https://doi.org/10.22435/mgmi.v13i1.5670;

FUNGSI TIROID DAN KESEHATAN MENTAL PADA WANITA USIA SUBUR

Thyroid Function and The Mental Health in Childbearing Age Women

Suryati Kumorowulan[1*], Yusi Dwi Nurcahyani[1], Leny Latifah[1], Diah Yunitawati[1]
[1]Magelang Health Research and Development Center
Kapling Jayan, Borobudur, Magelang, Central Java, Indonesia
*e-mail:suryatiyk@yahoo.co.id

Submitted: October 15th, 2021, revised: November 27th, 2021, approved: December 1st, 2021

ABSTRACT

Background*. Thyroid dysfunction is frequently associated with psychiatric problems, such as anxiety or depression. On the other hand, thyroid dysfunction patients have little reason to be concerned about their mental health. Childbearing age women are included in the priority category because they require excellent health conditions to prepare for pregnancy and parenthood.* ***Objective.*** *This study aimed to investigate relationship between thyroid function (as evaluated by thyroid hormone levels and thyroid stimulating hormone (TSH) levels) with mental health in childbearing age women.* ***Method.*** *This study is a cross sectional study, with childbearing age women (aged 15 years and up) who are already menstruating but have not yet reached menopause. The research was conducted in Yogyakarta City and Bukittinggi City with a total sample of 487 people. This study's independent variables were TSH and free T4 levels. The dependent variables were anxiety and depression. Other things to consider are height, body weight, and age. Blood samples had used to measure TSH and free T4 levels. All respondents were interviewed to assess whether they were depressed or anxious using the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI).* ***Results.*** *There is a significant difference in score of BAI (21.1±11,67 vs 19.7±11.18, p<0.000) and BDI (10.1±8.06 vs 9.50±7.36, p<0.000) between groups. Other results found that disfunction thyroid hormone levels (TSH <0.3 mIU/mL) was related to depression (OR 2.324 95% CI 1.072–5.041, p<0.05; AOR 2.718 95% CI 1.028–7.186, p<0.05), but not associated with anxiety.* ***Conclusion****. Thyroid dysfunction, particularly low thyroid stimulating hormone levels, has been linked to higher risk of depression in childbearing age women.*

Keywords*: anxiety, depression, free T4, TSH*

ABSTRAK

Latar Belakang. Disfungsi tiroid sering terkait dengan masalah kejiwaan, seperti kecemasan atau depresi. Di sisi lain, penderita disfungsi tiroid memiliki sedikit alasan untuk mengkhawatirkan kesehatan mental mereka. Wanita usia subur (WUS) termasuk dalam kelompok prioritas karena kondisi kesehatan yang optimal diperlukan dalam persiapan untuk kehamilan dan pengasuhan. **Tujuan**. Penelitian bertujuan untuk menyelidiki hubungan fungsi tiroid (berdasarkan kadar hormon tiroid *free* T4 dan TSH) dengan kesehatan mental pada WUS. **Metode**. Penelitian ini merupakan penelitian potong lintang, dengan subjek wanita usia subur (usia 15 tahun ke atas), sudah menstruasi, dan belum mengalami menopause. Penelitian dilakukan di Kota Yogyakarta dan Kota Bukittinggi dengan jumlah sampel 487 orang. Variabel bebas dalam penelitian adalah kadar TSH dan *free* T4. Variabel tergantung adalah kecemasan dan depresi. Variabel lain meliputi tinggi badan, berat badan, dan usia. Sampel darah diambil untuk mengukur kadar TSH dan *free* T4. Semua responden diwawancara untuk mengetahui status depresi dengan *Beck Depression Inventory* (BDI) dan kecemasan dengan *Beck Anxiety Inventory* (BAI). **Hasil**. Terdapat perbedaan yang signifikan pada skor BAI (21,1±11,67 vs 19,7±11,18, *p*<0,000) dan BDI (10,1±8,06 vs 9,50±7,36, *p*<0,000) antar kelompok. Penelitian ini menemukan bahwa disfungsi kadar hormon tiroid (TSH <0,3 mIU/mL) berhubungan dengan depresi (OR 2,324 95% CI

1,072–5,041, *p*<0,05; AOR 2,718 95% CI 1,028–7,186, *p*<0,05), tetapi tidak berhubungan dengan kecemasan. Hipertensi berhubungan dengan BDI (OR 0,339, 95% CI 0,178-0,645, *p*<0,05; AOR 0,216, 95% CI 0,100-0,644, *p*<0,000). **Kesimpulan**. Disfungsi tiroid khususnya kadar hormon TSH yang rendah berhubungan dengan semakin tingginya risiko depresi pada WUS.

