

Suboptimal Thyroid Hormone Replacement Is Associated With Worse Hospital Outcomes

Matthew D. Ettleson,¹ Antonio C. Bianco,¹ Wen Wan,² and Neda Laiteerapong,²

¹Section of Endocrinology, Diabetes, and Metabolism, University of Chicago, Chicago, Illinois 60637, USA; and

²Section of General Internal Medicine, University of Chicago, Chicago, Illinois 60637, USA

Correspondence: Matthew D. Ettleson, MD, Section of Adult and Pediatric Endocrinology, Diabetes, and Metabolism, University of Chicago, 5841 S Maryland Ave, MC1027, Chicago, IL 60637, USA. Email: Matthew.Ettleson@uchospitals.edu.

Abstract

Context: Many patients with hypothyroidism receive suboptimal treatment that may affect hospital outcomes.

Objective: This work aimed to identify differences in hospital outcomes between patients with and without hypothyroidism.

Methods: A retrospective cohort study, using the propensity score-based fine stratification method to balance covariates, was conducted using a large, US-based, commercial claims database from January 1, 2008 to December 31, 2015. Participants included patients aged 64 years and younger who had a thyrotropin (TSH) level collected before a hospital admission. Covariates included age, sex, US region, type of admission, year of admission, and comorbidities. Exposure included clinical hypothyroidism, which was divided into 4 subgroups based on prehospitalization TSH level: low (TSH < 0.40 mIU/L), normal (TSH 0.40–4.50 mIU/L), intermediate (TSH 4.51–10.00 mIU/L), and high (TSH > 10.00 mIU/L). Main outcome measures included length of stay (LOS), in-hospital mortality, and readmission outcomes.

Results: A total of 43 478 patients were included in the final study population, of whom 8873 had a diagnosis of hypothyroidism. Those with a high prehospitalization TSH level had an LOS that was 1.2 days longer (95% CI, 1.1–1.3; $P = .003$), a 49% higher risk of 30-day readmission (relative risk [RR] 1.49; 95% CI, 1.20–1.85; $P < .001$), and a 43% higher rate of 90-day readmission (RR 1.43; 95% CI, 1.21–1.67; $P < .001$) compared to balanced controls. Patients with normal TSH levels exhibited decreased risk of in-hospital mortality (RR 0.46; 95% CI, 0.27–0.79; $P = .004$) and 90-day readmission (RR 0.92; 95% CI, 0.85–0.99; $P = .02$).

Conclusion: The results suggest suboptimal treatment of hypothyroidism is associated with worse hospital outcomes, including longer LOS and higher rate of readmission.

Key Words: hypothyroidism, quality of care, hospital outcomes, MarketScan

Abbreviations: DTE, desiccated thyroid extract; ESS, effective sample size; FS, fine stratification; ICD-9-CM, International Classification of Diseases, Ninth Revision; IQR, interquartile range; LOS, length of stay; PS, propensity score; RR, relative risk; TSH, thyrotropin.

Primary hypothyroidism occurs when the thyroid gland is unable to produce a sufficient level of thyroid hormone to maintain normal organ system functions. It is a common disease, with an estimated 7% of the US population taking thyroid hormone replacement and an additional 4% with undiagnosed disease (1, 2). The main tool for both diagnosis and monitoring of patients with primary hypothyroidism is the serum thyrotropin (TSH) level, which is inversely related to the level of circulating thyroid hormones. The standard of care for the treatment of primary hypothyroidism is levothyroxine, with the goal of maintaining the serum TSH level within the normal reference range (3–5). TSH levels that are persistently above the reference range often indicate undertreatment with thyroid hormone. Conversely, TSH levels below the reference range may indicate overtreatment.

Despite the general consensus, off-target serum TSH levels during thyroid hormone replacement have been found in more than one-third of patients with primary hypothyroidism in many observational studies (6–10). There are several potential challenges to being on target, including (but not limited to) inconsistent monitoring, irregular adherence to thyroid hormone therapy, body weight changes, pregnancy

status, impaired absorption due to interactions with other medications or food, and changes in formulations of thyroid hormone (11).

Sustained off-target serum TSH levels can lead to changes in thyroid hormone action throughout the body over time, which can result in serious harm to patients. Serum TSH levels both significantly above (> 10 mIU/L) and below (< 0.1 mIU/L) the normal reference range have been associated with increased risk of heart failure, stroke, and overall excess mortality (12–14). Despite the high proportion of patients with off-target TSH levels who are at risk for poor health outcomes, very little evidence-based guidance on monitoring patients taking levothyroxine is available (15). In this study, we explored whether the suboptimal treatment of primary hypothyroidism may lead to adverse hospitalization outcomes.

Materials and Methods

In this retrospective cohort study, we compared the hospital outcomes of patients with hypothyroidism and those without hypothyroidism. We analyzed inpatient, pharmaceutical, and laboratory insurance claims from patients

Received: 16 February 2022. Editorial Decision: 1 April 2022. Corrected and Typeset: 28 April 2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the Endocrine Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

admitted to the hospital with available thyroid function tests in the IBM MarketScan Commercial Claims and Encounters Database from 2008 to 2015. The year 2015 was the last year that mortality data were included in the database. This database consists of deidentified claims data from millions of privately insured patients younger than 65 years in the United States. The database includes demographic information (age, sex, US geographic region), clinical variables (including laboratory test results and International Classification of Diseases, Ninth Revision [ICD-9-CM] diagnosis codes associated with encounters), and pharmaceutical claims. This study was deemed to have exempt status by the University of Chicago Biological Sciences Division's Institutional Review Board.

Identification of Study Population and Index Admission

The clinical laboratory database for each year was examined to identify all patients aged 18 years and older who had at least one TSH result (LOINC code 3016-3) and a subsequent hospital admission the same year (Fig. 1). For those patients with multiple admissions and/or TSH values collected

in a given year, only the admission and TSH pair that represented the smallest time difference were included in the study. This admission was defined as the index admission, and the TSH value was defined as the prehospitalization TSH level. Only TSH levels that were collected at least 7 days before admission were included, to minimize the potential effect of nonthyroidal illness on the prehospitalization TSH level. If a patient was admitted in multiple years, only the first admission was included in the study.

