

# Association between free thyroxine levels and clinical phenotype in first-episode psychosis: a prospective observational study (#79714)

1

First submission

## Guidance from your Editor

Please submit by **20 Jan 2023** for the benefit of the authors (and your token reward) .



### Structure and Criteria

Please read the 'Structure and Criteria' page for general guidance.



### Custom checks

Make sure you include the custom checks shown below, in your review.



### Raw data check

Review the raw data.



### Image check

Check that figures and images have not been inappropriately manipulated.

Privacy reminder: If uploading an annotated PDF, remove identifiable information to remain anonymous.

## Files

Download and review all files from the [materials page](#).

- 1 Figure file(s)
- 2 Table file(s)
- 1 Raw data file(s)
- 2 Other file(s)

## ! Custom checks

### Human participant/human tissue checks

- ! Have you checked the authors [ethical approval statement](#)?
- ! Does the study meet our [article requirements](#)?
- ! Has identifiable info been removed from all files?
- ! Were the experiments necessary and ethical?




# Structure and Criteria

## Structure your review

The review form is divided into 5 sections. Please consider these when composing your review:

1. BASIC REPORTING
2. EXPERIMENTAL DESIGN
3. VALIDITY OF THE FINDINGS
4. General comments
5. Confidential notes to the editor






 You can also annotate this PDF and upload it as part of your review

When ready [submit online](#).





## Editorial Criteria

Use these criteria points to structure your review. The full detailed editorial criteria is on your [guidance page](#).




### BASIC REPORTING

-  Clear, unambiguous, professional English language used throughout.
-  Intro & background to show context. Literature well referenced & relevant.
-  Structure conforms to [PeerJ standards](#), discipline norm, or improved for clarity.
-  Figures are relevant, high quality, well labelled & described.
-  Raw data supplied (see [PeerJ policy](#)).

### EXPERIMENTAL DESIGN

-  Original primary research within [Scope of the journal](#).
-  Research question well defined, relevant & meaningful. It is stated how the research fills an identified knowledge gap.
-  Rigorous investigation performed to a high technical & ethical standard.
-  Methods described with sufficient detail & information to replicate.

### VALIDITY OF THE FINDINGS

-  Impact and novelty not assessed. *Meaningful* replication encouraged where rationale & benefit to literature is clearly stated.
-  All underlying data have been provided; they are robust, statistically sound, & controlled.
-  Conclusions are well stated, linked to original research question & limited to supporting results.



The best reviewers use these techniques

## Tip

## Example

**Support criticisms with evidence from the text or from other sources**

*Smith et al (J of Methodology, 2005, V3, pp 123) have shown that the analysis you use in Lines 241-250 is not the most appropriate for this situation. Please explain why you used this method.*

**Give specific suggestions on how to improve the manuscript**

*Your introduction needs more detail. I suggest that you improve the description at lines 57- 86 to provide more justification for your study (specifically, you should expand upon the knowledge gap being filled).*

**Comment on language and grammar issues**

*The English language should be improved to ensure that an international audience can clearly understand your text. Some examples where the language could be improved include lines 23, 77, 121, 128 – the current phrasing makes comprehension difficult. I suggest you have a colleague who is proficient in English and familiar with the subject matter review your manuscript, or contact a professional editing service.*

**Organize by importance of the issues, and number your points**

1. Your most important issue
2. The next most important item
3. ...
4. The least important points

**Please provide constructive criticism, and avoid personal opinions**

*I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC*

**Comment on strengths (as well as weaknesses) of the manuscript**

*I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.*

# Association between free thyroxine levels and clinical phenotype in first-episode psychosis: a prospective observational study

Eloi Gine-Serven<sup>Corresp., 1</sup>, Maria Martinez-Ramirez<sup>1</sup>, Ester Boix-Quintana<sup>1</sup>, Eva Davi-Loscos<sup>1</sup>, Nicolau Guanyabens<sup>2</sup>, Virginia Casado<sup>2</sup>, Desiree Muriana<sup>2</sup>, Cristina Torres-Rivas<sup>1</sup>, Mj Cuesta<sup>3,4</sup>, Javier Labad<sup>1,5,6</sup>

<sup>1</sup> Department of Mental Health, Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain

<sup>2</sup> Department of Neurology, Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain

<sup>3</sup> Department of Psychiatry, Complejo Hospitalario de Navarra, Pamplona, Spain

<sup>4</sup> IdiSNA, Navarra Institute for Health Research, Pamplona, Spain

<sup>5</sup> Translational Neuroscience Research Unit I3PT-INC-UAB, Institut de Innovació i Investigació Parc Taulí (I3PT), Institut de Neurociències, Universitat Autònoma de Barcelona, Barcelona, Spain

<sup>6</sup> Centro de Investigación en Red de Salud Mental (CIBERSAM), Madrid, Spain

Corresponding Author: Eloi Gine-Serven

Email address: elogi69@gmail.com

**Aim:** To determine whether thyroid hormone levels are associated with a specific clinical phenotype in patients with first-episode psychosis (FEP). **Methods:** Ninety-eight inpatients experiencing FEP and with less than 6 weeks of antipsychotic treatment were included in the study and were followed up for one year. Baseline psychiatric evaluation included assessment of prodromal symptoms, positive and negative symptoms, depressive symptoms, stressful life events and cycloid psychosis criteria. Thyroid function (thyroid-stimulating hormone [TSH] and free thyroxine [FT4]) was determined at admission. Spearman correlation was conducted to analyse the correlation between levels of TSH/FT4 and symptoms. Logistic regression was performed to explore the association between psychopathological symptoms, 12-month diagnoses and thyroid hormones while adjusting for covariates. **Results:** Patients with prodromal symptomatology showed lower baseline FT4 levels (OR = 0.128;  $p = 0.05$ ). The duration of untreated psychosis (DUP) was inversely associated with FT4 concentrations ( $r = -0.251$ ;  $p = 0.039$ ). FEP patients with sudden onset of psychotic symptoms (criteria B, cycloid psychosis) showed higher FT4 levels at admission (OR = 10.485;  $p = 0.040$ ). Patients diagnosed with affective psychotic disorders (BD or MDD) at the 12-month follow-up showed higher free thyroxine levels at admission than patients diagnosed with nonaffective psychosis (schizophrenia, schizoaffective) (OR = 0.117;  $p = 0.042$ ). **Conclusions:** Our study suggests that higher free-thyroxine levels are associated with a specific clinical phenotype of FEP patients (fewer prodromal symptoms, shorter DUP duration and sudden onset of psychosis) and with affective psychosis

diagnoses at the 12-month follow-up.

