BMC Endocrine Disorders

RESEARCH

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Thyroid hormone levels in patients with bipolar disorder: a systematic review and meta-analysis

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Abstract

Purpose To investigate the difference in blood (serum/plasma) thyroid hormone (TH) levels, including thyroid-stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4), and free triiodothyronine (FT3), in bipolar disorder (BD) during different mood episodes (depression and mania) compared with healthy control (HC) and between manic episodes (BD-M) and depressive episodes (BD-D).

Methods As of September 1, 2024, the electronic databases PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, China Science and Technology Journal Database, Wanfang Database, and Clinical Trials. Gov were systematically searched with no language limitations. Standardized mean differences (SMD) with 95% confidence interval (CI) were summarized using a random effects model. The chi-squared-based Q test and the I^2 test assessed the size of heterogeneity.

Results The 21 studies included a total of 3696 participants, Of the 2942 BD patients, 1583 were in depressive episodes 1359 were in manic episodes. The status of measuring blood TH levels included 2 studies in plasma and 19 in serum. Combined with the results of the sensitivity analyses, we obtained the following relatively reliable results: serum T3 (SMD: -0.63, 95%CI: -1.09 to -0.17) and FT3 (SMD: -0.42, 95%CI: -0.83 to -0.00) levels decreased significantly in BD-D compared to HC; serum T3 (SMD: -0.91, 95%CI: -1.49 to -0.32) levels decreased significantly and serum FT4 (SMD: 0.37, 95%CI: 0.14 to 0.60) levels increased significantly in BD-M than in HC; serum T3 (SMD: 0.87, 95%CI: 0.24 to 1.49) and FT3 (SMD: 0.27, 95%CI: 0.13 to 0.42) levels demonstrated a significant elevation in BD-M compared to BD-D. In the group of euthyroidism, apart from serum FT4 (SMD: 0.21, 95%CI: -0.15 to 0.58) levels showed no significant difference between BD-M and HC, other results above remained consistent.

Conclusion Serum T3 and FT3 levels decreased significantly in BD-D compared to HC. Serum T3 levels decreased significantly and serum FT4 levels increased significantly in BD-M compared to HC. Serum T3 and FT3 levels increased significantly in BD-M than in BD-D. The temporality of changes in TH levels and BD progression demands further longitudinal studies to illustrate.

Trial registration Number and date of registration for prospectively registered trials No. CRD42022378530.

Keywords Bipolar disorder, Depression, Mania, Thyroid hormone, Meta-analysis

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Introduction

Bipolar disorder (BD) is a chronic, recurrent mental illness characterized by fluctuating mood states and energy, mainly manifested by alternating episodes of mania or hypomania (BD-M) and depression (BD-D), affecting 1–3% of the global population [1–3]. The psychosocial functioning of BD is greatly reduced, and suicide is one of the main causes of its high mortality rate, with a reduction in potential life expectancy of about 10–20 years [4]. According to the World Health Organization (WHO) World Mental Health (WMH) surveys, the days out of the role in BD was the second-highest among ten chronic physical disorders and nine mental disorders [5]. However, the diagnosis and treatment of BD continue to face challenges in clinical practice [3]. So, it is necessary to explore potential biomarkers for the disease.

Hypothalamic-pituitary-thyroid (HPT) axis dysfunction is considered to be related to the mechanism of BD [6]. Thyroid dysfunction (TD) increases the risk of BD and contributes to its worsening clinical course [7]. It was reported that BD patients were 2.55 times more likely to develop TD than the general population [8]. Even mild alterations in thyroid function are associated with the risk of BD [9]. Thyroid hormone (TH), which is involved in central nervous system (CNS)—related processes such as neuronal survival and differentiation, energy expenditure, synapse establishment, and myelin formation, has a fundamental effect on brain development [10, 11]. It is well established that TH is critical for mood regulation and abnormal TH levels may play an important role in the pathophysiology or management of mood disorders [12, 13]. Kuś et al. [9] concluded that each standard deviation (SD) increase in free thyroxine (FT4) levels was associated with an 11% reduction in the overall risk of BD. Amann et al. [14] indicated that higher blood thyroid-stimulating hormone (TSH) levels increase the risk of manic episodes in BD. The results of the study by Krishna et al. [8] noted that mean triiodothyronine (T3) values were significantly higher in BD patients compared with age and sex-matched controls. Furthermore, there is also some evidence that TH-assisted therapy is beneficial to the remission of BD [15, 16]. These findings affirm that the pathophysiologic mechanism of BD involves the disturbance of TH levels [8]. Several studies have examined changes in TH levels of BD patients, but a consensus has not yet been met. Lai et al. [12] found that serum TSH levels were significantly decreased in BD-D compared to healthy control (HC), and the result of Albeh et al. [17] demonstrated serum TSH levels in BD-M were significantly elevated compared to HC, but inconsistent results were reported by Song et al. [18]. Additionally, Zhao et al. [19] reported a significant increase in serum-free triiodothyronine (FT3) levels in BD-M than in BD-D, which is different from the outcome of Li et al. [20]. Therefore, this study aimed to investigate the differences in blood (serum/plasma) TH levels, including TSH, thyroxine (T4), T3, FT4, and FT3, between BD-D or BD-M and HC, as well as between BD-M and BD-D.

Methods

The study was according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S6) [21]. It has been registered in the PROSPERO (https://www.crd.york.ac.uk/prospero/), the International Prospective Register of Systematic Reviews platform with the number CRD42022378530.

Search strategy

The electronic databases PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Chinese Biomedical Literature Database, China Science and Technology Journal Database, Wanfang Database, and Clinical Trials. Gov were searched from inception to 1 September 2024, without language restriction. To ensure the quality of publication in Chinese form, we only included studies published in core or higher-tier publications recognized by Peking University. We also manually searched the references of relevant literature to avoid omissions. For studies where full text or useful data were not available, we tried to get it by contacting the authors. The search strategy was (bipolar disorder) AND (Thyroid hormones OR Thyrotropin OR TSH OR Thyroxine OR T4 OR Triiodothyronine OR T3 OR FT4 OR FT3) (Table S1).

Inclusion and exclusion criteria

Inclusion criteria were as follows:(1) studies provided diagnostic criteria for BD (current a depressive episode or a manic episode); (2) studies comparing blood TH levels between BD during depressive episodes or manic episodes and HC, or between depressive episodes and manic episodes in BD; (3) studies provided TH levels as mean and SD (or can be calculated).

Exclusion criteria were as follows: (1) reviews, conference abstracts, letters, and other non-primary studies; (2) non-human research, such as animal experiments; (3) the object of studies accompanied by other mental illness (such as schizophrenia); (4) rapid cycling BD; (5) studies during pregnancy or lactation; (6) treatment-induced changes in TH levels, such as lithium; (7) data or full text was not available.

Data collection and extraction

Data was extracted using a pre-designed form by two reviewers independently and disagreements were reconciled by discussing with a third author. The extracted

information was included as follows: the first author, publication year, location, design type, diagnostic criteria for BD, demographic characteristics of participants (sample size, gender, age, education), outcome indicators, TH measurement method, thyroid function, treatments, reference range of TH levels, and any scale to assess the severity of depression or mania.

Quality assessment

The quality of the included studies was assessed independently by two reviewers and any differences were resolved by a third reviewer. The quality assessment of case–control or cohort studies with the Newcastle Ottawa Scale (NOS) [22] and cross-sectional studies with the Agency for Healthcare Research and Quality Scale (AHRQ) [23], of 0–3, 4–6, 7–9 stars in NOS and 0–3,4–7,8–11 in AHRQ scores represent the highest risk of bias and the lowest quality, the medium risk of bias and the medium quality, the lowest risk of bias and the highest quality, respectively.