The study population was subject to several exclusion criteria. All patients with an admission codiagnosis of thyroid cancer, hyperthyroidism, hypopituitarism, or pregnancy were excluded. Only patients with admissions categorized as "surgical" or "medical" were included to limit the potential mediating effect of other admission types (eg, maternity, psychiatric) on outcomes. Owing to a high frequency of insurance disenrollment from year to year, annual databases were not linked. Thus, only readmissions that occurred in the same year as the index admission were counted. Because 90-day readmission was an outcome, only patients with an admission before September 30 (regardless of year) were included to minimize missing data (Fig. 2).

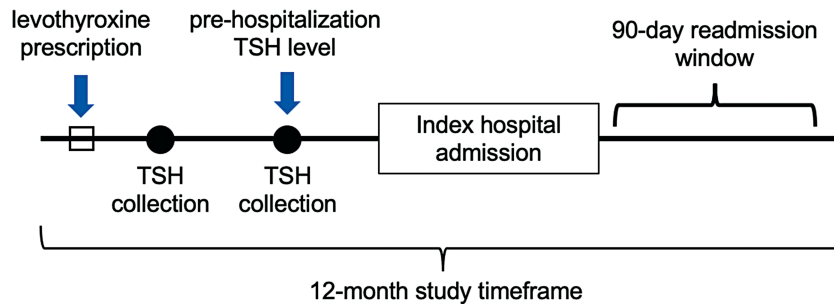


Figure 1. Diagram of the selection of prehospitalization thyrotropin (TSH) level, the index hospital admission and the readmission window. The TSH level and hospital admission pair that represented the smallest time difference were selected as the prehospitalization TSH level and the index hospital admission (with a minimum time difference of 7 days). The horizontal line represents the 12-month time frame of the study period.

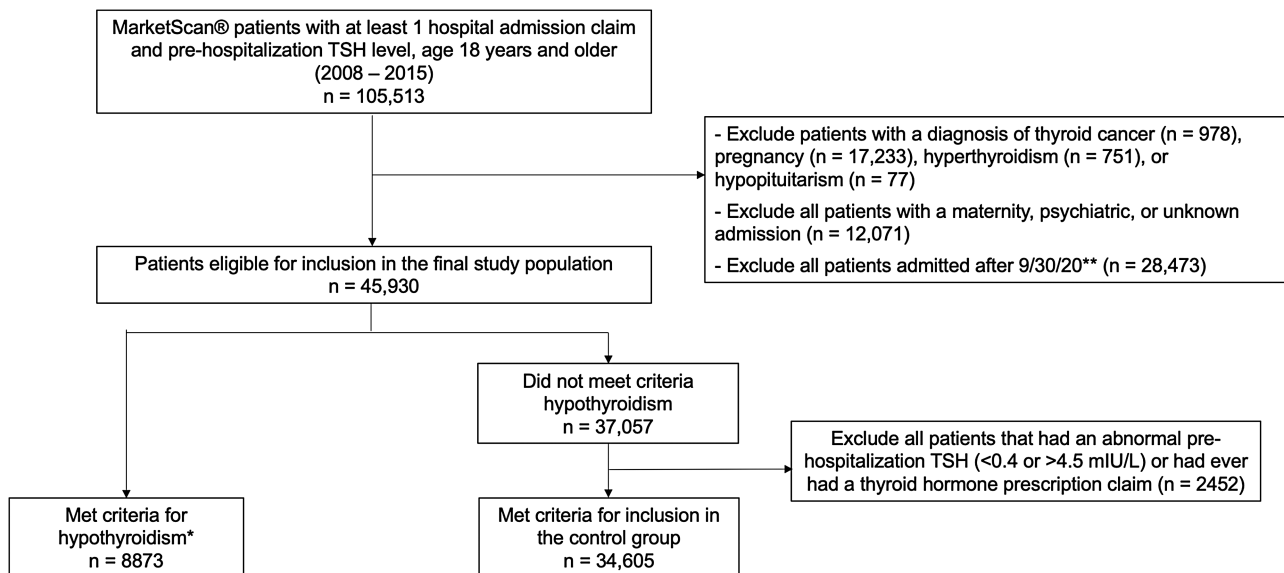


Figure 2. Flowchart of study population selection of patients with and without hypothyroidism. *Inclusion criteria for hypothyroidism: 1) at least 1 prescription claim for levothyroxine prior to the admission date; 2) a prehospitalization thyrotropin (TSH) value greater than 10.00 mIU/L; or 3) a diagnosis of hypothyroidism during the index hospital admission (confirmed by presence of diagnosis code for acquired hypothyroidism [International Classification of Diseases, Ninth Revision; ICD-9-CM 244.x] or chronic lymphocytic thyroiditis [ICD-9-CM 245.2]). 20** represents any single year from 2008 to 2015.

Primary Exposure and Thyrotropin Subgroups

The primary exposure of this study was primary hypothyroidism. All patients included in the analysis were considered to have hypothyroidism if they met at least 1 of 3 inclusion criteria: 1) at least 1 prescription claim for levothyroxine prior to the admission date during the same calendar as the hospital admission; 2) a prehospitalization TSH value greater than 10.00 mIU/L; or 3) a diagnosis of hypothyroidism during the index hospital admission (confirmed by the presence of the diagnosis code for acquired hypothyroidism [ICD-9-CM 244.x] or chronic lymphocytic thyroiditis [ICD-9-CM 245.2]). Prescription claims used to assign patients to the hypothyroidism group were limited to levothyroxine to exclude patients prescribed other types of thyroid hormone (eg, liothyronine, desiccated thyroid extract) for diagnoses other than hypothyroidism. The number of patients prescribed other types of thyroid hormone in addition to levothyroxine are included in Table 1.