Kata kunci: kecemasan, depresi, free T4, TSH

INTRODUCTION

Thyroid dysfunction is the second most common endocrine disorder in childbearing age women. It is because the thyroid hormone is involved in controlling of the menstrual cycle and the achievement of fertility. It influences follicle stimulating hormone and luteinizing hormone on steroid biosynthesis by specific triiodothyronine sites on oocytes during the fertility process. This process shows that the thyroid hormone has an impact on all aspects of reproduction.[1] Although thyroid dysfunction is common in childbearing age women, it is frequently discovered as a new diagnosis during pregnancy.[2,3,4] In early pregnancy, fetal dependence on maternal thyroxine delivery coincides with critical developmental periods such as neuronal proliferation, migration, and neural tube formation.[5] Maternal thyroid dysfunction in early pregnancy can have a permanent impact on the child's neurodevelopment. It is evident in the neurologic consequences of uncorrected congenital hypothyroidism or severe iodine deficiency.[6] So ensuring normal thyroid hormone levels in childbearing age women, especially before pregnancy, is critical for optimizing reproductive function, fetal growth, and development in pregnant women.

Thyroid hormone is associated with mental health problems and its association with reproductive function due to the role of thyroid hormone in metabolism in the brain. The research on the neurobiological effects of the thyroid axis on mood modulation supports the theory of thyroid function in mental health. On the other hand, studies on the role of thyroid function in the pathophysiology or treatment of mental health disorders are being conducted.[7] The mental health issues associated with primary thyroid disorders, such as hypothyroidism and hyperthyroidism, are diverse. Thyroid dysfunction can be accompanied by a variety of manifestations of mental health issues. Patients with thyroid dysfunction exhibit symptoms ranging from mild depression, anxiety to psychosis. Classic neuropsychiatric symptoms of hyperthyroidism or thyrotoxicosis include dysphoria, anxiety, irritability, emotional lability, and impaired concentration.[8] The mental health aspects studied were depression and anxiety, particularly in childbearing age women.

One of the consistent findings in epidemiological research is that women have a higher prevalence of depression and anxiety than men, particularly during reproductive years. Women have more components of anxiety and depression. The explanations for gender differences cover a wide range of topics. Aside from the effects of the menstrual cycle, pregnancy, and perimenopause on women's childbearing, the hormonal status may be an important variable.[9] According to the National Basic Health Research (Riskesdas) 2018 data, childbearing age women are more prone to depression. Women have a 7.4 percent higher prevalence of depression than men, which shows a prevalence 4.7 percent.[10] These findings

point to a dual vulnerability in women, namely susceptibility to thyroid function problems and mental health issues, particularly depression and anxiety.

Conventional health care practice in patients concludes that hypothyroidism is associated with reversible depression. Medical guidelines for clinical practice, issued by the American Association of Clinical Endocrinologists, state that a 'subclinical or clinical diagnosis' of hypothyroidism should be considered in every patient with depression. Many patients present to primary care providers with neuropsychiatric symptoms such as fatigue, anxiety, depression, or cognitive difficulties. Thyroid stimulating hormone (TSH) levels are typically measured over time as part of the evaluation. Thyroid stimulating hormone (TSH) that is slightly outside the normal range is referred to as mild thyroid dysfunction (subclinical), and it is associated with nonspecific neuropsychiatric symptoms. Thyroid function therapy is usually prescribed. Currently, levothyroxine is often prescribed for mild hypothyroidism.[8,11] However, there is a risk of subclinical hypothyroidism, defined as elevated TSH levels above normal limits, with thyroxine levels within the normal range for mental health problems.

