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Depressive symptoms, thyroid hormone and autoimmunity in a population-based cohort from Sardinia

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Abstract

Objective—To evaluate the association between depressive symptoms and thyroid autoimmunity, and the effect of thyroid hormone on the risk of depression.

Methods—We included 3138 individuals from SardiNIA project, none of whom was taking thyroid medication and antidepressants. Thyrotropin (TSH), free thyroxine (FT4), and antibodies against thyroperoxidase (TPOAb) were measured in all the sample. Depressive symptoms were assessed with Center for Epidemiologic Studies Depression Scale (CES-D).

Results—We found no association between TPOAb and depressive symptoms and no linear association between TSH or FT4 levels and depressive symptoms. However, individuals in the lowest and highest FT4 quintiles showed a higher CES-D score compared to individuals in the middle quintile. In addition, participants in the lowest and highest FT4 quintiles had an increased risk of CES-D 16 with odds ratios of 1.44 (95% CI = 1.09–1.89) and 1.33 (95% CI = 1.01–1.77), respectively.

Limitations—cross-sectional design of the study.

Conclusions—A U-shaped relation was found between FT4 and depressive symptoms: compared to average FT4 values, both high and low thyroid function was associated with more

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depressive symptoms. Further studies are necessary to determine the exact cause-effect relation of this association.

Keywords

free thyroxine; depression; thyroid hormone; depressive symptoms; Center for Epidemiologic Studies Depression Scale

1. Introduction

Thyroid hormones are fundamental for metabolism and growth (Santisteban & Bernal, 2005). Thyroid hormones are crucial in the developing nervous system, and they continue to be important in the adult brain. Prominent clinical signs of thyroid hormone deficiency or excess are manifested as alterations in central nervous system functioning, including mood and cognition. Indeed, research and clinical practice suggest that thyroid dysfunction is related to mood disorders and in particular to depression (Bauer et al., 2008). Both hypothyroidism and depression are common in primary care practice (Hueston, 2001) and these two conditions present with significant symptoms overlap (including fatigue, weight change, and depressed mood). Nevertheless only a small number of the depressed individuals shows overt thyroid disease (Gold et al., 1981). In most cases, hypothyroidism has autoimmune origin, and antibodies against thyroperoxidase (TPOAb) are commonly present in these patients (Delitala et al., 2014). Autoimmune thyroid disease has also been associated with an increased risk of depression: in particular, TPOAb was linked with depressed mood in several reports (Pop et al., 1998; Carta et al., 2004; Ott et al., 2011; Watt et al., 2012). However, other studies have found no such association, either cross-sectionally or longitudinally (Medici et al., 2014). The literature is also mixed on the association between subclinical levels of thyrotropin (TSH), free thyroxine (FT4), and depression (Engum et al., 2002; Forman-Hoffman & Philibert 2006; Hage & Azar, 2012; van de ven et al. 2012). One complication is an apparent “U shaped” relation with mood, with hyperthyroidism also found to be associated with depression (Thomsen et al., 2005). A recent study showed that this relation was significant even in the higher tertile of TSH within the normal range (Medici et al., 2014), suggesting a continuum between normal and pathological thyroid status.

Using data from a large population-based cohort, this study examined the association of depressive symptoms with thyroid autoimmunity, determined by the presence of TPOAb, and with thyroid hormones, determined by the level free FT4 and TSH. The study examined both linear and curvilinear (U-shaped) relations between thyroid hormones and depressive symptoms. The analyses considered continuous and dichotomous depressive symptom scores, and examined which symptoms of depression (e.g., somatic complaints vs. depressed affect) are related to thyroid function.

