Original Investigation

Falling Threshold for Treatment of Borderline Elevated Thyrotropin Levels—Balancing Benefits and Risks
Evidence From a Large Community-Based Study

Peter N. Taylor, MSc, MRCP; Ahmed Iqbal, MRCP; Caroline Minassian, MSc; Adrian Sayers, MSc; Mohd S. Draman, MRCP; Rosemary Greenwood, MSc; William Hamilton, MD; Onyebuchi Okosieme, MD, FRCP; Vijay Panicker, PhD; Sara L. Thomas, PhD; Colin Dayan, PhD, FRCP

IMPORTANCE Rates of thyroid hormone prescribing in the United States and the United Kingdom have increased substantially. If some of the increase is due to lowering the thyrotropin threshold for treatment, this may result in less benefit and greater harm.

OBJECTIVE To define trends in thyrotropin levels at the initiation of levothyroxine sodium therapy and the risk of developing a suppressed thyrotropin level following treatment.

DESIGN, SETTING, PARTICIPANTS, AND EXPOSURE Retrospective cohort study using data from the United Kingdom Clinical Practice Research Datalink. Among 52 298 individuals who received a prescription for levothyroxine between January 1, 2001, and October 30, 2009, we extracted data about the thyrotropin level before levothyroxine therapy initiation, clinical symptoms, and thyrotropin levels up to 5 years after levothyroxine was initiated. We excluded persons who had a history of hyperthyroidism, pituitary disease, or thyroid surgery; those who were taking thyroid-altering medication or if the levothyroxine prescription was related to pregnancy; and those who did not have a thyrotropin level measured within 3 months before the initiation of levothyroxine.

MAIN OUTCOMES AND MEASURES The median thyrotropin level at the time of the index levothyroxine prescription, the odds of initiation of levothyroxine therapy at thyrotropin levels of 10.0 mIU/L or less, and the age-stratified odds of developing a low or suppressed thyrotropin level after levothyroxine therapy.

RESULTS Between 2001 and 2009, the median thyrotropin level at the initiation of levothyroxine therapy fell from 8.7 to 7.9 mIU/L. The odds ratio for prescribing levothyroxine at thyrotropin levels of 10.0 mIU/L or less in 2009 compared with 2001 (adjusted for changes in population demographics) was 1.30 (95% CI, 1.19-1.42; $P < .001$). Older individuals and individuals with cardiac risk factors had higher odds of initiation of levothyroxine therapy with a thyrotropin level 10.0 mIU/L or less. At 5 years after levothyroxine initiation, 5.8% of individuals had a thyrotropin level of <0.1 mIU/L. Individuals with depression or tiredness at baseline had increased odds of developing a suppressed thyrotropin level, whereas individuals with cardiac risk factors (eg, atrial fibrillation, diabetes mellitus, hypertension, and raised lipid levels) did not.

CONCLUSIONS AND RELEVANCE We observed a trend toward levothyroxine treatment of more marginal degrees of hypothyroidism and a substantial risk of developing a suppressed thyrotropin level following therapy. Large-scale prospective studies are required to assess the risk-benefit ratio of current practice.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Peter N. Taylor, MSc, MRCP, Thyroid Research Group, Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, C2 Link Corridor, University Hospital of Wales, Heath Park, Cardiff CF14 4XN, United Kingdom (taylorpn@cardiff.ac.uk).

Primary hypothyroidism is one of the most common chronic disorders in Western populations[1,2] and is largely managed in primary care.[3,4] Levothyroxine sodium prescriptions in the United States have increased substantially in recent years (from 49.8 million in 2006 to 70.5 million in 2010).[5] A similar increase has been observed in England and Wales, with levothyroxine prescriptions rising from 17.1 million (in 2006) to 23.4 million (in 2010),[6] up from only 7 million prescriptions in 1998 data.[7,8]

Several factors have probably contributed to this rise. In England and Wales, a proportion may be attributed to a fall in the mean duration of prescriptions from 60 to 45 days.[8] Thyroid function testing has also increased substantially,[9,10] and in any year 18% to 25% of individuals have their thyroid function tested,[4,9,11] likely resulting in increased case finding. However, an additional factor may be a lowering of the thyrotropin threshold at which levothyroxine is initiated. This practice would be important to identify because it might be associated with more marginal benefits and with increased relative risk of patient harm. The results of studies published before 2001 suggested that between 15% and 20% of individuals taking levothyroxine are overtreated and develop a low thyrotropin level,[12,13] most likely because of inadequate monitoring. Overtreatment is associated with an increased risk of fractures[14] and atrial fibrillation.[15]

