Thyroid Function Within the Normal Range and the Risk of Depression: A Population-Based Cohort Study

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Context: Overt hypo- and hyperthyroidism are associated with an increased risk of depression. Little is known about the effects of variation in thyroid function within the normal range on the risk of depression.

Objective: The objective of the study was to examine the association between normal-range thyroid function and the risk of depression.

Design, Setting, and Participants: This was a cohort study in 1503 Dutch men and women, aged 70.6 (7.3) (mean [SD]) years. At baseline, serum TSH, thyroperoxidase antibody levels, and depressive symptoms [Center for Epidemiologic Studies Depression Scale (CES-D)] were assessed. A CES-D of 16 or greater is indicative of a depressive disorder. During follow-up (mean 8.0 y), participants were continuously monitored for the occurrence of incident depressive syndromes (n = 156).

Results: Cross-sectionally, persons in the lowest TSH tertile (0.3–1.0 mU/L) had more depressive symptoms [CES-D score (mean): 7.95 vs 6.63, $P = .014$] as well as an increased risk of a CES-D of 16 or greater [10.7% vs 5.0%, odds ratio (95% confidence interval) 2.22 (1.18–4.17)], compared with persons in the highest normal range TSH tertile (1.6–4.0 mU/L). In the prospective analyses, persons in the lowest TSH tertile who were depression free at baseline had a higher risk of incident depressive syndromes [12.3% vs 7.6%, odds ratio (95% confidence interval) 1.85 (1.10–3.11)]. Thyroid autoimmunity (thyroperoxidase antibody positivity) was not associated with CES-D scores or incident depressive syndromes.

Conclusions: Elderly persons with low-normal TSH levels have more concurrent depressive symptoms as well as a substantially increased risk of developing a depressive syndrome in the subsequent years. This study identifies low-normal TSH as an important risk factor for depression in the elderly. **(*J Clin Endocrinol Metab* 99: 1213–1219, 2014)**

Thyroid abnormalities are associated with the occurrence of psychiatric diseases, including depression (1, 2). Classically, hypothyroidism is associated with an increased risk of depression. However, a number of studies have also shown an increased risk of depression in patients with hyperthyroidism (1, 3–5). In this context it is remarkable to note that only limited and mainly cross-sectional data are available on the effects of variation in thyroid function within the normal range on the risk of depression.

Thyroperoxidase antibodies (TPOAbs) are antibodies against thyroperoxidase, which plays a key role in thyroid hormone (TH) synthesis. TPOAb-positive persons have an increased risk of developing hypothyroidism. Various autoimmune diseases have been associated with an increased risk of depression (6, 7). Although TPOAb-positivity is a common finding in the general population, the relationship between depression and TPOAb-positivity has been studied in only a limited number of studies, with conflicting results (8–12).

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Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, version 4; FT4, free T_4; GP, general practitioner; NTIS, nonthyroidal illness syndrome; OR, odds ratio; TH, thyroid hormone; TPOAb, thyroperoxidase antibody.

Although severe thyroid dysfunction has been shown to influence the risk of depression, depression itself may also have an effect on thyroid parameters (1, 2). Decreased food intake and chronic illness can cause important changes in thyroid function tests, known as the nonthyroidal illness syndrome (13, 14). It is therefore of importance to study the relation between thyroid function and depression not only cross-sectionally but also in a prospective study design.

For these reasons, we studied the effects of variation in thyroid function within the normal range on depression, both cross-sectionally and prospectively, in a population-based cohort study. In addition, the relationship between thyroid autoimmunity and depression was studied.

Materials and Methods

Study population

The Rotterdam Study is a prospective, population-based cohort study in 7983 Caucasians aged 55 years or older from Rotterdam, The Netherlands. Depressive symptoms and syndromes were assessed from the second examination round (September 1993 through December 1995) onward, which constituted the baseline of the present study (15).

The Medical Ethics Committee of the Erasmus Medical Center (Rotterdam, The Netherlands) approved the study, and written informed consent was obtained from all adult participants.