2. Materials and methods

2.1. Subjects

The sample examined in this study was part of the SardiNIA project, an ongoing longitudinal study in a population-based cohort from the island of Sardinia, Italy (Scuteri A

et al., 2014). Features of this project have been described elsewhere (Pilia G et al., 2006). Briefly, all residents from four towns (Lanusei, Arzana, Ilbono, and Elini) in a valley in Sardinia (Italy) were invited to participate. Since November 2001, participants had visited and their blood samples analyzed about every 3 years, generating three complete surveys. Depressive symptoms were first assessed during the third survey of the SardiNIA project. From the 4839 subjects who had the medical visit, we excluded those who reported taking drugs influencing thyroid function (levothyroxine, thyrostatics), those on antidepressants, according to the Anatomical Therapeutic Chemical (ATC) classification system (WHO Collaborating Center for drug statistic methodology, 2007), and subjects who refused the test. The final sample of the original cohort included 3,138 subjects (1,763 female and 1375 male). Smoking habits were divided in three groups: never, past, and current. Education was considered on a scale from 1 (no education) to 5 (university degree). Body mass index (BMI) was calculated as weight (kg) / height²(m²).

Each participant signed an informed consent. All study methods were conducted according to the principles expressed in the Declaration of Helsinki and were approved by the governing Ethics Committee, ASL4.

2.2. Assessment of depression

Depressive symptoms were assessed using the Center for Epidemiological Studies-Depression scale (CES-D) (Radloff, 1977), a widely used self-reported screening test. The CES-D comprises a 20-item scale assessing the frequency of depressive symptoms within the previous week. Each item is rated on a 4-point scale ranging from 0 (rarely or none of the time - less than 1 day -) to 3 (most or all of the time - 5/7 days -). Total CES-D scores ranges from 0 to 60, and is computed as the sum of items, with items 4, 8, 12, and 16 reversed. A cut-off score 16 is often used as threshold used to define depressed mood (Beekman et al., 1997). CES-D 16 aids in identifying individuals at risk for clinical depression, with good sensitivity and specificity and high internal consistency. In addition to the total CES-D score, we examined 4 subscales that assess different domains of depressive symptoms: depressed affect (7 items; e.g., “I felt sad”), somatic complaints (7 items; e.g., “I did not feel like eating; my appetite was poor”), anhedonia (4 items; e.g., “I was happy”), and interpersonal problems (2 items; e.g., “I felt that people disliked me”)(Sutin et al., 2013).

2.3. Biochemical and hormone assays

Blood venous samples were drawn between 7 and 8 a.m. after an overnight fast. Serum samples were assayed for TSH, FT4, and TPOAb using an automated chemiluminescence assay system (Immulite 2000, Siemens, Germany), as described elsewhere (Delitala et al., 2015). Normal values are as follows: TSH, 0.4–4.0 µIU/ml; FT4, 0.89–1.76 ng/dl; TPOAb, < 35 IU/ml.

Overt hypothyroidism was defined as serum TSH level above the upper limit of reference range and serum FT4 level below the lower limit. Overt hyperthyroidism was diagnosed in subjects who had serum TSH level below the lower limit of the reference range and serum FT4 level above the upper limit. We defined subclinical thyroid dysfunction as the presence

of serum FT4 level in the normal reference range together with high serum TSH (subclinical hypothyroidism) or low serum TSH (subclinical hyperthyroidism). Euthyroid were subjects with TSH value within the reference range.

2.4. Statistical analysis

Normal distribution was assessed with the Shapiro-Wilk test. Distributions of continuously measured variables that were not normally distributed are expressed as median and 25th–75th percentiles. Distributions of categorical variables are expressed as percentages.

In order to study the association between thyroid autoimmunity and depression, we tested whether the presence of TPOAb or its titer could influence mood. In addition, we evaluated the CES-D scores as a continuous variable in the multiple regression, and as a dichotomous variable (0= CES-D < 16; 1= CES-D ≥ 16) in the logistic regression. To test the relation of thyroid hormones with continuous CES-D, we included FT4 and TSH (continuous traits) as exposure variables in the multiple linear regression analysis. In addition, because previous studies demonstrated that both reduced and increased thyroid function, even within euthyroid subjects, were related to depressed mood (Thomsen et al., 2005; Medici et al., 2014), we divided FT4 into quintiles (Quintile 1= lowest, Quintile 3= reference, Quintile 5= highest) and TSH into 5 categories (subclinical and overt disorders and euthyroidism) and tested them in the multiple linear regression analyses. Further, we tested separately the association between FT4 (continuous and divided into quintiles) and TSH (continuous and divided into 5 categories) and the risk of CES-D scores ≥ 16 (0=CES-D < 16; 1= CES-D ≥ 16). Finally, we tested distinct models for each subscale of CES-D. Because the dependent count variables (depressive affect, anhedonia, somatic complaints, and interpersonal relation) indicated a non-normal and overdispersed distribution (variance > mean), we used a negative binomial regression.