American Thyroid Association guidelines[16] recommend consideration of levothyroxine therapy at thyrotropin levels of 10.0 mIU/L or less when there are clear symptoms of hypothyroidism, positive thyroid autoantibodies, or evidence of atherosclerotic cardiovascular disease or heart failure (evidence level B). Data from Scotland in 2001 indicated that most patients had levothyroxine initiated at thyrotropin levels of 10.0 mIU/L or less, with 45% to 48% of patients having therapy commenced with a thyrotropin level less than 6.0 mIU/L.[10]

In this study, we used a large United Kingdom (UK) population-based database to examine trends in thyrotropin levels before and after levothyroxine therapy initiation since 2001 and assessed the potential for adverse outcomes from current practice.

Methods

Regulatory Approval

Access to the General Practice Research Database (GPRD) data set (now called the Clinical Practice Research Datalink [www.CPRD.com]) was obtained via the Medical Research Council license. The study protocol was approved by the Independent Scientific Advisory Group of the UK Medicines and Healthcare Products Regulatory Agency.

Cohort

Clinical data, dates of levothyroxine prescriptions, and thyrotropin levels were extracted in primary care patients from the GPRD, which has been well described previously[17] and is the largest computerized database of anonymized medical records from primary care linked with other health care data. It is well validated for research on clinical diagnoses[18,19] and drug exposure and patient safety.[20-22]

At the time of this study, the GPRD contained computerized medical records of more than 5 million persons from 508 primary care practices throughout the United Kingdom. We included persons who had initiated levothyroxine treatment between January 1, 2001, and October 30, 2009, and excluded those who had a history of hyperthyroidism, pituitary disease, or thyroid surgery; those who were taking thyroid-altering medication or if the levothyroxine prescription was related to pregnancy; and those who did not have a thyrotropin level measured within 3 months before initiation of levothyroxine. Details of our data set are provided in the eMethods in the Supplement.

Identification of Thyrotropin and Free Thyroxine Results Generating the First Levothyroxine Prescription

We studied incident (first) levothyroxine prescriptions. A thyrotropin or free thyroxine (FT_4) level was relevant if it occurred within 90 days before levothyroxine initiation.

If more than 1 result was available, then the result closest to the date of levothyroxine initiation was used. Prescribing rates were calculated using baseline GPRD denominator data and were adjusted after removing from the denominator the person-time of individuals prescribed levothyroxine after 2001 (from the date of their levothyroxine prescription until the end of the study period or their exit from the GPRD). Excluded individuals (eg, those prescribed levothyroxine in pregnancy) were also removed from the person-years at risk.

Identification of Factors Potentially Relevant to Prescribing Levothyroxine at the Time of Initiation of Treatment

Medical codes were studied for each patient within 60 days before the relevant thyrotropin test. Codes regarding symptoms, examination findings, diagnoses, clinic appointments, and investigations were grouped into categories specified a priori (eTable 3 in the Supplement). For example, the atrial fibrillation or tachycardia category had several medical codes, including *atrial fibrillation*, *AF*, and *paroxysmal AF* pertaining to it. Individuals could be assigned to more than 1 category but would only be counted once within a category.

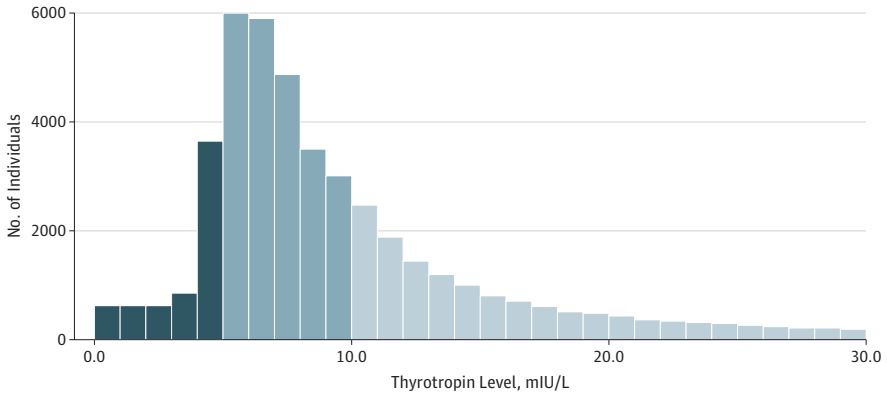
Thyrotropin Levels After Levothyroxine Initiation