Population for analysis

For the TSH analyses, data on Center for Epidemiologic Studies Depression Scale (CES-D) scores and incident depressive syndromes were complete for 1093 and 1369 persons with available TSH data. TPOAb-positive subjects, those on thyroid therapy, or those with abnormal TSH levels (see *Statistical analyses*) were excluded. Persons with dementia were also excluded because depression is difficult to assess in demented persons, and thyroid dysfunction has been associated with dementia (16). In the incident depressive syndrome analyses, only those persons who were depression free at baseline were included. Thus, in total, 943 and 1110 persons were included in the cross-sectional and prospective analyses, respectively.

For the TPOAb analyses, data on CES-D scores and incident depressive syndromes were complete for 1273 and 1503 dementia-free persons, respectively.

Assessment of thyroid function

In 2009, serum TSH (TSH Lumitest; Henning) and TPOAb (ELISA; Milenia; Diagnostic Products Corp) levels were determined in a random subset of the baseline serum samples. TSH and TPOAb levels were available in 1110 and 1503 persons, respectively. TPOAb levels greater than 10 IU/mL were regarded as positive.

In an examination round after baseline of the current study [4.27 (0.44) y], serum TSH (TSH Lumitest; Henning) and free T_4 (FT4; Vitros, ECI Immunodiagnostic System; Ortho-Clinical Diagnostics) levels were determined in 1071 samples.

As shown in Table 1, the use of thyroid medication was almost 10-fold higher in women compared with men, whereas the prevalence of TPOAb positivity was only 2.7 times higher in women. This may (in part) be explained by the fact that not only Hashimoto's thyroiditis but also other thyroid diseases are more prevalent among women. These include, for example, Graves' disease and thyroid cancer, which are, respectively, 7 and 3 times more common in women than in men (17, 18). We did not have specific data on these diseases, but it is unlikely that this has affected our analyses because we restricted our TSH analyses to TPOAb-negative persons with normal-range TSH levels and excluded all persons using thyroid medication.

Assessment of depression

At baseline, assessment of depressive symptoms was performed using the validated Dutch version of the CES-D (15). The CES-D is a 20-item, self-report measure of depressive symptoms experienced in the last week. Items are scored on a scale of 0 to 3 points. A score of 16 or greater is considered indicative of a depressive disorder (15, 19).

During follow-up, from baseline until October 2005 (mean 8.0 y), depressive episodes were identified using different methods, as has been described in detail previously (15). During the

Table 1. Population Characteristics

	Total (n = 1503)	Men (n = 576)	Women (n = 927)	*P* Value
Age, y, mean (SD)	70.6 (7.3)	70.2 (7.1)	70.8 (7.4)	.133
BMI, kg/m^2, mean (SD)	26.5 (3.6)	26.0 (2.9)	26.7 (4.0)	<.001
Smoking status, %				
Current	19.9%	23.6%	17.5%	.004
Past	44.0%	65.8%	30.1%	<.001
Never	36.1%	10.6%	52.4%	<.001
Dementia, %	0.9%	1.2%	0.7%	.23
TSH, mU/L, median (IQR)	1.30 (0.90–2.00)	1.30 (0.90–1.90)	1.40 (0.90–2.00)	.032
TPOAb-positivity, %	5.1%	2.5%	6.8%	<.001
Thyroid therapy, %	3.3%	0.5%	4.9%	<.001
CES-D score, mean (SD)	7.63 (6.98)	6.52 (6.21)	8.42 (7.38)	<.001
Incident depressive syndromes, %	9.2%	6.6%	10.9%	.005

Abbreviation: IQR, interquartile range. BMI was calculated as weight in kilograms divided by height in meters squared; TPOAb positive subjects were defined as those with TPOAb greater than 10 IU/mL.

two follow-up examination rounds (March 1997 through December 1999 and January 2002 through July 2004), participants were screened with the CES-D, and screen-positive participants were invited for a clinical psychiatric interview to diagnose depression. A psychiatrist, psychogeriatrician, or clinical psychologist, each with extensive clinical experience, conducted the interview using the Dutch version of the Present State Examination (15). This is a semistructured psychiatric interview included in the Schedules for Clinical Assessment in Neuropsychiatry. Scoring of items is conservative and relies on clinical judgment instead of the participant's answer only. Each interviewer was trained in the certified Dutch World Health Organization center. With a computerized diagnostic algorithm based on the item scores, major and minor depressive disorders and dysthymia were classified according to *Diagnostic and Statistical Manual of Mental Disorders*, version 4 (DSM-IV) criteria.

