Original Article

Methimazole plus levothyroxine for treating hyperthyroidism in children: a systematic review and meta-analysis

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Background: Hyperthyroidism is a disease of excessive synthesis and secretion of thyroid hormones, and there is a lack of studies that have systematically evaluated the efficacy of the combination in treating hyperthyroidism. This study aimed to systematically evaluate the effectiveness and safety of methimazole combined with levothyroxine for treating hyperthyroidism in children.

Methods: We searched PubMed, CNKI, Wanfang Database, EMBASE, Web of Science, and other online electronic databases to find correlation studies of methimazole combined with levothyroxine in treating hyperthyroidism in children from 2010 to 2021. Meta-analysis was performed using Stata 16 software.

Results: Finally, 15 relevant articles were included comprising 1,718 pediatric patients. Meta-analysis results indicated that compared with methimazole alone (control group), the experimental group administered methimazole + levothyroxine had no evident difference in the level of thyroid-stimulating hormone [standardized mean difference (SMD) =–0.34, 95% confidence interval (CI): –1.02, 0.35, P=0.33], but notably improved the efficacy of clinical treatment of hyperthyroidism in children [odds ratio (OR) =5.77, 95% CI: 2.62, 12.74, P<0.001]. Meanwhile, the experimental group had lower adverse reaction rates (OR =0.28, 95%CI: 0.19, 0.40, P<0.001), free triiodothyronine (FT3) level (SMD =–0.85, 95% CI: –1.57, 0.13, P=0.02), free tetraiodothyronine (FT4) level (SMD =–0.94, 95% CI: –1.59, –0.30, P=0.004) and reduced thyroid volume (SMD =–1.3, 95% CI: –1.67, 0.93, P<0.001).

Discussion: Using methimazole + levothyroxine to treat hyperthyroidism in children can raise the levels of FT3 and FT4, reduce the thyroid volume, improve clinical efficacy, and lower the adverse reaction rate of patients.

Keywords: Hyperthyroidism; levothyroxine; meta-analysis; methimazole

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Introduction

Hyperthyroidism is a disease of excessive synthesis and secretion of thyroid hormones, inducing symptoms such as goiter, hot flashes of the skin and metabolic disorders (1). Thyroid stimulating antibody binds competitively with thyroid stimulating hormone (TSH) to the TSH receptor (TSHR)-α subunit, activating the adenylate cyclase signaling system, leading to thyroid follicular epithelial hyperplasia and excess thyroid hormone production. It is a rare but

severe disease with a high possibility of complications. The incidence of fetal or childhood disease is between 0.0025% and 0.025% (2,3). The onset of hyperthyroidism in children is insidious, because they are less self-aware, and its early symptoms and abnormal emotional expression of the child are easily overlooked, losing the opportunity for treatment in the early stage (4).

At present, there are three approaches to treating hyperthyroidism: antithyroid medications, subtotal or near-total thyroidectomy, and nuclide iodine therapy (5). Surgery is difficult with high risk, so for children, the first choice is drug therapy. Methimazole and levothyroxine are commonly used antithyroid drugs. Methimazole inhibits the synthesis of thyroid hormones at different stages in the thyroid and peripheral tissues to reduce the levels of thyroid hormones (6). Levothyroxine has a similar function to the human endogenous hormones. It is metabolized by deiodination and glucuronidation, thereby ameliorating symptoms (7). The treatment mechanisms and effects of the two drugs are completely different. Studies have shown that initial use of high-dose methimazole is harmful to children and adolescents (8), but long-term administration is an effective and safe treatment that also prevents recurrence of hyperthyroidism (9-11). The use of methimazole alone can easily cause secondary attenuation to thyroid function, which levothyroxine can ameliorate (12-14); therefore, their combination for long-term treatment may not only effectively treat the disease, but also reduce the incidence of functional attenuation. However, currently there is a lack of studies that have systematically evaluated the efficacy of the combination in treating hyperthyroidism, so we systematically analyzed the effectiveness and safety of methimazole combined with levothyroxine in treating hyperthyroidism in children through a meta-analysis. We present the following article in accordance with the PRISMA reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-21-497/rc).

Methods

Literature search

We followed the guidelines of the systematic review and meta-analysis (PRISMA-P) protocol statement (15), using "methimazole", "treatment" and "hyperthyroidism" as keywords and Boolean logic, to search for relevant articles from 2010 to 2021 in PubMed, CNKI, Wanfang, EMBASE, and Web of Science, including dissertations, conference reports, and journal articles with no language restriction.

Screening criteria

Our inclusion criteria were as follows: (I) research subjects under 18 years of age and meeting the diagnostic criteria for hyperthyroidism, with no sex or nationality restrictions; (II) research type: randomized controlled trial (RCT) of drug treatment of hyperthyroidism, with no consideration of any blinding method; (III) intervention measures: experimental group administered methimazole + levothyroxine, and a control group treated with methimazole alone; (IV) outcome indicators: treatment efficacy and adverse reaction rate; levels of free triiodothyronine (FT3), free tetraiodothyronine (FT4), and thyroid-stimulating hormone (TSH), and thyroid volume before and after treatment in both the experimental and control groups.

Exclusion criteria: (I) case reports, news reports, and meta-analyses; (II) patients with other major diseases such as tumors; (III) studies with poorly defined processes and unclear conclusions.

Data extraction

Two researchers independently completed the literature search using NoteExpress3.2 literature management software and determined whether the studies met the inclusion criteria based on the title, abstract, and methods. Then they evaluated the full text, and re-screened the literature based on the inclusion and exclusion criteria, and finally selected the articles for data extraction. The two researchers cross-checked relevant data and other materials. If there was any disagreement, they attempted to reach a consensus or consulted a third reviewer.

The data extraction details mainly included: (I) baseline information: name of the first author, publication year, and duration of the study; (II) subject information: duration of treatment, total number of subjects, age and sex of subjects; (III) experimental type: RCT; (IV) outcome indicators: treatment efficacy, adverse reaction rate, FT3, FT4, TSH, thyroid volume before and after treatment in both the experimental and control groups.

Statistical analysis

Meta-analysis was performed using Stata 16 software. Binary variables used odds ratio (OR) and 95% confidence interval (CI), standardized mean differences (SMDs) with the 95% CI were used as summary statistics for continuous variables. The P value was used to analyze and evaluate the heterogeneity between studies, and the Chi-

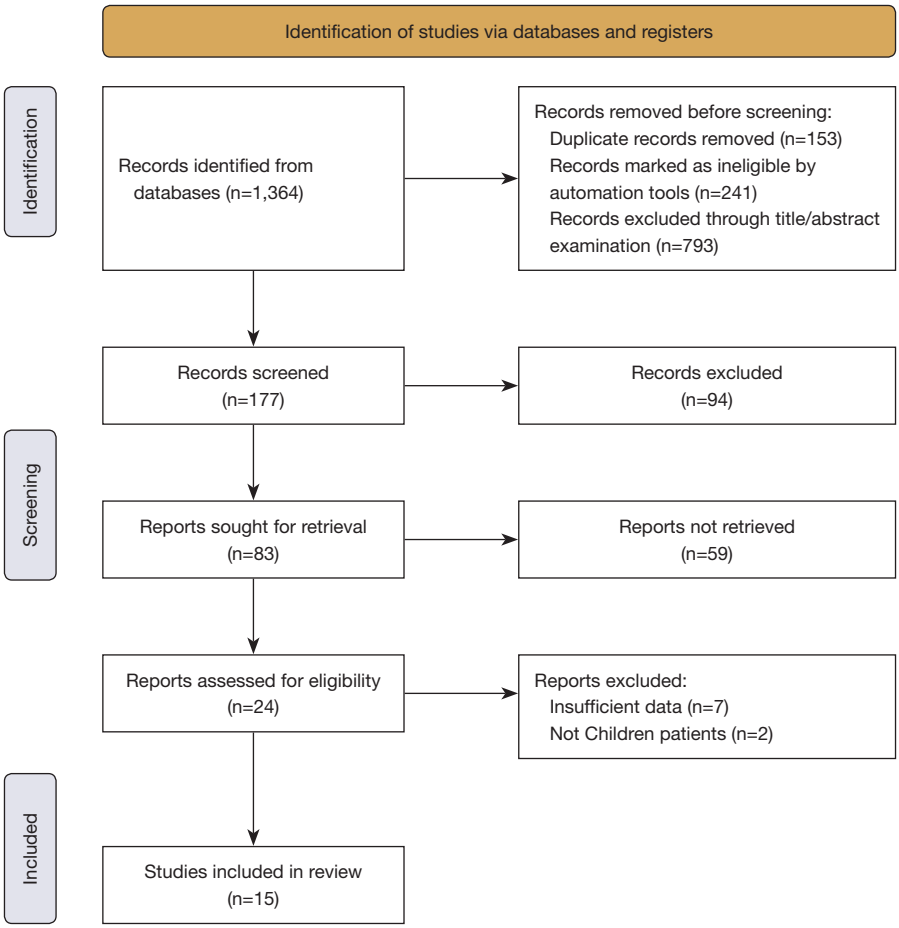


Figure 1 Flow chart of the literature search and screening process.