As a supplementary investigation, we repeated the above analyses in more selected samples. In particular, in one model, we included only TPOAb negative subjects and in a separate model those with TSH within the reference range.

All analyses were adjusted for age, age², education (continuous variables), sex, obesity (dichotomic variable), and smoking status (categorical variable). Due to its skewed distribution, the dependent variable CES-D score was transformed prior to running the regression. Significance was set at $p < 0.05$ in Stata 12.0.

Results

Descriptive statistics for the cohort are provided in Table 1. Female had also an increased frequency of CES-D score ≥ 16 in comparison to male (27.8% vs. 13.6%, $p < 0.001$). In regression models that accounted for covariates (age, age², sex, obesity, smoking status, and education), neither TPOAb titer nor TPOAb positivity showed an association with depressive symptoms (Table 2). In regression models that accounted for the same covariates, we found no linear associations between FT4 ($\beta = 0.025$; $p = 0.742$) or TSH ($\beta = 0.006$; $p = 0.573$) and CES-D scores. Similarly, FT4 and TSH did not predict a CES-D ≥ 16 (FT4: OR = 1.02, 95% CI = 0.70–1.51; $p = 0.893$; TSH: OR = 0.98, 95% CI = 0.92–1.05; $p = 0.584$).

Given previous reports of sex specific effects (Forman-Hoffman & Philibert 2006; Kritz-Silverstein et al., 2009; Williams et al., 2009), we tested, in additional analyses, sex interactions (TPOAb by sex, FT4 by sex, and TSH by sex) and found no significant differences between men and women in the associations of TPOAb, TSH, and FT4 with CES-D.

In addition to the above linear models, we tested whether individuals in the lowest and the highest FT4 quintiles had higher CES-D scores compared to individuals in the middle FT4 quintile. In regression models that accounted for covariates, we found that individuals in the lowest and highest FT4 quintiles reported significantly higher levels of depressive symptoms compared to those in the middle FT4 quintile (Table 3). Furthermore, a logistic regression analysis showed that subjects in the lowest and in the highest FT4 quintiles had an increased risk of a CES-D ≥ 16 with an odds ratio of 1.44 (95% CI = 1.09–1.89) and 1.33 (95% CI = 1.01–1.77), respectively (Table 4). Similar analyses found no U-shaped associations between TSH and CES-D scores.

We further examined whether FT4 had differential associations with a subscale of the CES-D. In negative binomial regression analysis adjusted for covariates, we found that participants with the lowest and highest FT4 quintiles had higher scores on the anhedonia subscale (Quintile 1: Coeff. = 0.076, $p = 0.012$; Quintile 5: Coeff. = 0.072, $p = 0.019$) (Table 5). There was a similar trend for the somatic complaints subscale, but the lowest quintile did not reach statistical significance (Quintile 1: Coeff. = 0.083, $p = 0.097$; Quintile 5: Coeff. = 0.111, $p = 0.029$). The depressive affect and interpersonal relation subscales showed no association with FT4 levels. We also found no association between the CES-D subscale and the TSH or the TPOAb (data not shown).

To test whether the FT4 effect on depressive symptoms was in part due to the presence of circulating TPOAb, we repeated the same above analysis in TPOAb negative subjects. After adjusting for covariates, subjects in the lowest and highest FT4 quintiles showed a direct association with CES-D scores compared to subjects in the middle quintile ($\beta = 0.162$, $p = 0.005$ and $\beta = 0.194$, $p = 0.001$, respectively) (Table S1). Furthermore, a logistic regression analysis showed that subjects in the lowest and highest FT4 quintiles had an increased risk of a CES-D ≥ 16 with an odds ratio of 1.57 (95% CI = 1.18 – 2.11, $p = 0.002$) and 1.47 (95% CI = 1.10 – 1.98, $p = 0.010$), respectively (Table S2). Finally, the results of the adjusted negative binomial regression analysis for each subscale of the CES-D indicated that participants with the lowest and highest FT4 quintiles had higher scores on the anhedonia (Quintile 1: Coeff. = 0.084, $p = 0.009$; Quintile 5: Coeff. = 0.079, $p = 0.015$) and somatic complaints subscales (Quintile 1: Coeff. = 0.110, $p = 0.041$; Quintile 5: Coeff. = 0.155, $p = 0.004$) (Table S3). There was a similar pattern for the depressed affect subscale, but it was weaker and non-significant. Still, the interpersonal relation subscale showed no association with FT4 level.

