

Systematic Review

# Dysregulation of Thyroid, Growth, and Appetite Hormones in Children and Adolescents With Neurodevelopmental Disorders: A Meta-analysis

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## Abstract

**Background:** Neurodevelopmental disorders [NDDs, including attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and tic disorder] usually arise during childhood or adolescence, but impact quality of life throughout the whole life cycle. Therefore, early diagnosis of NDDs is necessary; however, its etiology remains unclear. This study aimed to evaluate levels of thyroid, growth, and appetite hormones between children and adolescents with NDDs and healthy controls (HCs) by a meta-analysis of all evidence that demonstrated the importance of these indicators, but yielded controversial results. **Methods:** Five online databases were searched to retrieve relevant articles published before March 1, 2025. Mean and standard deviation data were collected and pooled using Stata 15.0 software to generate standardized mean difference (SMD) with 95% confidence intervals (CIs) as the effect size (ES) measure. **Results:** Fifty-four studies were included. The overall meta-analysis, subgroup, and trim-and-fill adjusting revealed that compared with HCs, levels of thyroid hormone free triiodothyronine (FT3) (SMD = 0.22; 95% CI = 0.04 to 0.40;  $p_{ES} = 0.015$ ), total triiodothyronine (TT3) (SMD = 0.82; 95% CI = 0.36 to 1.28;  $p_{ES} < 0.001$ ), and thyroid peroxidase antibody (TPO-Ab) (SMD = 0.37; 95% CI = 0.08 to 0.67;  $p_{ES} = 0.014$ ) were significantly increased, while free thyroxine (FT4) (SMD = -0.67; 95% CI = -0.69 to -0.64;  $p_{ES} < 0.001$ ), total thyroxine (TT4) (SMD = -0.35; 95% CI = -0.50 to -0.20;  $p_{ES} < 0.001$ ), and thyroid stimulating hormone (TSH) (SMD = -0.22; 95% CI = -0.41 to -0.03;  $p_{ES} = 0.026$ ) were significantly decreased in children and adolescents with NDDs. These changes were mainly observed in ADHD patients, with TPO-Ab increased only in ASD patients. Levels of the appetite hormone leptin were significantly elevated in male NDDs (SMD = 0.74; 95% CI = 0.10 to 1.38;  $p_{ES} = 0.023$ ) and ASD patients (SMD = 0.46; 95% CI = 0.17 to 0.74;  $p_{ES} = 0.002$ ) relative to HCs, but not in ADHD cases. Growth factor IGF-1 (insulin-like growth factor-1) was only significantly lower in the cerebrospinal fluids of ASD patients when compared with HCs (SMD = -0.89; 95% CI = -1.42 to -0.36;  $p_{ES} = 0.001$ ). **Conclusions:** Thyroid hormones and IGF-1/leptin may respectively represent promising biomarkers for predicting ADHD and ASD in children and adolescents.

**Keywords:** neurodevelopmental disorders; thyroid hormones; insulin-like growth factor I; appetite regulation; inflammation; meta-analysis

## 1. Introduction

Neurodevelopmental disorders (NDDs) represent a group of complex and heterogeneous conditions that manifest as impairments in cognition, communication, behavior and motor skills due to abnormal neural development [1]. Common NDDs usually have their initial-onset during childhood and adolescence, with an estimated global prevalence rate of 2–5.7% for attention deficit hyperactivity disorder (ADHD), 0.4–4.4% for autism spectrum disorder (ASD) and 0.3–0.8% for tic disorder (TD) [2,3]. Children and adolescents with these disorders are at increased risk for poor long-term outcomes, including lower levels of educational attainment, employment status and high rates of substance abuse, delinquency and psychiatric comorbidity (e.g., anxiety and depression), which not only significantly affect their quality of life, but also impose a tremendous stress on families and society [4,5]. This highlights the urgent need for early diagnosis and interventions, in chil-

dren and adolescents with NDDs, to prevent serious consequences.

Although the etiology of NDDs is considered to be multifactorial, existing evidence suggests thyroid dysfunction as a probable trigger [6]. There have been meta-analyses that demonstrate a significant association exists between maternal thyroid dysfunction and NDDs in children [6,7]. Pooling of 29 articles by Ge *et al.* [6] showed the risk of ADHD in offspring was increased in mothers with thyroid hormones outside the normal range during pregnancy, including hyperthyroidism [odds ratio (OR) = 1.18; 95% confidence interval (CI) = 1.04 to 1.34] or hypothyroidism (OR = 1.14; 95% CI = 1.03 to 1.26). Maternal hypothyroidism (OR = 1.41; 95% CI = 1.05 to 1.90) [6] or autoimmune thyroid diseases (OR = 1.28; 95% CI = 1.14 to 1.44) [7] was also found to elevate the prevalence ratio of ASD in children through integration of 29 [6] or 6 [7] studies, respectively. Additionally, mice overexpress-



ing thyroid hormone-responsive protein or lacking thyroid hormone receptors (THRB or THRA) typically manifested with ADHD [8–10]. An animal model of hypothyroidism by treatment with propylthiouracil exhibited developmental cerebellar defects and autism-like behaviors [11,12]. All these observations imply thyroid function status-related parameters in children and adolescents [such as free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4), thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPO-Ab) or thyroglobulin antibody (TG-Ab)] may represent potential biomarkers for predicting the development of NDDs. This hypothesis has been supported by some studies: Meng *et al.* [13] found FT3 was significantly increased, while FT4 was significantly decreased in children with ADHD, ASD and TD compared to healthy controls (HCs). Furthermore, both TT3 and TT4 were significantly lower in children with ADHD/TD than those in HCs, while TG-Ab was significantly reduced in children with TD/ASD relative to HCs. A receiver operating characteristic (ROC) curve analysis demonstrated FT4 was of high clinical value in the diagnosis of children with NDDs, with an area under the curve (AUC) of 0.76 [13]. Singh *et al.* [14] found the TSH level was 30% lower in male children with ASD than that in typically developing boys. The diagnostic accuracy and AUC for ASD based upon TSH levels was 76% and 0.674, respectively [14]. However, controversial results were also reported, including significantly higher levels of TSH and lower levels of FT4 in children with ASD [15,16] and no statistical differences in TSH and TT4 between ADHD/ASD cases and HCs [17,18]. Therefore, the relationship between thyroid hormones and NDDs in children and adolescents still requires further evaluation.

It furthermore has been reported that overweight and obesity are more prevalent among children and adolescents with NDDs [19]. Patients with hypothyroidism are often obese [20], which on one hand may be a consequence of lowered energy expenditure due to a decrease in the basal metabolic rate [21] or on the other hand associated with uncontrolled food intake due to disruptions in growth [insulin, insulin-like growth factor-1 (IGF-1) or IGF-binding protein 3 (IGFBP-3)] [22] and appetite (leptin, ghrelin or adiponectin) [23] hormone signaling pathways, ultimately facilitating weight gain. Thus, growth and appetite hormone-related parameters may serve as underlying diagnostic biomarkers for NDDs. Unfortunately, there were also conflicting findings in these indicators among different studies, including reduced [17,24,25], increased [26,27] and non-significance [28,29] of the various possible.

To further elucidate the link between the development of NDDs and levels of thyroid, growth and appetite hormones in children and adolescents, a meta-analysis that integrated all relevant evidence was conducted here. The sample size and statistical power can be increased through

pooling of data from multiple individual studies, which may thus provide more convincing conclusions.

## 2. Materials and Methods

### 2.1 Search Strategy

This analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (**Supplementary material PRISMA\_2020\_checklist**) [30]. Electronic databases of PubMed, EMBASE, Cochrane Library, the China National Knowledge Infrastructure (CNKI, Chinese) and Wanfang (Chinese) were searched for relevant studies published before March 1, 2025. The search keywords included: (“thyroid function” OR “thyroid hormones” OR “thyroid-stimulating hormone” OR “free triiodothyronine” OR “free thyroxine” OR “TSH” OR “FT3” OR “FT4” OR “iodine” OR “thyroid peroxidase antibody” OR “Anti-TPO” OR “TPO-Ab” OR “thyroglobulin antibody” OR “TG-Ab” OR “hypothyroidism” OR “hyperthyroidism” OR “insulin” OR “insulin-like growth factor” OR “IGF-1” OR “IGFBP-3” OR “leptin” OR “ghrelin” OR “adiponectin”) AND (“children” OR “child” OR “childhood” OR “adolescents” OR “pediatric”) AND (“attention deficit hyperactivity disorder” OR “autism” OR “Tourette syndrome” OR “tic disorder” OR “neurobehavioral disorders”). The language or publication status was not restricted and the reference lists of included studies and reviews were reviewed to retrieve additional literature.

### 2.2 Selection Criteria

Studies were included if they met the following criteria: (1) Detected levels of thyroid (FT3, FT4, TT3, TT4, TSH, TPO-Ab or TG-Ab), growth (IGF-1 or IGFBP-3) and appetite (leptin, ghrelin or adiponectin) hormones in children (<14 years) and adolescents (<19 years); (2) Compared the differences in these indicators between NDD cases (including ADHD, ASD and TD) and HCs; (3) NDD cases belonged to first-diagnosis, drug-naïve or NDD medications stopped before detection; (4) Collected samples of bodily fluids [e.g., blood, urine or cerebrospinal fluid (CSF)]; and (5) Provided the mean and standard deviation (SD).

Exclusion criteria included: (1) Duplicates; (2) Non-original articles (e.g., case reports, reviews, meta-analysis or conference abstract); (3) Articles or data not peer-reviewed (online preprints or results of clinical trial registries); (4) Cell, animal, neonatal or adult studies; (5) Lack of HCs; (6) Cases with ongoing pharmacotherapy; (7) Tissue samples analyzed; (8) Full-text or data unavailability; and (9) Other irrelevant topics.

### 2.3 Data Extraction

A standardized Microsoft Excel (version 2019; Microsoft Corporation, Redmond, WA, USA) spreadsheet was

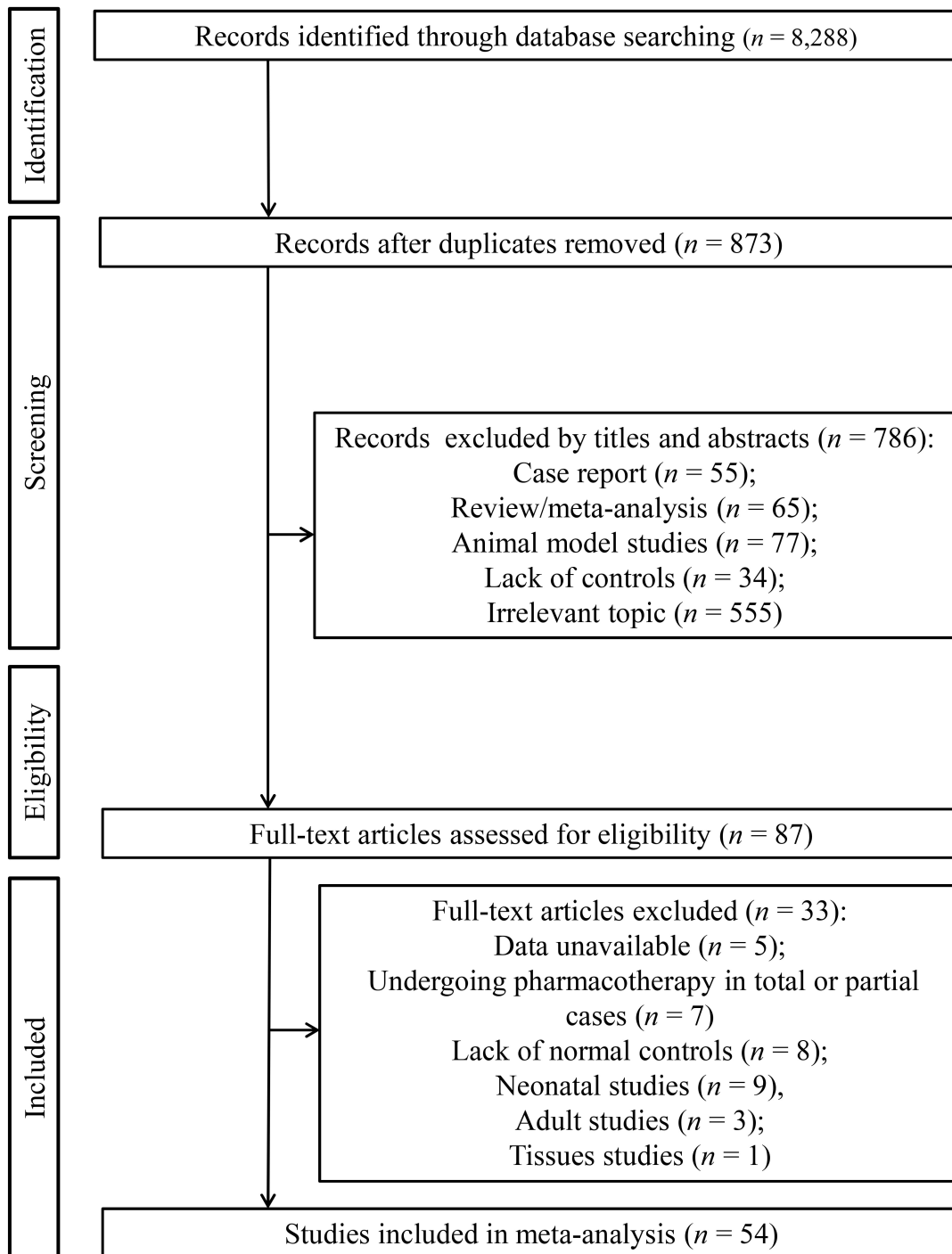


Fig. 1. Flow chart showing the process of study selection.

used to extract data from each study, which included the first author, publication year, country, study design, disease type, diagnosis criteria, number of cases and HCs, their sex, age, sample source and test levels for each indicator. The data in tables and texts were directly retrieved, while those in figures were estimated by using the Get-Data Graph digitizer software (version 2.26; getdata-graph-digitizer, Moscow, Russia; <https://getdata-graph-digitizer.software.informer.com/>). The quality of included stud-

ies was assessed using the Newcastle-Ottawa Scale (NOS) [31], with the scores ranging from 0 to 9 and studies of higher methodological quality were defined as NOS scores >6. Two reviewers independently extracted these data and the discrepancies were resolved through discussion until a consensus was reached.