# Association between free thyroxine levels and clinical phenotype in first-episode psychosis: a prospective observational study

Eloi Giné-Servén<sup>1</sup>, Maria Martinez-Ramirez<sup>1</sup>, Ester Boix-Quintana<sup>1</sup>, Eva Davi-Loscos<sup>1</sup>, Nicolau Guanyabens<sup>2</sup>, Virginia Casado<sup>2</sup>, Desiree Muriana<sup>2</sup>, Cristina Torres-Rivas<sup>1</sup>, Manuel J Cuesta<sup>3,4</sup>, Javier Labad<sup>1,5,6</sup>

<sup>1</sup>Department of Mental Health, Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain

<sup>2</sup>Department of Neurology, Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain

<sup>3</sup>Department of Psychiatry, Complejo Hospitalario de Navarra, Pamplona, Spain

<sup>4</sup>IdiSNA, Navarra Institute for Health Research, Pamplona, Spain.

<sup>5</sup>Translational Neuroscience Research Unit I3PT-INc-UAB, Institut de Innovació i Investigació Parc Taulí (I3PT), Institut de Neurociències, Universitat Autònoma de Barcelona

<sup>6</sup>Centro de Investigación en Red de Salud Mental (CIBERSAM)

**Abstract** word count, 240; **Text word** count, 2721; **References**, 48; **Figures**, 1; **Tables**, 2. **Supplementary material**: 1 figure and one table.

Running Title: Biomarkers in first episode psychosis

Key words: biomarkers, first episode, psychosis, thyroid, TSH, FT4

- 23    **Correspondence:** Eloi Giné Servén MD, Psychiatry Department, Hospital de Mataró Consorci Sanitari del
- 24    Maresme, Mataró, Spain, Carretera de la Cirera s/n, Mataró 08340 (Spain). Email: [elogi69@gmail.com](mailto:elogi69@gmail.com)

# ABSTRACT

**Aim:** To determine whether thyroid hormone levels are associated with a specific clinical phenotype in patients with first-episode psychosis (FEP).

**Methods:** Ninety-eight inpatients experiencing FEP and with less than 6 weeks of antipsychotic treatment were included in the study and were followed up for one year. Baseline psychiatric evaluation included assessment of prodromal symptoms, positive and negative symptoms, depressive symptoms, stressful life events and cycloid psychosis criteria. Thyroid function (thyroid-stimulating hormone [TSH] and free thyroxine [FT4]) was determined at admission. Spearman correlation was conducted to analyse the correlation between levels of TSH/FT4 and symptoms. Logistic regression was performed to explore the association between psychopathological symptoms, 12-month diagnoses and thyroid hormones while adjusting for covariates.

**Results:** Patients with prodromal symptomatology showed lower baseline FT4 levels (OR = 0.128;  $p=0.05$ ). The duration of untreated psychosis (DUP) was inversely associated with FT4 concentrations ( $r = -0.251$ ;  $p=0.039$ ). FEP patients with sudden onset of psychotic symptoms (criteria B, cycloid psychosis) showed higher FT4 levels at admission (OR = 10.485;  $p=0.040$ ). Patients diagnosed with affective psychotic disorders (BD or MDD) at the 12-month follow-up showed higher free thyroxine levels at admission than patients diagnosed with nonaffective psychosis (schizophrenia, schizoaffective) (OR = 0.117;  $p=0.042$ ).

**Conclusions:** Our study suggests that higher free-thyroxine levels are associated with a specific clinical phenotype of FEP patients (fewer prodromal symptoms, shorter DUP duration and sudden onset of psychosis) and with affective psychosis diagnoses at the 12-month follow-up.



# INTRODUCTION

First-episode psychosis (FEP) refers to heterogeneous clinical conditions representing the symptomatic emergence of myriad disorders, for instance, schizophrenia, schizoaffective disorder or bipolar disorder (Giné-Servén et al., 2021). Such disorders are predominantly preceded by a prodromal phase, commonly lasting months or years, in which faint symptoms show and are concurrent with a reduction of functionality in different areas, including sociofamiliar relationships or academic and occupational performance (Woodberry et al., 2016). This prodromal phase, as well as the duration of untreated psychosis (DUP) and the duration of untreated illness (DUI), is persistently related to functional recovery in patients with FEP (Santesteban-Echarri et al., 2017).

Not yet completely understood are the aetiology and pathogenesis of psychosis, however the overwhelming evidence points to a contribution from a combination of genetic and environmental factors (Brown, 2011; Tsuang et al., 2004). The lack of biomarkers adds to diagnostic delay as well as obstructing disease stratification, prediction of outcomes and therapeutic choice (Weickert et al., 2013).

Some studies have indicated that hormone deregulation may play a role in the development of psychosis (Hayes et al., 2012). Patients with schizophrenia usually develop endocrine abnormalities, such as hyperprolactinemia (Labad, 2019; González-Blanco et al., 2016), dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis or release of neurosteroids and appetite-regulating hormones (Misiak et al., 2021). Individual-level risk factors, such as poor dietary habits, sedentary behaviour and adverse effects of antipsychotics, also determine whether these patients will develop endocrine abnormalities (Misiak et al., 2021). Nevertheless, some groups (González-Blanco et al., 2016; Hubbard and Miller, 2019; Lis et al., 2020) have hypothesized that hyperprolactinemia, insulin resistance and HPA axis alterations might be related to intrinsic pathophysiological mechanisms and could also occur in early psychosis.

