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Clinical Research Article

Association of Low-Normal Free T4 Levels With Future Major Depression Development

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Abstract

Context: Hyperthyroidism and overt and subclinical hypothyroidism are associated with major depression; however, the association of major depression across the spectrum of thyroid function within the normal range is unknown.

Objective: We investigated whether higher or lower levels of free thyroxine (T4) and thyrotropin (TSH) within the normal range are associated with major depression.

Methods: This was a retrospective cohort study of 66 960 participants with normal thyroid function who visited for health checkups (St. Luke's International Hospital, 2005-2018). The primary outcome was the development of major depression during the follow-up period. Participants were divided into 3 equal groups based on baseline free T4 or TSH values (low-, middle-, or high-normal), and the incidence of major depression was compared using the Cox proportional hazard model after adjusting for potential covariates.

Results: During the median follow-up of 1883 days, 1363 (2.0%) patients developed major depression. The low-normal free T4 group had a significantly higher risk of major depression (adjusted HR 1.15; 95% CI, 1.01-1.31), but not the high-normal free T4 group or TSH groups. The association between low-normal free T4 and the development of major depression was maintained, rather more obvious, upon exclusion of participants whose thyroid hormone levels became abnormal during follow-up compared with data from all participants (adjusted HR 1.24; 95% CI, 1.07-1.43).

Conclusion: In this cohort, low-normal free T4 was associated with an increased risk of future major depression, even if subsequent hormone levels were maintained within the normal range. The magnitude of the impact of low-normal free T4 was relatively mild.

Key Words: depression, thyroid hormone, hypothyroidism, diabetes, clinical trial, data base

Abbreviations: BMI, body mass index; DSM, Diagnostic and Statistical Manual of Mental Disorders; HR, hazard ratio; IQR, interquartile range; T4, thyroxine; TSH, thyrotropin (thyroid-stimulating hormone).

Depression is a common health condition that has a substantial impact on individuals and society; it has received significant attention as an immediate global priority [1]. Depression can cause distress leading to premature death, and it has been reported to be significantly associated with excess all-cause mortality [2]. Prevention is essential to reduce the incidence of depression, and early detection and intervention are necessary [1]. Despite the importance of translating knowledge into practice, a considerable amount of evidence on prevention of depression remains unapplied in clinical settings. Researchers must also identify novel and underused prevention targets [1].

The association between thyroid dysfunction and psychiatric symptoms, particularly depression, has been discussed for a long time [3, 4]. While it has been clinically observed that thyroid function is closely associated with psychiatric disorders, such as mood disturbances and cognitive impairment, the role of thyroid hormones in brain function has not been fully elucidated. Advanced techniques, including functional neuroimaging, have revealed the influence of thyroid hormones on brain functions. It is now widely accepted that thyroid hormones play an important role in brain function and affect mood and cognition, although the exact mechanisms by which thyroid hormone affect brain functions are not fully understood [5, 6].

Both excessive and insufficient levels of thyroid hormone may be associated with psychiatric abnormalities. Patients with hyperthyroidism have been reported to be more likely to develop depressive symptoms [7, 8]. Overt hypothyroidism is characterized by elevated serum thyrotropin (thyroid-stimulating hormone, TSH) accompanied by low serum free thyroxine (T4) concentrations, while subclinical hypothyroidism is characterized by elevated TSH accompanied by a normal free T4 concentration [9, 10]. The association between hypothyroidism, either subclinical or overt, and depression has been discussed for decades; however, the findings remain inconclusive. Some studies

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have revealed an association between hypothyroidism and depression [8, 11], while others have failed to demonstrate this association [12-14]. However, a recent meta-analysis [5] concluded that overt hypothyroidism was associated with an increased incidence of depression. Furthermore, another meta-analysis reported that even subclinical hypothyroidism had a higher risk of depression than euthyroid controls [15], although some reported that there was no association between subclinical hypothyroidism and depression [16, 17], and the conclusions still remain controversial [5]. However, the risk of depression in people with normal thyroid function (both free T4 and TSH are within the normal range) is less well understood. Some studies have reported an association between thyroid hormones within the normal range and depression or depressive symptoms [18-24], but others focused on the relationship between subclinical hypothyroidism (free T4 was within the normal range, but TSH was higher) and depression [16, 17]. Although some of these studies have reported a positive association of TSH levels [22], a negative association of TSH levels [19, 21, 23], a positive association of free T4 levels [24], or no association of free T4/TSH levels [20] with depression in the general population, the association between depression and normal thyroid function remains controversial. Studies in which both free T4 and TSH are within the normal range and both values have been measured are still lacking. We hypothesized that even within normal limits, relatively high or low thyroid function may be associated with depression.

To determine whether low-normal (lower levels within the normal reference range, first tertile) or high-normal (higher levels within the normal reference range, third tertile) serum free T4 and TSH levels were associated with major depression, we investigated the risk of future development of major depression among individuals with both normal free T4 and normal TSH levels. We also investigated the association between conventional risk factors and depression.

Methods

This retrospective cohort study was conducted at St. Luke's International Hospital, Tokyo, Japan, from 2005 to 2018. The data of all the participants who visited the Center for Preventive Medicine at the hospital for voluntary health checkups, were included from the St. Luke's Health Checkup Database. Children were excluded. Pregnant women were excluded from this study, because health checkups excluded pregnant women, due to the inclusion of radiograph examinations. We excluded patients with a medical history of hyperthyroidism and hypothyroidism (including Hashimoto thyroiditis) at baseline, including those on thyroid hormone therapy, even if they were in the euthyroid state at the time. We also excluded those who had abnormal values for serum free T4 (<1.00 ng/dL or > 1.64 ng/dL) or TSH (<0.45 μIU/mL or >4.95 μIU/mL) based on the normal reference range in the hospital during their first blood exam as part of the health checkups at the center during the study periods, because our study population focused on those who had normal thyroid function. We also excluded patients with a medical history of major depression at baseline. Our primary outcome was the development of major depression during follow-up. We divided the participants into 3 equal groups based on the levels of free T4 or TSH at baseline and examined the outcomes of the groups (3 groups by free T4 levels and 3 groups by TSH levels, for a total of 3 groups for each). The St. Luke's Ethics Committee Institutional Review Board approved this study (approval number: 18-R197; comprehensive approval for studying the association between thyroid function and clinical outcomes).

