Subclinical Hypothyroidism and Incident Depression in Young and Middle-Age Adults

Ji Sun Kim,[1,2]* Yiyi Zhang,[3]* Yoosoo Chang,[4,5,6] Seungho Ryu,[4,5,6] Eliseo Guallar,[3,5] Young-Chul Shin,[1,7] Hocheol Shin,[8] Se-Won Lim,[1,7] and Juhee Cho[3,4,5]

[1]Workplace Mental Health Institute, Kangbuk Samsung Hospital, Seoul 04514, Republic of Korea; [2]Department of Psychiatry, Soonchunhyang University Cheonan Hospital, Cheonan 31151, Republic of Korea; [3]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205; [4]Center for Cohort Study, Total Healthcare Center, Kangbuk Samsung Hospital, Seoul 04514, Republic of Korea; [5]Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences & Technology, Sungkyunkwan University, Seoul 06351, Republic of Korea; [6]Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, 03181 Republic of Korea; [7]Department of Psychiatry, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 03181, Republic of Korea; and [8]Department of Family Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul 03181, Republic of Korea

Background: The role of subclinical hypothyroidism in the development of depression remains controversial. We examined the prospective association between subclinical hypothyroidism and incident depressive symptoms.

Methods: We conducted a prospective cohort study of 220,545 middle-age adults without depression who had undergone at least two comprehensive health examinations between 1 January 2011 and 31 December 2014. Thyroid-stimulating hormone, free triiodothyronine (FT3), and free thyroxine (FT4) levels were measured using an electrochemiluminescent immunoassay. The study outcome was incident depressive symptoms, defined as a Center for Epidemiologic Studies-Depression score >16.

Results: During a median follow-up period of 2 years, incident depressive symptoms occurred in 7323 participants. The multivariable-adjusted hazard ratio for incident depressive symptoms comparing subclinical hypothyroid and euthyroid participants was 0.97 (95% confidence interval, 0.87 to 1.09). Similarly, among euthyroid participants (n = 87,822), no apparent association was found between thyroid hormone levels and an increased risk of incident depressive symptoms.

Conclusions: No apparent association was found between subclinical hypothyroidism and incident depressive symptoms in a large prospective cohort of middle-age men and women. (***J Clin Endocrinol Metab*** **103: 1827–1833, 2018)**

Subclinical hypothyroidism is highly prevalent among individuals with depression (1, 2), and thyroid hormone supplementation might increase the effectiveness of antidepressants in the treatment of depression (3, 4). Although a previous meta-analysis (5) showed a possible link of thyroid function with incident depression among middle-age men, the role of subclinical hypothyroidism in the development of depression remains controversial. Additionally, the effectiveness of thyroid hormone supplementation in the treatment of depression remains controversial, with some positive (4, 6, 7), but also, some null studies (8).

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Abbreviations: BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies-Depression; CI, confidence interval; FT3, free triiodothyronine; FT4, free thyroxine; HR, hazard ratio; TSH, thyroid-stimulating hormone.

Studies of the association between subclinical hypothyroidism and depressive symptoms have been mostly cross-sectional, and their findings were inconclusive, with some studies reporting a positive association (9, 10) and others no association (11–14). Although some cohort studies have evaluated the association between subclinical hypothyroidism and depression (15, 16), most of these studies focused on elderly populations, and evidence for an association between subclinical hypothyroidism and depression in young and middle-age populations is scarce.

In the present study, we examined the prospective association between subclinical hypothyroidism and incident depressive symptoms in a large cohort of middle-age apparently healthy men and women. We hypothesized that the incidence of depressive symptoms would be greater in those participants with subclinical hypothyroidism than in those with euthyroid function.

Materials and Methods

Study population

The Kangbuk Samsung Health Study is a cohort study of South Korean men and women aged ≥18 years who have undergone a comprehensive annual or biennial health examination at the Kangbuk Samsung Hospital Total Health Care Center Clinics in Seoul and Suwon, South Korea (17). Details of the study design have been described previously (17, 18). More than 80% of participants were employees of various companies and local governmental organizations and their spouses. In South Korea, the Industrial Safety and Health Law requires annual or biennial health screening examinations of all employees, offered free of charge. The remaining participants voluntarily purchased screening examinations at the health screening center.

The present analysis included participants who had undergone at least two comprehensive health examinations between 1 January 2011 and 31 December 2014 (n = 220,545; Fig. 1). We excluded participants who had clinically significant depressive symptoms [defined as a Center for Epidemiologic Studies-Depression (CES-D) score >16; n = 32,707], overt hypothyroidism, overt or subclinical hyperthyroidism (n = 24,249), or a history of cancer (n = 5476) at baseline. We further excluded those participants who had not completed the CES-D questionnaire (n = 30,933) and those who did not have thyroid hormone measurements (n = 34,425) or other covariate data (n = 549) available at baseline. The final sample size was 92,206 participants (62,047 men and 30,159 women). The institutional review board of the Kangbuk Samsung Hospital approved the study and waived the informed consent requirement, because we only used de-identified data routinely collected during health screening examinations.