Thyroid hormones could very well play vital roles in the development and correct function of the CNS, supporting the development of neurons, oligodendrocytes, astrocytes and microglia and additionally, the modulation of proinflammatory feedback (Noda, 2015). Since neuroinflammation is said to have been associated with the pathogenesis of schizophrenia (Howes & McCutcheon, 2017), thyroid hormones might

also assist in the pathogenesis and clinical expression of schizophrenia and psychotic disorders by virtue of a proinflammatory mechanism.

Altered hypothalamic-pituitary-thyroid system function has been described in schizophrenia and bipolar and depressive disorders (Bičíkova et al., 2011; Othman et al., 1994; Santos et al., 2012), but very little research has been done in the early stages of these psychiatric disorders. In cross-sectional (Barbero et al., 2015) and prospective (Labad et al., 2016) studies carried out by our team, although within the normal range, higher free thyroxine (FT4) levels were associated with better attention and vigilance in early-stage psychotic disorders. Higher FT4 levels have been described in patients with affective psychosis than in those with nonaffective psychosis (Barbero et al., 2015). No associations were found by another group between thyroid function and positive, negative or general symptoms in drug-naïve male patients with schizophrenia (Jose et al., 2015).

However, few studies have explored the relationship between the clinical expression and thyroid hormones in first-episode psychosis (FEP). Previously carried out investigation highlights the necessity to perform research on biomarkers in the early stages of psychosis, which it is thought could provide crucial clues to the mechanisms underlying psychotic disorders and in turn, permitting the minimalization of confounders, in particular, antipsychotic exposure and the neurodegenerative evolution of the disease.

In the current study, we aimed to determine if thyroid hormones in patients with FEP relate to a distinct 12-month follow-up diagnoses and a differentiated clinical phenotype. We hypothesized that thyroid hormone levels were associated with clinical diagnosis one year after the onset of psychosis, with higher FT4 concentrations in affective psychoses than in nonaffective psychoses. As a secondary aim, we explored whether thyroid hormone levels were associated with distinct phenotypes (sudden onset, severity) in FEP patients.

## Methods

Data were collected as previously described in Giné-Servén et al., 2021.

### *Study design and participants*

Ninety-eight patients experiencing FEP were included in the study. These patients were admitted to acute inpatient units (adult or child and adolescent units) from the Department of Mental Health at the Hospital of Mataró between 1 June 2018 and 31 March 2020. FEP was defined as new-onset disorganized behaviour accompanied by delusions or hallucinations not caused by drugs that met DSM-IV criteria for a psychotic disorder (schizophrenia, bipolar disorder or unipolar major depression with psychotic features, schizophreniform disorder, brief psychotic disorder, delusional disorder, psychotic not otherwise specified). Patients were excluded if they had (1) positive symptoms of psychosis lasting more than 6 months; (2) treatment with antipsychotics, antidepressants or mood stabilizers for more than 6 weeks; (3) a past history of positive symptoms of psychosis; (4) a previous diagnosis of intellectual disability ( $IQ < 70$ ), or (5) active medical or neurological diseases that could explain the current symptoms.

The study received approval from the local **ethics committees** (Hospital of Mataró, Barcelona, Spain). All participants were informed about the nature of the study and gave written informed consent for participating in the study.

### *Clinical assessment*

During the first week of hospital admission, all patients underwent psychiatric and neurological evaluations. The description of the clinical and biological assessment is described in Figure 1 of the supplementary material (Figure S1). Two trained attending psychiatrists carried out diagnostic interviews using the Structured Clinical Interview for DSM-IV-TR (SCID-I) (First et al., 1994) for patients  $\geq 18$  years, the Schedule for Affective Disorders and Schizophrenia for school-age children and the Present and Lifetime version (K-SADS-PL) (KAUFMAN et al., 1997) for patients  $< 18$  years.

The onset of prodromal and psychotic symptoms was assessed retrospectively by means of a semistructured interview with a specific ad hoc inventory (Quick Psychosis Onset and Prodromal Symptoms Inventory [Q-POPSI]) that was designed for administration to patients and family and/or close relatives (Giné-Servén et al., 2021). The DUI and DUP were calculated. DUI was defined as the difference in time between the onset of the first symptom (prodromal or psychotic) of the illness and the start of the antipsychotic treatment. DUP was defined as the difference in time between the onset of the first positive

psychotic symptom and the start of antipsychotic treatment. A full explanation of the Q-POPSI inventory is described elsewhere (Giné-Servén et al., 2021).

Psychopathology at admission was assessed using three psychometric scales. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used to assess positive, negative and general psychopathology symptoms. Symptoms were recoded into five subscales following the Wallwork et al. (Wallwork et al., 2012) consensus: positive, negative, disorganized/concrete, excited and depressed factors. Acute psychosis onset was assessed with cycloid psychosis criteria (Table S1: Perris and Brockington's diagnostic criteria for cycloid psychosis) (Brockington et al., 1982; Perris, 1974). The Young Mania Rating Scale (YMRS) (Lukasiewicz et al., 2013; Young et al., 1978) was administered to assess manic symptoms. The Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960; Zimmerman et al., 2013) was also administered to assess depressive symptoms.

Stressful life events that occurred during the 6 months prior to admission were assessed using The List of Threatening Experiences (Brugha and Cragg, 1990), a subset of 12 life event categories that are associated with considerable long-term contextual threat.

Functional outcome was assessed at admission and discharge from the Acute Inpatient Unit using the Global Assessment of Functioning Scale (GAF) (Hall, 1995) for patients  $\geq 18$  years and the Children's Global Assessment Scale (C-GAS) (Shaffer, 1983) for patients  $< 18$  years.