## 2.4 Statistical Analysis

Stata software (v15.0; Stata Corporation, College Station, TX, USA) was used to perform the meta-analysis. All continuous outcomes were expressed as the standardized mean difference (SMD) with 95% CI to represent the pooled effect size (ES). A  $p_{ES}$ -value  $< 0.05$  determined by Z-test was regarded statistically significant. Cochrane's Q test and  $I^2$  statistics were used to assess the heterogeneity (H) between studies. The  $p_H$ -value  $< 0.1$  and  $I^2 > 50\%$  indicated the presence of a heterogeneity across studies and thus, a random-effect model was adopted to calculate the composite results; otherwise, a fixed-effect model was utilized. Subgroup analysis stratified by disease type, sex, age, weight, study design and sample source, was conducted to explore the sources of heterogeneity. A sensitivity analysis was conducted using the leave-one-out method to examine the robustness of pooled analyses. Publication bias (PB) was evaluated by Egger's linear regression test. The trim-and-fill method was employed to adjust the pooled ES if PB was detected ( $p_{PB}$ -value  $< 0.05$ ).

## 3. Results

### 3.1 Literature Search

The initial search of electronic databases yielded 8288 records. A total of 7415 studies were duplicate papers and removed. The remaining 873 non-duplicate studies were screened based on title and abstract. Of them, 786 did not meet the inclusion criteria because they were reviews/meta-analyses ( $n = 65$ ), case reports ( $n = 55$ ), animal model studies ( $n = 77$ ), lack of HCs ( $n = 34$ ) and irrelevant topic ( $n = 555$ ). The full-text of 87 studies was downloaded and read, after which 33 were excluded because of data unavailability ( $n = 5$ ), undergoing pharmacotherapy in all or a part of cases ( $n = 7$ ), lack of HCs ( $n = 8$ ), neonatal ( $n = 9$ ), adult studies ( $n = 3$ ) or tissue sample studies ( $n = 1$ ). Finally, 54 eligible studies (**Supplementary File 1**) were selected for this meta-analysis (Fig. 1).

### 3.2 Study Characteristics

The detailed characteristics of included studies are summarized in Table 1 and **Supplementary Table 1**. These studies were published from 1994 to 2025. Patients and HCs were enrolled from 16 countries, including China ( $n = 13$ ), Turkey ( $n = 12$ ), USA ( $n = 8$ ), Poland ( $n = 5$ ), Japan ( $n = 3$ ), Germany ( $n = 2$ ), Finland ( $n = 2$ ), Greece ( $n = 1$ ), Italy ( $n = 1$ ), Iran ( $n = 1$ ), India ( $n = 1$ ), Egypt ( $n = 1$ ), Korea ( $n = 1$ ), Saudi Arabia ( $n = 1$ ), Serbia ( $n = 1$ ) and Canada ( $n = 1$ ). Most studies ( $n = 46$ ) were performed in a single center and only eight studies used multi-centered designs. Biomarkers were analyzed for ADHD in 22 studies, for ASD in 29 studies, for both ADHD and ASD in two studies, for ADHD, ASD and TD in one study. NDDs were diagnosed mainly according to the diagnostic and statistical manual of mental disorders (DSM) (third, fourth or

fifth version), with some studies involving supplementary criteria, such as autism diagnostic interview-revised (ADI-R), autism diagnostic observation schedule (ADOS), childhood autism rating scale (CARS), kiddie schedule for affective disorders and schizophrenia of school-age children-present and lifetime version (K-SADS-PL), diagnostic interview and disruptive behavior disorder rating scale (DBDRS), international statistical classification of diseases and related health problems 10th revision (ICD-10) or Chinese classification of mental disorders (CCMD). Blood samples (serum or plasma) were collected for all thyroid function status- and appetite-related indicators, while urine, blood and CSF were for IGF-1 and IGFBP-3. Most studies did not address the weight difference, except two that divided the cases and HCs into overweight and normal weight. Some studies provided the results of all cases and cases with specific sex (female or male) or age ( $< 14$  years or  $> 14$  years). They were respectively used for overall and subgroup meta-analyses, which was the reason for inconsistency in the number of datasets during two analyses (**Supplementary Table 1**). According to the quality assessment results from NOS (ranging from 7 to 9), all articles were designated as high quality (Table 1).

### 3.3 Meta-analysis of Levels of Thyroid Function Indicators Between NDDs and HCs

#### 3.3.1 FT3

Twelve studies with 19 experimental datasets provided the mean and SD of FT3 concentration in NDD cases and HCs (**Supplementary Table 1**). There was significant heterogeneity between studies ( $I^2 = 96.3\%$ ,  $p_H < 0.001$ ), which led to a random-effect model chosen to pool the results (Table 2). The meta-analysis showed that compared to HCs, FT3 levels were significantly increased in patients with NDDs (SMD = 0.22; 95% CI = 0.04 to 0.40;  $p_{ES} = 0.015$ ) (Table 2; Fig. 2). Subgroup analysis revealed this increase in FT3 was mainly detected in studies with a single-center design and un-stratified sex or weight (Table 2).

A further independent analysis was performed for ADHD and ASD subjects. Results showed a significant increase in FT3 levels between subjects with ADHD and HCs (SMD = 0.43; 95% CI = 0.12 to 0.75;  $p_{ES} = 0.007$ ) (Table 3; Fig. 2), while no significant alterations in ASD subjects were found relative to HCs (SMD = 0.04; 95% CI = -0.29 to 0.38;  $p_{ES} = 0.800$ ) (Table 4; Fig. 2). Similar results were also obtained in subgroup analysis for ADHD (single-center,  $p_{ES} = 0.034$ ; mixed-sex,  $p_{ES} < 0.001$ ; mixed-weight,  $p_{ES} < 0.001$ ) and ASD ( $p_{ES} > 0.05$  in all subgroups). According to the symptoms, ADHD is clinically divided into the predominantly inattentive type (ADHD-IT), the predominantly hyperactive/impulsive type (ADHD-HIT) and combined types (ADHD-CT). Three studies also investigated the differences in FT3 between each ADHD type and HCs. Pooled data analysis indicated FT3 was only significantly elevated in ADHD-IT cases when compared to HCs

Table 1. Characteristics of included articles.

First author@	Year	Country	Design	Disease	Diagnosis criteria	Case			Control			Outcomes	NOS
						No.	Age	Gender (M/F)	No.	Age	Gender (M/F)		
Lukovac T	2024	Serbia	Single-center	ADHD	DSM-IV	67	10.13 ± 1.41	67/0	66	9.94 ± 1.52	66/0	FT4, TSH*	9
Langrock C	2018	Germany	Multicenter	ADHD (OW)	ICD; DSM	26	8.7 ± 1.8	17/9	66	10.0 ± 1.5	28/38	FT3, FT4, TSH, leptin*	8
	2018	Germany	Multicenter	ADHD (NW)	ICD; DSM	56	9.0 ± 1.7	44/12	82	9.1 ± 1.7	51/31	FT3, FT4, TSH, leptin*	
Kuppili PP	2017	India	Single-center	ADHD	DSM-IV-TR	30	9.47 ± 2.43	28/2	30	10.30 ± 2.79	28/2	TT3, TT4, TSH*	9
Albrecht D	2020	Germany	Multicenter	ADHD	ICD-10	420	10.6 (8.8–12.5)	336/84	8265	8.8 (6.1–11.5)	4465/3800	FT3, FT4, TSH*	8
	2020	Germany	Multicenter	ADHD	ICD-10	152	15.6 (14.4–16.7)	120/32	2751	15.6 (14.4–16.7)	1272/1479	FT3, FT4, TSH*	
Wang LJ	2023	China	Single-center	ADHD	DSM-V	144	8.9 ± 2.2	110/34	70	9.2 ± 2.2	46/24	TT3, FT4, TT4, TSH, IGF-1, IGFBP3*	9
Öz E	2023	Turkey	Single-center	ADHD	DSM-V	22	8.3 (7.0–9.3)	14/8	21	5.0 (3.4–13.6)	11/10	FT4, TSH*	9
Stein MA	2003	USA	Single-center	ADHD-CT	DSM-IV	195	8.9 ± 3.1	-	84	8.7 ± 3.04	-	TSH*	8
	2003	USA	Single-center	ADHD-IT	DSM-IV	54	10.6 ± 3.3	-	84	8.7 ± 3.04	-	TSH*	
Kim WJ	2020	Korea	Multicenter	ADHD	DSM-IV	41	8.81 ± 1.52	41/0	79	9.2 ± 1.65	79/0	FT4, TSH, IGF-1*	9
	2020	Korea	Multicenter	ADHD	DSM-IV	23	9.22 ± 1.51	0/23	33	9.36 ± 1.44	0/33	FT4, TSH, IGF-1*	
Singh S	2017	USA	Single-center	ASD	DSM-IV	43	2–8	43/0	37	2–8	37/0	TSH*	9
Desoky T	2017	Egypt	Single-center	ASD	CARS	60	7.03 ± 2.34	55/5	40	7.91 ± 3.21	20/20	FT3, FT4, TSH*	8
Błażewicz A	2021	Poland	Single-center	ASD	DSM-V; ADI-R; CARS	53	14.09 ± 1.42	41/12	77	14.71 ± 1.19	46/31	FT3, FT4, TSH*	9
Frye RE	2017	USA	Single-center	ASD	ADI-R; DSM	87	6.8 ± 3.0	70/17	12	8.2 ± 5.2	-	FT4, TSH*	7
Błażewicz A	2022	Poland	Single-center	ASD	ADOS-2; ADI-R;	129	14.1 ± 1.4	108/21	86	14.7 ± 1.2	54/32	FT3, FT4, TSH*	7
					ICD-10; DSM-V								
Błażewicz A	2016	Poland	Single-center	ASD	DSM-IV	40	7.2 (2–17)	40/0	40	9.9 (2–17)	40/0	FT3, FT4, TSH*	8
Elia J	1994	USA	Single-center	ADHD	DSM-III	53	9.16 ± 1.65	53/0	42	-	42/0	TSH, TT3, TT4*	8
Bala KA	2016	Turkey	Single-center	ASD	DSM-V; DSM-IV; CARS	16	7.88 ± 5.18	10/6	27	9.80 ± 4.01	13/14	TSH, T4, TPO-Ab*	9
	2016	Turkey	Single-center	ADHD	DSM-V; DSM-IV; DBDRS	34	7.68 ± 3.20	23/11	27	9.80 ± 4.01	13/14	TSH, FT4, TPO-Ab*	
Han L	2024	China	Single-center	ADHD (total, CT, IT, HIT)	CCMD-IV	81	8.04 ± 2.19	46/35	79	7.74 ± 2.25	45/34	FT3*	9
Chen JJ	2019	China	Single-center	ADHD	CCMD-III	48	9.38 ± 4.20	32/16	60	9.53 ± 3.97	34/26	FT3, FT4, TSH*	9
Jiang L	2021	China	Single-center	ADHD (total, CT, IT, HIT)	DSM-V	35	9.5 ± 2.6	29/6	18	9.3 ± 2.5	15/3	FT3, FT4, TT3, TT4, TSH*	9
Fan LP	2007	China	Single-center	ADHD (total, CT, IT, HIT)	DSM-IV	32	9–15	28/4	15	6.5–14.5	13/2	FT3, FT4, TT3, TT4, TSH*	9
Meng HJ	2024	China	Single-center	ADHD, ASD, TD	-	7035	6.53 ± 2.72	5680/1355	4801	6.34 ± 3.62	2771/2030	FT3, FT4, TT3, TT4, TSH, TPO-Ab*	8