Using the date of the index levothyroxine prescription as time zero, the thyrotropin levels after levothyroxine therapy were studied for up to 5 years. Time bands were split into 6-month intervals. Individuals could only be assigned once in each time band. If 2 or more thyrotropin values were available for a patient in the same 6-month period, the later thyrotropin level was used. We studied thyrotropin values 30 to 36 months and 54 to 60 months after levothyroxine initiation. Thyrotropin levels below 0.5 mIU/L were regarded as low, and values below 0.1 mIU/L were regarded as suppressed in keeping with previous regional UK studies.[10,15]

Statistical Analysis

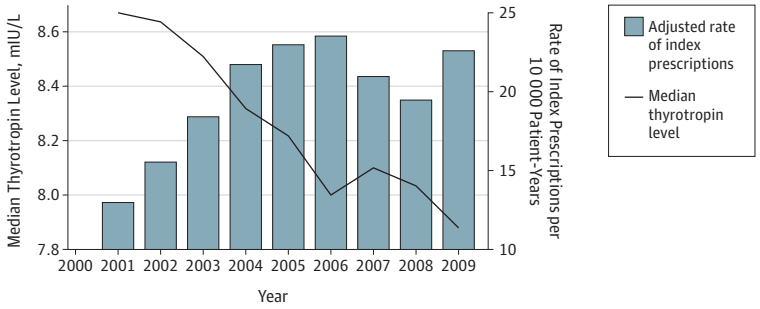
The median thyrotropin levels at levothyroxine initiation were calculated by year between 2001 and 2009. Logistic regression was undertaken to assess the odds ratio (OR) for having a levothyroxine prescription with thyrotropin levels of 10.0

Figure 1. Thyrotropin Levels at the Time of the Index Prescription of Levothyroxine



Dark bars indicate thyrotropin levels less than 4.0 mIU/L; medium bars, 4.0 to 10.0 mIU/L; and light bars, greater than 10.0 mIU/L. Levothyroxine given as levothyroxine sodium.

Figure 2. Median Thyrotropin Levels at the Time of the Index Prescription of Levothyroxine and Rate of Index Prescriptions by Year



The annual median thyrotropin level fell during the study period from 8.7 to 7.9 mIU/L. Levothyroxine given as levothyroxine sodium.

mIU/L or less using the odds of being prescribed levothyroxine with a thyrotropin level of 10.0 mIU/L or lower in 2001 as a baseline, with analyses adjusted for sex, clinical characteristics, and age at levothyroxine initiation.

Univariable logistic regression was also used to estimate the odds of developing a suppressed thyrotropin level at 5 years after levothyroxine initiation for sex, age, year of the index prescription, thyrotropin level at the time of the index levothyroxine prescription, and key clinical characteristics before levothyroxine therapy. Multivariable logistic regression was then undertaken, adjusting for sex, age, year of the index prescription of levothyroxine, and thyrotropin level at the time of the index levothyroxine prescription.

All statistical analyses were performed with commercially available software—STATA, version 12 (StataCorp LP).

Results

Characteristics of Individuals Prescribed Levothyroxine

The flow of patients in our data set is shown in eFigure 1 in the Supplement. We identified 52 298 individuals matching our inclusion criteria who had a levothyroxine prescription within 90 days after a documented thyrotropin level measurement. The median age at the time of the index levothyroxine prescription was 59 years (interquartile range, 47-72 years), with a male-female ratio of 1:3.74.

Prescribing Patterns in Initiation of Levothyroxine Therapy

Overall, the median thyrotropin level before the index levothyroxine prescription between 2001 and 2009 was 8.2 mIU/L (interquartile range, 5.9-13.9 mIU/L) (**Figure 1**). The annual median thyrotropin level fell during the study period from 8.7 to 7.9 mIU/L (**Figure 2**). This decrease reflected a reduction in individuals treated for an initial thyrotropin level greater than 10.0 mIU/L (42.1% to 35.6%) and a rise in those treated for a thyrotropin level in the range of 4.0 to 10.0 mIU/L (49.8% to 58.1%) (**Table 1**). Adjusting for sex, age, key clinical characteristics before levothyroxine therapy, and the presence of diabetes mellitus, hypertension, or raised lipid levels, the OR for having an index levothyroxine prescription with a thyrotropin level of 10.0 mIU/L or less in 2009 compared with 2001 was 1.30 (95% CI, 1.19-1.42; $P < .001$). Free thyroxine levels were available in 34 808 participants (66.6%) at the time of the index prescription of levothyroxine (eTable 4A, eTable 4B, and eFigure 2 in the Supplement). The odds of initiation of levo-

