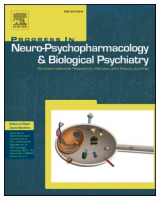
Progress in Neuropsychopharmacology & Biological Psychiatry 111 (2021) 110402

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp



Thyroid hormones in persons with schizophrenia: A systematic review and meta-analysis

Błażej Misiak [a,i,*], Bartłomiej Stańczykiewicz [b], Michał Wiśniewski [c], Francesco Bartoli [d,e], Giuseppe Carra [d,e,f], Daniele Cavaleri [d], Jerzy Samochowiec [g], Konrad Jarosz [h], Joanna Rosińczuk [b], Dorota Frydecka [i]

[a] Department of Psychiatry, Division of Consultation Psychiatry and Neuroscience, Wroclaw Medical University, Pasteura 10 Street, 50-367 Wroclaw, Poland
[b] Department of Nervous System Diseases, Wroclaw Medical University, Bartla 5 Street, 51-618 Wroclaw, Poland
[c] First Department of Psychiatry, Institute of Psychiatry and Neurology, Sobieskiego 9 Street, 02-957 Warsaw, Poland
[d] Department of Medicine and Surgery, University of Milano Bicocca, Monza, Italy
[e] Department of Mental Health & Addiction, ASST Nord Milano, Milano, Italy
[f] Division of Psychiatry, University College London, London, UK
[g] Department of Psychiatry, Pomeranian Medical University, Broniewskiego 26 Street, 71-460 Szczecin, Poland
[h] Department of Clinical Nursing, Pomeranian Medical University, Żołnierska 48 Street, 71-210 Szczecin, Poland
[i] Department of Psychiatry, Wroclaw Medical University, Pasteura 10 Street, 50-367 Wroclaw, Poland

ARTICLE INFO

Keywords:
Psychoneuroendocrinology
Thyroid gland
Psychotic disorders
Comorbidity

ABSTRACT

There is accumulating evidence that individuals with schizophrenia show altered levels of thyroid hormones. However, a qualitative and quantitative synthesis of findings in this field has not been performed so far. Therefore, we aimed to perform a systematic review and meta-analysis of studies investigating the levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), total thyroxine (tT4), free triiodothyronine (fT3) and total triiodothyronine (tT3) in multiple-episode schizophrenia (MES) and first-episode psychosis (FEP). Electronic databases were searched from their inception until 30th May 2020 by two independent reviewers. Random-effects meta-analyses and meta-regression analyses were performed. Altogether, 19 studies were included. Persons with FEP had significantly lower TSH levels (5 studies, $g = -0.26$, 95%CI: −0.47 to −0.06, $p = 0.013$, $I^2 = 21.3\%$), higher fT4 levels (3 studies, $g = 0.58$, 95%CI: 0.15–1.01, $p = 0.008$, $I^2 = 64.6\%$) and lower tT3 levels (2 studies, $g = -0.60$, 95%CI: −0.82 to −0.37, $p < 0.001$, $I^2 = 0\%$) compared to controls. Elevated TSH levels were found in persons with MES (13 studies, $g = 0.20$, 95%CI: 0.02–0.39, $p = 0.031$, $I^2 = 50.0\%$). Our findings imply that the levels of TSH might be decreased in persons with FEP and increased in those with MES. Other alterations need to be confirmed by additional studies. These findings imply the need to monitor the levels of TSH and thyroid hormones from the onset of psychosis.

1. Introduction

Physical health impairments are highly prevalent among persons with schizophrenia and largely contribute to reduced life expectancy (Piotrowski et al., 2017). Apart from cardiovascular diseases, persons with schizophrenia tend to develop several endocrine abnormalities related to the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, release of neurosteroids (Misiak et al., 2018) and appetite-regulating hormones (Misiak et al., 2019) as well as hyperprolactinemia (González-Blanco et al., 2016). Some of these alterations might also be associated with a risk of metabolic syndrome and its single components. The development of certain endocrine abnormalities is associated with individual level risk factors that include poor dietary habits, sedentary behavior and adverse effects of antipsychotics. However, some of them, e.g., hyperprolactinemia, insulin resistance and the HPA axis alterations, can also appear in early psychosis and might be related to intrinsic pathophysiological mechanisms (González-Blanco et al., 2016; Hubbard and Miller, 2019; Lis et al., 2020).

Less is known about the role of thyroid hormones in the pathophysiology of schizophrenia. In response to low levels of thyroid

* Corresponding author.
E-mail address: blazej.misiak@umed.wroc.pl (B. Misiak).

https://doi.org/10.1016/j.pnpbp.2021.110402
Received 6 April 2021; Received in revised form 9 July 2021; Accepted 12 July 2021
Available online 15 July 2021

hormones, including thyroxine (T4) and triiodothyronine (T3), the hypothalamus secrets thyrotropin-releasing hormone (TRH). Subsequently, TRH stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH) that activates the secretion of thyroid hormones. This regulation is called the hypothalamic-pituitary-thyroid axis and acts through a negative feedback. It is important to note that thyroid hormones play a role in neurodevelopmental processes, such as differentiation of neural cells, synaptogenesis and myelination. Indeed, T4 is the major thyroid gland hormone that can cross the blood-brain barrier; however, T3 can also enter the brain through complex transport mechanisms (Tost et al., 2020). Subsequently, T4 is converted to T3 by deionidase type 2 in astrocytes, and T3 can enter neurons (Noda, 2015). There are membrane and non-genomic intracytoplasmatic receptors for thyroid hormones, although the most well-characterized are genomic thyroid receptors (TRs), which regulate gene expression by acting as ligand-activated transcription factors. Notably, T3 exerts biological activity through the interactions with two isoforms TRs - TRα1 and TRβ1. However, the TRα1 isoforms represent 70–80% of all receptors and account for most effects of thyroid hormones in the brain, while TRβ1 exhibits more restricted tissue expression pattern in the brain (Bernal, 2007; Ercan-Fang et al., 1996). Although TRs are expressed early (TRα1) and later (TRβ1) in the embryonic development, they are also described as moderate to prominent in adult brain regions, mainly the cerebral cortex and the hippocampus (Bradley et al., 1989). Thyroid hormones have been shown to affect neurodevelopmental processes, such as neuronal proliferation, migration, differentiation and synapse formation (Dezonne et al., 2015), while in adult brain they interact with glial cells that modulate immune responses, regulate neurotransmitter release, and control neuron metabolism (Noda, 2018). Thyroid hormones are important for modulation of dopaminergic, serotonergic, glutamatergic, and GABAergic networks (Santos et al., 2012).

It has been reported that clinically relevant hyperthyroidism might manifest in people with psychotic symptoms, while hypothyroidism may give rise to mood symptoms that resemble negative symptoms of schizophrenia (MacDonald and Schulz, 2009; Marian et al., 2009; Snabboon et al., 2009). A recent population-based study demonstrated that a diagnosis of schizophrenia is significantly more prevalent in hypothyroid patients compared to controls (Sharif et al., 2018). However, studies investigating the levels of thyroid hormones in persons with psychotic disorders have provided mixed findings. Recognizing the pattern of alterations related to thyroid hormones in persons with schizophrenia might have important implications due to several clinical correlates. For instance, few cross-sectional studies have provided evidence for the association between altered levels of thyroid hormones and cognitive deficits or comorbid metabolic syndrome in persons with psychotic disorders (Ichioka et al., 2012; Kalinowska et al., 2019; Labad et al., 2016). Therefore, in this study we aimed to perform a systematic review and meta-analysis of studies investigating the levels of TSH and thyroid hormones in persons with schizophrenia and first-episode psychosis (FEP).

2. Materials and methods

2.1. Search strategy

Three reviewers were involved in searches of online databases from their inception until 30th May 2020 (see Supplementary Table 1 for details). Online searches were performed in agreement with the PRISMA guidelines (Moher et al., 2009), and the protocol of our systematic review and meta-analysis was registered in the PROSPERO database (registration number: CRD42020163283). The PRISMA checklist was presented in Supplementary Table 2.