Development of Major Depression

The primary outcome was the development of major depression during the study period. Information about the outcome was obtained from electronic medical records at St. Luke's International Hospital, and participants provided information on the history of major depression diagnosed in any of the other hospitals on a self-reported basis. Regarding the information from the electronic medical records, the diagnosis of major depression was made by the psychiatrist at the hospital based on the clinical information of the individuals. In addition, we obtained information regarding the development of major depression provided by participants on a self-reported basis, together with the information on other medical history, as a part of health checkups for all participants at each visit.

Serum Thyroid Function Test

As part of health checkups, serum free T4 and TSH levels were measured for all the participants, at every visit. Free T4 and TSH were routinely measured as a part of health checkups for all participants who presented to the clinic, whether or not they had any symptoms or were at risk for thyroid disease. Only the first thyroid function tests collected were used to categorize the participants. Those who developed hypothyroidism or hyperthyroidism during the study were not excluded, but we performed a subanalysis that excluded them. Free T3 levels were not measured. Serum free T4 and TSH levels were measured using electrochemiluminescence immunoassay (Roche Diagnostics). The normal reference range for serum free T4 was defined as 1.00 to 1.64 ng/dL, and that for TSH was defined as 0.45 to 4.95 μIU/mL based on the criteria at the hospital. According to the baseline free T4 or TSH levels, we divided the participants into 3 equal groups (first tertile defined as low-normal; second tertile defined as middle-normal; and third tertile defined as high-normal) and compared their outcomes, with the middle-normal group assigned as the reference group. The cutoff values for each tertile were as follows; free T4 (low-normal: ≥1.00 ng/dL to <1.22 ng/dL, middle-normal: ≥1.22 ng/dL to <1.35 ng/dL, and high-normal: ≥1.35 ng/dL to ≤1.64 ng/dL); TSH (low-normal: ≥0.45 μIU/mL to <1.39 μIU/mL, middle-normal: ≥1.39 μIU/mL to <2.16 μIU/mL, and high-normal: ≥2.16 μIU/mL to ≤4.95 μIU/mL).

Covariates

We also obtained data on participants' age, gender, body mass index (BMI), social habits, medical history, and family history of major depression as covariates. Social habits included smoking status (never, former, or current smoker), alcohol consumption status (abstainer, occasional drinker, or regular drinker), and exercise habits (almost none, 1-2 times a week, 3-5 times a week, or almost every day) based on self-reported responses to the questionnaire. We also obtained data regarding chronic diseases, including a medical history of any type of cancer, hypertension, diabetes, and dyslipidemia. Any family history of major depression was also obtained. BMI was categorized according to Asian criteria of the World Health Organization; underweight

(<18.5 kg/m^2), normal weight (>18.5 to ≤24.9 kg/m^2), and overweight/obese (>24.9 kg/m^2).

Statistical Methods

First, we summarized descriptive statistics regarding the participants' information by tertiles based on baseline serum free T4 levels or baseline serum TSH levels. The Kaplan–Meier curves for major depression-free survival based on free T4 or TSH groups were then drawn and examined by log-rank test, because the follow-up period varies among individuals. Separate analyses were conducted based on free T4 and TSH categories using the same population. We analyzed the risk of developing depression using the Cox proportional hazard model, after adjusting for covariates. We included free T4 and TSH as covariates and analyzed both free T4 and TSH categories. We calculated each Harrell's C concordance statistics and its statistical significance from Cox proportional hazard model to compare models with different covariates. Model 1 included participant age and gender; model 2 included social habits and BMI in addition to model 1; model 3 included past medical histories in addition to model 2; model 4 included family history of major depression in addition to model 3. For these models, we have included those that have been reported to be related in the past. We performed a subanalysis excluding participants who developed abnormal levels of free T4 or TSH at follow-up visits to evaluate whether depression could be directly related to low-normal free T4 levels or could be related to the development of hypothyroidism over time, for which a baseline low-normal free T4 is a predictor. We also followed subsequent free T4 and TSH levels at follow-up visits to evaluate future abnormal thyroid function according to the baseline free T4/TSH tertile groups and examined the results using the χ^2 test. Because thyroid function may fluctuate and be out of normal ranges incidentally, we performed the sensitivity analyses with the data dealing with those who had abnormal levels at least once, twice, and 3 times during the follow-up period. Participants were censored when they stopped coming to the hospital or taking the health checkups.

All analyses were performed using Stata MP 16.1 in 2021 (STATA Corp., College Station, TX, USA).

Results

Altogether, 66 960 participants were included in the study. The age range of the participants was 17 to 94 years, and the children were not included. The mean age of the participants was 46.6 years (SD: 11.4) and 33 586 (50.2%) participants were men. The mean value of free T4 was 1.29 ng/dL (SD: 0.14) and that of TSH was 1.92 μIU/mL (SD: 0.94). The participants were divided into 3 tertiles based on the baseline free T4 (low-normal: ≥1.00 ng/dL to <1.22 ng/dL, middle-normal: ≥1.22 ng/dL to <1.35 ng/dL, and high-normal: ≥1.35 ng/dL to ≤1.64 ng/dL) or TSH (low-normal: ≥0.45 μIU/mL to <1.39 μIU/mL, middle-normal: ≥1.39 μIU/mL to <2.16 μIU/mL, and high-normal: ≥2.16 μIU/mL to ≤4.95 μIU/mL).

Table 1 shows the baseline participant characteristics according to the baseline free T4 levels. Those who had lower baseline free T4 levels were more likely to be older, female, underweight, and had a healthier lifestyle ($P < .001$). In terms of medical history, they were more likely to have dyslipidemia or any type of cancer ($P < .001$). Regarding thyroid function, participants with lower free T4 levels tended to have slightly higher TSH levels ($P < .001$). Table 2 shows the baseline characteristics of the participants according to their TSH levels. Those with higher baseline TSH levels were more likely to be older and female, had a healthier lifestyle, hypertension, dyslipidemia, or any type of cancer ($P < .001$). The participants with higher TSH levels tended to have slightly lower free T4 levels ($P < .001$).