Table 1. Thyrotropin Levels Before the Index Prescription of Levothyroxine by Year and by the Odds of Initiating Therapy at Thyrotropin Levels of 10.0 mIU/L or Less Using Prescribing Data of Levothyroxine in 2001 as a Baseline[a]

	Thyrotropin Level, mIU/L			Model 1		Model 2		Model 3	
Year	<4.0	4.0-10.0	>10.0	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
2001	8.1	49.8	42.1	1 [Reference]	...	1 [Reference]		1 [Reference]	...
2002	5.6	53.1	41.3	1.03 (0.94-1.12)	.49	1.02 (0.94-1.12)	.59	1.02 (0.93-1.11)	.68
2003	5.5	53.3	41.2	1.04 (0.95- 1.12)	.41	1.04 (0.95-1.13)	.45	1.03 (0.94-1.12)	.53
2004	6.6	54.3	39.1	1.14 (1.04-1.23)	.003	1.14 (1.05-1.24)	.002	1.13 (1.04-1.22)	.005
2005	5.4	56.0	38.5	1.16 (1.04-1.25)	<.001	1.17 (1.08-1.27)	<.001	1.14 (1.05-1.24)	.001
2006	5.8	57.4	36.7	1.27 (1.15-1.35)	<.001	1.27 (1.17-1.38)	<.001	1.24 (1.14-1.34)	<.001
2007	5.2	57.3	37.4	1.22 (1.11-1.32)	<.001	1.23 (1.13-1.34)	<.001	1.19 (1.10-1.31)	<.001
2008	6.7	55.8	37.5	1.18 (1.11-1.32)	<.001	1.24 (1.14-1.35)	<.001	1.20 (1.10-1.31	<.001
2009	6.3	58.1	35.6	1.32 (1.20-1.43)	<.001	1.34 (1.23-1.46)	<.001	1.30 (1.19-1.42)	<.001

Abbreviation: OR, odds ratio.

[a] Among 52 298 individuals. *P* values are calculated using the Wald test. Model 1 gives crude values. Model 2 adjusts for sex and age at the index levothyroxine sodium prescription. Model 3 adjusts for sex, age at the index levothyroxine prescription, key clinical characteristics before levothyroxine therapy, and the presence of diabetes mellitus, hypertension, or raised lipid levels before levothyroxine initiation.

thyroxine therapy with a thyrotropin level 10.0 mIU/L or less at the end of the study in the subgroup of patients with an FT_4 level in the reference range was slightly lower (OR, 1.17; 95% CI, 1.00-1.36; $P = .05$) than in the analysis of the whole cohort (OR, 1.30; 95% CI, 1.19-1.42; $P < .001$).

Between 2001 and 2006, there was a 1.81-fold increase in the rate of index levothyroxine prescriptions (eTable 1 in the Supplement). After this time, the rate of new prescriptions did not substantially change despite a continuing decline in the median thyrotropin level at the time of the index levothyroxine prescription (Figure 2). Age-standardized rates comparing 2001 prescribing with 2006 prescribing revealed that there was still a 1.79-fold increase in the rate of index levothyroxine prescriptions after the change in age in the data set was taken into account. Age-stratified rates are given in eTable 2 in the Supplement.

Levothyroxine prescriptions were usually continued long term. Overall, 38 939 of 43 057 individuals (90.4%) still in the GPRD at the end of the study had received a repeat levothyroxine prescription during 2009.

Clinical Data Among Individuals Prescribed Levothyroxine

The symptoms and signs recorded in the 60-day period before initiation of levothyroxine are given in eTable 3 in the Supplement. The most common symptoms were tiredness (19.3%), weight gain or obesity (14.0%), and depression (5.8%). The median thyrotropin levels among individuals with recorded sleep apnea (23.1 mIU/L) or periorbital edema (32.7 mIU/L) were substantially greater than 10.0 mIU/L, consistent with the presence of more profound hypothyroidism.

