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[Intervention Review]

Recombinant human thyrotropin (rhTSH)-aided radioiodine treatment for non-toxic multinodular goitre

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ABSTRACT

Background

Multinodular goitre is common in women. Treatments for non-toxic multinodular goitre include surgery, levothyroxine suppressive therapy, and radioiodine. Radioiodine therapy is the only non-surgical alternative for non-toxic multinodular goitre. However, a high amount of radioiodine is needed to enable the thyroid nodules to adequately take up the radioiodine, because the multinodular goitre takes up a low amount of iodine. Recombinant human thyrotropin (rhTSH) has been used to increase radioiodine uptake and reduce thyroid volume of the multinodular goitre. Whether the improved reduction of the goitre resulting from rhTSH-stimulated radioiodine therapy is beneficial to the person remains controversial.

Objectives

To assess the effects of recombinant human thyrotropin-aided radioiodine treatment for non-toxic multinodular goitre.

Search methods

We searched the CENTRAL, MEDLINE, Scopus as well as ICTRP Search Portal and ClinicalTrials.gov. The date of the last search of all databases was 18 December 2020.

Selection criteria

We included randomised controlled clinical trials (RCTs) comparing the effects of rhTSH-aided radioiodine treatment compared with radioiodine alone for non-toxic multinodular goitre, with at least 12 months of follow-up.

Data collection and analysis

Two review authors independently screened titles and abstracts for relevance. Screening for inclusion, data extraction, and risk of bias assessment were carried out by one review author and checked by a second. Our main outcomes were health-related quality of life (QoL), hypothyroidism, adverse events, thyroid volume, all-cause mortality, and costs. We used a random-effects model to perform meta-analyses, and calculated risk ratios (RRs) for dichotomous outcomes, and mean differences (MDs) for continuous outcomes, using 95% confidence intervals (CIs) for effect estimates. We evaluated the certainty of the evidence using the GRADE approach.

Main results

We included six RCTs. A total of 197 participants were allocated to rhTSh-aided radioiodine therapy, and 124 participants were allocated to radioiodine. A single dose of radioiodine was administered 24 hours after the intramuscular injection of a single dose of rhTSH. The duration of follow-up ranged between 12 and 36 months.

Low-certainty evidence from one study, with 85 participants, showed uncertain effects for QoL for either intervention. RhTSH-aided radioiodine increased hypothyroidism compared with radioiodine alone (64/197 participants (32.5%) in the rhTSH-aided radioiodine group versus 15/124 participants (12.1%) in the radioiodine alone group; RR 2.53, 95% CI 1.52 to 4.20; 6 studies, 321 participants; moderate-certainty evidence in favour of radioiodine alone). A total of 118/197 participants (59.9%) in the rhTSH-aided radioiodine group compared with 60/124 participants (48.4%) in the radioiodine alone group experienced adverse events (random-effects RR 1.24, 95% CI 0.94 to 1.63; 6 studies, 321 participants; fixed-effect RR 1.23, 95% CI 1.02 to 1.49 in favour of radioiodine only; low-certainty evidence).

RhTSH-aided radioiodine reduced thyroid volume with a MD of 11.9% (95% CI 4.4 to 19.4; 6 studies, 268 participants; moderate-certainty evidence). One study with 28 participants reported one death in the radioiodine alone group (very-low certainty evidence). No study reported on costs.

Authors' conclusions

RhTSH-aided radioiodine treatment for non-toxic multinodular goitre, compared to radioiodine alone, probably increased the risk of hypothyroidism but probably led to a greater reduction in thyroid volume. Data on QoL and costs were sparse or missing.

PLAIN LANGUAGE SUMMARY

Recombinant human thyrotropin-aided radioiodine treatment for non-toxic multinodular goitre

Background

Goitre is an enlargement of the thyroid gland that can be classified as simple, diffuse goitre or multinodular goitre. Nodules (lumps) within the thyroid gland are common and usually benign. They are more frequent in women, the elderly, and in people who live in iodine-deficient areas. Thyroid nodules may occur as a single nodule or as multiple nodules (multinodular). Multinodular goitre can be 'toxic' (producing too much thyroid hormone), or non-toxic (normal thyroid function). Treatments for non-toxic multinodular goitre include surgery, thyroid hormone suppressive therapy, and radioiodine therapy. Usually, higher amounts of radioiodine are needed to enable an appropriate radioiodine uptake in the thyroid nodules. Genetically engineered recombinant human thyroid-stimulating hormone (rhTSH) has been used to increase radioiodine uptake.

We wanted to find out whether rhTSH-aided radioiodine treatment is better for people with non-toxic multinodular goitre compared with radioiodine treatment alone. The outcomes we were specifically interested in were health-related quality of life, underactive thyroid (hypothyroidism), side effects, reduction in thyroid volume, death from any cause, and costs.

What did we look for?

We searched medical databases for studies that:
— were randomised controlled trials (medical studies where participants are put randomly into one of the treatment groups);
— included people with non-toxic multinodular goitre;
— compared rhTSH-aided radioiodine treatment with radioiodine treatment alone;
— tracked participants (follow-up) for at least one year.

What did we find?

We found six studies that included a total of 321 participants. A single dose of radioiodine was administered 24 hours after the intramuscular injection of a single dose of rhTSH. Participants were followed up for 12 to 36 months.

Key results

One study with 85 participants showed there was not a clear beneficial or harmful effect on health-related quality of life for either intervention. Fewer people (53 to 377 of 1000 treated) receiving radioiodine alone experienced hypothyroidism compared with rhTSH-aided radioiodine therapy. It is possible that radioiodine alone resulted in fewer side effects, like discomfort and neck pain, than rhTSH-aided radioiodine, but we need more studies to confirm this finding. On the other hand, rhTSH-aided radioiodine reduced thyroid volume by, on average, 12% more than radioiodine treatment alone. One study, with 28 participants, reported one death in the radioiodine alone group. No study reported on costs.

Certainty of the evidence

We are moderately confident about the results for hypothyroidism and reduction of thyroid volume, mainly because there were only six studies with 268 to 321 participants. We are very uncertain about the results for health-related quality of life and death from any cause,

because there was just one study, with 85 participants that reported these outcomes. We are uncertain about the results for adverse events, mainly because there were not enough studies or participants to reliably evaluate this outcome.

How up to date is this review?
This evidence is up to date to 18 December 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Recombinant human thyrotropin-aided radioiodine compared with radioiodine for non-toxic multinodular goitre

Recombinant human thyrotropin-aided radioiodine compared with radioiodine for non-toxic multinodular goitre

Patient: people with non-toxic multinodular goitre

Settings: outpatients (5 studies); in hospital (1 study)

Intervention: recombinant human thyrotropin (rhTSH)-aided radioiodine

Comparison: radioiodine only

Outcomes	Risk with radioiodine only	Risk with rhTSH aided radioiodine	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Health-related quality of life Assessed with thyroid disease-specific questionnaire ThyPRO Follow-up: 36 months	See comment			85 (1)	⊕⊖⊖⊖ very low[a]	There were no clear differences in symptom improvement in the 17 goitre-specific questions and overall quality of life question among the treatment groups at 6 and 36 months
Hypothyroidism Follow-up: 12 to 36 months	**131 per 1000**	**306 per 1000** (184 to 508)	**RR 2.53** (1.52 to 4.20)	321 (6)	⊕⊕⊕⊖ moderate[b]	
Adverse events Follow-up: 12 to 36 months	**484 per 1000**	**600 per 1000** (455 to 789)	**RR 1.24** (0.94 to 1.63)	321 (6)	⊕⊕⊖⊖ **low**[c]	The fixed-effect model showed a RR of 1.23, 95% CI 1.02 to 1.49 in favour of radioiodine only
Thyroid volume Follow-up: 12 to 36 months	The mean reduction in thyroid volume ranged across control groups from 12.7% to 46.1%	The mean reduction in thyroid volume in the intervention groups was **11.9% higher** (4.4% higher to 19.4% higher)	—	268 (6)	⊕⊕⊕⊖ moderate[b]	

All-cause mortality Follow-up: 24 months	See comment	28 (1)	⊕⊖⊖⊖ very low[d]	Only 1 study reported deaths: 1/10 participants in the radioiodine only group died compared with 0/18 participants in the rhTSH aided radioiodine group
Costs	**Not reported**			

CI: confidence interval; **MD:** mean difference; **rhTSH:** recombinant human thyrotropin ; **RR:** risk ratio; **ThyPRO:** thyroid-related patient-reported outcomes.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Downgraded by three levels because of very serious imprecision (low median sample size, only 1 study reporting outcome)
[b]Downgraded by one level because of imprecision (low median sample size)
[c]Downgraded by two levels because of serious imprecision (low median sample size, CI consistent with benefit and harm)
[d]Downgraded by three levels because of very serious imprecision (one study only with small number of participants, very low number of events)

BACKGROUND

Description of the condition

Multinodular goitre

Goitre is an enlargement of the thyroid gland that can be classified as simple diffuse goitre, or multinodular goitre. Multinodular goitre is a clinically recognisable enlargement of the thyroid gland, characterised by excessive growth of more than one nodule (Medeiros-Neto 2012). Multinodular goitre can be divided into toxic (hyperthyroid), and non-toxic (euthyroid) multinodular goitre based on the thyroid function.

Epidemiology and pathogenesis of non-toxic multinodular goitre

Multinodular goitre is more common in women, with a female to male ratio of 4.5 to 1. The incidence of multinodular goitre in an adult UK population was about 15.5% (Tunbridge 1977). In the US Framingham study, where iodine intake was high (urinary iodine 246 mg/L), investigators detected multinodular goitre by palpation in only 1% of the examined adults (Vander 1954).

The major cause for multinodular goitre is iodine deficiency, and the incidence of multinodular goitre is increased in individuals with a history of chronic iodine deficiency (Medeiros-Neto 2012). It is estimated that about 6% of elderly people in a given population, previously suspected to have iodine deficiency, may have visible multinodular goitre (Berghout 1990). Other risk factors may relate to smoking (Laurberg 2004), natural goitrogens (e.g. cassava, millet, babassu coconut, vegetables from the genus Brassica, and soybean (Doerge 2002; Schröder-van der Elst 2003)), autoimmune disorders (e.g. Grave's disease, Hashimoto's thyroiditis (Pedersen 2001)), certain iodine-rich drugs (e.g. amiodarone (Vagenakis 1975)), and environmental agents (e.g. environmental chemicals, coal-derived pollutants, perchlorate (Braverman 2007; Lindsay 1992)). People with multinodular goitre often have a family history of goitre and surgical removal of nodules (Bayer 2004).

Clinical manifestations of non-toxic multinodular goitre

Most people with non-toxic multinodular goitre have few or no symptoms, except for those with large goitre. Many people are referred to hospital for cosmetic reasons or airway compression symptoms. Compression symptoms are more often seen in people with intrathoracic extensions of the multinodular goitre. Airway compression results in dyspnoea, stridor, cough, and a sensation of shock (Medeiros-Neto 2012). A few people may have a sudden transient pain, with enlargement of a side of the multinodular goitre, secondary to haemorrhage.

Diagnosis of non-toxic multinodular goitre

In people with large goitre, determination of thyroid hormones and imaging techniques are useful to establish the non-toxic nature of the multinodular goitre. The thyroid hormones free thyroxine (f)T4)), free triiodothyronine (f)T3)), thyroid stimulating hormone (TSH), and antithyroid peroxidase (anti-TPO) antibodies are frequently measured during the initial evaluation. Neck palpation is imprecise for both the assessment of thyroid morphology, and size (weight) determination (Medeiros-Neto 2012). Sonography provides an accurate estimate of the goitre and nodule volume, identifies thyroid nodules and cysts, detects microcalcification, and specifies the degree of echogenicity of the nodule. Diagnosis of non-toxic multinodular goitre is established by clinical signs, normal TSH (euthyroid state), and more than one nodule by sonography. Computed tomography (CT) and magnetic resonance imaging (MRI) are useful for assessing a multinodular goitre that extends to the upper mediastinum, and to evaluate the degree of tracheal compression.

Description of the intervention

Treatments for non-toxic multinodular goitre

Treatments for non-toxic multinodular goitre include surgery, levothyroxine suppression therapy, and radioiodine. Surgery efficiently reduces the goitre size, but carries a risk of both surgical and anaesthetic complications. Small multinodular goitres were preferentially treated with levothyroxine suppression therapy. However, levothyroxine suppression therapy seems to be on the wane, due to its low efficacy and adverse effects (Diehl 2005). This leaves radioiodine therapy as the only non-surgical alternative. Treatments vary in different countries. In the United States, surgery is the preferred treatment for people with large multinodular goitres (Bonnema 2000; Bonnema 2002). Radioiodine treatment of non-toxic multinodular goitre was introduced in some European countries about 25 years ago, and thyroidologists in Europe have tended to treat multinodular goitre with radioiodine as an alternative to surgery (Bonnema 2009; Hegedüs 1988).

Radioiodine treatment for non-toxic multinodular goitre

Radioactive iodine (^{131}I) is a β-γ emitting radionuclide with a physical half-life of 8.1 days, a principal γ−ray of 364 KeV, a principal β-particle with a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, and a range in tissue of 0.8 mm. Radioiodine is a good choice for those who decline, or are not fit for surgery. Fine-needle aspiration biopsy (FNAB) should be performed in multinodular goitres, to rule out thyroid malignancy before radioiodine therapy. If a nodule within a multinodular goitre has a cytologic diagnosis of papillary cancer, surgery should be performed. Radioiodine therapy for non-toxic multinodular goitre results in a mean thyroid volume reduction of approximately 40% to 50%, one year after treatment (Huysmans 2000; Le Moli 1999; Nygaard 1993; Wesche 2001). However, the individual response to radioiodine is variable, mostly because of low iodine uptake by the multinodular goitre. For large multinodular goitres, a high radioiodine dose is needed to achieve an adequate radioiodine accumulation in the thyroid nodules. Therefore, large activities of radioiodine are usually required. For this reason, people treated with radioiodine are often subject to hospitalisation, greater exposure to radiation, and higher treatment costs.

Recombinant human thyrotropin-aided radioiodine treatment for non-toxic multinodular goitre

Recombinant TSH is produced by recombinant DNA technology, which is a laboratory method to bring together genetic material from multiple sources. Thyroglobulin levels and radioiodine imaging stimulated by rhTSH were initially used in the diagnosis of metastatic disease of differentiated thyroid cancer, instead of thyroid hormone withdrawal. Later, it was found that rhTSH-aided iodine-131 thyroid remnant ablation, which is as effective as thyroid hormone withdrawal for people with differentiated thyroid cancer after surgery (Ma 2010). It was suggested that rhTSH might be used to increase radioiodine uptake in the various nodules of the multinodular goitre. RhTSH-aided radioiodine therapy for

multinodular goitre improves goitre volume reduction, reduces compression, and eliminates areas of thyroid autonomy (Ceccarelli 2010). It is easier to perform in an outpatient setting, with reduced costs to the public health system, particularly in countries with limited resources and a lack of high-volume thyroid surgeons.

Adverse effects of the intervention

Acute adverse effects include local tenderness, airway compression, and cardiac symptoms (rapid heart beat), which is caused by the surge of thyroid hormones in the blood, and an increase in the goitre volume (in the first 48 hours of radioiodine therapy). Glucocorticoids and β-blockers are used to minimise these acute adverse effects (Fast 2009). A number of studies suggested that these adverse effects are probably dose-dependent, and are negligible with lower rhTSH doses (Ceccarelli 2010; Ceccarelli 2011; Cubas 2009; Fast 2010; Fast 2011) .

The most common long-term adverse effect of rhTSH-aided radioiodine therapy for non-toxic multinodular goitre is permanent hypothyroidism (one third of people). In three reported randomised controlled studies, permanent hypothyroidism at one year was reported in 21%, 63%, and 65% of rhTSH-treated participants (Bonnema 2007; Hegedüs 1988; Silva 2004).

How the intervention might work

Radioactive iodine uptake by thyroid cells is mediated by a glycoprotein located on the cell membrane: the sodium/iodine (Na^+/I^-)symporter (NIS). NIS expression, as well as thyroglobulin production, is TSH-dependent. RhTSH is a heterodimeric glycoprotein, produced by recombinant DNA technology. It is obtained following transfection of a microorganism with genes encoding human TSH α and β subunits; rhTSH is then purified. The amino acid sequence of rhTSH is identical to that of human pituitary TSH, and shares its biochemical properties. It has been shown to stimulate thyroglobulin production and thyroid cell proliferation, as well as radioactive iodine uptake by thyroid cells.

RhTSH not only increases radioiodine uptake (Huysmans 2000; Nieuwlaat 2001), but also leads to a more homogeneous distribution of radioiodine in the gland, and to the thyroid cell activation that makes them more radiosensitive (Ceccarelli 2010). These properties may reduce the radioiodine activity required for the treatment of non-toxic multinodular goitre. RhTSH-aided radioiodine therapy for non-toxic multinodular goitre reduces goitre size by 35% to 55%, compared with radioiodine alone. RhTSH might be particularly useful in people with very large goitres, and in those with a low baseline thyroid radioiodine uptake.

Why it is important to do this review

Narrative reviews about rhTSH-aided radioiodine treatment for non-toxic multinodular goitre suggested that radioiodine therapy was effective for large non-toxic goitre in elderly people. Authors also stated that radioiodine therapy for multinodular goitres should be used in people with comorbidities or high operative risk, and in people with special professions (singers, teachers, speakers), or those who wish a non-invasive treatment modality (Dietlein 2006). Another review reported that rhTSH-stimulated radioiodine therapy of benign non-toxic multinodular goitre is significantly more effective than radioiodine alone, but is still an off-label use (Bonnema 2009).

Recombinant TSH can augment the reduction of a nodular goitre size after radioiodine therapy. However, hypothyroidism is a common complication, and acute airway compression may be a life-threatening complication. Whether the benefits outweigh the risks is controversial. Therefore, we will evaluate the effects of rhTSH-aided radioiodine treatment to help people make informed decisions.

OBJECTIVES

To assess the effects of recombinant human thyrotropin-aided radioiodine treatment for non-toxic multinodular goitre.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled clinical trials (RCTs).

Types of participants

Participants with non-toxic multinodular goitre, undergoing recombinant human thyrotropin (rhTSH)-aided radioiodine treatment.

Diagnostic criteria

Diagnosis of non-toxic multinodular goitre was based on enlargement of the thyroid, normal TSH (within the normal references), and nodules (≥ 2 nodules) identified with imaging techniques, including sonography, CT or MRI.

Types of interventions

We planned to investigate rhTSH plus radioiodine treatment compared with radioiodine alone.

Concomitant interventions had to be the same in both the intervention and comparator groups to establish fair comparisons.