During the median follow-up of 1883 days (interquartile range [IQR], 776-3610 days), 1363 (2.0%) participants developed major depression. Figure 1A shows the Kaplan–Meier curves for major depression-free survival according to the free T4 levels. The curve for the low-normal group had worse outcomes than that for the middle-normal group ($P < .01$). In contrast, Kaplan–Meier curves for major depression-free survival based on the TSH levels (Fig. 1B) showed similar results across all the groups ($P = .07$).

Table 3 shows the results of the analysis using a multivariable Cox proportional hazard model, including both free T4 and TSH categories. Harrell's C concordance statistics in each model was 0.54, 0.56, 0.57, 0.58 for model 1, 2, 3, 4, respectively. The *P* value for the difference of the model 2 and 1, 3 and 2, 4 and 3 was <0.01, <0.01, 0.08, respectively. Individuals in the low-normal free T4 group had a significantly higher risk of developing major depression during the study period than those in the middle-normal group (adjusted hazard ratio [HR] 1.15; 95% CI, 1.01-1.31), but those in the high-normal group (adjusted HR 1.10; 95% CI, 0.96-1.26) did not have a higher risk of developing major depression than those in the middle-normal group. Regarding TSH, both the low-normal (adjusted HR 1.03; 95% CI, 0.90-1.17) and the high-normal groups (adjusted HR 1.10; 95% CI, 0.96-1.25) had similar risk of developing major depression as the middle-normal group. In terms of social habits, a healthier lifestyle was associated with a lower risk of developing major depression, except for increased alcohol consumption. Those with any medical history tended to have a higher risk of developing major depression than those without it. We also analyzed the free T4 and TSH categories separately without including TSH and free T4 in the covariates, respectively, but in both analyses the results were not affected.

Table 4 shows the association between baseline free T4 and TSH levels and future abnormal free T4 or TSH levels. The data show the number of participants who had abnormal free T4 or TSH values at least once during any of the visits in the follow-up period. The median follow-up was 1883 days (IQR, 776-3610 days), and the median number of free T4 and TSH values collected was 4 times (IQR, 2-8 times). Table 4 (Free T4 or TSH) shows that those in the low tertile groups were more likely to progress to abnormally low values of free T4 or TSH, while those in the high tertile groups were more likely to progress to abnormally high free T4 or TSH levels. Remarkably, as many as 15.2% of those in the low-normal free T4 tertile group or 16.1% of those in the high-normal TSH tertile group developed abnormally low free T4 or high TSH values. The lower the baseline free T4 level, the higher the proportion of individuals with abnormally low future free T4 levels. The higher the baseline TSH level, the higher the proportion of patients with abnormally high TSH levels.

Table 4 (Free T4 and TSH) shows that the proportion of participants with both abnormally low free T4 and abnormally high TSH in the future, at least once each, during any of the

Table 1. Baseline characteristics of the participants according to free T4 levels

	Baseline free T4					
	Low-normal ≥1.00, <1.22 (n = 23 622)		Middle-normal ≥1.22, <1.35 (n = 21 951)		High-normal ≥1.35, <1.65 (n = 21 387)	
The development of major depression	526	(2.2)	417	(1.9)	420	(2.0)
Thyroid function						
Free T4, ng/dL, mean (SD)	1.14	(0.06)	1.29	(0.04)	1.46	(0.07)
TSH, μIU/mL, mean (SD)	2.07	(0.99)	1.89	(0.92)	1.78	(0.88)
Age, years, mean (SD)	48.1	(11.3)	46.9	(11.3)	44.7	(11.2)
Male, n (%)	8589	(36.4)	11 013	(50.2)	13 984	(65.4)
Alcohol consumption, n (%)						
Abstainer	9889	(41.9)	7951	(36.2)	6361	(29.7)
Occasional	4295	(18.2)	3957	(18.0)	3983	(18.6)
Regular	9438	(40.0)	10 043	(45.8)	11 043	(51.6)
Smoking status, n (%)						
Never smoker	15 721	(66.6)	13 294	(60.6)	11 634	(54.4)
Former smoker	5131	(21.7)	5140	(23.4)	5324	(24.9)
Current smoker	2770	(11.7)	3517	(16.0)	4429	(20.7)
Exercise habits, n (%)						
Almost none	8596	(36.4)	8243	(37.6)	8177	(38.2)
1-2 times a week	8508	(36.0)	8335	(38.0)	8491	(39.7)
3-5 times a week	4012	(17.0)	3331	(15.2)	2994	(14.0)
Almost everyday	2506	(10.6)	2042	(9.3)	1725	(8.1)
BMI, n (%)						
Underweight	2539	(10.8)	2005	(9.1)	1705	(8.0)
Normal weight	16 827	(71.2)	15 561	(70.9)	15 166	(71.0)
Overweight/obesity	4256	(18.0)	4385	(20.0)	4516	(21.1)
Medical history, n (%)						
Cancer bearing	1098	(4.7)	850	(3.9)	615	(2.9)
Hypertension	1777	(7.5)	1741	(7.9)	1650	(7.7)
Diabetes	419	(1.8)	449	(2.0)	431	(2.0)
Dyslipidemia	1190	(5.0)	1042	(4.8)	838	(3.9)
Family history of depression, n (%)	180	(0.8)	144	(0.7)	130	(0.6)

Participants were categorized into 3 tertile groups based on the baseline free T4 level (low-normal [first tertile]: ≥1.00 ng/dL to < 1.22 ng/dL, middle-normal [second tertile]: ≥1.22 ng/dL to <1.35 ng/dL, and high-normal [third tertile]: ≥1.35 ng/dL to ≤1.64 ng/dL). Data are presented as mean (SD) or number (%).
Abbreviations: BMI, body mass index; T4, thyroxine; TSH, thyrotropin.

visits, was significantly higher in the low-normal free T4 group (2.8%), and the percentage tended to increase as baseline free T4 levels decreased. Furthermore, participants with low-normal free T4 frequently experienced simultaneous low free T4 and high TSH levels in a single blood test taken during the same visit, in a future follow-up (0.8%).