To test whether all FT4 effects on depressive symptoms were due to subjects above the clinical cut-off, we performed additional analyses including subjects with TSH within the reference range. Table S4 shows the results of multiple regression analyses: participants in the lowest and highest FT4 quintiles had higher CES-D scores ($\beta = 0.136$, $p = 0.016$ and $\beta =$

0.150, $p = 0.009$, respectively), and had an increased risk of CES-D scores ≥ 16 (OR = 1.44, 95% CI = 1.08 – 1.91, $p = 0.012$ and OR = 1.35, 95% CI = 1.00 – 1.81, $p = 0.044$, respectively), as shown in Table S5. Furthermore, the subscale analysis confirmed the statistical significant U-shaped relation for anhedonia (Quintile 1: Coeff = 0.074, $p = 0.019$; Quintile 5: Coeff. = 0.066, $p = 0.035$) and the trend for somatic complaints (Quintile 1: Coeff = 0.087, $p = 0.096$; Quintile 5: Coeff. = 0.107, $p = 0.041$) (supplementary Table S6).

4. Discussion

This study found no support for an association between thyroid autoimmunity (TPOAb) and depressive symptoms in a community-based cohort. Similarly, there were no linear associations between depressive symptoms and the TSH and FT4 hormones. However, our findings suggest a U-shaped relation between FT4 and depressed mood: individuals within the lowest and highest FT4 quintiles reported more depressive symptoms compared to the group in the middle quintile. Our data also suggest that the U-shaped relation was mainly driven by greater anhedonia and somatic complaints among those with the lowest and highest FT4 quintiles.

In the present study, we showed that the presence of TPOAb positivity is not related to depressive symptoms. The association between thyroid autoimmunity and mental disorders has been postulated for decades but previous studies reported variable results, probably caused by the different cutoff used to define TPOAb positivity. The studies that found an association between depressed mood and the presence of TPOAb were generally based on small and/or selected samples (Carta et al., 2004; Fountoulakis et al., 2004). In addition, an association between antibodies against thyroid and post-partum depression was also documented (Kuijpers et al., 2001). However, current and other large studies reported no associations between thyroid autoimmunity and the depression scales (Engum et al., 2005; van de Ven et al., 2012; Medici et al., 2014).

Although we found no linear associations between TSH, FT4, and CES-D, the data from our large cohort indicates that serum FT4 level has a U-shaped relation with depressive symptoms. This finding was robust: more depressive symptoms in the groups with either high or low secreted thyroid hormones was found after accounting for the age, age², sex, BMI, education level, and smoking status, and the results did not change when we excluded from the analyses individuals with TSH above or below clinical thresholds. Compared to those with average FT4, those with either high or low FT4 had respectively 33% or 44% greater risks of reporting depressive symptoms equal or above the common threshold of 16, which is indicative of clinically significant symptoms of depression. These findings are thus consistent with the notion that thyroid dysfunction, either high or low level FT4, may result in depressive symptomatology.

The interface between the action of thyroid hormone and neuropsychiatric function is intricate, and several mechanisms of thyroid hormone uptake into the brain and influences on neurotransmitter generation have been identified (Bauer et al., 2008). Thyroid hormones are crucial in the developing nervous system, and they continue to be important in the adult brain as well, because the most prominent clinical effects of thyroid hormone deficiency and

excess are manifested as alterations in central nervous system function, including mood and cognition. In the brain most triiodothyronine (T3) is formed by local deiodination of the T4 precursor. The complex biological actions of thyroid hormones are initiated by the intracellular binding of T3 to nuclear receptor, resulting in alterations in gene expression that include stimulation or repression of transcription of various target genes (Bauer et al., 2008).