If a trial included multiple arms, we included any arm that met the review inclusion criteria.

Minimum duration of follow-up

Minimal duration of follow-up was one year.

We defined any follow-up period that extended beyond the original time frame for the primary outcome measure as specified in the power calculation of the trial's protocol, as an extended follow-up period, also called 'open-label extension study' (Buch 2011; Megan 2012).

Summary of specific exclusion criteria

We excluded studies of the following category of participants or study design.

- Case-control studies
- Studies with follow-up less than one year
- Participants with toxic goitre

Types of outcome measures

We planned to exclude a study if it did not report at least one of our primary or secondary outcome measures. We extracted the

following outcomes using the methods and time points specified below.

Primary outcomes

- Health-related quality of life
- Hypothyroidism
- Adverse events

Secondary outcomes

- Thyroid volume
- All-cause mortality
- Costs

Method of outcome measurement

- Health-related quality of life: measured by a validated instrument
- Hypothyroidism: defined as low serum-free thyroxine, a high TSH, or both
- Adverse events: e.g. number of participants with cervical discomfort, localised pain, or cardiac problems
- Thyroid volume: measured by CT, or MRI, or ultrasonography
- All-cause mortality: defined as death from any cause
- Costs: based on costs for inpatient clinics, and the number of visits to the outpatient clinics for each group, plus additional costs for services, such as surgery.

Timing of outcome measurement

The follow-up of radioiodine therapy for non-toxic multinodular goitre had to be at least one year for all outcome measures.

Search methods for identification of studies

Electronic searches

We searched the following sources.

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies Online (searched 21 December 2020)
- MEDLINE Ovid (MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily; 1946 to December 18, 2020; searched 21 December 2020)
- Scopus (searched 21 December 2020)
- ClinicalTrials.gov (www.clinicaltrials.gov; searched 21 December 2020)
- World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch/; searched 21 December 2020)

For detailed search strategies, see Appendix 1. We placed no restrictions on the language of publication when searching the electronic databases, or reviewing reference lists of included studies.

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included studies, systematic reviews, meta-analyses, and health technology assessment reports. In addition, we planned to contact authors of included studies to identify any additional information on the retrieved studies, and establish whether we may have missed further studies.

We did not use abstracts or conference proceedings for data extraction, unless full data were available from study authors, because this information source does not fulfil the CONSORT requirements, which consist of "an evidence-based, minimum set of recommendations for reporting randomised trials" (Moher 2010). We planned to present information on abstracts or conference proceedings in the Characteristics of studies awaiting classification table. We defined grey literature as records detected in ClinicalTrials.gov or WHO ICTRP.

Data collection and analysis

Selection of studies

Three review authors (CM, JX, HYL) independently screened the abstracts and titles of every record retrieved by the literature searches, to determine which records we should assess further. We obtained the full-text of all potentially relevant records. In the case of disagreement, we consulted the remainder of the review team, and made a judgment based on consensus. If we could not resolve a disagreement, we planned to categorise the trial as a 'study awaiting classification', and contact the study authors for clarification. We presented an adapted PRISMA flow diagram to show the process of study selection (Moher 2010). We listed all articles excluded after full-text assessment in a Characteristics of excluded studies table and provided the reasons for exclusion.

Data extraction and management

For studies that fulfilled our inclusion criteria, two review authors (CM, SC) independently abstracted relevant population and intervention characteristics, using standard data extraction templates (for details see Characteristics of included studies; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14). In the case of disagreement, we consulted the remainder of the review team, and made a judgment based on consensus. We reported data on efficacy outcomes and adverse events, using standardised data extraction sheets from the Cochrane Metabolic and Endocrine Disorders Group Group.

We provided information about potentially relevant ongoing trials, including the trial identifiers, in the Characteristics of ongoing studies table, and in Appendix 9, a Matrix of trial endpoints (publications and trial documents). We tried to find the protocol for each included trial, and we compared primary, secondary, and other outcomes with the data in publications.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximised the information yield by collating all available data, and we used the most complete data set aggregated across all known publications. We listed duplicate publications, companion documents, multiple reports of a primary study, and trial documents of included studies (such as trial registry information) as secondary references under the study ID of the included study. We also listed duplicate publications, companion documents, multiple reports of a study, and trial

documents of excluded studies (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trials registers

If data from included trials were available as study results in clinical trials registers, such as ClinicalTrials.gov, or similar sources, we made full use of this information and extracted the data. If there was also a full publication of the study, we collated and critically appraised all available data. If an included study was marked as a completed study in a clinical trial register but no additional information (study results, publication or both) was available, we added this study to the Characteristics of studies awaiting classification table.

Assessment of risk of bias in included studies

Three review authors (HW, SQ, HYL) independently assessed the risk of bias for each included trial. In the case of disagreement, we consulted the remainder of the review team, and made a judgment based on consensus. If adequate information was unavailable from the publications, trial protocols, or other sources, we planned to contact the study authors for more detail for risk of bias items.

We used the Cochrane RoB 1 assessment tool, and assigned assessments of low, high, or unclear risk of bias (Corbett 2014; Higgins 2017); for details see Appendix 2; Appendix 3. We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions,* according to the criteria and associated categorisations contained therein *(*Higgins 2017).

Summary assessment of risk of bias

We presented a risk of bias graph and a risk of bias summary figure.

We distinguished between self-reported and investigator-assessed, and adjudicated outcome measures.

We considered the following to be self-reported outcomes.

- Health-related quality of life
- Adverse events

We considered the following outcomes to be investigator-assessed.

- Hypothyroidism
- Thyroid volume
- All-cause mortality
- Costs

Risk of bias for a studies across outcomes

Some risk of bias domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a study. In case**s** of high risk of selection bias, we marked all endpoints investigated in the associated study as being at high risk. Otherwise, we did not perform a summary assessment of the risk of bias across all outcomes for a study.

Risk of bias for an outcome within a study and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both study-level entries and outcome-specific entries). We considered low risk of bias to denote a low risk of bias for all key domains, unclear risk to denote an unclear risk of bias for one or more key domains, and high risk to denote a high risk of bias for one or more key domains.

Risk of bias for an outcome across studies and across domains

These are the main summary assessments that we incorporated into our judgments about the certainty of the evidence in the summary of findings tables. We defined outcomes at low risk of bias when most information came from studies at low risk of bias, unclear risk when most information came from studies at low or unclear risk of bias, and high risk when a sufficient proportion of information came from studies at high risk of bias.

Measures of treatment effect

When at least two included studies were available for a comparison and a given outcome, we expressed dichotomous data as a risk ratio (RR) or odds ratio (OR) with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. thyroid volume in mL), we estimated the intervention effect using the mean difference (MD) with 95% CIs. For continuous outcomes that measured the same underlying concept (e.g. health-related quality of life) but used different measurement scales, we planned to calculate the standardised mean difference (SMD). We planned to express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over studies, cluster-randomised studies, and multiple observations for the same outcome. If more than one comparison from the same study was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison, or appropriately reduced the sample size so that the same participants did not contribute data to the meta-analysis more than once (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does not account for correlation arising from the same set of participants being in multiple comparisons.

We planned to attempt to re-analyse cluster-RCTs that did not appropriately adjusted for potential clustering of participants within clusters in their analyses. The variance of the intervention effects was to be inflated by a design effect. Calculation of a design effect involves estimation of an intra-cluster correlation coefficient (ICC). We planned to obtain estimates of ICCs by contacting study authors, or imputing the ICC values by using either estimates from other included studies that reported ICCs, or external estimates from empirical research (e.g. Bell 2013). We planned to examine the impact of clustering using sensitivity analyses.

Dealing with missing data

If possible, we obtained missing data from the authors of the included studies. We carefully evaluated important numerical data, such as screened, randomly assigned participants, as well as intention-to-treat, as-treated, and per-protocol populations. We investigated attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we critically appraised issues concerning missing data and use of imputation methods (e.g. last observation carried forward).

In studies where the standard deviation (SD) of the outcome was not available at follow-up, or we could not recreate it, we planned to standardise by the mean of the pooled baseline SD from those studies that reported this information.

Where included studies did not report means and SDs for outcomes, and we did not receive the necessary information from study authors, we planned to impute these values by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005).

We planned to investigate the impact of imputation on meta-analyses by performing sensitivity analyses, and we planned to report which studies had imputed SDs, for every outcome.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we did not report study results as the pooled effect estimate in a meta-analysis. We identified heterogeneity (inconsistency) by visually inspecting the forest plots, and by using a standard Chi^2 test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). When we found heterogeneity, we planned to attempt to determine possible reasons for this, by examining individual study and subgroup characteristics.

Assessment of reporting biases

If we included 10 or more studies that investigated a particular outcome, we planned to use funnel plots to assess small-study effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small studies), and publication bias (Sterne 2017). Therefore, we wanted to interpret the results carefully (Sterne 2011).

Data synthesis

We planned to undertake a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. Unless good evidence showed homogeneous effects across trials of different methodological quality, we primarily summarised low risk of bias data using a random-effects model (Wood 2008). We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects, and planned to present a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2009). A prediction interval requires 10 studies to be calculated, and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011).

For rare events, such as event rates below 1%, we planned to use the Peto odds ratio method, provided there was no substantial imbalance between intervention and comparator group sizes, and intervention effects were not exceptionally large. We performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and we planned to carry out the following subgroup analyses, including investigation of interactions (Altman 2003).

- Age (depending on data)
- Dose of rhTSH
- Dose of radioiodine

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes, by restricting analysis to the following.

- Published studies
- Effect of risk of bias, as specified in the Assessment of risk of bias in included studies section
- Very long, or large studies to establish the extent to which they dominate the results
- Use of the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), or country

We planned to test the robustness of results by repeating analyses using different measures of effect size (i.e. RR, OR, etc.), and different statistical models (fixed-effect and random-effects models).

Summary of findings and assessment of the certainty of the evidence

We presented the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias), and external validity, such as directness of results. Two review authors (JX, SC) independently rated the certainty of evidence for each outcome. We resolved differences in assessment by discussion, or by consultation with a third review author (CM).

We included a checklist to aid consistency and reproducibility of GRADE assessments (Appendix 14), to help with standardisation of the summary of findings tables (Meader 2014). Alternatively, we planned to present evidence profile tables, created with GRADEpro GDT, as an appendix (GRADEpro GDT). We presented results for outcomes as described in the Types of outcome measures section. If a meta-analysis was not possible, we presented the results in a narrative format in the summary of findings table. We justified all decisions to downgrade the certainty of the evidence by using footnotes, and we made comments to aid the reader's understanding of the Cochrane Review when necessary.

The summary of findings table provides key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences, for each comparison of alternative management strategies, numbers of participants and studies that addressed each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the summary of findings table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), Review Manager 5 table editor (Review Manager 2020), and GRADEpro GDT (GRADEpro GDT).

Interventions presented in the summary of findings table were recombinant TSH plus radioiodine, compared to radioiodine alone.

We reported the following outcomes, listed according to priority.

1. Health-related quality of life
2. Hypothyroidism
3. Adverse events
4. All-cause mortality
5. Thyroid volume
6. Costs

RESULTS

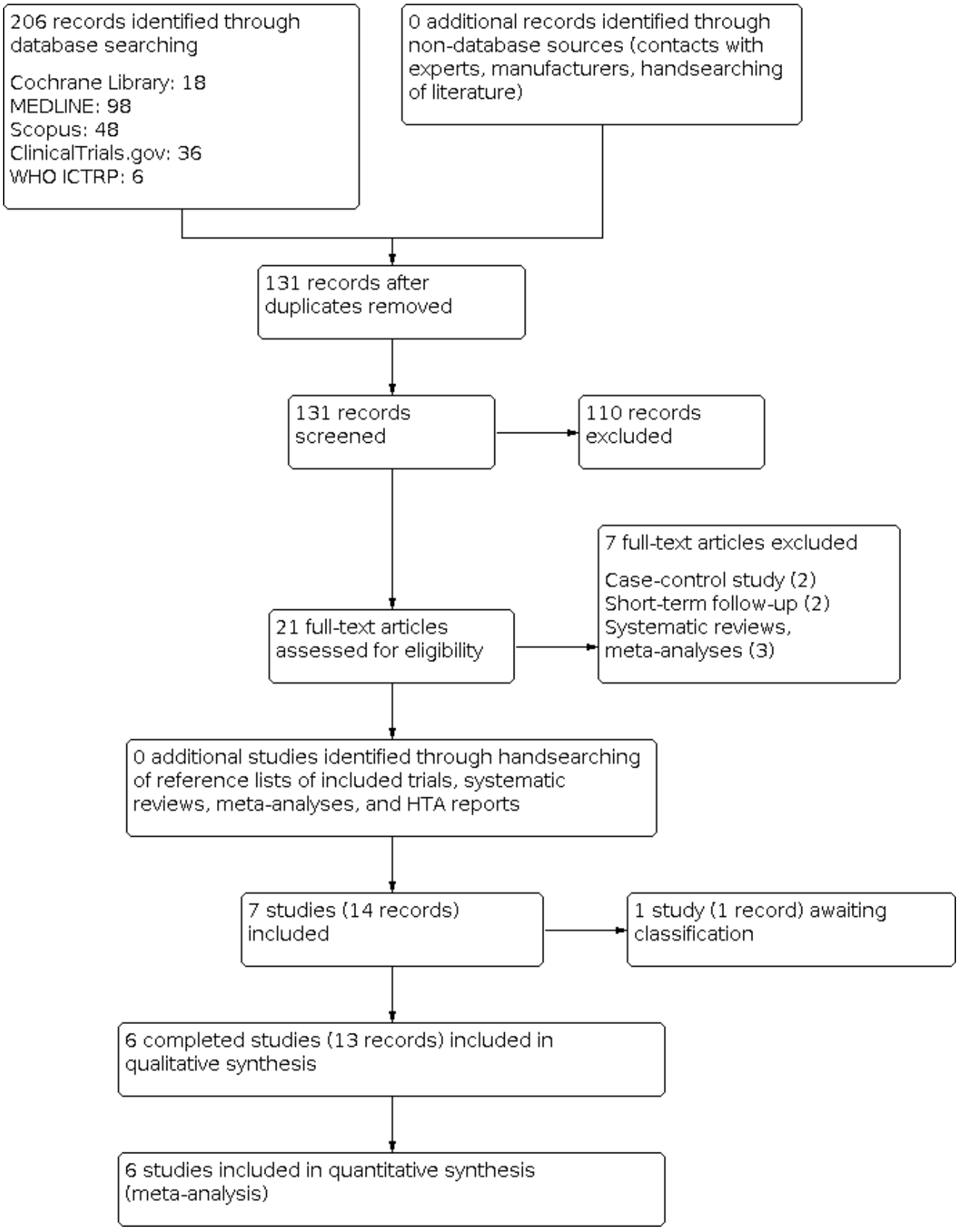
Description of studies

For a detailed description of studies, see Characteristics of included studies, Characteristics of excluded studies, and Characteristics of studies awaiting classification.

Results of the search

Our search identified a total of 206 records. We excluded most of the references on the basis of their titles and abstracts because they clearly did not meet the inclusion criteria. We included six studies, published in 13 records (Albino 2010; Bonnema 2007; Cubas 2009; Fast 2014; Nielsen 2006; Fast 2010), one study is awaiting assessment (NCT00454220; Figure 1).

Figure 1. PRISMA study flow diagram



Included studies

A detailed description of the characteristics of included studies is presented elsewhere (see Characteristics of included studies and appendices). The following is a succinct overview.

Source of data

We obtained all data from the published literature.

Comparisons

The included studies compared recombinant human thyrotropin (rhTSH)-aided radioiodine therapy with radioiodine therapy alone (plus placebo, usually isotonic saline).

Overview of study populations

Six studies included a total of 321 participants; 197 participants were randomised to rhTSH-aided radioiodine, and 124 participants to radioiodine alone. With the exception of one study, all randomised participants finished the studies as planned (Cubas 2009). The individual sample size ranged from 22 to 95.

Study design

All included studies adopted a parallel-group superiority design, and used a placebo control.

Five trials were conducted in single centre (Albino 2010; Bonnema 2007; Cubas 2009; Fast 2010; Nielsen 2006); one study was conducted in 13 centres from six countries (Fast 2014).

Four studies were double-blinded for participants and personnel (Albino 2010; Bonnema 2007; Fast 2010; Nielsen 2006), one study was single-blinded for participants (Fast 2014), and one study did not report blinding conditions (Cubas 2009). Outcome assessors were blinded in four studies (Albino 2010; Bonnema 2007; Fast 2010; Nielsen 2006).

The studies were conducted between 2002 and 2014. The duration of follow-up ranged from 12 to 36 months. No study had a run-in period. No study was terminated early.

Settings

Two of the six studies were conducted in Brasil (Albino 2010; Cubas 2009); three were completed in Denmark (Bonnema 2007; Fast 2010; Nielsen 2006); one multicentre study was conducted in Denmark, Italy, Brazil, Germany, France, and Canada (Fast 2014).

Five studies were conducted in an outpatient setting (Albino 2010; Cubas 2009; Fast 2010; Fast 2014; Nielsen 2006); one in a hospital (Bonnema 2007).

Participants

Ethnic groups were not mentioned in five studies (Albino 2010; Bonnema 2007; Cubas 2009; Fast 2010; Nielsen 2006). The duration of the multinodular goitre was not reported. Women represented the majority of participants in all studies (71% to 100%). The mean age of participants in the studies ranged from 32 to 87 years. Three studies provided limited data on co-medications, co-interventions, or comorbidities (Albino 2010; Cubas 2009; Nielsen 2006).

Diagnosis

Participants were diagnosed with non-toxic multinodular goitre based on thyroid function tests and fine needle aspiration biopsy (Albino 2010), or thyroid function tests with thyroid scintigraphy and ultrasonography (Bonnema 2007; Cubas 2009; Fast 2010; Fast 2014; Nielsen 2006)

Interventions

Two studies reported treatment before the start of the study, which included the methimazole until euthyroidism was achieved (Fast 2010; Cubas 2009). No study had a titration period. Recombinant human thyrotropin was administered intramuscularly, in a single dose. The dose of rhTSH varied between 0.005 mg and 0.3 mg, with an average dose of 0.106 mg. The six studies used a matching placebo as the control intervention.

Outcomes

The six studies explicitly stated a primary endpoint and secondary endpoints.

One study evaluated health-related quality of life using a specific questionnaire (Fast 2014). Hypothyroidism and thyroid volume reduction were measured in all studies. All studies reported on adverse events. One study reported on deaths (Cubas 2009). No study investigated costs. For details see Appendix 10.

Excluded studies

We excluded seven studies after careful evaluation of the full publications. For further details, see Characteristics of excluded studies.