To examine the sustainability in abnormal levels of free T4 or TSH, in addition to those who had only a single abnormal hormone level (Table 4), we performed the sensitivity analyses with the data of those who had abnormal levels at least twice and at least 3 times (Table 5) as those with abnormal thyroid function. The results were similar to the results of the analysis of those with a single hormone abnormality; they showed the same tendency, although the numbers of participants were smaller overall.

Table 6 shows the results of the multivariable Cox proportional hazard model for future depression, excluding participants who developed abnormal levels of free T4 or TSH at follow-up visits to evaluate whether depression could be directly related to low-normal free T4 levels, or could be related to the development of hypothyroidism over time, for which a baseline low-normal free T4 is a predictor. The results were similar to the main results (Table 3), but with rather higher hazard ratios; individuals in the low-normal free T4 group had significantly higher HR than those in the middle-normal group (adjusted HR 1.24; 95% CI, 1.07-1.43). Furthermore, the individuals in the high-normal TSH group had a significantly higher HR than those in the middle-normal group (adjusted HR 1.18; 95% CI, 1.02-1.36).

Discussion

In this cohort study, we demonstrated an association between serum low-normal free T4 levels and increased future major depression development among participants with free T4 and TSH levels within the normal reference range. However,

Table 2. Baseline characteristics of the participants according to TSH levels

	Baseline TSH					
	Low-normal ≥0.45, <1.39 (n = 22 539)		**Middle-normal ≥1.39, <2.16 (n = 22 151)**		**High-normal ≥2.16, <4.96 (n = 22 270)**	
The development of major depression	443	(2.0)	430	(1.9)	490	(2.2)
Thyroid function						
Free T4, ng/dL, mean (SD)	1.31	(0.14)	1.29	(0.14)	1.27	(0.14)
TSH, μIU/mL, mean (SD)	1.02	(0.24)	1.74	(0.22)	3.01	(0.70)
Age, years, mean (SD)	45.3	(10.6)	46.3	(11.3)	48.2	(12.0)
Male, n (%)	11 715	(52.0)	11 184	(50.5)	10 687	(48.0)
Alcohol consumption, n (%)						
Abstainer	7718	(34.2)	7938	(35.8)	8545	(38.4)
Occasional	4177	(18.5)	4016	(18.1)	4042	(18.2)
Regular	10 644	(47.2)	10 197	(46.0)	9683	(43.5)
Smoking status, n (%)						
Never smoker	12 478	(55.4)	13 454	(60.7)	14 717	(66.1)
Former smoker	5065	(22.5)	5217	(23.6)	5313	(23.9)
Current smoker	4996	(22.2)	3480	(15.7)	2240	(10.1)
Exercise habits, n (%)						
Almost none	8799	(39.0)	8210	(37.1)	8007	(36.0)
1-2 times a week	8451	(37.5)	8502	(38.4)	8381	(37.6)
3-5 times a week	3196	(14.2)	3384	(15.3)	3757	(16.9)
Almost everyday	2093	(9.3)	2055	(9.3)	2125	(9.5)
BMI, n (%)						
Underweight	2178	(9.7)	2041	(9.2)	2030	(9.1)
Normal weight	16 038	(71.2)	15 692	(70.8)	15 824	(71.1)
Overweight/obesity	4323	(19.2)	4418	(19.9)	4416	(19.8)
Medical history, n (%)						
Cancer bearing	739	(3.3)	817	(3.7)	1007	(4.5)
Hypertension	1597	(7.1)	1599	(7.2)	1972	(8.9)
Diabetes	424	(1.9)	423	(1.9)	452	(2.0)
Dyslipidemia	869	(3.9)	957	(4.3)	1244	(5.6)
Family history of depression, n (%)	150	(0.7)	151	(0.7)	153	(0.7)

Participants were categorized into 3 tertile groups based on the baseline TSH level (low-normal [first tertile]: ≥0.45 μIU/mL to <1.39 μIU/mL, middle-normal [second tertile]: ≥ 1.39 μIU/mL to <2.16 μIU/mL, and high-normal [third tertile]: ≥ 2.16 μIU/mL to ≤ 4.95 μIU/mL). Data are presented as mean (SD) or number (%).
Abbreviations: BMI, body mass index; TSH, thyrotropin; T4, thyroxine.

TSH levels did not show such an association. Regarding other risk factors, those with a habit of exercise and alcohol consumption had a lower risk of major depression, while female subjects, those who were underweight, smokers, those with a medical history of cancer, hypertension, and diabetes, and a family history of depression had a higher risk of major depression development.

Our cohort study showed that participants with low-normal serum free T4 levels had a higher risk of future major depression. These findings suggest that not only overt and subclinical hypothyroidism, which have been evaluated in previous studies, but also low-normal thyroid function may be a potential risk factor for future major depression development. Therefore, these patients should be closely followed up for the diagnosis of major depression in the early stages. In contrast, there was a weak and non–statistically significant association between high-normal free T4 levels and major depression. Regarding TSH levels, an association with future major depression was not observed. A possible explanation for this result is that free T4 levels may directly reflect the amount of thyroid hormone, while TSH levels are regulated by the negative feedback loop of the hypothalamic-pituitary-thyroid axis [9, 25]. Most thyroid dysfunctions are caused by the thyroid itself (primary), and pituitary or hypothalamic (central) causes are rare. Central hyperthyroidism is a cause of less than 1% of total hyperthyroidism [26], and the prevalence of central hypothyroidism is much rarer than primary hypothyroidism [27-30]. As a result, TSH concentrations fluctuate substantially in accordance with small changes in free T4, and the TSH response to free T4 change differs between individuals [31].

