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REVIEW ARTICLE

Effect of Bariatric Surgery on Thyroid Function in Obese Patients: a Systematic Review and Meta-Analysis

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Abstract We aimed to make a meta-analysis regarding the effect of bariatric surgery on thyroid function in obese patients. PubMed, EMBASE, CENTRAL, and four Chinese databases were searched for clinical studies. Data were pooled using Review Manager 5.3, and subgroup and sensitivity analyses were performed if necessary and feasible. As a result, 24 articles were included into meta-analysis. Bariatric surgery was associated with significant decrease in TSH, FT3, and T3 levels. However, FT4, T4, and rT3 levels were not significantly changed postoperatively. In addition, bariatric surgery had a favorable effect on overt and subclinical hypothyroid, with reduction of thyroid hormone requirements postoperatively. In conclusion, TSH, FT3, and T3 decrease are expected following bariatric surgery, as well as non-significant change of T4, FT4, and rT3 levels.

Keywords Bariatric surgery · Thyroid function · Obesity · Systematic review · Meta-analysis

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Introduction

Obesity has become a major public health concern in many countries due to the development of economy and change of life style [1]. As a systemic disease, obesity can result in a series of comorbidities and affect multiple organ functions, including thyroid function [2–4]. Some researches have noted a positive correlation between serum thyroid-stimulating hormone (TSH), T3 level, and obesity [5, 6]. Others demonstrated that subclinical hypothyroidism (SH) and hypothyroidism are more common in obese patients than normal-weight patients [7].

Bariatric surgery has been proved to be the most effective treatment for patients with severe obesity, which can bring about long-term weight loss and excellent remission of associated comorbidities [8, 9]. Change in thyroid function has also been described in obese patients after bariatric surgery. However, the results of previous researches are not constant. Some reported decreased TSH and increased free thyroxine (FT4) after sleeve gastrectomy (SG) [5], some found elevated TSH and no alteration in free triiodothyronine (FT3) after Roux-en-Y gastric bypasses (RYGB) and biliopancreatic diversion (BPD) [10], while others observed insignificant modification in thyroid hormones after adjustable gastric band (AGB) [11]. Given these different evidence, it is hard for us to draw a conclusion about the exact effect of bariatric surgery on thyroid function.

To date, there have been some meta-analyses showing that bariatric surgery is beneficial to liver function, renal function, and cardiac function in obese patients [12–14]. With respect of thyroid hormone change after bariatric surgery, however, no relevant systemic review or meta-analysis has been published before. Therefore, the aim of this study was to make a meta-analysis regarding the effect of bariatric surgery on thyroid function in obese patients.

Methods

The meta-analysis was conducted based on the recommendations from The Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology (MOOSE) [15], together with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [16]. Ethical approval and informed consent were deemed to be exempt because no interventions were implemented on patients.

Literature Search

A computerized search was conducted in PubMed, EMBASE, the Cochrane Central Register of Controlled Trails (CENTRAL), China National Knowledge Infrastructure (CNKI), Database of Chinese Ministry of Science & Technology (Wangfang), China Biological Medicine Database (CBM), and Database of Chinese Science and Technology Periodicals (VIP) from inception to 26 April 2017, with no language limitations. Free terms and medical subject headings were used together during literature search, including (bariatric surgery OR metabolic surgery OR weight loss surgery OR obesity surgery OR gastric bypass OR sleeve gastrectomy OR gastric banding OR biliopancreatic diversion OR duodenojejunal bypass) AND (thyroid OR hyperthyroidism OR euthyroid OR hypothyroidism OR TSH OR triiodothyronine OR thyroxine) AND (obese OR obesity). The references of identified articles and reviews were also hand-searched for other relevant investigations.

Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis were as follows: (1) obese patients with BMI greater than 30 kg/m^2 and (2) provide pre-operative and post-operative thyroid function data (e.g., TSH, FT3, FT4, T3, T4, and rT3 levels).

Animal studies, case reports, letters, comments, and reviews were excluded. If similar studies adopted data from overlapping populations, only the study with the most information was included and the other was excluded.

The stages of study selection, data extraction and quality assessment were conducted by two investigators independently, and disagreements were resolved by discussion with a third investigator.

Data Extraction and Quality Assessment

Titles and abstracts of all articles identified by literature search were screened to determine whether they met inclusion criteria. Full-text was further reviewed if the information form abstract met eligibility criteria.

For all included studies, a pre-specified data extraction form was used for extracting the following data: the first author, publication year, country, study design, patients' characteristics, follow-up duration, type of bariatric surgery, and outcomes. In terms of missing data, we would contact the authors by email for complete information if possible. The quality of the included trials was assessed by a modified version of Newcastle-Ottawa scale. We removed the item regarding "Selection of the non-exposed cohort" because it was not applicable for cohort studies without control group.

Statistical Analysis

All statistical analyses were performed by Review Manager (RevMan) 5.3 and Stata (version 11.0). For continuous variables, mean difference (MD) or standardized mean difference (SMD) with corresponding 95% confidence interval (95% CI) were calculated when appropriate, according to whether or not the outcomes were measured by the same scales. In case that mean ± standard deviations (SDs) were not provided explicitly, they would be calculated by other available data. Between-study heterogeneity was evaluated by the Cochran Q-statistic and I^2 statistic. A p value < 0.1 and $I^2 > 50\%$ indicate significant heterogeneity, which meant that a random effects model would be chosen to pool results. Otherwise, a fixed effect model would be used. Subgroup and sensitivity analyses were planned to identify possible sources of heterogeneity among included studies if necessary and feasible. Pre-specified subgroup analyses included type of surgery (RYGB vs. BPD vs. SG vs. AGB), type of preoperative thyroid function (euthyroidism vs. hypothyroidism), and follow-up duration (> 12 months vs. ≤ 12 months). Sensitivity analyses were conducted by changing the pooling model (random effects model or fixed effect model) and using the one-study-out method. Possible publication bias was evaluated by the funnel plot, with the Begg and Egger tests using Stata software.

Results

Search Process, Study Characteristics, and Quality Assessment

A total of 566 relevant articles were retrieved from database searches and no other trials were added to the search result by manual search. After removing the duplicate investigations, 464 titles and abstracts were screened. Afterwards, 161 publications were identified for eligibility of inclusion criterion in full text. Then, 29 articles were included in qualitative synthesis, of which five had no data for quantitative synthesis [17–21]. Hence, the remaining 24 articles with a total of 1147 patients were incorporated into final meta-analysis [5–7, 10, 11, 22–40]. Of the included studies, four studies had two arms and one study had three arms; these arms were analyzed separately in this meta-analysis. The detailed process of study selection is shown in Fig. 1.

The study characteristics are presented in Table 1. The types of bariatric surgery were not consistent among these studies. Some adopted malabsorptive surgery (e.g., BPD), some used restrictive surgery (e.g., SG, AGB), and others employed mixed surgery (e.g., RYGB). Also, there patients had different thyroid function preoperatively (e.g., euthyroidism, SH, hypothyroidism), and the duration of follow-up ranges from 10 days to 108 months. The assessment of study quality is displayed in Table 2.