2.2. Eligibility criteria

Publication records were included if they met the following criteria: 1) reported the levels of TSH and/or thyroid hormones, including free thyroxine (fT4) and/or total thyroxine (tT4) and/or free triiodothyronine (fT3) and/or total triiodothyronine (tT3) in serum or plasma samples; 2) necessary data (mean and SD for the levels of TSH and thyroid hormones, the number of participants and medication status) were available in the manuscript or upon request (corresponding authors of eligible publications were contacted if necessary); 3) case-control studies comparing the levels of thyroid hormones between persons with schizophrenia, schizoaffective disorder or FEP and healthy controls; 4) English language articles. This systematic review was limited to case-control studies due to the fact that these studies often build first evidence between specific mechanisms and outcomes (Tenny et al., 2020). To our knowledge, a qualitative and quantitative synthesis of evidence in this field has not been performed so far. Moreover, the levels of TSH and thyroid hormones are related to various environmental exposures and comorbid physical health impairments that might be difficult to control in longitudinal studies (Ferrari et al., 2017). In case of overlapping samples, data were included from the study reporting results from the largest sample. We excluded animal model studies, studies without healthy controls, non-original studies (e.g., editorials, commentaries and reviews) and studies without necessary data to perform meta-analysis.

2.3. Data extraction

The following data were extracted from eligible publications (mean ± SD or the number of cases): 1) age; 2) sex; 3) body mass index (BMI); 4) the levels of TSH and thyroid hormones; 5) scores of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987); 6) medication status and 7) the type of assay used to determine the levels of hormones. Data provided as median and interquartile range (IQR) were converted to calculate mean and SD. More specifically, the median was used as an approximation of the mean (Higgins et al., 2019). In turn, SD was calculated by dividing IRQ by 1.35 (Hozo et al., 2005).

Quality assessment was performed using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000). The NOS is a “star system” that enables to assess three categories of quality: 1) the selection of study groups (the maximum score is 4 stars); 2) the comparability of study groups (the maximum score is 2 stars) and 3) the ascertainment of exposure or outcome of interest (the maximum score is 3 stars). The total NOS score ranges between 0 and 9 stars. Higher number of stars indicates better quality. Matching patients and healthy controls for age and sex was considered to allocate stars for the comparability of studied groups.

2.4. Data analysis

Heterogeneity was evaluated using the Cochran Q and I^2 statistics. Due to anticipated heterogeneity, random-effects models were used and standardized mean difference (Hedges' g) was calculated as the effect size estimate. Hedges' g was selected to dermine effect size estimates due to expected heterogeneity in the methods used to measure the levels of TSH and thyroid hormones (Ellis, 2010). Moreover, the use of Hedges' g is recommended in case of small studies ($n < 20$) (Lakens, 2013). A leave-one-out sensitivity analysis was performed to investigate if any single study contributed to heterogeneity. Subgroup analyses were performed to explore thyroid hormones alterations separately for drug- or antipsychotic-naïve persons with FEP and medicated or unmedicated individuals with multiple-episode schizophrenia (MES). Meta-regression analyses were performed for continuous moderators that were recorded by at least six studies (age of persons with FEP and MES as well as healthy controls, the percentage of males, illness duration and scores of the PANSS) and categorical moderators if each category was represented by at least four studies (type of assay used to determine the levels of thyroid hormones) (Fu et al., 2011). Publication bias was assessed using the Egger's test in case of analyses based on at least 10 studies (Sterne et al., 2008). Results of all analyses were considered significant if the *p*-

value was less than 0.05. The STATISTICA software, version 12.5, was used to conduct the analyses.

3. Results

Initial search identified 2582 publication records and 19 studies were finally included in systematic review and meta-analysis (Fig. 1) (Banki et al., 1984; Barbero et al., 2014; Baumgartner et al., 2000; Bičíková et al., 2011; Boral et al., 1980; Bratek et al., 2015; Del Cacho et al., 2019; Extein et al., 1982; Garcia-Rizo et al., 2012; Jose et al., 2015; Lin et al., 2019; Loosen et al., 1977; Petrikis et al., 2016; Prange et al., 1979; Roy et al., 1989; Wahby et al., 1988; Yazici et al., 2002; Zhu et al., 2020). General characteristics of eligible studies are shown in Table 1, while the levels of hormones are presented in Supplementary Table 3. Altogether, these studies investigated the levels of thyroid hormones in 1138 persons with FEP and MES as well as 730 healthy controls. In case of three publication records (Barbero et al., 2019, 2014; Labad et al., 2016), samples were overlapping and the corresponding author was contacted to provide data from the largest number of participants. This sample is further reported as Barbero et al. (2014).

The NOS score varied between 3 and 7 (4.00 ± 1.05, Supplementary Table 4). Persons with FEP or MES and healthy controls were matched for age and sex in the majority of studies, except for five studies (Boral et al., 1980; Extein et al., 1982; Lin et al., 2019; Loosen et al., 1977; Zhu et al., 2020). Only two studies controlled for the effects of BMI (Garcia-Rizo et al., 2012; Zhu et al., 2020). In the study by Zhu et al. (2020), persons with FEP and MES had significantly higher BMI compared to healthy controls. In turn, persons with FEP and controls had similar BMI in the study by Garcia-Rizo et al. (2012). There were six studies of persons with FEP (Bičíková et al., 2011; Del Cacho et al., 2019; Garcia-Rizo et al., 2012; Jose et al., 2015; Petrikis et al., 2016; Zhu et al., 2020). All of these studies were based on drug-naïve or antipsychotic-naïve persons. In one study, medicated persons with early psychosis were recruited (illness duration shorter than 3 years) (Barbero et al., 2014). Other studies were based on persons with MES, who had been drug- or antipsychotic-free (Banki et al., 1984; Baumgartner et al., 2000; Boral et al., 1980; Jose et al., 2015; Loosen et al., 1977; Prange et al., 1979; Roy et al., 1989; Wahby et al., 1988) or medicated (Bratek et al., 2015; Extein et al., 1982; Lin et al., 2019; Telo et al., 2016; Zhu et al., 2020). The minimum time period without pharmacological treatment in drug-free or antipsychotic-free persons with MES varied between 5 days (Prange et al., 1979) and 2 months (Jose et al., 2015).

3.1. TSH

All studies included in this systematic review and meta-analysis investigated the levels of TSH. Results of the Egger's test did not reach the significance threshold (regression intercept = 0.05, 95%CI = −1.95–2.04, $p = 0.960$) indicating no evidence of publication bias (see Supplementary Fig. 1 for funnel plot). Pooled data analysis revealed no significant differences [g = 0.001, 95%CI = −0.12–0.12, $p = 0.982$, $I^2 = 53.65\%$, Q = 23.7, p(Q) = 0.014] in the levels of TSH between patients and healthy controls (Table 2, Fig. 2, Supplementary Fig. 2). However, subgroup analysis showed significantly lower levels of TSH in drug-naïve or antipsychotic-naïve persons with FEP [g = −0.26, 95%CI = −0.47 - -0.06, $p = 0.013$, $I^2 = 21.3$, Q = 5.1, p(Q) = 0.279] as well as

