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Subclinical hypothyroidism and symptoms of depression: Evidence from the National Health and Nutrition Examination Surveys (NHANES)

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ABSTRACT

Background: Subclinical hypothyroidism has been associated with increased risk for depression, yet the findings remain controversial. It is possible that subclinical hypothyroidism is associated with some, but not all symptoms of depression. We examined symptom-specific associations between depression and subclinical hypothyroidism.
Methods: Participants ($N = 7683$ adults) were from the National Health and Nutrition Examination Surveys of 2007–2008, 2009–2010, and 2011–2012 We included participants who had data on their thyroid profile and depressive symptoms (measured using Patient Health Questionnaire), and excluded those with overt hypothyroidism or hyperthyroidism, and those on thyroid hormone replacement therapy. Logistic regression with sampling weights was used to examine the association between subclinical hypothyroidism and depression symptoms. We also ran sensitivity analysis using different cut-off points for defining subclinical hypothyroidism.
Results: Of all the participants, 208 (2.7%) had subclinical hypothyroidism and of them only six had depression. Subclinical hypothyroidism was not associated with depression (OR = 0.61, 95% CI 0.20–1.87) nor with the specific depression symptoms. Using lower criteria for subclinical hypothyroidism diagnosis resulted in similar findings.
Conclusions: In a nationally representative sample of US adults, we observed no association between subclinical hypothyroidism and overall depression risk or any of the individual symptoms of depression.

1. Introduction

Subclinical hypothyroidism (SCH) is a common disorder (prevalence rate 3–10%) that is induced by an autoimmune disorder of the thyroid gland [1]. It can be diagnosed based on elevated values of thyroid stimulating hormone (TSH) and normal values of thyroxine (T4) and triiodothyronine (T3). Autoimmune disorders have been associated with elevated risk of depression and anxiety [2] but findings have been inconsistent. As for SCH, two recent meta-analyses concluded that SCH was associated with higher odds of depression compared to healthy controls (OR = 2.35 (95% CI 1.84–3.02) and OR = 3.56 (95% CI, 2.14–5.94)) [3,4]. A third meta-analysis found no association between SCH and depression (OR = 1.52 (95% CI 0.95–2.3) [5]. An older meta-analysis from 2009 [6] reported that depression was associated with lower TSH (OR = 0.92, 95% CI = 0.88–0.97) and higher T4 (OR = 1.1, 95% CI = 1.02–1.22), which contradicts the hypothesis that SCH is related to elevated depression risk [6]. All the meta-analyses reported considerable heterogeneity across studies, which may be related to differences in the definitions of SCH [7,8] and assessment of depressive symptoms.

Depression is a heterogeneous disorder that includes somatic, affective, and cognitive symptoms [9], and the different symptoms may reflect different aspects of disease etiology [10]. Some of the non-specific symptoms associated with SCH may overlap with symptoms of depression, including low mood, fatigue, weight gain, and concentration problems [11], and this overlap may become interpreted as higher depression risk associated with SCH. A symptom-specific analysis of the association can provide additional information on whether SCH is related only to some of the symptoms of depression. It seems plausible that the associations between SCH and depression reported in previous studies might be driven by some of the symptoms, the non-specific somatic symptoms in particular, whereas other symptoms might be unrelated to SCH. Results from a randomized controlled clinical study of 60 patients support this view, as the treatment of SCH with levothyroxine

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improved somatic but not affective symptoms of depression [12]. Understanding the association between SCH and depression at the symptom level could therefore be beneficial for the accurate diagnosis and treatment of both disorders. However, no studies to date have examined whether SCH is differently associated with different symptoms of depression.

The current study examined whether SCH is associated with specific depressive symptoms. Based on the suggested symptomatic overlap between SCH and depression [11], we hypothesized that SCH is most strongly associated with the somatic symptoms of depression—fatigue, disturbed sleep, changes in appetite, and psychomotor retardation.