All patients meeting at least 1 criterion for having hypothyroidism were divided into 4 subgroups based on prehospitalization TSH level: low (TSH < 0.40 mIU/L), normal (TSH 0.40-4.50 mIU/L), intermediate (TSH 4.51-10.00 mIU/L), and high (TSH > 10.00 mIU/L). If the patient did not meet any of these criteria for having hypothyroidism, they were considered for inclusion in the control group. Patients were excluded from the control group if they had a prehospitalization TSH value of less than 0.40 or greater than 4.50 mIU/L to exclude those with possible transient suppression or elevation of TSH levels or subclinical hypothyroidism or hyperthyroidism. In addition, patients were excluded from the control group if they had ever received a prescription for any thyroid hormone in the years before or after the year of hospital admission.

Hospital Outcomes and Covariates of Interest

The study outcomes were hospital length of stay (LOS), in-hospital mortality, and hospital readmission rate. Readmission was defined as any hospitalization that occurred within 30 and 90 days of discharge from the index admission. Data on demographics (age, sex, US geographic region) and admission type (medical or surgical) were collected for each patient. Data on the presence of select comorbidities (myocardial infarction, congestive heart failure, stroke, rheumatologic disease, liver disease, diabetes mellitus [type 1 or 2], chronic kidney disease, peptic ulcer disease, and malignancy) were collected. These comorbidities were selected from those included in the Charlson comorbidity index and most likely to be associated clinically with the presence of hypothyroidism. The presence of each admission codiagnosis was determined using the ICD-9-CM codes outlined in the method proposed by Deyo et al (16) to estimate the Charlson comorbidity index with data from administrative databases.

Statistical Methods

For this observational study, to minimize the degree of model dependence on the statistical estimation of causal effects, we used the propensity score-based fine stratification method (FS) to balance the covariates between the hypothyroidism and nonhypothyroidism (control) groups (17-19). We stratified the analysis by TSH subgroup. For each subgroup, we performed the FS method to estimate the average treatment effect on the treated (ie, patients with hypothyroidism). Here,

we consider the population with hypothyroidism to be a vulnerable population that requires treatment, and the population without hypothyroidism does not require treatment. The appropriateness of treatment is captured in the categorization of TSH subgroups. To perform FS, first, propensity scores (PS) were estimated as the predicted probability of having hypothyroidism for all given covariates of a study participant using

Table 1. Patient characteristics and hospital outcomes in those with and without hypothyroidism before covariate balancing

Characteristics and outcomes	With hypothyroidism	Without hypothyroidism	P
	n = 8873	n = 34 605	
Age, median (IQR), y	55 (48-60)	52 (43-58)	< .001
Female, %	81.0	61.5	< .001
Region of US, %			< .001
Northeast	26.1	29.9	
North Central	20.6	15.0	
South	46.5	50.1	
West	6.8	5.1	
Unknown	0.1	0.0	
Admission type, %			
Medical, vs surgical	45.5	44.9	.28
Comorbidities, %			
Myocardial infarction	4.3	4.7	.10
Congestive heart failure	4.9	4.6	.26
Stroke	5.5	5.6	.75
Rheumatologic disease	3.3	2.0	< .001
Liver disease	1.5	1.4	.74
Diabetes mellitus	23.3	21.8	.003
Chronic kidney disease	4.2	3.7	.04
Peptic ulcer disease	0.9	1.1	.12
Malignancy	9.4	9.9	.15
Thyroid hormone type ^a , No.			–
Levothyroxine	6874	–	
Liothyronine	189	–	
DTE	117	–	
Time from TSH draw to admission			
Days, median (IQR)	56 (27, 102)	63 (29, 112)	< .001
Days, mean (SD)	70.6 (54.1)	76.9 (57.7)	< .001
Hospital outcomes			
Length of stay			
Days, median (IQR)	3 (2, 4)	2 (1, 4)	.06
Days, mean (SD)	3.5 (4.3)	3.6 (4.5)	.52
In-hospital mortality, %	0.4	0.6	.01
Readmission rate, %			
30 d	8.3	8.0	.45
90 d	13.3	13.7	.25

Abbreviations: DTE, desiccated thyroid extract; IQR, interquartile range; PS, propensity score; TSH, thyrotropin.

^aOnly patients with at least one prescription for levothyroxine met inclusion criteria for the hypothyroidism group. The numbers of patients with additional thyroid hormone prescription types are included in the table.

logistic regression. Covariates included age, sex, region, admission type, and all comorbidities individually. Second, we excluded individuals whose PS were in the nonoverlapping PS regions. Third, based on PS levels, we stratified all participants in the hypothyroidism group into a relatively large number of equally sized PS strata. Fourth, we assigned individuals in the control group to these strata based on their PS. Last, we assigned weights to participants per stratum based on the formula (17). The number of PS strata we chose was 20, indicating the stratification width of about 0.05 on average, which is smaller than the recommended maximum PS width of 0.2 (20). We used the “MatchIt” R package to run the FS method. Because patients within nonoverlapping PS regions were excluded, a control pseudo-group was created for each subgroup analysis (no hypothyroidism patients were excluded). See Tables 2 to 5 for pseudo-group effective sample sizes.

Continuous and categorical variables were compared using the Wilcoxon rank sum test and chi-square test with the Rao-Scott second-order correction, respectively. LOS was modeled via Poisson regression to account for its nonnormal distribution. In-hospital mortality and readmissions were modeled via logistic regression to account for the possibility of a balanced covariate confounding the effect of hypothyroidism on the hospital outcomes. We performed both univariate analyses (treatment effect without adjusting any covariates) and multivariable analyses (with adjusting covariates), which were conducted with weights using the “Survey” R package.

Table 2. Patient characteristics of those in the low thyrotropin subgroup and matched controls after balancing covariates by the fine stratification method

Characteristics	Low TSH subgroup n = 1282	Control group ESS = 21379	P
Age, median (IQR), y	55 (48-60)	55 (47-60)	.573
Female, %	85.3	85.1	.80
Region of US, %			≥ .999
Northeast	27.1	27.1	
North Central	21.1	21.0	
South	45.4	45.3	
West	6.3	6.4	
Unknown	0.2	0.1	
Admission type, %			
Medical, vs surgical	42.7	42.8	.92
Comorbidities, %			
Myocardial infarction	4.1	4.0	.98
Congestive heart failure	3.4	3.5	.93
Stroke	5.5	5.4	.97
Rheumatologic disease	3.5	3.5	.98
Liver disease	1.2	1.2	.98
Diabetes mellitus	20.0	20.1	.98
Chronic kidney disease	3.3	3.3	.99
Peptic ulcer disease	0.7	0.7	.94
Malignancy	8.6	8.7	.90

Low TSH subgroup: TSH < 0.4 mIU/L. Abbreviations: ESS, effective sample size; IQR, interquartile range; TSH, thyrotropin.