Data synthesis and analysis

Standardized mean difference (SMD) with 95% confidence interval (CI) was used to represent continuous variables. If data in the study was not expressed as mean and SD, they were converted according to the method given by McGrath et al. [24]. The size of heterogeneity was assessed by the chi-squared-based Q test and the I^2 test, studies with an I^2 value of < 25%, 25%-50%, 50%-75%, or 75%-100% were considered to have no, low, moderate, or high heterogeneity, respectively. A random effects model was chosen to combine effect size, regardless of heterogeneity. Subgroup analyses were conducted following treatment, gender, and location. Sensitivity analysis was performed by eliminating each study in turn. Additionally, we only included those studies that demonstrated all included patients were euthyroid sound for sensitivity analysis. The test of publication bias used a funnel plot (number of studies at least 10) and Egger's test. If publication bias existed, the trim-and-fill method was used to reconfirmation the stability of statistical results. A P value of < 0.05 was considered statistically significant. All of the above statistical analyses were performed in STATA/MP 15.

Result

Study search and inclusion

The flowchart of study selection is shown in Fig. 1. A total of 6011 studies were retrieved in this study. There were 2227 duplicated studies removed and 3751 studies inconsistent with the purpose of the study were excluded by reading the title and abstract. The remaining 33 studies excluded 12 by full-text reading for the following reasons: reviews ($n=1$), conference abstracts ($n=4$), no BD diagnostic criteria ($n=1$), not BD-D or BD-M ($n=4$), under the influence of drugs ($n=1$), no extractable data ($n=1$). Finally, 21 studies were included in the systematic review and meta-analysis.

Study characteristics and quality assessment

The detailed characterization of the study population is shown in Table 1. Of these 21 studies, all but one prospective cohort study [25] and five case–control studies [20, 25–28] were cross-sectional. The study sites included India [29], France [30–32], Egypt [17], Poland [33], Canada [26], America [34], and China. In terms of language, there were 17 English and 4 Chinese articles [35–38]. The sample size for the original studies ranged from 16 to 828. The 21 studies included a total of 3696 participants, Of the 2942 BD patients, 1583 were in depressive episodes 1359 were in manic episodes, and the remaining 754 were HC. After excluding 3 studies [32, 38, 39] that did not indicate the sex ratio of enrolled patients, the proportion of females of all remaining patients was 47%, the proportion of females was 46% during depressive episodes and 48% during manic episodes. Apart from 2 studies [31, 38] not mentioned, the mean age of subjects ranged from 17.3 to 53.3. It should be noted that BD-D and HC were not matched for age in 2 studies [12, 27] and BD-D and BD-M were not matched for age in 1 study [20]. The diagnostic criteria for BD included the Diagnostic and Statistical Manual of Mental Disorders, Third, Fourth, and Fifth Edition (DSM-III, DSM-IV, and DSM-V, respectively), the International Classification of Diseases Diagnostic Criteria, Edition 10 (ICD-10), the Chinese Classification of Mental Disorders, Edition 3 (CCMD-3), and Research Diagnostic Criteria for a Selected Group of Functional Pqchoses, Edition 3 (RDC-III). The main methods for measuring TH levels included electrochemiluminescence immunoassay (ECLIA), chemiluminescence immunoassay (CLIA), radioimmunoassay (RIA), and enzyme-linked immunosorbent assay (ELISA). The states in which blood TH levels were measured included plasma [31, 32] and serum. Apart from the 5 studies not mentioned [17, 27, 31, 37, 40] or 1 study unsure [34], and 3 studies [20, 29, 33] included subjects with TD, others described the thyroid status as "no endocrine disease", "excluded of history of thyroid diseases" or "Euthyroidism" and so on. Except for 3 studies unknown [25, 33, 37], in terms of drug expression, these included "drug-naïve or medication-free for at least 3 months before hospitalization" "excluded of who received treatment for thyroid disease" "not receiving lithium carbonate or quetiapine that significantly affects the health of the patient" and "not receiving any psychiatric treatment", etc.

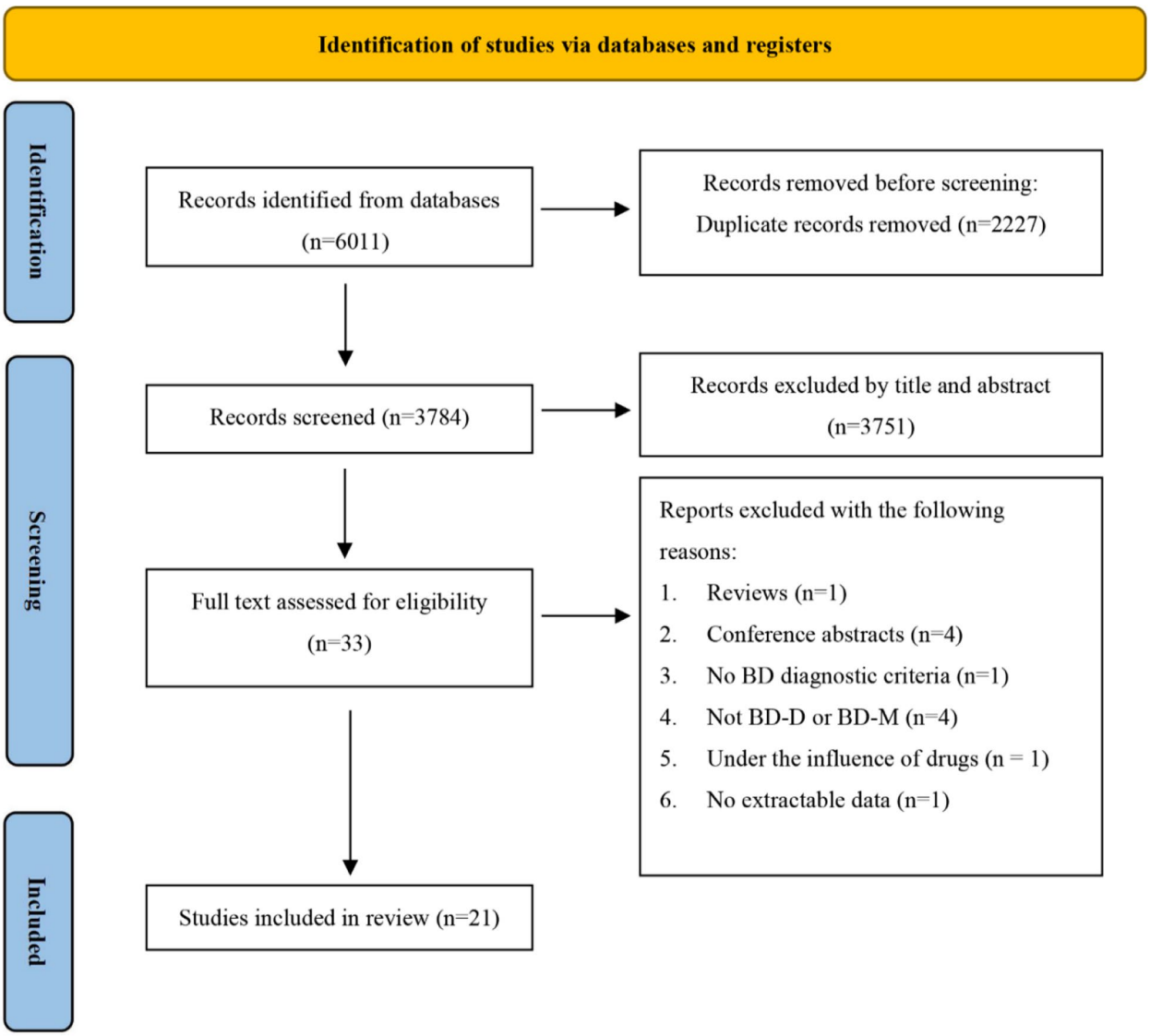

Fig. 1 Flow chart of study screening

The results of quality assessment by NOS for case–control or cohort studies showed a minimum of 6 stars and a maximum of 8 stars (Table S3), and AHRQ for cross-sectional studies showed a minimum score of 6 and a maximum score of 9 (Table S4). Overall, the included studies were medium to high.