2. Methods

2.1. Study design and participants

Participants were from the continuous cross-sectional US based National Health and Nutrition Examination Surveys (NHANES) of 2007–2008, 2009–2010, and 2011–2012, with different participants included in each wave. The NHANES is described in more detail elsewhere [13]. Other waves of NHANES were not used, as thyroid profiles were not measured in those waves. Sample selection flow chart is shown in Fig. 1. In 2007, thyroid profile measurements were taken from all participants aged 12 or older ($N = 6264$), and in 2009 ($N = 2364$) and 2011 ($N = 1970$) from one third of the participants aged 12 or older. We excluded participants younger than 18 years old and those with missing data on either thyroid profile, depressive symptoms or the covariates. We also excluded participants with hyperthyroidism (TSH $<$ 0.4mUI/L and normal or elevated ft4 levels) or overt hypothyroidism (TSH $>$ 10mUI/L and ft4 $<$ 9 pmol/L). Finally, we excluded any remaining participants who were receiving some kind of thyroid hormone replacement therapy (levothyroxine, liothyronine, thyroid desiccated, or other). Thus, our final sample consisted of 7683 participants. All participants of NHANES have provided written consent and study has been conducted according to the guidelines of the Helsinki declaration.

2.2. Measurements of hypothyroidism

All participants underwent laboratory measurements for a thorough thyroid profile. A complete description of the measurements is presented elsewhere [14]. The thyroid profile included tests for thyroid-stimulating hormone (TSH or thyrotropin) and free thyroxine (fT4). The American Association of Clinical Endocrinologists defined normal serum TSH levels between 0.4 and 4.5mUI/L according to its Medical Guidelines for Clinical Practice [15]. In our study, we defined SCH accordingly: serum TSH level over 4.5mIU/L and fT4 between 9 and 25 pmol/L. However, according to the corresponding European guidelines by the European Thyroid Association, SCH is categorized into two groups based on serum TSH levels: mild refers to 4-10mIU/L and severe to >10mUI/L [16]. Therefore, we also ran sensitivity analyses using these alternative cut-off points for defining mild and severe SCH. The cut-off points for SCH used in the main and sensitivity analyses, alongside the number of cases in each group, are presented in Table 1.

2.3. Measurement of depressive symptoms

The Patient Health Questionnaire (PHQ-9) [17] was used to measure depressive symptoms during the last two weeks. The PHQ-9 consists of nine items that are answered using a four-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), 3 (nearly every day). The individual items assess cognitive and emotional symptoms ("Have little interest in doing things", "Feeling down", "Feeling bad about self",

Table 1
Cut-off points for SCH used the analyses, and the number of cases in each group.

Main analyses	TSH (mIU/L)	fT4 (pmol/L)	Number of cases (%)
Reference group	0.4–4.49	9–25	7475 (97.3)
SCH	>4.5	9–25	208 (2.7)
Sensitivity analyses			
Reference group	0.4–3.99	9–25	7318 (96.1)
Mild SCH	4–9.99	9–25	294 (3.8)
Severe SCH	>10	9–25	8 (0.1)