Risk of bias in included studies

For details on risk of bias of included studies see Characteristics of included studies.

For an overview of review authors' judgments about each risk of bias item for individual studies and across all studies see Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

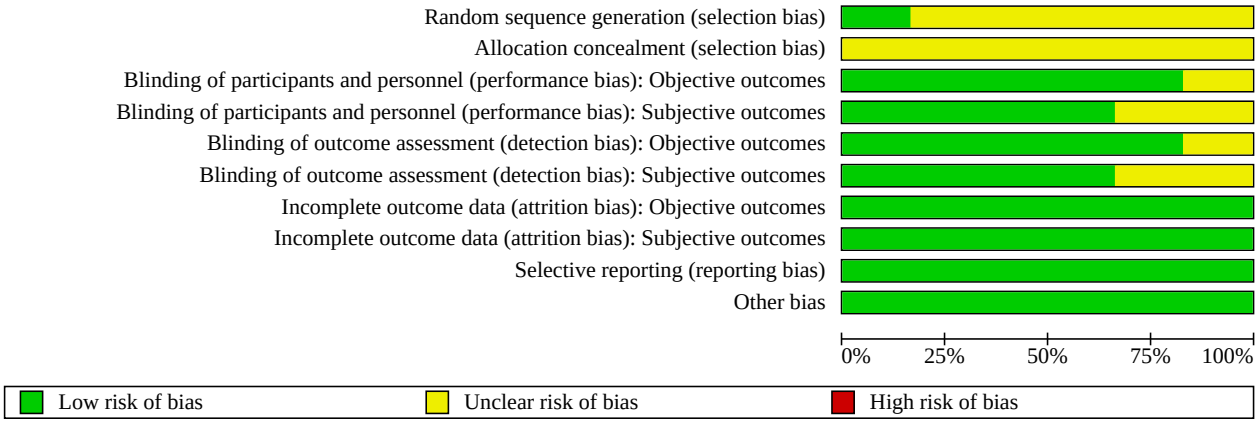
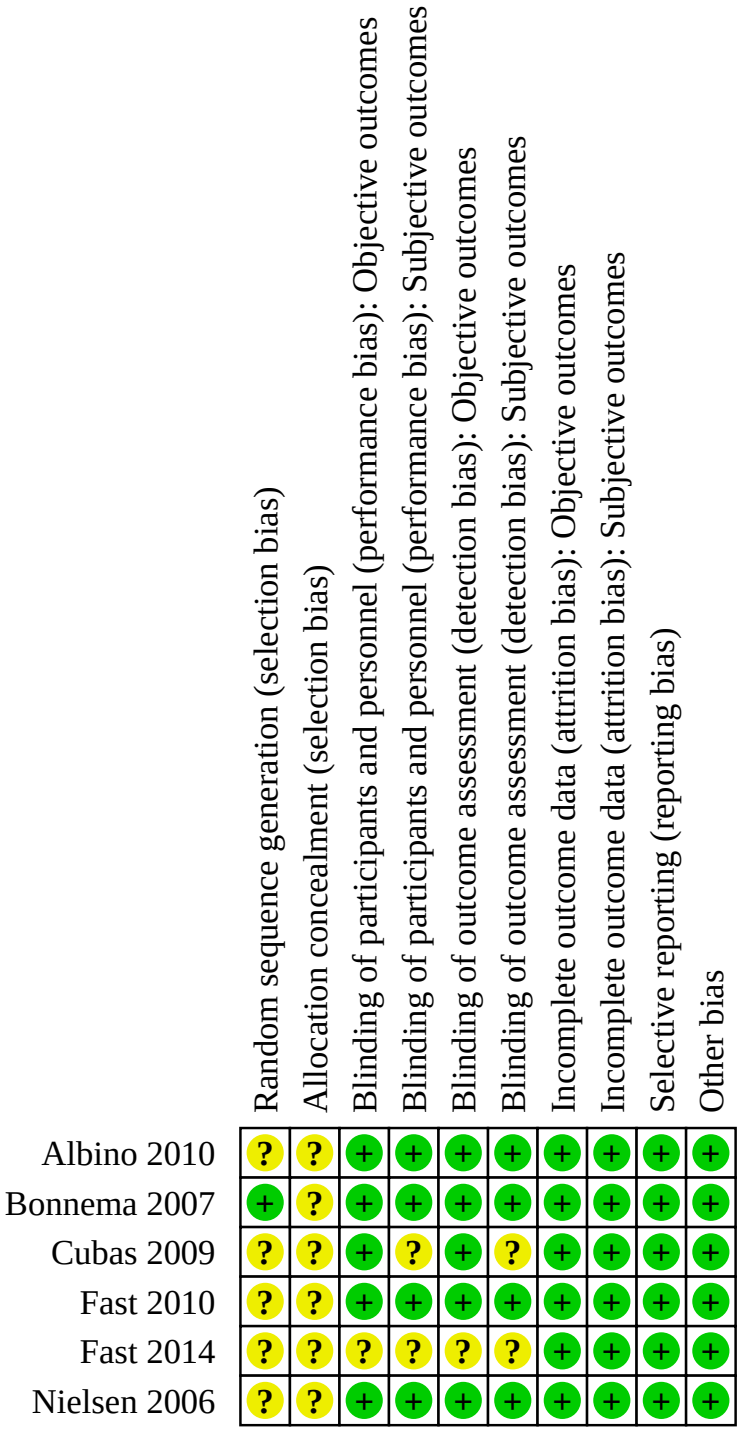


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



We investigated performance bias, detection bias, and attrition bias separately for objective and subjective outcome measures. We defined all-cause mortality, thyroid volume, hypothyroidism, and costs as objective outcome measures, and adverse events (e.g. local tenderness, tracheal compression, cardiac symptoms), and health-related quality of life as subjective outcomes.

Allocation

Randomisation sequence generation was unclear in all studies except one (Bonnema 2007). Allocation concealment was unclear in all studies.

Blinding

Four studies explicitly stated that blinding of the participants and personnel was undertaken, and we judged them as low risk of bias (Albino 2010; Bonnema 2007; Fast 2010; Nielsen 2006). Fast 2014 had a single-blind design with masking of the participants. Cubas 2009 did not report blinding conditions.

Incomplete outcome data

All studies described the number of study withdrawals, and study authors reported that they performed an intention-to-treat analysis. Overall, we judged attrition bias as low for all studies.

Selective reporting

We did not identify reporting bias for any of the included studies.

Other potential sources of bias

We did not identify any other bias for our included studies.

Effects of interventions

See: **Summary of findings 1** Recombinant human thyrotropin-aided radioiodine compared with radioiodine for non-toxic multinodular goitre

Baseline characteristics

For details of baseline characteristics, see Appendix 6 and Appendix 7.

Recombinant human thyrotropin-aided radioiodine compared with radioiodine alone

Primary outcomes

Health-related quality of life

There were no clear differences in symptom improvement in the 17 goitre-specific questions and overall quality of life question among the treatment groups at 6 and 36 months (1 study, 85 participants; very low-certainty evidence).

More than 50% of the participants reported no baseline symptoms for 9 of the 17 goitre-specific questionnaire items. Considering only participants who reported symptoms at baseline, the majority reported an improvement in symptoms after treatment for almost all goitre-specific items and in all treatment groups.

Hypothyroidism

A total of 64/197 participants (32.5%) in the rhTSH-aided radioiodine group and 15/124 participants (12.1%) in the radioiodine only group experienced hypothyroidism. Hypothyroidism increased following rhTSH-aided radioiodine treatment (risk ratio (RR) 2.53, 95% CI 1.52 to 4.20; P < 0.001; 6 studies, 321 participants; Analysis 1.1; moderate-certainty evidence).

Adverse effects

A total of 118/197 participants (59.9%) in the rhTSH-aided radioiodine group and 60/124 participants (48.4%) in the radioiodine only group experienced adverse events, such as mild cervical discomfort or localised pain (for details, see Appendix 13).

The random-effects model did not show evidence of a difference for adverse events (RR 1.24, 95% CI 0.94 to 1.63; P = 0.13; 6 studies, 321 participants; Analysis 1.2; low-certainty evidence). The fixed-effect model showed a RR of 1.23, 95% CI 1.02 to 1.49; P = 0.03 in favour of radioiodine only.

Secondary outcomes

Thyroid volume

RhTSH-aided radioiodine treatment reduced thyroid volume more than radioiodine only (mean difference (MD) 11.91%, 95% CI 4.43 to 19.40; P = 0.002; 6 studies, 268 participants; Analysis 1.3; moderate-certainty evidence).

All-cause mortality

Only one study reported deaths (Cubas 2009): one out of 10 participants in the radioiodine alone group died, compared with none out of 18 participants in the rhTSH-aided radioiodine group (very low-certainty evidence).

Costs

No study reported on this outcome measure.

Subgroup analyses

We did not perform subgroups analyses because there were not enough studies to estimate effects in various subgroups.

Sensitivity analyses

With the exception for the outcome adverse events we did not perform sensitivity analyses due to lack of data.

Assessment of reporting bias

We did not draw funnel plots due to limited number of studies.

Awaiting classification

We identified one single-blind study, planning to enrol approximately 96 participants, investigating 0.01 mg rhTSH or 0.03 mg rhTSH-aided radioiodine therapy versus radioiodine alone (NCT00454220). Study completion date was reported in ClinicalTrials.gov as July 2011; no publication was available.

DISCUSSION

Summary of main results

Only limited data were available from six studies that compared rhTSH-aided radioiodine therapy with radioiodine alone for non-toxic multinodular goitre (Summary of findings 1). rhTSH-aided radioiodine therapy reduced thyroid volume over radioiodine therapy alone, but it also increased hypothyroidism. Using a

random-effects model, the findings were inconclusive between groups regarding the risk of experiencing adverse events, which included mild cervical discomfort, localised pain, and cardiac problems. When we used a fixed-effect model, we got a similar estimate of risk, but the confidence interval shifted to the right, suggesting that rhTSH-aided radioiodine therapy might result in more adverse events.

Overall completeness and applicability of evidence

The included studies differed in terms of diagnosis of non-toxic multinodular goitre, and in medication used before enrolment, to ensure euthyroidism before therapy. Health-related quality of life was measured with a validated questionnaire in one study only (Fast 2010). Thyroid volume was measured in different ways, e.g. by ultrasonography or magnetic resonance imaging, limiting the comparability of intervention effects. Information on co-medications, co-interventions, and comorbidities was limited.

Quality of the evidence

The certainty of the evidence was moderate for hypothyroidism and reduction of thyroid volume, due to imprecision. We are very uncertain about the certainty of the evidence for health-related quality of life and all-cause mortality, due to very serious imprecision. The certainty of the evidence was low for adverse events due to serious imprecision.

Potential biases in the review process

Our body of evidence was limited because only six RCTs with follow-up of at least one year or longer were available. We could have identified more studies had we included shorter follow-up periods, however, the development of hypothyroidism and reduction of thyroid volume need time in non-toxic multinodular goitre. One study awaiting assessment, with long-term follow-up, could potentially contribute to the findings of our review, but it was never published. We did not have adequate information for a judgement of selection bias, because no publication provided enough details. We are uncertain about adverse effects, because our findings were not robust using different statistical models. Additional studies could provide a better picture of the risk-benefit ratio of rhTSH-aided radioiodine treatment compared with radioiodine alone.

Agreements and disagreements with other studies or reviews

Our review agrees with the findings of a recently published systematic review (Xu 2020): the authors of this review also reported a higher incidence of hypothyroidism following rhTSH-aided radioiodine therapy and a reduction in goitre volume especially after a higher dose of rhTSH.

A greater reduction in thyroid volume seems to be the most important effect of rhTSH administered before radioiodine (Giusti 2006). The dose of rhTSH for thyroid residual ablation was reported in a study as 0.45 mg per day, for two consecutive days, in people with differentiated thyroid cancer after thyroidectomy (Ma 2010). A flat dose-response curve existed over the range of rhTSH doses tested, with an approximate doubling of thyroid radioiodine uptake (Braverman 2008). The dose of rhTSH varied in the studies, ranging from 0.005 mg to 0.3 mg. We could not analyse the therapeutic effects of rhTSH doses, due to the limited number of included studies. A very low dose of 0.005 mg rhTSH was equally safe and effective as 0.1 mg rhTSH, followed by a fixed radiation dose of 1.11 GBq (Cubas 2009). A 0.3 mg rhTSH dose seemed to be as efficacious as a 0.9 mg dose in people with multinodular goitre (Duick 2003). In people with symptomatic toxic or nontoxic multinodular goitre, 0.1 mg and 0.3 mg of rhTSH were equally efficacious at inducing a quadrupling of the low, or low-normal baseline radioiodine values, at 72 hours after injection (Azorín 2017; Duick 2004). A recent RCT reported that a single dose of 0.03 mg rhTSH was well tolerated, and increased the radioiodine uptake in people with euthyroid, and subclinical hyperthyroid goitre (Mojsak 2016). A long-term controlled study demonstrated that 0.2 mg of rhTSH, on two consecutive days, increased the efficacy of ambulatory radioiodine dosages in treating non-toxic multinodular goitre in elderly people. However, high doses of rhTSH should be cautiously recommended for people with non-toxic multinodular goitre, who are elderly and sick.

RhTSH-aided radioiodine therapy for non-toxic multinodular goitre led to more adverse events, including cervical discomfort, localised pain, cardiac problems, and hypothyroidism, which were usually mild, transient, and readily treatable. These effects are probably dose-dependent. Acute adverse effects are due to the surge of the thyroid hormone in the blood, and to the increase in goitre volume, which cause cardiac symptoms and tracheal compression. In healthy individuals, rhTSH-induced thyroid swelling and hyperthyroidism is rapid and dose-dependent. For people with goitre, results suggested that these adverse effects are unlikely to be of clinical significance, following doses of rhTSH of 0.1 mg or less (Fast 2010). Theoretically, the rise in thyroid hormone levels and adverse effects after rhTSH doses of 0.1 mg or higher, might not be well tolerated in older or sicker people, and appear unjustified, given the lack of a increased rise in radioiodine uptake compared with the 0.03 mg dose (Duick 2004). Neither compression of the trachea, nor deterioration of the pulmonary function was observed in the acute phase, after rhTSH-augmented radioiodine therapy. In the long term, tracheal compression may diminish, and the inspiratory capacity improve, compared with radioiodine therapy alone (Bonnema 2008). RhTSH-stimulated radioiodine treatment of non-toxic multinodular goitre did not affect the structural and functional parameters of the heart, despite transient high serum levels of thyroid hormones (Barca 2007). The dose of rhTSH to achieve the most therapeutic effects and least adverse effects should be investigated in future studies.

No study reported long-term adverse effects (e.g. radiation-induced malignancy) of rhTSH-aided radioiodine treatment for non-toxic multinodular goitre. RhTSH not only increases the thyroid radioiodine uptake (Ceccarelli 2011), but per se potentiates the effect of radioiodine therapy, allowing a major reduction of the radioiodine activity without compromising efficacy. This approach is intriguing in terms of minimising the long-term risk of radiation-induced malignancy, and in reducing the costs and inconvenience of inpatient treatment (Fast 2010). The use of lower radioiodine activities reduces the radiation burden to the body, and the time of social life restriction. Moreover, depending on the radiation regulations of the different countries, radioiodine therapy could be carried out either as outpatients, or in a shorter hospitalisation period, implying a decrease of costs (Ceccarelli 2010).

AUTHORS' CONCLUSIONS

Implications for practice

Moderate-certainty evidence from six randomised controlled clinical trials, in 321 participants, suggested that recombinant human thyrotropin (rhTSH) radioiodine for nontoxic multinodular goitre reduces thyroid volume more than radioiodine alone. However, moderate-certainty evidence also showed radioiodine alone led to a lower risk of hypothyroidism.

Implications for research

Future randomised controlled trials (RCTs) should investigate the incidence of secondary malignancies following different radiation doses, as well as long-term health-related quality of life. RCTs should also try to identify the best rhTSH dose, and costs of rhTSH-aided radioiodine therapies for non-toxic multinodular goitre.

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REFERENCES

References to studies included in this review

Albino 2010 *{published data only}*

Albino CC, Graf H, Paz-Filho G, Diehl LA, Olandoski M, Sabbag A, et al. Radioiodine plus recombinant human thyrotropin do not cause acute airway compression and are effective in reducing multinodular goiter. *Brazilian Journal of Medical and Biological Research* 2010;**43**:303-9.

Bonnema 2007 *{published data only}*

Bonnema SJ, Nielsen VE, Boel-Jørgensen H, Grupe P, Andersen PB, Bastholt L, et al. Recombinant human thyrotropin-stimulated radioiodine therapy of large nodular goiters facilitates tracheal decompression and improves inspiration. *Journal of Clinical Endocrinology and Metabolism* 2008;**93**:3981-4.

* Bonnema SJ, Nielsen VE, Boel-Jorgensen H, Grupe P, Andersen PB, Bastholt L, et al. Improvement of goiter volume reduction after 0.3 mg recombinant human thyrotropin-stimulated radioiodine therapy in patients with a very large goiter: a double-blinded, randomized trial. *Journal of Clinical Endocrinology and Metabolism* 2007;**92**(9):3424-8. [PMID: 17566091]

Fast S, Nielsen VE, Grupe P, Boel-Jørgensen H, Bastholt L, Andersen PB, et al. Prestimulation with recombinant human thyrotropin (rhTSH) improves the long-term outcome of radioiodine therapy for multinodular nontoxic goiter. *Journal of Clinical Endocrinology and Metabolism* 2012;**97**:2653-60.

Cubas 2009 *{published data only}*

Cubas ER, Paz-Filho GJ, Olandoski M, Goedert CA, Woellner LC, Carvalho GA, et al. Recombinant human TSH increases the efficacy of a fixed activity of radioiodine for treatment of multinodular goitre. *International Journal of Clinical Practice* 2009;**63**(4):583-90.

Fast 2010 *{published data only}*

Bonnema SJ, Stovgaard ES, Fast S, Broedbaek K, Andersen JT, Weimann A, et al. Systemic oxidative stress to nucleic acids is unaltered following radioiodine therapy of patients with benign nodular goiter. *European Thyroid Journal* 2015;**4**(1):20-5.

* Fast S, Hegedüs L, Grupe P, Nielsen VE, Bluhme C, Bastholt L, et al. Recombinant human thyrotropin-stimulated radioiodine therapy of nodular goiter allows major reduction of the radiation burden with retained efficacy. *Journal of Clinical Endocrinology and Metabolism* 2010;**95**(8):3719-25.

NCT00275171. rhTSH, radioiodine uptake and goiter reduction following 131I therapy in patients with benign nontoxic nodular goiter. clinicaltrials.gov/ct2/show/NCT00275171 (first submitted 9 January 2006).