Inclusion of each covariate in multivariable analyses was based on statistical significance ($P < .05$) in the univariate analysis. Odds ratios were calculated through logistic regression and then corrected to relative risk (RR) using the method by Zhang and Yu (21) for an outcome whose incidence rate was greater than 10%. Data manipulation and analysis were completed using statistical software SAS (version 9.4) and R (version 4.1.2).

Results

A total of 43 478 patients were included in the final study population, of whom 8873 met the criteria for having primary hypothyroidism (Fig. 2). A total of 4770 (53.8%) patients had a prescription claim for levothyroxine and the diagnosis of hypothyroidism was associated with the admission claim. Of the remaining patients, 2104 (23.7%) had a levothyroxine prescription only and 1938 (21.8%) had a diagnosis of hypothyroidism only. The final 61 patients (0.7%) that met criteria for having hypothyroidism by having a prehospitalization TSH value greater than 10.00 mIU/L had a mean TSH value of 19.8 mIU/L. The median length of time between TSH collection and hospital admission was 56 days in the hypothyroidism group and 63 days in the control group. In the unbalanced univariate analysis, patients with hypothyroidism were older (median age, 55 years vs 52; $P < .001$), more likely to be women (81.0% vs 61.5%; $P < .001$), and had higher rates of rheumatologic disease,

Table 3. Patient characteristics of those in the normal thyrotropin subgroup and matched controls after balancing covariates by the fine stratification method

Characteristics	Normal TSH subgroup n = 5860	Control group ESS = 23 946	P
Age, median (IQR), y	55 (48-60)	55 (48-60)	.94
Female, %	82.5	82.1	.44
Region of US, %			≥ .999
Northeast	26.6	26.6	
North Central	20.7	20.9	
South	45.8	45.6	
West	6.9	6.9	
Unknown	0.1	0.1	
Admission type, %			
Medical, vs surgical	44.5	44.9	.59
Comorbidities, %			
Myocardial infarction	4.2	4.2	≥ .999
Congestive heart failure	4.2	4.2	.89
Stroke	5.3	5.3	.97
Rheumatologic disease	3.3	3.3	≥ .999
Liver disease	1.3	1.3	.99
Diabetes mellitus	23.4	23.7	.72
Chronic kidney disease	4.0	4.1	.97
Peptic ulcer disease	1.0	1.0	.90
Malignancy	9.4	9.3	.80

Normal TSH subgroup: TSH 0.40-4.50 mIU/L. Abbreviations: ESS, effective sample size; IQR, interquartile range; TSH, thyrotropin.

diabetes mellitus, and chronic kidney disease compared to the control group (see Table 1). Of note, patients with hypothyroidism had a lower in-hospital mortality rate (0.4% vs 0.6%; $P = .01$). The groups did not differ on average LOS or 30-day or 90-day readmission rates.

Univariate Analysis of Balanced Thyrotropin Subgroups and Control Groups

The patient characteristics of each TSH subgroup and the corresponding balanced control group are summarized and compared in Tables 2 to 5. The distributions of PS in each TSH subgroup and the control groups before and after covariate balancing are shown in Fig. 3. As a result of the FS protocol, the PS distribution of the “post-match” control group in each subgroup analysis mirrors the distribution of the corresponding hypothyroidism subgroup. In all cases, there were no significant differences in covariates (age, sex, region, admission type, and comorbidities) between each hypothyroidism subgroup and the corresponding balanced control group. The average prehospitalization TSH levels of each subgroup are presented in Table 6.

In general, hospital outcomes differed according to prehospitalization TSH level (Table 7). In the low TSH subgroup, there were no differences identified in LOS, in-hospital mortality, or readmission rates. In the normal TSH subgroup, the rate of in-hospital mortality was lower in those with hypothyroidism compared to the balanced

controls (0.3% vs 0.6%; $P = .004$). Also, the rate of 90-day readmissions was lower in the normal TSH subgroup compared to controls (12.6% vs 13.7%; $P = .004$). In the intermediate TSH subgroup, there were no differences in outcomes compared to the balanced control group. Finally, in the high TSH group, patients with hypothyroidism had a longer mean LOS (4.4 vs 3.7 days; $P = .005$) and higher 30- and 90-day readmission rates (13.3% vs 9.0%; $P < .001$ and 22.1% vs 15.7%; $P < .001$, respectively) compared to balanced controls.

Multivariable Analysis of Balanced Thyrotropin Subgroups and Control Groups

The results of the multivariable analysis were similar to those of the univariate analysis (Table 8). Adjustment for all comorbidities were included in each subgroup multivariable analysis. In the low TSH subgroup, having hypothyroidism was not associated with any differences in hospital outcomes compared to the balance control groups. In the normal TSH subgroup, hypothyroidism was associated with a lower risk of in-hospital mortality (RR 0.46; 95% CI, 0.27-0.79; $P = .004$) and 90-day readmission (RR 0.92; 95% CI, 0.85-0.99; $P = .02$). In the intermediate TSH subgroup, no differences in hospital outcomes were observed. Finally, those in the high TSH subgroup had a longer LOS (+1.2 days (95% CI, 1.1-1.3; $P = .003$), and higher risk of 30-day readmission (RR 1.49; 95% CI, 1.20-1.85; $P < .001$) and 90-day

Table 4. Patient characteristics of those in the intermediate thyrotropin subgroup and matched controls after balancing covariates by the fine stratification method

Characteristics	Intermediate TSH subgroup n = 1183	Control group ESS = 28 236	P
Age, median (IQR), y	54 (47-59)	54 (46-60)	.78
Female, %	72.6	72.3	.81
Region of US, %			≥ .999
Northeast	23.9	24.1	
North Central	20.3	20.6	
South	49.4	48.8	
West	6.3	6.4	
Unknown	0.1	0.1	
Admission type, %			
Medical, vs surgical	49.1	49.5	.80
Comorbidities, %			
Myocardial infarction	4.9	4.9	.99
Congestive heart failure	6.8	6.9	.82
Stroke	5.4	5.4	≥ .999
Rheumatologic disease	3.2	3.3	.87
Liver disease	2.1	2.2	.90
Diabetes mellitus	24.1	24.1	.97
Chronic kidney disease	4.5	4.5	.93
Peptic ulcer disease	0.5	0.6	.54
Malignancy	9.6	9.5	.95

Intermediate TSH subgroup: TSH 4.51-10.00 mIU/L. Abbreviations: ESS, effective sample size; IQR, interquartile range; TSH, thyrotropin.