#### *Thyroid function studies*

During the first 24-48 hours of admission, a fasted morning (between 8:30 and 9:30 AM) blood sample was obtained to determine thyroid hormone concentrations. Levels of TSH and FT4 were determined under routine conditions on the same day of the blood draw. The hormonal assay was performed in the Hospital de Mataró Testing Laboratory. TSH was determined by chemiluminescence (ECLIA); levels between 0.30–4.20 mcIU/mL were considered normal for both sexes. Free thyroxine (fT4) was evaluated by chemiluminescence (ECLIA); levels between 0.80-1.84 ng/dL were considered normal for both sexes (Cobas 8000 e801 (Roche)). TSH concentrations were determined in all patients, but FT4 was available in only 70 out of 98 patients.

# *Statistical analysis*

All data analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corporation, USA). Partial correlation analyses were used to explore the correlation between TSH and FT4 concentrations and continuous measures (DUI, DUP and psychometric scores) while adjusting for age and sex. Significance was set as a p value < 0.05 (bilateral).

Logistic regression was performed to explore the association between thyroid hormones (TSH, FT4) and affective psychosis while adjusting for sex and age. In this analysis, affective psychosis (defined as a diagnosis of bipolar disorder or psychotic depression confirmed at the follow-up visit at one year) was used as the dependent variable. The reference category for psychosis diagnosis was nonaffective psychosis (schizophrenia-spectrum diagnoses).

Further exploratory analyses were conducted to study the association between thyroid hormones and other clinical variables dealing with the presentation of first-episode psychosis (presence of prodromal symptoms; cycloid psychosis criteria) while adjusting for covariates. In these analyses, sex, age, cannabis use (defined as a positive cannabis test at admission) and stressful life events at onset were considered independent variables.

## **RESULTS**

The demographic, clinical and biochemical data of the sample at the baseline assessment are described in Table 1. Fifty-five FEP patients (56.1%) had prodromal symptoms. Thirty FEP patients (30.6%) had sudden onset of psychotic symptoms (criteria B, cycloid psychosis). Nine FEP patients (9.2%) met the full criteria for cycloid psychosis. Regarding thyroid hormone concentrations, the mean values for TSH and FT4 concentrations were within the normal limits. The ranges for TSH concentrations were 0.49 to 8.18 mIU/mL and 0.55 to 2.02 ng/dL for FT4. When the blood tests to determine thyroid function were performed, none of the patients were under lithium medication.

### **Clinical phenotype and free thyroxine levels at onset (exploratory analyses)**

Partial correlations (adjusted for age and sex) showed a negative significant association between TSH and FT4 concentrations ( $r = -0.371$ ,  $p = 0.002$ ). FT4 was negatively associated with DUP ( $r = -0.251$ ,  $p = 0.039$ )

but not DUI. TSH and FT4 concentrations were not associated with the severity of psychopathological scales, such as PANSS positive, negative, general psychopathology subscores, PANSS total score, YMRS or HAM-D (data not shown).

Patients with a positive cannabis test in urine at admission had higher FT4 concentrations ( $1.43 \pm 0.25$  vs.  $1.21 \pm 0.29$ ,  $p=0.002$ ; Figure 1), although they had similar TSH concentrations ( $1.73 \pm 1.51$  vs.  $1.92 \pm 1.10$ ,  $p= 0.502$ ).

The results of the logistic regression exploring the relationship between thyroid hormones and the clinical phenotype at the onset of psychosis are described in Table 2. FT4 (but not TSH) concentrations were associated with prodromal symptoms at the onset ( $OR= 0.06$ ,  $p= 0.018$ ) and B criteria of cycloid psychosis (sudden onset;  $OR= 10.49$ ,  $p= 0.040$ ). Other cycloid psychosis criteria (A, C, D and full criteria) were not associated with thyroid function.

#### **Diagnosis at the 12-month follow-up and free thyroxine levels at onset (main hypothesis)**

Fifty-four FEP patients (55.1%) were diagnosed with affective psychotic disorders (BD or MDD) at the 12-month follow-up. In the logistic regression analysis exploring the relationship between baseline thyroid hormone concentrations at admission and the diagnosis at follow-up (1 year) and adjusted for age and sex, FT4 concentrations were associated with affective psychosis ( $OR= 8.57$ ,  $p= 0.042$ ). TSH concentrations were not associated with the clinical diagnosis ( $OR= 1.26$ ,  $p= 0.273$ ).

## **DISCUSSION**

In our study, which included 98 FEP patients, higher (but in normal range) plasma FT4 concentrations at admission were associated with a specific clinical phenotype, characterized by fewer prodromal symptoms, shorter DUP duration and a sudden onset of psychosis. Cannabis use was associated with higher FT4 concentrations. Regarding the comparison between affective and nonaffective psychosis, patients diagnosed with affective psychosis (bipolar disorder or psychotic depression) at the 12-month follow-up showed higher free thyroxine levels at admission.

Higher free thyroxine was associated with sudden onset of psychosis, as assessed with Perris & Brockington cycloid psychosis criteria (Perris, 1974). Thyrotoxicosis and autoimmune thyroiditis have been

associated with acute and severe episode psychotic induction (Browlie et al., 2000; Menon et al., 2017). Possible mechanisms could involve excess thyroid hormone affecting neurotransmitters (serotonin, gaminobutyric acid and dopamine) or second messengers (adenyl cyclase and phospholipase-C systems). In a previous cross-sectional study (Barbero et al., 2015) including young (aged 18–35 years) early psychotic patients (less than 3 years of illness), better cognitive performance in the attention/vigilance domain was positively correlated with free T4 levels (but not TSH or thyroid antibodies). No other previous studies have explored how thyroid function correlates with clinical phenotype in FEP patients. Most studies have focused on other clinical aspects of the illness and have shown a close relationship between thyroid abnormalities and psychosis in general (Othman et al., 1994). Although we did not find a significant association between thyroid hormones and the full cycloid psychosis criteria, it is important to underscore that only 9 patients (9.2%) fulfilled all criteria for cycloid psychosis. Therefore, our sample might be underpowered for detecting significant associations with this outcome due to the low prevalence of cycloid psychosis. Further multicentre studies might overcome this limitation by increasing the number of patients with cycloid psychosis.