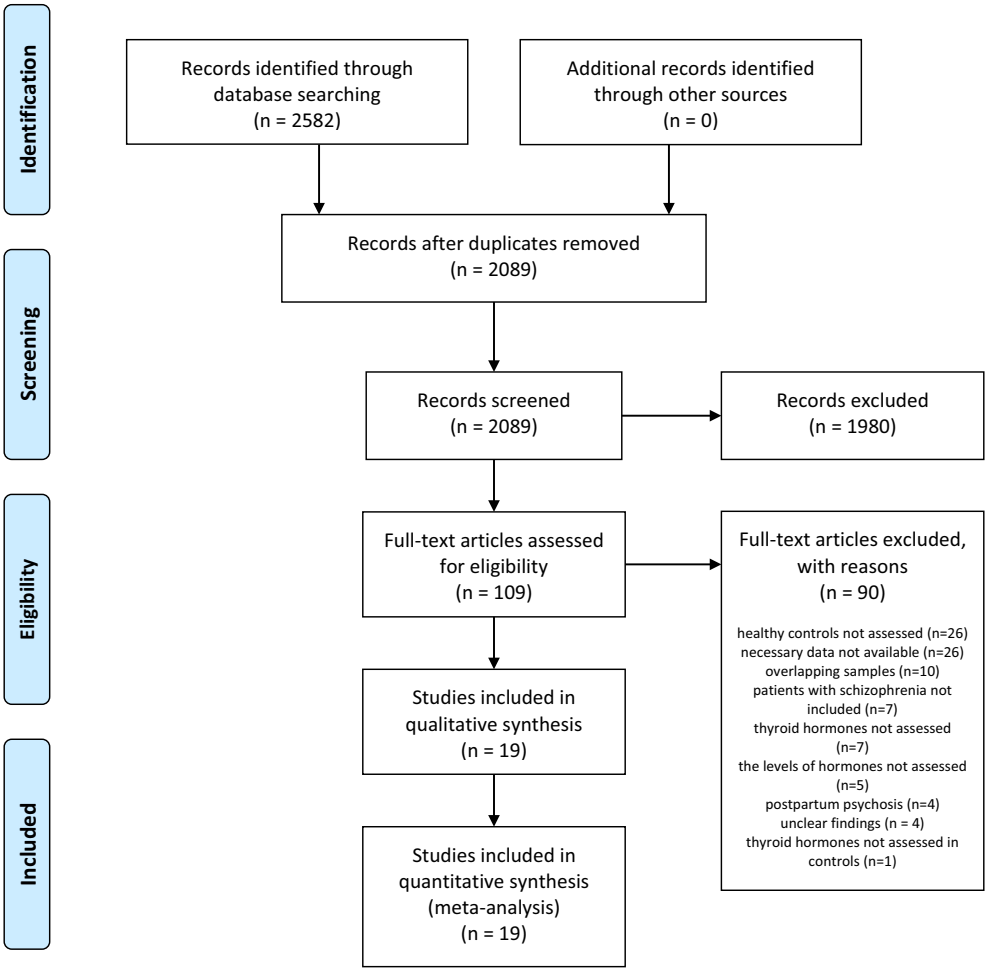


Fig. 1. Selection of studies (Moher et al., 2009).

Table 1
General characteristics of studies.

Study	Patients		Controls		Illness stage	Medication status	Hormones	Assay	NOS
	n (M/F)	Age, years[a]	n (M/F)	Age, years[a]					
Banki et al. (1984)	24 (0/24)	41.0 ± 13.0	15 (0/15)	42.0 ± 11.0	MES	Drug-free (≥30 days)	TSH	RIA	4
Barbero et al. (2014)	70 (43/27)	24.4 ± 5.2	50 (22/28)	23.8 ± 4.8	Early psychosis	Medicated	TSH and fT4	UK	5
Baumgartner et al. (2000)	31 (22/9)	29.2 ± 9.1	24 (17/7)	32.0 ± 4.6	MES	Drug-free (≥7 days)	TSH, tT4, tT3 and rT3	RIA	3
Bičíková et al. (2011)	22 (13/9)[b]	32.6 ± 7.4	47 (25/22)[b]	31.0 ± 5.9[c]	FES	Drug-naïve	TSH and fT4	CLA	5
Boral et al. (1980)	31 (16/15)	22–52	31 (16/15)	UK[d]	MES	Drug-free (≥15 days)	TSH, tT4 and tT3	RIA	3
Bratek et al. (2015)	15 (15/0)	36.6 ± 7.5	15 (15/0)	37.3 ± 7.8	MES	Medicated	TSH	UK	4
Del Cacho et al. (2019)	61 (38/23)	24.6 ± 9.3	45 (25/20)	27.6 ± 10.0	FEP	Drug-naïve	TSH	UK	4
Extein et al. (1982)	30 (22/8)	26.5 ± 8.5	20 (9/11)	29.9 ± 8.6	MES	Medicated	TSH and tT4	RIA	3
Garcia-Rizo et al. (2012)	33 (20/13)	28.6 ± 7.1	33 (21/12)	26.8 ± 5.5	FEP	Antipsychotic-naive	TSH	UK	5
Jose et al. (2015)	38 (38/0)	26.8 ± 4.4	38 (38/0)	29.0 ± 7.1	FES and MES	Drug-naïve and drug-free (at least 60 days)	TSH, fT4 and fT3	CLA	4
Lin et al. (2019)	69 (40/29)	41.8 ± 10.4	44 (13/31)	40.2 ± 8.6	MES	Medicated	TSH and tT3	UK	3
Loosen et al. (1977)	9 (0/9)	28.9 ± 2.0	40 (0/40)	35.9 ± 1.7	MES	Drug-free (≥7 days)	TSH	RIA	3
Petrikis et al. (2016)	40 (27/13)	32.5 ± 9.8	40 (27/13)	32.3 ± 9.1	FES	Drug-naïve	TSH, fT4 and T3	CLA	7
Prange et al. (1979)	17 (8/9)	28.0 ± 4.9	17 (8/9)	UK	MES	Drug-free (≥5 days)	TSH, tT4 and tT3	RIA	3
Roy et al. (1989)	14 (7/7)[e]	25.4 ± 4.4	14 (7/7)	UK[f]	MES	Drug-free (≥14 days) and medicated	TSH	RIA	5
Telo et al. (2016)	63 (31/32)	44.7 ± 10.4	53 (26/27)	41.6 ± 8.0	MES	Medicated	TSH, fT4 and fT3	CLA	4
Wahby et al. (1988)	37 (37/0)	35.5 ± 3.9	45 (45/0)	37.8 ± 1.7	MES	Drug-free (4–8 days)	TSH, tT4 and fT4	RIA	4
Zhu et al. (2020)	486 (292/194)	39.3 ± 12.6	154 (93/61)	37.3 ± 8.1	FES and MES	Antipsychotic-naïve and medicated	TSH, tT4, fT4, tT3 and fT3	CLA	4
Yazici et al. (2002)	58 (35/23)	32.5 ± 11.4	30 (15/15)	33.0 ± 10.0	MES	Drug-free (≥7 days)	TSH, tT4, fT4, tT3 and fT3	UK	3

Abbreviations: CLA – chemiluminescent assay; FEP – first-episode psychosis; FES – first-episode schizophrenia; fT3 – free triiodothyronine; fT4 – free thyroxine; MES – multiple-episode schizophrenia; NOS – the Newcastle-Ottawa Scale; RIA – radioimmunoassay; TSH – thyroid stimulating hormone; tT3 – total triiodothyronine; tT4 – total thyroxine; UK – unknown.

[a] Data expressed as mean ± SD or range.

[b] The levels of hormones reported for 13 male patients and 22 male controls.

[c] SD calculated according to the formula: SD = Interquartile range/1.35.

[d] Patients and controls were reported to be matched for age; however, descriptive statistics for age of controls were not provided.

[e] The levels of hormones reported for 13 patients and 13 controls.

[f] Patients and controls were reported to be matched for gender; however, the numbers of male and female controls were not provided.

Table 2
Main and subgroup analyses.

Hormone	Analysis	k	Meta-analysis			Heterogeneity analysis		
			g	95%CI	p	I^2	Q	p(Q)
TSH	Pooled analysis	20	0.001	−0.12–0.12	0.982	53.65%	23.7	**0.014**
	FEP (AP/drug-naïve)	5	−0.26	−0.47 to −0.06	**0.013**	21.3%	5.1	0.279
	MES (medicated and unmedicated)	13	0.20	0.02–0.39	**0.031**	50.0%	24.0	**0.020**
tT4	Pooled analysis	8	−0.03	−0.62–0.56	0.931	94.4%	125.9	**<0.001**
	MES (medicated and unmedicated)	7	0.08	−0.66–0.83	0.824	95.1%	121.9	**<0.001**
fT4	Pooled analysis	9	0.36	0.09–0.62	**0.009**	79.5%	39.1	**<0.001**
	FEP (AP/drug-naïve)	3	0.58	0.15–1.01	**0.008**	64.6%	5.65	0.059
	MES (medicated and unmedicated)	4	0.22	−0.24–0.68	0.357	85.2%	20.2	**<0.001**
tT3	Pooled analysis	8	−0.55	−0.76 to −0.34	**<0.001**	89.0%	63.6	**<0.001**
	FEP (AP/drug-naïve)	2	−0.60	−0.82 to −0.37	**<0.001**	0%	0.01	0.933
	MES (medicated and unmedicated)	6	−0.20	−0.79–0.39	0.504	92.0%	62.4	**<0.001**
fT3	Pooled analysis	5	0.07	−0.06–0.20	0.293	0%	3.2	0.525

k refers to the number of comparisons.

Significant effect size estimates or heterogeneity measures ($p < 0.05$) were marked with bold characters.

Abbreviations: AP – antipsychotic; FEP – first-episode psychosis; MES – multiple-episode schizophrenia; fT3 – free triiodothyronine; fT4 – free thyroxine; TSH – thyroid stimulating hormone; tT3 – total triiodothyronine; tT4 – total thyroxine.