Fast 2014 *{published data only}*

* Fast S, Hegedüs L, Pacini F, Pinchera A, Leung AM, Vaisman M, et al. Long-term efficacy of modified-release recombinant human thyrotropin augmented radioiodine therapy for benign multinodular goiter: results from a multicenter, international, randomized, placebo-controlled, dose-selection study. *Thyroid* 2014;**24**(4):727-35.

Graf H, Fast S, Pacini F, Pinchera A, Leung A, Vaisman M, et al. Modified-release recombinant human TSH (MRrhTSH) augments the effect of (131)I therapy in benign multinodular goiter: results from a multicenter international, randomized, placebo-controlled study. *The Journal of Clinical Endocrinology and Metabolism* 2011;**96**:1368-76.

Nielsen 2006 *{published data only}*

Fast S, Nielsen VE, Grupe P, Boel-Jørgensen H, Bastholt L, Andersen PB, et al. Prestimulation with recombinant human thyrotropin (rhTSH) improves the long-term outcome of radioiodine therapy for multinodular nontoxic goiter. *Journal of Clinical Endocrinology and Metabolism* 2012;**97**:2653-60.

NCT00145366. rhTSH, thyroid size, and radioiodine therapy in benign goiter. clinicaltrials.gov/ct2/show/NCT00145366 (first submitted 2 September 2005).

* Nielsen VE, Bonnema SJ, Boel-Jorgensen H, Grupe P, Hegedus L. Stimulation with 0.3-mg recombinant human thyrotropin prior to iodine 131 therapy to improve the size reduction of benign nontoxic nodular goiter: a prospective randomized double-blind trial. *Archives of Internal Medicine* 2006;**166**(14):1476-82. [PMID: 16864757]

Nielsen VE, Bonnema SJ, Jorgensen HB, Grupe P, Hegedus L. Stimulation with 0,3 mg recombinant human thyrotropin (rhTSH) increases the effect of 131I therapy in patients with nontoxic nodular goiter. A prospective, randomized, double-blind trial--secondary publication. *Ugeskrift for Laeger* 2006;**168**(47):4098-101.

References to studies excluded from this review

Azorín 2017 *{published data only}*

Belda MA, Caballero AM, Ardila GF, Ramírez MM, Jaramillo CG, Ardit JD, et al. Recombinant human thyrotropin stimulation prior to 131I therapy in toxic multinodular goitre with low radioactive iodine uptake. *Revista Espanola de Medicina Nuclear e Imagen Nuclear (English Edition)* 2017;**36**(1):7-12.

Lee 2015 *{published data only}*

Lee YY, Tam KW, Lin YM, Leu WJ, Chang JC, Hsiao CL, et al. Recombinant human thyrotropin before (131)I therapy in patients with nodular goitre: a meta-analysis of randomized controlled trials. *Clinical Endocrinology* 2015;**83**(5):702-10.

Mojsak 2016 *{published data only}*

Mojsak MN, Abdelrazek S, Szumowski P, Rogowski F, Sykała M, Kostecki J, et al. Single, very low dose (0.03 mg) of recombinant human thyrotropin (rhTSH) effectively increases radioiodine uptake in the I-131 treatment of large nontoxic multinodular goiter. *Nuclear Medicine Review. Central & Eastern Europe* 2016;**19**(1):3-11.

Nieuwlaat 2003 *{published data only}*

Nieuwlaat WA, Huysmans DA, van den Bosch HC, Sweep CG, Ross HA, Corstens FH, et al. Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. *The Journal of Clinical Endocrinology and Metabolism* 2003;**88**:3121-9.

Silva 2004 *{published data only}*

Silva MN, Rubió IG, Romão R, Gebrin EM, Buchpiguel C, Tomimori E. Administration of a single dose of recombinant human thyrotrophin enhances the efficacy of radioiodine treatment of large compressive multinodular goitres. *Clinical Endocrinology* 2004;**60**:300-8.

Tang 2016 *{published data only}*

Tang L, Ma T, Wu F. Recombinant human thyrotropin stimulated 131I treatment for multinodular goiter. *Nuklearmedizin* 2016;**55**(6):228-35.

References to studies awaiting assessment

NCT00454220 *{unpublished data only}*

* NCT00454220. Study to determine the dose, the safety and effectiveness of a new drug, modified release rhTSH, in patients with multinodular goiter. clinicaltrials.gov/ct2/show/NCT00454220 (first received 30 March 2007).

Additional references

Altman 2003

Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;**326**(7382):219. [PMID: 12543843]

Barca 2007

Barca MF, Gruppi C, Oliveira MT, Romao R, Cardia MS, Rubio I, et al. Cardiovascular assessment of hyperthyroid patients with multinodular goiter before and after radioiodine treatment preceded by stimulation with recombinant human TSH. *Endocrine* 2007;**32**:175-81.

Bayer 2004

Bayer Y, Neumann S, Meyer B, Rüschendorf F, Reske A, Brix T, et al. Genome-wide linkage analysis reveals evidence for four new susceptibility loci for familial euthyroid goitre. *Journal of Clinical Endocrinology and Metabolism* 2004;**89**:4044-52.

Bell 2013

Bell ML, McKenzie JE. Designing psycho-oncology randomised trials and cluster randomised trials: variance components and intra-cluster correlation of commonly used psychosocial measures. *Psycho-oncology* 2013;**22**:1738-47.

Berghout 1990

Berghout A, Wiersinga WM, Smits NJ, Touber JL. Interrelationships between age, thyroid volume, thyroid nodularity, and thyroid function in patients with sporadic nontoxic goiter. *American Journal of Medicine* 1990;**89**:602-8.

Bonnema 2000

Bonnema SJ, Bennedbaek FN, Wiersinga WM, Hegedüs L. Management of the nontoxic multinodular goitre: a European questionnaire study. *Clinical Endocrinology* 2000;**53**:5-12.

Bonnema 2002

Bonnema SJ, Bennedbaek FN, Ladenson PW, Hegedüs L. Management of the nontoxic multinodular goiter: a North American survey. *Journal of Clinical Endocrinology and Metabolism* 2002;**87**:112-7.

Bonnema 2008

Bonnema SJ, Nielsen VE, Boel-Jørgensen H, Grupe P, Andersen PB, Bastholt L, et al. Recombinant human thyrotropin-stimulated radioiodine therapy of large nodular goiters facilitates tracheal decompression and improves inspiration. *Journal of Clinical Endocrinology and Metabolism* 2008;**93**:3981-4.

Bonnema 2009

Bonnema SJ, Hegedüs L. A 30-year perspective on radioiodine therapy of benign nontoxic multinodular goiter. *Current Opinion in Endocrinology, Diabetes, and Obesity* 2009;**16**:379-84.

Borenstein 2017a

Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Research Synthesis Methods* 2017;**8**(1):5-18.

Borenstein 2017b

Borenstein M. Prediction intervals. www.meta-analysis.com/prediction (accessed 3 July 2017).

Braverman 2007

Braverman LE. Clinical studies of exposure to perchlorate in the United States. *Thyroid* 2007;**17**:819-22.

Braverman 2008

Braverman L, Kloos RT, Law B Jr, Kipnes M, Dionne M, Magner J. Evaluation of various doses of recombinant human thyrotropin in patients with multinodular goiters. *Endocrine Practice* 2008;**14**:832-9.

Buch 2011

Buch MH, Aletaha D, Emery P, Smolen JS. Reporting of long-term extension studies: lack of consistency calls for consensus. *Annals of the Rheumatic Diseases* 2011;**70**(6):886-90.

Ceccarelli 2010

Ceccarelli C, Brozzi F, Bianchi F, Santini P. Role of recombinant human TSH in the management of large euthyroid multinodular goitre: a new therapeutic option? Pros and cons. *Minerva Endocrinologica* 2010;**35**:161-71.

Ceccarelli 2011

Ceccarelli C, Antonangeli L, Brozzi F, Bianchi F, Tonacchera M, Santini P. Radioiodine 131I treatment for large nodular goiter: recombinant human thyrotropin allows the reduction of radioiodine 131I activity to be administered in patients with low uptake. *Thyroid* 2011;**21**:759-64.

Corbett 2014

Corbett MS, Higgins JP, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. *Research Synthesis Methods* 2014;**5**(1):79-85.

Deeks 2017

Deeks JJ, Higgins JP, Altman DG, editor(s), on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Diehl 2005

Diehl LA, Garcia V, Bonnema SJ, Hegedüs L, Albino CC, Graf H, et al. Management of the nontoxic multinodular goiter in Latin America: comparison with North America and Europe, an electronic survey. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**:117-23.

Dietlein 2006

Dietlein M, Dederichs B, Kobe C, Theissen P, Schmidt M, Schicha H. Therapy for non-toxic multinodular goiter: radioiodine therapy as attractive alternative to surgery. *Nuklearmedizin* 2006;**45**(01):21-34; quiz N1-2.

Doerge 2002

Doerge DR, Chang HC. Inactivation of thyroid peroxidase by soy isoflavones, in vitro and in vivo. *Journal of Chromatography* 2002;**777**(1-2):269-79.

Duick 2003

Duick DS, Baskin HJ. Utility of recombinant human thyrotropin for augmentation of radioiodine uptake and treatment of nontoxic and toxic multinodular goiters. *Endocrine Practice* 2003;**9**:204-9.

Duick 2004

Duick DS, Baskin HJ. Significance of radioiodine uptake at 72 hours versus 24 hours after pretreatment with recombinant human thyrotropin for enhancement of radioiodine therapy in patients with symptomatic nontoxic or toxic multinodular goiter. *Endocrine Practice* 2004;**10**:253-60.

Fast 2009

Fast S, Nielsen VE, Bonnema SJ, Hegedüs L. Time to reconsider nonsurgical therapy of benign non-toxic multinodular goitre: focus on recombinant human TSH augmented radioiodine therapy. *European Journal of Endocrinology / European Federation of Endocrine Societies* 2009;**160**:517-28.

Fast 2011

Fast S, Bonnema SJ, Hegedüs L. Radioiodine therapy of benign non-toxic goitre. Potential role of recombinant human TSH. *Annales D'endocrinologie* 2011;**72**:129-35.

Giusti 2006

Giusti M, Cappi C, Santaniello B, Ceresola E, Augeri C, Lagasio C, et al. Safety and efficacy of administering 0.2 mg of recombinant human TSH for two consecutive days as an adjuvant to therapy with low radioiodine doses in elderly out-patients with large nontoxic multinodular goiter. *Minerva Endocrinologica* 2006;**31**:191-209.

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 09 July 2019. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Hegedüs 1988

Hegedüs L, Hansen BM, Knudsen N, Hansen JM. Reduction of size of thyroid with radioactive iodine in multinodular non-toxic goitre. *BMJ (Clinical Research ed.)* 1988;**297**:661-2.

Higgins 2002

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539-58.

Higgins 2003

Higgins JT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**(7414):557-60.

Higgins 2009

Higgins JT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2009;**172**(1):137-59.

Higgins 2017

Higgins JT, Altman DG, Sterne JA, editor(s), on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JT, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from training.cochrane.org/handbook.

Hozo 2005

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5**:13. [DOI: 10.1186/1471-2288-5-13]

Huysmans 2000

Huysmans DA, Nieuwlaat WA, Erdtsieck RJ, Schellekens AP, Bus JW, Bravenboer B, et al. Administration of a single low dose of recombinant human thyrotropin significantly enhances thyroid radioiodide uptake in nontoxic nodular goiter. *Journal of Clinical Endocrinology and Metabolism* 2000;**85**(10):3592-6.

Laurberg 2004

Laurberg P, Nøhr SB, Pedersen KM, Fuglsang E. Iodine nutrition in breast-fed infants is impaired by maternal smoking. *Journal of Clinical Endocrinology and Metabolism* 2004;**89**:181-7.

Le Moli 1999

Le Moli R, Wesche MF, Tiel-Van Buul MM, Wiersinga WM. Determinants of long term outcome of radioiodine therapy of sporadic non-toxic goitre. *Clinical Endocrinology* 1999;**50**:783-9.

Lindsay 1992

Lindsay RH, Hill JB, Gaitan E, Cooksey RC, Jolley RL. Antithyroid effects of coal-derived pollutants. *Journal of Toxicology and Environmental Health* 1992;**37**:467-81.

Ma 2010

Ma C, Xie J, Liu W, Wang G, Zuo S, Wang X, et al. Recombinant human thyrotropin (rhTSH) aided radioiodine treatment for residual or metastatic differentiated thyroid cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 11. Art. No: CD008302. [DOI: 10.1002/14651858.CD008302.pub2]

Meader 2014

Meader N, King K, Llewellyn A, Norman G, Brown J, Rodgers M, et al. A checklist designed to aid consistency and reproducibility of GRADE assessments: development and pilot validation. *Systematic Reviews* 2014;**24**(3):82. [DOI: 10.1186/2046-4053-3-82] [PMID: 25056145]

Medeiros-Neto 2012

Medeiros-Neto G, Camargo RY, Tomimori EK. Approach to and treatment of goiters. *Medical Clinics of North America* 2012;**96**:351-68.

Megan 2012

Megan B, Pickering RM, Weatherall M. Design, objectives, execution and reporting of published open-label extension studies. *Journal of Evaluation in Clinical Practice* 2012;**18**(2):209-15.

Moher 2010

Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;**340**:c332. [DOI: 10.1136/bmj.c869]

Nieuwlaat 2001

Nieuwlaat WA, Hermus AR, Sivro-Prndelj F, Corstens FH, Huysmans DA. Pretreatment with recombinant human TSH changes the regional distribution of radioiodine on thyroid scintigrams of nodular goiters. *Journal of Clinical Endocrinology and Metabolism* 2001;**86**:5330-6.

Nygaard 1993

Nygaard B, Hegedüs L, Gervil M, Hjalgrim H, Søe-Jensen P, Hansen JM, et al. Radioiodine treatment of multinodular non-toxic goitre. *BMJ (Clinical research ed.)* 1993;**307**:828-32.

Pedersen 2001

Pedersen IB, Knudsen N, Perrild H, Ovesen L, Laurberg P. TSH-receptor antibody measurement for differentiation of hyperthyroidism into Graves' disease and multinodular toxic goitre: a comparison of two competitive binding assays. *Clinical Endocrinology* 2001;**55**:381-90.

Review Manager 2020 [Computer program]

The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. The Cochrane Collaboration, 2020.

Riley 2011

Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;**342**:d549.

Schröder-van der Elst 2003

Schröder-van der Elst JP, Smit JW, Romijn HA, van der Heide D. Dietary flavonoids and iodine metabolism. *BioFactors (Oxford, England)* 2003;**19**:171-6.

Schünemann 2017

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Akl E, et al, on behalf of the Cochrane GRADEing Methods Group and the Cochrane Statistical Methods Group. Chapter 11: Completing 'Summary of findings' tables and grading the confidence in or quality of the evidence. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017). Cochrane, 2017. Available from training.cochrane.org/handbook.

Sterne 2011

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.

Sterne 2017

Sterne JA, Egger M, Moher D, Boutron I, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JP, Churchill R, Chandler J, Cumpston MS, editor(s), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Tunbridge 1977

Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F. The spectrum of thyroid disease in a community: the Whickham survey. *Clinical Endocrinology* 1977;**7**:481-93.

Vagenakis 1975

Vagenakis AG, Braverman LE. Adverse effects of iodides on thyroid function. *Medical Clinics of North America* 1975;**59**:1075-88.

Vander 1954

Vander JB, Gaston EA, Dawber TR. Significance of solitary nontoxic thyroid nodules; preliminary report. *New England Journal of Medicine* 1954;**251**:970-3.

Wesche 2001

Wesche MF, Tiel-V Buul MM, Lips P, Smits NJ, Wiersinga WM. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. *Journal of Clinical Endocrinology and Metabolism* 2001;**86**:998-1005.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336**(7644):601-5.

Xu 2020

Xu C, Wang P, Miao H, Xie T, Zhou X, Zhang Q, et al. Recombinant human thyrotropin-stimulated radioiodine therapy in patients with multinodular goiters: a meta-analysis of randomized controlled trials. *Hormone & Metabolic Research* 2020;**52**(12):841-9.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Albino 2010

Study characteristics	
Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: participants had euthyroid goitres larger than 40 mL and either had a contraindication for surgery or declined surgery. None of the participants had previous surgery or treatment with radioiodine. Prior to the treatment, malignancy was excluded by ultrasound-guided fine needle aspiration biopsy of the dominant and suspect nodules, and by cytology studies. Normal levels of creatinine, transaminases, and fasting glucose, as well as normal electrocardiogram excluded the presence of comorbidities. None of the participants had used amiodarone or iodinated contrast in the past 12 months **Exclusion criteria**: participants with below normal TSH levels **Diagnostic criteria**: participants with normal TSH levels, multinodular goitre, and malignancy excluded **Setting**: outpatients **Age group**: adults **Gender distribution**: 91% female **Country where trial was performed**: Brazil
Interventions	**Intervention(s)**: 1.0 mL of the solution (0.01 mg or 0.1 mg rhTSH) was intramuscularly injected 24 hr prior to the radioiodine treatment **Comparator(s)**: 1.0 mL isotonic saline was intramuscularly injected 24 hr prior to the radioiodine treatment **Duration of intervention**: 2 days **Duration of follow-up**: 12 months **Run-in period**: none **Number of trial centres**: 1
Outcomes	**Reported outcome(s) in full text of publication**: thyroid function tests, TSH receptor antibodies, anti-thyroperoxidase antibodies (TPOAb), antithyroglobulin antibodies, thyroid volume, tracheal compression, adverse effects (clinical assessment and frequent measures of thyroid hormone levels)
Study details	**Trial identifier**: not reported **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: non-commercial funding **Publication status**: peer-reviewed journal

Albino 2010 *(Continued)*

Stated aim for study	**Quote**: "we assessed the efficacy and safety (including airway compression) of different doses of rhTSH associated with a fixed activity of ^{131}I for treating multinodular goitre"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "Patients were randomly and consecutively selected from the thyroid outpatient clinic" **Quote**: "This was a prospective, randomised, double-blind, placebo-controlled study" **Quote**: "Patients were assigned to a previously predefined treatment group by simple randomization" **Comment**: no details
Allocation concealment (selection bias)	Unclear risk	**Comment**: no details
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote**: "Patients and investigators were blind to the treatment throughout the study, including the physicians responsible for the interpretation of the results"
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote**: "Patients and investigators were blind to the treatment throughout the study, including the physicians responsible for the interpretation of the results"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote**: "Investigators were blind to the treatment throughout the study, including the physicians responsible for the interpretation of the results"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote**: "Investigators were blind to the treatment throughout the study, including the physicians responsible for the interpretation of the results"
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Quote**: "No case was lost during follow-up"
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Quote**: "No case was lost during follow-up"
Selective reporting (reporting bias)	Low risk	**Comment**: none detected
Other bias	Low risk	**Comment**: none detected