Meta-Analysis of TSH

Twenty-nine trials involving 1114 patients reported the outcome of TSH. Because of significant heterogeneity among these studies ($p < 0.00001$, $I^2 = 91\%$), a random effects model was used to pool result. The result showed that bariatric surgery could significantly decrease the TSH level of obese patients (SMD = 0.52, 95% CI 0.20 to 0.83, $p = 0.001$) (Fig. 2).

In order to explore the possible source of heterogeneity, we performed subgroup analyses by type of bariatric surgery, type of preoperative thyroid function, and follow-up duration (Table 3). Grouping the studies by type of bariatric surgery and type of preoperative thyroid function did not resolve heterogeneity, but the pooled results showed that RYGB, not BPD or AGB had a positive effect on TSH reduction. When we looked at the subgroup based on follow-up duration, a significant pooled result (SMD = 0.77, 95% CI 0.33 to 1.20, $p = 0.0006$) was observed for the articles with short-term

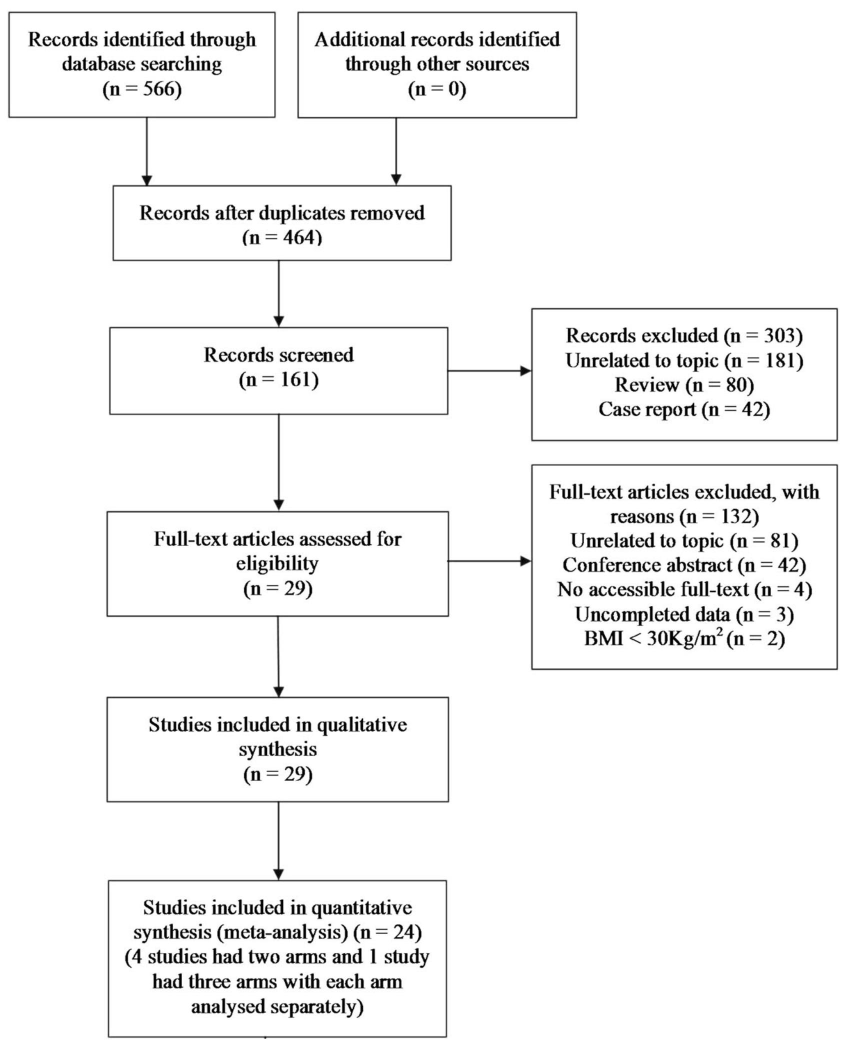

Fig. 1 Flow diagram of study selection

Table 1 Characteristic of included studies

Authors	Year	Country	Design	Preoperative thyroid function	Intervention	Number (M/F)	Age (years)	BMI (kg/m^2)	Follow-up (months)	Outcomes
Bawahab [22]	2017	Saudi Arabia	Prospective	NR	SG	50	20–45	45–50	12	TSH, T4
Fallahi (1) [10]	2017	Italy	Retrospective	Hypothyroidism	RYGB	13 (4/9)	45 ± 9	42.9 ± 3.5	3–11	TSH, FT3, FT4
Fallahi (2) [10]	2017	Italy	Retrospective	Hypothyroidism	BPD	4 (3/1)	42 ± 7	44.1 ± 4.4	3–11	TSH, FT3, FT4
Zendel [23]	2017	Israel	Retrospective	Hypothyroidism	RYGB, SG	93 (8/85)	46.6 ± 11.2	43.7 ± 6.4	12	TSH, FT4
Xing [24]	2017	China	Retrospective	NR	SG	10	31.6 ± 2.9	39.4 ± 6.8	1	TSH, FT3, FT4, T3, T4
Fierabracci [25]	2016	Italy	Retrospective	Hypothyroidism	RYGB, SG, AGB	93 (3/90)	48 ± 89	45.9 ± 5.6	28 ± 8	TSH, FT3, FT4
Abu-Ghanem [5]	2015	Israel	Prospective	Euthyroidism	SG	38 (10/28)	20–60	42.6 ± 3.58	6–12	TSH, FT4
Janssen [7]	2015	Netherlands	Retrospective	SH	RYGB	61	42 ± 13	47.1 ± 7.8	12	TSH, FT4
Butte [26]	2015	USA	Prospective	NR	RYGB	11 (3/8)	16.5 ± 0.8	57.0 ± 10.5	12	TSH, FT3, FT4, T3, T4, rT3
Hasani [11]	2015	Iran	Prospective	NR	LGP	21 (2/19)	34.33 ± 8.55	41.45 ± 5.68	3	TSH, T3, T4
Michalaki [27]	2014	Greece	NR	NR	RYGB, BPD-LL	35	43.4 ± 8.6	50.7 ± 8.5	6	TSH, T3, T4
Lips [6]	2013	Netherlands	Prospective	NR	RYGB	31 (0/31)	NR	43.9 ± 3.7	3	TSH, T3, FT4, rT3
Gkotsina (1) [28]	2013	Greece	NR	Euthyroidism	SG	10	32.5 ± 6.5	42.1 ± 2.1	35 days	TSH, T3, T4
Gkotsina (2) [28]	2013	Greece	NR	Euthyroidism	RYGB	7	35.9 ± 7.6	44.1 ± 2.5	35 days	TSH, T3, T4
Gkotsina (3) [28]	2013	Greece	NR	Euthyroidism	BPD-LL	15	32.8 ± 11	52.9 ± 7.1	35 days	TSH, T3, T4
Sundaram [29]	2013	USA	Retrospective	Hypothyroidism	RYGB, SG, GB	74 (8/66)	NR	NR	3–108	TSH
MacCuish [30]	2012	UK	Retrospective	Euthyroidism	RYGB	55 (13/42)	18–64	48.1 ± 1.6	24	TSH, FT4
Dall'Asta [31]	2010	Italy	Retrospective	Euthyroidism	AGB	258 (42/216)	41.1 ± 0.66	44.1 ± 0.41	24	TSH, FT3, FT4
Gniuli [32]	2010	Italy	NR	Euthyroidism and SH	BPD	45 (15/30)	41.5 ± 11.02	50.28 ± 8.87	24	TSH, FT3, FT4
Camastra [33]	2009	Italy	NR	NR	BPD	7 (3/4)	36 ± 4	49.0 ± 2.0	6	TSH, FT3, FT4
Nannipieri (1) [34]	2009	Italy	Prospective	NR	RYGB	14 (0/14)	40 ± 8	46.4 ± 6.3	12	TSH, FT3, FT4
Nannipieri (2) [34]	2009	Italy	Prospective	NR	RYGB	13 (6/7)	47 ± 5	44.9 ± 4.6	12	TSH, FT3, FT4
Moulin (1) [35]	2005	Brazil	Prospective	Euthyroidism	RYGB	54 (8/46)	20–64	35.9–87.5	12	TSH, T3, FT4
Moulin (2) [35]	2005	Brazil	Prospective	SH	RYGB	18 (2/16)	40.3 ± 10.5	35.9–87.5	12	TSH, T3, FT4
Alagna (1) [36]	2003	Italy	NR	Euthyroidism	BPD	12 (12/0)	35–63	49.0 ± 8.04	12	TSH, FT3, FT4
Alagna (2) [36]	2003	Italy	NR	Euthyroidism	BPD	26 (0/26)	25–56	46.1 ± 11.5	12	TSH, FT3, FT4
Dittmar [37]	2003	Germany	Prospective	NR	AGB	26 (8/18)	39.0 ± 9.38	48.1 ± 4.24	17 ± 2.2	TSH
Vettor [38]	2003	Italy	NR	NR	BPD	10 (7/3)	NR	49.8 ± 2.51	18 ± 2	TSH, FT3, FT4
Yashkov [39]	2000	Russian	Retrospective	NR	VBG	33	NR	NR	10–14 day	FT3, FT4
Buscemi [40]	1997	Italy	Retrospective	NR	BPD	10 (4/6)	37 ± 6	53.8 ± 6.5	36–48	TSH, FT3, FT4, T3, T4
Backes [17]	2016	Brazil	NR	Hypothyroidism and else	RYGB, BPD-DS	69 (6/63)	42.3 ± 10.4	51.1 ± 7.8	6	NR
Ruiz-Tovar [18]	2014	Spain	Retrospective	SH and else	SG	60 (7/53)	43.3 ± 10.4	50.6 ± 6.9	12	NR