Data collection

Baseline and follow-up examinations were conducted at the clinics of the Kangbuk Samsung Hospital Health Total Health Care Center in Seoul and Suwon. At each comprehensive health examination, we collected data on demographic characteristics, smoking status, alcohol consumption, physical activity, medical history, and medication use through standardized self-administered questionnaires. Smoking status was categorized as never, former, or current smoker. Current alcohol intake was categorized as none, moderate (≤30 g/d for men and ≤20 g/d for women), or high (>30 g/d for men and >20 g/d for women). The frequency of vigorous physical activity was categorized as 0, 1 to 3, or >3 times weekly.

Height, weight, and sitting blood pressure were measured by trained nurses. The body mass index was calculated as the weight in kilograms divided by the height in meters squared. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the current use of antihypertensive medications. Blood specimens were sampled

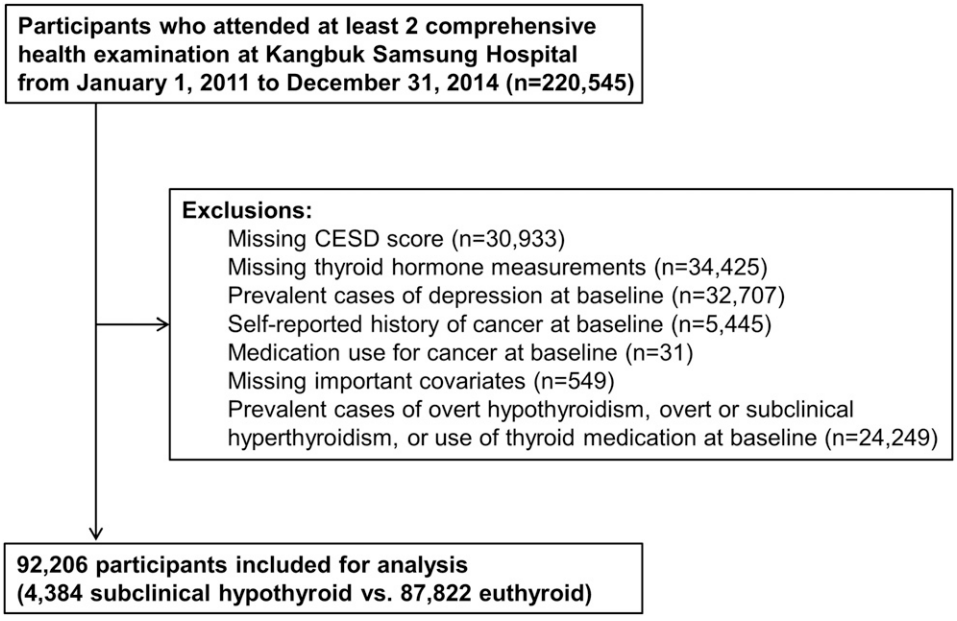

Figure 1. Study design flowchart.

from the antecubital vein after ≥10 hours of fasting. Diabetes was defined as a fasting serum glucose of ≥126 mg/dL, a self-reported history of diabetes mellitus, or the current use of antidiabetic medications.

Serum free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH) levels were measured using an electrochemiluminescent immunoassay (Roche, Tokyo, Japan) with a lower limit detection of 0.023 pg/dL, 0.26 pg/mL, and 0.005 μIU/mL, respectively. The coefficients of variation for low- and high-quality control specimens were 1.6% to 2.6% and 1.9% to 3.6% for FT4, 1.2% to 3.9% and 1.7% to 4.1% for FT3, and 2.1% to 3.2% and 2.2% to 3.1% for TSH, respectively. The normal range was 0.93 to 1.7 ng/dL for FT4, 2.0 to 4.4 pg/mL for FT3, and 0.25 to 5.0 μIU/mL for TSH. Subclinical hypothyroidism was defined as an FT4 within the normal range and TSH >5.0 μIU/mL. Although subclinical hypothyroidism is commonly defined using a TSH level of ≥4.5 μU/mL (19), we considered the ethnicity and age of the study participants (Asian midlife subjects) and defined euthyroid status using a TSH reference range of 0.25 to 5.0 μU/mL, as in previous studies of this type of population (20, 21). Euthyroid status was defined as FT4, FT3, and TSH levels within the corresponding normal range, no self-reported history of thyroid disease, and no current use of thyroid medications.