Meta-analysis

Comparison of TH levels between BD-D and HC

A total of 12 studies [12, 18, 25, 27, 30–32, 34–36, 39, 40] compared TH levels between BD-D and HC. The pooled result of 11 studies showed no significant differences in the blood (9 in serum and 2 in plasma) TSH levels between BD-D and HC (SMD: -0.20, 95%CI: -0.44 to 0.03, $I^2=72.10\%$, $P=0.089$). A total of 8 studies comparing serum T4 and T3 levels, the pooled results displayed that T4 and T3 levels decreased significantly in BD-D compared to HC ((SMD: -0.44, 95%CI: -0.79 to -0.08, $I^2=87.50\%$, $P=0.017$), (SMD: -0.63, 95%CI: -1.09 to -0.17, $I^2=92.30\%$, $P=0.007$, Fig. 2), respectively). Nine studies showed serum FT4 and FT3 levels, no significant difference was observed in FT4 levels, while FT3 levels displayed a significant decrease in BD-D compared to HC ((SMD: 0.12, 95%CI: -0.16 to 0.40), $I^2=81.80\%$, $P=0.403$), (SMD: -0.42, 95%CI: -0.83 to -0.00, $I^2=91.20\%$, $P=0.049$), respectively) (Table 2).

For sensitivity analysis in the group of euthyroidism, the pooled results of TSH, T4, T3, FT4, and FT3 levels

Table 1 Characteristics of the included population

Study	Location	Design type	Diagnostic criteria for BD	State	Number (Male/Female)	Average age(years)	Education(years)	Outcome indicators	THs measurement method	Thyroid function in BD	Treatments in BD	Rating scale (Mean ± SD)	Reference range of TH
Zhang et al. 2024 [25]	China	Longitudinal prospective cohort	ICD-10	BD-D	2627 (126/136)	37.18 ± 14.04	NA	TSH, T4, T3, FT4, FT3	Electrochemiluminescence	Those who had a history or current thyroid disease were excluded	Excluded of who received treatment for thyroid disease	MADRS (28.90 ± 11.92)	TSH: 0.27–4.2mu/L T4: 62–164 nmol/L T3: 1.3–3.1 nmol/L FT4: 12–22 pmol/L FT3: 3.60–7.50 pmol/L
				BD-M	238 (120/118)	36.70 ± 12.78						YMRS (29.15 ± 14.02)	
				HC	119 (61/58)	38.48 ± 9.37						NA	
Song et al. 2023 [18]	China	Cross-sectional	ICD-10	BD-D	60 (0/60)	29.9 ± 12.8	NA	TSH, T4, T3, FT4, FT3	Electrochemiluminescence	Exclusion of endocrine diseases	Not receiving lithium carbonate or quetiapine significantly affects the level of thyroid function before admission	HAMD (28.0 ± 4.9)	NA
				BD-M	60 (0/60)	31.3 ± 9.4						YMRS (21.0 ± 3.2)	
				HC	60 (0/60)	30.2 ± 6.4						NA	
Chen et al. 2022 [40]	China	Cross-sectional	DSM-V	BD-D	59 (23/26)	23.81 ± 5.87	14.04 ± 2.44	TSH, T4, T3, FT4, FT3	Chemiluminescence	No description of thyroid function	All patients were either medication naïve or were not medicated for at least six months	HDRS (27.05 ± 5.87)	TSH: 0.49–4.91mIU/L T4: 69.97–152.52 nmol/L T3: 1.01–2.48 nmol/L FT4: 7.64–16.03 pmol/L FT3: 3.09–7.42 pmol/L
				HC	52 (27/25)	24.62 ± 5.55	15.58 ± 2.53					HDRS (1.80 ± 2.34)	
Zhao et al. 2021 [19]	China	Cross-sectional	ICD-10	BD-D	128 (53/75)	26.91 ± 7.04	NA	TSH, T4, T3, FT4, FT3	TSH was detected by the electrochemical luminescence double antibody sandwich method, and T3, FT3, T4, and FT4 were determined by electrochemical luminescence	Exclusion of those who have a history of thyroid disease	Drug-naïve before hospitalization	MADRS (25.74 ± 11.79)	TSH: 0.27–4.20mIU/L T4: 62.00–164.00 nmol/L T3: 1.30–3.10 nmol/L FT4: 12.00–22.00 pmol/L FT3: 3.60–7.50 pmol/L
				BD-M	136 (71/65)	27.81 ± 8.62						YMRS (28.57 ± 12.00)	
Lai et al. 2021 [12]	China	Cross-sectional	DSM-IV	BD-D	69 (32/37)	26.23 ± 8.98	13.62 ± 2.65	TSH, T4, T3, FT4, FT3	Direct chemiluminescence method	Excluded any physical illness demonstrated by personal history or clinical or laboratory examinations	Excluded a history of the use of any psychotropic medication, psychotherapy, or electroconvulsive therapy	HDRS (26.72 ± 5.76)	TSH: 0.49–4.91mIU/L T4: 69.97–152.52 μg/dl T3: 1.01–2.48 ng/ml FT4: 7.64–16.03 ng/dl FT3: 3.09–7.42 pg/ml
				HC	53 (29/24)	36.23 ± 13.95	14.49 ± 3.12					HDRS (2.49 ± 2.05)	

Table 1 (continued)

Study	Location	Design type	Diagnostic criteria for BD	State	Number (Male/Female)	Average age(years)	Education(years)	Outcome indicators	THs measurement method	Thyroid function in BD	Treatments in BD	Rating scale (Mean ± SD)	Reference range of TH
Han et al. 2021 [28]	China	Case–control	ICD-10	BD-M	70 (35/35)	24.3 ± 5.1	N/A	TSH, T4, T3, FT4, FT3	Electrochemiluminescence immunoassay	Excluded history of thyroid diseases	Excluded (1) taking levothyroxine, antithyroid, glucocorticoid, estrogen, progestin, oral contraceptive, bromocriptine, or other medicine related to pituitary diseases in the past six months; (2) history of antipsychotic medications; (3) taking antipsychotic or mood stabilizer within two weeks	YMRS (28.2 ± 3.4)	TSH: 0.27–4.20mIU/L T4: 66–181 nmol/L T3: 1.3–3.1 nmol/L FT4: 12–22 pmol/L FT3: 2.8–7.1 pmol/L
				HC	70 (35/35)	24.7 ± 4.3						NA	
Goyal et al. 2021 [29]	India	Cross-sectional	ICD-10	BD-M	40 (25/15)	24.88 ± 6.10	NA	TSH, FT4, FT3	NA	Exclusion known case of thyroid disorder. Among a total of 40 patients of mania, 7.5% were found to be of hyperthyroidism while 5% had subclinical hyperthyroidism. In contrast, normal controls showed 5% and 10% prevalence of hypothyroidism and subclinical hypothyroidism, respectively	Excluded any past history of psychiatric illness and treatment; any history of taking psychotropic drug for other reasons	YMRS (35.85 ± 7.15)	TSH: 0.35–5.5 uIU/ml FT4: 0.89–1.76 ng/dl FT3: 2.3–4.2 pg/ml
				HC	40 (25/15)	27.23 ± 5.59						NA	

Table 1 (continued)