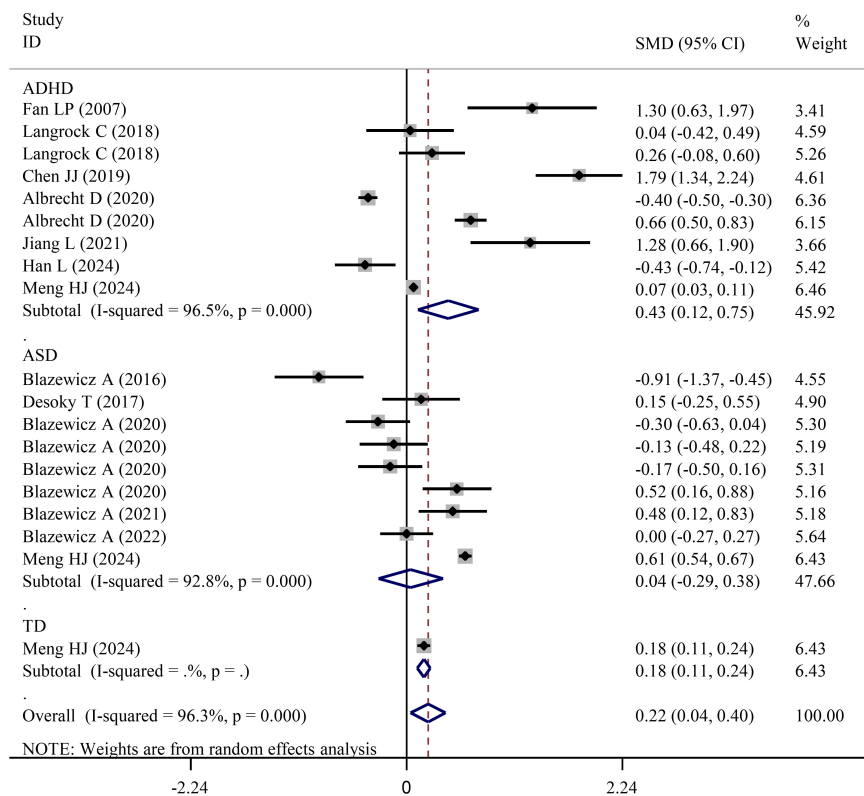
Table 1. Continued.

First author <sup>@</sup>	Year	Country	Design	Disease	Diagnosis criteria	Case			Control			Outcomes	NOS
						No.	Age	Gender (M/F)	No.	Age	Gender (M/F)		
Błażewicz A	2020	Poland	Single-center	ASD (OW); ASD (NW)	ADI-R; DSM-V; CARS	102 (OW); 50 (NW)	7.98 ± 1.46; 7.96 ± 1.39	-	53 (OW); 82 (NW)	8.06 ± 1.31; 8.6 ± 1.24	-	FT3, FT4, TSH*	9
	2020	Poland	Single-center	ASD (OW); ASD (NW)	ADI-R; DSM-V; CARS	76 (OW); 53 (NW)	14.07 ± 1.46; 14.08 ± 1.26	-	47 (OW); 82 (NW)	14.09 ± 1.42; 14.6 ± 1.24	-	FT3, FT4, TSH*	
Iwata K	2011	Japan	Single-center	ASD	DSM-IV-TR; ADI-R	32	12.3 ± 3.2	-	34	12.4 ± 2.6	-	TSH*	9
Lai KY	2024	China	Single-center	ADHD	DSM-V	77	8.2 ± 2.0	54/23	87	9.3 ± 2.6	49/38	Leptin, ghrelin, adiponectin*	7
Gurbuz F	2016	Turkey	Single-center	ADHD	DSM-IV	48	7–14	48/0	41	7–14	41/0	Leptin, IGF-1, IGFBP-3, ghrelin*	9
Baykal S	2019	Turkey	Single-center	ADHD	DSM-V	56	8.66 ± 2.77	39/17	40	7.93 ± 1.98	28/12	Ghrelin*	9
Hao YY	2020	China	Single-center	ADHD	DSM-IV	100	9.43 ± 2.15	56/44	100	9.56 ± 2.31	52/12	Ghrelin*	9
Petropoulos A	2024	Greece	Single-center	ADHD	DSM-IV	40	7.55 ± 1.85	23/17	40	8.07 ± 2.03	20/20	Leptin*	8
	2024	Greece	Single-center	ASD	DSM-IV	42	8.56 ± 2.03	38/4	40	8.07 ± 2.03	20/20	Leptin*	
Özcan Ö	2018	Turkey	Single-center	ADHD	DSM-IV; K-SADS-PL	36	9.30 ± 1.78	29/7	40	8.87 ± 2.13	29/11	Leptin, adiponectin*	9
Sahin S	2014	Turkey	Single-center	ADHD	DSM-IV; K-SADS-PL-TR	30	9.54 ± 2.83	24/6	20	9.65 ± 2.29	18/2	Leptin, ghrelin, adiponectin*	9
Zhang CJ	2024	China	Single-center	ASD	DSM-V; ADOS	56	3.0 (2.3–4.1)	51/5	30	2.8 (2.3–3.3)	25/5	IGF-1*	9
Robinson- Agramonte MLA	2022	Canada	Multicenter	ASD	DSM-V	22	9.45 ± 0.63	17/5	29	8.68 ± 0.54	21/8	IGF-1*	9
Anlar B	2007	Turkey	Single-center	ASD	DSM-IV	34	3.1 ± 0.9	26/8	29	3.3 ± 1.2	25/4	IGF-1, IGFBP-3 <sup>#</sup>	9
Şimşek F	2021	Turkey	Single-center	ASD	DSM-V	40	6.98 ± 2.58	37/3	40	7.79 ± 2.05	37/3	IGF-1*	9
Li Z	2022	China	Single-center	ASD	DSM-V	150	4 ± 1.3	113/37	165	4.17 ± 1.67	124/41	IGF-1, IGFBP-3*	9
Mills JL	2007	USA	Single-center	ASD	DSM-IV; ADOS	71	6.6 ± 1.5	71/0	59	6.5 ± 1.2	59/0	IGF-1, IGFBP-3*	9
Vanhala R	2001	Finland	Multicenter	ASD	DSM-III	11	3.8 ± 1.1	7/4	11	3.8 ± 1.3	5/6	IGF-1 <sup>&amp;</sup>	8
Riikonen R	2006	Finland	Multicenter	ASD	DSM-III	25	5.42 (1.92–15.83)	20/5	16	7.33 (1.08–15.17)	8/8	IGF-1 <sup>&amp;</sup>	7
Blardi P	2010	Italy	Single-center	ASD	DSM-IV; CARS ADOS	35	14.1 ± 5.4	21/14	35	-	-	Leptin, adiponectin*	8
Chen L	2024	China	Single-center	ASD	DSM-V	42	3.68 ± 1.54	20/22	42	4.02 ± 1.69	21/21	Leptin*	9
Ashwood P	2008	USA	Multicenter	ASD	ADOS; ADI-R	70	4.25 (2.4–15.5)	32/5	50	4.33 (2.2–14.7)	38/12	Leptin*	9
Maekawa M	2020	Japan	Single-center	ASD	DSM-IV	21	5.7 ± 0.21	18/3	26	6.05 ± 0.13	14/12	Leptin, adiponectin*	8
	2020	Japan	Single-center	ASD	DSM-IV	101	10.1 ± 0.15	92/9	66	10.47 ± 1.7	55/11	Leptin, adiponectin*	
Al-Zaid FS	2014	Saudi Arabia	Single-center	ASD	DSM-IV; CARS ADOS	31	5.60 ± 0.31	31/0	28	5.44 ± 0.23	28/0	Leptin*	9

**Table 1. Continued.**

First author <sup>@</sup>	Year	Country	Design	Disease	Diagnosis criteria	Case			Control			Outcomes	NOS
						No.	Age	Gender (M/F)	No.	Age	Gender (M/F)		
Wang BJ	2025	China	Single-center	ASD	DSM-V	36	6.4 ± 3.0	24/12	18	6.8 ± 3.5	12/6	Leptin, adiponectin*	9
Skórzyńska-Dziduszek KE	2023	Poland	Single-center	ASD	DSM-V; CARS ADI-R	102 (OW)	8.09 ± 1.36	86/16	53	8.09 ± 1.36	25/28	Leptin*	9
	2023	Poland	Single-center	ASD	DSM-V; CARS ADI-R	50 (NW)	8.09 ± 1.36	41/9	82	8.09 ± 1.36	53/29	Leptin*	
	2023	Poland	Single-center	ASD	DSM-V; CARS; ADI-R	76 (OW)	14.26 ± 1.37	67/9	47	14.26 ± 1.37	25/22	Leptin*	
	2023	Poland	Single-center	ASD	DSM-V; CARS ADI-R	53 (NW)	14.26 ± 1.37	12/41	82	14.26 ± 1.37	49/33	Leptin*	
Çelikkol Sadıç Ç	2021	Turkey	Single-center	ASD	DSM-V	44	2.86 ± 0.88	38/6	44	3.03 ± 0.98	35/9	Leptin, ghrelin*	9
Nehir Yazıcı Ö	2024	Turkey	Single-center	ASD	DSM-V	40	3.95 ± 1.46	29/11	40	4.42 ± 1.61	23/17	Leptin, ghrelin*	9
Ertürk E	2024	Turkey	Single-center	ADHD	DSM-V	40	9.87 ± 1.32	24/16	40	9.94 ± 1.58	24/16	IGF-1*	9
Toren P	1997	USA	Multicenter	ADHD	DSM-III-R	21	6–16	21/0	30	6–16	30/0	IGF-1*	9
Abedini M	2022	Iran	Single-center	ASD	DSM-IV	200	6.6 ± 4.1	-	198	6.8 ± 3.2	-	IGF-1*	8
Işeri E	2007	Turkey	Single-center	ADHD	DSM-IV	20	6–12	20/0	12	6–12	12/0	Leptin*	9
Fujita-Shimizu A	2010	Japan	Single-center	ASD	DSM-IV-TR; ADI-R	31	11.6 ± 2.9	31/0	31	12.1 ± 2.4	31/0	Adiponectin*	9
Raghavan	2019	USA	Single-center	ASD	-	36	1.59 (0.86–4.1)	-	602	1.59 (0.86–4.1)	-	Adiponectin*	8
Quan L	2021	China	Single-center	ASD	DSM-V	88	4.3 ± 1.2	68/20	88	4.3 ± 1.2	68/20	Adiponectin*	9

M, male; F, female; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; TD, tic disorder; OW, overweight; NW, normal weight; IT, inattentive type; HIT, hyperactive/impulsive type; CT, combined types; DSM, diagnostic and statistical manual of mental disorders; ADI-R, autism diagnostic interview-revised; ADOS, autism diagnostic observation schedule; CARS, childhood autism rating scale; K-SADS-PL, kiddie schedule for affective disorders and schizophrenia of school-age children-present and lifetime version; K-SADS-PL-TR, K-SADS-PL Turkish version; DBDRS, diagnostic interview and disruptive behavior disorder rating scale; ICD-10, international statistical classification of diseases and related health problems 10th revision; CCMD, Chinese classification of mental disorders; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TT3, total triiodothyronine; TT4, total thyroxine; TPO-Ab, thyroid peroxidase antibody; IGF-1, insulin-like growth factor 1; IGFBP3, insulin-like growth factor binding protein 3; CSF, cerebrospinal fluid; \*blood samples; #urinary samples; &CSF samples; @the references for these authors can be seen in **Supplementary File 1**; - indicated the information unknown.



**Fig. 2. Forest plots showing significantly higher FT3 levels in NDD (or ADHD) patients than in HCs.** NDD, neurodevelopmental disorders; HCs, healthy controls; ASD, autism spectrum disorder.

(SMD = 1.52; 95% CI = 0.80 to 2.23;  $p_{ES} < 0.001$ ), but not for ADHD-HIT ( $p_{ES} = 0.422$ ) and ADHD-CT ( $p_{ES} = 0.961$ ) (Table 3).