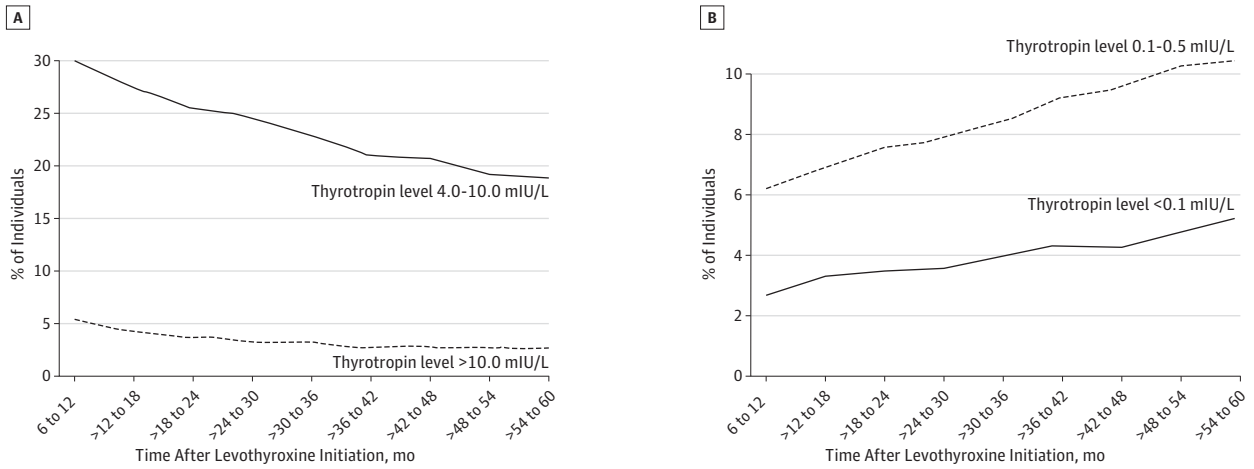
In 34 808 individuals with an FT_4 level available, 10 939 (31.4%) had levothyroxine prescribed with a thyrotropin level of 10.0 mIU/L or less and a normal FT_4 level despite no previous cardiovascular risk factors or classic hypothyroid symptoms, and were potentially overtreated. In addition, individuals in whom levothyroxine was initiated with a thyrotropin level in the range of 4.0 to 10.0 mIU/L and a normal FT_4 level rather than a low FT_4 level were more likely to be older and have cardiovascular risk factors but were not more likely to manifest tiredness, weight gain or obesity, or depression at baseline (eTable 4A in the Supplement). In contrast, individuals prescribed levothyroxine with a thyrotropin level between 4.0 and 10.0 mIU/L instead of exceeding 10.0 mIU/L were more likely to be female, have cardiovascular risk factors, and been older than 70 years when prescribed levothyroxine after 2004, with trends also observed for tiredness and depression (eTable 4B in the Supplement).

Thyrotropin Levels After Initiation of Levothyroxine Therapy

Trends in thyrotropin levels after initiation of levothyroxine therapy are shown in **Figure 3**. Not all individuals had measurement of thyrotropin levels repeated regularly. The data set was created in 2010, at which time we had thyrotropin levels at 3 follow-up years in 17 154 individuals (51.5% of those with 3 follow-up years) and at 5 follow-up years in 9252 individuals (39.7% of those with 5 follow-up years). During the period 6 months to 5 years after levothyroxine therapy initiation, the percentage of those with a thyrotropin level less than 0.1 mIU/L increased from 2.7% to 5.8%, and the percentage of those with a thyrotropin level between 0.1 and 0.5 mIU/L increased from 6.3% to 10.2%. This was accompanied by a decrease in those with a thyrotropin level between 5.0 and 10.0 mIU/L from 29.8% to 18.8%. Overall, 2.7% of individuals still had a thyrotropin level greater than 10.0 mIU/L at 5 years after levothyroxine was initiated.

Individuals' baseline characteristics seemed to substantially influence the odds of developing suppressed thyrotropin levels at 5 years after levothyroxine initiation (**Table 2**): these included female sex (OR, 1.57; 95% CI, 1.18-2.08; $P = .002$), tiredness (1.51; 1.13-2.01; $P = .005$) or depression (1.63; 1.02-2.60; $P = .04$), and a thyrotropin level at the index levothyroxine prescription of less than 4.0 mIU/L (1.83; 1.35-2.47; $P < .001$) or greater than 10.0 mIU/L (2.68; 2.07-3.44; $P < .001$). Having cardiovascular risk factors at baseline was generally associated with reduced odds of a low thyrotropin level at 5 follow-up years, although the presence of atrial fibrillation or diabetes mellitus had wide CIs that included equality.