Table 1 (continued)

Authors	Year	Country	Design	Preoperative thyroid function	Intervention	Number (M/F)	Age (years)	BMI (kg/m^2)	Follow-up (months)	Outcomes
Fazylov [19]	2008	USA	Retrospective	Hypothyroidism	RYGB	20 (0/20)	21–66	38–58.5	24	NR
Chikunguwo [20]	2007	USA	Retrospective	SH and else	RYGB,AGB	86 (18/68)	33–68	30–67	12	NR
Raftopoulos [21]	2004	USA	Retrospective	Hypothyroidism	RYGB	23 (3/20)	25–65	45	5.5–31	NR

NR not reported, *SH* subclinical hypothyroidism, *TSH* thyroid-stimulating hormone, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *BPD* biliopancreatic diversion, *BPD-DS* biliopancreatic diversion and duodenal switch, *AGB* adjustable gastric band, *LGP* laparoscopic gastric placation, *BPD-LL* biliopancreatic diversion with long-limb, *GB* gastric banding, *VBG* vertical banded gastroplasty

follow-up (≤ 12 months), but not for the studies with long-term follow-up (> 12 months).

In sensitivity analysis, the effective influence of bariatric surgery was confirmed by changing the random effects model to a fixed effect model (SMD = 0.31, 95% CI, 0.22 to 0.40, $p < 0.00001$). Also, the pooled results did not markedly alter when any one research was excluded in turn, with a range from 0.45 (95% CI 0.14 to 0.77) to 0.56 (95% CI 0.25 to 0.88). No significant publication bias was seen with Begg ($p = 0.722$) or Egger ($p = 0.106$) test.

Meta-Analysis of FT3

Fifteen studies including 559 patients were incorporated in the meta-analysis of FT3. Significant heterogeneity was identified across these studies ($p < 0.00001$, $I^2 = 98\%$), and the random effects model showed that bariatric surgery was associated with decreased FT3 in obese patients (SMD = 1.59, 95% CI 0.35 to 2.84, $p = 0.01$) (Fig. 3). Grouping these researches by type of bariatric surgery did not resolve heterogeneity (Table 3), but we found that RYGB and BPD were superior to SG in FT3 reduction. However, stratifying the studies by type of preoperative thyroid function led to homogeneous result for three researches focusing on preoperative hypothyroid patients (MD = 0.29, 95% CI 0.15 to 0.43, $p < 0.0001$), but not for the three studies focusing on euthyroid patients preoperatively (MD = 1.06, 95% CI 0.29 to 1.83, $p = 0.007$). In addition, when we looked at the subgroup of follow-up duration, both the two subgroups had no homogeneous results.

In the sensitivity analysis using the one-study-out method, the pooled results were not significantly altered, with a range from 0.95 (95% CI 0.62 to 1.28) to 1.70 (95% CI 0.38 to 3.02). Also, the pooled estimate from the random effects analyses were confirmed by the fixed effect analyses (SMD = 1.44, 95% CI 1.27 to 1.60, $p < 0.00001$). There was no evidence for publication bias (Begg, $p = 0.138$; Egger, $p = 0.646$).

Meta-Analysis of FT4

Twenty-two studies incorporating 909 patients were enrolled in the meta-analysis of FT4. Because of between-study heterogeneity, random effects model was used to pool result and showed that bariatric surgery did not lead to significant change in FT4 (SMD = −0.11, 95% CI −0.77 to 0.55, $p = 0.74$) (Fig. 4).