### 3.3.2 FT4

Eighteen studies with 26 experimental datasets examined the concentration of FT4 in NDD cases and HCs (Supplementary Table 1). Pooling all related data under a random-effect model ( $I^2 = 95.9%$ ,  $p_H < 0.001$ ) did not detect a significant difference in FT4 levels between NDD cases and HCs (SMD = -0.02; 95% CI = -0.19 to 0.15;  $p_{ES} = 0.808$ ) (Table 2). No significant differences were also found in most of subgroups except for studies with a multicenter design that suggested FT4 levels were significantly lower in NDD cases than in HCs (SMD = -0.29; 95% CI = -0.52 to -0.06;  $p_{ES} = 0.013$ ) (Table 2; Fig. 3).

No statistical significance was found during the independent meta-analysis of FT4 for ADHD (SMD = -0.07; 95% CI = -0.34 to 0.20;  $p_{ES} = 0.612$ ) (Table 3) and ASD cases (SMD = 0.14; 95% CI = -0.32 to 0.60;  $p_{ES} = 0.558$ ) (Table 4). However, subgroup analysis showed FT4 levels were significantly decreased either for male ADHD cases (SMD = -0.26; 95% CI = -0.52 to -0.01;  $p_{ES} = 0.042$ ) or for analysis of studies with a multicenter design (SMD = -0.29; 95% CI = -0.52 to -0.06;  $p_{ES} = 0.013$ ) (Table 3). Similarly to these subgroup analysis results, a lower concentration of FT4 was observed in ADHD-IT cases when

compared to HCs (SMD = -0.78; 95% CI = -1.36 to -0.19;  $p_{ES} = 0.009$ ). Different from the results of ADHD, FT4 was found to be higher in female ASD patients when compared to HCs (SMD = 0.44; 95% CI = 0.006 to 0.86;  $p_{ES} = 0.047$ ) (Table 4), but this conclusion requires further investigation as the  $p_{ES}$ -value was approximately 0.05.

### 3.3.3 TT3

Six studies with eight experimental datasets compared the average level of TT3 in NDD cases and HCs (Supplementary Table 1). Under a random-effect model ( $I^2 = 99.4%$ ,  $p_H < 0.001$ ), the combined results revealed TT3 levels in NDD cases were not significantly different when compared to HCs (SMD = -0.07; 95% CI = -0.59 to 0.45;  $p_{ES} = 0.804$ ) (Table 2). However, subgroup analysis of mixed-age populations indicated a significant increase in TT3 levels within the NDD group when compared to HCs (SMD = 0.82; 95% CI = 0.36 to 1.28;  $p_{ES} < 0.001$ ) (Table 2).

All these six studies explored TT3 in ADHD and one study simultaneously included ASD and TD patients; thus, both pooled and subgroup meta-analyses were only performed for ADHD. No significant variations in levels of TT3 were found between ADHD cases and HCs in overall meta-analysis (SMD = 0.22; 95% CI = -0.85 to 1.29;  $p_{ES} = 0.681$ ), but TT3 levels were significantly increased in mixed-age populations in the subgroup analysis (SMD =

**Table 2. Altered levels of thyroid, growth and appetite hormones in children and adolescents with neurodevelopmental disorders.**

Variables	No.	SMD	95% CI	$p_{ES}$	$I^2$	$p_H$	Model	$p_{PB}$		
FT3 (pmol/L)	Overall	19	0.22	0.04, 0.40	<b>0.015</b>	96.3	<0.001	R	0.765	
	Sex	Male	3	-0.05	-0.85, 0.75	0.906	91.5	<0.001	R	
		Female	2	0.19	-0.24, 0.61	0.385	0.0	0.674	F	
	Design	Mix	16	0.28	0.09, 0.48	<b>0.004</b>	96.7	<0.001	R	
		Multicenter	4	0.14	-0.51, 0.79	0.673	97.6	<0.001	R	
	Age	Single-center	15	0.24	0.05, 0.43	<b>0.012</b>	95.6	<0.001	R	
		Children	11	0.004	-0.21, 0.21	0.971	97.1	<0.001	R	
	Weight	Adolescents	4	0.27	-0.16, 0.69	0.223	88.7	<0.001	R	
		Mix	5	0.78	-0.18, 1.73	0.110	94.8	<0.001	R	
		OW	3	-0.18	-0.39, 0.03	0.100	0.0	<0.001	F	
	FT4 (pmol/L)	Overall	26	-0.02	-0.19, 0.15	0.808	95.9	<0.001	R	<0.001
		Sex	Male	5	-0.02	-0.41, 0.37	0.907	81.0	<0.001	R
Female			3	0.23	-0.19, 0.64	0.283	33.8	0.221	F	
Design		Mix	20	-0.02	-0.21, 0.17	0.827	96.3	<0.001	R	
		Multicenter	6	-0.29	-0.52, -0.06	<b>0.013</b>	79.4	<0.001	R	
Age		Single-center	20	0.07	-0.13, 0.26	0.501	96.1	<0.001	R	
		Children	18	-0.07	-0.26, 0.12	0.463	96.2	<0.001	R	
Weight		Adolescents	4	0.01	-0.48, 0.50	0.957	91.4	<0.001	R	
		Mix	5	0.16	-0.25, 0.58	0.442	75.5	0.003	R	
		OW	3	-0.18	-0.93, 0.58	0.646	91.7	<0.001	R	
Weight		NW	3	0.28	-0.11, 0.68	0.162	73.7	0.022	R	
		Mix	20	-0.06	-0.24, 0.13	0.553	96.0	<0.001	R	
TT3 (ng/mL)	Overall	8	-0.07	-0.59, 0.45	0.804	99.4	<0.001	R	0.188	
	Sex	Male	1	-0.04	-0.45, 0.37	0.854	-	-	R	
		Mix	7	-0.07	-0.62, 0.48	0.804	99.5	<0.001	R	
	Age	Children	5	-0.54	-1.16, 0.07	0.084	99.6	<0.001	R	
		Mix	3	0.82	0.36, 1.28	< <b>0.001</b>	45.4	0.160	F	
TT4 (ng/mL)	Overall	8	-0.35	-0.50, -0.20	< <b>0.001</b>	91.0	<0.001	R	0.170	
	Sex	Male	1	-0.07	-0.47, 0.34	0.752	-	-	R	
		Mix	7	-0.38	-0.54, -0.22	< <b>0.001</b>	91.7	<0.001	R	
	Age	Children	5	-0.37	-0.53, -0.21	< <b>0.001</b>	94.2	<0.001	R	
		Mix	3	-0.26	-0.86, 0.33	0.386	69.4	0.038	R	
TSH ( $\mu$ IU/mL)	Overall	32	-0.08	-0.23, 0.08	0.326	95.0	<0.001	R	0.435	
	Sex	Male	6	-0.46	-1.24, 0.31	0.241	95.8	<0.001	R	
		Female	3	-0.16	-0.50, 0.19	0.369	4.5	0.351	F	
	Design	Mix	24	-0.02	-0.18, 0.14	0.831	95.0	<0.001	R	
		Multicenter	6	-0.19	-0.63, 0.24	0.387	94.9	<0.001	R	
	Age	Single-center	26	-0.04	-0.20, 0.12	0.619	94.2	<0.001	R	
		Children	20	-0.22	-0.41, -0.03	<b>0.026</b>	96.4	<0.001	R	
	Weight	Adolescents	4	0.21	-0.19, 0.61	0.304	86.9	<0.001	R	
		Mix	9	0.20	-0.12, 0.52	0.215	81.2	<0.001	R	
		OW	3	0.03	-0.18, 0.24	0.802	0.0	0.568	R	
	Weight	NW	3	0.02	-0.75, 0.78	0.962	92.8	<0.001	R	
		Mix	26	-0.10	-0.23, 0.07	0.261	95.7	<0.001	R	
TPO-Ab (IU/mL)	Overall	5	0.37	0.08, 0.67	<b>0.014</b>	98.3	<0.001	R	0.762	
IGF-1 (ng/mL)	Overall	15	-0.41	-1.14, 0.33	0.275	97.8	<0.001	R	0.640	
	Sex	Male	4	0.21	-0.04, 0.46	0.094	31.6	0.223	F	
		Female	1	0.40	-0.14, 0.94	0.146	-	-	R	
	Mix	10	-0.74	-1.78, 0.31	0.167	98.3	<0.001	R		

**Table 2. Continued.**

Variables		No.	SMD	95% CI	$p_{ES}$	$I^2$	$p_H$	Model	$p_{PB}$	
	Design	Multicenter	7	-0.21	-1.26, 0.83	0.691	94.9	<0.001	R	0.273
		Single-center	8	-0.58	-1.62, 0.47	0.280	98.6	<0.001	R	
	Age	Children	10	-0.73	-1.67, 0.21	0.127	98.4	<0.001	R	
		Mix	5	0.24	-0.74, 1.22	0.632	91.1	<0.001	R	
	Source	Blood	12	-0.09	-0.90, 0.73	0.830	98.1	<0.001	R	
		Urinary	1	-3.37	-4.14, -2.59	<0.001	-	-	R	
		CSF	2	-0.89	-1.42, -0.36	<b>0.001</b>	0.0	0.566	F	
	Overall	5	-0.51	-1.29, 0.28	0.204	96.0	<0.001	R		
	Sex	Male	2	0.31	-0.61, 1.23	0.512	91.1	<0.001	R	
		Mix	3	-1.12	-2.37, 0.13	0.079	97.5	<0.001	R	
IGFBP-3 (µg/mL)	Design	Multicenter	1	-3.78	-4.62, -2.95	<0.001	-	-	R	
		Single-center	4	0.17	-0.22, 0.56	0.394	84.5	<0.001	R	
	Age	Children	4	-0.62	-1.60, 0.36	0.215	97.0	<0.001	R	
		Mix	1	-0.17	-0.59, 0.25	0.430	-	-	R	
	Source	Blood	4	0.17	-0.22, 0.56	0.394	84.5	<0.001	R	
		Urinary	1	-3.78	-4.62, -2.95	<0.001	-	-	R	
	Overall	24	0.10	-0.33, 0.53	0.645	95.2	<0.001	R	0.305	
	Sex	Male	6	0.74	0.10, 1.38	<b>0.023</b>	87.7	<0.001	R	
		Female	3	0.18	-1.77, 2.12	0.860	93.7	<0.001	R	
	Mix	Mix	16	-0.08	-0.66, 0.50	0.787	96.5	<0.001	R	
Multicenter		3	-0.27	-2.47, 1.94	0.811	98.6	<0.001	R		
Design	Single-center	21	0.14	-0.27, 0.56	0.496	93.9	<0.001	R		
	Children	17	-0.007	-0.62, 0.60	0.982	96.4	<0.001	R		
Age	Adolescents	2	0.04	-0.21, 0.29	0.741	0.0	0.818	F		
	Mix	5	0.53	0.02, 1.04	<b>0.042</b>	82.1	<0.001	R		
Weight	OW	3	-0.95	-2.54, 0.64	0.240	97.7	<0.001	R		
	NW	3	0.80	0.007, 1.60	<b>0.048</b>	93.0	<0.001	R		
Mix	Mix	18	0.16	-0.36, 0.67	0.547	94.7	<0.001	R		
Leptin (ng/mL)	Overall	7	0.62	-0.38, 1.62	0.226	97.5	<0.001	R	0.218	
	Sex	Male	2	1.03	0.01, 2.04	<b>0.047</b>	89.2	<0.001	R	
		Mix	5	0.44	-0.89, 1.77	0.519	98.1	<0.001	R	
	Age	Children	3	1.21	-0.88, 3.30	0.256	98.5	<0.001	R	
		Mix	4	0.17	-0.74, 1.08	0.713	94.7	<0.001	R	
	Overall	10	-0.16	-0.58, 0.25	0.437	89.8	<0.001	R	0.957	
Adiponectin (µg/mL)	Sex	Male	1	-0.75	-1.26, -0.23	0.005	-	-	R	
		Mix	9	-0.10	-0.54, 0.34	0.650	90.4	<0.001	R	
	Age	Children	6	-0.33	-0.89, 0.23	0.249	92.9	<0.001	R	
		Mix	4	0.10	-0.49, 0.69	0.740	79.8	0.002	R	

SMD, standardized mean difference; ES, effect size; 95% CI, 95% confidence intervals; H, heterogeneity; R, random-effect; F, fixed-effect; PB, publication bias. Bold indicates indicators with the  $p_{ES}$ -value < 0.05 by analysis of more than one dataset.