In our data, exercise habits and alcohol drinking habits lowered the risk of major depression, while female subjects, those who were underweight, those with smoking habits, family history of depression, medical history of cancer, hypertension,

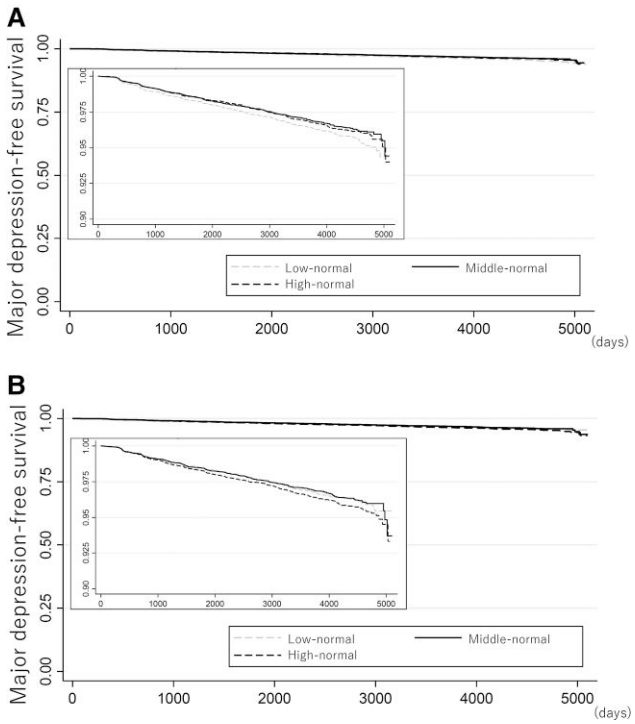

Figure 1. a: Major depression-free survival curves according to free T4 levels. Low-normal [first tertile]: ≥1.00 ng/dL to <1.22 ng/dL, middle-normal [second tertile]: ≥1.22 ng/dL to <1.35 ng/dL, and high-normal [third tertile]: ≥1.35 ng/dL to ≤1.64 ng/dL. b: Major depression-free survival curves according to the TSH levels. Low-normal [first tertile]: ≥0.45 μIU/mL to <1.39 μIU/mL, middle-normal [second tertile]: ≥1.39 μIU/mL to <2.16 μIU/mL, and high-normal [third tertile]: ≥2.16 μIU/mL to ≤4.95 μIU/mL.

Table 3. Results of the multivariable Cox proportional hazard model for future depression

	Adjusted hazard ratio (95% CI)
Thyroid function	
Baseline free T4	
Low-normal	**1.15 (1.01-1.31)**
Middle-normal	Reference
High-normal	1.10 (0.96-1.26)
Baseline TSH	
Low-normal	1.03 (0.90-1.17)
Middle-normal	Reference
High-normal	1.10 (0.96-1.25)
Age, years	**1.01 (1.01-1.02)**
Female	**1.25 (1.09-1.43)**
Alcohol consumption	
Abstainer	Reference
Occasional	**0.80 (0.68-0.93)**
Regular	**0.81 (0.71-0.92)**
Smoking status	
Never smoker	Reference
Former smoker	**1.21 (1.05-1.39)**
Current smoker	**1.22 (1.03-1.44)**
Exercise habits	
Almost none	Reference
1-2 times a week	**0.86 (0.76-0.98)**
3-5 times a week	0.89 (0.76-1.04)
Almost everyday	**0.81 (0.66-0.98)**
Body mass index	
Underweight	**1.25 (1.06-1.48)**
Normal weight	Reference
Overweight/obesity	0.94 (0.81-1.09)
Medical history, n (%)	
Cancer bearing	**1.37 (1.09-1.71)**
Hypertension	**1.33 (1.10-1.60)**
Diabetes	**1.75 (1.33-2.31)**
Dyslipidemia	1.18 (0.95-1.48)
Family history of depression, n (%)	**2.04 (1.30-3.21)**

Baseline free T4 level (low-normal [first tertile]: ≥1.00 ng/dL to <1.22 ng/dL, middle-normal [second tertile]: ≥1.22 ng/dL to <1.35 ng/dL, and high-normal [third tertile]: ≥1.35 ng/dL to ≤1.64 ng/dL) and the baseline TSH level (low-normal [first tertile]: ≥0.45 μIU/mL to <1.39 μIU/mL, middle-normal [second tertile]: ≥1.39 μIU/mL to <2.16 μIU/mL, and high-normal [third tertile]: ≥2.16 μIU/mL to ≤4.95 μIU/mL).
Models were adjusted for participant age, gender, body mass index, social history (alcohol consumption, smoking status, and exercise habits), medical history of cancer, hypertension, diabetes, dyslipidemia, and family history of depression.
Abbreviations: T4, thyroxine; TSH, thyrotropin.
The numbers in bold represents that its *P* value is less than 0.05.

and diabetes had an increased risk of major depression, which was consistent with previous observations [32-41].

There are 2 possible explanations for the association between low-normal free T4 levels and an increased risk of major depression. First, low-normal free T4 levels are not adequate for some individuals, although they are within the normal laboratory reference range. A previous study reported that individual free T4 levels are maintained within a narrower range than the population-based reference range [9, 42], and that individual thyroid function set points are largely genetically determined [43], indicating that low-normal free T4 levels could be too low for some individuals. Our results suggest that serum low-normal free T4 levels are a risk factor for the development of future major depression.

Another possibility is that the serum free T4 concentration, which was within the normal reference range at baseline, decreased further below the lower limit of the normal reference range during the follow-up period. It has been previously reported that subclinical hypothyroidism is usually progressive, and most cases regress to a euthyroid state, while some progress to overt hypothyroidism [10]. Likewise, low-normal thyroid function at baseline could progress to hypothyroidism in the future. As expected, our results indicate that some people with low-normal free T4 levels show a further decrease in serum free T4 levels over time to levels below the normal reference range, and some develop overt hypothyroidism. In some people with serum high-normal TSH levels, TSH levels increase to higher levels over time, resulting in overt or subclinical hypothyroidism. Among those with low-normal free T4 levels at baseline, the proportion of participants with both decreased free T4 and increased TSH levels at least once was 2.8%. This decreasing trend of free T4 and the rate of progression to overt hypothyroidism were in accordance with previous reports, which showed a common clinical course from the euthyroid state to overt hypothyroidism via subclinical hypothyroidism [10]. The reported annual rate of progression to overt hypothyroidism was approximately 1% to 5%,

Table 4. Association between baseline free T4 and TSH levels and future abnormal free T4 and TSH levels