Study	Location	Design type	Diagnostic criteria for BD	State	Number (Male/Female)	Average age(years)	Education(years)	Outcome indicators	THs measurement method	Thyroid function in BD	Treatments in BD	Rating scale (Mean ± SD)	Reference range of TH
Duval et al. 2020 [30]	France	Cross-sectional	DSM-IV	BD-D	13 (13/0)	34.3 ± 10.8	N/A	TSH, FT4, FT3	Immunoassay techniques based on enhanced luminescence	Without a history of endocrinopathy. All subjects had basal TSH, FT4, and FT3 values within the normal range	Before testing, patients were medication-free for at least 2 weeks. No patient had received long-acting neuroleptics, electroconvulsive therapy, lithium salts, fluoxetine, or monoamine oxidase inhibitor antidepressants within 2 years of testing	NA	NA
				HC	13 (13/0)	33.2 ± 9.2							
Wu et al. 2020 [37]	China	Cross-sectional	ICD-10	BD-D	352 (129/123)	34.59 ± 15.57	N/A	TSH, T4, T3, FT4, FT3	NA	No description on thyroid function	First hospitalization. No description of history of treatment prior to hospitalization	NA	TSH: 0.27–4.20 mIU/L T4: 66-181 nmol/L T3: 1.3–3.1 nmol/L FT4: 12-22 pmol/L FT3: 3.1–6.8 pmol/L
				BD-M	476 (217/259)	32.70 ± 12.60							
Zhong et al. 2019 [39]	China	Cross-sectional	DSM-V	BD-D	57	26.74 ± 8.73	14.03 ± 2.83	TSH, T4, T3, FT4, FT3	Direct chemiluminescence method	Excluded of any history/current thyroid disease	Excluded treatment of thyroid disease, such as anti-thyroid drug therapy, and ^{131}I treatment. At the time of blood testing, all patients either had not been administered medication or were not medicated for at least 6 months	HDRS (27.10 ± 5.69)	TSH: 0.38–4.31mIU/L T4: 4.9–11.0 μg/dl T3: 0.79–1.58 ng/ml FT4: 0.82–1.63 ng/dl FT3: 2.10–3.80 pg/ml
				HC	20	28.32 ± 9.01	14.72 ± 2.76					NA	
Su et al. 2019 [27]	China	Case–control	DSM-V	BD-D	92 (42/50)	24.76 ± 12.75	NA	TSH, T4, T3, FT4, FT3	NA	No description of thyroid function	Unmedicated patients	NA	NA
				HC	89 (25/64)	47.34 ± 13.05							

Table 1 (continued)

Study	Location	Design type	Diagnostic criteria for BD	State	Number (Male/Female)	Average age(years)	Education(years)	Outcome indicators	THs measurement method	Thyroid function in BD	Treatments in BD	Rating scale (Mean ± SD)	Reference range of TH
Li et al. 2019 [20]	China	Case–control	DSM-V	BD-D BD-M	58 (31/27) 28 (15/13)	20.7 ± 6.7 29.5 ± 8.9	NA	TSH, T4, T3, FT4, FT3	NA	The thyroid profiles of all BD-mania were within the normal limits. In the BD-depression, the baseline TSH value of three patients was lower than the normal below limit, and for one patient it was higher than the normal upper limit	Drug-naïve or medication-free for at least 3 months before hospitalization	N3A	TSH: 0.38–4.34mu/L T4: 55.47–161.25 nmol/L T3: 1.02–2.96 nmol/L FT4: 10.45–24.38 pmol/L FT3: 2.77–6.31 pmol/L
Khaled et al. 2018 [17]	Egypt	Cross-sectional	DSM-IV	BD-M HC	30 (21/9) 15	23.6 ± 6.2 24.4 ± 6.5	NA	TSH, T4, T3	Chemiluminescent immunoassay	No description of thyroid function	Not receiving any psychiatric treatment	NA	NA
Jin et al. 2017 [35]	China	Cross-sectional	ICD-10	BD-D BD-M HC	71 (27/44) 62 (26/36) 203 (78/125)	25.62 ± 11.15 26.58 ± 13.12 25.13 ± 8.62	NA	TSH, T4, T3, FT4, FT3	Chemiluminescent immunoassay	Exclusion of endocrine diseases	Not receiving electroconvulsive therapy within one year; not receiving lithium treatment within 6 months	NA	NA
Su et al. 2016 [38]	China	Cross-sectional	ICD-10	BD-D BD-M	109 86	NA	NA	TSH, T4, T3, FT4, FT3	Enzyme-linked immunosorbent assay	Excluded severe somatic diseases and endocrine disorders affecting TH levels	No lithium taken in six months	NA	NA
Adam et al. 2014 [33]	Poland	Cross-sectional	ICD-10	BD-D BD-M	203 (57/146) 61 (25/36)	52.8 ± 18.4 45.3 ± 19.8	NA	TSH	Automatic analyzer Dirui CS-400	The overall rate of patients with BD-D who were above or below the normal range of TH levels was 12.2%, and 11.4% for BD-M patients	No information regarding patients treatment	NA	TSH: (1) 0.4–5.0 IIU/Ml (2) 0.3–3.0 IIU/mL (3) 0.4–2.5 IIU/mL

Table 1 (continued)

Study	Location	Design type	Diagnostic criteria for BD	State	Number (Male/Female)	Average age(years)	Education(years)	Outcome indicators	THs measurement method	Thyroid function in BD	Treatments in BD	Rating scale (Mean ± SD)	Reference range of TH
Li et al. 2003 [36]	China	Cross-sectional	CCMD-3	BD-D HC	25 (11/14) 30 (13/17)	33 ± 9 34 ± 10	NA	TSH, FT4, FT3	Enzyme-linked immunosorbent assay	Exclusion of endocrine diseases	No antipsychotics or antidepressants for at least 2 weeks at enrollment	NA	NA
Sokolov et al. 1994 [26]	Canada	Case–control	DSM-III	BD-M HC	13 (6/7) 13 (5/8)	17.3 ± 1.2 17.3 ± 1.6	NA	TSH, T4, T3, FT4	TSH-ImmunoEnzymatic Assay; T4, T3-Immunofluorescence; FT4-Radioimmunoassay	Thyroid indices within the normal laboratory reference range	Excluded those who had received any of the following medications within the month before admission: lithium carbonate, carbamazepine, valproic acid, any antidepressant, or the oral contraceptive pill; or if they had at any time received electroconvulsive therapy or thyroid hormone replacement	NA	NA
Souetre et al. 1988 [31]	France	Cross-sectional	DSM-III	BD-D HC	8 (2/6) 8	52.8 ± 7.4 N/A	NA	TSH	Radioimmunoassay	No description of thyroid function	The investigations took place after an initial 2-week period of drug withdrawal for the patients	HDRS (24.4 ± 3.8) HDRS (9.6 ± 4.9)	NA
Souetre et al. 1986 [32]	France	Cross-sectional	DSM-III	BD-D HC	8 13 (8/5)	53.3 ± 4.49 48.85 ± 6.91	NA	TSH	Radioimmunoassay	Euthyroid status	The investigations took place after an initial 2-week period of drug withdrawal (no patient was previously under Lithium therapy)	HDRS (22.89 ± 4.7) HDRS (5.7 ± 2.3)	NA

Table 1 (continued)

Study	Location	Design type	Diagnostic criteria for BD	State	Number (Male/Female)	Average age(years)	Education(years)	Outcome indicators	THs measurement method	Thyroid function in BD	Treatments in BD	Rating scale (Mean ± SD)	Reference range of TH
Linnoila et al. 1982 [34]	America	Cross-sectional	RDC-III	BD-D	9 (0/9)	38.3 ± 17.6	NA	T4, T3	Radioimmunoassay	Serum T4 and T3 concentrations were within the normal range of the National Institutes of Health Clinical Chemistry Laboratory	All patients had been free of treatment with lithium for a minimum of 8 weeks, and they had not received any psychotropic drugs for 2 weeks	NA	NA
				BD-M	7 (0/7)								
				HC	8 (0/8)	37.0 + 10.4							

ICD-10 International Classification of Diseases Diagnostic Criteria, Edition 10, *DSM-V* Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, *DSM-III* Diagnostic and Statistical Manual of Mental Disorders, Third Edition, *CCMD-3* Chinese Classification of Mental Disorders, Edition 3, *RDC-III* Research Diagnostic Criteria for a Selected Group of Functional Pqchoses, Edition 3, *BD* Bipolar disorder, *BD-D* Bipolar depression, *BD-M* Bipolar mania, *HC* Healthy control, *TH* Thyroid hormone, *TSH* Thyroid-stimulating hormone, *T4* Thyroxine, *T3* Triiodothyronine, *FT4* Free thyroxine, *FT3* Free triiodothyronine, *MADRS* Montgomery-Asberg Depression Rating Scale, *YMRS* Young Mania Rating Scale, *HDRS* Hamilton Depression Rating Scale, *N/A* Not available