square test and I^2 statistic were used to assess the extent of the heterogeneity. P<0.10 and I^2>50% represented heterogeneity between the studies, and the random-effects model was used for meta-analysis; otherwise, the fixed-effects model was selected. When the meta-analysis contained ≥10, a funnel plot and Begg's test were used to judge the publication bias. Sensitivity analysis examined the stability of the overall results. P<0.05 suggested a marked difference.

Results

Literature search

Using the described retrieval method, 1,364 related articles were initially retrieved, and 177 documents remained after excluding duplicate records. By reading the title and abstract, irrelevant studies were eliminated, and then the full text was examined according to the inclusion and exclusion criteria. Finally, 15 studies (16-30) were selected for this meta-analysis. *Figure 1* shows the literature search and screening process.

General situation of the included studies

The 15 articles included 1,718 children diagnosed with hyperthyroidism. All studies were RCTs, of which 866 comprised the experimental (treatment) group and 852 were the control group. Treatment efficacy was the main outcome indicator. All 15 articles described the adverse reaction rate and FT3 and FT4 levels before and after treatment. There were 14 articles related to TSH before treatment and after treatment, and 12 articles recorded the thyroid volume before and after treatment. *Table 1* shows the basic characteristics of the included studies.

Table 1 Basic characteristics of included studies for a meta-analysis

Study	Year	Study duration	Cases treat/ control	Age (years)		Disease (months)		Sex (male/female)		Study design	Outcome measures
				Treatment group	Control group	Treatment group	Control group	Treatment group	Control group		
Zhang & Yang (25)	2019	2016.01–2019.01	400/400	9.7±1.5	9.8±1.3	7.7±1.3	7.5±1.2	210/190	218/182	RCT	①②③④⑤⑥⑦⑧⑨⑩
Huang *et al.* (17)	2018	2016.05–2018.05	40/40	10.1±1.5	9.9±1.6	6.2±1.7	6.1±1.5	13/27	12/28	RCT	①②③④⑤⑥⑦⑧⑨⑩
Zhang *et al.* (29)	2016	2010.10–2014.10	50/35	6.3±1.9	5.7±1.4	5.9±2.0	5.7±1.6	30/20	20/15	RCT	②③④⑤⑥⑦⑧
Du *et al.* (27)	2015	2013.05–2015.01	60/60	4–14	4–14	10.2±1.5	10.1±1.5	15/45	23/17	RCT	②③④⑤⑥⑦⑧⑨⑩
Ren *et al.* (28)	2020	2018.09–2019.09	44/44	10.3±1.0	11.2±0.8	6.8±1.7	6.9±1.9	20/24	14/30	RCT	①②③④⑤⑥⑦⑧
Meng *et al.* (18)	2016	2007.01–2014.01	20/20	10.3±2.1	9.2±1.9	6.1±2.4	7.2±2.1	9/11	8/12	RCT	②③④⑤⑥⑨⑩
Chen *et al.* (23)	2019	2017.02–2018.06	42/42	8.7±1.3	8.5±1.3	6.5±0.7	6.3±0.7	25/17	26/16	RCT	②③④⑤⑥⑦⑧
Li & Liao (19)	2017	2016.02–2017.03	25/25	9.7±1.7	9.7±1.8	6.1±0.8	6.0±0.7	11/14	10/15	RCT	②③④⑤⑥⑦⑧⑨⑩
Xie *et al.* (22)	2015	2012.01–2014.04	24/23	9.5±1.3	9.6±1.5	2–12	2–11	9/15	9/14	RCT	②③④⑤⑥⑦⑧⑨⑩
Bai *et al.* (26)	2017	2015.07–2016.07	25/25	8.2±3.4	8.1±3.5	6.3±3.4	6.2±3.4	11/14	10/15	RCT	①②③④⑤⑥⑦⑧⑨⑩
Gu & Zhao (16)	2019	2015.02–2017.08	30/30	10.3±1.4	10.2±1.4	NP	NP	13/17	14/16	RCT	②③④⑤⑥⑦⑧⑨⑩
Wang *et al.* (30)	2018	2015.10–2016.10	40/40	9.7±2.1	9.6±1.9	6.5±0.7	6.5±0.5	17/23	18/22	RCT	①②③④⑤⑥⑦⑧⑨⑩
Wang *et al.* (20)	2018	2011.03–2017.01	15/15	9±1.4	10.5±1.6	10.5±3.1	10±3.6	8/7	6/9	RCT	②③④⑤⑥⑦⑧⑨⑩
Zhang *et al.* (24)	2014	2010.09–2012.09	29/29	10.5±4.2	10.5±4.2	3–17	3–17	11/18	10/19	RCT	②③④⑤⑥⑦⑧⑨⑩
Yang *et al.* (21)	2010	2002.01–2005.01	22/24	4–14	4–14	2–16	2–16	4/18	4/20	RCT	②③④⑤⑥⑦⑧⑨⑩

①, treatment efficacy; ②, adverse reaction rate; ③, FT3 level before treatment; ④, FT3 level after treatment; ⑤, FT4 level before treatment;⑥, FT4 level after treatment; ⑦, TSH level before treatment and after treatment; ⑨, thyroid volume before treatment; ⑩ thyroid volume after treatment. FT3, free triiodothyronine; FT4, free thyroxine; RCT, randomized controlled trial; TSH, thyroid-stimulating hormone; NR, not reported.