Bonnema 2007

Study characteristics

Bonnema 2007 *(Continued)*

Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: people with a very large nodular goitre, resulting in cervical compression or cosmetic discomfort, or both; surgery was not feasible because of concomitant medical disorders, previous neck surgery, personal aversions, or a combination **Exclusion criteria**: a history of cardiac failure or ventricular arrhythmias, previous malignant disease, or physical or psychiatric disabilities suggestive of difficulties in adherence to the protocol **Diagnostic criteria**: the diagnosis was based on clinical examination, ultrasonography, and 99 mTc-pertechnetate thyroid scintigraphy. Fine-needle aspiration biopsy of any scintigraphically dominant hypoactive nodule was performed to exclude malignancy **Setting**: inpatients **Age group**: adults **Gender distribution**: 76% female **Country where trial was performed**: Denmark
Interventions	**Intervention(s)**: 1.0 mL of the solution (0.3 mg rhTSH) was intramuscularly injected into the gluteal region, 24 hr before ^{131}I therapy **Comparator(s)**: 1.0 mL isotonic saline was intramuscularly injected 24 hr prior to the ^{131}I therapy **Duration of intervention**: 1 day **Duration of follow-up**: 12 months **Run-in period**: none **Number of trial centres**: 1
Outcomes	**Reported outcome(s) in full text of publication**: goitre volume reduction, thyroid function tests, adverse effects (thyroid pain and cervical compression), patient satisfaction, all cause mortality
Study details	**Trial identifier**: not reported **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: The Agnes and Knut Mørk Foundation, Hans Skouby's and Wife Emma Skouby's Foundation, Dagmar Marshall's Foundation, King Christian the X's Foundation, Oda Pedersens Research Foundation, Frode V. Nyegaard and Wife's Foundation, The Research Foundation of the County of Funen, The Institute of Clinical Research-University of Southern Denmark, The National Thyroid League, The Novo Nordisk Foundation, and The A. P. Møller Relief Foundation **Publication status**: peer-reviewed journal
Stated aim for study	**Quote**: "to evaluate the principle of rhTSH stimulated 131I therapy in patients with a very large goiter"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	**Quote**: "Randomization was performed by an independent pharmacist at the hospital, using a random number generator"

Bonnema 2007 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	**Comment**: no details
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote**: "The study was performed in a randomised, placebo-controlled, double-blinded set-up"
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote**: "The study was performed in a randomised, placebo-controlled, double-blinded set-up"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote**: "The study was performed in a randomised, placebo-controlled, double-blinded set-up"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote**: "The study was performed in a randomised, placebo-controlled, double-blinded set-up"
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Quote**: "No patient dropped out during the study period"
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Quote**: "No patient dropped out during the study period"
Selective reporting (reporting bias)	Low risk	**Comment**: none detected
Other bias	Low risk	**Comment**: none detected

Cubas 2009

Study characteristics	
Methods	**Study design**:parallel randomised controlled trial
Participants	**Inclusion criteria**: people with diagnosis of multinodular goitre; all of them had subclinical hyperthyroidism (which was treated with methimazole), or were euthyroid **Exclusion criteria**: people had previous surgery, TSH-suppressive therapy with T4, or radioactive iodine treatment, serious medical conditions **Diagnostic criteria**: the diagnosis was based on either by palpation or US, and 131I thyroid scintigraphy. US-guided fine needle aspiration biopsy of suspicious and dominant nodules to exclude malignancy **Setting**: outpatients **Age group**: adults **Gender distribution**: 93% female **Country where trial was performed**: Brazil

Cubas 2009 *(Continued)*

Interventions	**Intervention(s)**: participants in group A (N = 9)received a single intramuscular dose of 1.0 mL (0.1 mg) of rhTSH; participants in group B (N = 9) received 0.005 mg of rhTSH, also in a single intramuscular injection, 24 hr before ^{131}I therapy **Comparator(s)**: 1.0 mL isotonic saline was intramuscularly injected 24 hr prior to the ^{131}I therapy **Duration of intervention**: 1 day **Duration of follow-up**: 24 months **Run-in period**: none **Number of trial centres**: 1
Outcomes	**Reported outcome(s) in full text of publication**: thyroid volume reduction, radioactive iodine uptake, thyroid function tests, adverse effects (hyperthyroidism and thyroid enlargement)
Study details	**Trial identifier**: not reported **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: Genzyme do Brasil **Publication status**: peer-reviewed journal
Stated aim for study	**Quote**: "to evaluate whether rhTSH increases the efficacy of a fixed activity of 131I for the treatment of multinodular goitre"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "three treatment protocols were designed and patients were randomly assigned" **Comment**: not enough details
Allocation concealment (selection bias)	Unclear risk	**Comment**: no details
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Comment**: outcomes unlikely influenced by lack of blinding
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Comment**: no details
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Comment**: outcomes unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	**Comment**: no details

Cubas 2009 *(Continued)*

Subjective outcomes		
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Quote**: "In the placebo group, a 71-year-old female died 8 months after treatment of complications of an unrelated ischemic cerebral stroke"
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Quote**: "In the placebo group, a 71-year-old female died 8 months after treatment of complications of an unrelated ischemic cerebral stroke"
Selective reporting (reporting bias)	Low risk	**Comment**: none detected
Other bias	Low risk	**Comment**: none detected

Fast 2010

Study characteristics	
Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: non-pregnant, non-lactating participants older than 18 yr, with a nontoxic nodular goitre (i.e. thyroid volume more than 28 mL, and two or more nodules larger than 1 cm), and the presence of goitre-related symptoms (i.e. pressure or cosmetic complaints, or both), or subclinical hyperthyroidism (i.e. serum TSH < 0.30 mU/L and normal serum T4 and T3 levels), or a combination **Exclusion criteria**: participants with subclinical hyperthyroidism could not have hyperthyroid symptoms necessitating antithyroid drugs or blockers **Diagnostic criteria**: the diagnostic set-up included clinical examination, thyroid function tests, ^{99m}Tc scintigraphy, and ultrasonography **Setting**: outpatient clinic **Age group**: adults (> 18 years) **Gender distribution**: 87% female **Country where trial was performed**: Denmark
Interventions	**Intervention(s)**: a vial containing 0.9 mg rhTSH was reconstituted to a concentration of 0.1 mg/mL (administered in the gluteal region), followed by a thyroid dose of 50 Gy. RhTSH was given 24 hr, 48 hr, or 72 hr before radioiodine **Comparator(s)**: placebo injection constituted 1 mL isotonic saline, followed by a thyroid dose of 100 Gy. Placebo was given 24 hr, 48 hr, or 72 hr before radioiodine **Duration of intervention**: 1 to 3 days **Duration of follow-up**: 12 months **Run-in period**: none **Number of trial centres**: 1
Outcomes	**Reported outcome(s) in full text of publication**: goitre volume reduction, hospitalisation, goitre-related symptoms, thyroid function tests, thyroid peroxidase antibodies, TSH receptor antibodies, thyroid size, patient satisfaction (visual analogue scale), prevalence of myxoedema

Fast 2010 *(Continued)*

Study details	**Trial identifier**: NCT00275171 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial and non-commercial funding (Novo Nordisk Foundation, The Strategic Research Council at Odense University Hospital, The Agnes and Knut MørkFoundation, The National Thyroid League, The Institute of Clinical Research at University of Southern Denmark, The Hans Skouby and wife Emma Skouby Foundation, Dagmar Marshalls Foundation, Oda Pedersen's Research Foundation, The Ingemann O. Buck Foundation, The Else Poulsen Memorial Foundation, Desirée and Niels Yde Foundation, and the Danish Agency for Science Technology and Innovation) **Publication status**: peer-reviewed journal
Stated aim for study	**Quote**: "to evaluate whether a reduced thyroid dose of 50 Gy, in combination with 0.1 mg rhTSH would result in a GVR comparable to that of a conventional dose of 100 Gy without rhTSH stimulation (placebo). Furthermore, the impact of the interval between rhTSH and 131I-therapy on GVR was examined"
Notes	"Only one of the 60 patients (2%) receiving rhTSH had to be hospitalized for 1 d, whereas hospitalization between 1 and 3 d was required in 14 of the 30 patients (47%) in the placebo group (P < 0.0001 between groups). Importantly, 37 patients in the combined rhTSH group compared with zero in the placebo group could be treated without any post-therapeutic restrictions (P < 0.0001). The maximum131I-activity that can be employed without any patient restrictions in Denmark is 200 MBq"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "In a two-factorial design, patients were randomised (by an independent pharmacist) to receive either 0.1 mg of rhTSH (N = 60) followed by a thyroid dose of 50 Gy, or placebo followed by 100 Gy (N = 30). Furthermore, patients were randomised to receive rhTSH or placebo 24, 48, or 72 h before 131I-therapy" **Comment**: not enough details
Allocation concealment (selection bias)	Unclear risk	**Comment**: no details
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote from ClinicalTrials.gov:** "masking: quadruple (participant, care provider, investigator, outcomes assessor)"
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote from ClinicalTrials.gov:** "masking: quadruple (participant, care provider, investigator, outcomes assessor)"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote from ClinicalTrials.gov:** "masking: quadruple (participant, care provider, investigator, outcomes assessor)"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote from ClinicalTrials.gov:** "masking: quadruple (participant, care provider, investigator, outcomes assessor)"

Fast 2010 *(Continued)*

Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Quote**: "Of the 93 patients who had signed informed consent, 90 completed the protocol (three patients withdrew their informed consent before randomization)"
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Quote**: "Of the 93 patients who had signed informed consent, 90 completed the protocol (three patients withdrew their informed consent before randomization)"
Selective reporting (reporting bias)	Low risk	**Comment**: data available on ClinicalTrials.gov
Other bias	Low risk	**Comment**: none detected

Fast 2014

Study characteristics	
Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: a clinical diagnosis of multinodular goitre, 40 mL to 140 mL in size (by ultrasound (US) and palpation); age 35 to 80 years; serum free thyroxine (T4) index (fTI) and total triiodothyronine (T3) within the normal range, and serum TSH from undetectable to the upper limit of the normal range; no suspicion of thyroid malignancy as determined by fine needle aspiration biopsy. All participants had an indication for treatment, based on either cosmetic or compressive complaints, or both **Exclusion criteria**: people with previous partial or near total thyroidectomy, a history of ^{131}I therapy, or both **Diagnostic criteria**: the diagnostic set-up included clinical examination, thyroid function tests, and ultrasonography **Setting**: outpatient clinic **Age group**: adults (> 18 years) **Gender distribution**: 85% female **Countries where trial was performed**: Denmark, Italy, Brazil, Germany, France, Canada
Interventions	**Intervention(s)**: 0.01 mg rhTSH or 0.03 mg rhTSH was administered by intramuscular injection in the gluteal region, in equal volumes, 24 hr before 131I therapy **Comparator(s)**: placebo injection was 0.5 mL of the same concentration of sodium carboxymethylcellulose **Duration of intervention**: 1 to 3 days **Duration of follow-up**: 36 months **Run-in period**: none **Number of trial centres**: 13
Outcomes	**Reported outcome(s) in full text of publication**: goitre volume reduction, smallest cross-sectional area of trachea, quality of life, thyroid function tests
Study details	**Trial identifier**: not reported

Fast 2014 *(Continued)*

	Trial terminated early: no
Publication details	**Language of publication**: English **Funding**: this work was supported by a research grant from Genzyme Corp., Cambridge, Massachusetts **Publication status**: peer-reviewed journal
Stated aim for study	**Quote**: "to compare the long-term efficacy and safety of two low doses of modified release rhTSH (MR-rhTSH) in combination with ^{131}I therapy"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "In this phase II, randomised, single-blinded, placebo controlled, three-arm, parallel group, dose-selection study, ninety-five patients were randomised (single-blinded) to receive placebo, 0.01 mg rhTSH, or 0.03 mg rhTSH I.M., 24 hr before oral ^{131}I therapy. Investigators were unblinded from the randomization scheme" **Comment**: not enough details
Allocation concealment (selection bias)	Unclear risk	**Comment**: no details
Blinding of participants and personnel (performance bias) Objective outcomes	Unclear risk	**Quote**: "Investigators were unblinded towards the randomization scheme to facilitate study execution; only patients were blinded"
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	**Quote**: "Investigators were unblinded towards the randomization scheme to facilitate study execution; only patients were blinded"
Blinding of outcome assessment (detection bias) Objective outcomes	Unclear risk	**Quote**: "Investigators were unblinded towards the randomization scheme to facilitate study execution; only patients were blinded"
Blinding of outcome assessment (detection bias) Subjective outcomes	Unclear risk	**Quote**: "Investigators were unblinded towards the randomization scheme to facilitate study execution; only patients were blinded"
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Quote**: "No patient dropped out during the study period"
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Quote**: "No patient dropped out during the study period"
Selective reporting (reporting bias)	Low risk	**Comment**: none detected
Other bias	Low risk	**Comment**: none detected

Nielsen 2006

Study characteristics	
Methods	**Study design**: parallel randomised controlled trial
Participants	**Inclusion criteria**: participants with symptoms of cervical compression, cosmetic discomfort, or subclinical hyperthyroidism (serum thyroid-stimulating hormone (TSH) 0.10 mU/L, and normal serum thyroxine (T4) and serum triiodothyronine (T3) levels), or a combination **Exclusion criteria**: participants who were averse to any treatment, younger than 18 years, had nodules suggestive of malignancy, had intrathoracic goitre > 100 mL, had previous ^{131}I therapy, were unable to complete follow-up, had a 24-hr thyroid ^{131}I uptake < 20% **Diagnostic criteria**: the diagnosis was obtained by clinical examination, ultrasonography, and sodium pertechnetate 99 m Tc thyroid scintigraphy **Setting**: outpatient clinic **Age group**: adults (> 18 years) **Gender distribution**: 89% female **Country where trial was performed**: Denmark
Interventions	**Intervention(s)**: each participant received 0.3 mg of recombinant human thyrotropin injected intramuscularly, into the gluteal region, 24 hr prior to ^{131}I therapy **Comparator(s)**: placebo injection constituted 1 mL isotonic saline into the gluteal region, 24 hr prior to ^{131}I therapy **Duration of intervention**: 1 to 2 days **Duration of follow-up**: 12 months **Run-in period**: none **Number of trial centres**: 1
Outcomes	**Reported outcome(s) in full text of publication**: T3, T4, TSH
Study details	**Trial identifier**: NCT00145366 **Trial terminated early**: no
Publication details	**Language of publication**: English **Funding**: commercial and non-commercial funding (research grants from The Agnes and Knut Mørk Foundation, Hans Skouby and Wife Emma Skouby Foundation, Dagmar Marshall Foundation, King Christian the X Foundation, Oda Pedersens Research Foundation, Frode V. Nyegaard and Wife Foundation, The Research Foundation of the County of Funen, The Institute of Clinical Research – University of Southern Denmark, The National Thyroid League, The Novo Nordisk Foundation, and The A. P. Møller Relief Foundation **Publication status**: peer-reviewed journal
Stated aim for study	**Quote**: "to evaluate, in a double-blind, placebo controlled set-up, the goiter-reducing effect and adverse effects of prestimulation with 0.3 mg of recombinant human thyrotropin 24 hours prior to 131I therapy, in a homogeneous, well-characterized group of patients with nontoxic nodular goiter"
Notes	

Nielsen 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	**Quote**: "The study was performed in a randomised, placebo controlled double-blinded set-up" **Comment**: no details
Allocation concealment (selection bias)	Unclear risk	**Comment**: no details
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	**Quote**: "The study was performed in a randomised, placebo controlled double-blinded set-up"
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	**Quote**: "The study was performed in a randomised, placebo controlled double-blinded set-up"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	**Quote**: "The study was performed in a randomised, placebo controlled double-blinded set-up"
Blinding of outcome assessment (detection bias) Subjective outcomes	Low risk	**Quote**: "The study was performed in a randomised, placebo controlled double-blinded set-up"
Incomplete outcome data (attrition bias) Objective outcomes	Low risk	**Quote**: "No patient dropped out during the study period"
Incomplete outcome data (attrition bias) Subjective outcomes	Low risk	**Quote**: "No patient dropped out during the study period"
Selective reporting (reporting bias)	Low risk	**Comment**: none detected
Other bias	Low risk	**Comment**: none detected

—: denotes not reported
Note: where the judgement is 'unclear' and the description is blank, the trial did not report that particular outcome
Gy: Gray; **^{131}I**: radioiodine; **rhTSH**: recombinant human thyrotropin; **T3:** triiodothyronine;**T4**: thyroxine; **Tc**: technetium; **TSH**: thyroid stimulating hormone; **US:** ultrasound

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Azorín 2017	Controlled clinical trial, participants had toxic multinodular goitres
Lee 2015	Review of meta-analysis
Mojsak 2016	Short follow-up of eight weeks

Study	Reason for exclusion
Nieuwlaat 2003	Uncontrolled clinical trial
Silva 2004	Most participants had toxic multinodular goitres
Tang 2016	Review of meta-analysis

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT00454220

Methods	**Type of study:** efficacy study **Allocation**: randomised **Intervention model**: parallel assignment **Masking**: single-blind (participants) **Primary purpose**: treatment
Participants	**Condition**: multinodular goitre **Enrolment**: estimated 96 **Inclusion criteria**: • clinical diagnosis of multinodular goitre, judged clinically and by ultrasound at screening to be at least 40 mL, but ≤ 140 mL in size • clinically free of thyroid cancer as determined by Fine Needle Aspiration (FNA) of all dominant, or highly suspicious cold nodules in the goitre, and cytology reports as negative for thyroid cancer (Note: results of FNA and cytology reports that were performed within 18 months prior to commencing screening procedures and met these criteria were acceptable for inclusion) • principal Investigator believes there is a minimal risk of coexistent thyroid cancer • principal Investigator feels the participant's iodine intake or levels will not significantly impact the results of the study (urinary iodine assay at screening and low-iodine diet were optional and associated data will not be collected for study purposes) • baseline serum level of free thyroxine index (FTI) within the normal range, as determined by central lab • baseline serum level of thyroid stimulating hormone (TSH) ranges from undetectable to the upper limit of the normal range, as determined by central lab • females of child-bearing potential must be on a stable hormonal contraceptive regimen (i.e. > 6 months continuous use), or use a double barrier method (i.e. condom and foam) through to visit 8 (i.e. the end of the core study) • through to visit 8 (6 months) for male participation in the study, it is recommended that his sexual partner(s), who are females of child-bearing potential, use the above described methods of contraception. • negative pregnancy tests for all women of child-bearing potential prior to participating in the study • women aged 50 years and above and considered postmenopausal (defined as > 2 years since last menstrual period) will not need to have a pregnancy test • routine blood laboratory values within normal range at screening, as determined by central lab • abnormal values considered not clinically significant by the Principal Investigator are acceptable for inclusion • electrocardiogram (ECG; 12 lead, 2 minute rhythm strip) within normal limits at screening as determined by a designated study cardiologist or appropriately qualified physician at each site. Exclusion - evidence of an old myocardial infarction (MI); ECG findings of occasional premature atri-

NCT00454220 *(Continued)*

al beats, abnormal PR intervals not associated with supra ventricular tachycardia (SVT) or heart block, right bundle branch block, and heart rates ≤ 100 beats per minute (BPM), and ≥ 50 BPM
- committed to follow all protocol-required study procedures, as evidenced by providing written informed consent within 21 days prior to screening period 2.