When evaluating based on specific surgical group, between-study heterogeneity could only be resolved for the two studies adopted SG surgery (SMD = 0.65, 95% CI 0.24 to 1.06, $p = 0.0002$), but the pooled result was significant for the seven adopted BPD surgery (SMD = 0.70, 95%

Table 2 Quality assessment of included studies by modified Newcastle-Ottawa Scales

Study authors	Selection			Comparability	Outcome		
	Exposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up
Bawahab [22]	*	*	*	*	*	*	*
Fallahi (1) [10]	*	*	*	*	*	*	*
Fallahi (2) [10]	*	*	*	*	*	*	*
Zendel [23]	*	*	*	*	*	*	*
Xing [24]	*	*	*	*	*	–	–
Fierabracci [25]	*	*	*	*	*	*	*
Abu-Ghanem [5]	*	*	*	*	*	*	*
Janssen [7]	*	*	*	*	*	*	*
Butte [26]	*	*	*	*	*	*	*
Hasani [11]	*	*	*	*	*	–	–
Michalaki [27]	*	*	*	*	*	*	*
Lips [6]	*	*	*	*	*	–	–
Gkotsina (1) [28]	*	*	*	*	*	–	–
Gkotsina (2) [28]	*	*	*	*	*	–	–
Gkotsina (3) [28]	*	*	*	*	*	–	–
Sundaram [29]	*	*	*	*	*	*	*
MacCuish [30]	*	*	*	*	*	*	*
Dall'Asta [31]	*	*	*	*	*	*	*
Gniuli [32]	*	*	*	*	*	*	*
Camastra [33]	*	*	*	*	*	*	*
Nannipieri (1) [34]	*	*	*	*	*	*	*
Nannipieri (2) [34]	*	*	*	*	*	*	*
Moulin (1) [35]	*	*	*	*	*	*	*
Moulin (2) [35]	*	*	*	*	*	*	*
Alagna (1) [36]	*	*	*	*	*	*	*
Alagna (2) [36]	*	*	*	*	*	*	*
Dittmar [37]	*	*	*	*	*	*	*
Vettor [38]	*	*	*	*	*	*	*
Yashkov [39]	*	*	*	*	*	–	–
Buscemi [40]	*	*	*	*	*	*	*
Backes [17]	*	*	*	*	*	*	*
Ruiz-Tovar [18]	*	*	*	*	*	*	*
Fazylov [19]	*	*	*	*	*	*	*
Chikunguwo [20]	*	*	*	*	*	*	*
Raftopoulos [21]	*	*	*	*	*	*	*

CI 0.03 to 1.37, $p = 0.004$). Also, grouping these studies by type of preoperative thyroid function could only resolved between-study heterogeneity for the four studies focusing on patients with preoperative hypothyroidism ($p = 0.41$, $I^2 = 0\%$). Regardless of short-term follow-up (≤ 12 months) or long-term follow-up (> 12 months), the pooled results did not reach statistical significance.

Study or Subgroup	Before surgery Mean	SD	Total	After surgery Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Abu-Ghanem 2015	2.45	0.17	38	1.82	0.18	38	3.4%	3.56 [2.83, 4.30]
Alagna (1) 2003	1.55	0.693	12	1.4	0.294	12	3.3%	0.27 [-0.53, 1.08]
Alagna (2) 2003	1.5	0.91	26	1.65	0.59	26	3.7%	-0.19 [-0.74, 0.35]
Bawahab 2017	3.369	0.62	50	2.39	0.4	50	3.8%	1.86 [1.39, 2.33]
Buscemi 1997	1.14	0.32	10	1.28	0.74	10	3.2%	-0.24 [-1.12, 0.65]
Butte 2015	3.05	1.36	11	1.65	0.94	11	3.1%	1.15 [0.24, 2.07]
Camastra 2009	1.94	0.22	7	1.49	0.18	7	2.3%	2.10 [0.70, 3.49]
Dall'Asta 2010	1.9	0.07	258	1.93	0.12	220	4.1%	-0.31 [-0.49, -0.13]
Dittmar 2003	1.38	0.76	26	1.27	0.52	26	3.7%	0.17 [-0.38, 0.71]
Fallahi (1) 2017	2.21	0.91	13	3.8	1.83	13	3.2%	-1.07 [-1.90, -0.23]
Fallahi (2) 2017	2.65	0.86	4	3.12	1.33	4	2.3%	-0.36 [-1.77, 1.04]
Fierabracci 2016	1.56	1.47	93	0.84	1.03	93	4.0%	0.56 [0.27, 0.86]
Gkotsina (1) 2013	2.56	1.14	10	2.37	1.17	10	3.2%	0.16 [-0.72, 1.04]
Gkotsina (2) 2013	1.88	0.94	7	2.02	0.95	7	2.9%	-0.14 [-1.19, 0.91]
Gkotsina (3) 2013	2.57	1.01	15	3.07	1.26	15	3.4%	-0.43 [-1.15, 0.30]
Gniuli 2010	2.96	4.11	45	4.59	9.05	45	3.9%	-0.23 [-0.64, 0.18]
Hasani 2015	2.47	1	21	2.25	1.09	21	3.6%	0.21 [-0.40, 0.81]
Janssen 2015	5.82	2.05	61	2.78	1.31	61	3.9%	1.76 [1.34, 2.18]
Lips 2013	3.4	1.7	31	2	1.1	31	3.7%	0.97 [0.44, 1.49]
MacCuish 2012	2	0.14	55	2.02	0.22	55	3.9%	-0.11 [-0.48, 0.27]
Michalaki 2014	2.02	0.97	35	2.4	1.06	35	3.8%	-0.37 [-0.84, 0.10]
Moulin (1) 2005	2.28	0.88	54	1.74	0.97	54	3.9%	0.58 [0.19, 0.96]
Moulin (2) 2005	5.27	1.22	18	2.68	0.89	18	3.2%	2.37 [1.50, 3.25]
Nannipieri (1) 2009	1.4	0.52	14	1.1	0.74	14	3.4%	0.46 [-0.30, 1.21]
Nannipieri (2) 2009	2	0.67	13	0.9	0.74	13	3.1%	1.51 [0.62, 2.40]
Sundaram 2013	2.64	1.83	74	2	1.43	74	4.0%	0.39 [0.06, 0.71]
Vettor 2003	1.76	0.22	10	2	0.21	10	3.0%	-1.07 [-2.02, -0.12]
Xing 2017	3.13	1.3	10	1.62	0.4	10	2.9%	1.50 [0.48, 2.52]
Zendel 2017	3.9	2.8	93	3	2.6	93	4.0%	0.33 [0.04, 0.62]
Total (95% CI)			**1114**			**1076**	**100.0%**	**0.52 [0.20, 0.83]**

Heterogeneity: Tau² = 0.62; Chi² = 310.49, df = 28 (P < 0.00001); I² = 91%
Test for overall effect: Z = 3.19 (P = 0.001)

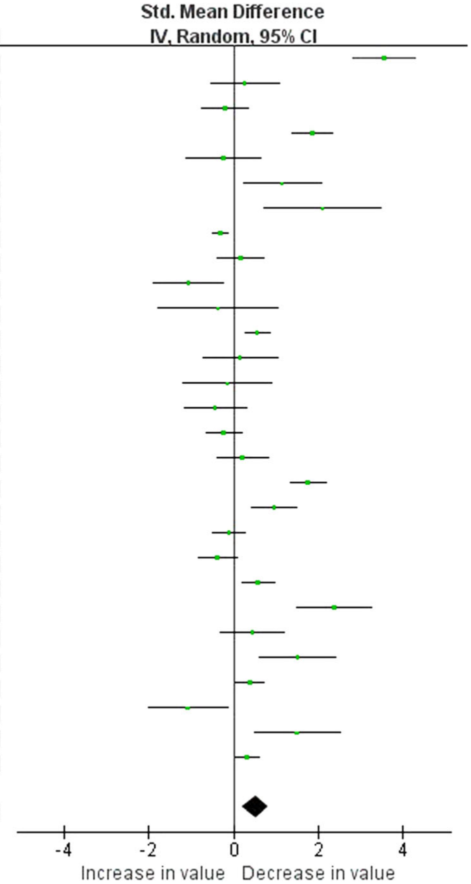

Fig. 2 Forest plots demonstrating changes in TSH

When omitting any one study out in turn, the pooled estimate were not observably changed, with a range from − 0.27 (95% CI − 0.93 to 0.39) to 0.06 (95% CI − 0.57 to 0.70). However, when changing the random effects model to the fixed effect model, the pooled result became statistically significant (SMD = − 0.51, 95% CI – 0.62 to − 0.41, $p < 0.00001$), which means that bariatric surgery could increase the level of FT4. So, the effect of bariatric surgery on FT4 level needs to be further studied. For this outcome, publication bias was not found (Begg, $p = 0.693$; Egger, $p = 0.252$).