We used the Korean version of the CES-D scale (22, 23) to evaluate depressive symptoms. The development of clinically significant depressive symptoms was defined as a CES-D score >16. This cutoff has been established and validated in previous studies (24–26). Because stress could be an important confounder for the development of depressive symptoms, perceived stress was assessed using the stress questionnaire developed and validated for use in the general Korean population by the Korean Center for Disease Control (27).

Statistical analysis

The study endpoint was the development of incident depressive symptoms. Participants were followed up from the baseline visit to the visit for the development of depressive symptoms or the last available visit. Because incident depressive symptoms occurred at an unknown point between the visit of diagnosis and the previous visit, we used flexible parametric proportional hazards models to account for interval censored events (28). We first compared the risk of incident depressive symptoms among participants with subclinical hypothyroidism to that of euthyroid participants. We then assessed the dose-response relationship between thyroid hormone levels and depressive symptoms among euthyroid participants using two approaches. First, we categorized each thyroid hormone into quartiles. Second, we modeled thyroid hormones using restricted quadratic splines with knots at the 5th, 50th, and 95th percentiles of their sample distributions.

To control for potential confounders, we used three multivariable models with a progressive degree of adjustment. The first model was adjusted for age, sex, year of baseline examination, and study center. The second model was further adjusted for body mass index, smoking status, alcohol consumption, vigorous exercise, total cholesterol, high-density lipoprotein cholesterol, triglycerides, hypertension, and diabetes. The third model was further adjusted for stress level. As a sensitivity analysis, we divided subclinical hypothyroidism by TSH level (≤10 μU/mL and >10 μU/mL). We also performed a sensitivity analysis using repeated measurements of thyroid hormones to examine subclinical hypothyroidism status as a time-varying variable using pooled logistic regression. In addition, we performed prespecified subgroup analyses stratified by age (≤50 vs >50 years) and sex (male vs female). However, no statistically significant interaction was found (data not shown). All analyses were performed using STATA, version 12 (StataCorp LP, College Station, TX).

Results

The average age ± standard deviation of the study participants was 39.9 ± 6.7 years, and 32.7% were women (Table 1). The average levels of TSH, FT4, and FT3 were 2.2 ± 1.5 μlU/mL, 1.3 ± 0.2 ng/dL, and 3.2 ± 0.4 pg/mL, respectively. The Spearman correlation coefficients between thyroid hormone levels were −0.08 between TSH and FT3, −0.15 between TSH and FT4, and 0.44 between FT3 and FT4. The prevalence of subclinical hypothyroidism at baseline was 4.7%. Participants with subclinical hypothyroidism were slightly older, were more likely to be women, nonsmokers, and nonalcohol users, and to have a lower body mass index, lower stress level, and higher high-density lipoprotein cholesterol level.

During a median follow-up period of 2 years, incident depressive symptoms occurred in 7323 participants. The multivariable-adjusted hazard ratio (HR) for incident depressive symptoms comparing subclinical hypothyroid and euthyroid participants was 0.95 [95% confidence interval (CI), 0.85 to 1.06; Table 2]. When further adjusted for stress levels, the HR was 0.97 (95% CI, 0.87 to 1.09). Among the 4384 participants with subclinical hypothyroidism, 326 (7%) had TSH levels >10 μU/mL (range, 5 to 57 μU/mL; 5th to 95th percentile, 5 to 11 μU/mL). In the sensitivity analyses further dividing subclinical hypothyroidism by TSH level, similar associations were found with depression for those with TSH levels ≤10 and TSH >10 μU/mL (Supplemental Table 1). The conclusions were similar when we examined subclinical hypothyroidism status as a time-varying variable (Supplemental Table 2).

Similarly, among euthyroid participants (n = 87,822), no apparent association was found between thyroid hormone levels and an increased risk of incident depressive symptoms (Table 3, Fig. 2). In the fully adjusted models, the HRs for incident depressive symptoms comparing the highest and lowest quartiles were 0.92 (95% CI, 0.86 to 0.99; *P* for trend = 0.09) for TSH, 0.97 (95% CI, 0.90 to 1.05; *P* for trend = 0.62) for FT4, and 1.00 (95% CI, 0.92 to 1.08; *P* for trend = 0.76) for FT3.