Exclusion criteria:

- history of thyroid cancer
- previous partial or near total thyroidectomy
- clinical history, signs or symptoms that make thyroid cancer a higher than usual probability, such as positive immediate family history of thyroid cancer, history of head or neck irradiation, a stone-hard nodule, or suspicious growth of a nodule in recent months, palpable cervical lymph nodes, or nodes that on ultrasound have features suspicious for metastases (unless ruled out by biopsy or FNA)
- during the 45 days before administration of MRrhTSH or placebo (i.e. screening periods 1 and 2), use of propylthiouracil, methimazole or thyroxine, vitamins or supplements containing kelp or iodine (taking a multivitamin that does not contain iodine or kelp is acceptable), medications that significantly affect iodine handling, such as high dose corticosteroids, high dose diuretics, or lithium (low or moderate dose diuretic use is acceptable)
- currently or within the past 60 days used retinoic acid
- serum calcitonin above the upper limit of normal at screening, as determined by central lab
- use of amiodarone within the prior 2 years
- received iodine-containing contrast agent within the past 3 months
- inability to complete all required visits
- conditions in which use of beta-blockers are medically contraindicated, such as recently active asthma or clinically significant chronic obstructive pulmonary disease
- currently, or within the past 5 years, have a history of malignancy, other than squamous or basal cell carcinoma of the skin, or carcinoma in situ of the cervix
- prior MI, even if remote; stroke within 6 months; atrial fibrillation or clinically significant arrhythmia within 6 months (person may have mild hypertension or chronic cardiac illnesses that are well controlled on a medication regimen: blood pressure (BP) less than 140/90 mmHg after resting 5 minutes)
- concurrent major medical disorder (e.g. documented significant cardiac disease, debilitating cardiopulmonary disease, advanced renal failure, advanced liver disease, advanced pulmonary disease, or advanced cerebral vascular disorder) that may have an impact on the capability of the person to adequately comply with the requirements of this study
- women who are pregnant or lactating
- recent history of alcoholism, drug abuse, or other disorder that might affect compliance with the protocol
- received investigational study medication within 30 days prior to signing informed consent, or intends to participate in another clinical study involving the use of an investigational drug over the course of study participation.
- taking anticoagulants, except for aspirin
- at the time of screening, know to be human immunodeficiency virus (HIV) antibody positive or hepatitis B antigen positive (no screening for HIV or hepatitis B should be done in the study).
- hyperthyroid symptom scale (HSS) ≥ 20
- people who have received 131I in the past, and have had a lifetime exposure believed to be >10 mCi (0.37GBq) of 131I
- history of allergy to thyrogen, sodium carboxymethylcellulose (NaCMC; including prior history of anaphylaxis following topical lidocaine, barium sulfate ingestion, or intra-articular or parenteral corticosteroid).
- smallest cross-sectional area of the trachea (SCAT) discovered on CT to be < 60 mm^2

Interventions	**Intervention(s)**: 0.01 mg rhTSH, 0.03 mg rhTSH **Comparator(s)**: placebo

NCT00454220 *(Continued)*

Outcomes	**Primary outcome(s)**: change from baseline to 6, 36 months in goitre size by computer tomography (CT) scan **Secondary outcome(s)**: change in goitre size from baseline to 6 months in smallest cross sectional area of the trachea, the percentage of participants in each group who attained a goitre volume shrinkage at 6,12, 36 months of 28% or greater, thyroid Quality of Life Questionnaire, thyroid stimulating hormone (TSH), free thyroxine (FT4), total thyroxine (TT4), FT1, free triiodothyronine (FT3), total T3 (TT3), physical exams, vitals, adverse events, respiratory symptoms, tracheal diameter measurements determined by ultrasound, electrocardiogram (ECG), treatment-emergent hyperthyroidism
Study details	NCT00454220
Publication details	Study to evaluate the dose, safety, and effectiveness of modified-release recombinant human thyroid stimulating hormone (MRrhTSH), when used in conjunction with radioiodine for the treatment of multinodular goitre
Stated aim of study	**Quote**: "to determine the safety and effectiveness of 2 different doses of modified-release recombinant human thyroid stimulating hormone (MRrhTSH) when administered with radioiodine in patients with multinodular goiter, a condition that involves the enlargement of the thyroid gland. We will also evaluate the safety and effectiveness of radioiodine therapy alone in these patients"
Notes	

DATA AND ANALYSES

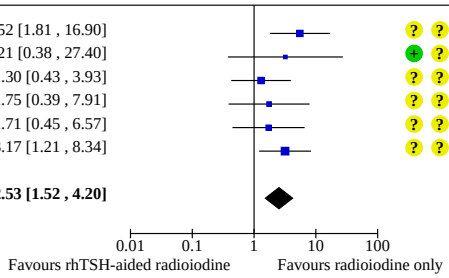
Comparison 1. rhTSH-aided radioiodine versus radioiodine only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Hypothyroidism	6	321	Risk Ratio (M-H, Random, 95% CI)	2.53 [1.52, 4.20]
1.2 Adverse events	6	321	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.94, 1.63]
1.3 % of thyroid volume reduction	6	268	Mean Difference (IV, Random, 95% CI)	11.91 [4.43, 19.40]

Analysis 1.1. Comparison 1: rhTSH-aided radioiodine versus radioiodine only, Outcome 1: Hypothyroidism

Study or Subgroup	rhTSH-aided radioiodine Events	Total	Radioiodine only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Nielsen 2006	16	28	3	29	20.5%	5.52 [1.81 , 16.90]	? ? + + + + +
Bonnema 2007	3	14	1	15	5.6%	3.21 [0.38 , 27.40]	+ ? + + + + +
Cubas 2009 (1)	7	18	3	10	20.9%	1.30 [0.43 , 3.93]	? ? + + + + +
Fast 2010	7	60	2	30	11.3%	1.75 [0.39 , 7.91]	? ? + + + + +
Albino 2010 (2)	6	14	2	8	14.2%	1.71 [0.45 , 6.57]	? ? + + + + +
Fast 2014 (3)	25	63	4	32	27.5%	3.17 [1.21 , 8.34]	? ? ? ? + + +
Total (95% CI)		**197**		**124**	**100.0%**	**2.53 [1.52 , 4.20]**	
Total events:	64		15				

Heterogeneity: Tau² = 0.00; Chi² = 4.18, df = 5 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.59 (P = 0.0003)
Test for subgroup differences: Not applicable



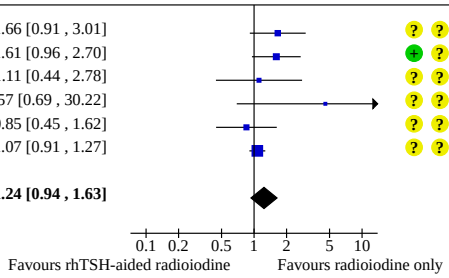
Footnotes
(1) Group 1 and 2 combined (0.005 mg rhTSH and 0.1 mg rhTSH)
(2) N = 3/6 with 0.01 mg rhTSH & N = 3/8 with 0.1 mg rhTSH
(3) Combined group 0.01 mg rhTSH and 0.03 mg rhTSH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Objective outcomes
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Objective outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: rhTSH-aided radioiodine versus radioiodine only, Outcome 2: Adverse events

Study or Subgroup	rhTSH-aided radioiodine Events	Total	Radioiodine only Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F G
Nielsen 2006	16	28	10	29	15.3%	1.66 [0.91 , 3.01]	? ? + + + + +
Bonnema 2007	12	14	8	15	18.3%	1.61 [0.96 , 2.70]	+ ? + + + + +
Cubas 2009 (1)	8	18	4	10	7.8%	1.11 [0.44 , 2.78]	? ? ? ? + + +
Albino 2010 (2)	8	14	1	8	2.1%	4.57 [0.69 , 30.22]	? ? + + + + +
Fast 2010	17	60	10	30	13.6%	0.85 [0.45 , 1.62]	? ? + + + + +
Fast 2014 (3)	57	63	27	32	43.0%	1.07 [0.91 , 1.27]	? ? ? ? + + +
Total (95% CI)		**197**		**124**	**100.0%**	**1.24 [0.94 , 1.63]**	
Total events:	118		60				

Heterogeneity: Tau² = 0.04; Chi² = 7.67, df = 5 (P = 0.18); I² = 35%
Test for overall effect: Z = 1.49 (P = 0.13)
Test for subgroup differences: Not applicable



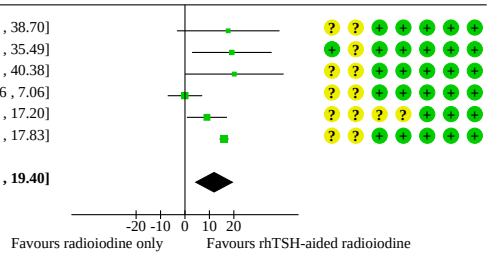
Footnotes
(1) Group 1 and 2 combined (0.005 mg rhTSH and 0.1 mg rhTSH)
(2) N = 4/6 with 0.01 mg rhTSH & N = 4/8 with 0.1 mg rhTSH
(3) Combined group 0.01 mg rhTSH and 0.03 mg rhTSH

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Subjective outcomes
(D) Blinding of outcome assessment (detection bias): Subjective outcomes
(E) Incomplete outcome data (attrition bias): Subjective outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: rhTSH-aided radioiodine versus radioiodine only, Outcome 3: % of thyroid volume reduction

Study or Subgroup	rhTSH-aided radioiodine Mean [%]	SD [%]	Total	Radioiodine only Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
Albino 2010 (1)	36.7	18.1	8	19	24.3	8	8.7%	17.70 [-3.30 , 38.70]
Bonnema 2007	53.3	3.3	14	34.1	32	15	12.0%	19.20 [2.91 , 35.49]
Cubas 2009	32.9	23.2	9	12.7	21.5	10	9.2%	20.20 [0.02 , 40.38]
Fast 2010 (2)	35	15.5	60	35	16.4	30	22.2%	0.00 [-7.06 , 7.06]
Fast 2014 (3)	53	18.6	30	44	12.7	27	20.8%	9.00 [0.80 , 17.20]
Nielsen 2006	62.1	3	28	46.1	4	29	27.2%	16.00 [14.17 , 17.83]
Total (95% CI)			**149**			**119**	**100.0%**	**11.91 [4.43 , 19.40]**

Heterogeneity: Tau² = 52.71; Chi² = 21.09, df = 5 (P = 0.0008); I² = 76%
Test for overall effect: Z = 3.12 (P = 0.002)
Test for subgroup differences: Not applicable



Footnotes

(1) 12-month follow-up (N = 8 with 0.1 mg rhTSH)
(2) 12-month follow-up (combined rhTSH groups - rhTSH 24/48/72h)
(3) CT scan results refer to 86/91 randomised participants (0.03 mg rHTSH group)

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Objective outcomes
(D) Blinding of outcome assessment (detection bias): Objective outcomes
(E) Incomplete outcome data (attrition bias): Objective outcomes
(F) Selective reporting (reporting bias)
(G) Other bias

ADDITIONAL TABLES

Table 1. Overview of study populations

Trial ID (trial design)	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/ eligible (N)	Randomised (N)	Analysed (primary outcome) (N)	Finished study (N)	Randomised finished study (%)	Follow-up
Albino 2010 (parallel RCT)	I1: 0.1 mg rhTSH + radioiodine (1.11 GBq)	—	—	8	8	8	100	12 months
	I2: 0.01 mg rhTSH + radioiodine (1.11 GBq)			6	6	6	100	
	C: isotonic saline + radioiodine (1.11 GBq)			8	8	8	100	
	total:			**22**	**22**	**22**	**100**	
Bonnema 2007 (parallel RCT)	I: 0.3 mg rhTSH + radioiodine (aiming at a thyroid dose of 100 Gy)	"Accepting a type I error of 5%, a type II error of 10%, and assuming a SD of 20% on the percent goiter volume reduction, at least 13 patients in each randomization group were required to detect a difference of 25%"	—	14	14	14	100	12 months
	C: isotonic saline + radioiodine (aiming at a thyroid dose of 100 Gy)			15	15	15	100	
	total:			**29**	**29**	**29**	**100**	
Cubas 2009 (parallel RCT)	I1: 0.005 mg rhTSH + radioiodine (1.11 GBq)	—	—	9	9	9	100	24 months
	I2: 0.1 mg rhTSH + radioiodine (1.11 GBq)			9	9	9	100	
	C: isotonic saline + radioiodine (1.11 GBq)			10	10	9	100	
	total:			**28**	**28**	**27**	**96**	

Table 1. Overview of study populations *(Continued)*

Fast 2010[a] (parallel RCT)	I: 0.1 mg rhTSH + radioiodine (50 Gy)	—	594/282	60	60	60	100	12 months
	C: placebo + radioiodine (100 Gy)			30	30	30	100	
	total:			**90**	**90**	**90**	**100**	
Fast 2014 (parallel RCT)	I1: 0.01 mg rhTSH + radioiodine (100 Gy)	"Using a two-sided t-test, this study required 29 patients per arm to have an 80% power for the detection of the group difference at a 0.05 significance level"	141/95	30	30	30	100	36 months[b]
	I2: 0.03 mg rhTSH + radioiodine (100 Gy)			33	33	33	100	
	C: sodium carboxymethylcellulose + radioiodine (100 Gy)			32	32	32	100	
	total:			**95**	**95**	**95**	**100**	
Nielsen 2006 (parallel RCT)	I: 0.3 mg rhTSH + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	"Accepting a type I error of 5% and a type II error of 10% and assuming an SD of 20% on the percentage of goiter volume reduction, at least 21 patients in each randomization group were required to detect a difference of 20%"	—	28	28	28	100	12 months
	C: isotonic saline + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)			29	29	29	100	
	total:			**57**	**57**	**57**	**100**	
Total	**All interventions**			**197**		**197**		
	All comparators			**124**		**123**		
	All interventions and comparators			**321**		**320**		

— denotes not reported

[a]Placebo group: N = 30; rhTSH group combined: N = 60 (rhTSH 24 hr before radioiodine: N = 20; rhTSH 48 hr before radioiodine: N = 20; rhTSH 72 hr before radioiodine: N = 20)

[b]Extension phase of the original study lasting 6 months (10 participants withdrew during the extension phase)

^{131}I: radioactive iodine; **C:** comparator; **GBq**: gigabecquerel; **Gy**: Gray; **I:** intervention; **RCT**: randomised controlled trial; **SD**: standard deviation

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)
1. MESH DESCRIPTOR Goiter, Nodular
2. MESH DESCRIPTOR Thyroid Nodule
3. (thyroid ADJ3 nodule*):TI,AB,KY
4. ((goiter* OR goitre*) ADJ6 (nodular OR multinodular OR multi-nodular OR nontoxic OR non-toxic)):TI,AB,KY
5. #1 OR #2 OR #3 OR #4
6. MESH DESCRIPTOR Iodine Radioisotopes
7. MESH DESCRIPTOR Radiopharmaceuticals
8. (radioiodine* or radioactive iodine*):TI,AB,KY
9. (131J OR J131 OR I131 OR 131I):TI,AB,KY
10. #6 OR #7 OR #8 OR #9
11. MESH DESCRIPTOR Thyrotropin alfa
12. (thyrotropin alfa):TI,AB,KY
13. rhTSH*:TI,AB,KY
14. (recombinant ADJ6 ("human TSH" OR thyrotropin*)):TI,AB,KY
15. #11 OR #12 OR #13 OR #14
16. #5 AND #10 AND #15

MEDLINE Ovid
1. Goiter, Nodular/
2. Thyroid Nodule/
3. (thyroid adj3 nodule?).tw.
4. (goiter? adj6 (nodular or multinodular or multi-nodular or nontoxic or non-toxic)).tw.
5. (goitre? adj6 (nodular or multinodular or multi-nodular or nontoxic or non-toxic)).tw.
6. or/1-5
7. Iodine Radioisotopes/
8. Radiopharmaceuticals/
9. (radioiodine* or radioactive iodine*).tw.
10. (131J or J131 or I131 or 131I).tw.
11. or/7-10
12. Thyrotropin Alfa/

(Continued)

13. thyrotropin alfa.tw.

14. rhTSH?.tw.

15. (recombinant adj6 (human TSH or thyrotropin*)).tw.

16. or/12-15

17. 6 and 11 and 16

Scopus
1. TITLE-ABS("thyroid nodule*" OR ((goiter* OR goitre*) W/6 (nodular OR multinodular OR multi-nodular OR nontoxic OR non-toxic)))
2. TITLE-ABS(radioiodine* OR "radioactive iodine*" OR 131J OR J131 OR I131 OR 131I OR 131)
3. TITLE-ABS("thyrotropin alfa" OR rhTSH* OR (recombinant W/6 ("human TSH" OR thyrotropin*)))
4. #1 AND #2 AND #3
5. TITLE-ABS-KEY(random* OR "clinical trial*" OR "double blind*" OR placebo*)
6. #4 AND #5

WHO ICTRP Search Portal (standard search)
goiter* AND thyrotropin* OR
goiter* AND recombinant OR
goiter* AND rhTSH OR
goitre* AND thyrotropin* OR
goitre* AND recombinant OR
goitre* AND rhTSH OR
nodule* AND thyrotropin* OR
nodule* AND recombinant OR
nodule* AND rhTSH

ClinicalTrials.gov (expert search)
(goiter OR goitre OR goiters OR goitres OR "thyroid nodule" OR "thyroid nodules") AND (thyrotropin OR rhTSH OR recombinant)

Appendix 2. Selection bias decisions

Selection bias decisions for studies that reported unadjusted analyses: comparison of results obtained using method details alone versus results obtained using method details and study baseline information[a]			
Reported randomisation and allocation concealment methods	**Risk of bias judgement using methods reporting**	**Information gained from study characteristics data**	**Risk of bias using baseline information and methods reporting**

(Continued)

Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	**High risk**
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	**Unclear risk**[b]
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables[c]	Low risk
		No baseline details	**Unclear risk**
Sequence is not truly randomised or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	**Low risk**
		Limited baseline details, showing balance in some important prognostic variables[c]	**Unclear risk**
		No baseline details	High risk

[a]Taken from Corbett 2014; judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias compared with using methods reporting alone.
[b]Imbalance was identified that appears likely to be due to chance.
[c]Details for the remaining important prognostic variables are not reported.