Thyroid dysfunction findings have been mostly associated with affective psychosis (bipolar disorder) rather than with nonaffective psychosis (schizophrenia) (Carta et al., 2004). We found that patients diagnosed with affective psychosis at 12 months showed higher free thyroxine levels at onset than nonaffective psychosis patients. This result would be in line with that found in a previous study (Barbero et al., 2015), where an exploratory analysis by psychotic subtypes suggested that subjects with affective psychoses (BD or schizoaffective disorder) had increased FT4 levels and a better cognitive profile than those with nonaffective psychosis (schizophreniform disorder or schizophrenia). However, in a recent study (Petruzzielli et al., 2020) with child and adolescent patients, those diagnosed with first affective spectrum disorder showed lower free thyroxine levels than those with first schizophrenia spectrum disorder.

We did not find an association between the severity of psychopathology and thyroid function, which is in accordance with previous studies including patients with FEP (Barbero et al., 2020; Jose et al., 2015) or bipolar disorder (Goyal et al., 2021; Barbero et al., 2014). However, in previous studies including patients

with schizophrenia, the severity of illness showed a positive correlation with thyroxine levels (T4) (Baumgartner et al., 2000) and a negative correlation with free T3 levels (Ichioka et al., 2012).

Tetrahydrocannabinol, the main psychoactive constituent present in cannabis, acutely alters several hormones, including suppression of luteinizing hormone (Cone et al., 1986), testosterone (Barnett et al., 1983), and triiodothyronine (T3) (Parshad et al., 1983). Cannabinoids also suppress the hypothalamic–pituitary–adrenal (HPA) axis at the pituitary level and thyroid gland (Chakrabarti et al., 2011). Despite this, there are limited human data regarding the effects of cannabis on thyroid hormone levels. Two previous studies found lower TSH and T3 levels in acute cannabis users (Malhotra et al., Parshad et al., 1983), but these changes were not seen in chronic users (Bonnet et al., 2013) or in cannabis-related psychosis patients (Muzaffar et al., 2021). In our study, we found that FEP patients with a positive cannabis test in urine at admission had higher FT4 concentrations, although they maintained similar TSH concentrations than FEP patients with a negative cannabis test. To our knowledge, this is the first time these results have been found in a sample of FEP patients.

Some limitations of our study need to be addressed. First, we only determined thyroid function once (one morning sample collected under fasting conditions). Second, we did not assess thyroid autoimmune status, which might be associated with the clinical phenotype of FEP (Barbero et al., 2020). Third, as already mentioned, the sample size of our study might be too small for detecting associations between thyroid hormones and low-prevalence phenotypes (e.g., cycloid psychosis).

In summary, our study suggests that higher free-thyroxine levels are associated with a specific clinical phenotype of FEP patients (fewer prodromal symptoms, shorter DUP duration and sudden onset of psychosis) and with affective psychosis diagnoses at the 12-month follow-up.

## ACKNOWLEDGMENTS

The authors thank the Adult and the Child and Adolescent Psychiatry Services of Hospital de Mataró for their care of patients and collaboration with the study. We are indebted to the patients and their families who participated in the study.



254 **CONFLICT OF INTEREST**

255 The authors declare no conflict of interest regarding this work.

256

# REFERENCES

- Barbero, J.D., Garcia-Parés, G., Llorens, M., Tost, M., Cobo, J., Palao, D., Labad, J., 2014. Thyroglobulin antibodies and risk of readmission at one year in subjects with bipolar disorder. *Psychiatry Res.* 219, 109–113. <https://doi.org/10.1016/j.psychres.2014.05.028>
- Barbero, J.D., Gutiérrez-Zotes, A., Montalvo, I., Creus, M., Cabezas, Á., Solé, M., Algora, M.J., Garcia-Parés, G., Vilella, E., Labad, J., 2015. Free thyroxine levels are associated with cognitive abilities in subjects with early psychosis. *Schizophr. Res.* 166, 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., 2020. Association between anti-thyroid antibodies and negative symptoms in early psychosis. *Early Interv. Psychiatry* 14, 470–475. <https://doi.org/10.1111/eip.12873>
- Barnett, G., Chiang, C.-W.N., Licko, V., 1983. Effects of marijuana on testosterone in male subjects. *J. Theor. Biol.* 104, 685–692. [https://doi.org/10.1016/0022-5193\(83\)90255-2](https://doi.org/10.1016/0022-5193(83)90255-2)
- Baumgartner, A., Pietzcker, A., Gaebel, W., 2000. The hypothalamic–pituitary–thyroid axis in patients with schizophrenia. *Schizophr. Res.* 44, 233–243. [https://doi.org/10.1016/S0920-9964\(99\)00187-5](https://doi.org/10.1016/S0920-9964(99)00187-5)
- Bicikova, M., Hampl, R., Hill, M., Ripova, D., Mohr, P., Putz, Z., 2011. Neuro- and immunomodulatory steroids and other biochemical markers in drug-naïve schizophrenia patients and the effect of treatment with atypical antipsychotics. *Neuro Endocrinol. Lett.* 32, 141–7.
- Bonnet, U., 2012. Chronic Cannabis Abuse, Delta-9-tetrahydrocannabinol and Thyroid Function. *Pharmacopsychiatry* 46, 35–36. <https://doi.org/10.1055/s-0032-1316342>
- Brockington, I.F., Perris, C., Kendell, R.E., Hillier, V.E., Wainwright, S., 1982. The course and outcome of cycloid psychosis. *Psychol. Med.* 12, 97–105. <https://doi.org/10.1017/S0033291700043336>
- Brown, A.S., 2011. The environment and susceptibility to schizophrenia. *Prog. Neurobiol.* 93, 23–58. <https://doi.org/10.1016/j.pneurobio.2010.09.003>
- Brownlie, B., Rae, A., Walshe, J., Wells, J., 2000. Psychoses associated with thyrotoxicosis - “thyrotoxic psychosis.” A report of 18 cases, with statistical analysis of incidence. *Eur. J. Endocrinol.* 438–444. <https://doi.org/10.1530/eje.0.1420438>
- Brugha, T.S., Cragg, D., 1990. The List of Threatening Experiences: the reliability and validity of a brief life events questionnaire. *Acta Psychiatr. Scand.* 82, 77–81. <https://doi.org/10.1111/j.1600-0447.1990.tb01360.x>
- Carta, M.G., Loviselli, A., Hardoy, M.C., Massa, S., Cadeddu, M., Sardu, C., Carpiniello, B., Dell’Osso, L., Mariotti, S., 2004. The link between thyroid autoimmunity (antithyroid peroxidase autoantibodies) with anxiety and mood disorders in the community: a field of interest for public health in the future. *BMC Psychiatry* 4, 25. <https://doi.org/10.1186/1471-244X-4-25>
- Chakrabarti, S., 2011. Thyroid Functions and Bipolar Affective Disorder. *J. Thyroid Res.* 2011, 1–13. <https://doi.org/10.4061/2011/306367>