Figure 3. Thyrotropin Levels After Initiation of Levothyroxine



A, Undertreated. B, Overtreated. Levothyroxine given as levothyroxine sodium.

Discussion

Our results show that the annual rate of new levothyroxine prescriptions increased 1.74-fold during the study period. There was also a decline in the median thyrotropin threshold at the time of the index levothyroxine prescription from 8.7 to 7.9 mIU/L, with a 28.0% increase in the odds of having levothyroxine initiated at a thyrotropin level of 10.0 mIU/L or less.

This increase in rate was not simply due to an aging population because age-adjusted and age-stratified rates also demonstrated a rise (eTables 1 and 2 in the Supplement). Furthermore, it was not because of shorter prescriptions because we only counted the first (incident) prescription a patient ever received. An increase in case finding due to more thyroid tests being ordered,[4,9,23] in combination with the observed fall in the thyrotropin threshold for initiation of treatment, could explain this increase. Because our data set does not contain information about individuals who never received levothyroxine therapy, we cannot calculate the relative contribution of these 2 factors.

Although it may only partly account for the overall increase in the number of persons in whom levothyroxine was prescribed, the reduction in the thyrotropin threshold is important because it implies that the net benefits of levothyroxine therapy may be more marginal. For example, the highest age-adjusted and age-stratified rates of new levothyroxine prescribing (even with a normal FT_4 level) were observed in older persons (eTable 2 in the Supplement), who also had the highest odds of being prescribed levothyroxine with a thyrotropin level between 4.0 and 10.0 mIU/L (eTable 4B in the Supplement). A substantial number of these prescriptions may be unwarranted because mild thyrotropin elevations may be a normal manifestation of aging.[24] Furthermore, evidence shows that treatment of subclinical hypothyroidism in individuals older than 70 years has less cardiovascular benefit than that in younger persons,[25] and overtreatment in older patients may cause net harm.[14,26]

The marked increase in new levothyroxine prescriptions since 2002 may have been an unintended consequence of the Quality and Outcome Framework,[27] which required UK primary care physicians to maintain a database of patients with hypothyroidism and to monitor thyrotropin levels annually. This may have drawn more attention to thyroid function testing and to levothyroxine therapy, resulting in increased case finding and enthusiasm to initiate treatment. New prescription rates have stabilized since 2007 despite a continued fall in the median thyrotropin levels, which may indicate that this enthusiasm for case finding began to wane at this stage.

Most patients (61.1%) in our data set initiated levothyroxine therapy with a thyrotropin level of 10.0 mIU/L or less (Figure 1). Furthermore, in 34 808 individuals with an FT_4 level available, 31.4% had levothyroxine prescribed with a thyrotropin level of 10.0 mIU/L or less and a normal FT_4 level despite no previous cardiovascular risk factors or classic hypothyroid symptoms. These individuals were potentially overtreated according to recent guidelines.[16] This percentage may be an overestimate because data about thyroid antibody status were unavailable, and we could not identify symptoms relevant to hypothyroidism before the thyrotropin test that resulted in the index levothyroxine prescription in 47.9% of individuals.

Free thyroxine values were available in 68.3% of individuals prescribed levothyroxine with a thyrotropin level between 4.0 and 10.0 mIU/L, and 82.7% of this group had FT_4 values within the reference range, consistent with a diagnosis of subclinical hypothyroidism (eTable 4A in the Supplement). The evidence for clinical benefit of treatment in this range outside of pregnancy is weak.[16] Only 39.4% of individuals prescribed levothyroxine for subclinical hypothyroidism had a history of diabetes mellitus, hypertension, raised lipid levels, or atrial fibrillation before levothyroxine initiation, with 46.9%

Table 2. Odds of Developing a Suppressed Thyrotropin Level 5 Years After Levothyroxine Therapy by Sex, Age Group, Index Thyrotropin Level, the Presence of Cardiovascular Risk Factors, and the Clinical Reasons for Prescribing