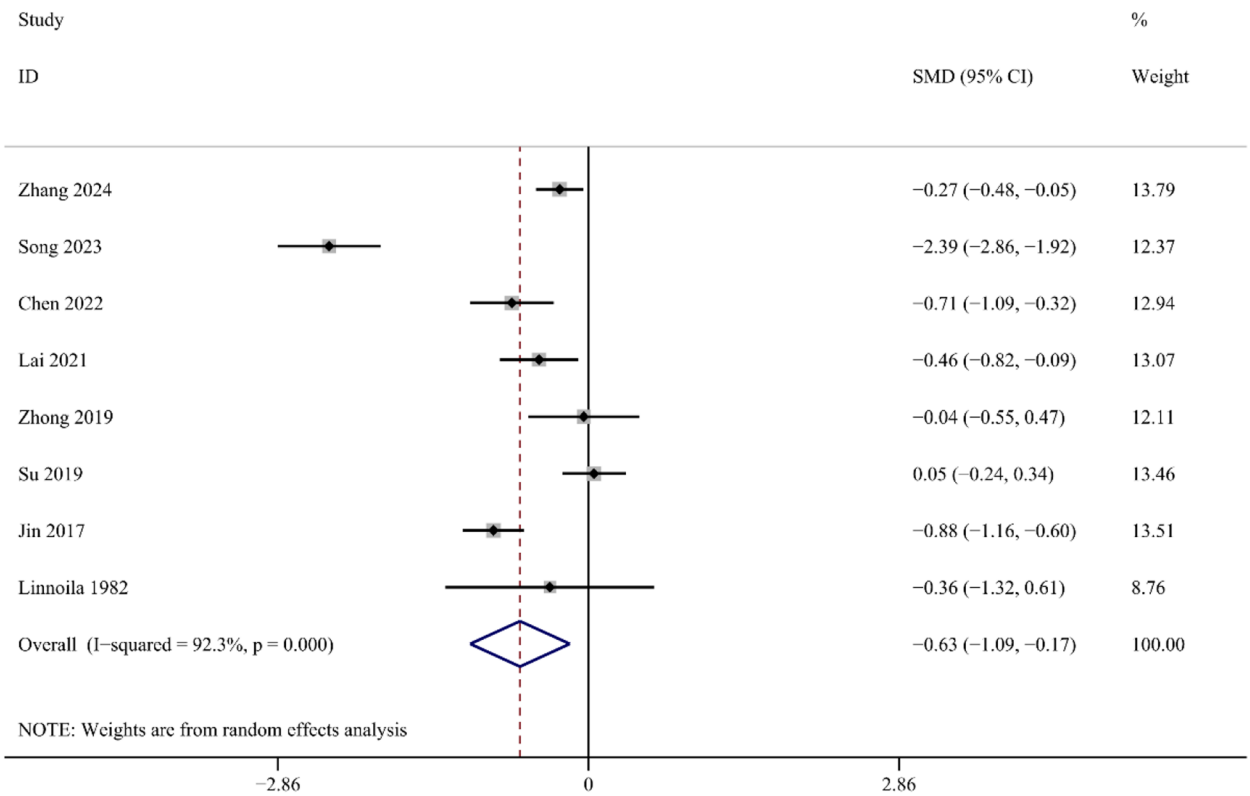

Fig. 2 Forest plot for comparing serum T3 levels in BD-D and HC (SMD: standard mean difference; CI: confidence interval)

all remained consistent with the original results ((SMD: -0.18, 95%CI: -0.48 to 0.11, $I^2=76.20\%$, $P=0.224$), (SMD: -0.58, 95%CI: -1.03 to -0.12, $I^2=89.60\%$, $P=0.014$), (SMD: -0.80, 95%CI: -1.44 to -0.15, $I^2=94.50\%$, $P=0.015$), (SMD: 0.01, 95%CI: -0.30 to 0.31, $I^2=77.90\%$, $P=0.969$), (SMD: -0.47, 95%CI: -0.82 to -0.12, $I^2=83.00\%$, $P=0.009$), respectively) (Table 3).

Comparison of TH levels between BD-M and HC

A total of 8 studies [17, 18, 25, 26, 28, 34, 35, 38] compared TH levels between BD-M and HC. The pooled result of 7 studies showed no significant differences in serum TSH levels between BD-M and HC (SMD: -0.03, 95%CI: -0.48 to 0.41, $I^2=89.90\%$, $P=0.878$). A total of 7 studies comparing serum T4 and T3 levels, the pooled results displayed that T4 and T3 levels had no significant differences between BD-M and HC ((SMD: -0.34, 95%CI: -0.91 to 0.24, $I^2=92.60\%$, $P=0.252$), (SMD: -0.51, 95%CI: -1.12 to 0.09, $I^2=93.30\%$, $P=0.096$), respectively). Six studies showed serum FT4 levels, no significant difference was observed in FT4 levels between BD-M and HC (SMD: 0.23, 95%CI: -0.08 to 0.55, $I^2=77.90\%$, $P=0.144$). The pooled results of 5 studies displayed showed no significant differences in serum FT3 levels between BD-M and HC (SMD: 0.04, 95%CI: -0.09 to 0.18, $I^2=0.00\%$, $P=0.537$) (Table 2).

For sensitivity analysis in the group of euthyroidism, the pooled results of TSH, T4, FT4, and FT3 levels were consistent with the original results ((SMD: 0.05, 95%CI: -0.40 to 0.49, $I^2=88.20\%$, $P=0.839$), (SMD: -0.10, 95%CI: -0.64 to 0.43, $I^2=91.70\%$, $P=0.708$), (SMD: 0.21, 95%CI: -0.15 to 0.58, $I^2=81.90\%$, $P=0.255$), (SMD: 0.02, 95%CI: -0.12 to 0.16, $I^2=0.00\%$, $P=0.779$), respectively); however, T3 levels decreased significantly in BD-M compared to HC (SMD: -0.74, 95%CI: -1.47 to -0.01, $I^2=95.30\%$, $P=0.048$) (Table 3).

Comparison of TH levels between BD-M and BD-D

A total of 9 studies [18–20, 25, 33–35, 37, 38] compared TH levels between BD-M and BD-D. The pooled result of 8 studies showed no significant differences in serum TSH levels between BD-M and BD-D (SMD: 0.06, 95%CI: -0.12 to 0.23, $I^2=73.00\%$, $P=0.514$). A total of 8 studies comparing serum T4 and T3 levels, the pooled results displayed that T4 and T3 levels demonstrated a significant elevation in BD-M compared to BD-D ((SMD: 0.67, 95%CI: 0.08 to 1.26, $I^2=97.20\%$, $P=0.026$), (SMD: 0.87, 95%CI: 0.24 to 1.49, $I^2=97.50\%$, $P=0.007$, Fig. 3), respectively). Seven studies showed serum FT4 and

Table 2 Presentation of outcome indicators in all subjects

Outcome indicators	BD-D and HC					BD-M and HC					BD-M and BD-D				
	N	SMD	95%CI	I^2 (%)	*P*-value	N	SMD	95%CI	I^2 (%)	*P*-value	N	SMD	95%CI	I^2 (%)	*P*-value
TSH	11	-0.20	(-0.44 to 0.03)	72.10	0.089	7	-0.03	(-0.48 to 0.41)	89.90	0.878	8	0.06	(-0.12 to 0.23)	73.00	0.514
T4	8	-0.44	(-0.79 to -0.08)	87.50	0.017	7	-0.34	(-0.91 to 0.24)	92.60	0.252	8	0.67	(0.08 to 1.26)	97.20	0.026
T3	8	-0.63	(-1.09 to -0.17)	92.30	0.007	7	-0.51	(-1.12 to 0.09)	93.30	0.096	8	0.87	(0.24 to 1.49)	97.50	0.007
FT4	9	0.12	(-0.16 to 0.40)	81.80	0.403	6	0.23	(-0.08 to 0.55)	77.90	0.144	7	0.48	(-0.06 to 1.03)	96.90	0.083
FT3	9	-0.42	(-0.83 to -0.00)	91.20	0.049	5	0.04	(-0.09 to 0.18)	0.00	0.537	7	0.27	(0.13 to 0.42)	54.70	0.000