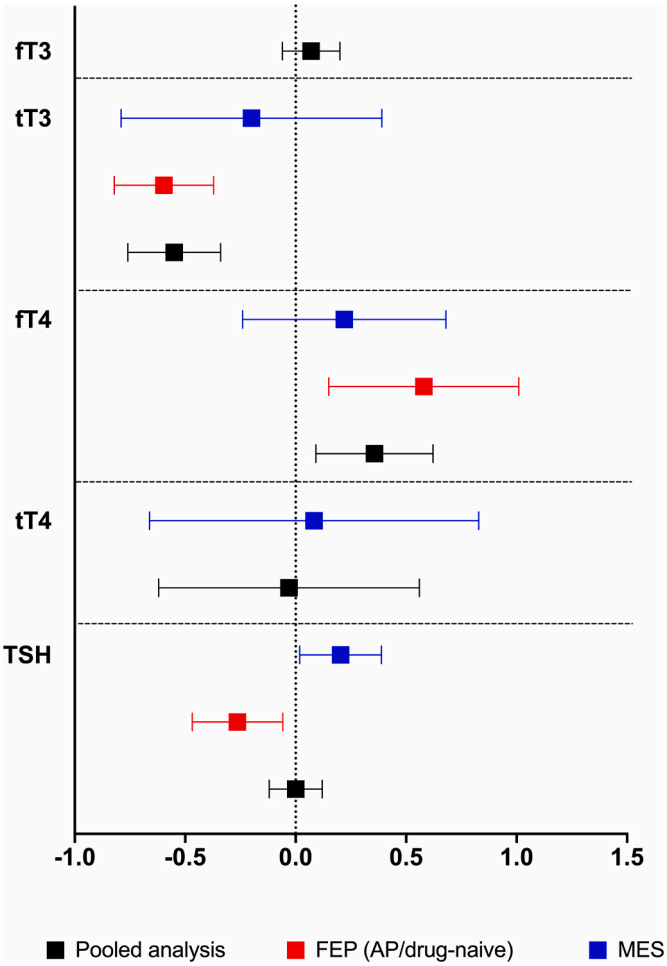


Fig. 2. Summary of effect size estimates for differences in the levels of hypothalamic-pituitary-thyroid axis hormones between persons with schizophrenia and healthy controls. Abbreviations: AP – antipsychotic; FEP – first-episode psychosis; fT3 – free triiodothyronine; fT4 – free thyroxine; MES – multiple-episode schizophrenia; TSH – thyroid stimulating hormone; tT3 – total triiodothyronine; tT4 – total thyroxine.

significantly higher levels of TSH in medicated and unmedicated persons with MES [g = 0.20, 95%CI = 0.02–0.39, $p = 0.031$, $I^2 = 50.0\%$, Q = 24.0, p(Q) = 0.020]. Sensitivity analysis demonstrated that after removing single studies from the subgroup analysis of persons with FEP (Del Cacho et al., 2019) or MES (Prange et al., 1979; Roy et al., 1989; Zhu et al., 2020), there were trends toward significant between-group differences in TSH levels (Supplementary Table 5). Moreover, sensitivity analysis revealed that after removing two single studies (Boral et al., 1980; Lin et al., 2019), the levels of TSH remained significantly lower in persons with MES compared to healthy controls with not significant heterogeneity. However, meta-regression analysis (Table 3) revealed no significant moderators in the analysis of TSH levels.

3.2. tT4

The levels of tT4 were assessed by seven studies (Baumgartner et al., 2000; Boral et al., 1980; Extein et al., 1982; Prange et al., 1979; Wahby et al., 1988; Yazici et al., 2002; Zhu et al., 2020). Pooled analysis of these studies (Table 2, Supplementary Fig. 3) revealed no significant between-group differences in the levels of tT4 [g = −0.03, 95%CI = −0.62–0.56, $p = 0.931$, $I^2 = 94.4\%$, Q = 125.9, p(Q) < 0.001]. No significant differences in tT4 levels between persons with MES and healthy controls were found [g = 0.08, 95%CI = −0.66–0.83, $p = 0.824$, $I^2 = 95.1\%$, Q = 121.9, $p < 0.001$]. Sensitivity analysis demonstrated that differences in the levels of tT4 between individuals with MES and healthy controls remained not significant after removing single studies (Supplementary Table 5). No single study was found to account for heterogeneity. There was only one study that assessed the levels of tT4 in persons with FEP.

Meta-regression analysis demonstrated significant negative correlations of the NOS score (β = −0.57, 95%CI = −1.11 to −0.04, $p = 0.035$) and age of healthy controls (β = −0.20, 95%CI = −0.38 to −0.01, p = 0.035) with effect size estimates in the pooled analysis (Table 3). After limiting the subgroup analysis to studies of individuals with MES and the NOS score ≥ 4 (Wahby et al., 1988; Zhu et al., 2020), between group differences in tT4 levels were not significant and heterogeneity remained significant [g = −0.57, 95%CI = −1.26–0.11, $p = 0.101$, $I^2 = 88.1\%$, Q = 8.4, p(Q) = 0.004].

3.3. fT4

The levels of fT4 were determined by eight studies (Barbero et al., 2014; Bičíková et al., 2011; Jose et al., 2015; Petrikis et al., 2016; Telo et al., 2016; Wahby et al., 1988; Yazici et al., 2002; Zhu et al., 2020). Pooled [g = 0.36, 95%CI = 0.09–0.62, $p = 0.009$, $I^2 = 79.5\%$, Q = 39.1, p < 0.001] and subgroup analysis of drug-naïve or antipsychotic-naïve persons with FEP [g = 0.58, 95%CI = 0.15–1.01, $p = 0.008$, $I^2 = 64.6\%$, Q = 5.7, p (Q) = 0.059] revealed significantly elevated levels of fT4 in the group of patients compared to healthy controls (Table 2, Fig. 2, Supplementary Fig. 4). Persons with MES and healthy controls had similar levels of fT4 [g = 0.22, 95%CI = −0.24–0.68, $p = 0.357$, $I^2 = 85.2$, Q = 20.2, p(Q) < 0.001]. The difference in fT4 levels between drug-naïve or antipsychotic-naïve persons with FEP and healthy controls appeared to be not significant after removing the studies by Bičíková et al. (2011) [g = 0.44, 95%CI = −0.01–0.89, $p = 0.053$, $I^2 = 68.4\%$, Q = 3.2, p(Q) = 0.075] or Zhu et al. (2020) [g = 0.60, 95%CI = −0.32–1.52, $p = 0.199$, $I^2 = 79.3\%$, Q = 4.8, p(Q) = 0.028] (Supplementary Table 5). Differences in the levels of fT4 between persons with MES and healthy controls remained not significant after removing any single study (Supplementary Table 5). Moreover, heterogeneity remained significant in sensitivity analysis of studies based on persons with MES. Meta-regression analysis did not identify any significant moderators for the levels of fT4 (Table 3).

3.4. tT3

The levels of tT3 were assessed by seven studies (Baumgartner et al., 2000; Boral et al., 1980; Lin et al., 2019; Petrikis et al., 2016; Prange et al., 1979; Yazici et al., 2002; Zhu et al., 2020). The levels of tT3 were significantly lower in the group of patients based on the pooled analysis [g = −0.55, 95%CI = −0.76–0.34, p < 0.001, $I^2 = 89.0\%$, Q = 63.6, p (Q) < 0.001]. More specifically, this difference was significant in drug- or antipsychotic-naïve persons with FEP [g = −0.60, 95%CI = −0.82 to −0.37, p < 0.001, $I^2 = 0\%$, Q = 0.01, p(Q) = 0.933] but not in subjects with MES [g = −0.20, 95%CI = −0.79–0.39, $p = 0.504$, $I^2 = 92.0$, Q = 62.4, p(Q) < 0.001] (Table 2, Fig. 2, Supplementary Fig. 5). However, the subgroup analysis of persons with FEP was based on two studies (Petrikis et al., 2016; Zhu et al., 2020). No single study accounted for heterogeneity in subgroup analysis of persons with MES (Supplementary Table 5). Moreover, differences in tT3 levels between persons with MES and healthy controls remained not significant after removing any single study. No significant moderators were found in meta-regression analyses.

3.5. fT3

The levels of fT3 were measured by four studies (Jose et al., 2015; Telo et al., 2016; Yazici et al., 2002; Zhu et al., 2020). Due to low number of studies, subgroup and meta-regression analyses were not performed. There were no significant differences between persons with

Table 3
Meta-regression analysis.