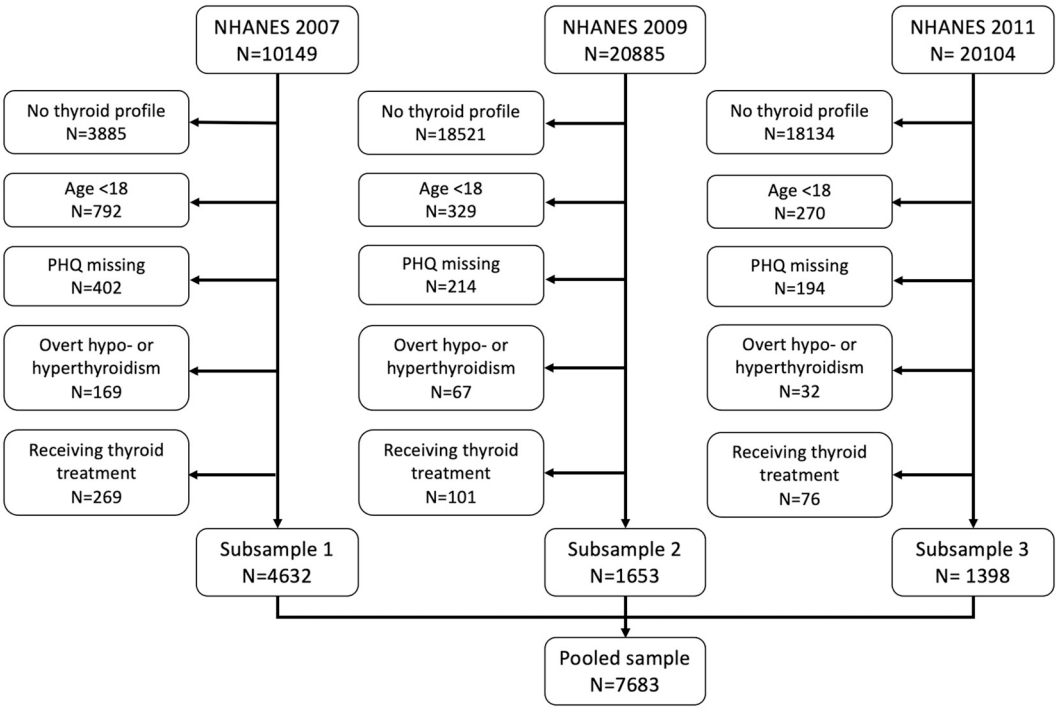

Fig. 1. Sample selection flowchart.

"Trouble concentrating", "Thought to be better off dead") and somatic symptoms ("Trouble sleeping", "Feeling tired", "Appetite change", "Moving/speaking slowly"). We dichotomized the items so that values 0 and 1 were coded as not having the symptom, and values 2 and 3 were coded as having the symptom. For the item "Thought to be better off dead" values from 1 to 3 were coded as having the symptom. We then computed a sum score for depression. Participants with a sum score of ≥5 were considered to screen positive for a depressive episode, following the standard (PHQ) cut-off values [17]. In sensitivity analyses, we also used a sum score ≥ 2 as a cut-off for depression. Furthermore, we computed a sum score for depression using the four-point scale and used cut-off points of ≥5 and ≥ 10 to define mild depression and moderate depression for further sensitivity analysis.

2.4. Covariates

Sociodemographic characteristics (age, sex, ethnicity and education) in NHANES were recorded in household interviews. We included age as a linear and squared variable to account for the potential non-linear association of age with depression and depressive symptoms. Self-reported ethnicity was coded as non-Hispanic white, non-Hispanic black, Hispanic, and other. Education was measured as the self-reported highest grade attained or degree received and categorized into five groups: 1 - less than 9th grade, 2–9-11th grade with no diploma, 3 - high school graduate or equivalent, 4 – some college, 5 – college graduate or higher.

2.5. Statistical analysis

Sampling weight, stratum, and cluster variables were used in all analyses to adjust for the unequal probabilities of selection, over-sampling, and non-response. We pooled the three NHANES cohorts together and used logistic regression to analyze the associations between SCH and [1] a dichotomous indicator of depression (PHQ ≥ 5), and [2] each of the symptoms of depression (yes/no) separately. Symptom-level analyses were conducted in two steps. First, each depressive symptom was separately regressed on SCH as defined by the American Association of Clinical Endocrinologists, adjusting for age, age squared, sex, ethnicity, and education (a total of nine separate models). Second, we ran a mutually adjusted model by further adjusting the symptom-specific associations for all the other depressive symptoms (besides the outcome symptom) to examine the independent associations between SCH and symptoms of depression. For the sensitivity analysis we ran the same models as in the main analyses, but defined SCH using the guidelines by the European Thyroid Association. Third, for symptom-level sensitivity analysis, we ran similar models using ordinal logistic regression analysis and the original four-point scale answers for each symptom, and the American Association of Clinical Endocrinologists definition for SCH. Lastly, we also examined if depression was more strongly associated with overt hypothyroidism than with SCH. For this, we reintroduced participants with overt hypothyroidism to our analysis sample ($N = 48$).

3. Results

Descriptive statistics are shown in Table 2. There were 208 participants with SCH, and only six of them had a PHQ score of five or higher. SCH was not associated with depression (OR = 0.61, 95% CI 0.20–1.87). Using a PHQ score of two or more as the cut-off point ($n = 31$ depression cases), the OR was 0.78 (95% CI 0.40–1.50). The results were similar when using a continuous sum score for PHQ (mild depression: OR = 0.92, 95% CI 0.56–1.51; moderate depression: OR = 0.98, 95% CI 0.39–2.43: Supplementary Table B), and the European Thyroid Association's definition for mild and severe SCH (Supplementary Table C).