BD-D Bipolar depression, *BD-M* Bipolar mania, *HC* Healthy control, *TSH* Thyroid-stimulating hormone, *T4* Thyroxine, *T3* Triiodothyronine, *FT4* Free thyroxine, *FT3* Free triiodothyronine, *N* Number, *SMD* Standard mean difference, *CI* Confidence interval

Table 3 Presentation of outcome indicators in the group of euthyroidism in sensitivity analysis

Outcome indicators	BD-D and HC					BD-M and HC					BD-M and BD-D				
	N	SMD	95%CI	I^2 (%)	*P*-value	N	SMD	95%CI	I^2 (%)	*P*-value	N	SMD	95%CI	I^2 (%)	*P*-value
TSH	8	-0.18	(-0.48 to 0.11)	76.20	0.224	5	0.05	(-0.40 to 0.49)	88.20	0.839	5	0.04	(-0.20 to 0.28)	75.10	0.739
T4	5	-0.58	(-1.03 to -0.12)	89.60	0.014	5	-0.10	(-0.64 to 0.43)	91.70	0.708	5	0.94	(0.03 to 1.86)	98.00	0.043
T3	5	-0.80	(-1.44 to -0.15)	94.50	0.015	5	-0.74	(-1.47 to -0.01)	95.30	0.048	5	1.36	(0.33 to 2.40)	98.40	0.010
FT4	7	0.01	(-0.30 to 0.31)	77.90	0.969	5	0.21	(-0.15 to 0.58)	81.90	0.255	5	0.73	(-0.08 to 1.55)	97.60	0.078
FT3	7	-0.47	(-0.82 to -0.12)	83.00	0.009	4	0.02	(-0.12 to 0.16)	0.00	0.779	5	0.37	(0.26 to 0.49)	0.00	0.000

BD-D Bipolar depression, *BD-M* Bipolar mania, *HC* Healthy control, *TSH* Thyroid-stimulating hormone, *T4* Thyroxine, *T3* Triiodothyronine, *FT4* Free thyroxine, *FT3* Free triiodothyronine, *N* Number, *SMD* Standard mean difference, *CI* Confidence interval

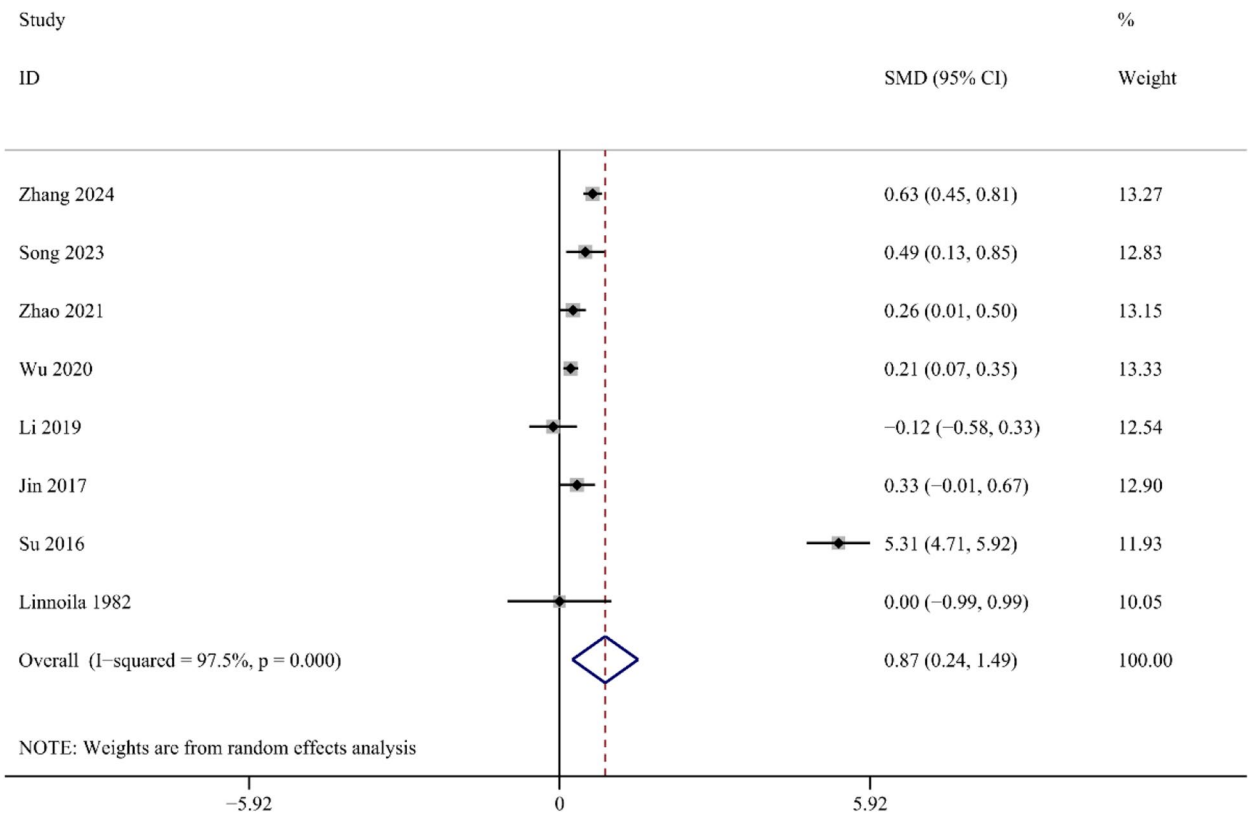

Fig. 3 Forest plot for comparing serum T3 levels in BD-M and BD-D (SMD: standard mean difference; CI: confidence interval)

FT3 levels, no significant difference was observed in FT4 levels (SMD: 0.48, 95%CI: -0.06 to 1.03, $I^2=96.90\%$, $P=0.083$), however, FT3 levels had significant elevation in BD-M compared to BD-D (SMD: 0.27, 95%CI: 0.13 to 0.42, $I^2=54.70\%$, $P=0.000$, Fig. 4) (Table 2).

For sensitivity analysis in the group of euthyroidism, the pooled results of TSH, T4, T3, FT4, and FT3 levels were consistent with the original results ((SMD: 0.04, 95%CI: -0.20 to 0.28, $I^2=75.10\%$, $P=0.739$), (SMD: 0.94, 95%CI: 0.03 to 1.86, $I^2=98.00\%$, $P=0.043$), (SMD: 1.36, 95%CI: 0.33 to 2.40, $I^2=98.40\%$, $P=0.010$), (SMD: 0.73, 95%CI: -0.08 to 1.55, $I^2=97.60\%$, $P=0.078$), (SMD: 0.37, 95%CI: 0.26 to 0.49, $I^2=0.00\%$, $P=0.000$), respectively) (Table 3).

Subgroup analysis

Subgroup analyses were based on treatment, gender, and location. There were significant differences in TSH and FT4 levels in the subgroup of treatment. T4, T3, and FT3 levels had significant intergroup differences in the subgroups of treatment, gender, and location (Table S5).

Sensitivity analysis and publication *bias*

The results of the sensitivity analysis are shown in Fig. S1. As demonstrated in Table 4, after omitting unstable studies in the sensitivity analysis, the following results have not changed, indicating relative stability: TSH levels showed no significant differences and FT3 levels showed a decrease significantly in BD-D compared with HC ((SMD: -0.16, 95%CI: -0.38 to 0.07, $I^2=44.00\%$, $P=0.172$), (SMD: -0.77, 95%CI: -1.12 to -0.42, $I^2=83.90\%$, $P=0.000$), respectively); but the following results have changed, indicating instability: (1) T4 levels had no significant differences between BD-D and HC (SMD: -0.06, 95%CI: -0.32 to 0.20, $I^2=44.40\%$, $P=0.649$); (2) T3 levels showed decreased significantly and FT4 levels showed elevated significantly in BD-M than in HC ((SMD: -0.91, 95%CI: -1.49 to -0.32, $I^2=86.20\%$, $P=0.002$), (SMD: 0.37, 95%CI: 0.14 to 0.60, $I^2=40.00\%$, $P=0.002$), respectively); (3) T4 levels showed no significant differences between BD-M and BD-D (SMD: 0.16, 95%CI: -0.12 to 0.43, $I^2=77.60\%$, $P=0.267$); sensitivity analyses indicated that the re-pooled results above after removing unstable studies were relatively robust (Fig. S2). Both the funnel plot (Fig. S3) and Egger's test (Table S2) showed that all results were free of publication bias.