Appendix 3. Risk of bias assessment

Risk of bias domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: study authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person, who was not otherwise involved in the study, performed this. We considered the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

(Continued)

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

For each included study, we described the method used to conceal allocation to interventions prior to assignment, and we assessed whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, internet-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes
- Unclear risk of bias: insufficient information about the allocation concealment
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure

We also evaluated study baseline data to incorporate assessment of baseline imbalance into the risk of bias judgement for selection bias (Corbett 2014).

Chance imbalances may also affect judgements on the risk of attrition bias. In the case of unadjusted analyses, we distinguished between studies that we rated as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies that we judged as being at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We reclassified judgements of unclear, low, or high risk of selection bias as specified in Appendix 3.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the study)

We evaluated the risk of detection bias separately for each outcome. We noted whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judged that the outcome was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the study did not address this outcome
- High risk of bias: no blinding or incomplete blinding, and the outcome was likely to have been influenced by lack of blinding; blinding of study participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome was likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We evaluated the risk of detection bias separately for each outcome. We noted whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment was ensured, and it was unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judged that the outcome measurement was unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the study did not address this outcome
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to quantity, nature, or handling of incomplete outcome data)

For each included study, or each outcome, or both, we described the completeness of data, including attrition and exclusions from the analyses. We stated whether the study reported attrition and exclusions, and we reported the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We also noted if the study reported the reasons for attrition or exclusion, and whether missing data were balanced across groups, or were related to outcomes. We considered the implications of missing outcome data per outcome, such as high dropout rates (e.g. above 15%), or disparate attrition rates (e.g. difference of 10% or more between study arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.

(Continued)

- Unclear risk of bias: insufficient information to assess whether missing data, in combination with the method used to handle missing data, were likely to induce bias; the study did not address this outcome
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated', or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We assessed outcome reporting bias by evaluating the results of the appendix 'Matrix of study endpoints (publications and trial documents).'

- Low risk of bias: the study protocol was available, and all the study's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes.
- Unclear risk of bias: insufficient information about selective reporting
- High risk of bias: not all the study's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely, so that we could not enter them into a meta-analysis; the study report failed to include results for a key outcome that we would expect to have been reported for such a study.

Other bias

- Low risk of bias: the study appeared to be free from other sources of bias.
- Unclear risk of bias: information was insufficient to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias
- High risk of bias: the study had a potential source of bias related to the specific study design used; the study was claimed to be fraudulent; or the study had some other serious problem.

Appendix 4. Descriptions of participants

Study ID	Criteria	Description
Albino 2010	Inclusion criteria	Participants with euthyroid benign goitres
	Exclusion criteria	Participants with below normal TSH levels
	Diagnostic criteria	Participants with normal TSH levels, multinodular goitre and excluded malignancy (fine needle aspiration biopsy of the dominant and/or suspect nodules and by cytology studies)
Bonnema 2007	Inclusion criteria	Participants with euthyroid benign goitres
	Exclusion criteria	Participants with a history of cardiac failure or ventricular arrhythmias, previous malignant disease, or physical or psychiatric disabilities suggestive of difficulties in adherence to the protocol
	Diagnostic criteria	The diagnosis was based on clinical examination, ^{99m}Tc scintigraphy, and ultrasonography
Cubas 2009	Inclusion criteria	Participants with euthyroid benign goitres

(Continued)

	Exclusion criteria	Participants with previous surgery, TSH-suppressive therapy with T4, or radioactive iodine treatment, serious medical conditions
	Diagnostic criteria	The diagnostic setup included clinical examination, ^{131}I thyroid scintigraphy, and ultrasonography
Fast 2010	Inclusion criteria	Non-pregnant, non-lactating participants older than 18 yr, with a nontoxic nodular goitre (i.e. thyroid volume above 28 mL and two or more nodules larger than 1 cm), the presence of goitre-related symptoms (i.e. pressure, cosmetic complaints, or both), subclinical hyperthyroidism (i.e. serum TSH < 0.30 mU/L and normal serum T4 and T3 levels), or subclinical hyperthyroidism alone
	Exclusion criteria	Participants with subclinical hyperthyroidism were required to have hyperthyroid symptoms that did not necessitate the use of antithyroid drugs or -blockers
	Diagnostic criteria	The diagnostic setup included clinical examination, thyroid function tests, ^{99m}Tc scintigraphy, and ultrasonography
Fast 2014	Inclusion criteria	Participants with euthyroid benign goitres
	Exclusion criteria	Participants with previous partial or near total thyroidectomy, a history of ^{131}I therapy, or a history of therapy alone
	Diagnostic criteria	The diagnostic setup included clinical examination, thyroid function tests, and ultrasonography
Nielsen 2006	Inclusion criteria	Participants with euthyroid or subclinical hyperthyroid benign goitres
	Exclusion criteria	Participants who were averse to any treatment, were younger than 18 years, had intrathoracic goitre > 100 mL, had previous ^{131}I therapy, were unable to complete follow-up, had a 24-hour thyroid 131I uptake < 20%
	Diagnostic criteria	The diagnostic setup included clinical examination, thyroid function tests, ^{99m}Tc scintigraphy, and ultrasonography

T3: triiodothyronine;**T4**: thyroxine;**^{99m}Tc**: Technetium-99m; **TSH**: thyroid stimulating hormone

Appendix 5. Description of interventions

Study ID	Intervention(s)	Comparator
Albino 2010	I1: a 1.1 mg vial of rhTSH was diluted with 1.2 mL sterile water for injection, resulting in a 1 mL drawable solution of rhTSH concentrated at 0.9 ng/mL. A 1.0 mL aliquot of this solution was then diluted with 9 mL sterile water for injection, which resulted in a 0.1 mg/mL solution, which was intramuscularly injected 24 hours prior to radioiodine treatment	1.0 mL isotonic saline was intramuscularly injected 24 hours prior to radioiodine treatment
	I2: in order to obtain the 0.01 mg/mL solution of rhTSH, 1 mL of the 0.1 mg solution was diluted with 9 mL sterile water, which was intramuscularly injected 24 hours prior to radioiodine treatment	

(Continued)

Bonnema 2007	1.0 mL of the solution (0.3 mg rhTSH) was intramuscularly injected in the gluteal region 24 hours before ^{131}I therapy	1.0 mL isotonic saline was intramuscularly injected 24 hours prior to the ^{131}I therapy
Cubas 2009	I1: a single dose of 1.0 ml (0.1 mg) of rhTSH, which was intramuscularly injected 24 hours prior to radioiodine treatment	1.0 mL isotonic saline was intramuscularly injected 24 hours prior to the ^{131}I therapy
	I2: a single dose of 1.0 mL (0.005 mg) of rhTSH, which was intramuscularly injected 24 hours prior to radioiodine treatment	
Fast 2010	A vial containing 0.9 mg rhTSH was reconstituted to a concentration of 0.1 mg/mL (administered in the gluteal region), followed by a thyroid dose of 50 Gy. RhTSH was given 24 hours, 48 hours, or 72 hours before radioiodine	1 mL isotonic saline, followed by a thyroid dose of 100 Gy. Placebo was given 24 hours, 48 hours or 72 hours before radioiodine
Fast 2014	I1: 0.01 mg rhTSH was administered by intramuscular injection in the gluteal region 24 hours before ^{131}I therapy	The placebo injection was 0.5 mL of the same concentration of sodium carboxymethylcellulose
	I2: 0.03 mg rhTSH was administered by intramuscular injection in the gluteal region 24 hr before ^{131}I therapy	
Nielsen 2006	0.3 mg of rhTSH was injected intramuscularly into the gluteal region 24 hours prior to ^{131}I therapy	The placebo injection constituted 1 mL isotonic saline in the gluteal region 24 hours prior to ^{131}I therapy

GBq: giga Becquerel; **Gy**: Gray; **I**: intervention; **rhTSH**: recombinant human thyrotropin.

Appendix 6. Baseline characteristics (I)

Study ID	Intervention(s) and comparator(s)	Duration of follow-up	Participants	Study period	Country	Setting	Ethnic groups (%)	Duration of goitre
Albino 2010	I1: 0.1 mg rhTSH + radioiodine (1.11 GBq) I2: 0.01 mg rhTSH + radioiodine (1.11 GBq) C: placebo and radioiodine (1.11 GBq)	12 months	participants with multinodular goitre	—	Brazil	outpatients	—	—
Bonnema 2007	I: 0.3 mg rhTSH + radioiodine (aiming at a thyroid dose of 100 Gy) C: isotonic saline + radioiodine (aiming at a thyroid dose of 100 Gy)	12 months	participants with euthyroid benign goitres	2002 to 2005	Denmark	inpatients	—	—
Cubas 2009	I1: 0.005 mg rhTSH + radioiodine (1.11 GBq) I2: 0.1 mg rhTSH + radioiodine (1.11 GBq) C: placebo and radioiodine (1.11 GBq)	24 months	participants with euthyroid benign goitres	—	Brazil	outpatients	—	—
Fast 2010	I: 0.1 mg rhTSH + radioiodine (50 Gy) C: placebo + radioiodine (100 Gy)	12 months	participants with nontoxic nodular goitre with 2 or more nodules larger than 1 cm, and the presence of goitre-related symptoms (pressure or cosmetic complaints, or both), subclinical hyperthyroidism, or subclinical hyperthyroidism alone	2006 to 2008	Denmark	outpatients	—	—

(Continued)

Fast 2014	I1: 0.01 mg rhTSH + radioiodine (100 Gy) I2: 0.03 mg rhTSH + radioiodine (100 Gy) C: placebo and radioiodine (100 Gy)	36 months	participants with euthyroid benign goitres	—	Denmark, Italy, Brazil, Germany, France, Canada	outpatients	Black (9), white (88), mixed (3)	—
Nielsen 2006	I: 0.3 mg rhTSH + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake and ^{131}I half-life) C: placebo + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake and ^{131}I half-life)	12 months	participants with euthyroid benign goitres	2002 to 2004	Denmark	outpatients	—	—

—: denotes not reported

^{131}I: radioactive iodine; **C**: comparator; **GBq**: giga Becquerel; **Gy**: Gray; **I**: intervention; **rhTSH**: recombinant human thyrotropin

Appendix 7. Baseline characteristics (II)

Study ID	Intervention and comparator	% women	Age (mean/ range years (SD))	Comedications / Cointerventions / Comorbidities
Albino 2010	I1: 0.1 mg rhTSH + radioiodine (1.11 GBq)	88	62 (44 to 74)	All participants were advised to follow a low-iodine diet, starting 2 weeks prior to the administration of the diagnostic and therapeutic activities of radioiodine
	I2: 0.01 mg rhTSH + radioiodine (1.11 GBq)	100	61 (52 to 72)	
	C: placebo and radioiodine (1.11 GBq)	88	60 (33 to 72)	
Bonnema 2007	I: 0.3 mg rhTSH + radioiodine (aiming at a thyroid dose of 100 Gy)	71	57 (42 to 84)	—
	C: isotonic saline + radioiodine (aiming at a thyroid dose of 100 Gy)	80	65 (37 to 87)	
Cubas 2009	I1: 0.005 mg rhTSH + radioiodine (1.11 GBq)	100	60 (48 to 73)	None of the participants had serious medical conditions and all of them had subclinical hyperthyroidism (which was treated with methimazole), or were euthyroid
	I2: 0.1 mg rhTSH + radioiodine (1.11 GBq)	100	61 (49 to 73)	
	C: placebo and radioiodine (1.11 GBq)	80	62 (45 to 86)	
Fast 2010	I: 0.1 mg rhTSH + radioiodine (50 Gy)	83	52 (22 to 83)	—
	C: placebo + radioiodine (100 Gy)	93	55 (27 to 78)	—
Fast 2014	I1: 0.01 mg rhTSH + radioiodine (100 Gy)	97	57.3 (10.2)	—
	I2: 0.03 mg rhTSH + radioiodine (100 Gy)	76	56.9 ± 10.3	
	C: placebo and radioiodine (100 Gy)	84	57.5 (8.7)	
Nielsen 2006	I: 0.3 mg rhTSH + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	86	52 (32 to 68)	6% of participants had previous thyroidectomy
	C: placebo + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	93	52 (26 to 77)	5% of participants had previous thyroidectomy

—: denotes not reported

^{131}I: radioactive iodine; **C**: comparator; **GBq**: giga Becquerel; **Gy**: Gray; **I**: intervention; **rhTSH**: recombinant human thyrotropin; **SD**: standard deviation

Appendix 8. Time points of outcome measurements

Study ID	Outcomes	Time points of measurement
Albino 2010	**Review's primary outcomes**	
	Health-related quality of life	—
	Hypothyroidism	3 d, 10 d, 30 d, 90 d, 180 d, 360 d
	Adverse events	3 d, 10 d, 30 d, 90 d, 180 d, 360 d
	Review's secondary outcomes	
	Thyroid volume	2 d, 7 d, 180 d, 360 d
	All-cause mortality	—
	Costs	—
Bonnema 2007	**Review's primary outcomes**	
	Health-related quality of life	—
	Hypothyroidism	1 wk, 3 wk, 9 wk, 12 wk, 6 mo, 9 mo, 12 mo
	Adverse events	1 wk, 3 wk, 9 wk, 12 wk, 6 mo,12 mo
	Review's secondary outcomes	
	Thyroid volume	1 wk, 12 mo
	All-cause mortality	—
	Costs	—
Cubas 2009	**Review's primary outcomes**	
	Health-related quality of life	—
	Hypothyroidism	24 hr, 72 hr, 1 mo, 2 mo, 3 mo, 6 mo, 12 mo, 24 mo
	Adverse events	24 mo
	Review's secondary outcomes	
	Thyroid volume	6 mo, 12 mo, 24 mo
	All-cause mortality	6 mo, 12 mo, 24 mo
	Costs	—
Fast 2010	**Review's primary outcomes**	
	Health-related quality of life	—

(Continued)

	Hypothyroidism	3 wk, 6 wk, 3 mo, 6 mo, 9 mo, 12 mo
	Adverse events	12 mo
	Review's secondary outcomes	
	Thyroid volume	3 mo, 12 mo
	All-cause mortality	—
	Costs	—
Fast 2014	**Review's primary outcomes**	
	Health-related quality of life	12 mo, 24 mo, 36 mo
	Hypothyroidism	Every 3 mo until 36 mo
	Adverse events	Continuously monitored for 36 mo
	Review's secondary outcomes	
	Thyroid volume	6 mo, 36 mo
	All-cause mortality	—
	Costs	—
Nielsen 2006	**Review's primary outcomes**	
	Health-related quality of life	—
	Hypothyroidism	3 wk, 6 wk, 12 wk, 3 mo, 6 mo, 9 mo, 12 mo
	Adverse events	3 wk, 6 wk, 12wk, 3 mo, 6 mo, 9 mo, 12 mo
	Review's secondary outcomes	
	Thyroid volume	3 mo, 6 mo, 9 mo, 12 mo
	All-cause mortality	—
	Costs	—

—: denotes not reported

hr: hours;**d**: days; **mo**: months; **wk**: weeks.

Appendix 9. Matrix of study endpoints (publications and trial documents)

Study ID

(Continued)

Albino 2010	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): thyroid volume, tracheal compression (tracheal cross-sectional area), antithyroid antibodies, and thyroid hormones, hypothyroidism
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): thyroid function tests, TSH receptor antibodies, thyroid peroxidase antibodies (TPOAb), antithyroglobulin antibodies, thyroid volume, tracheal compression, adverse effects (clinical assessment and frequent measures of thyroid hormone levels)
Bonnema 2007	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): 1. Permanent hypothyroid 2. Adverse effects related to thyroid pain and cervical compression
	Secondary outcome measure(s): 1. Goitre volume reduction
	Other outcome measure(s): thyroid function tests, TSH receptor antibodies, thyroid peroxidase antibodies (TPOAb), antithyroglobulin antibodies, patient satisfaction
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): 1. Adverse effects related to thyroid pain and cervical compression 2. Hypothyroidism
	Secondary outcome measure(s): 1. Goitre volume reduction
	Other outcome measure(s): thyroid function tests, TSH receptor antibodies, thyroid peroxidase antibodies (TPOAb), antithyroglobulin antibodies, thyroid volume, tracheal compression, adverse effects (clinical assessment and frequent measures of thyroid hormone levels)

(Continued)

Cubas 2009	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c] **Source:** NT **Endpoints quoted in publication(s)[b,c]** **Primary outcome measure(s)**: 1. Hypothyroidism 2. Adverse events related to radioiodine treatment **Secondary outcome measure(s)**: 1. Thyroid volume reduction **Other outcome measure(s)**: thyroid function tests, thyroglobulin, thyroid volume, adverse effects (clinical assessment and frequent measures of thyroid hormone levels), all cause mortality **Endpoints quoted in abstract of publication(s)[b,c]** **Primary outcome measure(s)**: 1. Hypothyroidism 2. Hyperthyroidism related to radioiodine treatment **Secondary outcome measure(s)**: 1. Thyroid volume reduction **Other outcome measure(s)**: thyroid function tests, thyroglobulin, thyroid volume, adverse effects (clinical assessment and frequent measures of thyroid hormone levels), all cause mortality
Fast 2010	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c] **Source:** NCT00275171 **Primary outcome measure(s)**: 1. An intra-individual comparison of the thyroid 131I-uptake before and after stimulation with rhTSH /placebo; time frame: 24 and 96 hours after tracer administration 2. An inter-individual comparison of the thyroid 131I uptake between those who receive placebo and those who receive rhTSH; time frame: 24 and 96 hours after tracer administration 3. An estimation of which time interval, injecting rhTSH, that is more favourable before 131I therapy (24 hours, 48 hours, or 72 hours); time frame: 24 and 96 hours after tracer administration 4. A comparison of the degree of goitre reduction when patients are pre-stimulated with rhTSH, and receive a thyroid 131I dose of 50 Gy; or when receiving conventional 131I, receiving a thyroid dose of 100 Gy; time frame: 3, 6, 9, and 12 months after 131I therapy **Secondary outcome measure(s)**: 1. A registration of adverse effects following rhTSH/placebo; time frame: all adverse effects occurring within one year of follow-up 2. Patient satisfaction (visual analogue scale) before, 3 months post 131I therapy, and at the end of follow-up (1 year); time frame: baseline, 3, and 12 months after 131I therapy 3. Development of TPOab or TSHRab; time frame: at 12-month follow-up 4. Thyroid function; time frame: at 12-month follow-up

(Continued)

	Other outcome measure(s): —
	Trial results available in trial register: no
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): goitre volume reduction, hospitalisation, goitre-related symptoms, thyroid function tests, thyroid peroxidase antibodies, TSH receptor antibodies, thyroid size, patient satisfaction (visual analogue scale)
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): goitre volume reduction, hospitalisation (according to the official radiation regulation), goitre-related symptoms, prevalence of myxoedema
Fast 2014	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NT
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s): 1. The ThyQoL questionnaire contained17 goitre-specific items and several overall quality-of life items before and after stimulation with rhTSH or placebo 2. Thyroid function was monitored every three months, until 36 months. Antibodies against the TSH receptor were measured at baseline and repeated at six months 3. Adverse events were continuously monitored, and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v10.0 or higher
	Secondary outcome measure(s): 1. Thyroid volume was monitored by computed tomography (CT) scan of the neck, and performed at baseline, six months, and 36 months following therapy
	Other outcome measure(s): thyroid antithyroid antibodies, cross-sectional area of trachea
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): 1. The quality of life was improved 2. Permanent hypothyroidism at 3 years
	Secondary outcome measure(s): 1. Thyroid volume reduction at 6 mo and 36 mo
	Other outcome measure(s): radioiodine uptake, cross-sectional area of trachea

(Continued)

Nielsen 2006	**Endpoints quoted in trial document(s)** (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)[a,c]
	Source: NCT00145366
	Primary outcome measure(s):
	1. Permanent hypothyroidism after treatment
	2. Adverse effects related to hyperthyroid
	Secondary outcome measure(s):
	1. Goitre volume reduction
	Other outcome measure(s): TSH receptor antibodies, thyroid peroxidase antibodies (TPOAb), antithyroglobulin antibodies, patient satisfaction
	Trial results available in trial register: no
	Endpoints quoted in publication(s)[b,c]
	Primary outcome measure(s):
	1. Permanent hypothyroidism after treatment
	2. Adverse effects related to hyperthyroid
	Secondary outcome measure(s):
	1. Goitre volume reduction
	Other outcome measure(s): patient satisfaction
	Endpoints quoted in abstract of publication(s)[b,c]
	Primary outcome measure(s): —
	Secondary outcome measure(s): —
	Other outcome measure(s): —

— denotes not reported
[a]Trial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers).
[b]Publication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents, or multiple reports of a primary trial).
[c]Primary and secondary outcomes refer to verbatim specifications in publication/records. Unspecified outcome measures refer to all outcomes not described as primary or secondary outcome measures.