Additionally, a medical history was taken to assess whether depressive episodes had occurred between follow-up rounds. From baseline onward, trained research assistants systematically scrutinized all information contained in the medical records of the general practitioners (GPs), for instance, hospital discharge letters, specialist reports, and notes of the GP, for a number of predefined cues such as symptoms of depression, prescriptions of psychiatric medication, the occurrence of major life events, and psychosocial problems. Next, two physicians and a research psychologist independently read all information and categorized each depression according to a predefined protocol. All discordant categorizations were discussed in consensus meetings (15).

Using the above-mentioned methods, we recorded depression that fulfilled *DSM-IV* criteria as well as depressive episodes that were clinically relevant but did not fulfill *DSM-IV* criteria. The GPs frequently diagnosed depression without using or documenting the formal *DSM-IV* criteria. Depressive syndromes therefore included DSM-IV major depressive disorder and dysthymia as well as depression recorded by a GP or a physician, self-reported depression for which the participant consulted a GP or mental health professional, and DSM-IV minor depression. Grief, adjustment disorder, and burnout, characterized by emotional exhaustion and reduced satisfaction in personal accomplishment, were not regarded as depression.

Covariates

Information on smoking status and thyroid therapy were obtained by questionnaires at baseline and during follow-up examination rounds. Smoking was categorized as never, past, and current. Height and weight were measured to calculate body mass index (BMI; kilograms per square meter). The presence of dementia was assessed at baseline and during follow-up, as has been described in detail previously (20).

Statistical analyses

The TSH reference range was 0.3–4.0 mU/L, defined as the range between the 2.5th and 97.5th percentiles after exclusion of subjects with thyroid therapy or TPOAb-positivity. The group with normal-range TSH levels was divided in tertiles. Due to the skewed distribution of TSH and high clustering of TSH levels around 1.0 mU/L, it was not possible to make three equal-sized groups. At baseline, the cross-sectional relationships between TSH tertiles, continuous CES-D scores, and the risk of a CES-D score of 16 or greater were studied using analysis of covariance and logistic regression analyses, respectively. In the prospective analysis, logistic regression was used to study the relation between TSH tertiles and the incidence of depressive syndromes.

Similarly, TPOAb status was studied in relationship to CES-D using an analysis of covariance. Logistic regression was used to study the relationship between TPOAb status, the risk of a CES-D score of 16 or greater, and the incidence of depressive syndromes.

Analyses were additionally corrected for gender, age, BMI, and smoking status. All analyses were repeated in men and women separately and gender*TSH tertile interaction terms were calculated to investigate the presence of gender-specific effects.

IBM SPSS Statistics for Windows, version 20.0 (IBM Corp) was used for all analyses.

Power calculations

Power calculations for detectable effect sizes were performed at $\beta = .80$ and $\alpha = .05$. For the TSH tertiles analyses, we had power to detect differences in CES-D of 0.15 SD (1 SD = 6.98) and to detect odds ratios (ORs) of 1.79 and 1.72 for CES-D scores of 16 or greater and depressive syndromes, respectively. For the TPOAb-positivity analyses, we had power to detect differences in CES-D of 0.26 SD (1 SD = 6.98) and to detect ORs of 2.37 and 2.29 for CES-D scores of 16 or greater and depressive syndromes, respectively.

Results

Characteristics of the studied population are shown in Table 1. Compared with men, women had a higher BMI, smoked less, and had a higher median TSH level as well as more TPOAb-positivity and thyroid therapy. In addition, women had a higher mean CES-D score and a higher incidence of depressive syndromes. All further analyses were performed in nondemented persons who were not on thyroid therapy.