Meta-Analysis of T3

Eleven studies examined the effect of bariatric surgery on T3, with a total of 222 participants. The impact measure SMD was chosen because the measurement scales used were different among these studies. There was homogeneity across these researches ($P = 0.29$, $I^2 = 17\%$) (Fig. 5), so a fixed effect model was selected for analysis. The pooled result suggested that T3 level decreased after bariatric surgery as compared with that before surgery (SMD = 1.05, 95% CI 0.85 to 1.25, $p < 0.00001$). Subgroup analysis was not performed because of between-study homogeneity. To verify the robustness of pooled estimate, we conduct sensitivity analysis by using different pooled models. The random-effects model also indicated that bariatric surgery could reduce the T3 level in obese patients (SMD = 1.07, 95% CI 0.84 to 1.30, $p < 0.00001$), which means that the summary effect size is robust. No matter which study was removed, the pooled result kept statistically significant. There was no publication bias for this outcome from Begg and Egger tests.

Meta-Analysis of T4

Nine trails with 169 patients were included in the meta-analysis calculating T4 concentration. No significant heterogeneity was seen between studies, so we used the fixed effect model to summarize mean effect size and found that bariatric surgery did not result in significant variation in T4 (SMD = 0.12, 95% CI – 0.10 to 0.34, $p = 0.28$) (Fig. 6). In the sensitivity analysis, a random effects model yielded a similar result (SMD = 0.10, 95% CI − 0.18 to 0.39,

Table 3 Subgroup analyses of TSH, FT3, and FT4 levels

Subgroup	Stratification	No. of studies	P value for heterogeneity	I^2	Pooled standardized mean differences	*P* value for pooled results
TSH						
Bariatric surgery						
	RYGB	10	< 0.00001	89%	0.75 [0.17, 1.33]	0.01
	BPD	7	0.02	60%	− 0.08 [− 0.55, 0.40]	0.75
	SG	4	< 0.00001	92%	1.79 [0.52, 3.06]	0.006
	AGB	2	0.10	62%	− 0.14 [− 0.59, 0.30]	0.53
Preoperative thyroid function						
	Euthyroidism	9	< 0.00001	93%	0.36 [− 0.24, 0.97]	0.24
	SH	2	0.21	35%	1.94 [1.39, 2.49]	< 0.00001
	Hypothyroidism	5	0.006	72%	0.19 [− 0.18, 0.57]	0.31
Follow-up duration						
	> 12 months	7	< 0.00001	80%	− 0.10 [− 0.44, 0.25]	0.58
	≤ 12 months	21	< 0.00001	90%	0.77 [0.33, 1.20]	0.0006
FT3						
Bariatric surgery						
	RYGB	4	0.11	51%	0.72 [0.14, 1.31]	0.02
	BPD	7	0.001	73%	1.32 [0.68, 1.97]	< 0.0001
	SG	1	–	–	0.77 [− 0.15, 1.68]	0.10
	AGB	1	–	–	9.19 [8.57,9.80]	< 0.00001
Preoperative thyroid function						
	Euthyroidism	3	< 0.00001	95%	1.06 [0.29, 1.83]*	0.007
	Hypothyroidism	3	0.88	0%	0.29 [0.15, 0.43]*	< 0.0001
Follow-up duration						
	> 12 months	5	< 0.00001	99%	2.89 [− 0.26, 6.03]	0.07
	≤ 12 months	10	0.004	63%	0.92 [0.47, 1.36]	< 0.0001
FT4						
Bariatric surgery						
	RYGB	9	< 0.00001	95%	− 0.49 [− 1.32, 0.33]	0.24
	BPD	7	0.0001	78%	0.70 [0.03, 1.37]	0.004
	SG	2	0.61	0%	0.65 [0.24, 1.06]	0.002
	AGB	1	–	–	− 3.88 [− 4.19, − 3.58]	< 0.00001
Preoperative thyroid function						
	Euthyroidism	6	< 0.00001	99%	− 1.07 [− 2.97, 0.84]	0.27
	SH	2	0.03	80%	0.11 [− 0.72, 0.95]	0.79
	Hypothyroidism	4	0.41	0%	− 0.13 [− 0.32, 0.07]	0.20
Follow-up duration						
	> 12 months	6	< 0.00001	99%	− 0.73 [− 2.63, 1.17]	0.45
	≤ 12 months	16	0.0003	63%	0.11 [− 0.14, 0.36]	0.39

*Pooled mean differences

$p = 0.47$) with the fixed effect analysis. What's more, when using the one-study-out method, we observed that no research could change the pooled results remarkably, so bariatric surgery has no significant effect on T4 level. Because the number of included studies was less than 10, publication bias was not checked for this outcome.

Meta-Analysis of rT3

Two studies were included in the meta-analysis of rT3, with 42 patients overall. Because of between-study heterogeneity ($p = 0.14$, $I^2 = 54\%$) (Fig. 7), a random effects model was chosen to pool results and showed that rT3 concentration did