Table 5. Patient characteristics of those in the high thyrotropin subgroup and matched controls after balancing covariates by the fine stratification method

Characteristics	High TSH subgroup n = 548	Control group ESS = 24 410	P
Age, median (IQR), y	54 (45-59)	54 (46-60)	.73
Female, %	72.1	72.6	.79
Region of US, %			≥ .999
Northeast	23.0	22.7	
North Central	18.8	18.9	
South	50.7	50.8	
West	7.5	7.5	
Unknown	0.0	0.0	
Admission type, %			
Medical, vs surgical)	54.9	55.1	.93
Comorbidities, %			
Myocardial infarction	4.7	4.7	.95
Congestive heart failure	11.5	10.9	.65
Stroke	8.6	8.5	.94
Rheumatologic disease	2.7	2.8	.97
Liver disease	2.4	2.3	.93
Diabetes mellitus	27.2	27.2	.99
Chronic kidney disease	7.1	6.7	.71
Peptic ulcer disease	0.7	0.7	.98
Malignancy	11.1	11.1	.99

High TSH subgroup: TSH greater than 10.00 mIU/L. Abbreviations: ESS, effective sample size; IQR, interquartile range; TSH, thyrotropin.

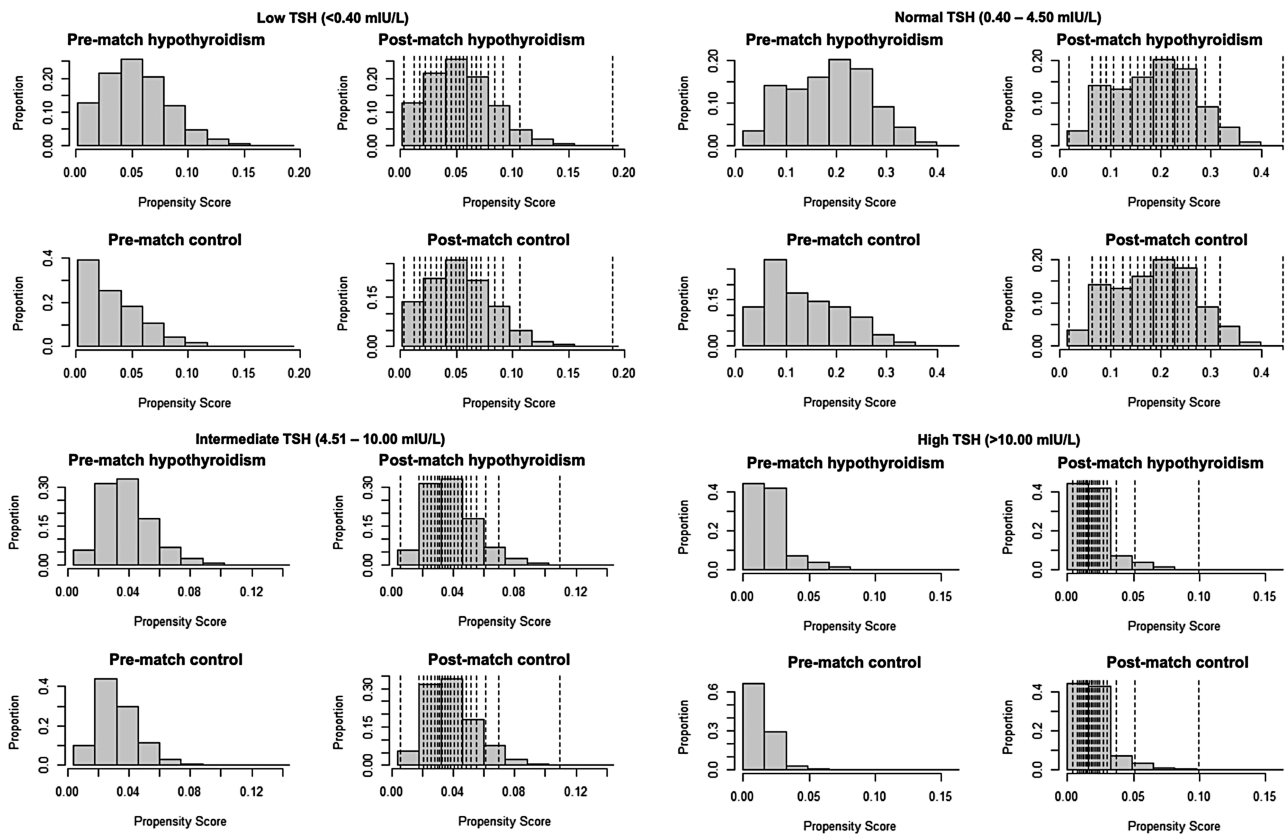


Figure 3. Distribution of propensity scores pre match and post match in each thyrotropin (TSH) subgroup and the control group. Dotted lines distinguish the 20 strata that were generated during the match process to optimize the balancing of covariates.

readmission (RR 1.43; 95% CI, 1.21-1.67; $P < .001$) compared to balanced controls.

Discussion

We found several differences in hospital outcomes in patients with and without primary hypothyroidism, primarily in those with high (> 10.00 mIU/L) TSH levels before hospitalization. Those patients were more likely to have a longer LOS and more likely to be readmitted after hospital discharge compared to balanced controls without hypothyroidism. Conversely, those with a normal prehospitalization TSH level (0.40-4.50 mIU/L) had a decreased risk of in-hospital mortality and readmission within 30 days of discharge. These results were similar across both univariate and multivariable analyses.