Normal range TSH levels and depression

Table 2 shows the cross-sectional relationships between normal range TSH tertiles, continuous CES-D scores, and the risk of a CES-D score of 16 or greater as well as the longitudinal relationship between normal range TSH tertiles and the incidence of depressive syndromes. At baseline, persons with lower normal range TSH levels had higher CES-D scores, also after correction for gender, age, BMI, and smoking status. Persons in the lowest normal range TSH tertile had a higher risk of a CES-D score of 16 or greater [OR 2.09 (95% confidence interval [CI] 1.16–3.76), $P = .015$], compared with persons in the highest tertile. These effects remained similar after correction for gender, age, BMI, and smoking status (OR 2.22 (95% CI 1.18–4.17), $P = .013$).

In the prospective analyses of persons free of depression at baseline, those in the lowest normal range TSH tertile had a higher incidence of depressive syndromes during

Table 2. Normal-Range TSH Levels, CES-D Scores, and the Risk of Incident Depressive Disorders

		TSH Tertiles				
		Tertile 1, 0.30–1.00 mU/L	Tertile 2, 1.01–1.60 mU/L	Tertile 3, 1.61–4.00 mU/L	OR (95% CI)	*P* Value
Cross-sectional analyses						
	n	365	273	305		
CES-D score (continuous)	Model 1, mean (SE)[a]	8.03 (0.35)	7.24 (0.41)	6.83 (0.39)		.025
	Model 2, mean (SE)[b]	7.95 (0.36)	7.37 (0.42)	6.63 (0.39)		.014
	n	365	273	305		
CES-D 16 or greater	Model 1, % (SE)[a]	11.0 (1.4)	6.7 (1.6)	5.6 (1.5)	2.09 (1.16–3.76)	.015
	Model 2, % (SE)[b]	10.7 (1.5)	7.6 (1.7)	5.0 (1.6)	2.22 (1.18–4.17)	.013
Prospective analyses						
	n	416	327	367		
Incident Depressive	Model 1, % (SE)[a]	12.0 (1.4)	8.3 (1.6)	7.6 (1.6)	1.75 (1.06–2.88)	.029
Syndromes	Model 2, % (SE)[b]	12.3 (1.5)	8.9 (1.7)	7.6 (1.6)	1.85 (1.10–3.11)	.020

Analyses were performed in TPOAb-negative, nondemented persons who were not on thyroid therapy. Normal-range TSH tertiles were compared with CES-D scores, the risk of a CES-D score of 16 or greater, and the risk of incident depressive syndromes (in baseline depression free subjects). Subjects receiving thyroid therapy, TPOAb-positive subjects, subjects with abnormal TSH levels, and dementia cases were excluded. The OR comparing low-normal with high-normal TSH levels is indicated.

[a] Model 1 had no adjustments.

[b] Model 2 was adjusted for gender, age, BMI, and smoking status.

follow-up [OR 1.75 (95% CI 1.06–2.88), $P = .029$]. This association remained significant after correction for gender, age, BMI, and smoking status [OR 1.85 (95% CI 1.10–3.11), $P = .020$].

No gender-specific effects were observed in the TSH tertile vs CES-D score of 16 or greater, and incident depressive syndrome analyses, with gender*TSH tertile interaction term *P* values of $P = .28$ and $P = .82$, respectively. The association between TSH tertiles and CES-D scores was mainly driven by women (gender*TSH tertile interaction term $P = .012$): CES-D scores in the low, middle, and high TSH tertiles were 6.36 (0.44) [mean (SE)], 6.11 (0.51), and 6.58 (0.51) in men ($P = .75$) and 9.49 (0.52), 8.22 (0.60), and 7.00 (0.55) in women ($P = .002$).

In the examination round after baseline of the current study, TSH and FT4 levels were negatively correlated [$r = -0.19$, $P = 1.5 \times 10^{-8}$; $\beta = .06$ (0.01) mU/pmol, $P < .001$].