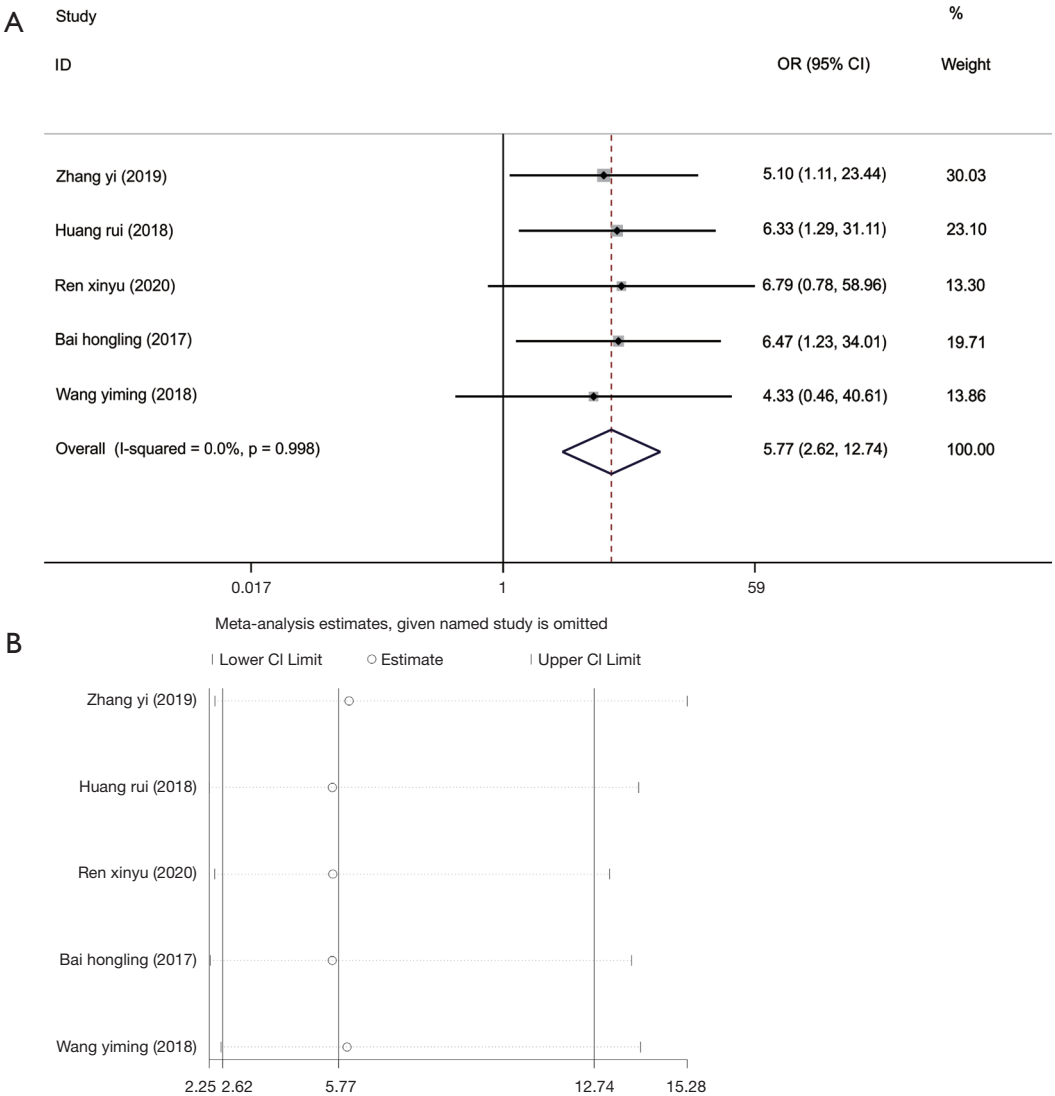


Figure 2 Meta-analysis of treatment efficacy for juvenile hyperthyroidism. (A) Forest chart and (B) sensitivity analysis of treatment efficacy. CI, confidence interval; OR, odds ratio.

Treatment efficacy

A total of five articles (17,25,26,28,30) reported the efficacy of methimazole + levothyroxine in treating patients with hyperthyroidism. The included studies dis not have marked heterogeneity (I^2=0.0%, P=0.998), so the fixed-effects model was selected for further analysis, and it showed that methimazole + levothyroxine was more effective than methimazole alone in treating hyperthyroidism in children (OR =5.77, 95% CI: 2.62, 12.74, P<0.001) (*Figure 2A*). In order to re-estimate the pooled effect size, the research literature was eliminated one by one for sensitivity analysis, suggesting that the results before and after elimination did not change distinctly (*Figure 2B*), indicating low sensitivity and reliable and stable results.

Adverse reaction rate

All 15 studies (16-30) reported adverse reactions, but each

had a different description of different adverse reactions. There was no distinct heterogeneity among the studies (I^2=8.3%, P=0.36), so we chose a fixed-effects model for meta-analysis. The results revealed fewer adverse events in patients from the experimental group (OR =0.28, 95% CI: 0.19, 0.40, P<0.001) (*Figure 3A*), indicating that treating with methimazole + levothyroxine was more universal than treating with methimazole alone. To explore the publication bias, a funnel plot was drawn based on the adverse reaction rate. All the studies were within the 95% CI except for one, and the plot was symmetrical. The P value of the Begg's test was 0.66, suggesting no publication bias (*Figure 3B*). Sensitivity analysis of the adverse reaction rate revealed that the pooled effect size did not change evidently, so the results were stable (*Figure 3C*).

Evaluation of FT3 and FT4 levels before and after treatment

The level of FT3 is not affected by thyroid-binding globulin, and its reference level in the normal human body is 2.3–4.2 pg/mL (31). FT4 is a sensitive index for *in vitro* tests of thyroid function, which directly reflect thyroid function, and the level in patients with hyperthyroidism is generally >23 pmol/L (32). Recording the levels of FT3 and FT4 before and after treatment is an evaluation of treatment efficacy. All 15 studies (17-30,33) recorded the changes in FT3 and FT4 before and after treatment, with no distinct heterogeneity between the studies for FT3 and FT4 levels before treatment (I^2=0%, P=0.999). The combined analysis results of the fixed-effect model showed that the experimental and control groups had no notable differences in FT3 or FT4 levels before treatment (FT3: SMD =0.01, 95% CI: –0.09, 0.10, P=0.869; FT4: SMD =0.01, 95% CI: –0.09, 0.10, P=0.872) (*Figure 4A*,*4B*). However, after treatment, there was high heterogeneity between studies for the levels of FT3 and FT4, and the random-effects model was used to combine the effect size. From the results, both the FT3 (SMD =–0.85, 95% CI: –1.57, 0.13, P=0.02) and FT4 (SMD =–0.94, 95% CI: –1.59, –0.30, P=0.004) levels of the experimental group were markedly lower than those of the control group (*Figure 4C*,*4D*).

Publication bias analysis was performed by drawing the funnel plot of FT3 and FT4 before and after treatment, and the results indicated that all the effect values were within the 95% CI (*Figure 5*), and the Begg's linear regression test results revealed that the study had no notable publication bias. The sensitivity analysis results of FT3 and FT4 levels before and after treatment all showed that the combined results of the study had low sensitivity and the results were stable (*Figure 6*).

Evaluation of TSH level and thyroid volume before and after treatment

There were 14 studies (16,17,19-30) that measured the TSH levels in the plasma of patients before and after treatment, and 12 (16-22,24-27,30) compared the thyroid volume before and after treatment. The included studies showed no notable heterogeneity (thyroid volume: I^2=0%, P=0.985; TSH level: I^2=0%, P=0.493), so a fixed-effects model was selected for analysis, which revealed that the thyroid volume (SMD =0.098, 95% CI: –0.004, 0.20, P=0.06) and the level of TSH in plasma (SMD =0.07, 95% CI: –0.02, 0.17, P=0.13) showed no evident differences between the two groups before treatment (*Figure 7A*,*7B*). After treatment, we selected a random-effects model for the analysis (thyroid volume: I^2=86.4%, P=0.00; TSH level: I^2=97.1%, P=0.00), and the results suggested that the thyroid volume of patients from the experimental group (SMD =–1.3, 95% CI: –1.67, 0.93, P<0.001) was markedly lower than the control group, but there was no distinct difference in TSH level between the two groups (SMD =–0.34, 95% CI: –1.02, 0.35, P=0.33) (*Figure 7C*,*7D*).

Publication bias analyses of thyroid volume and TSH level before and after treatment were conducted. The funnel plot results revealed that before and after treatment all the research points in the graph were concentrated within the 95% CI, with some symmetry and no publication bias (*Figure 8A*,*8B*). For thyroid volume before and after treatment, both the funnel plot and graph distributed asymmetrically before treatment, and P=0.015 from the Begg's test (*Figure 8C*), indicating publication bias existed. However, the funnel plot of thyroid volume after treatment showed that all research points were distributed within the 95% CI, and P=0.061, suggesting no publication bias (*Figure 8D*).

Sensitivity analyses of thyroid volume and TSH level before and after treatment demonstrated that the combined results of thyroid volume and TSH level before and after treatment had low sensitivity and were reliable and stable (*Figure 9*).