Hormone	Analysis	Moderator	k	β	95%CI	p	Adj. R^2
TSH	Pooled analysis	Age of patients	17	0.01	−0.01–0.03	0.176	35.15%
		Age of controls	17	0.01	−0.02–0.03	0.669	0%
		% of male patients	17	−0.34	−1.01–0.34	0.328	0%
		% of male controls	16	−0.33	−0.98–0.32	0.321	0%
		Illness duration	7	−0.0001	−0.003–0.003	0.849	0%
		PANSS-P	7	−0.01	−0.04–0.01	0.399	0%
		PANSS-N	7	0.004	−0.03–0.04	0.803	0%
		NOS	20	−0.13	−0.29–0.04	0.127	4.80%
		Assay (CLA)	14	−0.39	−0.79–0.02	0.063	4.15%
	MES	Age of patients	11	0.002	−0.02–0.02	0.865	0%
		Age of controls	10	0.0003	−0.04–0.04	0.988	0%
		% of male patients	12	−0.05	−0.84–0.74	0.897	0%
		% of male controls	11	−0.02	−0.84–0.80	0.954	0%
		Illness duration	7	−0.001	−0.003–0.003	0.849	0%
		Minimum time without treatment	7	−0.01	−0.03–0.02	0.442	0%
		NOS	14	−0.08	−0.25–0.08	0.320	0%
tT4	Pooled analysis	Age of patients	7	−0.05	−0.20–0.10	0.516	0%
		Age of controls	6	−0.20	−0.38 - -0.01	**0.035**	44.96%
		% of male patients	6	−0.39	−4.79–4.01	0.862	0%
		NOS	8	−0.57	−1.11 to −0.04	**0.035**	39.74%
	MES	Age of patients	6	−0.08	−0.22–0.05	0.230	29.65%
		% of male patients	6	−0.39	−4.79–4.01	0.862	0%
		NOS	7	−0.61	−1.53–0.30	0.190	17.65%
fT4	Pooled analysis	Age of patients	9	−0.03	−0.07–0.01	0.160	5.63%
		Age of controls	9	−0.02	−0.08–0.03	0.389	0%
		% of male patients	7	0.44	−1.26–2.14	0.614	0%
		% of male controls	7	0.01	−0.01–0.02	0.239	1.51%
		PANSS-P	6	0.01	−0.03–0.05	0.562	0%
		PANSS-N	6	−0.02	−0.07–0.02	0.309	5.59%
		NOS	9	−0.08	−0.35–0.19	0.552	0%
tT3	Pooled analysis	Age of patients	7	−0.004	−0.09–0.09	0.937	0%
		Age of controls	6	−0.06	−0.22–0.09	0.427	0%
		% of male patients	6	0.28	−4.74–5.31	0.912	0%
		NOS	8	−0.16	−0.46–0.15	0.313	6.16%
	MES	NOS	6	−0.80	−2.08–0.49	0.223	28.96%

k refers to the number of comparisons.
Significant moderators ($p < 0.05$) were marked with bold characters.
Abbreviations: CLA – chemiluminescence; fT4 – free thyroxine; TSH – thyroid stimulating hormone; tT3 – total triiodothyronine; tT4 – total thyroxine; PANSS-N – the Positive and Negative Syndrome Scale (subscale of negative symptoms); PANSS-P - the Positive and Negative Syndrome Scale (subscale of positive symptoms).

MES or FEP and healthy controls [g = 0.07, 95%CI = −0.06–0.20, p = 0.293, I^2 = 0%, Q = 3.2, p(Q) = 0.525] (Table 2, Fig. 2, Supplementary Fig. 6). These findings and heterogeneity measures remained not significant in sensitivity analysis (Supplementary Table 5).

4. Discussion

Our meta-analysis revealed that drug-naïve or antipsychotic-naïve persons with FEP have lower levels of TSH compared to healthy controls with no evidence of heterogeneity. However, after removing a single study (Del Cacho et al., 2019), only a trend toward significantly lower TSH levels in unmedicated individuals with FEP was observed. Moreover, we found significantly higher levels of fT4 and significantly lower levels of tT3 in unmedicated subjects with FEP. At this point, it is important to note that the analysis of tT3 levels was based on two studies, and thus sensitivity analysis was not performed. In turn, the difference in fT4 levels was not significant after removing two single studies (Bičíková et al., 2011; Zhu et al., 2020). The study by Zhu et al. (2020) was based on the largest sample of antipsychotic-naïve persons with FEP (n = 92) and healthy controls (n = 154). In turn, Bičíková et al. (2011) assessed a small and relatively homogenous sample of male individuals with FEP (n = 13) and male controls (n = 22).

The mechanisms of alterations in the levels of thyroid hormones in unmedicated persons with FEP remain unknown. Alterations observed in subjects with FEP (decreased levels of tT3 and TSH as well as elevated levels of fT4) resemble those reported in patients with the non-thyroidal illness syndrome (NTIS) characterized by altered negative feedback between TSH and thyroid hormones. The development of NTIS has been reported in severe somatic illnesses but also in conditions caused by acute or chronic stress, especially in hospitalized patients (Pappa et al., 2011). The NTIS captures deranged profile of thyroid hormones manifesting in low levels of tT3 and/or fT3 (Pappa et al., 2011). In some cases, altered levels of TSH, tT4 and fT4 have been demonstrated (Adler and Wartofsky, 2007). For instance, elevated fT4 levels may appear in patients with NTIS during starvation or prolonged fasting that induce the release of fatty acids inhibiting protein bonding (Lim et al., 1993). Stress-induced NTIS may also manifest in reduced levels of TSH and increased levels of fT4 due to the suppressing effects of glucocorticoids on TSH secretion and conversion of T4 to T3 (Adler and Wartofsky, 2007). Importantly, elevated blood cortisol levels have been widely reported in subjects with FEP (Hubbard and Miller, 2019). At this point, it is also important to note that peripheral inflammation, observed in FEP (Upthegrove et al., 2014), can also contribute to alterations observed in NTIS (De Luca et al., 2021). However, the role of intrinsic mechanisms should also be considered. For instance, DeLisi et al. (1991) found that a history of thyroid disorders is significantly more frequent in first-degree relatives of persons with FEP compared to healthy controls. It has also been shown that variation in the *HOPA* gene, encoding the thyroid receptor co-activator protein, may impact a risk of schizophrenia (DeLisi et al., 2000; Sandhu et al., 2003). A series of case reports presented hyperthyroidism-induced psychosis (Kimoto et al., 2019; Shaikh et al., 2020). Moreover, autoimmune encephalitis with clinical manifestation resembling schizophreniform psychosis might be associated with the presence of anti-thyroid antibodies (Endres et al., 2020). Similarly, the clinical manifestation of Hashimoto's thyroiditis might include psychosis (Churilov et al., 2019). Another possibility is that

available evidence is not sufficient to conclude that individuals with FEP show elevated levels of fT4 and decreased levels of tT3 due to low number of studies and the observation that these findings were not significant after removing single studies.

The levels of TSH were elevated in persons with MES with significant heterogeneity. After removing two single studies (Boral et al., 1980; Lin et al., 2019), this difference remained significant with no evidence for heterogeneity. It is likely that the difference in our findings on the levels of TSH and thyroid hormones between individuals with MES and those with FEP is due to greater exposure to antipsychotic treatment. Importantly, our analysis also included studies of unmedicated individuals with MES. However, a minimum time period without medications was relatively short (between 3 and 30 days) and was not associated with effect size estimates for the levels of TSH and tT4. Nevertheless, this observation does not preclude a potential impact of antipsychotics on the levels of TSH and thyroid hormones as some antipsychotics might exert long half-time (e.g., 75 h for oral aripiprazole) (Broder et al., 2012). Moreover, the majority of individuals with MES included in our meta-analysis were medicated with antipsychotics ($n = 515$, 79.5%). It has repeatedly been shown that antipsychotics may impact the levels of thyroid hormones. Vedal et al. (2018) found that the use of antipsychotics was associated with lower levels of fT4 in a large sample of persons with severe mental disorders ($n = 1345$). This association was mainly driven by the use of quetiapine and olanzapine. Similarly, a large retrospective cohort study demonstrated that acute treatment with quetiapine is strongly associated with the development of new-onset hypothyroidism (Zhao et al., 2021). Other studies have shown that phenothiazine and amisulpride may increase the levels of TSH after stimulation by thyrotropin-releasing hormone (TRH) (Gründer et al., 1999; Khalil and Richa, 2011; Wetzel et al., 1994; Zatelli et al., 2014). In turn, clozapine has been found to decrease TRH-stimulated level of TSH (Paunovlć et al., 1991). Furthermore, other medications, including mood stabilizers and antidepressants may also affect the levels of thyroid hormones (Hennessey and Jackson, 1996). A recent population-based study showed increased rate of hypothyroidism in patients with schizophrenia after, but not before, the onset of psychosis (Melamed et al., 2020). However, it remains largely unknown whether antipsychotics directly impact functioning of the hypothalamic-pituitary-thyroid axis. It cannot be excluded that antipsychotic-induced weight gain and subsequent obesity contribute to the development of hypothyroioidism. Indeed, there is evidence that obesity may induce thyroid autoimmunity and hypothyroidism (Song et al., 2019). Finally, given that NTIS can appear in the course of severe medical conditions, it cannot be excluded that observed differences in the profile of TSH and thyroid hormones between individuals with FEP and those with MES are secondary to differences in the severity of psychopathological manifestation.