- 294 Cone, E.J., Johnson, R.E., Moore, J.D., Roache, J.D., 1986. Acute effects of smoking marijuana on  
295 hormones, subjective effects and performance in male human subjects. *Pharmacol. Biochem. Behav.*  
296 24, 1749–1754. [https://doi.org/10.1016/0091-3057\(86\)90515-0](https://doi.org/10.1016/0091-3057(86)90515-0)
- 297 First M, Spitzer R, Gibbon M. Structured clinical interview for DSM-IV axis I disorders. Washington, DC:  
298 American Psychiatric Press (1994).
- 299 Giné-Servén, E., Martínez-Ramírez, M., Boix-Quintana, E., Davi-Loscos, E., Guanyabens, N., Casado, V.,  
300 Muriana, D., Torres-Rivas, C., Crespo-Facorro, B., Labad, J., 2022. Routine cerebrospinal fluid  
301 parameters as biomarkers in first-episode psychosis: A prospective observational study. *Prog. Neuro-*  
302 *Psychopharmacology Biol. Psychiatry* 112, 110424. <https://doi.org/10.1016/j.pnpbp.2021.110424>
- 303 González-Blanco, L., Greenhalgh, A.M.D., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B.J., Kirkpatrick,  
304 B., 2016. Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related  
305 disorders: A meta-analysis. *Schizophr. Res.* 174, 156–160.  
306 <https://doi.org/10.1016/j.schres.2016.03.018>
- 307 Goyal, M., Yadav, K., Solanki, R., 2021. A study of thyroid profile in patients suffering from the first episode  
308 of mania: A cross-sectional study. *Indian J. Psychiatry* 63, 395.  
309 [https://doi.org/10.4103/psychiatry.IndianJPsychiatry\\_33\\_20](https://doi.org/10.4103/psychiatry.IndianJPsychiatry_33_20)
- 310 Hall, R.C.W., 1995. Global Assessment of Functioning. *Psychosomatics* 36, 267–275.  
311 [https://doi.org/10.1016/S0033-3182\(95\)71666-8](https://doi.org/10.1016/S0033-3182(95)71666-8)
- 312 Hamilton, M., 1960. A RATING SCALE FOR DEPRESSION. *J. Neurol. Neurosurg. Psychiatry* 23, 56–62.  
313 <https://doi.org/10.1136/jnnp.23.1.56>
- 314 Hayes, E., Gavrilidis, E., Kulkarni, J., 2012. The Role of Oestrogen and Other Hormones in the  
315 Pathophysiology and Treatment of Schizophrenia. *Schizophr. Res. Treatment* 2012, 1–8.  
316 <https://doi.org/10.1155/2012/540273>
- 317 Howes, O.D., McCutcheon, R., 2017. Inflammation and the neural diathesis-stress hypothesis of  
318 schizophrenia: a reconceptualization. *Transl. Psychiatry* 7, e1024–e1024.  
319 <https://doi.org/10.1038/tp.2016.278>
- 320 Hubbard, D.B., Miller, B.J., 2019. Meta-analysis of blood cortisol levels in individuals with first-episode  
321 psychosis. *Psychoneuroendocrinology* 104, 269–275.  
322 <https://doi.org/10.1016/j.psyneuen.2019.03.014>
- 323 Ichioka, S., Terao, T., Hoaki, N., Matsushita, T., Hoaki, T., 2012. Triiodothyronine may be possibly  
324 associated with better cognitive function and less extrapyramidal symptoms in chronic schizophrenia.  
325 *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 39, 170–174.  
326 <https://doi.org/10.1016/j.pnpbp.2012.06.008>
- 327 Jose, J., Nandeesha, H., Kattimani, S., Meiyappan, K., Sarkar, S., Sivasankar, D., 2015. Association  
328 between prolactin and thyroid hormones with severity of psychopathology and suicide risk in drug free  
329 male schizophrenia. *Clin. Chim. Acta* 444, 78–80. <https://doi.org/10.1016/j.cca.2015.02.003>
- 330 KAUFMAN, J., BIRMAHER, B., BRENT, D., RAO, U., FLYNN, C., MORECI, P., WILLIAMSON, D., RYAN,  
331 N., 1997. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and  
332 Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *J. Am. Acad. Child Adolesc.*  
333 *Psychiatry* 36, 980–988. <https://doi.org/10.1097/00004583-199707000-00021>