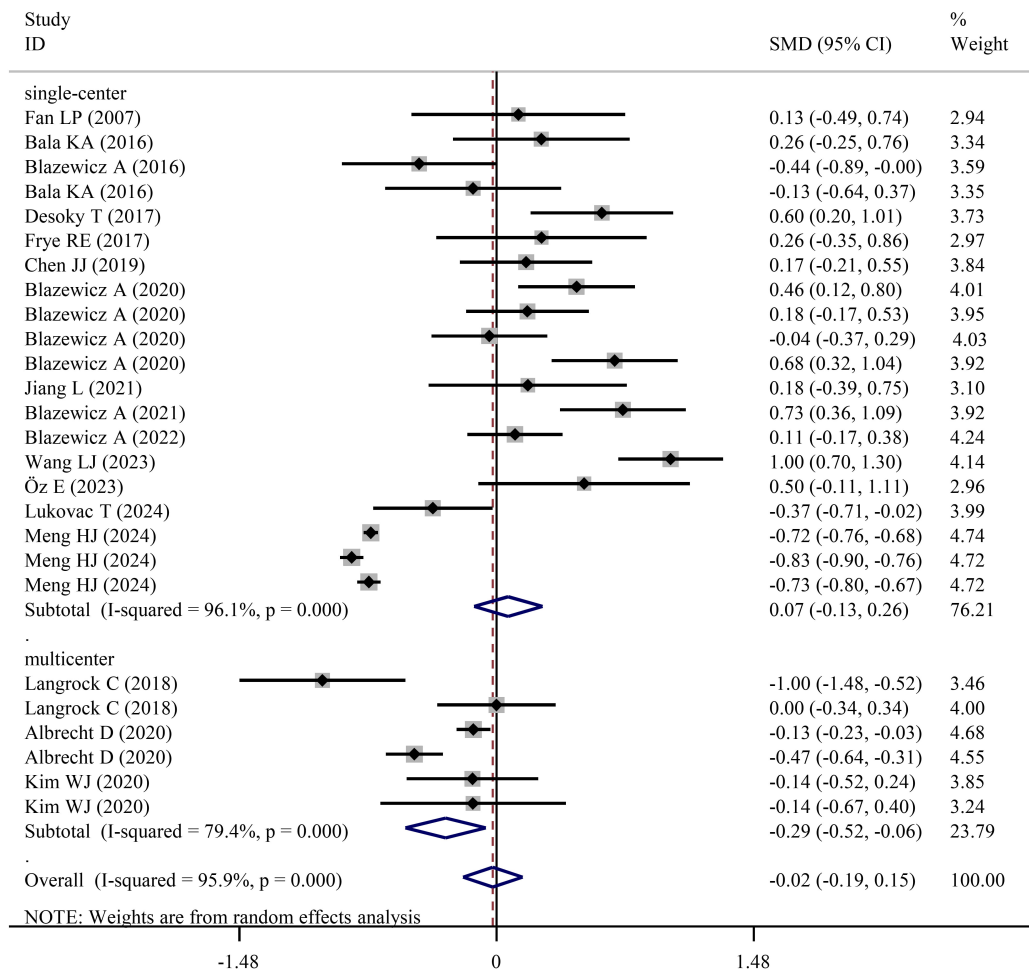
0.82; 95% CI = 0.36 to 1.28;  $p_{ES}$  < 0.001). Additionally, TT3 levels were found to be higher in all three ADHD subtypes, including ADHD-IT (SMD = 0.83; 95% CI = 0.24 to 1.41;  $p_{ES}$  = 0.006), ADHD-HIT (SMD = 1.50; 95% CI = 0.69 to 2.31;  $p_{ES}$  < 0.001) and ADHD-CT (SMD = 1.06; 95% CI = 0.56 to 1.56;  $p_{ES}$  < 0.001) (Table 3).

### 3.3.4 TT4

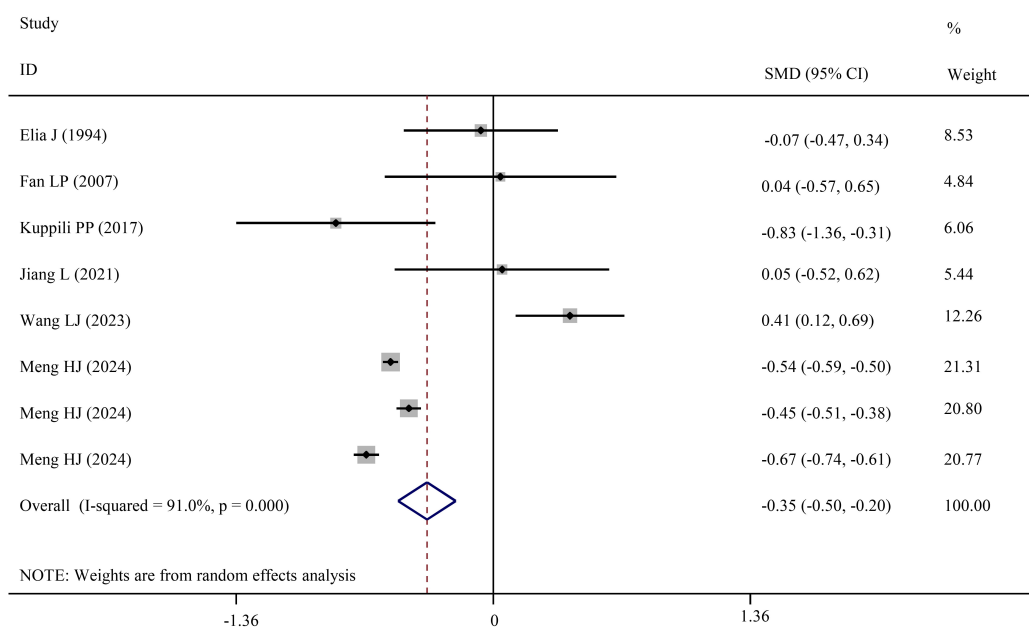
The meta-analysis of TT4 levels encompassed six studies with eight experimental datasets (Supplementary Table 1). The combined results which were analyzed based

on a random-effect model ( $I^2$  = 91%,  $p_H$  < 0.001), showed NDD patients had reduced levels of TT4 when compared to HCs (SMD = -0.35; 95% CI = -0.50 to -0.20;  $p_{ES}$  < 0.001) (Table 2; Fig. 4). This declining trend in TT4 levels specifically occurred in populations with mixed-sex (SMD = -0.38; 95% CI = -0.54 to -0.22;  $p_{ES}$  < 0.001) and children (age < 14 years) (SMD = -0.37; 95% CI = -0.53 to -0.21;  $p_{ES}$  < 0.001) (Table 2).

Although pooled and subgroup analyses did not detect significant changes in TT4 levels between ADHD and HCs, the combined analysis of two studies revealed TT4 levels



**Fig. 3. Forest plots showing significantly lower FT4 levels in NDD patients than in HCs when studies with a multicenter design were pooled.**



**Fig. 4. Forest plots showing significantly lower TT4 levels in NDD patients than in HCs.**

**Table 3. Altered levels of thyroid, growth and appetite hormones in children and adolescents with ADHD.**

Variables	No.	SMD	95% CI	<i>p</i> <sub>ES</sub>	<i>I</i> <sup>2</sup>	<i>p</i> <sub>H</sub>	Model	<i>p</i> <sub>PB</sub>		
FT3 (pmol/L)	Overall (ADHD)	9	0.43	0.12, 0.75	<b>0.007</b>	96.5	<0.001	R	0.341	
	Design	Multicenter	4	0.14	-0.51, 0.79	0.673	97.6	<0.001	R	
		Single-center	5	0.76	0.06, 1.47	<b>0.034</b>	95.7	<0.001	R	
	Age	Children	5	-0.10	-0.40, 0.20	0.494	95.3	<0.001	R	
		Adolescents	1	0.66	0.50, 0.83	<0.001	-	-	R	
	Mix	Mix	3	1.53	1.18, 1.88	< <b>0.001</b>	13.9	0.313	R	
		OW	1	0.04	-0.42, 0.49	0.875	-	-	R	
	Weight	NW	1	0.26	-0.08, 0.60	0.132	-	-	R	
		Mix	7	0.52	0.15, 0.89	<b>0.006</b>	97.4	<0.001	R	
	ADHD-IT	3	1.52	0.80, 2.23	< <b>0.001</b>	62.2	0.071	R	0.102	
ADHD-HIT	3	0.63	-0.90, 2.16	0.422	84.1	0.002	R	0.248		
ADHD-CT	3	0.06	-2.39, 2.52	0.961	97.8	<0.001	R	0.077		
FT4 (pmol/L)	Overall (ADHD)	14	-0.07	-0.34, 0.20	0.612	95.7	<0.001	R	0.008	
	Sex	Male	2	-0.26	-0.52, -0.01	<b>0.042</b>	0.0	0.380	R	
		Female	1	-0.14	-0.67, 0.40	0.619	-	-	R	
	Mix	Mix	11	-0.03	-0.34, 0.29	0.856	96.6	<0.001	R	
		Multicenter	6	-0.29	-0.52, -0.06	<b>0.013</b>	79.4	<0.001	R	
	Design	Single-center	8	0.13	-0.44, 0.71	0.647	96.3	<0.001	R	
		Children	10	-0.08	-0.43, 0.26	0.632	96.8	<0.001	R	
	Age	Adolescents	1	-0.47	-0.64, -0.31	<0.001	-	-	R	
		Mix	3	0.16	-0.12, 0.44	0.256	0.0	0.991	R	
	OW	OW	1	-1.00	-1.48, -0.52	<0.001	-	-	R	
		NW	1	<0.001	-0.34, 0.34	1.000	-	-	R	
	Weight	Mix	12	-0.003	-0.30, 0.29	0.985	96.2	<0.001	R	
		ADHD-IT	2	-0.78	-1.36, -0.19	<b>0.009</b>	0.0	0.869	F	-
ADHD-HIT	2	0.59	-0.16, 1.34	0.125	0.0	0.931	F	-		
ADHD-CT	2	0.43	-0.04, 0.90	0.070	0.0	0.928	F	-		
TT3 (ng/mL)	Overall (ADHD)	6	0.22	-0.85, 1.29	0.681	98.6	<0.001	R	0.002	
	Sex	Male	1	-0.04	-0.45, 0.37	0.854	-	-	R	
		Mix	5	0.28	-0.97, 1.53	0.661	98.7	<0.001	R	
	Age	Children	3	-0.38	-1.72, 0.97	0.583	98.9	<0.001	R	
		Mix	3	0.82	0.36, 1.28	< <b>0.001</b>	45.4	0.160	R	
	ADHD-IT	2	0.83	0.24, 1.41	<b>0.006</b>	0.0	0.476	R	-	
	ADHD-HIT	2	1.50	0.69, 2.31	< <b>0.001</b>	0.0	0.590	F	-	
	ADHD-CT	2	1.06	0.56, 1.56	< <b>0.001</b>	12.9	0.284	F	-	
TT4 (ng/mL)	Overall (ADHD)	6	-0.16	-0.59, 0.27	0.462	90.8	<0.001	R	0.150	
	Sex	Male	1	-0.07	-0.47, 0.34	0.752	-	-	R	
		Mix	5	-0.18	-0.69, 0.33	0.485	91.9	<0.001	R	
	Age	Children	3	-0.08	-0.74, 0.59	0.817	95.6	<0.001	R	
		Mix	3	-0.26	-0.86, 0.33	0.386	69.4	0.038	R	
	ADHD-IT	2	-1.07	-1.67, -0.46	<b>0.001</b>	0.0	0.988	F	-	
	ADHD-HIT	2	0.75	-0.008, 1.50	0.053	0.0	0.984	F	-	
	ADHD-CT	2	0.27	-0.20, 0.73	0.262	0.0	0.991	F	-	
TSH (μIU/mL)	Overall (ADHD)	18	-0.04	-0.26, 0.18	0.723	94.1	<0.001	R	0.406	
	Sex	Male	3	0.07	-0.14, 0.29	0.515	0.0	0.946	R	
		Female	1	-0.46	-1.00, 0.08	0.094	-	-	R	
	Mix	Mix	14	-0.04	-0.29, 0.22	0.783	95.4	<0.001	R	
		Multicenter	6	-0.19	-0.63, 0.24	0.387	94.9	<0.001	R	
	Design	Single-center	12	0.04	-0.18, 0.26	0.701	83.7	<0.001	R	
		Children	11	-0.25	-0.55, 0.05	0.108	95.9	<0.001	R	
	Age	Adolescents	1	0.33	0.17, 0.49	<0.001	-	-	R	
		Mix	6	0.29	-0.06, 0.64	0.107	76.5	0.001	R	