Several studies have found an association between hypothyroidism and depression[11,12,13,14] and anxiety.[12,14] Other studies, on the contrary, have found an association with increased depression in hyperthyroidism subjects.[7,12,15] A study in a large sample of the general population in Norway found no association between thyroid dysfunction and the appearance of anxiety and depression.[16] A population-based study in Korea showed that thyroid dysfunction was associated with a different response to depression. TSH levels can be used to predict the appearance of depressive symptoms in women and as one of the risk factors for depression because normal thyroid function to low is associated with the risk of developing depression in women.[7]

Based on these considerations, the purpose of this study is to sharpen the analysis by selecting childbearing age women targets. It is due to the fact that childbearing age women is a population that epidemiologically has a higher risk for thyroid function disorders and mental health problems, this study measures two indicators of mental health problems, depression and anxiety, and how they relate to thyroid function. Changes in TSH and thyroid hormone levels are used to diagnose thyroid dysfunction.[17] The purpose of this study is to determine whether women with thyroid dysfunction are more at risk for depression and anxiety.

METHODS

This study was a cross sectional study in 2017. Because this study is part of an epidemiological study to determine the status of iodine and salt adequacy, the sampling was designed to be representative of the region.[18] The study was conducted in Yogyakarta City (Yogyakarta Special Region Province) and Bukittinggi City (West Sumatra Province). Surveys are designed to provide representative information by the sub national domain (strata), defined based on administrative or programmatic relevance. The primary sampling unit (PSU) was chosen using the proportional probability sampling (PPS) methodology, which involved a systematic random selection of the number of households required in each PSU.

The population was childbearing age women, aged 15 years and up, still had menstruation, and

not yet menopause. The sample had selected by simple random sampling method and obtained 245 for Yogyakarta City and 242 for Bukittinggi City. The total number of samples collected was 487.

The independent variables in this study were TSH and free T4 levels represent thyroid function. Dependent variables were anxiety and depression, representing mental health status. Body's weight, height, and age were also collected as probable confounding variables. The age range is categorized into three levels according to the definition of the Ministry of Health (2009), namely adolescents (15–25 years), adults (26–45 years), and elderly more than 45 years.[19] Clinical examination by an expert doctor was used to obtain data on physical markers, health status, and disease history. Nutritional status was measured and collected by anthropometric examination; height was measured using microtoise, and body weight was measured using a digital scale (Seca). Thyroid function was analyzed by measuring TSH and free T4 levels using the enzyme linked immunosorbent assay (ELISA) method. The reference values were free T4: 0.8–2.0 ng/dL and TSH: 0.3–4.0 mIU/L.

Non-fasting venous blood samples were collected from the subjects and drawn into vacutainers refrigerated immediately after collection and sent to the Biochemical Laboratory of Magelang Health Research and Development Center located in Magelang Regency, Central Java. After the process, serum and plasma samples were stored at −20°C until analysis was done.

The instrument used to measure the level of anxiety is the Beck Anxiety Inventory (BAI). The Beck Anxiety Inventory has 21 items that measure physical, cognitive, and emotional aspects. Subjects were asked what they felt during the last four weeks then put in a score that has a ranging from 0 to 3. The total score will indicate the subject's level of anxiety. The score used as a cut-off was 8.[20] The Beck Depression Inventory (BDI) was applied to assess the level of depression of respondents. It has 21 items, rated on 4 point scale ranging from 0–3. The Beck Depression Inventory measures the prolonged disruption of mood and emotional conditions that involving thinking, behaving, and feeling processes that generally arise due to loss of hope or feelings of helplessness. The Beck Depression Inventory has a cut-off score of 14.[21]

The National Institute of Health Research and Development (NIHRD) ethics committe gave their clearance, numbering it LB.02.01/2/KE.149/2017. Written informed consent was obtained from subjects.

RESULTS

The mean age of samples (n=487) was 35.4±8.17; 75.5 percent were 25–45 years old (adult category). Subjects with TSH level <0.3 mIU/mL were significantly older average than the normal groups (0.3–2.5 mIU/mL) ($p<0.05$). The proportion of depression was significantly higher (46.4%) in the TSH level <0.3 mIU/mL than in the normal groups (27.6%) ($p<0.05$). But the score of BDI average was significantly lower in the TSH level >4.0 mIU/mL groups than in the normal groups. Free T4 levels were significantly lower in the TSH >4.0 mIU/mL groups than in normal groups (Table 1).