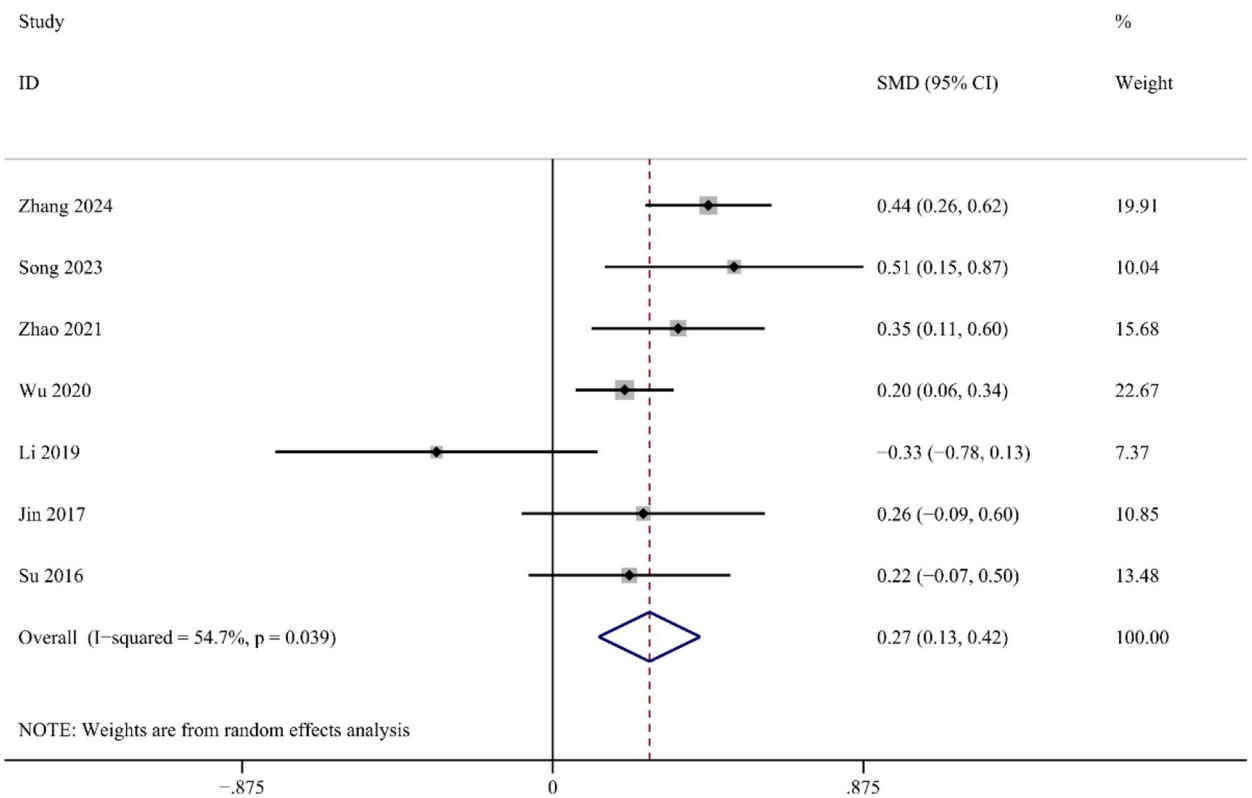

Fig. 4 Forest plot for comparing serum FT3 levels in BD-M and BD-D (SMD: standard mean difference; CI: confidence interval)

Table 4 Presentation of outcome indicators after omitting unstable studies in the sensitivity analysis

	Outcome indicators	Number of studies omitted	The pooled results after omitting unstable studies				
			N	SMD	95%CI	I^2 (%)	*P*-value
BD-D and HC	TSH	3	8	-0.16	(-0.38 to 0.07)	44.00	0.172
	T4	3	5	-0.06	(-0.32 to 0.20)	44.40	0.649
	FT3	3	6	-0.77	(-1.12 to -0.42)	83.90	0.000
BD-M and HC	T3	2	5	-0.91	(-1.49 to -0.32)	86.20	0.002
	FT4	1	5	0.37	(0.14 to 0.60)	40.00	0.002
BD-M and BD-D	T4	2	6	0.16	(-0.12 to 0.43)	77.60	0.267

BD-D Bipolar depression, *BD-M* Bipolar mania, *HC* Healthy control, *TSH* Thyroid-stimulating hormone, *T4* Thyroxine, *T3* Triiodothyronine, *FT4* Free thyroxine, *FT3* Free triiodothyronine, *N* Number, *SMD* Standard mean difference, *CI* Confidence interval

Discussion

In this meta-analysis, we systematically compared blood TH levels between BD-D or BD-M and HC as well as between BD-M and BD-D, then the following relatively robust results were obtained: serum T3 and FT3 levels decreased significantly in BD-D compared to HC; serum T3 levels decreased significantly and serum FT4 levels increased significantly in BD-M compared to HC; serum T3 and FT3 levels were significantly higher in BD-M than in BD-D; there were no significant differences in other TH levels. Overall, the results of the present study deepened the understanding of the relationship between BD and thyroid function, which may be helpful in the diagnosis and treatment of BD in clinical practice.

In this study, serum T3 levels were significantly decreased in both BD-D and BD-M compared to HC, which was coherent with those of Song et al. [18]. It is a fact that significant cognitive impairment exists in BD [41]. The thyroid gland is stimulated by TSH to secrete TH, of which 93% are T4 and 7% are T3, and inactive T4 is converted to active T3 by types I, II iodothyronine deiodinase (D1, D2) [42, 43]. T3 is essential for the development and differentiation of neurons and neuroglia [44, 45]. T3 in the brain comes from a dual source of T4 in the circulation (D1) and astrocytes (D2), which functions by acting on thyroid receptors (TR) [46, 47]. TR is abundant in the hippocampus [48, 49]. T3 induces hippocampal neurogenesis by affecting Type 2b and Type 3 progenitors in the dentate gyrus [49–51]. It is well-established that hippocampal neurogenesis and cognitive function have an association [52]. Additionally, the lack of T3 decreases the growth rate of the hippocampus and the number of granule cells in the dentate gyrus [53, 54]. Of note, a reduction in hippocampal volume is a hallmark of BD [55]. Furthermore, T3 is sufficient to activate TR-specific gene pathways in the amygdala, and infusion of T3 into the amygdala is sufficient to rescue cognitive deficits in a mouse model of systemic hypothyroidism [56]. In brief, T3 levels in BD patients may be related to their cognitive function. Besides, we found that serum FT3 levels were significantly decreased in BD-D compared to HC, which was consistent with other studies [12, 18, 25, 40]. It has been found that T3 levels were negatively correlated with the Hamilton Depression Rating Scale (HAMD) in BD-D and the Young Mania Rating Scale (YMRS) in BD-M [18, 40]. However, the results of Zhang et al. [25] showed a positive correlation between FT3 levels and the Montgomery and Asberg Depression Rating Scale (MADRS) in BD-D. Moreover, depressive episodes are the most typical clinical feature of BD patients, leading to a high rate of misdiagnosis of BD due to its high similarity to unipolar depression [3]. Su et al. [27] noted that serum T3 and FT3 levels may represent biological differences between unipolar and bipolar depression. Therefore, measuring serum T3 or FT3 levels in BD may be beneficial in diagnosis as well as prediction and prevention of serious consequences in future disease processes.