**Table 3. Continued.**

Variables	No.	SMD	95% CI	$p_{ES}$	$I^2$	$p_H$	Model	$p_{PB}$		
Weight	OW	1	-0.17	-0.62, 0.29	0.469	-	-	R		
	NW	1	-0.34	-0.68, 0.005	0.054	-	-	R		
	Mix	16	-0.01	-0.25, 0.2	0.919	94.7	<0.001	R		
	ADHD-IT	3	0.41	-0.31, 1.13	0.265	72.2	0.027	R	0.052	
	ADHD-HIT	2	0.91	0.15, 1.68	<b>0.019</b>	0.0	0.969	F	-	
	ADHD-CT	3	0.67	0.44, 0.90	<b>&lt;0.001</b>	0.0	0.801	F	-	
TPO-Ab (IU/mL)	Overall	2	0.22	0.18, 0.25	<b>&lt;0.001</b>	0.0	0.876	F	-	
IGF-1 (ng/mL)	Overall	6	-0.57	-1.93, 0.80	0.414	98.1	<0.001	R	0.683	
	Sex	Male	3	0.08	-0.17, 0.33	0.533	0.0	0.691	R	
		Female	1	0.40	-0.14, 0.94	0.146	-	-	R	
		Mix	2	-2.07	-6.40, 2.27	0.350	99.4	<0.001	R	
	Design	Multicenter	3	0.21	-0.06, 0.48	0.129	0.0	0.633	R	
		Single-center	3	-1.39	-4.07, 1.29	0.310	99.1	<0.001	R	
	Age	Children	4	-0.91	-2.98, 1.16	0.388	98.8	<0.001	R	
Mix		2	0.07	-0.26, 0.41	0.672	0.0	0.391	R		
IGFBP-3 (µg/mL)	Overall	2	0.05	-0.32, 0.42	0.773	54.4	0.139	R	-	
Leptin (ng/mL)	Overall	9	-0.59	-1.74, 0.56	0.316	97.7	<0.001	R	0.223	
	Sex	Male	2	0.32	-0.07, 0.71	0.107	18.7	0.267	R	
		Female	1	-1.01	-1.70, -0.32	0.004	-	-	R	
		Mix	6	-0.81	-2.52, 0.90	0.356	98.5	<0.001	R	
	Design	Multicenter	2	-0.97	-5.25, 3.30	0.655	99.2	<0.001	R	
		Single-center	7	-0.48	-1.69, 0.73	0.434	97.1	<0.001	R	
	Age	Children	7	-0.80	-2.31, 0.72	0.304	98.2	<0.001	R	
		Mix	2	0.15	-0.53, 0.83	0.659	73.0	0.054	R	
	Weight	OW	1	-3.16	-3.81, -2.51	<0.001	-	-	R	
		NW	1	1.20	0.83, 1.57	<0.001	-	-	R	
Mix		7	-0.48	-1.69, 0.73	0.434	97.1	<0.001	R		
Ghrelin (ng/mL)	Overall	5	-1.32	-3.15, 0.52	0.161	98.8	<0.001	R	0.409	
	Sex	Male	1	1.55	1.07, 2.02	<0.001	-	-	R	
		Mix	4	0.63	-1.07, 2.32	0.468	98.5	<0.001	R	
	Age	Children	1	3.36	2.88, 3.83	<0.001	-	-	R	
		Mix	4	0.17	-0.74, 1.08	0.713	94.7	<0.001	R	
Adiponectin (µg/mL)	Overall	3	0.16	-0.73, 1.04	0.730	91.7	<0.001	R	0.735	

ADHD, attention deficit hyperactivity disorder; IT, inattentive type; HIT, hyperactive-impulsive type; CT, combined type; H, heterogeneity; R, random-effect; F, fixed-effect; PB, publication bias. Bold indicates indicators with the  $p_{ES}$ -value < 0.05 by analysis of more than one dataset.

were decreased in ADHD-IT when compared to HCs (SMD = -1.07; 95% CI = -1.67 to -0.46;  $p_{ES}$  = 0.001) (Table 3).

### 3.3.5 TSH

Twenty-three studies with 32 datasets recorded the TSH levels in NDD patients and HCs (**Supplementary Table 1**). A random-effect meta-analysis demonstrated TSH levels in NDD patients were not significantly different from those of HCs (SMD = -0.08; 95% CI = -0.23 to 0.08;  $p_{ES}$  = 0.326;  $I^2$  = 95%,  $p_H$  < 0.001) (Table 2). However, subgroups analysis of children less than 14 years old implied TSH levels were decreased in the NDD group relative to HCs (SMD = -0.22; 95% CI = -0.41 to -0.03;  $p_{ES}$  = 0.026) (Table 2).

Pooled and subgroup meta-analyses did not identify the association of TSH levels for both ADHD (Table 3) and

ASD (Table 4) patients. However, children and adolescents with ADHD-HIT (SMD = 0.91; 95% CI = 0.15 to 1.68;  $p_{ES}$  = 0.019) and ADHD-CT (SMD = 0.67; 95% CI = 0.44 to 0.90;  $p_{ES}$  < 0.001) were observed to have a higher TSH than HCs (Table 3).

### 3.3.6 TPO-Ab

Two studies with five datasets reported TPO-Ab levels in NDD patients and HCs (**Supplementary Table 1**). Combined results showed TPO-Ab levels were significantly increased in NDD patients when compared to HCs (SMD = 0.37; 95% CI = 0.08 to 0.67;  $p_{ES}$  = 0.014) (Table 2). A similar result was also obtained for ADHD (SMD = 0.22; 95% CI = 0.18 to 0.25;  $p_{ES}$  < 0.001) (Table 3) and ASD cases (SMD = 0.14; 95% CI = 0.08 to 0.21;  $p_{ES}$  < 0.001) (Table 4).

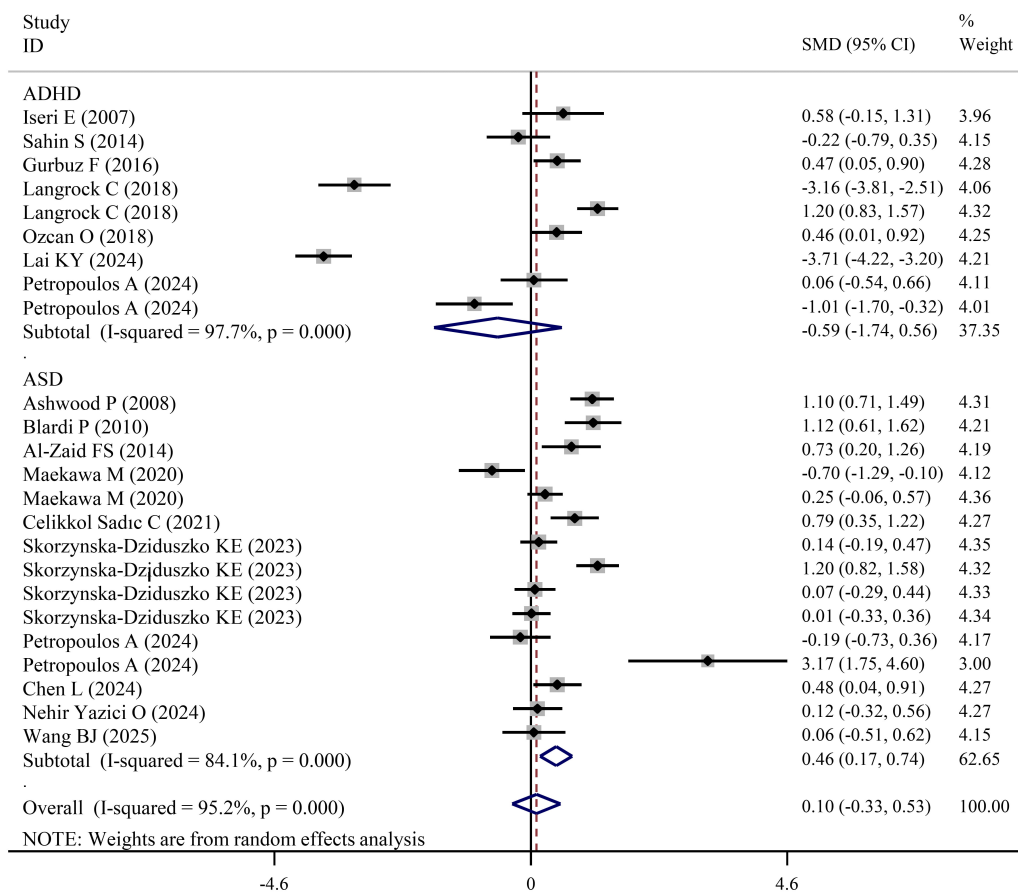
**Table 4. Altered levels of thyroid, growth and appetite hormones in children and adolescents with ASD.**

Variables		No.	SMD	95% CI	<i>p</i> <sub>ES</sub>	<i>I</i> <sup>2</sup>	<i>p</i> <sub>H</sub>	Model	<i>p</i> <sub>PB</sub>	
FT3 (pmol/L)	Overall	9	0.04	-0.29, 0.38	0.800	92.8	<0.001	R	0.005	
	Sex	Male	3	-0.05	-0.85, 0.75	0.906	91.5	<0.001	R	
		Female	2	0.19	-0.24, 0.61	0.385	0.0	0.674	F	
	Age	Mix	6	0.12	-0.26, 0.51	0.530	92.0	<0.001	R	
		Children	5	0.06	-0.41, 0.52	0.810	92.5	<0.001	R	
	Weight	Adolescents	3	0.11	-0.29, 0.52	0.582	75.6	0.016	R	
		Mix	2	-0.21	-1.57, 1.15	0.766	95.4	<0.001	R	
		OW	2	-0.23	-0.47, 0.003	0.053	0.0	0.599	R	
	Weight	NW	2	0.19	-0.45, 0.84	0.554	84.7	0.011	R	
		Mix	5	0.09	-0.37, 0.55	0.695	93.4	<0.001	R	
FT4 (pmol/L)	Overall	11	0.14	-0.32, 0.60	0.558	96.5	<0.001	R	<0.001	
	Sex	Male	3	0.14	-0.50, 0.77	0.670	86.7	0.001	R	
		Female	2	0.44	0.006, 0.86	<b>0.047</b>	0.0	0.553	F	
	Age	Mix	8	0.14	-0.42, 0.70	0.627	96.6	<0.001	R	
		Children	7	0.11	-0.49, 0.72	0.714	96.2	<0.001	R	
	Weight	Adolescents	3	0.19	-0.27, 0.65	0.419	81.5	0.005	R	
		Mix	2	0.15	-1.00, 1.29	0.800	93.8	<0.001	R	
		OW	2	0.21	-0.28, 0.70	0.406	76.9	0.038	R	
	Weight	NW	2	0.43	-0.06, 0.92	0.089	73.6	0.052	R	
		Mix	7	0.03	-0.55, 0.62	0.913	96.3	<0.001	R	
TT3 (ng/mL)	Overall	1	-0.21	-0.27, -0.14	<0.001	-	-	F	-	
TT4 (ng/mL)	Overall	1	-0.45	-0.51, -0.38	<0.001	-	-	F	-	
TSH (μIU/mL)	Overall	13	-0.24	-0.62, 0.14	0.209	94.8	<0.001	R	0.621	
	Sex	Male	4	-0.96	-2.61, 0.69	0.253	97.9	<0.001	R	
		Female	2	0.03	-0.39, 0.46	0.885	0.0	0.733	F	
	Age	Mix	9	-0.02	-0.34, 0.30	0.914	89.1	<0.001	R	
		Children	8	-0.44	-1.07, 0.19	0.173	96.3	<0.001	R	
	Weight	Adolescents	3	0.16	-0.49, 0.82	0.626	90.6	<0.001	R	
		Mix	3	0.03	-0.65, 0.71	0.926	86.9	<0.001	R	
		OW	2	0.08	-0.16, 0.31	0.512	0.0	0.626	R	
	Weight	NW	2	0.20	-1.00, 1.40	0.747	95.5	<0.001	R	
		Mix	9	-0.46	-1.00, 0.08	0.097	95.8	<0.001	R	
TPO-Ab (IU/mL)	Overall	2	0.14	0.08, 0.21	<b>&lt;0.001</b>	24.9	0.249	F	-	
IGF-1 (ng/mL)	Overall	9	-0.30	-1.24, 0.64	0.528	97.8	<0.001	R	0.573	
	Sex	Male	1	0.50	0.15, 0.85	0.005	-	-	R	
		Mix	8	-0.40	-1.44, 0.63	0.446	97.8	<0.001	R	
	Design	Multicenter	4	-0.55	-2.86, 1.77	0.644	96.8	<0.001	R	
		Single-center	5	-0.10	-1.25, 1.06	0.870	98.5	<0.001	R	
	Source	Children	6	-0.61	-1.74, 0.51	0.285	98.4	<0.001	R	
		Mix	3	0.40	-1.94, 2.73	0.739	95.5	<0.001	R	
		Blood	6	0.39	-0.74, 1.53	0.499	98.4	<0.001	R	
	Source	Urinary	1	-3.37	-4.14, -2.59	<0.001	-	-	R	
		CSF	2	-0.89	-1.42, -0.36	<b>0.001</b>	0.0	0.566	F	
IGFBP-3 (μg/mL)	Overall	3	-0.97	-2.54, 0.60	0.224	97.9	<0.001	R	0.562	
Leptin (ng/mL)	Overall	15	0.46	0.17, 0.74	<b>0.002</b>	84.1	<0.001	R	0.383	
	Sex	Male	4	1.03	0.006, 2.05	<b>0.049</b>	91.9	<0.001	R	
		Female	2	0.91	-3.43, 5.25	0.681	96.7	<0.001	R	
	Design	Mix	10	0.35	0.01, 0.69	<b>0.044</b>	85.9	<0.001	R	
		Multicenter	1	1.10	0.71, 1.49	<0.001	-	-	R	
	Single-center	14	0.40	0.12, 0.69	<b>0.006</b>	82.6	<0.001	R		