Table 1. Characteristics of Subjects based on TSH level

Variables	TSH level			
	0.3–2.5 mIU/mL (n=312)	<0.3 mIU/mL (n=28)	2.5–4.0 mIU/mL (n=93)	>4.0 mIU/mL (n=54)
Years of age, mean±SD	34.9±8.15	38.8±7.3*	35.9±8.45	35.6±7.96
Age categories (years),%				
<25	13.8 (43)	8.3 (2)	12.4 (11)	10.6 (6)
25–45	75.6 (236)	70.8 (20)	74.2 (69)	80.9 (44)
>45	10.6 (33)	20.6 (6)	13.5 (13)	8.5 (5)
Weight (kg), mean±SD	58.9±12.19	56.2±8.96	60.1±12.13	60.2±12.59
BMI (kg/m^2), mean±SD	25.3±4.91	24.1±3.62	26.1±4.69	26.0±5.26
Categories of BMI (%)				
Underweight	5.9 (18)	3.6 (1)	5.4 (5)	5.6 (3)
Overweight	33.3 (104)	42.9 (12)	34.4 (32)	38.9 (21)
Obese	16.0 (50)	3.6 (1)	23.7 (22)	22.2 (12)
Normal weight (reff)	44.8 (140)	50.0 (14)	36.6 (34)	33.3 (18)
Biochemistry				
TSH (mIU/mL), median (min–max)	1.38 (0.33–2.5)	0.08 (0.01–0.27)***	3.05 (2.51–4.00)***	5.21 (4.06–31.05)***
free T4 (ng/dL), median (min–max)	1.19 (0.67–2.13)	1.3 (0.63–3.34)	1.18 (0.59–1.97)	1.06 (0.10–1.70)***
Psychology				
Anxiety scores, mean±SD	20.7±11.34	22.35±13.42	20.4±11.29	17.2±10.82
Anxiety				
Yes	84.9 (265)	85.7 (24)	88.2 (82)	77.8 (42)
No	15.1 (47)	14.3 (4)	11.8 (11)	22.2 (12)
Depression scores, mean±SD	9.9±7.69	11.7±7.67	9.2±7.86	9.1±7.61*
Depression				
Yes	27.6 (86)	46.4 (13)*	25.8 (24)	24.1 (13)
No	72.4 (226)	53.6 (15)	74.2 (69)	75.9 (41)

p values are for comparison with normal TSH (0.3–2.5 mIU/mL), * p<0.05, ** p<0.001, ***p<0.000; Anxiety= BAI score >7; Depression= BDI score >13

Subject with free T4 level >2.0 ng/dL was significantly lower BMI than the reference groups (p<0.05). In the groups based on free T4 levels, there was no statistically significant difference in BAI and BDI scores (Table 2).

Table 2. Characteristics of Subjects based on Free T4 Level

Variables	Free T4 level		
	0.8–2.0 ng/dL (n=463)	>2.0 ng/dL (n=7)	<0.8 ng/dL (n=17)
Years of age, mean±SD	35.4±8.20	38.1±7.19	34.3±8.05
Age categories (years),%			
<25	13.2 (61)	8.3 (2)	12.4 (11)
25–45	75.1 (348)	70.8 (20)	74.2 (69)
>45	11.7 (54)	20.6 (6)	13.5 (13)
Weight (kg), mean±SD	59.2±12.17	52.9±8.40	59.4±10.27
BMI (kg/m^2), mean±SD	25.5±4.89	22.0±3.22*	25.7±4.05
Categories of BMI (%)			
Underweight	5.7 (26)	14.3 (1)	0.0 (0)
Overweight	35.5 (164)	14.3 (1)	23.5 (4)
Obese	17.8 (82)	0.0 (0)	17.6 (3)
Normal weight (reff)	41.0 (190)	71.4 (5)	58.8 (10)
Biochemistry			
TSH (mIU/mL), median (min–max)	1.81 (0.01–15.07)	0.06 (0.01–1.70)***	3.40 (0.13–31.05)***
free T4 (ng/dL), median (min–max)	1.19 (0.80–1.99)	2.59 (2.08–3.34)**	0.70 (0.10–0.79)***
Psychology			
Anxiety scores, mean±SD	20.3±7.71	22.1±7.38	23.0±13.46
Anxiety			
Yes	84.7 (392)	100.0 (7)	82.4 (14)
No	15.3 (71)	0.0 (0)	17.6 (3)
Depression scores, mean±SD	9.8±7.71	11.0±9.75	10.6±7.47
Depression			
Yes	27.4 (127)	42.9 (3)	35.3 (6)
No	72.6 (336)	57.1 (4)	64.7 (11)

p values are for comparison with normal free T4 (0.8–2.0 ng/dL), * p<0.05, ** p<0.001, *** p<0.000; Anxiety= BAI scores >7; Depression= BDI scores >13