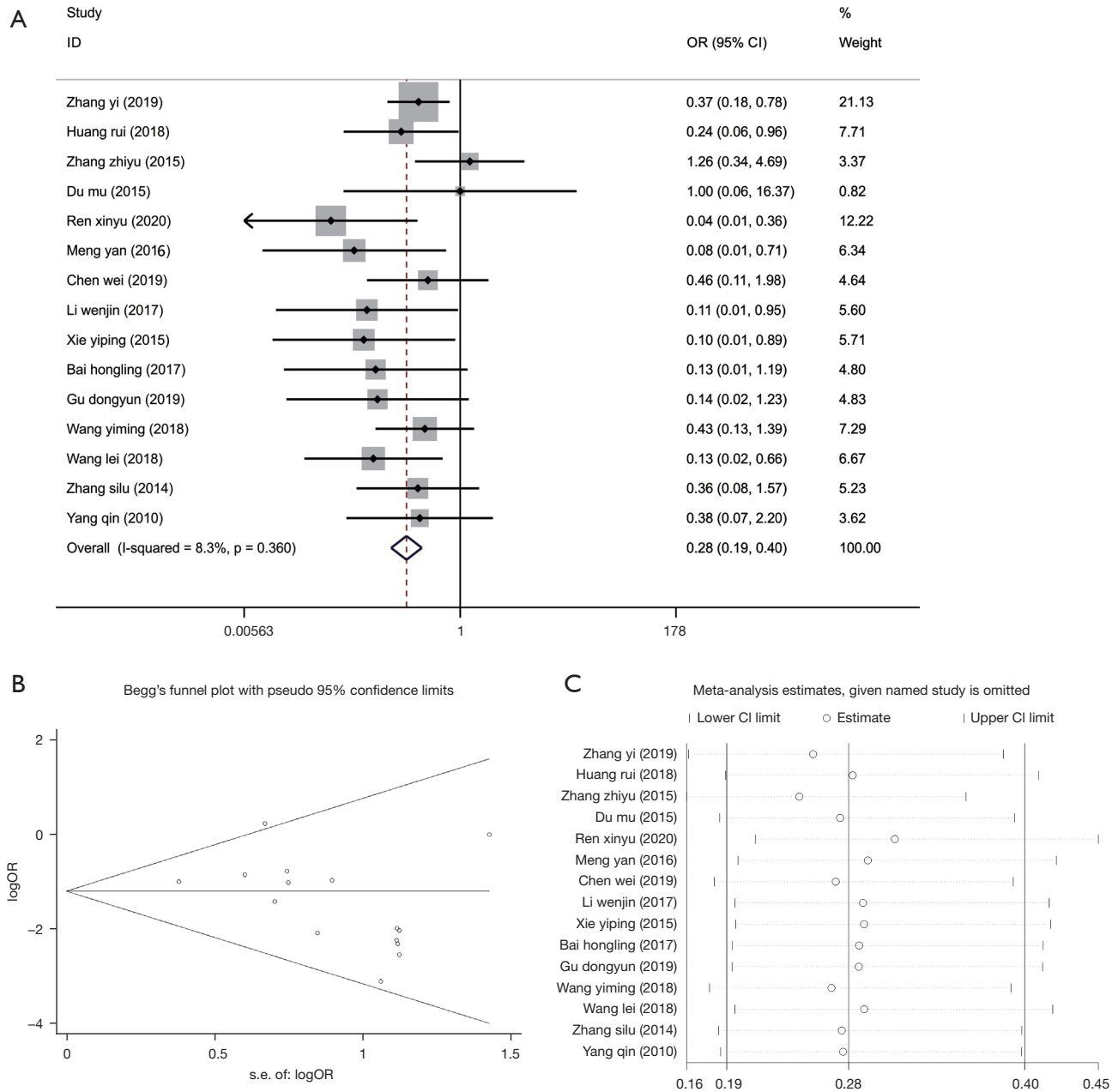
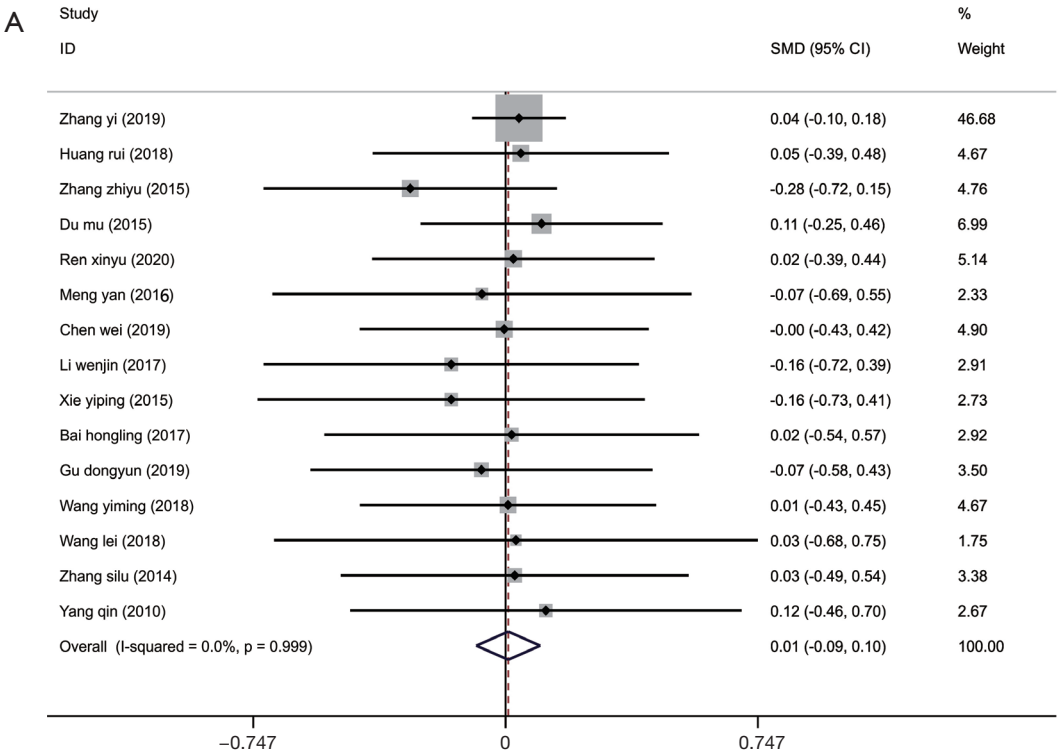
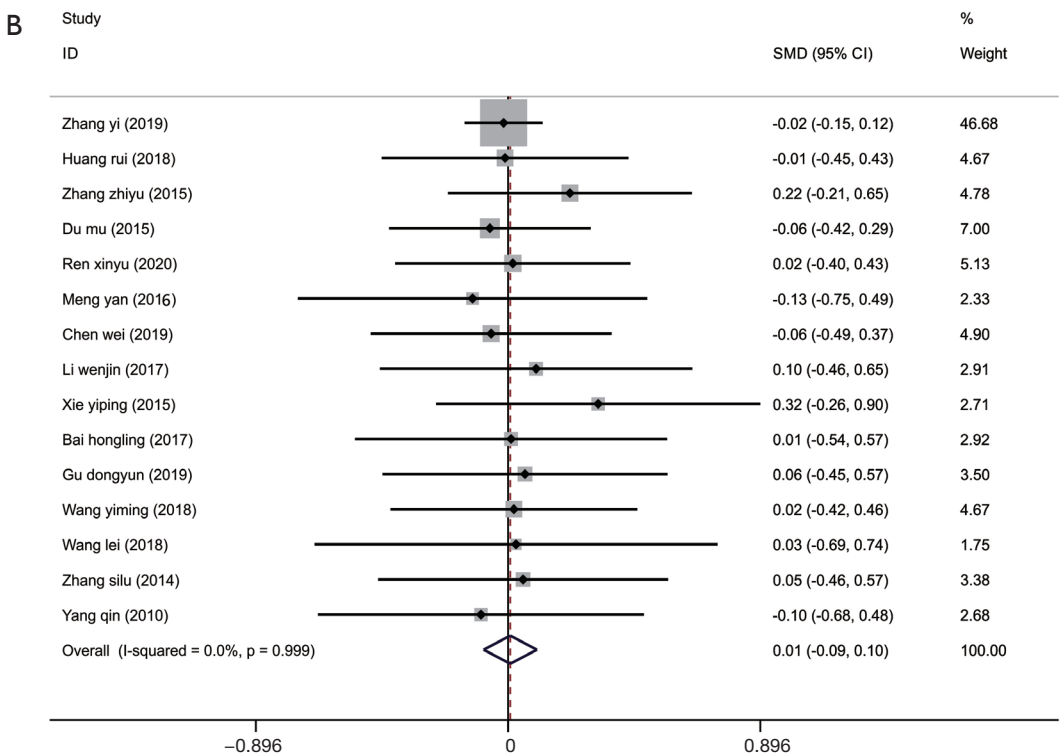


Figure 3 Meta-analysis of the adverse reaction rate after treatment of juvenile hyperthyroidism. (A) Forest diagram, (B) funnel plot and (C) sensitivity analysis of the adverse reaction rate. CI, confidence interval; OR, odds ratio.