**Table 4. Continued.**

Variables	No.	SMD	95% CI	$p_{ES}$	$I^2$	$p_H$	Model	$p_{PB}$	
Age	Children	10	0.46	0.08, 0.83	<b>0.016</b>	84.6	<0.001	R	
	Adolescents	2	0.04	-0.21, 0.29	0.741	0.0	0.818	F	
	Mix	3	0.78	0.15, 1.41	<b>0.015</b>	80.4	0.006	R	
	OW	2	0.11	-0.13, 0.36	0.375	0.0	0.783	R	
	NW	2	0.60	-0.56, 1.77	0.308	95.1	<0.001	R	
	Mix	11	0.51	0.14, 0.87	<b>0.006</b>	83.3	<0.001	R	
Ghrelin (ng/mL)	Overall	2	0.14	-0.74, 1.02	0.752	87.8	0.004	R	-
Adiponectin ( $\mu\text{g/mL}$ )	Overall	7	-0.30	-0.75, 0.14	0.184	87.4	<0.001	R	0.773
	Sex	Male	1	-0.75	-1.26, -0.23	0.005	-	-	R
	Mix	6	-0.23	-0.73, 0.27	0.363	88.9	<0.001	R	
	Age	Children	4	-0.47	-1.08, 0.14	0.128	90.9	<0.001	R
	Mix	3	-0.06	-0.75, 0.64	0.875	81.5	0.004	R	

Bold indicates indicators with the  $p_{ES}$ -value < 0.05 by analysis of more than one dataset.



**Fig. 5. Forest plots showing significantly higher leptin levels in ASD patients than in HCs.**

### 3.4 Meta-analysis of Levels of Growth Indicators Between NDDs and HCs

#### 3.4.1 IGF-1

Fourteen studies with 15 datasets measured IGF-1 concentration in NDD patients and HCs (**Supplementary Table 1**). The overall meta-analysis did not detect a significant difference in IGF-1 between two groups (SMD = -0.41; 95% CI = -1.14 to 0.33;  $p_{ES}$  = 0.275). However,

subgroup analysis of studies with CSF samples found IGF-1 levels were significantly reduced in NDD patients relative to HCs (SMD = -0.89; 95% CI = -1.42 to -0.36;  $p_{ES}$  = 0.001) (Table 2).

Six and nine datasets were respectively used to determine the difference in levels of IGF-1 between ADHD/ASD and HCs. Similarly to NDDs, IGF-1 levels were not significantly different between ADHD (SMD = -0.57; 95% CI =

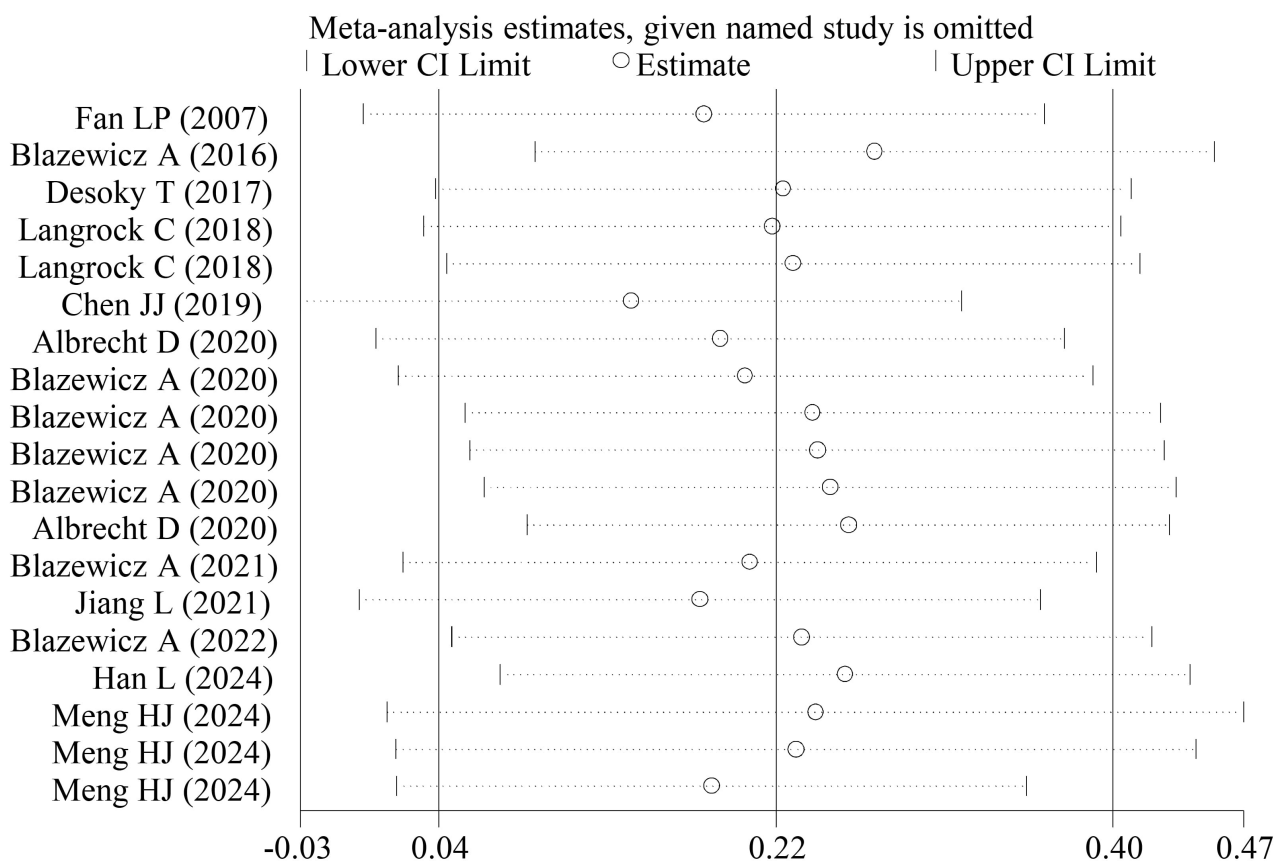


Fig. 6. Sensitivity analysis for FT3.

-1.93 to 0.80;  $p_{ES} = 0.414$ )/ASD (SMD = -0.30; 95% CI = -1.24 to 0.64;  $p_{ES} = 0.528$ ) and HCs in the overall meta-analysis (Tables 3,4). Reduced IGF-1 levels were only observed in ASD patients in subgroup analysis of studies with CSF samples (SMD = -0.89; 95% CI = -1.42 to -0.36;  $p_{ES} = 0.001$ ) (Table 4).

### 3.4.2 IGFBP-3

The concentration of IGFBP-3 in NDD patients and HCs were determined and compared in five studies (Supplementary Table 1). Regardless of total NDDs (SMD = -0.51; 95% CI = -1.29 to 0.28;  $p_{ES} = 0.204$ ) (Table 2) or specific ADHD (SMD = 0.05; 95% CI = -0.32 to 0.42;  $p_{ES} = 0.773$ ) (Table 3)/ASD cases (SMD = -0.97; 95% CI = -2.54 to 0.60;  $p_{ES} = 0.224$ ) (Table 4), IGFBP-3 levels were not found to be significantly altered when compared to HCs.

## 3.5 Meta-analysis of Levels of Appetite Indicators Between NDDs and HCs

### 3.5.1 Leptin

The difference in the concentration of leptin between NDD patients and HCs was evaluated by 17 studies that included 24 datasets (Supplementary Table 1). Pooled analysis uncovered no significant disparities in levels of leptin between NDD patients and HCs (SMD = 0.10; 95% CI =

0.33 to 0.53;  $p_{ES} = 0.645$ ) (Table 2; Fig. 5). However, subgroup analysis showed leptin levels were significantly increased in male (SMD = 0.74; 95% CI = 0.10 to 1.38;  $p_{ES} = 0.023$ ), normal weight (SMD = 0.80; 95% CI = 0.007 to 1.60;  $p_{ES} = 0.048$ ), mixed-age (SMD = 0.53; 95% CI = 0.02 to 1.04;  $p_{ES} = 0.042$ ) NDDs when compared to HCs (Table 2).

Independent meta-analysis for ADHD cases did not detect significant changes in levels of leptin regardless of pooled or subgroup analysis (Table 3; Fig. 5). However, compared with HCs, leptin levels were significantly increased in ASD patients (SMD = 0.46; 95% CI = 0.17 to 0.74;  $p_{ES} = 0.002$ ) (Table 4; Fig. 5). Subgroup analysis of studies with male (SMD = 1.03,  $p_{ES} = 0.049$ ), mixed-sex (SMD = 0.35,  $p_{ES} = 0.044$ ), a single-center design (SMD = 0.4,  $p_{ES} = 0.006$ ), children (SMD = 0.46,  $p_{ES} = 0.016$ ), mixed-age (SMD = 0.78,  $p_{ES} = 0.015$ ) and mixed-weight (SMD = 0.51,  $p_{ES} = 0.006$ ) cases also confirmed significantly high levels of leptin in ASD cases (Table 4).

### 3.5.2 Ghrelin

Seven studies investigated levels of ghrelin in NDD patients and HCs (Supplementary Table 1). The meta-analysis of these studies found no significant difference in ghrelin levels between the two groups. Subgroup analysis observed a significant increase in ghrelin levels in male

NDD patients relative to HCs, although the  $p$ -value was approximately 0.05 (SMD = 1.03; 95% CI = 0.01 to 2.04;  $p_{ES} = 0.047$ ) (Table 2). Non-significant results were also detected during independent meta-analysis of ADHD (Table 3) and ASD cases (Table 4).

### 3.5.3 Adiponectin

Nine studies with ten datasets examined levels of adiponectin in NDD patients and HCs (**Supplementary Table 1**), which were used for the meta-analysis. Results showed adiponectin levels were not significantly changed in total NDD patients (Table 2), ADHD (Table 3) and ASD (Table 4) patients when compared to HCs. Subgroup analysis also obtained non-significant results for all cases.

### 3.6 PB and Sensitivity Analysis

Egger's linear regression test was used to determine the PB for each variable. As shown in Tables 2,3,4, there was evidence of PB for analysis of FT4 in total NDD patients ( $p_{PB} < 0.001$ ), FT4 ( $p_{PB} = 0.008$ ), TT3 ( $p_{PB} = 0.002$ ) in ADHD patients, FT3 ( $p_{PB} = 0.005$ ) and FT4 ( $p_{PB} < 0.001$ ) in ASD patients. A trim-and-fill analysis was then performed for them to adjust the ES. Consequently, FT4 levels were found to be significantly reduced in NDD (random-effect: SMD =  $-0.57$ ; 95% CI =  $-0.74$  to  $-0.41$ ;  $p_{ES} < 0.001$ ; fixed-effect: SMD =  $-0.67$ ; 95% CI =  $-0.69$  to  $-0.64$ ;  $p_{ES} < 0.001$ ), ADHD (random-effect: SMD =  $-0.55$ ; 95% CI =  $-0.81$  to  $-0.29$ ;  $p_{ES} < 0.001$ ; fixed-effect: SMD =  $-0.62$ ; 95% CI =  $-0.65$  to  $-0.58$ ;  $p_{ES} < 0.001$ ) and ASD (random-effect: SMD =  $-0.60$ ; 95% CI =  $-1.02$  to  $-0.17$ ;  $p_{ES} = 0.006$ ; fixed-effect: SMD =  $-0.74$ ; 95% CI =  $-0.79$  to  $-0.68$ ;  $p_{ES} < 0.001$ ) patients when compared to HCs; TT3 levels were found to be significantly reduced in ADHD patients under a fixed-effect model (SMD =  $-1.38$ ; 95% CI =  $-1.42$  to  $-1.34$ ;  $p_{ES} < 0.001$ ); the changes in FT3 levels of ASD patients were the same as pre-adjusted results.

Sensitivity analyses showed that by individually excluding the studies in a series of leave-one-out analyses, no significant changes were obtained in the effect estimates for all variables, providing support for the robustness of the meta-analysis conclusion (Fig. 6).