There are certainly potential mechanisms of thyroid hormone action on mood and cognition. Many of the limbic system structures where thyroid hormone receptors are prevalent have been implicated in the pathogenesis of mood disorders. Moreover, interactions of thyroid function with neurotransmitter systems -- mainly norepinephrine and serotonin, directly implicated in mood and behavior regulation -- could contribute to brain function (Whybrow and Prange, 1981; Mason et al., 1987). Animal studies demonstrate that thyroid hormones modulate the serotonergic system through an increase in serotonergic neurotransmission, because brain serotonin levels correlated positively with T3 levels (Cleare et al., 1995). D2 activity may also be depressed by the elevated cortisol levels seen in depression and stress, resulting in decreased brain T3 levels (Jackson, 1998). There also indications that selective serotonin reuptake inhibitors and tricyclic antidepressants promote the activity of D2, thus resulting in increased conversion of T4 to T3 within the brain (Hage and Azar, 2012). Interactions with other neurotransmitters, including dopamine, have also been considered (Henley and Koehnle, 1997; Mano et al., 1998).

Additional suggestive evidence linking thyroid function to mood are the observations that in depressed individuals, the nocturnal surge of TSH is frequently absent, resulting in a reduction in thyroid hormone secretion (Souetre et al., 1988) and a blunted TSH response to thyrotropin releasing hormone (TRH) (Jackson, 1998), indicating that functional central hypothyroidism might occur in some depressed patients.

Overall, the available data, taken together, strongly support both thyroid hormone effects on brain development and function and neuropsychiatric manifestations of overt hypothyroidism and hyperthyroidism. It is not clear, however, whether the abnormal concentration of thyroid hormone might be a cause or a consequence of the depression. One hypothesis is that the hypercortisolemia described in some depressed patients may increase TRH neuronal activity, thus reducing the effect of TRH at the pituitary level. The net result is a reduced TSH response to protirelin seen in depressed individuals (Duval et al., 2006). On the other hand, although T3 and T4 concentrations within the brain are preserved within a narrow range, independently of fluctuations in the bloodstream (Bahls and de Carvalho, 2004), hypothyroid subjects may complain of depression, which improved after thyroxine supplementation therapy (Cleare et al., 1996). Hence, the association between thyroid hormone and depression is extremely complex, and other hormones, such as cortisol and sex hormones, may modulate them.

In humans, data are largely limited to the frequency of thyroid dysfunctions in depressed subjects. Thus far, the more recent availability of population surveys are providing the opportunity to study this association on subjects randomly selected from the general population, but still with divergent results. In one study, higher levels of T4 in the normal

range were associated with an increased risk of depression in men (Williams et al., 2009). In the Rancho-Bernardo Study an association between thyroid function and depressed mood with a gender-specific pattern was found (Kritz-Silverstein et al., 2009). In another study, Medici et al. found an association between low-normal TSH within the reference range and risk of developing depression independently of gender, and confirmed in prospective analysis (Medici et al., 2014). But other studies found no association between thyroid dysfunction and depression (Beydoun et al., 2013; Engum et al., 2005; Fjællegaard et al., 2015; Saltevo et al., 2015; van de Ven et al., 2012). The methodological approaches, the test used to assess the depression, and the different sample size used in the various studies might partly justify the contrasting results. Indeed, it should be noted that including subjects under antidepressant therapy can cause a misinterpretation of the thyroid hormones (Bou Khalil et al., 2011). Considering that the prevalence of antidepressant usage increases with age, and that more than 15% of women over 70 are chronic users (Lawrenson et al., 2000), the effect could be considerable.