Our study has important limitations that need to be acknowledged. First, the majority of eligible studies were based on small samples with questionable representativeness. Certain subgroup analyses were also performed on a low number of eligible studies. Similarly, it should be noted that the effects of some moderators, e.g., symptomatic manifestation or illness duration, were tested by a limited number of studies. Moreover, the majority of eligible studies did not record potential confounding factors, e.g., those related to adiposity, the type and dosage of antipsychotics. It cannot be excluded that these factors contributed to heterogeneity that was high in some analyses. Although we found that quality of studies and age of healthy controls were associated with effect size estimates for tT4 levels, no significant moderators were found for other analyses. It is likely that due to unavailability of detailed clinical data, we were unable to find other factors explaining heterogeneity. Another point is that we were not able to disentangle whether observed differences in the levels of thyroid hormones are clinically relevant due to a lack of reporting the proportion of participants with abnormal levels of hormones. It should also be noted that we were unable to perform more detailed analyses of medication effects due to unavailability of necessary data. Finally, causal associations between altered levels of thyroid hormones and schizophrenia cannot be established due to a lack of longitudinal studies included in our meta-analysis.

In sum, results of this meta-analysis imply that decreased levels of TSH might be present at the onset of psychosis, while elevated levels of TSH might appear in persons with MES. Other hormonal alterations related to the activity of the hypothalamic-pituitary-thyroid axis require additional, population-based studies, controlling for the effects of various confounding factors. Moreover, longitudinal studies are needed to provide insights into causal associations between thyroid hormones and the development of psychosis as well as to dissect the role of antipsychotics in the development of thyroid disorders. Nevertheless, our observations support the need of monitoring thyroid function from the onset of psychotic disorders.

Author contribution

BM – protocol of systematic review and meta-analysis, online search, data analysis and manuscript writing; BS and MW – protocol of systematic review and meta-analysis, online search; FB and GC – manuscript writing; JS, KJ and JR – corrections and revisions of the manuscript; DF – data analysis and manuscript writing.

Declaration of competing interest

None to declare.

Acknowledgements

Authors are deeply grateful to all corresponding authors of eligible studies who provided necessary data to perform this systematic review and meta-analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110402.

References

Adler, S.M., Wartofsky, L., 2007. The nonthyroidal illness syndrome. Endocrinol. Metab. Clin. N. Am. 36 (3), 657–672. https://doi.org/10.1016/j.ecl.2007.04.007.

Banki, C.M., Arato, M., Papp, Z., 1984. Thyroid stimulation test in healthy subjects and psychiatric patients. Acta Psychiatr. Scand. 70 (4), 295–303. https://doi.org/10.1111/j.1600-0447.1984.tb01212.x.

Barbero, J.D., Gutiérrez-Zotes, A., Montalvo, I., Creus, M., Cabezas, Á., Solé, M., Algora, M.J., Garcia-Parés, G., Vilella, E., Labad, J., 2014. Free thyroxine levels are associated with cognitive abilities in subjects with early psychosis. Schizophr. Res. 166 (1–3), 37–42. https://doi.org/10.1016/j.schres.2015.04.030.

Barbero, J.D., Palacín, A., Serra, P., Solé, M., Ortega, L., Cabezas, Á., Montalvo, I., Algora, M.J., Martorell, L., Vilella, E., Sánchez-Gistau, V., Labad, J., 2019. Association between anti-thyroid antibodies and negative symptoms in early psychosis. Early Interv. Psychiatry. https://doi.org/10.1111/eip.12873.

Baumgartner, A., Pietzcker, A., Gaebel, W., 2000. The hypothalamic-pituitary-thyroid axis in patients with schizophrenia. Schizophr. Res. 44 (3), 233–243. https://doi.org/10.1016/S0920-9964(99)00187-5.

Bernal, J., 2007. Thyroid hormone receptors in brain development and function. Nat. Clin. Pract. Endocrinol. Metab. 3, 249–259. https://doi.org/10.1038/ncpendmet0424.

Bičíková, M., Hampl, R., Hill, M., Řípová, D., Mohr, P., Putz, Z., Vanuga, P., 2011. Neuro- and immunomodulatory steroids and other biochemical markers in drug-naive schizophrenia patients and the effect of treatment with atypical antipsychotics. Neuroendocrinol. Lett. 32 (2), 141–147.

Boral, G.C., Ghosh, A.B., Pal, S.K., 1980. Thyroid function in different psychiatric disorders. Indian J. Psychiatry 22 (2), 200–202.

Bradley, D.J., Young, W.S., Weinberger, C., 1989. Differential expression of α and β thyroid hormone receptor genes in rat brain and pituitary. Proc. Natl. Acad. Sci. U. S. A. 86, 7250–7254. https://doi.org/10.1073/pnas.86.18.7250.

Bratek, A., Koźmin-Burzyńska, A., Krysta, K., Cierpka-Wiszniewska, K., Krupka-Matuszczyk, I., 2015. Effects of hormones on cognition in schizophrenic male patients—preliminary results. Psychiatr. Danub. 27, 261–265.

Broder, M.S., Bates, J.A., Jing, Y., Hebden, T., Forbes, R.A., Chang, E., 2012. Association between second-generation antipsychotic medication half-life and hospitalization in the community treatment of adult schizophrenia. J. Med. Econ. 15 (1), 105–111.

Churilov, L.P., Sobolevskaia, P.A., Stroev, Y.I., 2019. Thyroid gland and brain: enigma of Hashimoto's encephalopathy. Best Pract. Res. Clin. Endocrinol. Metab. 33 (6), 101364. https://doi.org/10.1016/j.beem.2019.101364.

De Luca, R., Davis, P.J., Lin, H.Y., Gionfra, F., Percario, Z.A., Affabris, E., Pedersen, J.Z., Marchese, C., Trivedi, P., Anastasiadou, E., Negro, R., Incerpi, S., 2021. Thyroid hormones interaction with immune response, inflammation and non-thyroidal illness syndrome. Front. Cell. Dev. Biol. 8, 614030. https://doi.org/10.3389/fcell.2020.614030.

Del Cacho, N., Butjosa, A., Vila-Badia, R., Cuadras, D., Kaplan, M., Rubio-Abadal, E., Pardo, M., Muñoz-Samons, D., Cuevas-Esteban, J., Saenz-Navarrete, G., Usall, J., 2019. Prolactin levels in drug-naïve first episode nonaffective psychosis patients compared with healthy controls. Sex differences. Psychiatry Res. 276, 218–222. https://doi.org/10.1016/j.psychres.2019.03.027.

DeLisi, L.E., Boccio, A.M., Riordan, H., Hoff, A.L., Dorfman, A., McClelland, J., Kushner, M., Van Eyl, O., Oden, N., 1991. Familial thyroid disease and delayed language development in first admission patients with schizophrenia. Psychiatry Res. 38 (1), 39–50. https://doi.org/10.1016/0165-1781(91)90051-P.

DeLisi, L.E., Smith, A.B., Razi, K., Stewart, J., Wang, Z., Sandhu, H.K., Philibert, R.A., 2000. Investigation of a candidate gene for schizophrenia on Xq13 previously associated with mental retardation and hypothyroidism. Am. J. Med. Genet. Neuropsychiatr. Genet. https://doi.org/10.1002/1096-8628(20000612)96:3<398::AID-AJMG30>3.0.CO;2-Z.

Dezonne, R.S., Lima, F.R.S., Trentin, A.G., Gomes, F.C., 2015. Thyroid hormone and astroglia: endocrine control of the neural environment. J. Neuroendocrinol. 27, 435–445. https://doi.org/10.1111/jne.12283.

Ellis, P., 2010. The Essential Guide to Effect Sizes: Statistical Power, Meta-Analysis, and the Interpretation of Research Results. Cambridge University Press, Cambridge.