	Baseline free T4				Baseline TSH			
	Low-normal (n = 23 622)	Middle-normal (n = 21 951)	High-normal (n = 21 387)	*P* value	Low-normal (n = 22 539)	Middle-normal (n = 22 151)	High-normal (n = 22 270)	*P* value
Free T4 or TSH								
Elevated free T4	209 (0.9)	383 (1.7)	1963 (9.2)	<.01	992 (4.4)	854 (3.9)	709 (3.2)	<.01
Decreased free T4	3600 (15.2)	736 (3.4)	195 (0.9)	<.01	1140 (5.1)	1403 (6.3)	1988 (8.9)	<.01
Elevated TSH	1900 (8.0)	1311 (6.0)	920 (4.3)	<.01	112 (0.5)	440 (2.0)	3579 (16.1)	<.01
Decreased TSH	600 (2.5)	595 (2.7)	666 (3.1)	<.01	1243 (5.5)	321 (1.5)	297 (1.3)	<.01
Free T4 and TSH								
Elevated free T4 and								
Elevated TSH	35 (0.2)	49 (0.2)	103 (0.5)	<.01	24 (0.1)	34 (0.2)	129 (0.6)	<.01
Normal TSH	44 (0.2)	178 (0.8)	1650 (7.7)	<.01	750 (3.3)	679 (3.1)	443 (2.0)	<.01
Decreased TSH	159 (0.7)	190 (0.9)	235 (1.1)	<.01	237 (1.1)	154 (0.7)	193 (0.9)	<.01
Decreased free T4 and								
Elevated TSH	666 (2.8)	168 (0.8)	65 (0.3)	<.01	44 (0.2)	111 (0.5)	744 (3.3)	<.01
Normal TSH	2832 (12.0)	538 (2.5)	119 (0.6)	<.01	1011 (4.5)	1254 (5.7)	1224 (5.5)	<.01
Decreased TSH	132 (0.6)	47 (0.2)	20 (0.1)	<.01	97 (0.4)	45 (0.2)	57 (0.3)	<.01

Data represent the number of participants with abnormal free T4/TSH values at least once during any of the visits in the follow-up period.
Elevated free T4 indicates a value > 1.64 ng/dL; decreased free T4 indicates a value < 1.00 ng/dL; elevated TSH indicates a value > 4.95 μIU/mL; decreased TSH indicates a value < 0.45 μIU/mL, at least once during any of the visits in the follow-up period.
Normal free T4 was between 1.64 and 1.00 ng/dL; normal TSH was between 0.45 and 4.95 μIU/mL, throughout the follow-up period and during all visits.
Data are presented as numbers (%). The (%) indicates the percentage of participants in the total number of each of the 3 tertile groups.
Baseline free T4 level (low-normal [first tertile]: ≥ 1.00 ng/dL to < 1.22 ng/dL, middle-normal [second tertile]: ≥ 1.22 ng/dL to < 1.35 ng/dL, and high-normal [third tertile]: ≥ 1.35 ng/dL to ≤ 1.64 ng/dL) and the baseline TSH level (low-normal [first tertile]: ≥ 0.45 μIU/mL < 1.39 μIU/mL, middle-normal [second tertile]: ≥ 1.39 μIU/mL to < 2.16 μIU/mL, and high-normal [third tertile]: ≥ 2.16 μIU/mL to ≤ 4.95 μIU/mL).
Abbreviations: T4, thyroxine; TSH, thyrotropin.

although the previously reported rate was from subclinical hypothyroidism [10]. Taken together, this suggests that it is possible that low-normal free T4 levels are associated with future major depression development because these free T4 levels decrease further over time, possibly leading to hypothyroidism, which is reported to be associated with major depression. Similarly, those with high-normal free T4 levels at baseline tended to have increased free T4 levels over time, which is also consistent with a previous report [10].

Interestingly, based on the finding that the association between the development of major depression and low-normal free T4 was more obvious when we excluded participants who developed abnormal thyroid function at the follow-up visit, the development of major depression may be directly related to low-normal free T4 levels itself, not to the subsequent decrease in free T4 levels.

The question of an association between normal thyroid function (both free T4 and TSH are within the normal range) and depression is less well understood. There are a number of studies that address this issue in the general population, including genome-wide association studies on normal range TSH and free T4 levels [20], and a study on a possible modification by depressive symptoms in the association between thyroid hormones and cognitive performance [18]. Some studies examine the association with subclinical hypothyroidism, in which TSH is higher than normal [16, 17] or examine individuals with normal thyroid function, only discussing the ranges of TSH levels but not free T4 levels [19, 21-23]. Studies directly examining the association between depression and free T4 levels are even more limited; there is a report that higher free T4 levels are associated with a higher risk of depression [24]. However, this is a meta-analysis that includes 4 studies that examine the relationship between free T4 and depression, but since the only study that shows a significant difference is the one that shows a relationship between higher levels of free T4 and the current depressive syndrome [44], this result is not a finding on the risk of future development of depression. More research is needed to determine the association with the future onset of depression. Our study is the first to demonstrate the association between low-normal free T4 levels and the future development of depression in the general population with normal thyroid function, measuring both free T4 and TSH. Furthermore, repeated measurement of free T4 and TSH and subsequent long-term follow-up are also new data.