There are likely multiple causes underlying worse hospital outcomes in those with hypothyroidism and higher than normal TSH levels. Those with undertreatment of or undiagnosed hypothyroidism may be more likely to have suboptimal treatment of other medical conditions that contribute to worse hospital outcomes. An elevated TSH level may be a sign of either poor adherence to or poor absorption of daily thyroid hormone therapy, which may extend to other regular medical therapies. Low thyroid hormone may also more directly influence hospital outcomes, which may be suggested by the difference in outcomes between those with intermediate and high prehospitalization TSH levels. In general, the systemic effects of hypothyroidism on multiple organ systems may contribute to cardiovascular, respiratory,

and/or cognitive decompensation in the hospitalized patient (22-24). Specifically, clinical hypothyroidism has been associated with several perioperative complications, including intraoperative hypotension, heart failure, and minor gastrointestinal and neuropsychiatric postoperative complications (25). Several studies have identified an association between hypothyroidism and atrial fibrillation following cardiac surgery, which may contribute to worse hospital outcomes (26-28). Hypothyroidism may also put patients at risk for intraoperative bleeding, which could delay discharge or increase the risk of hospital readmission (29, 30).

However, the reasons why patients with a normal prehospitalization TSH level may have improved hospital outcomes compared to those without hypothyroidism are less clear. It is unlikely that thyroid hormone replacement would provide an advantage over endogenous thyroid hormone production in hospital outcomes. In-range TSH values may be a surrogate for regular health care and adherence to medical therapy, which likely leads to better hospital outcomes. We have previously shown in a study of the National Health and Nutrition Examination Survey that lack of access to routine health care is associated with suboptimal treatment of hypothyroidism (31). It is important to recognize that other factors that are difficult to determine from the data available from insurance claims, such as the severity of the medical or surgical problem leading to hospital admission, may be playing a role in this observation, as well. It is also noteworthy that although no adverse hospital outcomes were associated with low TSH levels in this study, adverse cardiovascular and fracture outcomes have both been observed in patients on thyroid

Table 6. Average prehospitalization thyrotropin values of each hypothyroidism subgroup

Average TSH value	TSH subgroup			
	Low ^d	Normal	Intermediate	High
	(n = 1282)	(n = 5860)	(n = 1183)	(n = 548)
Mean (SD)	0.14 (0.12)	2.00 (1.08)	6.17 (1.43)	28.52 (26.18)
Median (IQR)	0.10 (0.03-0.24)	1.83 (1.11-2.80)	5.70 (5.00-7.15)	17.25 (12.44-33.08)

Low subgroup: TSH less than 0.40 mIU/L. Normal subgroup: TSH 0.40-4.50 mIU/L. Intermediate subgroup: TSH 4.51-10.00 mIU/L. High subgroup: TSH greater than 10.00 mIU/L. All TSH value units are mIU/L.

Abbreviation: TSH, thyrotropin.

^dOf the 1282 patients in the low subgroup, 122 patients had a prehospitalization TSH value less than .01 mIU/L.

Table 7. Univariate analysis of hospital outcomes after balancing covariates, stratified by thyrotropin subgroup before admission

Outcomes	TSH subgroup											
	Low	Control	P	Normal	Control	P	Inter	Control	P	High	Control	P
(n/ ESS)	(1282)	(21 379)		(5860)	(23 946)		(1183)	(28 236)		(548)	(24 410)	
Length of stay												
Median (IQR)	2 (2-4)	2 (2-4)	.88	2 (2-4)	3 (2-4)	.09	3 (2-4)	3 (2-4)	.23	3 (2-5)	3 (2-4)	< .001
Mean (SD)	3.5 (5.2)	3.5 (4.1)	.54	3.5 (4.1)	3.6 (4.2)	.07	3.7 (3.7)	3.6 (4.3)	.74	4.4 (5.4)	3.7 (4.4)	.005
In-hospital mortality	0.2	0.5	.15	0.3	0.6	.004	0.7	0.6	.78	1.1	0.7	.27
30-d readmission	7.8	7.6	.80	7.8	7.8	.84	9.0	8.3	.45	13.3	9.0	< .001
90-d readmission	12.16	13.3	.50	12.6	13.7	.03	12.9	14.5	.14	22.1	15.7	< .001

Length of stay in days, presented as median and mean. All other outcomes presented as percentages. Low subgroup: TSH less than 0.40 mIU/L. Normal subgroup: TSH 0.40-4.50 mIU/L. Intermediate subgroup: TSH 4.51-10.00 mIU/L. High subgroup: TSH greater than 10.00 mIU/L. P values determined by Wilcoxon rank sum and t tests (length of stay) and chi-square test with the Rao-Scott second-order correction.

Abbreviations: ESS, effective sample size of control group; Inter, Intermediate; n, number of patients in TSH subgroup; TSH, thyrotropin.

Table 8. Multivariable analysis of hospital outcomes after balancing covariates, stratified by thyrotropin subgroup before admission

Outcomes	TSH subgroup											
	Low			Normal			Intermediate			High		
	(n = 1282)			(n = 5860)			(n = 1183)			(n = 548)		
	Coefficient (SE)	P	Coefficient (SE)	P	Coefficient (SE)	P	Coefficient (SE)	P	Coefficient (SE)	P		
Length of stay ^d	-0.024 (0.042)	.57	-0.031 (0.017)	.06	0.012 (0.030)	.69	0.154 (0.051)	.003				
	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P				
In-hospital mortality ^a	0.44 (0.14-1.42)	.17	0.46 (0.27-0.79)	.004	1.13 (0.55-2.33)	.73	1.45 (0.61-3.42)	.40				
30-d readmission ^b	1.03 (0.85-1.25)	.76	0.99 (0.90-1.09)	.84	1.07 (0.89-1.29) ^c	.45	1.49 (1.20-1.85) ^c	< .001				
90-d readmission ^b	0.94 (0.80-1.10)	.52	0.92 (0.85-0.99)	.02	0.89 (0.76-1.03)	.13	1.43 (1.21-1.67)	< .001				

Low subgroup: TSH less than 0.40 mIU/L. Normal subgroup: TSH 0.40-4.50 mIU/L. Intermediate subgroup: TSH 4.51-10.00 mIU/L. High subgroup: TSH greater than 10.00 mIU/L.