EMA: European Medicines Agency; **FDA**: Food and Drug Administration (US); **NT**: no trial document available.

Appendix 10. Definition of endpoint measurement

Study ID	Health-related quality of life	Hypothyroidism	Adverse events	Thyroid volume	All-cause mortality	Costs

(Continued)

Albino 2010	NR	T3, (f)T4, TSH measurements	Adverse effects were evaluated by clinical assessment, and by frequent measurements of thyroid hormone levels, goitre enlargement, compressive symptoms	Thyroid volume was measured by MRI. The thyroid limits were manually drawn, and the thyroid area was calculated by the built-in (dedicated) software	NR	NR
Bonnema 2007	NR	T3, (f/t)T4, TSH measurements	Goitre-related symptoms	Goitre size was estimated by MRI	NR	NR
Cubas 2009	NR	T3, (f)T4, TSH measurements	Symptoms of hyperthyroidism; enlargement of the thyroid without compressive symptoms, or moderate cervical pain	CT scan	death	NR
Fast 2010	NR	(f/t)T3, (f/t)T4, TSH measurements	Proportion of participants experiencing adverse effects, such as goitre-related pressure symptoms (i.e. cervical obstructive symptoms)	In 70 participants, a planimetric ultrasonic scanning procedure was performed; in the remaining 20 participants, retroclavicular extension of the gland impeded an accurate ultrasonic assessment – in these participants, planimetric measurements were based on MRI	NR	NR
Fast 2014	Thyroid disease-specific questionnaire ThyPRO	(f/t)T3, (f/t)T4, TSH measurements	Participants were continuously monitored for adverse events (AEs), which were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v 10.0 or higher	CT scan	NR	NR
Nielsen 2006	NR	(f/t)T3, (f/t)T4, TSH measurements	ND	Ultrasonography	NR	NR

CT: computed tomography; **ND**: not defined; **NR**: not reported; **MRI**: magnetic resonance imaging; **(f/t)T3**: (free) triiodothyronine; (**f/t)T4**: (free/total) thyroxine; **THyPRO**: thyroid-related patient-reported outcomes; **TSH**: thyroid-stimulating hormone.

Appendix 11. Adverse events (I)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Deaths (N)	Deaths (% of participants)	Participants with at least one adverse event (N)	Participants with at least one adverse event (%)	Participants with at least one severe/serious adverse event (N)	Participants with at least one severe/serious adverse event (%)
Albino 2010	I1: 0.1 mg rhTSH + radioiodine (1.11 GBq)	8	—	—	4	50	—	—
	I2: 0.01 mg rhTSH + radioiodine (1.11 GBq)	6	0	0	4	66.7	—	—
	C: placebo and radioiodine (1.11 GBq)	8	0	0	3	37.5	—	—
Bonnema 2007	I: 0.3 mg rhTSH + radioiodine (aiming at a thyroid dose of 100 Gy)	14	—	—	12	85.7	—	—
	C: isotonic saline + radioiodine (aiming at a thyroid dose of 100 Gy)	15	—	—	8	53.3	—	—
Cubas 2009	I1: 0.005 mg rhTSH + radioiodine (1.11 GBq)	9	0	0	6	66.6	—	—
	I2: 0.1 mg rhTSH + radioiodine (1.11 GBq)	9	0	0	2	22.2	—	—
	C: placebo and radioiodine (1.11 GBq)	10	1	10	4	40	—	—
Fast 2010	I: 0.1 mg rhTSH + radioiodine (50 Gy)	60	—	—	17	28.3	—	—
	C: placebo + radioiodine (100 Gy)	30	—	—	10	33.3	—	—
Fast 2014	I1: 0.01 mg rhTSH + radioiodine (100 Gy)	30	—	—	26	86.7	—	—
	I2: 0.03 mg rhTSH + radioiodine (100 Gy)	33	—	—	31	93.9	—	—
	C: placebo and radioiodine (100 Gy)	32	—	—	27	84.4	—	—
Nielsen 2006	I: 0.3 mg rhTSH + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	28	—	—	16	53.6	—	—

(Continued)

C: placebo + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	29	—	—	10	34.5	—	—

—: denotes not reported

^{131}I: radioactive iodine; **C**: comparator; **GBq**: giga Becquerel; **Gy**: Gray; **I**: intervention; **rhTSH**: recombinant human thyrotropin

Appendix 12. Adverse events (II)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants discontinuing study due to an adverse event (N)	Participants discontinuing study due to an adverse event (%)	Participants with at least one hospitalisation (N)	Participants with at least one hospitalisation (%)
Albino 2010	I1: 0.1 mg rhTSH + radioiodine (1.11 GBq)	8	0	0	—	—
	I2: 0.01 mg rhTSH + radioiodine (1.11 GBq)	6	0	0	—	—
	C: placebo and radioiodine (1.11 GBq)	8	0	—	—	—
Bonnema 2007	I: 0.3 mg rhTSH + radioiodine (aiming at a thyroid dose of 100 Gy)	14	0	0	1	7.1
	C: isotonic saline + radioiodine (aiming at a thyroid dose of 100 Gy)	15	0	0	—	—
Cubas 2009	I1: 0.005 mg rhTSH + radioiodine (1.11 GBq)	9	—	—	—	—
	I2: 0.1 mg rhTSH + radioiodine (1.11 GBq)	9	—	—	—	—
	C: placebo and radioiodine (1.11 GBq)	10	—	—	—	—
Fast 2010	I: 0.1 mg rhTSH + radioiodine (50 Gy)	60	0	0	1[a]	1.7
	C: placebo + radioiodine (100 Gy)	30	0	0	14[a]	46.7
Fast 2014	I1: 0.01 mg rhTSH + radioiodine (100 Gy)	30	0	0	—	—
	I2: 0.03 mg rhTSH + radioiodine (100 Gy)	33	0	0	—	—
	C: placebo and radioiodine (100 Gy)	32	—	—	—	—
Nielsen 2006	I: 0.3 mg rhTSH + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	28	0	0	—	—
	C: placebo + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	29	0	0	—	—

—: denotes not reported

a"^{131}I-activity was limited to 600 MBq to avoid hospitalisation, as required by the official radiation regulation in Denmark. Shortly after study initiation, the protocol was extended to allow activities up to 3700 MBq given in hospital, because limitation of the administered ^{131}I-activity to 600 MBq would not allow us to deliver the intended 100 Gy in a considerable proportion of patients in the placebo group. Before this protocol extension, the administered ^{131}I-activity had been limited in two patients in the placebo group (from 1192 to 629 MBq and 884 to 626 MBq)"

^{131}I: radioactive iodine; **C**: comparator; **GBq**: giga Becquerel; **Gy**: Gray; **I**: intervention; **rhTSH**: recombinant human thyrotropin

Appendix 13. Adverse events (III)

Study ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants with a specific adverse event (description)	Participants with at least one specific adverse events (N)	Participants with at least one specific adverse event (%)
Albino 2010	I1: 0.1 mg rhTSH + radioiodine (1.11 GBq)	8	(a) hypothyroidism (b) mild cervical discomfort, localised pain, and palpitations (c) goitre enlargement and/or compressive symptoms with respiratory difficulty	(a) 3 (b) 1 (c) 3	(a) 37.5 (b) 12.5 (c) 37.5
	I2: 0.01 mg rhTSH + radioiodine (1.11 GBq)	6	(a) hypothyroidism (b) mild cervical discomfort, localised pain and palpitations (c) goitre enlargement, or compressive symptoms, or both, with respiratory difficulty	(a) 3 (b) 1 (c) 2	(a) 50 (b) 16.7 (c) 33.3
	C: placebo and radioiodine (1.11 GBq)	8	(a) hypothyroidism (b) mild cervical discomfort, localised pain and palpitations (c) goitre enlargement, or compressive symptoms, or both, with respiratory difficulty	(a) 2 (b) 1 (c) 2	(a) 25 (b) 12.5 (c) 25
Bonnema 2007	I: 0.3 mg rhTSH + radioiodine (aiming for a thyroid dose of 100 Gy)	14	—	—	—
	C: isotonic saline + radioiodine (aiming at a thyroid dose of 100 Gy)	15	—	—	—
Cubas 2009	I1: 0.005 mg rhTSH + radioiodine (1.11 GBq)	9	(a) symptoms of hyperthyroidism, such as palpitation, anxiety, headache, or asthenia (b) enlargement of the thyroid without compressive symptoms, moderate cervical pain	(a) 6 (b) 6	(a) 66.6 (b) 66.6
	I2: 0.1 mg rhTSH + radioiodine (1.11 GBq)	9	(a) symptoms of hyperthyroidism, such as palpitation, anxiety, headache, or asthenia	(a) 2 (b) 3	(a) 22.2 (b) 33.3

(Continued)

			(b) enlargement of the thyroid without compressive symptoms, or moderate cervical pain		
	C: placebo and radioiodine (1.11 GBq)	10	(a) symptoms of hyperthyroidism, such as palpitation, anxiety, headache, or asthenia	(a) 4	(a) 40
				(b) 0	(b) 0
			(b) enlargement of the thyroid without compressive symptoms, or moderate cervical pain		
Fast 2010	I: 0.1 mg rhTSH + radioiodine (50 Gy)	60	(a) hyperthyroidism symptoms	(a) 13	(a) 21.7
			(b) cervical discomfort or pain	(b) 5	(b) 8.3
			(c) biochemical hyperthyroidism	(c) 33	(c) 55
			(d) mild, transient thyroid-associated ophthalmopathy	(d) 2	(d) 3.3
				(e) 7	(e) 11.7
			(e) permanent hypothyroidism (1-year follow-up)	(f) 4	(f) 6.7
			(f) therapeutic failure (i.e. failure to relieve goitre-related symptoms, leading to subsequent thyroid surgery)		
	C: placebo + radioiodine (100 Gy)	30	(a) hyperthyroid symptoms	(a) 7	(a) 23.3
			(b) cervical discomfort/pain	(b) 4	(b) 13.3
			(c) biochemical hyperthyroidism	(c) 19	(c) 63.3
			(d) mild, transient thyroid-associated ophthalmopathy	(d) 0	(d) 0
				(e) 2	(e) 6.7
			(e) permanent hypothyroidism (1-year follow-up)	(f) 2	(f) 6.7
			(f) therapeutic failure (i.e. failure to relieve goitre-related symptoms, leading to subsequent thyroid surgery)		
Fast 2014	I1: 0.01 mg rhTSH + radioiodine (100 Gy)	30	(a) hyperthyroidism	(a) 8	(a) 26.7
			(b) hypothyroidism	(b) 10	(b) 33.3
			(c) thyroid pain	(c) 0	(c) 0
			(d) neck pain	(d) 3	(d) 10
	I2: 0.03 mg rhTSH + radioiodine (100 Gy)	33	(a) hyperthyroidism	(a) 11	(a) 33.3
			(b) hypothyroidism	(b) 15	(b) 45.5
			(c) thyroid pain	(c) 1	(c) 3
			(d) neck pain	(d) 6	(d) 18.2
	C: placebo and radioiodine (100 Gy)	32	(a) hyperthyroidism	(a) 2	(a) 6.3
			(b) hypothyroidism	(b) 4	(b) 12.5

(Continued)

			(c) thyroid pain	(c) 1	(c) 3.1
			(d) neck pain	(d) 3	(d) 9.4
Nielsen 2006	I: 0.3 mg rhTSH + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	28	(a) hyperthyroid symptoms	(a) 10	(a) 35.7%
			(b) cervical pain beyond 1 week	(b) 3	(b) 10.7%
			(c) permanent hypothyroidism	(c) 16	(c) 57.1
	C: placebo + radioiodine (calculated based on thyroid size, thyroid ^{131}I uptake, and ^{131}I half-life)	29	(a) hyperthyroid symptoms	(a) 6	(a) 20.7
			(b) cervical pain beyond 1 week	(b) 2	(b) 6.9
			(c) permanent hypothyroidism	(c) 3	(c) 10.3

—: denotes not reported

^{131}I: radioactive iodine; **C**: comparator; **GBq**: giga Becquerel; **Gy**: Gray; **I**: intervention; **rhTSH**: recombinant human thyrotropin.

Appendix 14. Checklist to aid consistency and reproducibility of GRADE assessments

Items		(1) Health-related quality of life	(2) Hypothyroidism	(3) Adverse events	(4) All-cause mortality	(4) Thyroid volume	(6) Costs
Trial limitations (risk of bias)[a]	Was random sequence generation used (i.e. no potential for selection bias)?	Unclear	Unclear	Unclear	Unclear	Unclear	Not reported
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear	Unclear	Unclear	Unclear	
	Was there blinding of participants and personnel (i.e. no potential for performance bias), or outcome not likely to be influenced by lack of blinding?	Yes (participants)	Yes	Yes	Yes	Yes	
	Was there blinding of outcome assessment (i.e. no potential for detection bias), or was outcome measurement not likely to be influenced by lack of blinding?	Yes (participants)	Yes	Yes	Yes	Yes	
	Was an objective outcome used?	Yes	Yes	Yes	Yes	Yes	
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)?[e]	Yes	Yes	Yes	Yes	Yes	
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes	Yes	Yes	Yes	
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes	Yes	Yes	Yes	
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes	Yes	Yes	Yes	
Inconsistency[b]	Point estimates did not vary widely?	NA	Yes	Yes	NA	Yes	
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at	NA	Substantial	Substantial	NA	Substantial	

(Continued)

	least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?					
	Was the direction of effect consistent?	NA	Yes	Yes	NA	Yes
	What was the magnitude of statistical heterogeneity (as measured by I^2) - low (I^2 < 40%), moderate (I^2 40% to 60%), high I^2 > 60%)?	NA	Low	Low	NA	High (↓)
	Was the test for heterogeneity statistically significant (P < 0.1)?	NA	Not statistically significant	Not statistically significant	NA	Statistically significant (↓)
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes
Imprecision[c]	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	NA	Yes	No (↓)	NA	Yes
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)?[e]	Low (↓)	Low (↓)	Low (↓)	Low (↓)	Low (↓)
	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5 to 10 studies, small: < 5 studies)?[e]	Small (↓)	Moderate	Moderate	Moderate	Moderate
	Was the outcome a common event (e.g. occurs more than 1/100)?	NA	Yes	Yes	NA	NA

(Continued)

Publication bias[d]	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	NA	NA	NA	NA	NA
	There was no discrepancy in findings between published and unpublished trials?	Unclear	Unclear	Unclear	Unclear	Unclear

[a]Questions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials.
[b]Questions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2.

[c]When judging the width of the confidence interval, it is recommended that one uses a clinical decision threshold to assess whether the imprecision is clinically meaningful.
[d]Questions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry, and discrepancies between published and unpublished trials.
[e]Depends on the context of the systematic review area.

(↓): key item for potential downgrading the certainty of the evidence (GRADE), as shown in the footnotes of the summary of findings table(s); **NA**: not applicable

HISTORY

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CONTRIBUTIONS OF AUTHORS

All review authors contributed to, read, and approved the final protocol draft.

Chao Ma (CM): protocol draft, search strategy development, data analysis, data interpretation, review draft, and future review update

Jiawei Xie (JX): trial selection and data extraction

Suyun Chen (SC): acquisition of trial copies, trial selection, data extraction, data analysis, and future review update

Hui Wang (HW): trial selection, data extraction, and data interpretation

Huo Yanlei (HYL): trial selection and assessment of each trial independently

DECLARATIONS OF INTEREST

YH: none known

JX: none known

SC: none known

QS: none known

HW: none known

CM: none known

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Because of the long time delay between publication of the protocol and review, all parts of the Cochrane Review were upgraded to the most recent Cochrane and CMED standards, by the Editorial Base.

NOTES

We based parts of the Methods, Appendix 1, Appendix 5, and Appendix 6 of the Cochrane Protocol on a standard template established by the CMED group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Goiter; Iodine Radioisotopes [therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic; Thyrotropin; *Thyrotropin Alfa

MeSH check words

Female; Humans