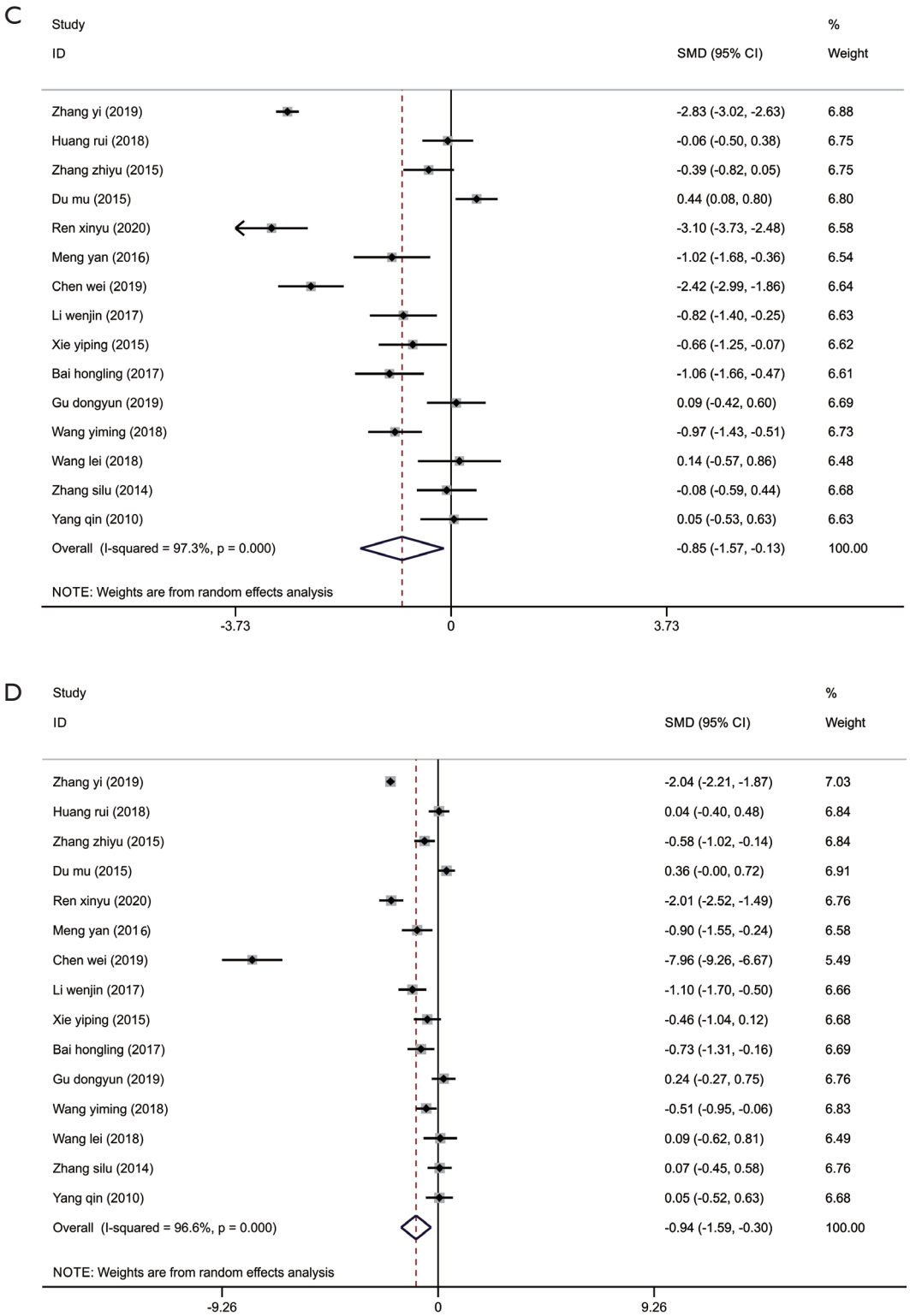


Figure 4 Forest plots of FT3 and FT4 levels before and after hyperthyroidism treatment. (A) FT3 levels before treatment; (B) FT4 levels before treatment; (C) FT3 levels before treatment; (D) FT4 levels after treatment. CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; SMD, standardized mean difference.

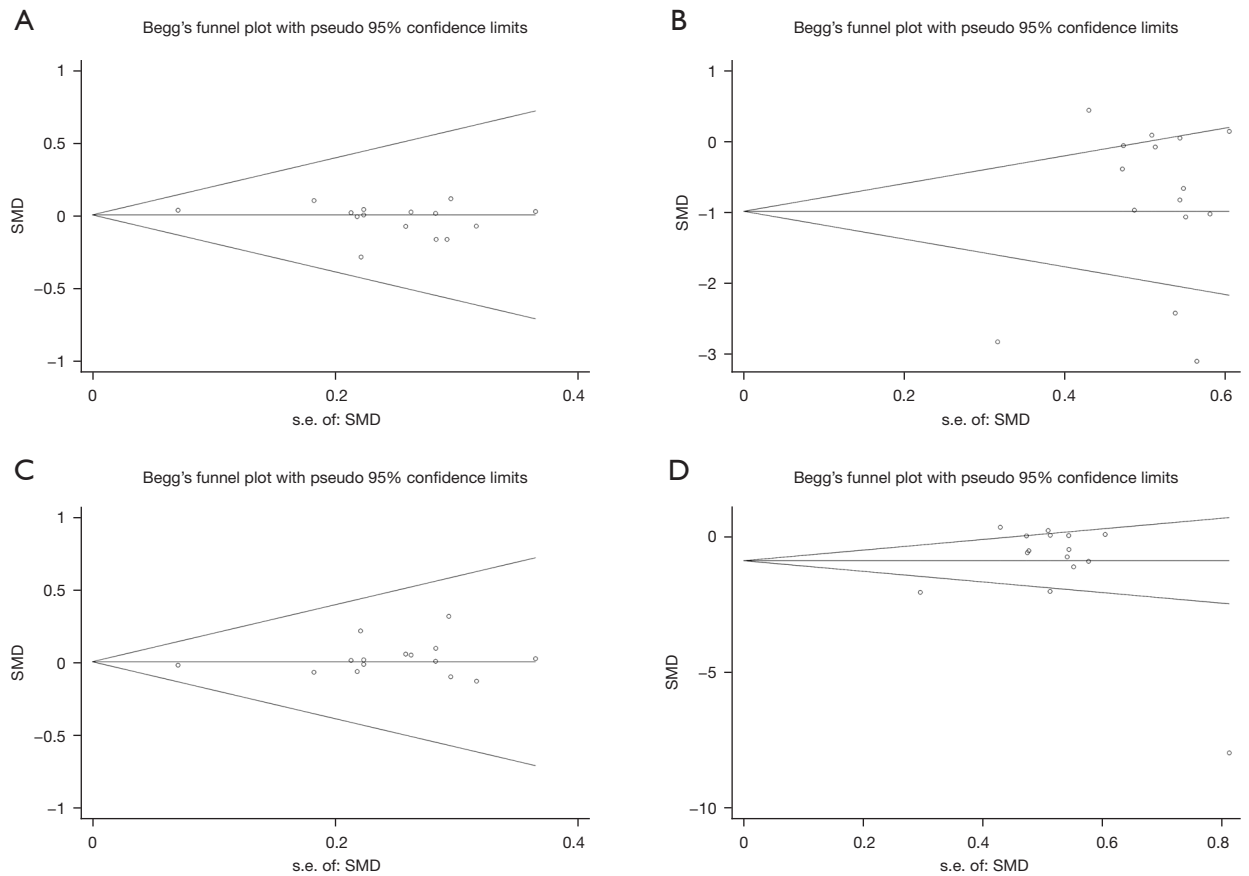


Figure 5 Publication bias funnel plots of biochemical indicators before and after hyperthyroidism treatment. FT3 levels (A) before and (B) after treatment. FT4 levels (C) before and (D) after treatment. FT3, free triiodothyronine; FT4, free thyroxine; SMD, standardized mean difference.