SCH was not associated with any of the specific symptoms of depression when examined separately (Fig. 2) or when adjusted for all the other symptoms of depression (Fig. 3). The same conclusion held when using the European Thyroid Association's definition for mild and severe SCH, and a four-point scale for depression symptoms (Supplementary Figs. A through D). Finally, overt hypothyroidism was also not associated with depression (Supplementary Fig. E).

Table 2
Descriptive statistics. Frequency (percentage), unless otherwise stated.

	No SCH (n = 7475)	SCH (n = 208)	p-value for difference
Sex			
Male	3547 (47)	94 (45)	0.58
Female	3928 (53)	114 (55)	
Age, mean (SD)	47.5 (18.4)	53.7 (19.0)	0.15
Ethnicity			
Non-hispanic white	3296 (44)	130 (63)	<0.01
Non-hispanic black	1562 (21)	12 (6)	
Hispanic	2124 (28)	54 (26)	
Other	493 (7)	12 (6)	
Education			
Less than 9th	830 (11)	43 (21)	0.43
9-11th grade	1197 (16)	29 (14)	
High school or equivalent	1662](22)	47 (23)	
Some college	1951 (26)	45 (22)	
College or higher	1451 (19)	37 (18)	
TSH. mean (SD)	1.75 (0.96)	6.17 (3.19)	<0.01
fT4, mean (SD)	10.20 (1.77)	10.20 (1.72)	0.75
Depression			
PHQ ≥ 2	1272 (17)	31 (15)	0.26
PHQ ≥ 5	317 (4)	6 (3)	0.27
Depressive symptoms			
Have little interest	565 (8)	10 (5)	0.16
Feeling down	565 (8)	16 (8)	0.31
Trouble sleeping	1220 (16)	36 (17)	0.76
Feeling tired	1231 (16)	29 (14)	0.62
Appetite change	676 (9)	16 (8)	0.55
Feeling bad about self	433 (6)	7 (3)	0.16
Trouble concentrating	419 (6)	15 (7)	0.67
Moving/speaking slowly	274 (4)	7 (3)	0.46
Better off dead	317 (4)	5 (2)	0.70

Subclinical hypothyroidism (SCH) defined as TSH >4.5mUI/L and fT4 9-25mUI/L.
Thyroid stimulating hormone (TSH).
Patient Health Questionnaire (PHQ).

4. Discussion

The nonspecific symptoms associated with subclinical hypothyroidism (SHC) overlap partly with symptoms of depression—especially with somatic symptoms of depression—and there is evidence to suggest an elevated risk of depression among individuals with SCH [3–5]. We examined whether SCH would be associated particularly strongly with specific symptoms of depression, and whether these associations would be sensitive to the cut-off values for defining SCH. In contrast to our hypothesis, SCH was not associated with an elevated risk of depression in general or with any of the individual symptoms of depression specifically. Further analyses that were based on different criteria for defining SCH, or different coding of depressive symptoms, all yielded similar results.

In addition to SCH not being associated with overall depression risk, the associations were in the opposite direction than expected, that is, SCH was associated with lower depression risk but not significantly so. This is also in contrast to the two meta-analyses that reported associations between SCH and depression [3,4]. However, the inverse association observed in our study is not unique. The meta-analysis from 2009 [6] also reported that lower TSH and higher T4 would be related to elevated depression, even though this inverse association of TSH was mostly based on one large cohort study [18]. Treatment of SCH with levothyroxine has been shown to reduce the somatic symptoms of