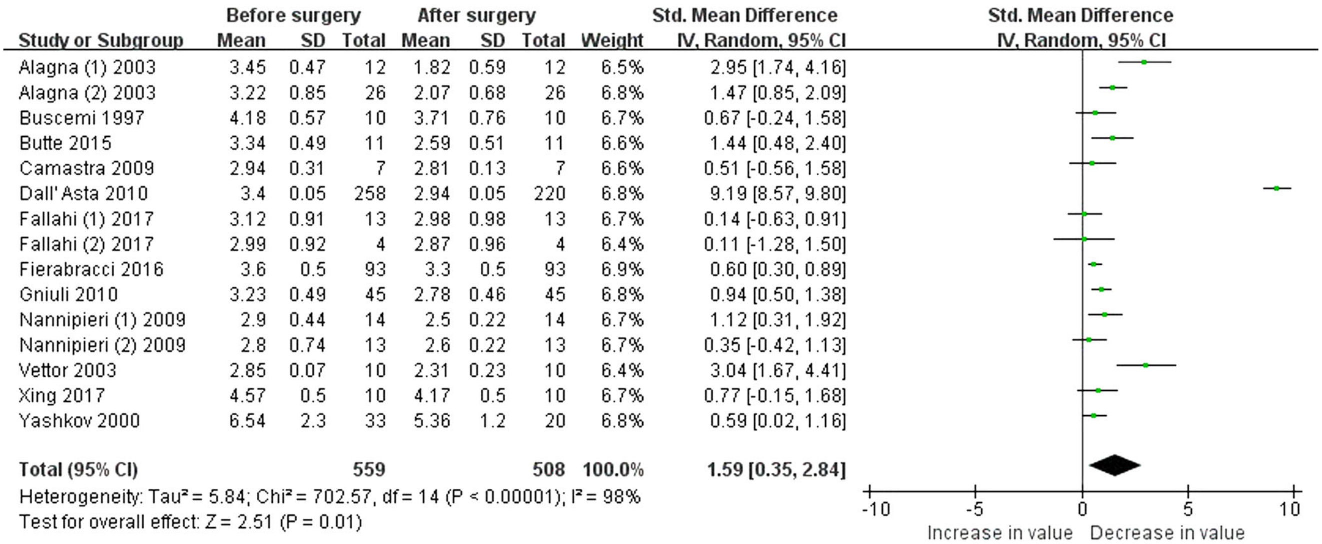

Fig. 3 Forest plots demonstrating changes in FT3

not change signally after bariatric surgery (MD = 0.03, 95% CI – 0.02 to 0.08, $p = 0.20$).

Remission of Overt and Subclinical Hypothyroidism

Ten studies described the remission rate of overt and subclinical hypothyroidism after bariatric surgery (Table 4). A favorable effect of bariatric surgery on overt and subclinical hypothyroid patients has been shown in most of these studies, which could be supported by remission or improvement rate of overt and subclinical hypothyroidism, together with lower requirement of LT4 dose postoperatively. However, Gniuli et al. studied 45 patients undergoing BPD and found an enhanced prevalence of subclinical and frank hypothyroidism postoperatively; however, most of these patients had preexisting thyroid disease preoperatively (e.g., multinodular,

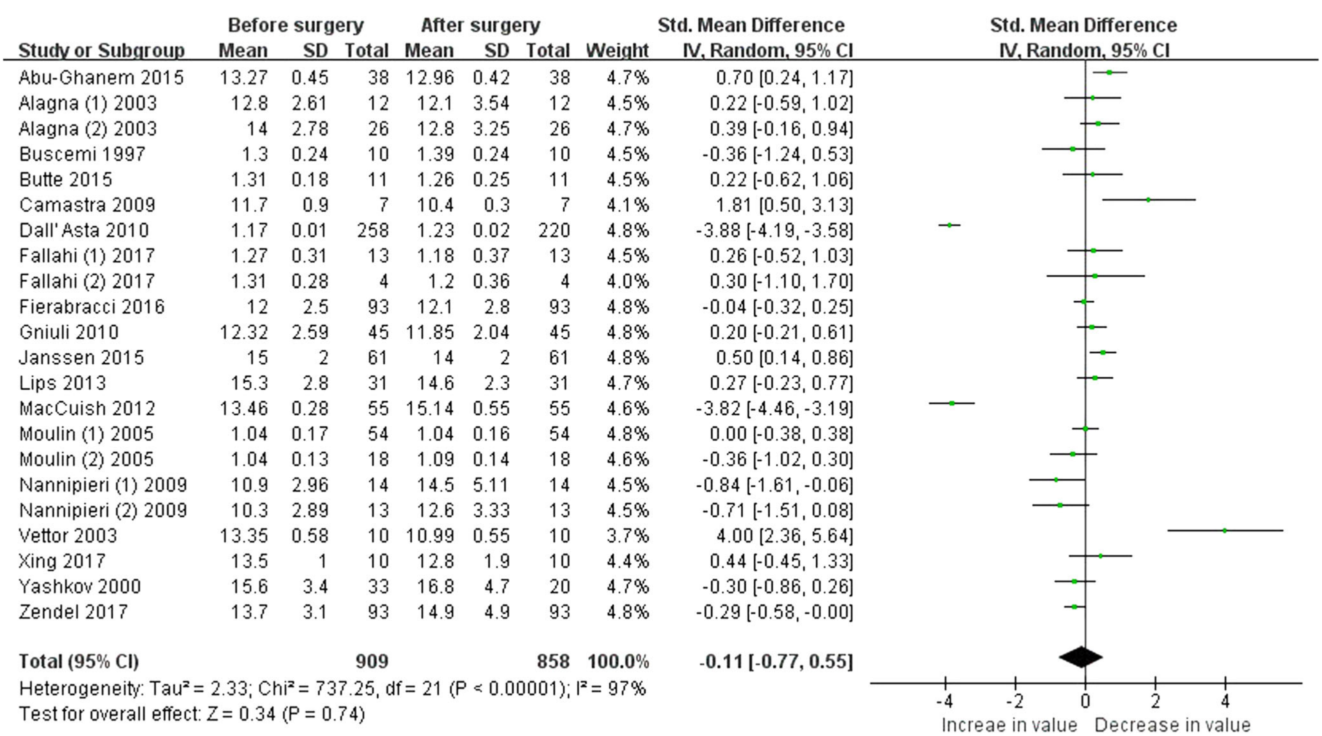

Fig. 4 Forest plots demonstrating changes in FT4

Study or Subgroup	Before surgery Mean	SD	Total	After surgery Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Buscemi 1997	1.37	0.21	10	1.27	0.14	10	5.1%	0.54 [-0.36, 1.43]
Butte 2015	115	30.7	11	77.7	17.9	11	4.4%	1.43 [0.47, 2.38]
Gkotsina (1) 2013	1.29	0.16	10	1.05	0.11	10	3.7%	1.67 [0.62, 2.72]
Gkotsina (2) 2013	1.44	0.28	7	1.18	0.21	7	3.2%	0.98 [-0.15, 2.12]
Gkotsina (3) 2013	1.4	0.12	15	1.15	0.12	15	5.0%	2.03 [1.12, 2.93]
Hasani 2015	1.52	0.63	21	1.21	0.41	21	10.6%	0.57 [-0.05, 1.19]
Lips 2013	1.9	0.3	31	1.6	0.2	31	13.9%	1.16 [0.62, 1.70]
Michalaki 2014	1.36	0.28	35	1.16	0.2	35	17.0%	0.81 [0.32, 1.30]
Moulin (1) 2005	133	24.5	54	112.1	16.5	54	25.3%	0.99 [0.59, 1.39]
Moulin (2) 2005	129.1	22.1	18	104.3	16.7	18	7.8%	1.24 [0.52, 1.96]
Xing 2017	1.7	0.2	10	1.4	0.2	10	4.0%	1.44 [0.43, 2.44]
Total (95% CI)			**222**			**222**	**100.0%**	**1.05 [0.85, 1.25]**

Heterogeneity: Chi² = 12.00, df = 10 (P = 0.29); I² = 17%
Test for overall effect: Z = 10.22 (P < 0.00001)

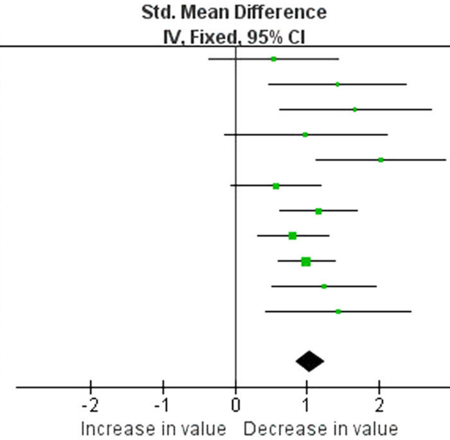

Fig. 5 Forest plots demonstrating changes in T3

thyroidal cysts), which means that the onset of subclinical and frank hypothyroidism could be considered as a natural progression of these thyroid diseases [32].