Discussion

In the present large prospective cohort of middle-age men and women, we found no apparent association between

Table 1. Baseline Characteristics of Study Participants

Characteristic	Total (n = 92,206)	Euthyroid (n = 87,822)	Subclinical Hypothyroidism (n = 4384)	*P* Value
Age, y	39.9 ± 6.7	39.8 ± 6.6	40.7 ± 7.2	< 0.001
Sex				< 0.001
Female	30,159 (32.7)	28,045 (31.9)	2114 (48.2)	
Male	62,047 (67.3)	59,777 (68.1)	2270 (51.8)	
Study center				< 0.001
Seoul	52,528 (57.0)	50,253 (57.2)	2275 (51.9)	
Suwon	39,678 (43.0)	37,569 (42.8)	2109 (48.1)	
Body mass index, kg/m^2	23.6 ± 3.2	23.6 ± 3.2	23.3 ± 3.3	< 0.001
Total cholesterol, mg/dL	196.8 ± 34.1	196.8 ± 34.1	197.1 ± 34.5	0.63
HDL cholesterol, mg/dL	56.4 ± 14.3	56.3 ± 14.3	57.4 ± 14.5	< 0.001
Triglycerides, mg/dL	120.2 ± 81.4	120.3 ± 81.6	118.9 ± 78.4	0.26
Smoking				< 0.001
Never	34,702 (37.6)	32,551 (37.1)	2151 (49.1)	
Former	22,934 (24.9)	21,863 (24.9)	1071 (24.4)	
Current	23,026 (25.0)	22,510 (25.6)	516 (11.8)	
Unknown	11,544 (12.5)	10,898 (12.4)	646 (14.7)	
Alcohol				< 0.001
None	9105 (9.9)	8532 (9.7)	573 (13.1)	
Moderate	62,873 (68.2)	59,956 (68.3)	2917 (66.5)	
High	14,495 (15.7)	13,985 (15.9)	510 (11.6)	
Unknown	5733 (6.2)	5349 (6.1)	384 (8.8)	
Vigorous exercise, times/wk				< 0.001
0	52,097 (56.5)	49,560 (56.4)	2537 (57.9)	
1–3	31,418 (34.1)	30,035 (34.2)	1383 (31.5)	
>3	6097 (6.6)	5798 (6.6)	299 (6.8)	
Unknown	2594 (2.8)	2429 (2.8)	165 (3.8)	
Hypertension	10,668 (11.6)	10,184 (11.6)	484 (11.0)	0.26
Diabetes	3377 (3.7)	3237 (3.7)	140 (3.2)	0.09
Stress score	15.8 ± 5.5	15.8 ± 5.5	15.4 ± 5.2	< 0.001
TSH, μIU/mL	2.2 ± 1.5	2.0 ± 0.9	6.9 ± 2.8	< 0.001
FT4, ng/dL	1.3 ± 0.2	1.3 ± 0.2	1.2 ± 0.2	< 0.001
FT3, pg/mL	3.2 ± 0.4	3.2 ± 0.4	3.1 ± 0.4	< 0.001
CESD score	5.1 ± 4.1	5.1 ± 4.1	5.0 ± 4.2	0.50

Data presented as mean ± standard deviation or n (%).

Abbreviation: HDL, high-density lipoprotein.

subclinical hypothyroidism and incident depressive symptoms. The lack of association was similar across age and sex groups and was not affected by adjustment for potential confounders.

The association between subclinical hypothyroidism and depression is controversial. In a study of 123 participants with subclinical hypothyroidism and 123 euthyroid controls, the prevalence of depressive symptoms was approximately double among the subclinical hypothyroid group (10). Positive associations between subclinical hypothyroidism and depression were also observed in another study of 248 elderly outpatients with subclinical hypothyroidism and 203 euthyroid controls with nonthyroidal disease (9) and in a cross-sectional study of 323 elderly subjects (29). However, more recent studies have found no association between subclinical hypothyroidism and the lifetime development of depression in women (30, 31). Furthermore, two larger cross-sectional studies of community-dwelling elderly men

Table 2. HRs and 95% CIx for Incident Depressive Symptoms Associated With Subclinical Hypothyroidism (n = 92,206)

Subclinical Hypothyroidism at Baseline	Events/Total N	Model 1[a]	Model 2[b]	Model 3[c]
No	6960/87,822	Reference	Reference	Reference
Yes	363/4384	0.95 (0.86–1.06)	0.95 (0.85–1.06)	0.97 (0.87–1.09)

[a]Model 1 adjusted for age, sex, and study center.

[b]Model 2 adjusted further for body mass index, smoking status, alcohol consumption, vigorous exercise, total cholesterol, high-density lipoprotein cholesterol, triglycerides, hypertension, diabetes, and use of thyroid medications.

[c]Model 3 adjusted further for stress level.