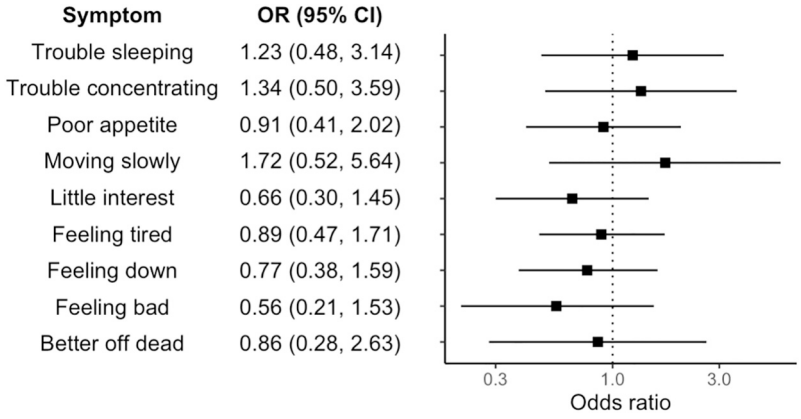

Fig. 2. Odds ratios for the associations between SCH and individual depressive symptoms, adjusted for age, age^2, sex, education and ethnicity.

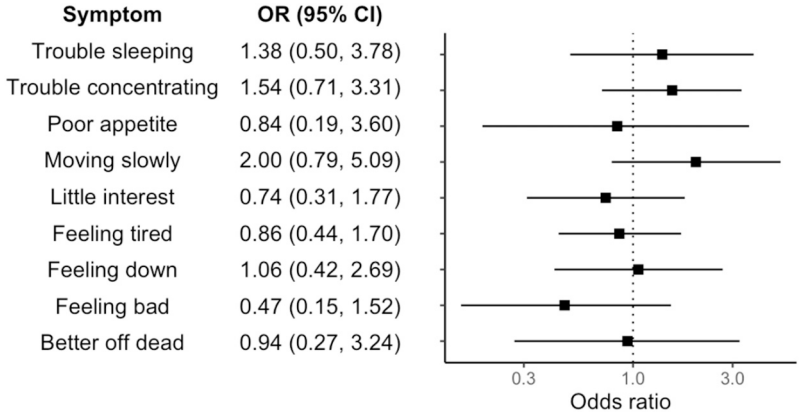

Fig. 3. Odds ratios for the associations between SCH and individual depressive symptoms, adjusted for age, age^2, sex, education, ethnicity and all other depressive symptoms besides the outcome symptom.

depression [12]. On the other hand, some studies have linked long-term thyroxine replacement therapy with worse overall psychological well-being of patients even when the patients' hypothyroidism had been under control (i.e. they were euthyroid) [19,20].

Examining the association between SCH and depression at symptom level is a strength of our study. However, we were limited in using cross-sectional data. This prevented us from examining time dependent association between SCH and depressive symptoms. Diagnosis of thyroid disorders may be complicated with the circadian and seasonal fluctuation of TSH [21]. However, relatively few longitudinal studies have been conducted on the association between SCH and depression, and none that could have controlled for circadian or seasonal fluctuation. Findings from a Korean study on young and middle-aged adults [22] and Dutch study on the elderly [23] suggested no association between SCH and depressive symptoms. Both studies took advantage of two to four repeated measurements of thyroid hormone and depressive symptom measurements. Both studies, however, only measured TSH annually or biannually, and also only examined the sum score of depressive symptoms as the outcome. As the TSH levels may fluctuate over time [15], we may have also under- or overestimated the prevalence of SCH within our sample as all the thyroid related laboratory tests were conducted only once per participant. Another issue that may have led to overestimation of SCH is that TSH levels have been noted to rise with age. An estimated 12% of people over 80 years of age have elevated TSH levels (>4.5mIU/L) without it actually reflecting thyroid disfunction [15]. Still, repeating the analyses with a sample restricted to participants aged 18–70 years did not change the results or the interpretations.

The heterogeneity in the associations between SCH and depression suggests that there may be other factors, such as comorbid diseases, that determine whether SCH becomes associated with depression risk. While the association between SCH and depression is cited in clinical guidelines and has at least some empirical evidence, there is very little research on plausible mechanisms that might explain why SCH specifically would increase depression risk. We hypothesized that this association would be explained largely by the somatic symptoms of depression, but SCH was not associated even with somatic complaints, such as fatigue, poor appetite, or psychomotor retardation. Given the many contradictory findings on the subject, there is an evident need for further examination of the association between SCH and depression. Studies taking advantage of large cohort samples using symptom level analyses is one such possibility when moving forward.