Thyroid autoimmunity (TPOAb-positivity) and depression

As shown in Table 3, TPOAb status did not show any associations with continuous CES-D scores, and the risk of a CES-D score of 16 or greater. Neither were there asso-

Table 3. TPOAb Status, CES-D Scores, and the Risk of Incident Depressive Disorders

		TPOAb-Negative Subjects	TPOAb-Positive Subjects	OR (95% CI)	*P* Value
Cross-sectional analyses					
	n	1201	72		
CES-D score (continuous)	Model 1, mean (SE)[a]	7.55 (0.20)	8.10 (0.82)		.51
	Model 2, mean (SE)[b]	7.52 (0.20)	7.52 (0.82)		.99
	n	1201	72		
CES-D of 16 or greater	Model 1, % (SE)[a]	8.6 (0.8)	12.5 (3.3)	1.52 (0.74–3.15)	.26
	Model 2, % (SE)[b]	8.7 (0.8)	11.4 (3.4)	1.31 (0.63–2.75)	.47
Prospective analyses					
	n	1427	76		
Incident depressive syndromes	Model 1, % (SE)[a]	9.2 (0.8)	9.2 (3.3)	1.12 (0.49–2.56)	.79
	Model 2, % (SE)[b]	9.4 (0.8)	8.5 (3.4)	1.04 (0.45–2.44)	.92

Analyses were performed in nondemented persons who were not on thyroid therapy. TPOAb status was compare with CES-D score, the risk of a CES-D score of 16 or greater, and the risk of incident depressive syndromes (in baseline depression free subjects). Dementia cases were excluded. TPOAb-positive subjects were defined as having TPOAb greater than 10 IU/mL.

[a] Model 1 had no adjustments.

[b] Model 2 was adjusted for gender, age, BMI, and smoking status.

ciations with the risk of incident depressive syndromes. No gender-specific effects were observed (data not shown).

Discussion

In the current study, we investigated the effects of variation in thyroid function within the normal range on the risk of depression as well as the relationship between thyroid autoimmunity and depression. Various studies have shown an increased risk of depression in both hypo- and hyperthyroidism, but little is known about the effects of normal-range thyroid function on depression (1–5). This is the first individual study to demonstrate a relationship between low-normal TSH levels and depression, and this relationship was demonstrated both cross-sectionally and longitudinally.

The only other study that has previously reported a relationship between high-normal thyroid function and depression concerned a meta-analysis of six studies (21), but the included studies in this meta-analysis differed substantially in age ranges (eg, 17–39 vs 85–89 y), type and sensitivity of depression scale, and assessment methods used, and no data on thyroid autoimmunity were available (21–26). Furthermore, only two of the included studies investigated the associations between thyroid status and the risk of depression prospectively (21, 24), whereas the other studies were cross-sectional (22, 23, 25, 26). These prospective studies were limited by the fact that they were either restricted to men (21) or included a smaller sample size with a shorter follow-up period (599 participants with follow-up of 3.7 y) (24). In the current study, we show an increased risk of depressive syndromes in persons with low-normal TSH levels by intensively monitoring a large group of elderly persons for 8 years for the occurrence of depressive episodes, and additionally taking the effects of potentially interfering factors such as TPOAbs, age, gender, dementia, and smoking into account. In addition, persons with low-normal TSH levels had more concurrent depressive symptoms and were more likely to have a CES-D score of 16 or greater, which is considered indicative of a depressive disorder (15, 19). These results show that even minor variation in thyroid function within the normal range can have important effects on affective behavior.

Based on the fact that both hypo- and hyperthyroidism have been associated with an increased risk of depression, one could expect a U-shaped relationship between thyroid function within the normal range and depression. However, such a relationship was not observed because only low-normal TSH levels were found to be associated with an increased risk of depression, both cross-sectionally and longitudinally. A number of conditions could underlie the observed low-normal TSH levels. Illness in general can lead to changes in thyroid parameters via a wide range of mechanisms (13, 14). This condition is called the nonthyroidal illness syndrome (NTIS) and is characterized by low serum T_3 levels. In addition, this condition can lead to a decrease in TSH and FT4 levels (13, 14). Therefore, the low-normal TSH levels in the current study could be a reflection of NTIS. Serum FT4 levels were not determined at baseline, but both TSH and FT4 levels were available 4.3 years after baseline. The fact that we observed an inverse correlation between TSH and FT4 at this time point makes NTIS a less likely explanation for the observed low-normal TSH levels and could point toward mild autonomous thyroid function, which is common in the elderly (27). In addition, in the previously discussed meta-analysis by Williams et al (21), higher normal-range FT4 levels were found to be positively associated with depression. Taken together, our data suggest a high-normal thyroid function in these subjects, and in this context it is interesting to note that TH regulates neuronal cell survival and interferes with serotonergic neurotransmission, which plays a key role in affective behavior (28, 29). However, the exact biological mechanism behind the association between a higher thyroid function, both outside and within the normal range, and depression remains to be clarified in future studies.