In this paper we also analyzed the four-item CES-D subscale. Interestingly, subjects with the lowest and with highest FT4 quintiles had a reduced capacity to derive pleasure from normally pleasurable stimuli, “anhedonia”, a key symptom of depression. This association might be explained by reduced brain metabolism in the limbic system noted by some authors. The limbic system is involved in emotion control and both hyperthyroidism (Schreckenberger et al., 2006) and mild hypothyroidism (Bauer et al., 2009) were associated with metabolic changes in well-defined brain areas, revealed by positron emission tomography. Like anhedonia, the subscale analysis further showed that somatic symptoms were associated with both reduced and increased thyroid function. This finding is consistent with previous studies in which thyroid hormone was associated with an increased frequency of somatic complaints in both hypothyroidism and hyperthyroidism (Paschke et al., 1990; Schlote et al., 1992; Bauer et al., 2009). Intriguingly, these symptoms improved after treatment of thyroid disorder (Paschke et al., 1990; Schlote et al., 1992). Of course, hypothyroid and hyperthyroid individuals have different symptoms that reflect the opposite metabolic states. Hyperthyroidism is usually associated with irritability, insomnia, and nervousness while fatigue, hyper-somnolence, and difficulty concentrating are found in hypothyroidism. As a further complication, older subjects often have so called apathetic hyperthyroidism, which may resemble symptoms of hypothyroidism (Levy, 1991). The subscale analysis also showed that, although not statistically associated, even the depressive affect subscale had a “U-shaped” relation with FT4 quintiles of borderline significance (Table 5), which may represent a trend underestimated by our strict exclusion criteria.

5. Limitations

In our study, in addition to depending on cross-sectional analyses that precluded temporality ascertainment, the single measurement of FT4 and TSH may result in transient abnormal thyroid disorders. However, the results are bolstered by the use of very strict exclusion criteria. We excluded those on thyrostatic and levothyroxine as well as those who reported taking anti-depressants. Although this can result in an underestimation of the number of depressed subjects, it avoids possible pharmacologic interference with the pituitary-thyroid axis, because antidepressants may significantly decrease FT4 concentration (Joffe and

Singer, 1990). The statistical approach was further strengthened by considering CES-D score both as a continuous and a dichotomous variable and by the use of FT4 in quintiles, regardless of thyroid function classes (hypothyroidism, hyperthyroidism and euthyroidism).

6. Conclusion

In conclusion, we found evidence that mood is influenced by FT4 concentration with a “U shaped” relation: increased or reduced thyroid function is a risk factor for depression. Although autoimmunity is the most common cause of hypothyroidism (Delitala et al., 2014), in the present paper the association between lower thyroid function and depressed mood is independent of its presence. Similar findings were found in euthyroid subjects suggesting that even a small variation in thyroid hormone may influence mood in a kind of continuum with abnormal thyroid hormone concentration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Mood disorders are not related to antibodies against thyroid
- Free thyroxine has a “U-shaped” relation with depressive symptoms
- Free thyroxine is related to depressed mood also in euthyroid subjects

Table 1

Characteristics of the sample

	FT4 (ng/dl)				
	Quintile 1 (n= 629) (< 0.95 ng/dl)	Quintile 2 (n= 660) (0.95–1.04 ng/dl)	FT4 (ng/dl) Quintile 3 (n= 629) (1.05–1.14 ng/dl)	Quintile 4 (n= 631) (1.15–1.30 ng/dl)	Quintile 5 (n= 589) (1.31 ng/dl)
Age (yrs.)	48.5 (39.0 – 60.7)	48.3 (38.5 – 61.4)	49.7 (36.3 – 63.9)	50.1 (37.8 – 64.0)	52.1 (37.8 – 64.7)
BMI (Kg/m ²)	25.3 (22.5 – 29.2)	25.8 (22.8 – 28.9)	25.3 (22.4 – 28.3)	25.9 (22.7 – 28.8)	25.5 (22.6 – 28.5)
BMI 30 (%)	22.1%	18.3%	16.7%	18.1%	16.5%
TSH (µIU/ml)	1.66 (1.17 – 2.53)	1.56 (1.09 – 2.46)	1.47 (1.06 – 2.15)	1.44 (1.00 – 2.03)	1.41 (0.93 – 2.09)
TPOAb positivity (%)	25.9%	20.9%	18.9%	18.4%	23.9%
Smoking status (%)					
Never	61.2%	57.0%	62.8%	57.5%	59.5%
Past	16.5%	17.6%	15.3%	15.7%	14.8%
Current	22.3%	25.5%	21.9%	26.8%	25.7%
Education	3.17 ± 0.93	3.13 ± 0.96	3.20 ± 1.02	3.14 ± 1.04	3.16 ± 1.03
CES-D score	10 (6 – 16)	9 (6 – 14)	9 (5 – 14)	9 (6 – 14)	10 (7 – 15)
CES-D 16 (%)	25.9%	20.9%	18.9%	18.4%	23.9%

Data are expressed as median and interquartile range, or percentage. Education is expressed as mean and standard deviation.