Similar to the findings of previous studies, we found that serum T3 and FT3 levels were significantly higher in BD-M than in BD-D [18, 19]. It has been reported that the mechanism by which BD fluctuates between polar and opposing emotional states has a hypothesis of the adrenergic-cholinergic, with depressive episodes based on increased cholinergic function and manic episodes based on increased catecholamine activity [57]. T3 is an aromatic amino acid analog of tyrosine that undergoes decarboxylation to form biogenic amine neurotransmitters such as dopamine (DA), norepinephrine (NE), and serotonin (5-HT), and so T3 is regarded as a precursor of catecholamine-like amines [58, 59]. Moreover, T3 has neurotransmitter-and/or neuromodulator-like effects in the adrenergic system of the brain [59]. Indeed, the pathophysiologic changes in depression are associated with 5-HT deficiency [60]. It is known that there is a link between 5-HT levels and circulating T3 levels, and that depressive-like behavior

in hypothyroid rats is strongly associated with reduced 5-HT levels [61–63]. Besides, previous studies have shown that depression can cause overactivation of the hypothalamic–pituitary–adrenal (HPA) axis and then increase cortisol levels, which in turn may reduce TH conversion in peripheral tissues by inhibiting deiodinase activity, leading to decreased T3 levels [30, 64, 65]. Khaled et al. [17] showed that cortisol levels reduced and 5-HT levels increased in BD-M. The excellent efficacy of T3 as an adjunctive treatment for BD-D has been reported, and the mechanism may be through the modulation of neurogenesis by affecting 5-HT and DA [66]. There was also evidence of a transition to manic symptoms in drug-resistant BD-D after adjuvant therapy with T3, which was speculated to be a TH-catecholamine receptor interaction [67]. Taken together, BD mood fluctuation may be associated with serum T3 and FT3 levels. Therefore, it is necessary to consider differences in TH levels in BD patients with different emotional states in clinical practice.

After omitting unstable studies of Zhang et al. [25] in the sensitivity analysis, serum FT4 levels displayed a significant increase in BD-M than in HC. At present, BD is mainly treated with drugs. It is known that psychotropic drugs affect the function of the HPT axis [68, 69]. Especially for lithium, has proven to be the treatment of choice for BD, but its effect on thyroid function is explicit [7, 70]. However, the treatment condition of BD patients was not shown in the study by Zhang et al. [25], which may be a reason for its instability. It is known that TH has a profound effect on mood and behavior. Elevated peripheral FT4 levels may be associated with symptoms specific to manic episodes in BD, such as elevated mood and increased activity [71]. A study by Li et al. [72] found that serum FT4 levels were a risk factor for the core features of BD-M (physical violence). Additionally, it was reported that FT4 levels were positively correlated with YMRS in BD-M patients [25]. Therefore, FT4 levels may correlate with disease severity during manic episodes in BD. Our results were similar to those of Han et al. [28]. Notely, Han et al. [28] indicated that there may be gender differences in the neuroendocrine regulation of BD-M, with elevated FT4 levels restricted to males, and that the specific changes in TH levels in females need to be explained by thyroid compensatory mechanisms. Classical neuroendocrine feedback theory suggests that physiologic feedback systems are regulated primarily by negative feedback and self-protection. BD-M has been reported to alleviate symptoms by lowering TH levels through self-regulatory mechanisms and stimulating regulation of the pituitary axis through a negative feedback mechanism, a process that increases TSH secretion as well as the sensitivity of the anterior pituitary gland [73–75]. Besides, Özerdem et al. [74] emphasized that female BD patients were more likely to have elevated TSH levels. However, due to the limitations of the included studies, further analysis by gender was not conducted in this study. Furthermore, several studies have reported that low TSH levels may be possibly associated with cognitive impairment in BD-D patients [12, 39, 40]. But, our study did not find significant changes in TSH levels in BD patients. Currently, studies on BD and thyroid-related studies focus on the therapeutic aspects, such as exploring the benefits of TH therapy for BD or exploring the effects of antipsychotics on thyroid function in BD patients, whereas there are a limited number of studies exploring the changes in TH levels in BD patients alone. Therefore, more future studies are necessary to explore TH levels in BD patients and then better testify to the potential value of TH for the diagnosis and treatment of BD.

The strengths of this meta-analysis were that it provided the most comprehensive and up-to-date assessment of blood TH levels in BD patients by rigorously quantifying and analyzing inconsistent results, leading to more persuasive conclusions. Additionally, we only included those studies that demonstrated all included patients were euthyroid sound for sensitivity analysis, which added to the reliability of our findings. Nonetheless, there were several limitations. Firstly, due to the cross-sectional nature of the included studies, the causal relationship between BD patients and TH levels cannot be well illustrated. Secondly, the small number of studies included may affect the robustness of the pooled results. Thirdly, the pooled results demonstrated high heterogeneity, which may be related to different subject characteristics such as age and gender. Fourthly, the generalizability of the results may be limited by the fact that the experimental study sites were mainly in China. For the above reasons, the results of this study need to be interpreted with caution. Thus, more relevant studies to verify the feasibility of our results are necessary.

The present study did have several questions that were not addressed owing to deficiencies in the design type, number, subject population, and location of included studies. Given these shortcomings, more large prospective cohort studies and clinical trials are needed to provide reference values for specific TH as circulating biomarkers for BD, encompassing specific age groups, different genders, and more ethnically diverse BD patients, respectively.

Conclusion

In conclusion, serum T3 and FT3 levels decreased significantly in BD-D compared to HC. Serum T3 levels decreased significantly and serum FT4 levels increased

significantly in BD-M compared to HC. Serum T3 and FT3 levels increased significantly in BD-M than in BD-D. Whether changes in TH levels occur after or before BD pathology needs to be assessed by longitudinal studies. TH levels in BD patients with different emotional states need to be considered in clinical management. Certainly, the clinical applicability of TH therapy for BD remains to be validated by additional large multicenter trials.

Abbreviations

BD	Bipolar disorder
BD-D	Bipolar depression
BD-M	Bipolar mania
HC	Healthy control
WHO	World Health Organization
WMH	World Mental Health
HPT	Hypothalamic-pituitary-thyroid
HPA	Hypothalamic–pituitary–adrenal
TD	Thyroid dysfunction
TH	Thyroid hormone
TSH	Thyroid-stimulating hormone
T4	Thyroxine
T3	Triiodothyronine
FT4	Free thyroxine
FT3	Free triiodothyronine
TR	Thyroid receptor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NOS	Newcastle Ottawa Scale
AHRQ	Agency for Healthcare Research and Quality Scale
SD	Standard deviation
SMD	Standardized mean difference
CI	Confidence interval
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD-10	International Classification of Diseases Diagnostic Criteria, Edition 10
CCMD-3	Chinese Classification of Mental Disorders, Edition 3
RDC-III	Research Diagnostic Criteria for a Selected Group of Functional Pqchoses, Edition 3
ECLIA	Electrochemiluminescence immunoassay
CLIA	Chemiluminescence immunoassay
RIA	Radioimmunoassay
ELISA	Enzyme-linked immunosorbent assay
D1	Types I iodothyronine deiodinase
D2	Types II iodothyronine deiodinase
YMRS	Young Mania Rating Scale
HAMD	Hamilton Depression Rating Scale
MADRS	Montgomery and Asberg Depression Rating Scale
CNS	Central nervous system
DA	Dopamine
NE	Norepinephrine
5-HT	Serotonin

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01776-1.

Supplementary Material 1.

Acknowledgements
We are grateful for the contributions of the researchers and study participants, and the grant from the National Natural Science Foundation of China (No.82060152).

Clinical trial number
Not applicable.

Authors' contributions
All authors were involved in the conception and design of the study. SL, XC and XL completed the data preparation, data extraction and data analysis. SL wrote the first draft. The draft was reviewed and revised by LT and XC. All authors read and finalized the final version of the manuscript.

Funding
This work was supported by a grant from the National Natural Science Foundation of China (No.82060152).

Data availability
All available data analyzed in this study are included in the manuscript and its supplementary materials.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 6 September 2023 Accepted: 4 November 2024
Published online: 18 November 2024

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