## 4. Discussion

Although there was one meta-analysis [13] that explored the link of thyroid hormones in children with the development of NDDs, this study only collected data of FT4 and TSH before August 23, 2024. In the present study, an updated meta-analysis that retrieved studies providing all thyroid hormones (e.g., FT3, FT4, TT3, TT4, TSH and TPO-Ab) in both children and adolescents with NDDs and HCs until March 1, 2025, was performed. Consequently, 26 and 32 datasets were respectively obtained for analysis of FT4 and TSH, the sample size of which was clearly larger than those of the study of Meng *et al.* [13] (FT4, 9; TSH, 14)

and thus, the conclusion may be more certain. As expected, the results of the overall meta-analysis were non-significant for both FT4 (SMD =  $-0.02$ ; 95% CI =  $-0.19$  to  $0.15$ ) and TSH (SMD =  $-0.08$ ; 95% CI =  $-0.23$  to  $0.08$ ), which was somewhat different from those of Meng *et al.* [13] (FT4: MD =  $-0.29$ , 95% CI:  $-0.50$  to  $-0.09$ , significant; TSH: MD =  $-0.07$ , 95% CI:  $-0.36$  to  $0.2$ , non-significant). However, significantly reduced FT4 was observed in the overall analysis for the ADHD-IT subtype, subgroup analyses for total NDDs/ADHD (multicenter studies) and trim-and-fill adjusted analysis for total NDDs, ADHD and ASD. More interestingly, subgroup analysis revealed lower TSH levels were associated with an increased risk for NDDs diagnosis in children, but not in adolescents. Furthermore, this study, for the first time, identified that compared to HCs, FT3 levels were significantly increased in total NDD and ADHD patients; TT4 levels were significantly decreased in total NDD and ADHD-IT patients; TT3 levels were only elevated in each ADHD subtype (ADHD-IT, ADHD-HIT, ADHD-CT); TPO-Ab levels were significantly increased in total NDD, ADHD and ASD patients. This suggests TSH, FT4 and TPO-Ab may represent potential biomarkers for diagnosing and monitoring children and/or adolescents with various NDDs (both ADHD and ASD), while FT3, TT3 and TT4 may be associated with the development of ADHD.

Thyroid hormones are synthesized and secreted by the thyroid gland. T4 is the major thyroid hormone secreted by this gland. However, T4 is a biologically inactive form that must be converted to T3 by iodothyronine deiodinases for biological activity in target cells. T4 and T3 can be free or bound to plasma proteins, among which, only FT4 and FT3 are pivotal for physiological functions [32]. Therefore, theoretically, the importance sequence of thyroid hormones for the development of diseases may be FT3 > FT4 > TT3 > TT4, which was demonstrated here (i.e., overall meta-analysis for NDDs and ADHD achieved significant results for FT3. Also, the number of analyzed data was more than six; while only subgroup or pooled analysis with a small number of datasets confirmed significant findings for other hormones). Existing evidence has demonstrated these thyroid hormones play fundamental roles in brain development. For example, mutations in THRB or THRA were reported to cause syndromes of resistance to thyroid hormone (RTHB or RTHA) in patients who exhibited an ADHD-like phenotype [33]. T3 functioned mainly via binding to THRB or THRA. THRB or THRA mutations may disrupt T3 binding and inactivate downstream signaling pathways, ultimately promoting elevated T3 levels in the blood [34]. Furthermore, the production and release of T3 are stimulated by TSH through the hypothalamic-pituitary thyroid axis. The T3 accumulated in the blood may exert a negative feedback effect on the anterior pituitary and thereby suppress TSH secretion [35]. Higher FT3, TT3 and lower TSH represent the status of hyperthyroidism which has several symptoms in common with ADHD, including hyper-

activity and inattention. It had been demonstrated that the prevalence ratio of ADHD in those with hyperthyroidism increased 1.7-fold when compared to the reference population [36]. An *in vitro* study also revealed that treatment with high-dose T3 reduced the viability of neural precursor cells and induced hyperactivity of cortical neurons as well as similar transcriptomic changes with ASD and ADHD patients [37]. Lower levels of T4 may be associated with increased expression and enzymatic activity of deiodinase 2 [38,39]. TPO-Ab is a thyroid autoimmune antibody. High levels of TPO-Ab indicate the presence of inflammatory diseases in the thyroid gland. Numerous studies have implied activation of inflammation may be a risk factor for the development of ADHD and ASD symptoms in adolescence [40,41], including increased number of M1 macrophages and secretion of pro-inflammatory cytokines [e.g., interleukin (IL)-1 $\beta$ , IL-6, IL-8 and tumor necrosis factor- $\alpha$ ] when compared to HCs [42]. Maternal hypothyroxinemia was also reported to induce ASD-like phenotypes in the offspring who simultaneously exhibited immune disorders manifested primarily by the significant increase in levels of pro-inflammatory cytokine IL-17A in blood and brain tissues, as well as the enhancement in the ratio of Th17/Treg cells and frequencies of M1-like macrophages in the spleen. Supplementation with T4 prevented maternal hypothyroxinemia-induced ASD phenotypes and immune responses [43]. Such findings may explain results reported here that high levels of TPO-Ab, FT3, TT3 and low levels of FT4, TT4, TSH predicted a high risk of ADHD and/or ASD.

Currently, there were no meta-analyses that investigated the association of IGF-1/IGFBP-3 with NDDs. In this study, six and nine datasets that respectively analyzed ADHD and ASD were, for the first time, integrated. Although the overall meta-analysis did not obtain significant differences between NDDs (ADHD and ASD) and HCs, subgroup analysis indicated significantly reduced IGF-1 levels in CSF samples of ASD when compared to HCs. IGF-1, a polypeptide hormone, was implicated in exerting neuro-protective roles in brain cells, including increasing cell viability and decreasing both proapoptotic caspase-3 activity and lactate dehydrogenase release through activation of the PI3K/AKT-YAP/TAZ cascade [44,45]. In SHANK3-deficient mice that mimicked ASD, daily intraperitoneal injections of IGF-1 or its derivative were observed to reverse deficits in hippocampal  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid signaling, long-term potentiation and motor performance [46]. Clinical trials found that treatment with IGF-1 triggered significant improvements in social impairment, restrictive behaviors and hyperactivity in SHANK3-deficient children [47,48]. These findings may support low levels of IGF-1 as a pathogenesis of ASD.

Chen *et al.* [49] used a meta-analysis to explore the changes of appetite hormones (including leptin,  $n = 11$ ;

ghrelin,  $n = 2$ ; adiponectin,  $n = 7$ ) in children with ASD, with leptin significantly increased to be identified. However, articles included in the study of Chen *et al.* [49] contained data from patients undergoing medical treatment (methylphenidate or atomoxetine) which may have influenced levels of those appetite hormones (e.g., increase leptin, ghrelin and adiponectin) [29,50]. In this study, all data were collected from drug-naïve patients with ADHD and ASD. When compared to Chen *et al.*' study [49], more or newly published [51–53] datasets were included for analysis of ASD (leptin:  $n = 15$ ; ghrelin:  $n = 2$ ; adiponectin:  $n = 7$ ). Moreover, appetite hormones were, for the first time, analyzed for ADHD patients (leptin:  $n = 9$ ; ghrelin:  $n = 5$ ; adiponectin:  $n = 3$ ). Regardless of pooled or subgroup analysis, no remarkably significant differences in levels of adiponectin were identified between total NDDs/ADHD/ASD and HCs. Leptin and ghrelin levels were found to be significantly increased in male NDDs (leptin: ADHD,  $n = 2$ ; ASD,  $n = 4$ ; ghrelin: ADHD,  $n = 1$ ; ASD,  $n = 1$ ); leptin levels were also higher in independent analyses of all ASD patients and several subgroups. Leptin was originally discovered to be secreted from adipose tissues into the blood and function as a regulator of body-weight by reducing food intake and increasing energy expenditure [54]. Administration of recombinant leptin was found to induce weight loss [55,56], which was similar to the symptoms of hyperthyroidism (FT3 increase) observed in ASD and ADHD. Additionally, leptin was previously identified to share structural and functional similarities with the IL-6 family of cytokines [57]. *In vitro* incubation with or *in vivo* injection of leptin was shown to stimulate the release of pro-inflammatory mediators (e.g., TNF- $\alpha$ , IL-1 $\beta$  or cyclooxygenase-2) in brain cells [58,59]. Therefore, high levels of leptin may impact the development of ASD by a pro-inflammatory mechanism, which was consistent with the result of the meta-analysis of high TPO-Ab in ASD.

Several limitations should be acknowledged. First, the number of published studies was relatively small for some indicators, such as TPO-Ab, IGFBP3, ghrelin and TG-Ab (only one study; thus, TG-Ab was not analyzed) [13]. Patients in female, adolescent and overweight subgroups were rarely enrolled, which led to the inconclusive ES estimate. Second, the mean and SD were provided for thyroid, growth and appetite hormones in NDDs. Whether the data of these indicators were outside the normal range and the corresponding proportion were very little described [60]. Third, few studies explored the diagnostic efficiency and threshold values of these biomarkers for predicting NDDs by ROC curve analysis and calculation of AUCs [13,14,61,62]. Fourth, few research evaluated clinical factors that affected levels of thyroid, growth and appetite hormones, such as dietary intake, nutrition (albumin) [63], genetics (polymorphism) [14,24,62] and environmental factors (perfluoroalkyl substances) [64]. Fifth, there was evidence of significant heterogeneity in the majority of pooled

analyses and it could not be eliminated after subgroup analyses. Sixth, considering the possibly same mechanisms for the development of various NDDs, the meta-analysis was firstly performed for the whole NDDs and then each NDD type. However, our research mainly focused on three types (ADHD, ASD and TD) of NDDs because of their high prevalence and relatively numerous studies. No studies reported the association of thyroid, growth and appetite hormones-related indicators with other types of NDDs [e.g., disorder of intellectual development (DID), developmental speech or language disorder (DSD) or developmental learning disorder (DLD)]. Seventh, the diagnosis criterion of NDDs was somewhat different among included studies (different DSM versions or others), which may influence prevalence rates of patients and levels of studied indicators in them. Therefore, more clinical trials with larger sample sizes and detailed information need to be designed to further understand the associations of these thyroid, growth and appetite biomarkers with various NDDs (including ADHD, ASD, TD, DID, DSD and DLD; classified using the same diagnosis criterion), and confirm their diagnostic thresholds and prediction performance before clinical generalization of these results.

## 5. Conclusions

The current meta-analysis showed a significant association of the high risk of NDDs in children and adolescents with significantly low levels of FT4, TT4, TSH, IGF-1 and high levels of FT3, TT3, TPO-Ab and leptin in bodily fluids. Thyroid hormones (FT3, FT4, TT3, TT4, TSH and TPO-A) were particularly suited as noninvasive biomarkers for monitoring the development of ADHD, while growth factor IGF-1 and the appetite hormone leptin (in addition to FT4 and TPO-Ab) may serve as more desirable biomarkers for predicting ASD.

## Abbreviations

NDDs, neurodevelopmental disorders; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; TD, tic disorder; OR, odds ratio; CI, confidence interval; THR, thyroid hormone receptor; FT3, free triiodothyronine; FT4, free thyroxine; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid stimulating hormone; TPO-Ab, thyroid peroxidase antibody; TG-Ab, thyroglobulin antibody; ROC, receiver operating characteristic; AUC, an area under the ROC curve; IGF-1, insulin-like growth factor-1; IGFBP-3, IGF-binding protein 3; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CSF, cerebrospinal fluid; NOS, Newcastle-Ottawa Scale; SMD, standardized mean difference; ES, effect size; H, heterogeneity; HC, healthy controls; DSM, diagnostic and statistical manual of mental disorders; ADI-R, autism diagnostic interview-revised; ADOS, autism diagnostic observation schedule; CARS, childhood autism rating scale; K-SADS-PL, kiddie sched-

ule for affective disorders and schizophrenia of school-age children-present and lifetime version; DBDRS, diagnostic interview and disruptive behavior disorder rating scale; ICD-10, international statistical classification of diseases and related health problems 10th revision; CCMD, Chinese classification of mental disorders; ADH-IT, ADHD-predominantly inattentive type; ADHD-HIT, ADHD-the predominantly hyperactive/impulsive type; ADHD-CT, ADHD-combined type.

## Availability of Data and Materials

The data used for meta-analysis in the study are displayed in **Supplementary Table 1**.

## Author Contributions

HW: Data curation, Formal analysis, Writing — original draft. KH: Data curation, Formal analysis, Writing — original draft. LZP: Conceptualization, Methodology, Supervision, Writing — review & editing. XCX: Conceptualization, Supervision, Writing — review & editing. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.31083/JIN39816>.

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