Discussion

In the past decades, a huge amount of interest has been devoted to the effect of bariatric surgery on weight loss, type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia. However, the impact of bariatric surgery on thyroid hormone parameters gained only limited attention, although thyroid hormones paly a very important role in regulating a series of metabolic processes in the human body, including macronutrient metabolism, energy metabolism, and so on [41, 42]. To the best of our knowledge, this is the first meta-analysis to evaluate the effect of bariatric surgery on thyroid function in obese patients. We found that bariatric surgery could reduce TSH, FT3, and T3 levels. However, postoperative FT4, T4, and rT3 concentrations were not significantly changed as compared with that before surgery.

Although an association between bariatric surgery and change of thyroid hormones has been found in this meta-analysis, the underlying reasons responsible for this are not well understood yet and may be explained by several mechanisms. First, it is about adipose tissue and adipokines. As the key component of obesity, adipose tissue can secrete a mass of adipocytokines (e.g., leptin), which have been proposed to have a stimulatory impact on thyroid activity and thereby increase TSH and T3 secretion [43]. Hence, surgery-induced weight loss could bring about a decline in the concentration of TSH and T3 [44]. Second, the surgery itself may also have an added impact besides weight reduction; this standpoint is supported by the evidence that TSH reduction was not correlated with percentage of excess weight loss (%EWL) in some studies [5, 35]. This phenomenon is similar with other effects of bariatric surgery, such as T2DM remissions, which is connected not only with weight loss but also with the surgery itself through other mechanisms, including mediation of gastrointestinal hormone [45]. With regard to this aspect, a recently published study has observed that serum ghrelin is positively related with TSH level, so reduction in ghrelin succeeding RYGB and SG would be contributed to TSH decrease [46].

Study or Subgroup	Before surgery Mean	SD	Total	After surgery Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bawahab 2017	15.34	1.66	50	15.08	0.65	50	30.1%	0.20 [-0.19, 0.60]
Buscemi 1997	8.84	1.33	10	8.04	0.81	10	5.6%	0.70 [-0.21, 1.60]
Butte 2015	7.77	1.65	11	7.32	1.23	11	6.6%	0.30 [-0.54, 1.14]
Gkotsina (1) 2013	7.71	0.83	10	8.32	1.24	10	5.8%	-0.55 [-1.45, 0.34]
Gkotsina (2) 2013	9.38	1.15	7	8.65	1.43	7	4.0%	0.53 [-0.55, 1.60]
Gkotsina (3) 2013	9.19	1.36	15	8.87	1	15	9.0%	0.26 [-0.46, 0.98]
Hasani 2015	8.1	1.45	21	9.04	1.33	21	12.0%	-0.66 [-1.29, -0.04]
Michalaki 2014	8.93	1.57	35	8.38	1.51	35	20.8%	0.35 [-0.12, 0.83]
Xing 2017	87	11.3	10	88.8	16	10	6.0%	-0.12 [-1.00, 0.75]
Total (95% CI)			**169**			**169**	**100.0%**	**0.12 [-0.10, 0.34]**

Heterogeneity: Chi² = 12.06, df = 8 (P = 0.15); I² = 34%
Test for overall effect: Z = 1.09 (P = 0.28)

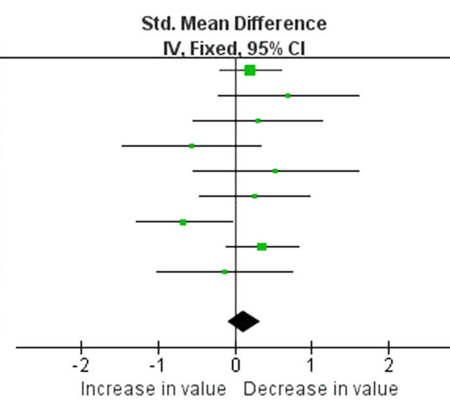

Fig. 6 Forest plots demonstrating changes in T4

Study or Subgroup	Before surgery Mean	SD	Total	After surgery Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Butte 2015	0.33	0.08	11	0.27	0.04	11	43.8%	0.06 [0.01, 0.11]
Lips 2013	0.28	0.09	31	0.27	0.07	31	56.2%	0.01 [-0.03, 0.05]
Total (95% CI)			**42**			**42**	**100.0%**	**0.03 [-0.02, 0.08]**

Heterogeneity: Tau² = 0.00; Chi² = 2.18, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 1.29 (P = 0.20)

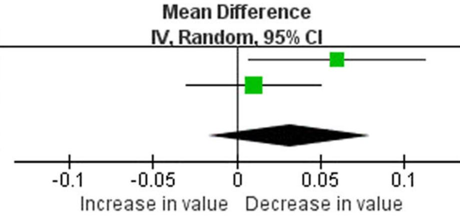

Fig. 7 Forest plots demonstrating changes in rT3

Third, alterations in deiodinase level induced by energy imbalance and nutritional change after weight loss may also make a contribution [32, 47, 48]; for instance, increased type 3 deiodinase (D3) activity and decreased type 2 deiodinase (D2) activity could lead to reduced conversion of T4 to T3 [6, 49]. Another noteworthy mechanism is that organochlorine compounds released into serum during lipid mobilization subsequent to weight loss play a role in T3 and FT3 reduction [50, 51].

Alteration in thyroid function following obesity surgery is a common phenomenon, but the reported results were not always similar between different studies and this may be partly due to different types of surgery performed. Of the various bariatric procedures which have emerged nowadays, RYGB, SG, AGB, and BPD are the most commonly used [52]. There is a paucity of data on direct comparison of thyroid function changes after different types of bariatric surgeries in the literature. Fallahi et al. examined patients who underwent RYGB and BPD and mentioned no significant difference in the variation of TSH between the two groups [10]. Fierabracci et al. described the modification in thyroid drug doses caused by either RYGB or SG was comparable [25]. Nonetheless, the sample sizes of both the two studies were small, which may affect the reliability of these results. Our pooled results demonstrated that the most widely studied type of bariatric surgery regarding thyroid hormone changes were RYGB and BPD. The subgroup analyses suggested that RYGB, not BPD or AGB, had a positive effect on TSH reduction. With respect of FT3 reduction, RYGB and BPD was superior to SG. This may be explained by the effect of entero-hepatic circulation; FT3 is mainly generated by T4 de-iodination in the liver, then excreted through the bile and reabsorbed by means of entero-hepatic circulation. After RYGB and BPD, the entero-hepatic circulation was destroyed to a certain degree, which would lead to FT3 decrease [53]. However, due to between-study heterogeneity and small patient samples in some subgroups, these pooled estimates should be cautiously treated. Furthermore, since we cannot recognize whether other types of bariatric surgery would have different effects, future research should focus on comparing different types of bariatric procedures and clarifying the mechanisms behind.