Various studies have found a higher prevalence of depression in women, which is in line with the results from the current study (30). Gender-related differences have been observed in various aspects of the pathophysiology of depression (31), and we therefore investigated the gender-specific effects of TSH levels and TPOAb status on depression. The association between a low-normal TSH and more depressive symptoms was found to be driven by women. However, these gender-specific differences were observed only for mean CES-D scores and not for the risk of CES-D scores of 16 or greater or incident depressive syndromes, which therefore seems to be of less clinical relevance.

Thyroid autoimmunity (TPOAb-positivity) is a common finding in the general population, especially in the elderly, with a prevalence in the current population of 5.1%. Autoimmune diseases, such as systemic lupus erythematosus and Sjogren's syndrome, have been associated with an increased risk of depression (7, 32), but little is known about the effects of TPOAb-positivity on the risk of depression. A few cross-sectional studies have investigated the relationship between TPOAb-positivity and depression, with conflicting results (8–12). The largest of these studies did not find an association between TPOAb-

positivity and depression in men and women (9). This is in line with the results from the current study, in which we did not find an association of TPOAb-positivity with concurrent depressive symptoms. We also did not find an association with the risk of incident depressive syndromes.

Our study has some limitations. As mentioned, no serum FT4 levels were available at baseline. Both serum TSH and FT4 levels were available 4.3 years after baseline, and their inverse correlation helped us to exclude NTIS as an important explanation for the observed low-normal TSH levels. However, we cannot exclude the possibility that there were persons with subclinical forms of pituitary insufficiency present in our analyses. Also, although we excluded persons using thyroid medication and there were no persons using amiodarone, we cannot exclude the possibility that our analyses still included subclinical persons using other thyroid interfering medication, such as glucocorticoids, because we did not have complete data on other medication use in our cohort.

Finally, we have not studied whether an increase of the low-normal TSH levels with antithyroid drugs reduces the risk of depression. This should be clarified in future studies.

The fact that the current study identifies low-normal TSH levels as an important risk factor for developing a depressive syndrome will likely be of clinical importance for various reasons. The treatment of depression with conventional therapies such as antidepressants and psychotherapy is suboptimal because 70% of treated depressed patients have residual symptoms, and 20% are treatment resistant (33, 34). To exclude underlying thyroid disease, clinical guidelines advise to measure serum TSH in persons with a new-onset depressive disorder (35). When TSH levels fall within the reference ranges, a thyroidal origin of the depression is excluded, and conventional depression treatment is started. Our results show that a low-normal TSH level results in an increased risk of depression, and it is tempting to speculate whether these persons may benefit from additional treatment with antithyroid drugs.

Furthermore, thyroid disorders are common in the general population, and the target of treatment of both hypo- and hyperthyroidism is to maintain TSH within the normal range (36). However, it has been shown that patients on T_4 therapy with a TSH within the normal range have a significant impairment in psychological well-being compared with controls of similar age and sex (37). Because the TSH reference range is wide (generally around 0.4–4.0 mU/L), it is remarkable to note that few data are available on the benefits of targeting treatment on low-normal vs high-normal TSH levels, especially with respect to the risk of affective complaints. Walsh et al (38) performed a double-blind, randomized, crossover trial in T_4-treated hypothyroid patients to investigate the effects of adjustments in T_4 dose. No differences in well-being and quality of life were found between patients with low-normal and high-normal TSH levels. However, this trial included only a limited number of patients (ie, 56 patients), no depression-specific questionnaires were used, and treatment and follow-up periods were short (ie, 8 wk). Saravanan et al (39) studied the relationship between TH parameters and well-being in 697 patients on T_4 therapy. A positive correlation between serum TSH levels and continuous depression scores, as measured by the Hospital Anxiety and Depression Scale, was found. However, this relationship was not seen when the Hospital Anxiety and Depression Scale depression score was used as a categorical variable, and no data on the incidence of depressive episodes were available. In a large study of more than 1000 women with thyroid disease who were taking T_4, Panicker et al (40) found that higher TSH levels were associated with more depression and anxiety. However, these results were based only on cross-sectional (and not prospective) analyses, and the study was unfortunately not powered to investigate these relations in men. Because this is the first individual study to demonstrate a relationship between low-normal TSH levels and depression in men and women, results should be first replicated in an independent study. If replicated, large randomized controlled trials should investigate the psychological well-being and risk of depressive syndromes when targeting patients on low-normal vs high-normal TSH levels.