Multivariate logistic regression analysis was conducted to analyze the relationship between TSH and free T4 thyroid function, with anxiety and depression, adjusted with BMI and age proved as confounding variables. The result showed significant odds ratio for the thyroid hormone levels (TSH <0.3 mIU/mL). Compared to the reference group, subjects with TSH levels less than 0.3 mIU/mL had 2.278 (95% CI 1.041–4.984) times the risk of depression (p<0.05). TSH levels below 0.3 mIU/mL were associated with a greater risk of depression (AOR 3.452 95% CI 1.286–9.286, p<0.05) after further adjustment for age and BMI factors (Table 3).

Table 3. Bivariate and Multivariate Logistic Regression Estimates for Factors Associated with Thyroid Hormone (TSH and free T4)

	Anxiety		Depression	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
TSH				
>4.0 mIU/mL	0.621 (0.304–1.266)	0.703 (0.315–1.571)	0.833 (0.426–1.631)	1.023 (0.476–2.199)
2.5–4.0 mIU/mL	1.322 (0.655–2.667)	1.476 (0.704–3.095)	0.914 (0.540–1.548)	0.875 (0.487–1.574)
<0.3 mIU/mL	1.064 (0.353–3.207)	0.515 (0.148–1.789)	2.278 (1.041–4.984)*	3.452 (1.286–9.286)*
free T4				
>2.0 ng/dL	NA	NA	1.984 (0.438–8.989)	1.639 (0.326–8.226)
<0.8 ng/dL	0.845 (0.237–3.017)	0.696 (0.181–2.682)	1.443 (0.523–3.984)	1.778 (0.596–5.306)

* p<0.05, ** p<0.001, *** p<0.000; Anxiety= BAI scores >7; Depression= BDI scores >13
OR= crude model, AOR= adjusted for age and BMI

DISCUSSION

The results in this study indicate that TSH <3 mIU/mL is associated with an increased risk of depression, but not associated with anxiety, and free T4 is not associated with anxiety and depression. It means that women with thyroid dysfunction, particularly concerning low TSH levels, have a 3.4 times higher risk of developing depression.

Several studies have shown that abnormal parameters in thyroid function have been associated with postpartum depression risk. Serum thyroid hormone concentrations have been reported to influence depression severity.[22] The severity or susceptibility of depression is associated with changes in TSH levels in response to administration of thyrotropin-releasing hormone (TRH), suggesting an association between the disorder and regulation of the hypothalamic-pituitary-thyroid (HPT) axis.[7]

The findings of another study in hypothyroid patients (TSH levels higher than normal) revealed that many patients with thyroid problems suffered from psychiatric disorders. Approximately 60 percent of respondents experienced depression problems, although to varying degrees. Anxiety was also reported by 63 percent of respondents at various levels of anxiety. Because thyroid hormone plays an important role in behavioural and mood problems, thyroid dysfunction can result in other comorbidities such as depression, anxiety, memory problems, and learning disabilities.[23]

This finding is different from the results in this study, with the general population without clear clinical symptoms of thyroid dysfunction. In results of hypothyroidism disorder, Itterman's study, which covered the general population, was also not in accordance with this study because it revealed that undiagnosed hypothyroidism is associated with depression and anxiety. In contrast, our study,-showed that TSH values above normal limits were not associated with anxiety and also depression. But, on the other hand, Itterman's research also found that untreated hyperthyroidism is associated with depression.[12] Our study found that only TSH levels below normal or a trend toward subclinical hyperthyroidism were associated with a significantly increased risk of depression.