Of the included studies, follow-up durations were different from each other. In comparison with the short-term follow-up (SMD = 0.92, 95% CI 0.47 to 1.36, $p < 0.0001$), the long-term follow-up (> 12 months) tended to have a more obvious effect on FT3 reduction (SMD = 2.89, 95% CI − 0.26 to 6.03), but its *p* value did not achieve statistical significance ($p = 0.07$). This may be ascribed to small sample sizes, because only five studies with 416 patients were enrolled in the subgroup of long-term follow-up, so long-term change in thyroid hormones caused by surgical weight reduction deserves further investigations. Another point that should be noted is that patients with different preoperative thyroid function may have different response to bariatric surgery. However, most of previous studies focused on only a specific group of patients (e.g., euthyroid, hypothyroid). And some studies even did not provide detailed data regarding this aspect. In the meta-analysis, a sub-group analysis was conducted according to patients' preoperative thyroid function. For obese patients with normal thyroid function, our pooled results showed a decrease of T3 and FT3 (data not shown) following bariatric surgery with no change of TSH level. Explanations of these vibrations might be provided by decreased type 1 deiodinase (D1) and type 2 deiodinase (D2) activities postoperatively [32].

The prevalence of hypothyroidism in obese patients has been documented ranging from 11.8 to 18% [2, 25, 29], of which the exact pathogenesis is multifactorial. A relatively reasonable explanation is that TSH secretion is not only controlled by stimulatory effect of TRH and the negative feedback of thyroid hormones, but also influenced by some other factors, including leptin, ghrelin, dopamine, etc. [54, 55]; all these factors synthetically make for a rise in TSH level and a decline in T3 and T4 levels [7]. It is noteworthy that a favorable effect of bariatric surgery on hypothyroid patients have been reported in most of the included studies [23, 25, 29], including improvement of thyroid function and decrease of thyroid drug requirements, although the clinical significance of the finding is not clear yet. But for the patients who had thyroid disease, including multinodular, thyroidal cysts, and autoimmune disease, we should keep an eye on the progression of these diseases. And for SH, the literature has demonstrated its prevalence between 10.5 and 25.0% in obese patients [20, 35], of which the data is obviously higher than that in the general population [56, 57]. However, it is described that obesity-related SH would not affect postsurgical weight loss [7]. Moreover, our pooled result showed that the TSH level of SH patients would decreased significantly after bariatric surgery (SMD = 1.94, 95% CI 1.39 to 2.49,

Table 4 Remission of overt and subclinical hypothyroidism in included studies

Included studies	Intervention	Follow-up (months)	Thyroid dysfunction before surgery (%, n)	Change in thyroid function after surgery (%, n)	LT4 users before surgery (%, n)	Change in LT4 dose after surgery (%, n)
Zendel [23]	RYGB, SG	12	Hypothyroid: 100% (93/93)	NR	89% (83/93)	13.2% (11/83) off medication 12% (10/83) require lower dose
Fierabracci [25]	RYGB, SG, AGB	28 ± 8	Hypothyroid: 100% (93/93)	NR	100% (93/93)	50% (47/93) require lower dose 37% (34/93) require unchanged dose 13% (12/93) require higher dose
Janssen [7]	RYGB	12	SH: 100% (61/61)	SH resolved: 86.9% (53/61)SH persistent: 13.1% (8/61)	NR	NR
Sundaram [29]	RYGB, SG, GB	3–108	Hypothyroid: 100% (74/74)	NR	100% (74/74)	26% (19/74) require lower dose 55% (41/74) require unchanged dose 19% (14/74) require higher dose
Gniuli [32]	BPD	24	SH: 23.4% (11/45)	SH: 42.4% (19/45) Hypothyroid: 6.3% (3/45)	NR	NR
Moulin (2) [35]	RYGB	12	SH: 25.0% (18/72)	NR	NR	NR
Backes [17]	RYGB, BPD-DS	6	Hypothyroid: 13% (9/69)	Hypothyroid: 9.4% (6/64)	NR	NR
Ruiz-Tovar [18]	SG	12	SH: 16.7% (10/60)	SH: 1.7% (1/60)	NR	NR
Fazylov [19]	RYGB	24	Hypothyroid: 100% (20/20)	Hypothyroid resolved: 25% (5/20) Hypothyroid improved: 10% (2/20) Hypothyroid unchanged: 40% (8/20) Hypothyroid worsened: 25% (5/20)	NR	NR
Chikunguwo [20]	RYGB, AGB	12	SH: 10.5% (9/86)	SH resolved: 100% (9/9)	NR	NR
Raftopoulos [21]	RYGB	5.5–31	Hypothyroid: 100% (23/23)	Hypothyroid resolved: 8.7% (2/23) hypothyroid improved: 34.8% (8/23) hypothyroid unchanged: 56.5% (13/23)	100% (23/23)	8.7% (2/23) off medication 34.8% (8/23) require lower dose 56.5% (13/23) require unchanged dose

NR not reported, *SH* subclinical hypothyroidism, *RYGB* Roux-en-Y gastric bypass, *SG* sleeve gastrectomy, *AGB* adjustable gastric band, *GB* gastric banding, *BPD* biliopancreatic diversion, *BPD-DS* biliopancreatic diversion and duodenal switch

$p < 0.00001$), with a high percentage of spontaneous recovery of SH. In view of current evidence, we believe that SH is more likely to be a consequence rather than a cause of obesity, and postoperative follow-up alone is sufficient for most bariatric surgery patients with SH, no longer needing thyroid hormone treatment; this viewpoint is supported by some other investigators [7, 35].

This study provides a quantifiable measure of thyroid function change after bariatric surgery. However, some limitations should be pointed out. First, it is the between-study heterogeneity; patient characteristics, type of bariatric surgery, and follow-up duration vary obviously between studies and may issue in reporting biases. Nonetheless, random effects model was adopted to pool estimations when appropriate, so as to give the most conservative estimates. Furthermore, subgroup analysis and sensitivity analysis were performed and indicated that the pooled results were relatively robust. However, future research should take patient characteristics into account, and determine the exact effect for different procedures. Another limitation is most of the included studies were observational studies, which are of suboptimal quality relative to experimental study. Therefore randomized controlled studies of bariatric surgery compared with medical treatment are warranted.

Conclusion

Based on the currently available evidence, TSH, FT3, and T3 decrease are expected following bariatric surgery, as well as non-significant change of T4, FT4, and rT3 levels. However, randomized prospective studies with larger samples and longer follow-up are needed.

Compliance with Ethical Standards

Ethical Approval For this type of study, formal consent is not required.

Conflict of Interest The authors declare that they have no conflict of interest.

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