Abbreviations: RR, relative risk; TSH, thyrotropin.

^aAdjusted for age, sex, region, year, admission type, and comorbidities.

^bAdjusted for age, sex, region, admission type, and comorbidities (except where otherwise noted).

^cAdjusted for age, sex, admission type, and comorbidities.

hormone with suppressed TSH levels (TSH < 0.03 mIU/L) (32).

To our knowledge, this is the first study to identify worse short-term hospital outcomes in individuals with hypothyroidism with off-target TSH levels. Akirov et al (33) found that high prehospitalization TSH levels were associated with increased mortality over 2 years of follow-up, but no difference in in-hospital mortality or LOS between groups. This study adds to the growing body of literature highlighting the

risk of overtreatment and undertreatment of hypothyroidism (12, 13). Two primary advantages of this study are 1) that TSH levels were collected on average 8 weeks before admission, thus the TSH level should not be affected by critical illness related to hospitalization; and 2) the robust balancing of covariates for each TSH subgroup and its corresponding control group minimized the effect of potential confounders (eg, age, comorbidities, admission type) that varied between the TSH subgroups.

The long- and short-term adverse health effects associated with off-target treatment of hypothyroidism, coupled with the high frequency of off-target treatment among the millions of patients in the United States on thyroid hormone suggest that a public health effort to improve the quality of care of hypothyroidism is necessary. However, there is currently no quality measure within the Centers for Medicare & Medicaid Services Merit-based Incentive Payment System pertaining to the appropriate treatment of hypothyroidism (34). The presence of guidelines alone may not be sufficient, as demonstrated by the inadequate application of guidelines for the use of levothyroxine in the treatment of thyroid cancer, a serious but much less common disease than clinical hypothyroidism (35).

This study has several important limitations. First, the claims database contained patient data on those with commercial insurance and those younger than 65 years, meaning the results of this study are not necessarily generalizable to an older population or those with nonprivate insurance. Owing to the upper limit of the normal TSH range increasing with age (36), the exclusion of older patients likely minimized the number of patients in the intermediate TSH subgroup that actually had a “normal” TSH for their age. Patient race/ethnicity data were not available in the database, thus no adjustment in the normal TSH range by race was made, as has been suggested by some but has not been adopted in clinical practice (37). Second, the study requirement that all patients (including controls) have a TSH collected before hospitalization eliminated many potential study patients. We assumed that most of these thyroid tests were performed for routine practice, but it is possible that the TSH requirement imposed a selection bias that made certain comorbidities associated with thyroid symptoms (eg, depression, obesity) more prevalent in the control group. Third, the decision to include a levothyroxine prescription or TSH value greater than 10.0 mIU/L as a criterion for having hypothyroidism may have led to the inclusion of some patients in the hypothyroidism group who did not truly have hypothyroidism. For example, a TSH level greater than 10.00 mIU/L may represent alternate diagnoses, such as the recovery phase of thyroiditis or nonthyroidal illness. Some patients are prescribed thyroid hormone that do meet the standard diagnostic criteria for clinical hypothyroidism (38). However, the decision was made to include these criteria to capture undiagnosed hypothyroidism and individuals for whom hypothyroidism was inappropriately missing as a codiagnosis on admission. Additionally, a TSH level greater than 10.00 mIU/L has been demonstrated to be a significant predictor of progression to overt hypothyroidism (39, 40).

Fourth, because this was a retrospective cohort study, the risk of covariates confounding the results was addressed with a robust balancing methodology that included covariate adjustment in the multivariable analysis. While the effects of confounding variables are impossible to eliminate, we believe we minimized the confounding effects of the measured covariates to the extent possible. Last, the lack of continuous enrollment precluded the counting of readmissions that occurred in the next calendar year. Missing readmission data were minimized by excluding admissions after September 30, but this could introduce selection bias.

To conclude, primary hypothyroidism with suboptimal treatment may increase the risk of worse hospital outcomes, including longer LOS and higher rate of readmission. These risks were no longer present in patients with adequate treatment. Unfortunately, suboptimal treatment is common among

the patient population with hypothyroidism. These findings add to the growing body of evidence demonstrating the serious adverse short- and long-term health effects associated with suboptimal treatment of hypothyroidism. The development and implementation of strategies to identify patients with hypothyroidism who are at risk for suboptimal treatment and provide them with treatment plans that maintain in-range TSH levels are needed.

Financial Support

This work was supported by the National Institute of Diabetes and Kidney Disease of the National Institutes of Health (award No. 5T32DK007011-46 to M.D.E.).

Disclosures

M.D.E., W.W., and N.L. have nothing to disclose. A.C.B. reports consulting fees from AbbVie, Allergan, Sention Therapeutics, Synthomics, and Thyron. These are not relevant to the content of this manuscript.

Data Availability

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

References

- Ross JS, Rohde S, Sangaralingham L, *et al*. Generic and brand-name thyroid hormone drug use among commercially insured and Medicare beneficiaries, 2007 through 2016. *J Clin Endocrinol Metab*. 2019;104(6):2305-2314.
- Hollowell JG, Staehling NW, Flanders WD, *et al*. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87(2):489-499.
- Okosieme O, Gilbert J, Abraham P, *et al*. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endocrinol (Oxf)*. 2016;84(6):799-808.
- Jonklaas J, Bianco AC, Bauer AJ, *et al*; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. *Thyroid*. 2014;24(12):1670-1751.
- Pearce SHS, Brabant G, Duntas LH, *et al*. 2013 ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J*. 2013;2(4):215-228.
- Okosieme OE, Belludi G, Spittle K, Kadiyala R, Richards J. Adequacy of thyroid hormone replacement in a general population. *QJM*. 2011;104(5):395-401.
- Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado Thyroid Disease Prevalence Study. *Arch Intern Med*. 2000;160(4):526-534.
- Somwaru LL, Arnold AM, Joshi N, Fried LP, Cappola AR. High frequency of and factors associated with thyroid hormone over-replacement and under-replacement in men and women aged 65 and over. *J Clin Endocrinol Metab*. 2009;94(4):1342-1345.
- la Cour JL, Medici BR, Grand MK, *et al*. Risk of over- and under-treatment with levothyroxine in primary care in Copenhagen, Denmark. *Eur J Endocrinol*. 2021;185(5):673-679.