Discussion

Because children are growing and their body structure and tissues are not fully developed, the conservative method of drug treatment is mainly adopted for juvenile hyperthyroidism. During treatment, the main indicators of FT3, FT4, and TSH levels, and thyroid volume reflect the efficacy of treatment. The 2016 Japanese guidelines for hyperthyroidism in children recommended that antithyroid drugs should be administered for at least 18–24 months, and to use biochemical indicators to monitor disease (32). It has been reported that the TSH level in serum should be used as the initial screening and diagnostic criterion and that it has the highest sensitivity and specificity in assessing whether there is hyperthyroidism (34). However, others such as Bahn Chair *et al.* (35) have demonstrated that serum TSH level is still suppressed several months after taking antithyroid drugs, so it is not a good parameter for early detection and treatment. After continuous medication for 12–18 months, when the TSH level becomes normal, then reducing the dosage of methimazole or withdrawal can be considered (35). The TSH level is an effective indicator for evaluate treatment efficacy in juvenile hyperthyroidism. Long-term use of methimazole, an antithyroid drug, can reduce TSH levels and treat hyperthyroidism. Our study results indicated that methimazole + levothyroxine markedly reduced FT3 and FT4 levels and thyroid volume, but had no distinct effect on TSH levels, possibly because the average of the included studies was 7 months, which was shorter than is recommended in the treatment guidelines,

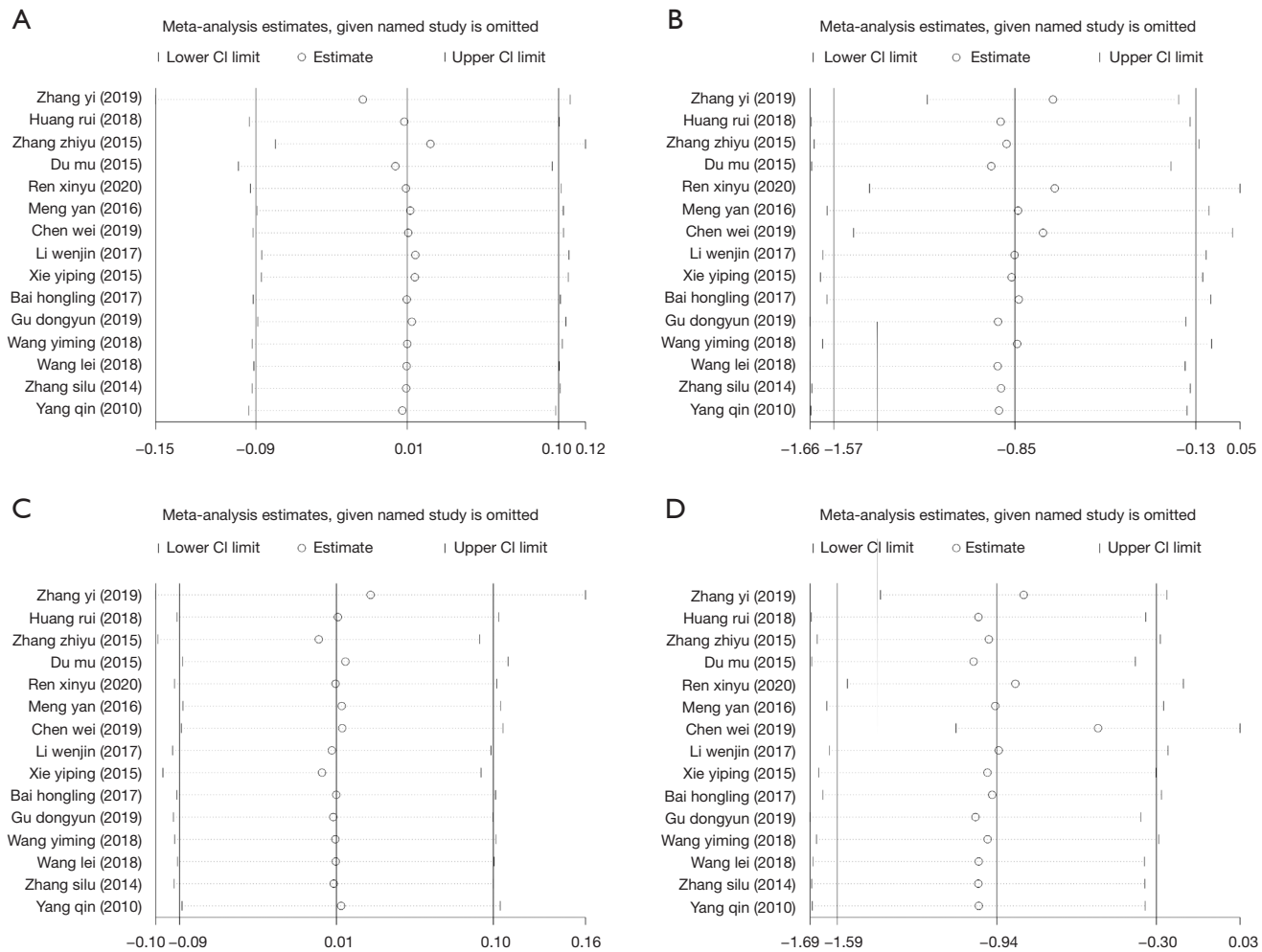
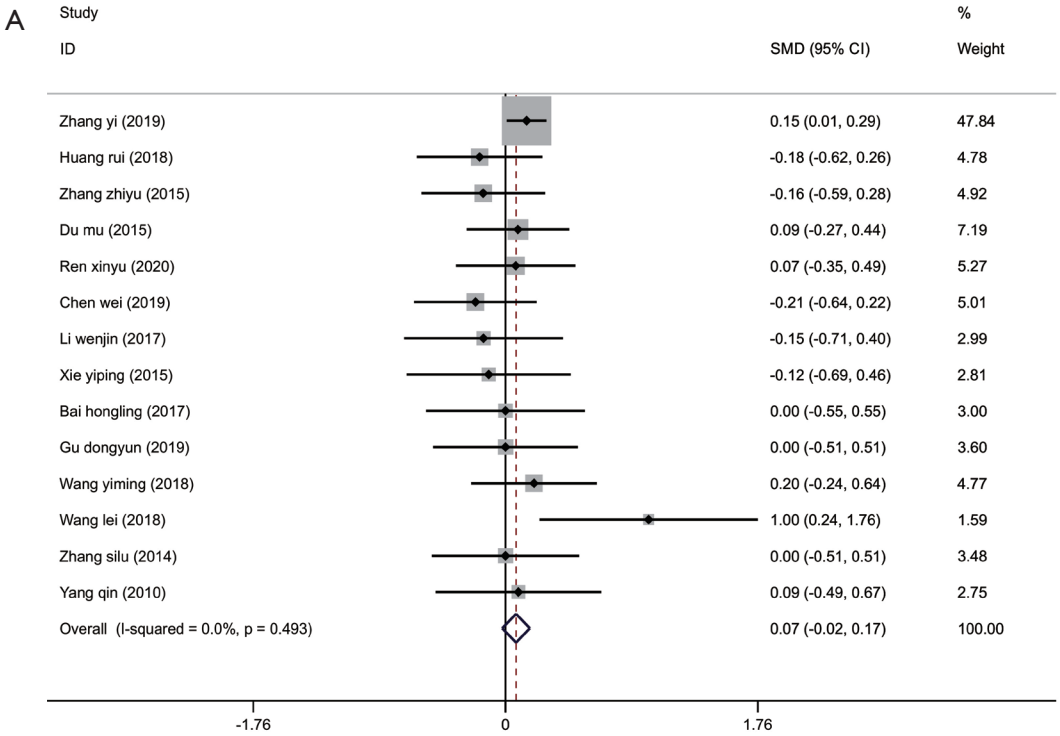