Table 3. HRs and 95% CIs for Incident Depressive Symptoms Stratified by Baseline Thyroid Hormone Levels Among Euthyroid Participants (n = 87,822)

Thyroid Hormone	Model 1[a]	Model 2[b]	Model 3[c]
TSH (μIU/mL)			
Quartile 1	Reference	Reference	Reference
Quartile 2	0.93 (0.87–1.00)	0.94 (0.88–1.01)	0.93 (0.87–0.99)
Quartile 3	0.95 (0.89–1.02)	0.97 (0.90–1.03)	0.98 (0.91–1.05)
Quartile 4	0.90 (0.84–0.96)	0.92 (0.86–0.99)	0.92 (0.86–0.99)
P for trend	0.01	0.05	0.09
90th vs 10th percentile	0.93 (0.87–0.99)	0.95 (0.89–1.01)	0.96 (0.90–1.02)
FT4 (ng/dL)			
Quartile 1	Reference	Reference	Reference
Quartile 2	0.97 (0.91–1.03)	0.97 (0.91–1.04)	0.97 (0.91–1.04)
Quartile 3	1.00 (0.94–1.07)	1.01 (0.94–1.08)	0.99 (0.92–1.06)
Quartile 4	1.00 (0.93–1.07)	1.00 (0.93–1.08)	0.97 (0.90–1.05)
P for trend	0.82	0.70	0.62
90th vs 10th percentile	0.98 (0.92–1.05)	0.99 (0.92–1.06)	0.96 (0.90–1.03)
FT3 (pg/mL)			
Quartile 1	Reference	Reference	Reference
Quartile 2	0.99 (0.92–1.06)	0.99 (0.92–1.06)	0.98 (0.92–1.05)
Quartile 3	0.95 (0.88–1.03)	0.94 (0.87–1.01)	0.94 (0.87–1.02)
Quartile 4	1.03 (0.95–1.11)	0.99 (0.92–1.07)	1.00 (0.92–1.08)
P for trend	0.57	0.68	0.76
90th vs 10th percentile	1.01 (0.94–1.08)	0.97 (0.90–1.04)	0.98 (0.91–1.05)

[a]Model 1 adjusted for age, sex, year of baseline examination, and study center.

[b]Model 2 adjusted further for body mass index, smoking status, alcohol consumption, vigorous exercise, total cholesterol, high-density lipoprotein cholesterol, triglycerides, hypertension, and diabetes.

[c]Model 3 adjusted further for stress level.

(n = 3,932) (11) and of elderly patients in primary care (n = 5,865) (14) did not find an association between subclinical hypothyroidism and depression. Finally, a recent Danish population study (n = 8214) reported that the prevalence of depression was similar in euthyroid individuals and individuals with subclinical hypothyroidism (32).

Very few cohort studies have evaluated the association between subclinical hypothyroidism and depression. Two small prospective studies, one of 606 adults aged 70 to 82 years (19) and another of 599 subjects aged ≥85 years found no association between thyroid status and depressive symptoms (33). In addition, in 918 participants aged ≥65 years, subclinical hypothyroidism was not associated with depression (16). A recent retrospective cohort study from Korea with younger (mean age 46.9 years) and generally healthy participants found a positive association between TSH levels and the risk of depressive symptoms in women but not in men (34). In contrast to our analysis, that study used the Beck Depression Inventory (BDI) to assess for depressive symptoms. The BDI emphasizes the cognitive component (35)

