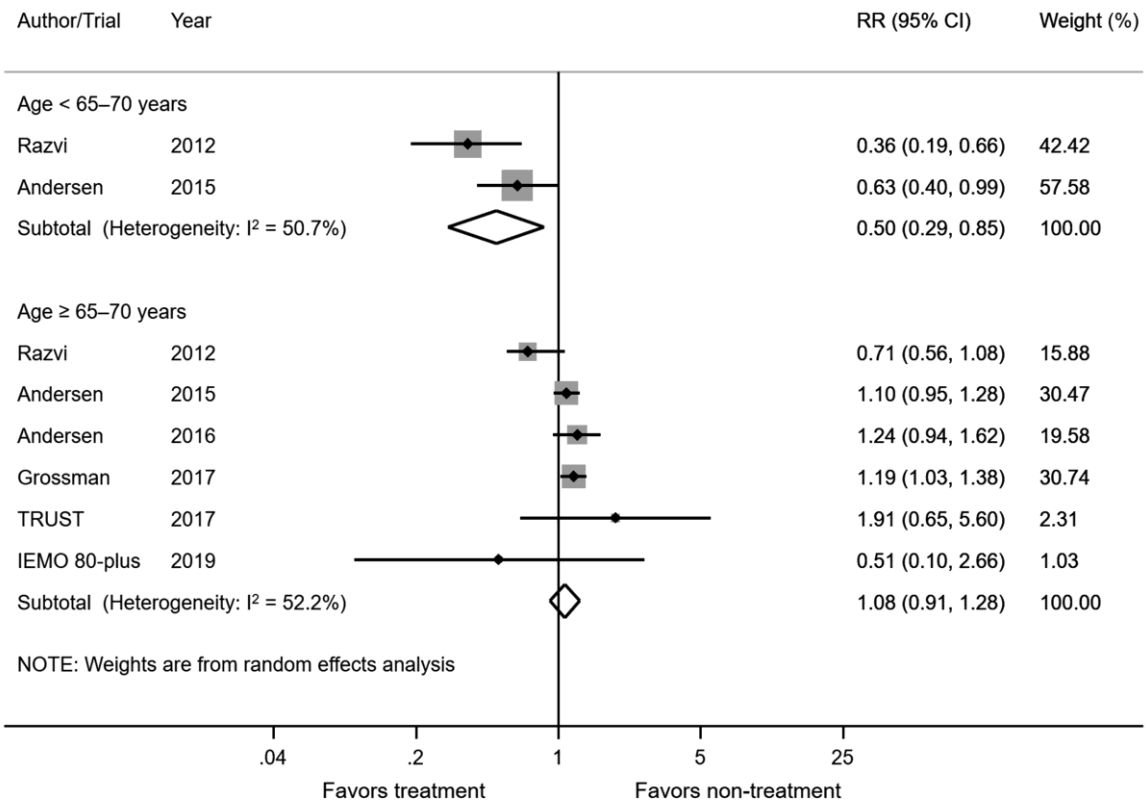

Figure 4

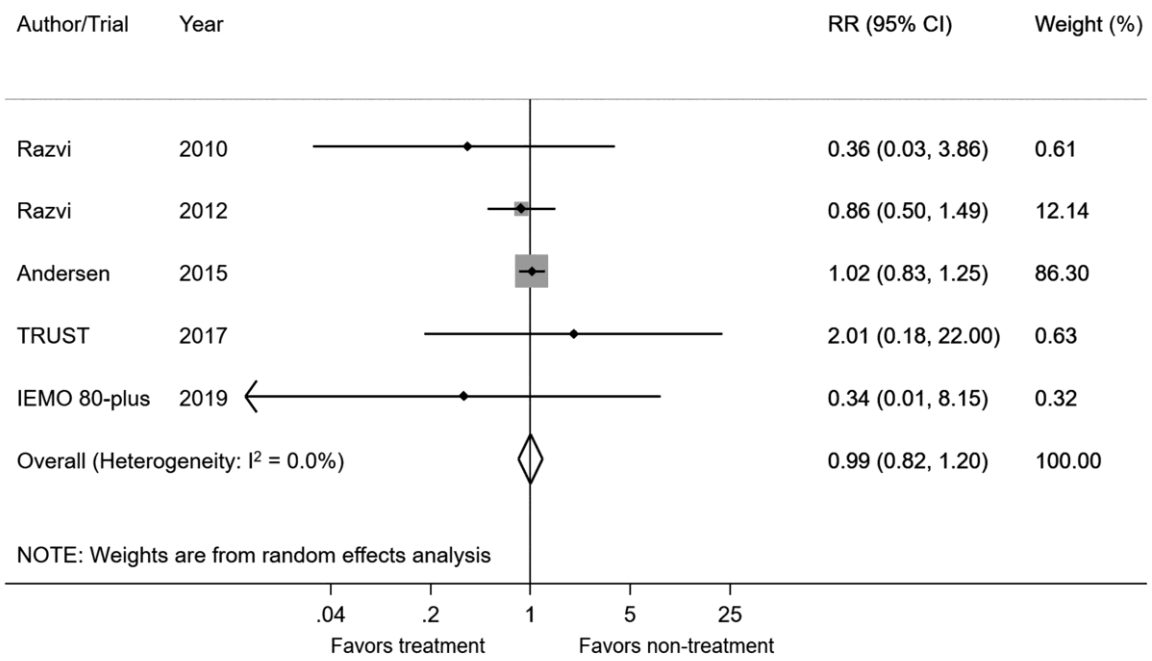

Figure 5