Endres, D., Leypoldt, F., Bechter, K., Hasan, A., Steiner, J., Domschke, K., Wandinger, K. P., Falkai, P., Arolt, V., Stich, O., Rauer, S., Prüss, H., van Elst, L.T., 2020. Autoimmune encephalitis as a differential diagnosis of schizophreniform psychosis: clinical symptomatology, pathophysiology, diagnostic approach, and therapeutic considerations. Eur. Arch. Psychiatry Clin. Neurosci. 270 (7), 803–818. https://doi.org/10.1007/s00406-020-01113-2.

Ercan-Fang, S., Schwartz, H.L., Oppenheimer, J.H., 1996. Isoform-specific 3,5,3′-triiodothyronine receptor binding capacity and messenger ribonucleic acid content in rat adenohypophysis: effect of thyroidal state and comparison with extrapituitary tissues. Endocrinology 137, 3228–3233. https://doi.org/10.1210/endo.137.8.8754744.

Extein, I., Pottash, A.L.C., Gold, M.S., Cowdry, R.W., 1982. Using the protirelin test to distinguish mania from schizophrenia. Arch. Gen. Psychiatry 39 (1), 77–81. https://doi.org/10.1001/archpsyc.1982.04290010053010.

Ferrari, S.M., Fallahi, P., Antonelli, A., Benvenga, S., 2017. Environmental issues in thyroid diseases. Front. Endocrinol. 8, 50. https://doi.org/10.3389/fendo.2017.00050.

Fu, R., Gartlehner, G., Grant, M., Shamliyan, T., Sedrakyan, A., Wilt, T.J., Griffith, L., Oremus, M., Raina, P., Ismaila, A., Santaguida, P., Lau, J., Trikalinos, T.A., 2011. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. J. Clin. Epidemiol. 64, 1187–1197. https://doi.org/10.1016/j.jclinepi.2010.08.010.

Garcia-Rizo, C., Fernandez-Egea, E., Oliveira, C., Justicia, A., Parellada, E., Bernardo, M., Kirkpatrick, B., 2012. Prolactin concentrations in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis. Schizophr. Res. 134 (1), 16–19. https://doi.org/10.1016/j.schres.2011.07.025.

González-Blanco, L., Greenhalgh, A.M.D., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B. J., Kirkpatrick, B., 2016. Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: a meta-analysis. Schizophr. Res. 174, 156–160. https://doi.org/10.1016/j.schres.2016.03.018.

Gründer, G., Wetzel, H., Schlösser, R., Anghelescu, I., Hillert, A., Lange, K., Hiemke, C., Benkert, O., 1999. Neuroendocrine response to antipsychotics: effects of drug type and gender. Biol. Psychiatry 28 (5), 461–473. https://doi.org/10.1016/S0006-3223(98)00125-5.

Hennessey, J.V., Jackson, I.M.D., 1996. The interface between thyroid hormones and psychiatry. Endocrinologist 6 (3), 214–223. https://doi.org/10.1097/00019616-199605000-00008.

Higgins, J.P.T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M.J., 2019. In: Welch, V.A. (Ed.), Cochrane Handbook for Systematic Reviews of Interventions, 2nd Edition. John Wiley & Sons, Chichester, UK.

Hozo, S.P., Djulbegovic, B., Hozo, I., 2005. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. 5, 13. https://doi.org/10.1186/1471-2288-5-13.

Hubbard, D.B., Miller, B.J., 2019. Meta-analysis of blood cortisol levels in individuals with first-episode psychosis. Psychoneuroendocrinology 104, 269–275. https://doi.org/10.1016/j.psyneuen.2019.03.014.

Ichioka, S., Terao, T., Hoaki, N., Matsushita, T., Hoaki, T., 2012. Triiodothyronine may be possibly associated with better cognitive function and less extrapyramidal symptoms in chronic schizophrenia. Prog. Neuro Psychopharmacol. Biol. Psychiatry 39 (1), 170–174. https://doi.org/10.1016/j.pnpbp.2012.06.008.

Jose, J., Nandeesha, H., Kattimani, S., Meiyappan, K., Sarkar, S., Sivasankar, D., 2015. Association between prolactin and thyroid hormones with severity of psychopathology and suicide risk in drug free male schizophrenia. Clin. Chim. Acta 444, 78–80. https://doi.org/10.1016/j.cca.2015.02.003.

Kalinowska, S., Trześniowska-Drukała, B., Safranow, K., Pełka-Wysiecka, J., Kłoda, K., Misiak, B., Samochowiec, J., 2019. Association between thyroid function and metabolic syndrome in male and female schizophrenia patients. Psychiatry Res. 274, 167–175. https://doi.org/10.1016/j.psychres.2019.02.029.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/SCHBUL/13.2.261.

Khalil, R.B., Richa, S., 2011. Thyroid adverse effects of psychotropic drugs: a review. Clin. Neuropharmacol. 34 (6), 248–255. https://doi.org/10.1097/WNF.0b013e31823429a7.

Kimoto, S., Yamamuro, K., Kishimoto, T., 2019. Acute psychosis in patients with subclinical hyperthyroidism. Psychiatry Clin. Neurosci. 73 (6), 348–349. https://doi.org/10.1111/pcn.12847.

Labad, J., Barbero, J.D., Gutiérrez-Zotes, A., Montalvo, I., Creus, M., Cabezas, Solé, Algora, M.J., Garcia-Parés, G., Vilella, E., 2016. Free thyroxine levels are associated with cognitive changes in individuals with a first episode of psychosis: a prospective 1-year follow-up study. Schizophr. Res. 171 (1–3), 182–186. https://doi.org/10.1016/j.schres.2016.01.036.

Lakens, D., 2013. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Front. Psychol. 4, 863. https://doi.org/10.3389/fpsyg.2013.00863.

Lim, C.F., Docter, R., Visser, T.J., Krenning, E.P., Bernard, B., van Toor, H., de Jong, M., Hennemann, G., 1993. Inhibition of thyroxine transport into cultured rat hepatocytes by serum of nonuremic critically ill patients: effects of bilirubin and nonesterified fatty acids. J. Clin. Endocrinol. Metab. 76 (5), 1165–1172. https://doi.org/10.1210/jcem.76.5.8496307.

Lin, C.H., Lin, C.Y., Wang, H.S., Lane, H.Y., 2019. Long-term use of clozapine is protective for bone density in patients with schizophrenia. Sci. Rep. 9 (1), 3895. https://doi.org/10.1038/s41598-019-40691-7.

Lis, M., Stańczykiewicz, B., Liśkiewicz, P., Misiak, B., 2020. Impaired hormonal regulation of appetite in schizophrenia: a narrative review dissecting intrinsic mechanisms and the effects of antipsychotics. Psychoneuroendocrinology 119, 104744. https://doi.org/10.1016/j.psyneuen.2020.104744.

Loosen, P.T., P. Jr., A.J., Wilson, I.C., Lara, P.P., Pettus, C., 1977. Thyroid stimulating hormone response after thyrotropin releasing hormone in depressed, schizophrenic and normal women. Psychoneuroendocrinology 2 (2), 137–148. https://doi.org/10.1016/0306-4530(77)90019-1.

MacDonald, A.W., Schulz, S.C., 2009. What we know: findings that every theory of schizophrenia should explain. Schizophr. Bull. 35 (3), 493–508. https://doi.org/10.1093/schbul/sbp017.

Marian, G., Nica, E.A., Ionescu, B.E., Ghinea, D., 2009. Hyperthyroidism–cause of depression and psychosis: a case report. J. Med. Life 2 (4), 440–442.

Melamed, S.B., Farfel, A., Gur, S., Krivoy, A., Weizman, S., Matalon, A., Feldhamer, I., Hermesh, H., Weizman, A., Meyerovitch, J., 2020. Thyroid function assessment before and after diagnosis of schizophrenia: a community-based study. Psychiatry Res. 293, 113356.

Misiak, B., Frydecka, D., Loska, O., Moustafa, A.A., Samochowiec, J., Kasznia, J., Stańczykiewicz, B., 2018. Testosterone, DHEA and DHEA-S in patients with schizophrenia: a systematic review and meta-analysis. Psychoneuroendocrinology 89, 92–102. https://doi.org/10.1016/j.psyneuen.2018.01.007.