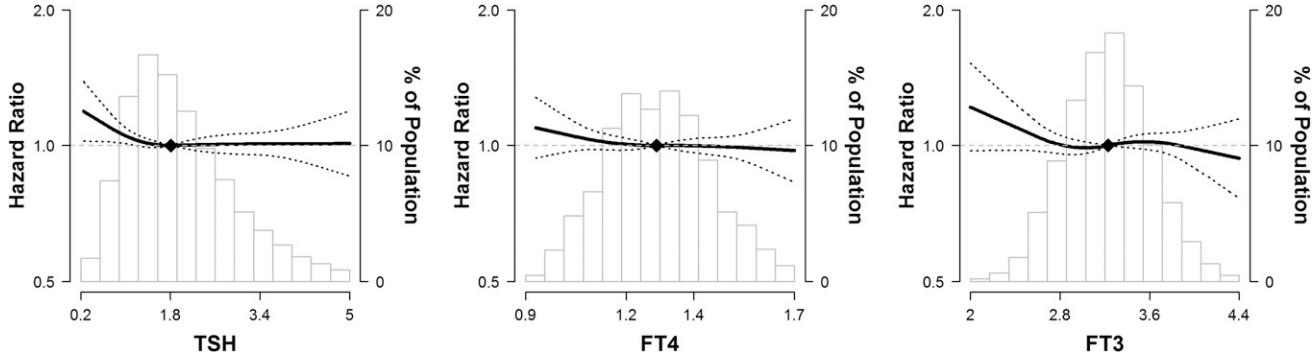

Figure 2. HRs for incident depressive symptoms stratified by thyroid hormone levels among euthyroid participants. Curves represent adjusted HRs (solid lines) and their 95% CIs (dashed lines) based on restricted quadratic splines for thyroid hormone levels at baseline, with knots at the 5th, 50th, and 95th percentiles of their sample distributions. The reference values (diamond dots) were set at the 50th percentile of the thyroid hormone distributions. Models were adjusted for age, sex, year of baseline examination, study center, body mass index, smoking status, alcohol consumption, vigorous exercise, total cholesterol, high-density lipoprotein cholesterol, triglycerides, hypertension, diabetes, and stress levels. Bars represent the frequency distribution of each thyroid hormone.

and the CES-D emphasizes the affective component of depression (23). The CES-D is generally recommended for primary screening of depression in community settings or in primary care (36) because it has shown greater sensitivity and specificity for the detection of depressive symptoms compared with the BDI (37), for both young (26, 38) and elderly (39) populations.

Several previous cross-sectional and cohort studies reporting positive associations between subclinical hypothyroidism and depression, especially the older studies, might have been limited by small sample sizes and/or selection bias. The larger studies, more recent and less prone to biases, have tended to report more negative results. Furthermore, some studies that reported a beneficial effect of thyroid hormone supplementation in the treatment of depression (4, 6, 7) were open label and potentially subject to a number of information and selection biases.

To the best of our knowledge, our study represents the largest prospective cohort study to evaluate the association between subclinical thyroid dysfunction and depressive symptoms. In addition, we included a detailed list of possible confounders such as age, sex, comorbidities, smoking, alcohol, and menopause status for female participants. Furthermore, to the best of our knowledge, ours is the first study to consider the role of stress in the association between thyroid function and depression. Stress might induce a wide variety of neurochemical and hormonal changes, including in the thyroid hormones (40–42). Simultaneously, repeated exposure to stressful events is also a potent risk factor for depression (43–45). In our analysis, however, further adjustment for stress did not materially change the results.

The present study had several limitations. We used self-reported questionnaires rather than structured clinical interviews for the identification of depressive symptoms. Also, although the CES-D questionnaires are well established for use in population studies and have good correlation with clinical diagnoses of depression (12), we could not exclude the possibility of misclassification of the outcome. Second, the follow-up period for our study was relatively short, although we were able to identify a large number of participants with incident depressive symptoms. It has been suggested that a mean follow-up duration of 3 years would be suitable to assess long-term changes in depressive symptoms (19). We have continued to follow up the participants, and future analyses with a longer follow-up period might provide additional insight into the longer term consequences of subclinical hypothyroidism. Our analysis did not exclude participants who developed thyroid disease during the follow-up, because this could mediate the development of depression. Future studies should identify the mechanisms involved in the development of depression associated with different thyroid hormone levels. Finally, our study consisted primarily of middle-age generally healthy men and women from Korea. Therefore, our findings might not be generalizable to other ethnic or age groups. Furthermore, most of our participants were workers employed by large companies, which could further limit the generalizability of our findings.

In conclusion, we found no apparent association between subclinical hypothyroidism and incident depressive symptoms in a large prospective cohort of middle-age men and women. Future prospective studies among other ethnic groups and with longer follow-up periods are needed to confirm our findings.

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Correspondence and Reprint Requests: Juhee Cho, PhD, Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul 06351, Republic of Korea. Email: jcho@skku.edu; or Se-Won Lim, MD, PhD, Department of Psychiatry, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea. E-mail: knappe@paran.com.

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References

1. Hage MP, Azar ST. The link between thyroid function and depression. *J Thyroid Res*. 2012;**2012**:590648.
2. Jain L, Arora H, Verma K, Singh H, Aswal S. A study of correlation between depression and hypothyroidism in female patients Delhi. *Psychiatry J*. 2013;**16**(2):283–287.
3. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*. 2008;**29**(1):76–131.
4. Monzani F, Del Guerra P, Caraccio N, Pruneti CA, Pucci E, Luisi M, Baschieri L. Subclinical hypothyroidism: neurobehavioral features and beneficial effect of L-thyroxine treatment. *Clin Investig*. 1993;**71**(5):367–371.
5. Williams MD, Harris R, Dayan CM, Evans J, Gallacher J, Ben-Shlomo Y. Thyroid function and the natural history of depression: findings from the Caerphilly Prospective Study (CaPS) and a meta-analysis. *Clin Endocrinol (Oxf)*. 2009;**70**(3):484–492.
6. Bono G, Fancellu R, Blandini F, Santoro G, Mauri M. Cognitive and affective status in mild hypothyroidism and interactions with L-thyroxine treatment. *Acta Neurol Scand*. 2004;**110**(1):59–66.
7. Gulseren S, Gulseren L, Hekimsoy Z, Cetinay P, Ozen C, Tokatlioglu B. Depression, anxiety, health-related quality of life, and disability in patients with overt and subclinical thyroid dysfunction. *Arch Med Res*. 2006;**37**(1):133–139.
8. Baldini IM, Vita A, Mauri MC, Amodei V, Carrisi M, Bravin S, Cantalamessa L. Psychopathological and cognitive features in subclinical hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry*. 1997;**21**(6):925–935.
9. Chueire VB, Silva ET, Perotta E, Romaldini JH, Ward LS. High serum TSH levels are associated with depression in the elderly. *Arch Gerontol Geriatr*. 2003;**36**(3):281–288.
10. Demartini B, Ranieri R, Masu A, Selle V, Scarone S, Gambini O. Depressive symptoms and major depressive disorder in patients affected by subclinical hypothyroidism: a cross-sectional study. *J Nerv Ment Dis*. 2014;**202**(8):603–607.