- 334 Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for  
335 Schizophrenia. *Schizophr. Bull.* 13, 261–276. <https://doi.org/10.1093/schbul/13.2.261>
- 336 Labad, J., Barbero, J.D., Gutiérrez-Zotes, A., Montalvo, I., Creus, M., Cabezas, Á., Solé, M., Algora, M.J.,  
337 García-Parés, G., Vilella, E., 2016. Free thyroxine levels are associated with cognitive changes in  
338 individuals with a first episode of psychosis: A prospective 1-year follow-up study. *Schizophr. Res.*  
339 171, 182–186. <https://doi.org/10.1016/j.schres.2016.01.036>
- 340 Labad, J., 2019. The role of cortisol and prolactin in the pathogenesis and clinical expression of psychotic  
341 disorders. *Psychoneuroendocrinology* 102, 24–36. <https://doi.org/10.1016/j.psyneuen.2018.11.028>
- 342 Lis, M., Stańczykiewicz, B., Liśkiewicz, P., Misiak, B., 2020. Impaired hormonal regulation of appetite in  
343 schizophrenia: A narrative review dissecting intrinsic mechanisms and the effects of antipsychotics.  
344 *Psychoneuroendocrinology* 119, 104744. <https://doi.org/10.1016/j.psyneuen.2020.104744>
- 345 Lukasiewicz, M., Gerard, S., Besnard, A., Falissard, B., Perrin, E., Sapin, H., Tohen, M., Reed, C., Azorin,  
346 J.-M., 2013. Young Mania Rating Scale: how to interpret the numbers? Determination of a severity  
347 threshold and of the minimal clinically significant difference in the EMBLEM cohort. *Int. J. Methods*  
348 *Psychiatr. Res.* 22, 46–58. <https://doi.org/10.1002/mpr.1379>
- 349 Malhotra, S., Heptulla, R.A., Homel, P., Motaghedi, R., 2017. Effect of Marijuana Use on Thyroid Function  
350 and Autoimmunity. *Thyroid* 27, 167–173. <https://doi.org/10.1089/thy.2016.0197>
- 351 Menon, V., Subramanian, K., Thamizh, J.S., 2017. Psychiatric Presentations Herald Hashimoto's  
352 Encephalopathy: A Systematic Review and Analysis of Cases Reported in Literature. *J. Neurosci.*  
353 *Rural Pract.* 08, 261–267. [https://doi.org/10.4103/jnrp.jnrp\\_440\\_16](https://doi.org/10.4103/jnrp.jnrp_440_16)
- 354 Misiak, B., Stańczykiewicz, B., Wiśniewski, M., Bartoli, F., Carra, G., Cavaleri, D., Samochowiec, J., Jarosz,  
355 K., Rosińczuk, J., Frydecka, D., 2021. Thyroid hormones in persons with schizophrenia: A systematic  
356 review and meta-analysis. *Prog. Neuro-Psychopharmacology Biol. Psychiatry* 111, 110402.  
357 <https://doi.org/10.1016/j.pnpbp.2021.110402>
- 358 Noda, M., 2015. Possible role of glial cells in the relationship between thyroid dysfunction and mental  
359 disorders. *Front. Cell. Neurosci.* 9. <https://doi.org/10.3389/fncel.2015.00194>
- 360 Othman, S.S., Kadir, K.A., Hassan, J., Hong, G.K., Singh, B.B., Raman, N., 1994. High Prevalence of  
361 Thyroid Function Test Abnormalities in Chronic Schizophrenia. *Aust. New Zeal. J. Psychiatry* 28, 620–  
362 624. <https://doi.org/10.3109/00048679409080785>
- 363 Parshad, O., Kumar, M., Melville, G.N., 1983. Thyroid-gonad relationship in marijuana smokers. A field  
364 study in Jamaica. *West Indian Med. J.* 32, 101–5.
- 365 Perris, C. (1974). A study of cycloid psychoses. *Acta Psychiatrica Scandinavica*, 253, 1–77. Retrieved from  
366 <http://www.ncbi.nlm.nih.gov/pubmed/4532463>
- 367 Petruzzelli, M.G., Marzulli, L., Giannico, O.V., Furente, F., Margari, M., Matera, E., Margari, F., 2020.  
368 Glucose Metabolism, Thyroid Function, and Prolactin Level in Adolescent Patients With First Episode  
369 of Schizophrenia and Affective Disorders. *Front. Psychiatry* 11.  
370 <https://doi.org/10.3389/fpsy.2020.00775>
- 371 Santesteban-Echarri, O., Paino, M., Rice, S., González-Blanch, C., McGorry, P., Gleeson, J., Alvarez-  
372 Jimenez, M., 2017. Predictors of functional recovery in first-episode psychosis: A systematic review

373 and meta-analysis of longitudinal studies. Clin. Psychol. Rev. 58, 59–75.  
374 <https://doi.org/10.1016/j.cpr.2017.09.007>

375

376 Santos, N.C., Costa, P., Ruano, D., Macedo, A., Soares, M.J., Valente, J., Pereira, A.T., Azevedo, M.H.,  
377 Palha, J.A., 2012. Revisiting Thyroid Hormones in Schizophrenia. J. Thyroid Res. 2012, 1–15.  
378 <https://doi.org/10.1155/2012/569147>

379 Shaffer, D., 1983. A Children's Global Assessment Scale (CGAS). Arch. Gen. Psychiatry 40, 1228.  
380 <https://doi.org/10.1001/archpsyc.1983.01790100074010>

381 Tsuang, M.T., Bar, J.L., Stone, W.S., Faraone, S. V, 2004. Gene-environment interactions in mental  
382 disorders. World Psychiatry 3, 73–83.