Table 5. Association between baseline free T4 and TSH levels and future abnormal free T4 and TSH levels

	Baseline free T4				Baseline TSH			
	Low-normal (n = 23 622)	Middle-normal (n = 21 951)	High-normal (n = 21 387)	*P* value	Low-normal (n = 22 539)	Middle-normal (n = 22 151)	High-normal (n = 22 270)	*P* value
At least twice								
Elevated free T4	19 (0.1)	48 (0.2)	479 (2.2)	<.01	239 (1.1)	177 (0.8)	130 (0.6)	<.01
Decreased free T4	1470 (6.2)	161 (0.7)	37 (0.2)	<.01	385 (1.7)	506 (2.3)	777 (3.5)	<.01
Elevated TSH	870 (3.7)	573 (2.6)	377 (1.8)	<.01	27 (0.1)	119 (0.5)	1674 (7.5)	<.01
Decreased TSH	148 (0.6)	138 (0.6)	163 (0.8)	.14	357 (1.6)	49 (0.2)	43 (0.2)	<.01
At least 3 times								
Elevated free T4	5 (0.0)	12 (0.1)	169 (0.8)	<.01	84 (0.4)	55 (0.3)	47 (0.2)	<.01
Decreased free T4	775 (3.3)	65 (0.3)	12 (0.1)	<.01	188 (0.8)	259 (1.2)	405 (1.8)	<.01
Elevated TSH	477 (2.0)	324 (1.5)	208 (1.0)	<.01	13 (0.1)	46 (0.2)	950 (4.3)	<.01
Decreased TSH	62 (0.3)	64 (0.3)	63 (0.3)	.77	161 (0.7)	15 (0.1)	13 (0.1)	<.01

Data represent the number of participants with abnormal free T4/TSH values at least twice or 3 times during any of the visits in the follow-up period.
Elevated free T4 indicates a value > 1.64 ng/dL; decreased free T4 indicates a value < 1.00 ng/dL; elevated TSH indicates a value > 4.95 μIU/mL; decreased TSH indicates a value < 0.45 μIU/mL, at least twice or 3 times during any of the visits in the follow-up period.
Normal free T4 was between 1.64 and 1.00 ng/dL; normal TSH was between 0.45 and 4.95 μIU/mL, throughout the follow-up period and during all visits.
Data are presented as numbers (%). The (%) indicates the percentage of participants in the total number of each of the 3 tertile groups.
Baseline free T4 level (low-normal [first tertile]: ≥ 1.00 ng/dL to < 1.22 ng/dL, middle-normal [second tertile]: ≥ 1.22 ng/dL to < 1.35 ng/dL, and high-normal [third tertile]: ≥ 1.35 ng/dL to ≤ 1.64 ng/dL) and the baseline TSH level (low-normal [first tertile]: ≥ 0.45 μIU/mL to < 1.39 μIU/mL, middle-normal [second tertile]: ≥ 1.39 μIU/mL to <2.16 μIU/mL, and high-normal [third tertile]: ≥ 2.16 μIU/mL to ≤ 4.95 μIU/mL).
Abbreviations: T4, thyroxine; TSH, thyrotropin.

It is reported that the risk of depression for hypothyroidism and subclinical hypothyroidism are 1.30 and 1.13, respectively [5]. The hazard ratio for developing depression in the low-normal free T4 group was 1.15 in this study, and it is considered to be as high as subclinical hypothyroidism, although the control groups are not exactly the same. Although low-normal free T4 was statistically associated with subsequent major depression, the magnitude of the impact was relatively mild compared to other risk factors. In fact, the adjusted HR of low-normal free T4 (1.15) was slightly smaller compared to those of underweight (adjusted HR 1.25), current smoking (adjusted HR 1.22), cancer (adjusted HR 1.37), hypertension (adjusted HR 1.33), diabetes (adjusted HR 1.75), and family history of major depression (adjusted HR 2.04). However, we believe that the additional new evidence from our study is still worthwhile for further research in this topic.

The clinical application of our study may be that people with serum low-normal free T4 concentrations should be carefully monitored, which may lead to early diagnosis and early treatment of major depression and contribute to reduce the development of major depression. Thyroid hormone replacement therapy may be associated with the prevention of depression [45]. It may be possible that early treatment of low-normal free T4 may contribute to the prevention of depression in the future.

The limitations of this study include the fact that it was conducted in a single center with a retrospective cohort design. Due to the relatively young median age of the cohort, these results may not be generalized to the older population, since there is a normal age-related increase in TSH levels. In this study, 1363 (2.0%) patients developed major depression, during the median follow-up of 1883 days. This 5-year incidence rate of 2.0% seems to be close to the previously reported lifetime prevalence of major depression in Japan (3%-7%) [46, 47]. It is also reported that the prevalence of major depression in Japan is much lower than in Western countries, and this is because patients with depression in Japan were less likely to seek medical treatment compared to patients in Western countries, due to a greater reluctance to report depression and use of mental health service [48]. The result of a 2.0% development of major depression is considered consistent with the previous reports in Japan but may be slightly less than these reports. This may be because in this study, the information of 51.8% of the patients was collected on a self-reported basis of the patients, this may have resulted in a greater underestimation due to hesitation to report major depression. Despite the possible underdiagnosis of major depression, our data showed a positive association. Another reason is that this cohort is relatively young, whereas major depression in Japan is reported to be more common in the elderly [46, 48]. In addition, the background of the participants may be another reason. As for the background of the participants in health checkups, 69.3% of those who underwent health checkups were participants in corporate health checkups. It has previously been reported that those who voluntarily underwent the health checkups at St. Luke's International Hospital have relatively higher socioeconomic status compared to the general population [49].

Table 6. Results of the multivariable Cox proportional hazard model for future depression (only participants who maintained a normal free T4 or TSH over the time course of the study)

	Adjusted hazard ratio (95% CI)
Thyroid function	
Baseline free T4	
Low-normal	**1.24 (1.07-1.43)**
Middle-normal	Reference
High-normal	1.16 (0.99-1.34)
Baseline TSH	
Low-normal	1.03 (0.89-1.19)
Middle-normal	Reference
High-normal	**1.18 (1.02-1.36)**
Age, years	**1.01 (1.01-1.02)**
Female	**1.20 (1.04-1.39)**
Alcohol consumption	
Abstainer	Reference
Occasional	**0.82 (0.69-0.97)**
Regular	**0.78 (0.68-0.90)**
Smoking status	
Never smoker	Reference
Former smoker	**1.21 (1.04-1.42)**
Current smoker	1.19 (0.99-1.43)
Exercise habits	
Almost none	Reference
1-2 times a week	**0.87 (0.75-0.99)**
3-5 times a week	0.88 (0.73-1.05)
Almost everyday	0.81 (0.65-1.01)
Body mass index	
Underweight	**1.26 (1.04-1.53)**
Normal weight	Reference
Overweight/obesity	0.93 (0.79-1.09)
Medical history, n (%)	
Cancer bearing	**1.38 (1.07-1.78)**
Hypertension	**1.35 (1.10-1.66)**
Diabetes	**1.82 (1.34-2.46)**
Dyslipidemia	1.21 (0.94-1.54)
Family history of depression, n (%)	**2.16 (1.32-3.55)**