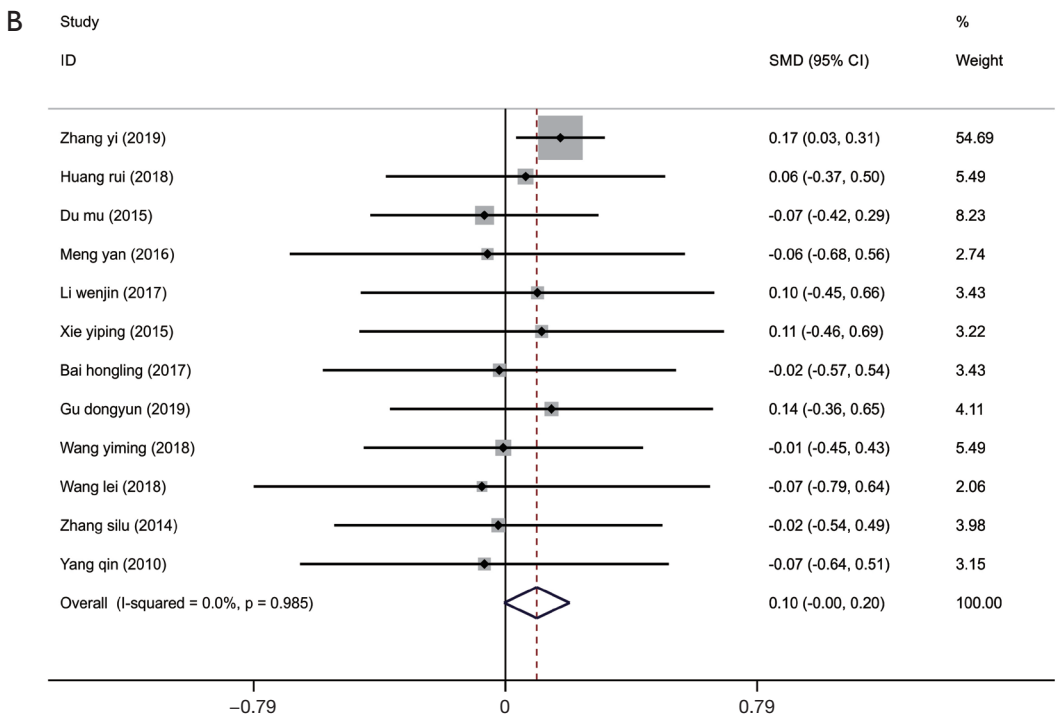
Figure 6 Sensitivity analyses of biochemical indicators before and after hyperthyroidism treatment. FT3 levels (A) before and (B) after treatment. FT4 levels (C) before and (D) after treatment. CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine.

thereby affecting our conclusions.

Methimazole inhibits the synthesis and secretion of thyroid peroxidase, and can reduce the volume of the thyroid as well as the FT3 and FT4 levels and other indicators during the treatment of hyperthyroidism. When it is administered in different stages of the disease, the TSH level can increase, causing adverse reactions. However, the efficacy when using it alone in treating hyperthyroidism is not obvious, and its dosage and using combinations need to be further investigated clinically (36). Levothyroxine is a sodium salt of tetraiodothyronine, which decomposes to tetraiodothyronine after oral administration and strengthens the function of the sympathetic-adrenal system, so it is adjuvant therapy for hyperthyroidism with high biological activity and fast onset (37). As far as we know, current clinical treatment with the combination of these two drugs has a significant effect, but prognostic meta-analyses of children with hyperthyroidism are rare. Our meta-analysis found that compared with using methimazole alone, administering methimazole combined with levothyroxine had a better therapeutic effect on children with hyperthyroidism, with fewer adverse reactions, and effectively reduced the FT3 and FT4 levels, as well as the thyroid volume, providing a great reference for treating hyperthyroidism in children.

Although the 15 studies included in this study were





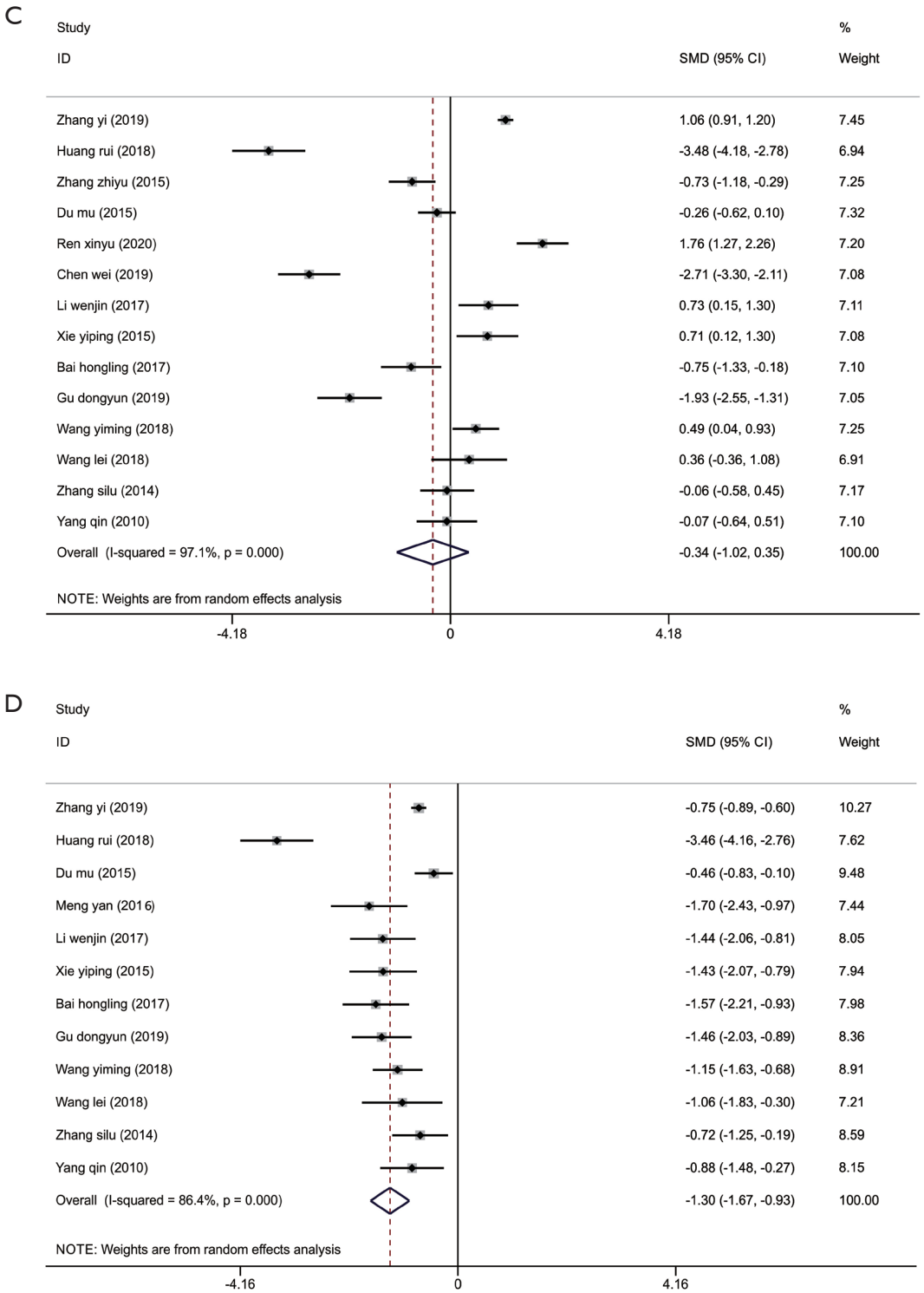


Figure 7 Forest plots of TSH levels and thyroid volume before and after hyperthyroidism treatment. (A) TSH levels before treatment; (B) thyroid volume before treatment; (C) TSH levels after treatment; (D) thyroid volume after treatment. TSH, thyroid-stimulating hormone; CI, confidence interval; SMD, standardized mean difference.