11. Almeida OP, Alfonso H, Flicker L, Hankey G, Chubb SA, Yeap BB. Thyroid hormones and depression: the Health in Men study. *Am J Geriatr Psychiatry*. 2011;**19**(9):763–770.
12. Dayan CM, Panicker V. Hypothyroidism and depression. *Eur Thyroid J*. 2013;**2**(3):168–179.
13. Pop VJ, Maartens LH, Leusink G, van Son MJ, Knottnerus AA, Ward AM, Metcalfe R, Weetman AP. Are autoimmune thyroid dysfunction and depression related? *J Clin Endocrinol Metab*. 1998;**83**(9):3194–3197.
14. Roberts LM, Pattison H, Roalfe A, Franklyn J, Wilson S, Hobbs FD, Parle JV. Is subclinical thyroid dysfunction in the elderly associated with depression or cognitive dysfunction? *Ann Intern Med*. 2006;**145**(8):573–581.
15. Manciet G, Dartigues JF, Decamps A, Barberger-Gateau P, Letenneur L, Latapie MJ, Latapie JL. The PAQUID survey and correlates of subclinical hypothyroidism in elderly community residents in the southwest of France. *Age Ageing*. 1995;**24**(3):235–241.
16. Park YJ, Lee EJ, Lee YJ, Choi SH, Park JH, Lee SB, Lim S, Lee WW, Jang HC, Cho BY, Woo JI, Kim KW. Subclinical hypothyroidism (SCH) is not associated with metabolic derangement, cognitive impairment, depression or poor quality of life (QoL) in elderly subjects. *Arch Gerontol Geriatr*. 2010;**50**(3):e68–e73.
17. Chang Y, Yun KE, Jung HS, Kim CW, Kwon MJ, Sung E, Ryu S. A1c and coronary artery calcification in nondiabetic men and women. *Arterioscler Thromb Vasc Biol*. 2013;**33**(8):2026–2031.
18. Zhang Y, Kim BK, Chang Y, Ryu S, Cho J, Lee WY, Rhee EJ, Kwon MJ, Rampal S, Zhao D, Pastor-Barriuso R, Lima JA, Shin H, Guallar E. Thyroid hormones and coronary artery calcification in euthyroid men and women. *Arterioscler Thromb Vasc Biol*. 2014; **34**(9):2128–2134.
19. Blum MR, Wijsman LW, Virgini VS, Bauer DC, den Elzen WP, Jukema JW, Buckley BM, de Craen AJ, Kearney PM, Stott DJ, Gussekloo J, Westendorp RG, Mooijaart SP, Rodondi N; PROSPER Study Group. Subclinical thyroid dysfunction and depressive symptoms among the elderly: a prospective cohort study. *Neuroendocrinology*. 2016;**103**(3-4):291–299.
20. Sarfo-Kantanka O, Kyei I, Sarfo FS, Ansah EO. Thyroid disorders in Central Ghana: the influence of 20 years of iodization. *J Thyroid Res*. 2017;**2017**:7843972.
21. Sowers M, Luborsky J, Perdue C, Araujo KL, Goldman MB, Harlow SD; SWAN. Thyroid stimulating hormone (TSH) concentrations and menopausal status in women at the mid-life: SWAN. *Clin Endocrinol (Oxf)*. 2003;**58**(3):340–347.
22. Kim MD, Hong SC, Lee CI, Kwak YS, Shin TK, Jang YH, Oh EH, Lee JW, Jeon BH, Hwang SE. Prevalence of depression and correlates of depressive symptoms for residents in the urban part of Jeju Island, Korea. *Int J Soc Psychiatry*. 2007;**53**(2):123–134.
23. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;**1**(3):385–401.
24. 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**(1):231–235.
25. de Jongh RT, Lips P, van Schoor NM, Rijs KJ, Deeg DJ, Comijs HC, Kramer MH, Vandenbroucke JP, Dekkers OM. Endogenous subclinical thyroid disorders, physical and cognitive function, depression, and mortality in older individuals. *Eur J Endocrinol*. 2011;**165**(4):545–554.
26. Cho MJ, Nam JJ, Suh GH. Prevalence of symptoms of depression in a nationwide sample of Korean adults. *Psychiatry Res*. 1998; **81**(3):341–352.
27. Lee ES, Shin HC, Lee JH, Yang YJ, Cho JJ, Ahn G, Yoon YS, Sung E. Development of the perceived stress inventory: a new questionnaire for Korean population surveys. *Korean J Fam Med*. 2015; **36**(6):286–293.
28. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med*. 2002;**21**(15):2175–2197.
29. Chueire VB, Romaldini JH, Ward LS. Subclinical hypothyroidism increases the risk for depression in the elderly. *Arch Gerontol Geriatr*. 2007;**44**(1):21–28.
30. Bell RJ, Rivera-Woll L, Davison SL, Topliss DJ, Donath S, Davis SR. Well-being, health-related quality of life and cardiovascular disease risk profile in women with subclinical thyroid disease—a community-based study. *Clin Endocrinol (Oxf)*. 2007;**66**(4): 548–556.
31. 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**(2):132–139.
32. Fjaellegaard K, Kvetny J, Allerup PN, Bech P, Ellervik C. Well-being and depression in individuals with subclinical hypothyroidism and thyroid autoimmunity—a general population study. *Nord J Psychiatry*. 2015;**69**(1):73–78.
33. Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frölich M, Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;**292**(21):2591–2599.
34. Kim EY, Kim SH, Rhee SJ, Huh I, Ha K, Kim J, Chang JS, Yoon DH, Park T, Ahn YM. Relationship between thyroid-stimulating hormone levels and risk of depression among the general population with normal free T4 levels. *Psychoneuroendocrinology*. 2015;**58**:114–119.
35. Santor DA, Zuroff DC, Ramsay JO, Cervantes P, Palacios J. Examining scale discriminability in the BDI and CES-D as a function of depressive severity. *Psychol Assess*. 1995;**7**(2):131–139.
36. Andriushchenko AV, Drobizhev MIu, Dobrovol'skiĭ AV. [A comparative validation of the scale CES-D, BDI, and HADS(d) in diagnosis of depressive disorders in general practice]. *Zh Nevrol Psikhiatr Im S S Korsakova*. 2003;**103**(5):11–18.
37. Whooley MA, Avins AL, Miranda J, Browner WS. Case-finding instruments for depression: two questions are as good as many. *J Gen Intern Med*. 1997;**12**(7):439–445.
38. Demirchyan A, Petrosyan V, Thompson ME. Psychometric value of the Center for Epidemiologic Studies Depression (CES-D) scale for screening of depressive symptoms in Armenian population. *J Affect Disord*. 2011;**133**(3):489–498.
39. Irwin M, Artin KH, Oxman MN. Screening for depression in the older adult: criterion validity of the 10-item Center for Epidemiological Studies Depression Scale (CES-D). *Arch Intern Med*. 1999; **159**(15):1701–1704.
40. Bauer M, Priebe S, Kürten I, Gräf KJ, Baumgartner A. Psychological and endocrine abnormalities in refugees from East Germany: part I. Prolonged stress, psychopathology, and hypothalamic-pituitary-thyroid axis activity. *Psychiatry Res*. 1994;**51**(1):61–73.
41. Lasser RA, Baldessarini RJ. Thyroid hormones in depressive disorders: a reappraisal of clinical utility. *Harv Rev Psychiatry*. 1997; **4**(6):291–305.
42. Mason J, Southwick S, Yehuda R, Wang S, Riney S, Bremner D, Johnson D, Lubin H, Blake D, Zhou G, et al. Elevation of serum free triiodothyronine, total triiodothyronine, thyroxine-binding globulin, and total thyroxine levels in combat-related posttraumatic stress disorder. *Arch Gen Psychiatry*. 1994;**51**(8):629–641.
43. Benjamin S, Prakasan P, Sreedharan S, Wright AD, Spener F. Pros and cons of CLA consumption: an insight from clinical evidences. *Nutr Metab (Lond)*. 2015;**12**(1):4.
44. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;**301**(5631):386–389.
45. Hammen C. Stress and depression. *Annu Rev Clin Psychol*. 2005; **1**(1):293–319.