Baseline free T4 level (low-normal [first tertile]: ≥ 1.00 ng/dL to < 1.22 ng/dL, middle-normal [second tertile]: ≥ 1.22 ng/dL to < 1.35 ng/dL, and high-normal [third tertile]: ≥ 1.35 ng/dL to ≤ 1.64 ng/dL) and the baseline TSH level (low-normal [first tertile]: ≥ 0.45 μIU/mL to < 1.39 μIU/mL, middle-normal [second tertile]: ≥ 1.39 μIU/mL to <2.16 μIU/mL, and high-normal [third tertile]: ≥ 2.16 μIU/mL to ≤ 4.95 μIU/mL).
Models were adjusted for participant age, gender, body mass index, social history (alcohol consumption, smoking status, and exercise habits), medical history of cancer, hypertension, diabetes, dyslipidemia, and family history of depression.
Abbreviations: T4, thyroxine; TSH, thyrotropin.
The numbers in bold represents that its *P* value is less than 0.05.

Regarding the diagnosis of major depression, among the 1363 patients who developed major depression, information on 706 (51.8%) patients was collected on a self-reported basis, which is the history of major depression diagnosed in the other hospitals. Because all clinical practices in Japan were provided under universal insurance, which requires diagnosis of the disease, in principle, all physicians are considered to make diagnoses in accordance with the guidelines. The information of the remaining 657 (48.2%) patients was collected from the electronic medical records at St. Luke's International Hospital. The diagnosis of these patients was made by a qualified psychiatrist in the hospital, considered to make diagnoses in accordance with the guidelines. In Japan, The Committee for Treatment Guidelines of Mood Disorders, Japanese Society of Mood Disorders published a Japanese guideline; Guidelines for Treatment of Depression [50, 51]. These guidelines are in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV or DSM-5. Because this study was not a prospective study, the accuracy of the diagnosis might not be perfect. However, each physician basically made a diagnosis according to the guidelines that comply with DSM-IV or DSM-5. In addition, variations in the diagnosis of major depression are considered as a random error, because both physician and participant would be considered not to pay special attention to their thyroid function within normal range. As a result, the variations might result in a nondifferential misclassification which produces bias toward the null. Therefore, although the accuracy of the diagnosis may not be fully guaranteed, our findings were considered to have certainty.

We excluded participants with a history of major depression, but we could not exclude participants who were taking antidepressants without a diagnosis of major depression and our dataset does not have the information on antidepressants, since the data was intended for health checkups rather than for this particular study. However, the number of participants taking antidepressants without the diagnosis of major depression would be limited, because all clinical practices in Japan were provided under universal insurance, which requires diagnosis of the disease. For other psychiatric disorders than major depression for which antidepressants could be prescribed, the reported lifetime prevalence of these disorders in Japan are not very high (eg, 8.1% for anxiety, 0.2% for bipolar, and 0.59% for schizophrenia) [52, 53].

In this study, our dataset does not have the information on other psychiatric disorders related to thyroid abnormalities, because the data was originally collected for health checkups rather than specifically for this study. According to the reported lifetime prevalence of anxiety, bipolar, and schizophrenia in Japan [52, 53], the impact of these disorders other than anxiety is considered limited, because the lifetime prevalences in Japan are relatively low. Regarding the impact of anxiety on the outcome, further research may be needed. Unfortunately, our dataset lacked the information on the participants taking medications that interfere with thyroid function tests (such as amiodarone, steroids, anti-epileptics etc.) or those with comorbidities that may have an impact on free T4 levels (such as eating disorders). However, we assumed that the number of such participants was limited because all our study population underwent voluntary health checkups without known major symptoms and had high socioeconomic status, expected to have healthier condition than general population. Even for the general population, the estimated prevalence of anorexia nervosa and bulimia nervosa in Japan was reported to be 4.79 and 1.02, respectively, per 100 000 females [54]. Thus, the effects of such conditions on our findings would be limited. Our dataset does not have the information on educational level and psychosocial factors, as the data was intended for the purpose of health checkups rather than this study. However, because these factors may not be related to thyroid function within normal limits, the effects may be limited.

The number of participants with decreased free T4 levels could be overestimated because we evaluated the number of those who experienced decreased free T4 levels at least once during the follow-up period, which could include people who recovered from decreased free T4 levels. Patients who developed abnormal values were recommended to visit any medical institution after health checkups. However, it is not known whether the patient initiated the treatment or not, as it is up to the patient whether or not to see the doctor, and diagnosis and treatment depend on the subsequent clinical course. We evaluated the number of participants who had both decreased free T4 and elevated TSH levels at least once each during any of the visits, but this number could be overestimated. Therefore, we also evaluated the number of participants with both decreased free T4 and elevated TSH levels in a single blood test at the same visit to identify participants with a confirmed diagnosis of overt hypothyroidism. We also performed the sensitivity analyses with the data of those who had abnormal levels at least twice and 3 times during the follow-up period.

Conclusion

In this large cohort study of the general population with normal thyroid function, we found an association between low-normal free T4 levels and future major depression. We reported that individuals with low-normal free T4 levels are at an increased risk of developing major depression, and follow-up analysis suggested that the development of major depression may be directly associated with low-normal free T4 levels itself, even if subsequent hormone levels are maintained within the normal ranges throughout, and not associated with a subsequent further decrease in free T4 levels. Our results suggest the potential for clinical application of low-normal free T4 levels as a new depression prevention target and that such patients should be closely monitored, which will contribute to a reduction in the development of major depression. Since prevention is an important part of reducing depression, even if there is no major need for treatment from an endocrine point of view, it is necessary to identify individuals with endocrinological risk factors other than the known conventional risk factors of major depression.

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Disclosures

The authors have no conflicts of interest to disclose.

Data Availability

Restrictions apply to the availability of all data analyzed during this study to preserve patient confidentiality. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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