In conclusion, this study identifies low-normal TSH as an important risk factor for depression in the elderly, which is independent of thyroid autoimmunity.

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References

1. **Bauer M, Goetz T, Glenn T, Whybrow PC.** The thyroid-brain interaction in thyroid disorders and mood disorders. *J Neuroendocrinol*. 2008;20:1101–1114.
2. **Bunevicius R.** Thyroid disorders in mental patients. *Curr Opin Psychiatry*. 2009;22:391–395.
3. **Placidi GP, Boldrini M, Patronelli A, et al.** Prevalence of psychiatric disorders in thyroid diseased patients. *Neuropsychobiology*. 1998; 38:222–225.
4. **Thomsen AF, Kvist TK, Andersen PK, Kessing LV.** Increased risk of affective disorder following hospitalisation with hyperthyroidism—a register-based study. *Eur J Endocrinol*. 2005;152:535–543.
5. **Trzepacz PT, McCue M, Klein I, Levey GS, Greenhouse J.** A psychiatric and neuropsychological study of patients with untreated Graves' disease. *Gen Hosp Psychiatry*. 1988;10:49–55.
6. **Maes M, Meltzer H, Jacobs J, et al.** Autoimmunity in depression: increased antiphospholipid autoantibodies. *Acta Psychiatr Scand*. 1993;87:160–166.
7. **Valtysdottir ST, Gudbjornsson B, Lindqvist U, Hallgren R, Hetta J.** Anxiety and depression in patients with primary Sjogren's syndrome. *J Rheumatol*. 2000;27:165–169.
8. **Carta MG, Loviselli A, Hardoy MC, et al.** 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*. 2004;4:25.
9. **Engum A, Bjoro T, Mykletun A, Dahl AA.** Thyroid autoimmunity, depression and anxiety: are there any connections? An epidemiological study of a large population. *J Psychosom Res*. 2005;59:263–268.
10. **Pop VJ, Maartens LH, Leusink G, van Son MJ, et al.** Are autoimmune thyroid dysfunction and depression related? *J Clin Endocrinol Metab*. 1998;83:3194–3197.
11. **Kirim S, Keskek SO, Koksal F, Haydardedeoglu FE, Bozkirli E, Toledano Y.** Depression in patients with euthyroid chronic autoimmune thyroiditis. *Endocr J*. 2012;59:705–708.
12. **van de Ven AC, Muntjewerff JW, Netea-Maier RT, et al.** Association between thyroid function, thyroid autoimmunity, and state and trait factors of depression. *Acta Psychiatr Scand*. 2012;126:377–384.
13. **Peeters RP.** Non thyroidal illness: to treat or not to treat? *Ann Endocrinol (Paris)*. 2007;68:224–228.
14. **Warner MH, Beckett GJ.** Mechanisms behind the non-thyroidal illness syndrome: an update. *J Endocrinol*. 2010;205:1–13.
15. **Luijendijk HJ, van den Berg JF, Dekker MJ, et al.** Incidence and recurrence of late-life depression. *Arch Gen Psychiatry*. 2008;65: 1394–1401.
16. **Tan ZS, Vasan RS.** Thyroid function and Alzheimer's disease. *J Alzheimers Dis*. 2009;16:503–507.
17. **Amur S, Parekh A, Mummaneni P.** Sex differences and genomics in autoimmune diseases. *J Autoimmun*. 2012;38:J254–J265.
18. **Rahbari R, Zhang L, Kebebew E.** Thyroid cancer gender disparity. *Future Oncol*. 2010;6:1771–1779.
19. **Beekman AT, Deeg DJ, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W.** Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med*. 1997; 27:231–235.
20. **Schrijvers EM, Direk N, Koudstaal PJ, et al.** Associations of serum cortisol with cognitive function and dementia: the Rotterdam Study. *J Alzheimers Dis*. 2011;25:671–677.