Abbreviations: BMI, body mass index; TSH, thyrotropin; FT4, free thyroxine; CES-D, Center for Epidemiological Studies-Depression scale.

Table 2

Relation of TPOAb and CES-D. Result of multiple regression analysis and logistic regression analysis.

CES-D continuous	β (se)	P Value*
TPOAb + vs. TPOAb –	–0.304 (0.394)	0.440
TPOAb titer	0.001 (0.001)	0.626
CES-D 16	OR (95% CI)	P Value*
TPOAb + vs. TPOAb –	1.40 (0.75–2.60)	0.126
TPOAb titer	1.00 (0.66–3.95)	0.300

* Adjusted for age, sex, obesity (BMI ≥ 30), smoke, and education.

Abbreviations: β , beta coefficient; se, standard error

Table 3

Association between FT4 quintiles and depressive symptom scores.

	β	Std. Err.	t	p value
Age	-0.021	0.007	-3.14	0.002
Age ²	0.000	0.000	2.61	0.009
Sex	-0.459	0.038	-12.20	<0.001
BMI ≥ 30	-0.071	0.046	-1.54	0.124
Current smokers	0.221	0.051	4.33	<0.001
Past smokers	0.108	0.044	2.44	0.015
Education	-0.079	0.022	-3.65	<0.001
FT4				
Quintile 1 (n= 629) (< 0.95 ng/dl)	0.132	0.055	2.41	0.016
Quintile 2 (n= 660) (0.95 – 1.04 ng/dl)	0.081	0.054	1.51	0.132
Quintile 3 (n= 629) (1.05 – 1.14 ng/dl)	-	-	-	Reference
Quintile 4 (n= 631) (1.15 – 1.30 ng/dl)	0.017	0.054	0.32	0.750
Quintile 5 (n= 589) (> 1.30 ng/dl)	0.140	0.055	2.53	0.011

Abbreviations: β , beta coefficient, Std. Err., standard error; t, t test; BMI, body mass index; FT4, free thyroxine

Table 4

Association between FT4 quintiles and CES-D 16.

FT4	CES-D 16		
	Odds Ratio	95% CI	p value
Quintile 1(n= 629) (< 0.95 ng/dl)	1.44	1.09 – 1.89	0.009
Quintile 2 (n= 660) (0.95 – 1.04 ng/dl)	1.07	0.81–1.41	0.647
Quintile 3 (n= 629) (1.05 – 1.14 ng/dl)	-	-	Reference
Quintile 4 (n= 631) (1.15 – 1.30 ng/dl)	0.95	0.71–1.27	0.749
Quintile 5 (n= 589) (> 1.30 ng/dl)	1.33	1.01–1.77	0.044

Analysis adjusted for age, age², sex, obesity (BMI ≥ 30), smoking status, and education.

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; FT4, free thyroxine; CI, confidence interval.

Table 5

Association between FT4 quintiles and CES-D subscales.

	Quintile 1 (n= 629) (< 0.95 ng/dl)		Quintile 2 (n= 660) (0.95–1.04 ng/dl)		Quintile 3 (n= 629) (1.05–1.14 ng/dl)	Quintile 4 (n= 631) (1.15 – 1.30 ng/dl)		Quintile 5 (n= 589) (1.31 ng/dl)	
	Coeff	p value	Coeff	p value	Reference	Coeff	p value	Coeff	p value
Depressive affect	0.081	0.246	0.018	0.801	-	-0.042	0.556	0.071	0.320
Anhedonia	0.076	0.012	0.053	0.079	-	0.012	0.702	0.072	0.019
Somatic complaints	0.083	0.097	0.010	0.846	-	0.022	0.664	0.111	0.029
Interpersonal relation	0.016	0.872	-0.111	0.261	-	-0.088	0.378	0.034	0.733

Analyses adjusted for age, age², sex, obesity (BMI ≥ 30), smoking status, and education.

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; Coeff, estimated Poisson regression coefficient.