383 Wallwork, R.S., Fortgang, R., Hashimoto, R., Weinberger, D.R., Dickinson, D., 2012. Searching for a  
384 consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia.  
385 Schizophr. Res. 137, 246–250. <https://doi.org/10.1016/j.schres.2012.01.031>

386 Weickert, C.S., Weickert, T.W., Pillai, A., Buckley, P.F., 2013. Biomarkers in Schizophrenia: A Brief  
387 Conceptual Consideration. Dis. Markers 35, 3–9. <https://doi.org/10.1155/2013/510402>

388 Woodberry, K.A., Shapiro, D.I., Bryant, C., Seidman, L.J., 2016. Progress and Future Directions in  
389 Research on the Psychosis Prodrome. Harv. Rev. Psychiatry 24, 87–103.  
390 <https://doi.org/10.1097/HRP.0000000000000109>

391 Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A Rating Scale for Mania: Reliability, Validity  
392 and Sensitivity. Br. J. Psychiatry 133, 429–435. <https://doi.org/10.1192/bjp.133.5.429>

393 Zimmerman, M., Martinez, J.H., Young, D., Chelminski, I., Dalrymple, K., 2013. Severity classification on  
394 the Hamilton depression rating scale. J. Affect. Disord. 150, 384–388.  
395 <https://doi.org/10.1016/j.jad.2013.04.028>

396

**Table 1** (on next page)

Clinical Biochemical Data

1 Table 1: Demographic, clinical and biochemical variables of 98 patients with first-episode psychosis

Age, mean (SD), years	34.7 (15.3)
Female sex, N (%)	40 (40.8%)
Previous history of psychiatric (nonpsychotic) disorders, N (%)	60 (61.9%)
Mood disorder	38 (38.7%)
Anxiety disorder	7 (7.1%)
Obsessive compulsive disorder	2 (2.0%)
Personality disorder	23 (23.5%)
Eating behaviour disorder	4 (4.1%)
Substance use disorder	28 (28.6%)
Others	7 (7.1%)
Smoking, N (%)	51 (52.0%)
Cannabis use (abuse or dependence), N (%)	48 (49.0%)
Alcohol use (abuse or dependence), N (%)	29 (29.6%)
First degree family history of psychiatric disease, N (%)	44 (44.9%)
Previous life stressful events, N (%)	41 (41.8%)
Prodromal symptoms, N (%)	55 (56.1)
Cognitive symptoms	22 (22.4%)
Negative symptoms	23 (23.5%)
Attenuated positive psychotic symptoms	28 (28.6%)
Mood symptoms	21 (21.4%)
Anxiety symptoms	24 (24.5%)
Obsessive-compulsive symptoms	4 (4.1%)
Duration of psychiatric prodromal symptoms, N (%)	
No prodromal symptoms	43 (43.9%)
<1 month	4 (4.1%)
1–6 months	24 (24.5%)
>6 months	27 (27.6%)
Duration of untreated illness, mean (SD), days	173.2 (257.1)
Duration of untreated psychosis, mean (SD), days	37.5 (50.9)
Treatment during hospital admission, N (%)	
Atypical antipsychotics	98 (100%)
Typical antipsychotics	8 (8.2%)
Mood stabilizers	48 (49.0%)
Electroconvulsive therapy	1 (1.0%)
PANSS, mean (SD)	
Total score	82.3 (20.0)
Wallwork factors:	
Positive factor	14.4 (3.5)
Negative factor	12.1 (7.0)
Disorganized/concrete factor	8.8 (2.9)
Excited factor	11.6 (4.1)
Depressed factor	8.2 (3.6)
YMRS, mean (SD)	26.7 (11.2)
HAM-D, mean (SD)	22.5 (9.7)
Cycloid psychosis complete phenotype, N (%)	9 (9.2%)
Acute psychotic episode	36 (36.7%)
Sudden onset	30 (30.6%)
Clinical profile (4 or more)	23 (23.5%)
Confusion	27 (27.6%)
Delusions	98 (100%)
Hallucinations	53 (54.1%)

Panxiety	24 (24.5%)
Happiness or ecstasy	40 (40.8%)
Motility disturbances	25 (25.5%)
Concern with death	8 (8.2%)
Oscillations of mood	10 (10.2%)
No fixed symptomatologic combination	11 (11.2%)
Suicidal attempt during FEP	9 (9.2%)
GAF, mean (SD)	
On admission	29.9 (6.6)
At discharge	62.5 (9.1)
Thyroid hormones levels	
Parameters, mean (SD)	
TSH (mIU/mL)	1.8 (1.2)
FT4 (ng/dL)	1.3 (0.2)

2

3 Abbreviations: SD, standard deviation; PANSS, positive and negative syndrome scale, YMRS, Young  
4 Mania Rating Scale, HAM-D, Hamilton Depressive Rating Scale for Depression; GAF, Global Assessment  
5 of Functioning, FEP, first-episode psychosis, TSH, thyroid stimulating hormone; FT4, free thyroxine.

6



# **Table 2**(on next page)

Thyroid logistic regression

1 **Table 2. Results of the logistic regression exploring the relationship between thyroid hormones and clinical phenotype at onset**

	Prodromal symptoms at onset		Criteria A cycloid psychosis		Criteria B cycloid psychosis		Criteria C cycloid psychosis		Criteria D cycloid psychosis		Full criteria cycloid psychosis	
	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value	OR	p value
TSH	1.026	0.903	1.114	0.584	1.440	0.086	0.848	0.507	0.958	0.899	0.925	0.840
FT4	0.059	0.018	2.252	0.428	10.485	0.040	2.056	0.523	1.900	0.671	1.779	0.714
Female gender	0.373	0.11	1.057	0.914	0.899	0.849	3.030	0.062	2.093	0.365	1.635	0.560
Age	0.921	0.001	0.989	0.552	0.976	0.251	0.975	0.250	0.955	0.166	0.950	0.158
SLE at onset	3338	0.063	1.478	0.454	1.863	0.279	1.236	0.719	1.152	0.866	1.575	0.606
Cannabis (positive urine test)	1676	0.426	0.613	0.406	0.339	0.104	0.783	0.707	0.329	0.244	0.355	0.289

2

3 Abbreviations: TSH, thyroid stimulating hormone; FT4, free thyroxine. SLE, stressful life events.

# Figure 1

Cannabis FT4