21. **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;70:484–492.
22. **Engum A, Bjoro T, Mykletun A, Dahl AA.** An association between depression, anxiety and thyroid function—a clinical fact or an artifact? *Acta Psychiatr Scand*. 2002;106:27–34.
23. **Forman-Hoffman V, Philibert RA.** Lower TSH and higher T4 levels are associated with current depressive syndrome in young adults. *Acta Psychiatr Scand*. 2006;114:132–139.
24. **Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG.** Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;292:2591–2599.
25. **Roberts LM, Pattison H, Roalfe A, et al.** Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? *Ann Intern Med*. 2006;145:573–581.
26. **van Boxtel MP, Menheere PP, Bekers O, Hogervorst E, Jolles J.** Thyroid function, depressed mood, and cognitive performance in older individuals: the Maastricht Aging Study. *Psychoneuroendocrinology*. 2004;29:891–898.
27. **Tonacchera M, Pinchera A, Vitti P.** Assessment of nodular goitre. *Best Pract Res Clin Endocrinol Metab*. 2010;24:51–61.
28. **Alva-Sanchez C, Sanchez-Huerta K, Arroyo-Helguera O, Anguiano B, Aceves C, Pacheco-Rosado J.** The maintenance of hippocampal pyramidal neuron populations is dependent on the modulation of specific cell cycle regulators by thyroid hormones. *Brain Res*. 2009; 1271:27–35.
29. **Bauer M, Heinz A, Whybrow PC.** Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *Mol Psychiatry*. 2002;7:140–156.
30. **Noble RE.** Depression in women. *Metabolism*. 2005;54:49–52.
31. **Halbreich U, Lumley LA.** The multiple interactional biological processes that might lead to depression and gender differences in its appearance. *J Affect Disord*. 1993;29:159–173.
32. **Julian LJ, Tonner C, Yelin E, et al.** Cardiovascular and disease-related predictors of depression in systemic lupus erythematosus. *Arthritis Care Res*. 2011;63:542–549.
33. **Little A.** Treatment-resistant depression. *Am Fam Physician*. 2009; 80:167–172.
34. **Rakofsky JJ, Holtzheimer PE, Nemeroff CB.** Emerging targets for antidepressant therapies. *Curr Opin Chem Biol*. 2009;13:291–302.
35. **Work Group on Psychiatric Evaluation, American Psychiatric Association Steering Committee on Practice Guidelines.** Psychiatric evaluation of adults. Second edition. *Am J Psychiatry* 2006;163:3–36.
36. **Baskin HJ, Cobin RH, Duick DS, et al.** American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. *Endocr Pract*. 2002;8:457–469.
37. **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 (Oxf)*. 2002;57:577–585.
38. **Walsh JP, Ward LC, Burke V, et al.** Small changes in thyroxine dosage do not produce measurable changes in hypothyroid symptoms, well-being, or quality of life: results of a double-blind, randomized clinical trial. *J Clin Endocrinol Metab*. 2006;91:2624–2630.
39. **Saravanan P, Visser TJ, Dayan CM.** Psychological well-being correlates with free thyroxine but not free 3,5,3′-triiodothyronine levels in patients on thyroid hormone replacement. *J Clin Endocrinol Metab*. 2006;91:3389–3393.
40. **Panicker V, Evans J, Bjoro T, Asvold BO, Dayan CM, Bjerkeset O.** A paradoxical difference in relationship between anxiety, depression and thyroid function in subjects on and not on T4: findings from the HUNT study. *Clin Endocrinol (Oxf)*. 2009;71:574–580.