5. Conclusions

Subclinical hypothyroidism has been suggested to manifest some of the symptoms that characterize depression. In a large sample of US adults, subclinical hypothyroidism was not associated with overall depression risk or any of the individual symptoms of depression.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2021.152253.

References

[1] Monzani A, Prodam F, Bellone S, Bona G. Subclinical hypothyroidism. N Engl J Med 2017;376:2556–65.
[2] Demartini B, Ranieri R, Masu A, Selle ÞV, Scarone S, Gambini O. Depressive symptoms and major depressive disorder in patients affected by subclinical hypothyroidism. J Nerv Ment Dis 2014;202(8):603–7.
[3] Siegmann EM, Müller HHO, Luecke C, Philipsen A, Kornhuber J, Grömer TW. Association of depression and anxiety disorders with autoimmune thyroiditis: a systematic review and meta-analysis. JAMA Psychiat 2018;75(6):577–84.
[4] Loh HH, Lim LL, Yee A, Loh HS. Association between subclinical hypothyroidism and depression: an updated systematic review and meta-analysis. BMC Psychiatry 2019;19(1):1–10.
[5] Zhao T, Chen BM, Zhao XM, Shan ZY. Subclinical hypothyroidism and depression: a meta-analysis. Transl Psychiatry 2018;8(239):1–8.
[6] 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 2009;70(3):484–92.
[7] Surks MI, Ortiz E, Daniels GH, Sawin CT, Cobin RH, Franklyn JA, et al. Subclinical thyroid disease - scientific review and guidelines for diagnosis and management. JAMA. 2004;291(2):228–38.
[8] Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012;379:1142–54.
[9] Fried EI. The 52 symptoms of major depression: lack of content overlap among seven common depression scales. J Affect Disord 2017;208:191–7.
[10] Jokela M, García-Velázquez R, Airaksinen J, Gluschkoff K, Kivimäki M, Rosenström T. Chronic diseases and social risk factors in relation to specific symptoms of depression: evidence from the U.S. national health and nutrition examination surveys. J Affect Disord 2019;251:242–7.
[11] Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: who to treat and how. Drugs. 2012;72(1):17–33.
[12] Najafi L, Malek M, Hadian A, Ebrahim Valojerdi A, Khamseh ME, Aghili R. Depressive symptoms in patients with subclinical hypothyroidism-the effect of treatment with levothyroxine: a double-blind randomized clinical trial. Endocr Res 2015;40(3):121–6.
[13] Määttänen I, Gluschkoff K, Komulainen K, Airaksinen J, Savelieva K, García-Velázquez R, et al. Testosterone and specific symptoms of depression: evidence from NHANES 2011–2016. Compr Psychoneuroendocrinol 2021;6:100044.
[14] NHANES Questionnaires, Datasets, and Related Documentation [Internet] [cited 2020 May 25]. Available from: https://wwwn.cdc.gov/nchs/nhanes/; 2020.
[15] Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract 2012;18(6):988–1028.
[16] Pearce SHS, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J 2013;2:215–28.
[17] Kroenke K, Spitzer RL, Williams JBW. The PHQ-9 - Validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606–13.
[18] 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.
[19] Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on "adequate" doses of L-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol 2002;57(5):577–85.
[20] Djurovic M, Pereira AM, Smit JWA, Vasovic O, Damjanovic S, Jemuovic Z, et al. Cognitive functioning and quality of life in patients with Hashimoto thyroiditis on long-term levothyroxine replacement. Endocrine. 2018;62(1):136–43.
[21] Wang D, Cheng X, Yu S, Qiu L, Lian X, Guo X, et al. Data mining: seasonal and temperature fluctuations in thyroid-stimulating hormone. Clin Biochem 2018;60:59–63.
[22] Kim JS, Zhang Y, Chang Y, Ryu S, Guallar E, Shin Y, et al. Subclinical hypothyroidism and incident depression in young and middle-age adults. J Clin Endocrinol Metab 2018;103(5):1827–33.
[23] Blum MR, Wijsman LW, Virgini VS, Bauer DC, den Elzen WPJ, Jukema JW, et al. Subclinical thyroid dysfunction and depressive symptoms among the elderly: a prospective cohort study. Neuroendocrinology 2016;103:291–9.