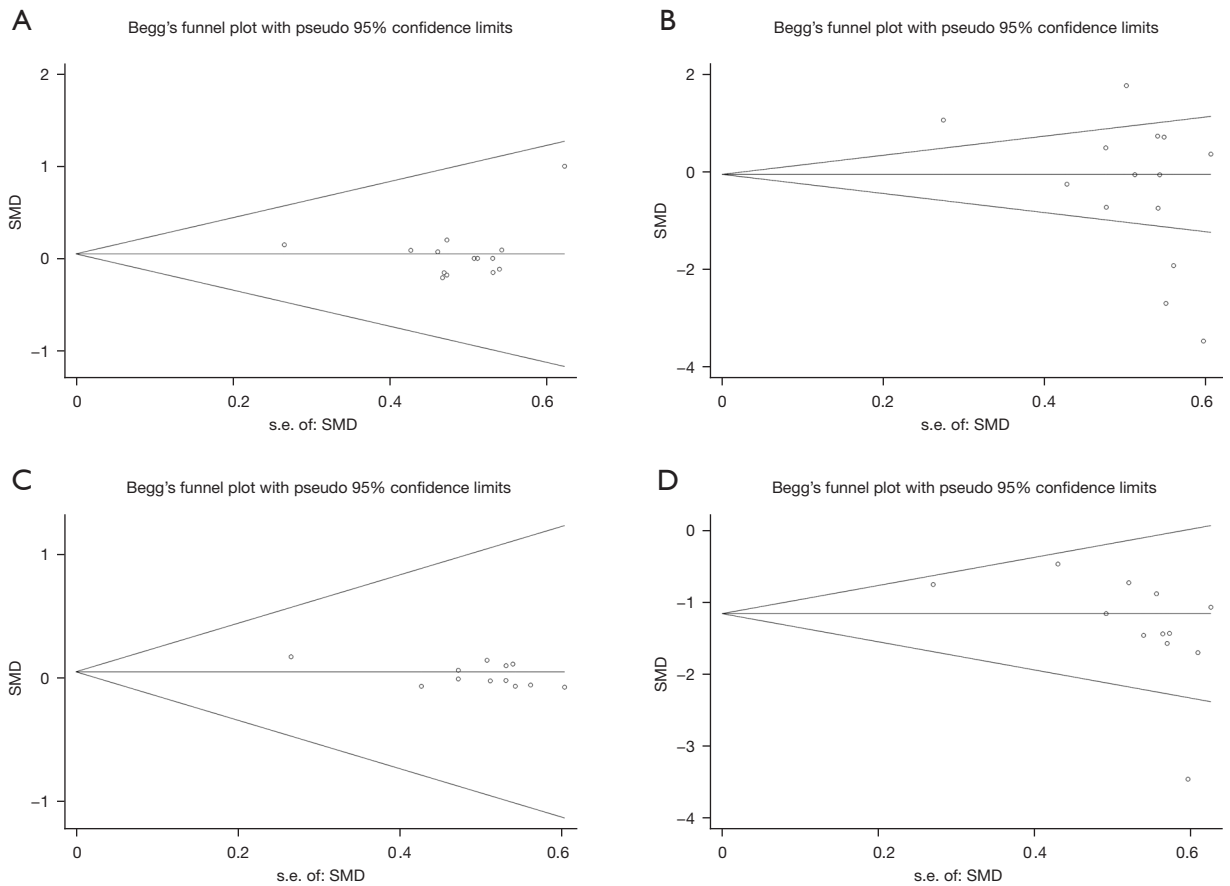


Figure 8 Begg's funnel plots of TSH levels and thyroid volume before and after hyperthyroidism treatment. Publication bias funnel plots of TSH (A) before and (B) after treatment. Publication bias funnel plots of thyroid volume (C) before and (D) after treatment. TSH, thyroid-stimulating hormone; SMD, standardized mean difference.

all RCTs, with a total of 1,718 children included for heterogeneity, publication bias, and sensitivity, there are still some limitations. (I) The included 15 studies cannot not be guaranteed to have the same drug manufacturers, dosages, or treatment durations, so there will be clinical heterogeneity. (II) The studies failed to conduct in-depth research on the previous medical history of the children and other treatment-related factors (whether surgery and other drug treatments had been performed), and there may be side effects and sequelae that will affect treatment efficacy in this study. (III) There were only five studies reporting treatment efficacy, and as funnel plot analysis was not performed, publication bias is possible. (IV) The duration of drug administration was relatively short in all studies, none of which reached the treatment duration recommended by thyroid associations, which may affect the evaluation of the indicators.

Conclusions

Our meta-analysis found that methimazole combined with levothyroxine therapy can markedly improve the treatment efficacy of hyperthyroidism in children, and has advantages in decreasing FT3 levels, FT4 levels, thyroid volume, and the adverse reaction rate. However, this study still has the limitation of a small sample size, and the results require a larger sample and well-designed research for further verification.

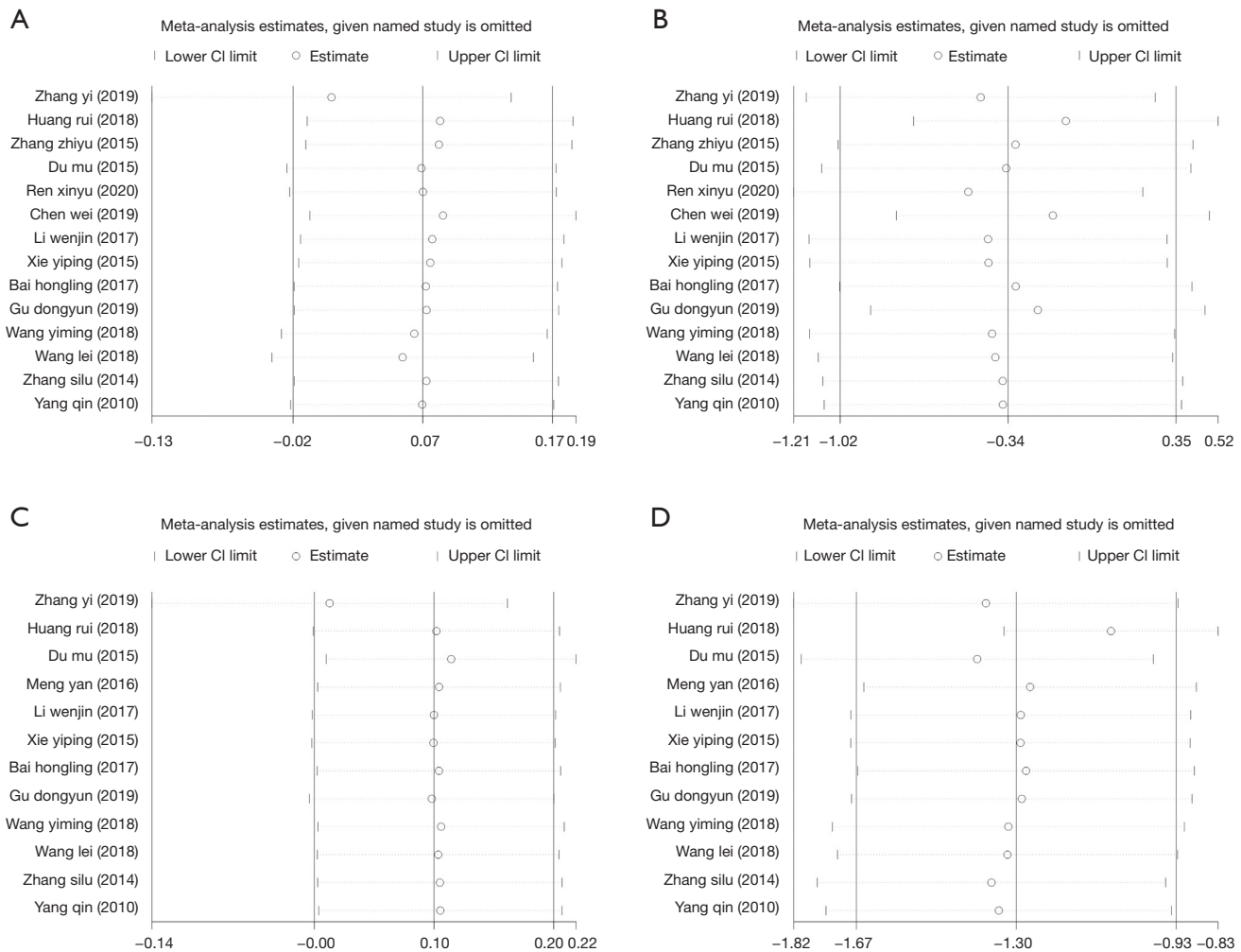


Figure 9 Sensitivity analysis of TSH levels and thyroid volume before and after hyperthyroidism treatment. Sensitivity analysis of TSH (A) before and (B) after treatment. Sensitivity analysis of thyroid volume (C) before and (D) after treatment. TSH, thyroid-stimulating hormone; SMD, standardized mean difference.

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Footnote

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