Several studies showed that serum TSH levels were associated with an increased risk of developing thyroid dysfunction.[24] Cross sectional study in Norwegia indicated that

hyperthyroidism and hypothyroidism were more likely to experience depression. It is possible that some individuals depend more on thyroid hormones for their psychological well-being.[16] Almeida et al. conducted a study on the relationship between thyroid hormones and depression in male respondents aged 69–87 years. The results indicated that subclinical thyroid disorders were not associated with the prevalence or incidence of depression. The study results indicated that serum TSH and free T4 levels were not associated with depression. So there are still differences between subclinical hypothyroidism or subclinical hyperthyroidism contributing to an increased risk of developing depression among male.[25]

Previous population-based studies were found the same result with this study. This result was in line as the general population based research of Brazil[26] and Korea.[7] Meta-analyses study also confirmed the findings, which showed TSH to be negatively correlated with depression.[11] More specifically, a Korean study also showed that higher than normal TSH was predictive of an increased risk of depression in women, rather than men. This study strengthens these findings.

This study also found a relatively high prevalence of depression, 29.7 percent. The result is higher than the 7.4 percent prevalence of depression in women (aged over 15 years) reported in the 2018 Riskesdas survey.[10] This could be due to differences in depression assessment tools. The *National* Basic *Health Research* (Riskesdas) used the Mini International Neuropsychiatric Interview (MINI), whereas this study used BDI, which is more rigid in its measurement. The prevalence results of this study are close to those of Peltzer and Pengpid, showing the prevalence of severe and moderate depression in Indonesia is 21.8 percent. The prevalence in males is 21.4 percent, and in females is 22.3 percent. This survey was conducted on respondents aged 15 years and over. The measuring instrument used to measure the level of depression is the Center for Epidemiological Studies Depression Scale (CES-D-10).[27] This study considers that TSH levels can be used to predict the appearance of depressive symptoms in women and as one of the risk factors for depression because lower TSH level is associated with the risk of developing depression in women.

CONCLUSION

Thyroid dysfunction, particularly lower TSH levels, was related to higher risk of depression in childbearing age women.

SUGGESTION

Efforts to obtain optimal health status for childbearing age women in various reproductive cycles are critical, including among others things, supporting adequate thyroid function. Other population-based studies that have found a link between thyroid dysfunction and depression have been undertaken in childbearing age women or men. Future research should concentrate on more sensitive reproductive cycles, such as a pregnancy and lactation.

ACKNOWLEDGEMENT

We want to thank the district health offices and community health centers in Yogyakarta City and Bukittinggi City for participating in this study.

REFERENCES

1. Medenica S, Nedeljkovic O, Radojevic N, Stojkovic M, Trbojevic B, Pajovic B. Thyroid Dysfunction and Thyroid Autoimmunity in Euthyroid Women in Achieving Fertility. *Eur Rev Med Pharmacol Sci*. 2015;19(6):977–87.
2. Taylor PN, Zouras S, Min T, Nagarahaj K, Lazarus JH, Okosieme O. Thyroid Screening

in Early Pregnancy: Pros and Cons. *Front Endocrinol (Lausanne)*. 2018;9:1–7.

3. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet*. 2017;390(10101):1550–62.
4. De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet*. 2016;388(10047):906–18.
5. Moog NK, Entringer S, Heim C, Wadhwa PD, Kathmann N, Buss C. Influence of Maternal Thyroid Hormones during Gestation on Fetal Brain Development. *Neuroscience*. 2017;342:68–100.
6. Eligar V, Taylor P, Okosieme O, Dayan C. Thyroid Hormone Replacement. In: Pfaff D, Joëls M, editors. *Hormones, Brain and Behavior, 3rd ed*. Oxford: Academic Press; 2017. p. 229–39.
7. Kim EY, Kim SH, Rhee SJ, Huh I, Ha K, Kim J, et al. Relationship between Thyroid-Stimulating Hormone Levels and Risk of Depression among The General Population with Normal Free T4 Levels. *Psychoneuroendocrinology*. 2015;58:114–9.
8. Hage MP, Azar ST. The Link between Thyroid Function and Depression. *J Thyroid Res*. 2012;2012:590648.
9. Grigoriadis S, Robinson GE. Gender Issues in Depression. *Ann Clin Psychiatry*. 2007;19(4):247–55.
10. Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan. *Laporan Nasional Riskedas 2018*. Jakarta: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan; 2019.
11. Williams MD, Harris R, Dayan CM, Evans J, Gallacher J, Ben-Shlomo Y. Thyroid Function and The Natural History of Depression: Findings from The Caerphilly Prospective Study (CaPS) and A Meta-Analysis. *Clin Endocrinol (Oxf)*. 2009;70(3):484–92.
12. Ittermann T, Völzke H, Baumeister SE, Appel K, Grabe HJ. Diagnosed Thyroid Disorders are Associated with Depression and Anxiety. *Soc Psychiatry Psychiatr Epidemiol*. 2015;50(9):1417–25.
13. Maes M, Meltzer HY, Cosyns P, Suy E, Schotte C. An Evaluation of Basal Hypothalamic-Pituitary-Thyroid Axis Function in Depression: Results of A Large-Scaled and Controlled Study. *Psychoneuroendocrinology*. 1993;18(8):607–20.
14. Romero-Gómez B, Guerrero-Alonso P, Carmona-Torres JM, Notario-Pacheco B, Cobo-Cuenca AI. Mood Disorders in Levothyroxine-Treated Hypothyroid Women. *Int J Environ Res Public Health*. 2019;16(23):4776.
15. Hong JW, Noh JH, Jun-Kim D. Association between Subclinical Thyroid Dysfunction and Depressive Symptoms in The Korean Adult Population: The 2014 Korea National Health and Nutrition Examination Survey. *PLoS One*. 2018;13(8):e0202258.
16. Engum A, Bjøro T, Mykletun A, Dahl AA. An Association between Depression, Anxiety and Thyroid Function--A Clinical Fact or An Artefact?. *Acta Psychiatr Scand*. 2002;106(1):27–34.
17. World Health Organization. *Assessment of Iodine Deficiency Disorders and Monitoring Their Elimination: A Guide For Programme Managers. 3rd ed.* Geneva: World Health Organization; 2007.
18. Kumorowulan S. Pengembangan Metode Alat Ukur Garam secara Kuantitatif di Daerah dengan Berbagai Tingkat Kecukupan Iodium. *Laporan Penelitian.* Magelang: Balai Penelitian dan Pengembangan Gangguan Akibat Kekurangan Iodium; 2017.
19. Departemen Kesehatan RI. *Profil Kesehatan Indonesia*. Jakarta: Departemen Kesehatan RI; 2009.

20. Carney CE, Moss TG, Harris AL, Edinger JD, Krystal AD. Should We be Anxious when Assessing Anxiety Using The Beck Anxiety Inventory in Clinical Insomnia Patients?. *J Psychiatr Res*. 2011;45(9):1243–9.
21. Alvi T, Assad F, Ramzan M KF. Depression, Anxiety and Their Associated Factors among Medical Students. *J Coll Physicians Surg Pak*. 2010;20(2):122–6.
22. Stohn JP, Martinez ME, Hernandez A. Decreased Anxiety and Depression Like Behaviors and Hyperactivity in A Type 3 Deiodinase-Deficient Mouse Showing Brain Thyrotoxicosis and Peripheral Hypothyroidism. *Psychoneuroendocrinology*. 2016;74:46–56.
23. Bathla M, Singh M, Relan P. Prevalence of Anxiety and Depressive Symptoms among Patients with Hypothyroidism. *Indian J Endocrinol Metab*. 2016;20(4):468–74.
24. Zimmermann MB. The Thyroid and Its Diseases. In: Luster M, Duntas LH, Wartofsky L, editors. *The Thyroid and Its Diseases. A Comprehensive Guide for the Clinician*. Cham: Springer International Publishing; 2019. p.101–108.
25. Almeida OP, Alfonso H, Flicker L, Hankey G, Chubb SAP, Yeap BB. Thyroid Hormones and Depression: The Health in Men Study. *Am J Geriatr Psychiatry*. 2011;19(9):763–70.
26. Varella AC, Benseñor IM, Janovsky CCPS, Goulart AC, Birck MG, Santos IS, et al. Thyroid Stimulating Hormone Levels and Incident Depression: Results from The ELSA-Brasil Study. *Clin Endocrinol (Oxf)*. 2021;94(5):858–65.
27. Peltzer K, Pengpid S. High Prevalence of Depressive Symptoms in A National Sample of Adults in Indonesia: Childhood Adversity, Sociodemographic Factors and Health Risk Behaviour. *Asian J Psychiatr*. 2018;33:52–9.