Misiak, B., Bartoli, F., Stramecki, F., Samochowiec, J., Lis, M., Kasznia, J., Jarosz, K., Stańczykiewicz, B., 2019. Appetite regulating hormones in first-episode psychosis: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 102, 362–370. https://doi.org/10.1016/j.neubiorev.2019.05.018.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J.A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J.J., Devereaux, P.J., Dickersin, K., Egger, M., Ernst, E., Gøtzsche, P.C., Grimshaw, J., Guyatt, G., Higgins, J., Ioannidis, J.P.A., Kleijnen, J., Lang, T., Magrini, N., McNamee, D., Moja, L., Mulrow, C., Napoli, M., Oxman, A., Pham, B., Rennie, D., Sampson, M., Schulz, K.F., Shekelle, P.G., Tovey, D., Tugwell, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6 (7), e1000097 https://doi.org/10.1371/journal.pmed.1000097.

Noda, M., 2015. Possible role of glial cells in the relationship between thyroid dysfunction and mental disorders. Front. Cell. Neurosci. 9, 194. https://doi.org/10.3389/fncel.2015.00194.

Noda, M., 2018. Thyroid hormone in the CNS: contribution of neuron–glia interaction. In: Vitamins and Hormones, 106, pp. 313–331. https://doi.org/10.1016/bs.vh.2017.05.005.

Pappa, T.A., Vagenakis, A.G., Alevizaki, M., 2011. The nonthyroidal illness syndrome in the non-critically ill patient. Eur. J. Clin. Investig. 41 (2), 212–220. https://doi.org/10.1111/j.1365-2362.2010.02395.x.

Paunovlć, V.R., Timotijević, I., Marinković, D., 1991. Neuroleptic actions on the thyroid axis: different effects of clozapine and haloperidol. Int. Clin. Psychopharmacol. 6 (3), 133–139. https://doi.org/10.1097/00004850-199100630-00001.

Petrikis, P., Tigas, S., Tzallas, A.T., Archimandriti, D.T., Skapinakis, P., Mavreas, V., 2016. Prolactin levels in drug-naïve patients with schizophrenia and other psychotic disorders. Int. J. Psychiatry Clin. Pract. 20 (3), 165–169. https://doi.org/10.1080/13651501.2016.1197274.

Piotrowski, P., Gondek, T.M., Królicka-Deręgowska, A., Misiak, B., Adamowski, T., Kiejna, A., 2017. Causes of mortality in schizophrenia: an updated review of European studies. Psychiatr. Danub. 29, 108–120.

Prange, A.J., Loosen, P.T., Wilson, I.C., Meltzer, H.Y., Fang, V.S., 1979. Behavioral and endocrine responses of schizophrenic patients to TRH (protirelin). Arch. Gen. Psychiatry 36 (10), 1086–1093. https://doi.org/10.1001/archpsyc.1979.01780100056005.

Roy, A., Wolkowitz, O., Doran, A., Pickar, D., 1989. TRH test in schizophrenic patients and controls. Biol. Psychiatry 25 (4), 523–526. https://doi.org/10.1016/0006-3223(89)90211-4.

Sandhu, H.K., Sarkar, M., Turner, B.M., Wassink, T.H., Philibert, R.A., 2003. Polymorphism analysis ofHOPA: a candidate gene for schizophrenia. Am. J. Med. Genet. 123B (1), 33–38. https://doi.org/10.1002/ajmg.b.20019.

Santos, N.C., Costa, P., Ruano, D., MacEdo, A., Soares, M.J., Valente, J., Pereira, A.T., Azevedo, M.H., Palha, J.A., 2012. Revisiting thyroid hormones in schizophrenia. J. Thyroid. Res. 569147 https://doi.org/10.1155/2012/569147.

Shaikh, A., Shah, K., Idowu, J., 2020. 109 hyperthyroidism-induced psychosis. CNS Spectr. 25 (2), 270–271. https://doi.org/10.1017/S1092852920000279.

Sharif, K., Tiosano, S., Watad, A., Comaneshter, D., Cohen, A.D., Shoenfeld, Y., Amital, H., 2018. The link between schizophrenia and hypothyroidism: a population-based study. Immunol. Res. 66 (6), 663–667. https://doi.org/10.1007/s12026-018-9030-7.

Snabboon, T., Khemkha, A., Chaiyaumporn, C., Lalitanantpong, D., Sridama, V., 2009. Psychosis as the first presentation of hyperthyroidism. Intern. Emerg. Med. 4 (4), 359–360. https://doi.org/10.1007/s11739-009-0259-y.

Song, R.H., Wang, B., Yao, Q.M., Li, Q., Jia, X., Zhang, J.A., 2019. The impact of obesity on thyroid autoimmunity and dysfunction: a systematic review and meta-analysis. Front. Immunol. 10, 2349.

Sterne, J.A., Egger, M., Moher, D., 2008. Addressing reporting biases. In: Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. https://doi.org/10.1002/9780470712184.ch10.

Telo, S., Bilgic, S., Karabulut, N., 2016. Thyroid hormone levels in chronic schizophrenic patients: association with psychopathology. West Indian Med. J. 65 (2), 312–315. https://doi.org/10.7727/wimj.2015.186.

Tenny, S., Kerndt, C.C., Hoffman, M.R., 2020. Case control studies. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL). Available from: https://www.ncbi.nlm.nih.gov/books/NBK448143/.

Tost, M., Monreal, J.A., Armario, A., Barbero, J.D., Cobo, J., García-Rizo, C., Bioque, M., Usall, J., Huerta-Ramos, E., Soria, V., Labad, J., Pilar, Á., Barbero, J.D., Bioque, M., Jesús, C., del Cacho, N., García-Rizo, C., Labad, J., Martín-Blanco, A., Monreal, J.A., Montalvo, I., Portella, M., Real, E., Rubio, E., Soria, V., Usall, J., 2020. Targeting hormones for improving cognition in major mood disorders and schizophrenia: thyroid hormones and prolactin. Clin. Drug Investig. 40, 1–14. https://doi.org/10.1007/s40261-019-00854-w.

Upthegrove, R., Manzanares-Teson, N., Barnes, N.M., 2014. 2014. Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis. Schizophr. Res. 155 (1–3), 101–108. https://doi.org/10.1016/j.schres.2014.03.005.

Vedal, T.S.J., Steen, N.E., Birkeland, K.I., Dieset, I., Reponen, E.J., Laskemoen, J.F., Rødevand, L., Melle, I., Andreassen, O.A., Molden, E., Jönsson, E.G., 2018. Free thyroxine and thyroid-stimulating hormone in severe mental disorders: a naturalistic study with focus on antipsychotic medication. J. Psychiatr. Res. 106, 74–81. https://doi.org/10.1016/j.jpsychires.2018.09.014.

Wahby, V.S., Ibrahim, G.A., Giller, E.L., Mason, J.W., Saddik, F.W., Adams, J.R., Martin, R.P., Milad, E.R., 1988. Thyrotropin response to thyrotropin-releasing hormone in RDC schizodepressed men. J. Affect. Disord. 15 (1), 81–85. https://doi.org/10.1016/0165-0327(88)90012-2.

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P., 2000. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Wetzel, H., Wiesner, J., Hiemke, C., Benkert, O., 1994. Acute antagonism of dopamine D2-like receptors by amisulpride: effects on hormone secretion in healthy volunteers. J. Psychiatr. Res. 28 (5), 461–473. https://doi.org/10.1016/0022-3956(94)90004-3.

Yazici, K., Yazici, A.E., Taneli, B., 2002. Different neuroendocrine profiles of remitted and nonremitted schizophrenic patients. Prog. Neuro Psychopharmacol. Biol. Psychiatry 26 (3), 579–584. https://doi.org/10.1016/S0278-5846(01)00311-6.

Zatelli, M.C., Ambrosio, M.R., Bondanelli, M., Degli Uberti, E., 2014. Pituitary side effects of old and new drugs. J. Endocrinol. Investig. 37 (10), 917–923. https://doi.org/10.1007/s40618-014-0133-2.

Zhao, Y., Wen, S.W., Li, M., Sun, Z., Yuan, X., Retnakaran, R., Zhang, R., Zhai, D., 2021. Dose-response association of acute-phase quetiapine treatment with risk of new-onset hypothyroidism in schizophrenia patients. Br. J. Clin. Pharmacol. https://doi.org/10.1111/bcp.14928.

Zhu, Y., Ji, H., Tao, L., Cai, Q., Wang, F., Ji, W., Li, G., Fang, Y., 2020. Functional status of hypothalamic–pituitary–thyroid and hypothalamic–pituitary–adrenal axes in hospitalized schizophrenics in Shanghai. Front. Psychiatry 11, 65. https://doi.org/10.3389/fpsyt.2020.00065.