10. Parle JV, Franklyn JA, Cross KW, Jones SR, Sheppard MC. Thyroxine prescription in the community: serum thyroid stimulating hormone level assays as an indicator of undertreatment or overtreatment. *Br J Gen Pract.* 1993;43(368):107-109.
11. Duntas LH, Jonklaas J. Levothyroxine dose adjustment to optimise therapy throughout a patient's lifetime. *Adv Ther.* 2019;36(Suppl 2):30-46.
12. Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. Over- and under-treatment of hypothyroidism is associated with excess mortality: a register-based cohort study. *Thyroid.* 2018;28(5):566-574.
13. Thayakaran R, Adderley NJ, Sainsbury C, et al. Thyroid replacement therapy, thyroid stimulating hormone concentrations, and long term health outcomes in patients with hypothyroidism: longitudinal study. *BMJ.* 2019;366:l4892.
14. Papaleontiou M, Levine DA, Reyes-Gastelum D, Hawley ST, Banerjee M, Haymart MR. Thyroid hormone therapy and incident stroke. *J Clin Endocrinol Metab.* 2021;106(10):e3890-e3900.
15. Baloch Z, Carayon P, Conte-Devolx B, et al; Guidelines Committee, National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid.* 2003;13(1):3-126.
16. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45(6):613-619.
17. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. Propensity-score-based fine stratification approach for confounding adjustment when exposure is infrequent. *Epidemiology.* 2017;28(2):249-257.
18. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ* 2019;367:l5657.
19. Imai K, King G, Nall C. The essential role of pair matching in cluster-randomized experiments, with application to the Mexican Universal Health Insurance Evaluation. *Stat Sci.* 2009;24(1):29-53.
20. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res.* 2011;46(3):399-424.
21. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA.* 1998;280(19):1690-1691.
22. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system: from theory to practice. *J Clin Endocrinol Metab.* 1994;78(5):1026-1027.
23. Ladenson PW, Goldenheim PD, Ridgway EC. Prediction and reversal of blunted ventilatory responsiveness in patients with hypothyroidism. *Am J Med.* 1988;84(5):877-883.
24. Osterweil D, Syndulko K, Cohen SN, et al. Cognitive function in non-demented older adults with hypothyroidism. *J Am Geriatr Soc.* 1992;40(4):325-335.
25. Ladenson PW, Levin AA, Ridgway EC, Daniels GH. Complications of surgery in hypothyroid patients. *Am J Med.* 1984;77(2):261-266.
26. Park YJ, Yoon JW, Kim KI, et al. Subclinical hypothyroidism might increase the risk of transient atrial fibrillation after coronary artery bypass grafting. *Ann Thorac Surg.* 2009;87(6):1846-1852.
27. Worku B, Tortolani AJ, Gulkarov I, Isom OW, Klein I. Preoperative hypothyroidism is a risk factor for postoperative atrial fibrillation in cardiac surgical patients. *J Card Surg.* 2015;30(4):307-312.
28. Martínez-Comendador J, Marcos-Vidal JM, Gualis J, et al. Subclinical hypothyroidism might increase the risk of postoperative atrial fibrillation after aortic valve replacement. *Thorac Cardiovasc Surg.* 2016;64(5):427-433.
29. Yuan M, Ling T, Ding Z, Mou P, Zhou Z. Does well-controlled overt hypothyroidism increase the risk of total knee arthroplasty? *ANZ J Surg.* 2020;90(10):2056-2060.
30. Subahi A, Yassin AS, Adegbola O, et al. Comparison of hospital outcomes of transcatheter aortic valve implantation with versus without hypothyroidism. *Am J Cardiol.* 2018;122(5):838-843.
31. Ertleson MD, Bianco AC, Zhu M, Laiteerapong N. Sociodemographic disparities in the treatment of hypothyroidism: NHANES 2007-2012. *J Endocr Soc.* 2021;5(7):bvab041.
32. Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab.* 2010;95(1):186-193.
33. Akirov A, Shochat T, Shechvitz A, Shimon I, Diker-Cohen T, Robenshtok E. Pre-admission TSH levels predict long-term mortality in adults treated for hypothyroidism. *Endocrine.* 2017;58(3):481-487.
34. Quality payment program: explore measures & activities. Accessed Dec 7, 2021. <https://qpp.cms.gov/mips/explore-measures?tab=qualityMeasures&py=2021#measures>
35. Martins de Almeida JF, Gonçalves Tsumura W, Vaisman M, Montalli Assumpção LV, Ward LS. Current recommendations for levothyroxine treatment of differentiated thyroid cancer patients are not properly implemented in clinical practice. *J Endocrinol Invest.* 2012;35(10):901-904.
36. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab.* 2007;92(12):4575-4582.
37. Boucai L, Surks MI. Reference limits of serum TSH and free T4 are significantly influenced by race and age in an urban outpatient medical practice. *Clin Endocrinol (Oxf).* 2009;70(5):788-793.
38. Brito JP, Ross JS, El Kawkgi OM, et al. Levothyroxine use in the United States, 2008-2018. *JAMA Intern Med.* 2021;181(10):1402-1405.
39. Huber G, Staub JJ, Meier C, et al. Prospective study of the spontaneous course of subclinical hypothyroidism: prognostic value of thyrotropin, thyroid reserve, and thyroid antibodies. *J Clin Endocrinol Metab.* 2002;87(7):3221-3226.
40. Somwaru LL, Rariy CM, Arnold AM, Cappola AR. The natural history of subclinical hypothyroidism in the elderly: the Cardiovascular Health Study. *J Clin Endocrinol Metab.* 2012;97(6):1962-1969.