Characteristic	Thyrotropin Level 0.1-0.5 mIU/L				Thyrotropin Level <0.1 mIU/L			
	OR (95% CI)	*P* Value[a]	OR (95% CI)[b]	*P* Value[a,b]	OR (95% CI)	*P* Value[a]	OR (95% CI)[b]	*P* Value[a,b]
Sex								
Male	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...
Female	1.40 (1.19-1.64)	<.001	1.45 (1.23-1.73)	<.001	1.55 (1.17-2.04)	.002	1.57 (1.18-2.08)	.002
Age group at levothyroxine sodium initiation, y								
18 to 45	1 [Reference]	...	...	...	1 [Reference]	...	1 [Reference]	...
>45 to 70	0.81 (0.70-0.93)	.003	0.82 (0.70-0.95)	.009	0.71 (0.58-0.89)	.002	0.76 (0.61-0.94)	.01
>70 to 99	0.52 (0.44-0.62)	<.001	0.54 (0.45-0.65)	<.001	0.38 (0.28-0.51)	<.001	0.41 (0.30-0.55)	<.001
Year of index prescription								
2001	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...
2002	0.95 (0.80-1.14)	.64	0.97 (0.80-1.18)	.78	1.03 (0.75-1.39)	.87	1.06 (0.78-1.45)	.70
2003	0.97 (0.82-1.16)	.79	0.98 (0.82-1.18)	.86	1.30 (0.98-1.72)	.07	1.37 (1.03-1.82)	.03
2004	0.75 (0.63-0.90)	.002	0.78 (0.65-0.94)	.009	0.91 (0.68-1.22)	.53	0.97 (0.72-1.30)	.83
Index thyrotropin level, mIU/L								
<4.0	1.49 (1.24-1.79)	<.001	1.44 (1.20-1.72)	<.001	1.96 (1.46-2.64)	<.001	1.83 (1.35-2.47)	<.001
4.0 to 7.0	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...
>7.0 to 10.0	1.18 (0.98-1.42)	.08	1.19 (0.99-1.41)	.002	1.21 (0.87-1.69)	.24	1.22 (0.88-1.71)	.21
>10.0	2.54 (2.19-2.94)	<.001	2.82 (2.22-2.99)	<.001	2.64 (2.05-3.39)	<.001	2.68 (2.07-3.44)	<.001
Presence of atrial fibrillation								
No	1 [Reference]	...	...	...	1 [Reference]	...	1 [Reference]	...
Yes	0.72 (0.53-0.98)	.04	0.87 (0.63-1.20)	.40	0.32 (0.15-0.68)	.003	0.42 (0.20-0.90)	.03
Hypertension or raised lipid levels								
No	1 [Reference]	...	...	...	1 [Reference]	...	1 [Reference]	...
Yes	0.70 (0.61-0.80)	<.001	0.81 (0.71- 0.94)	.004	0.55 (0.44-0.71)	<.001	0.68 (0.53-0.87)	.002
Presence of diabetes mellitus								
No	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...
Yes	0.63 (0.48-0.83)	.001	0.81 (0.61-1.07)	.15	0.59 (0.37-0.95)	.03	0.78 (0.48-1.27)	.32
Free thyroxine level at levothyroxine initiation								
Normal	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...	1 [Reference]	...
Low	2.02 (1.73-2.36)	<.001	1.60 1.36-1.89	<.001	1.81 (1.41-2.34)	.001	1.37 (1.04-1.81)	.02
Clinical reason for thyrotropin measurement								
Depression	1.91 (1.41-2.58)	<.001	1.64 (1.19-2.27)	.003	1.86 (1.18-2.95)	.008	1.63 (1.02-2.60)	.04
Tiredness	1.51 (1.25-1.82)	<.001	1.56 (1.28-1.89)	<.001	1.69 (1.27-2.24)	<.001	1.51 (1.13-2.01)	.005
Weight gain or obesity	1.31 (1.05-1.63)	.02	1.26 (1.00-1.59)	.05	1.10 (0.75-1.62)	.61	1.03 (0.70-1.51)	.89
Peripheral edema	0.78 (0.52-1.17)	.23	0.86 (0.57-1.30)	.49	0.50 (0.22-1.14)	.10	0.57 (0.25-1.29)	.18
Menstrual irregularities	1.29 (0.90-1.83)	.16	0.99 (0.68-1.42)	.94	1.68 (1.01-2.80)	.04	1.11 (0.66-1.87)	.69
Diabetes review	0.79 (0.55-1.15)	.23	0.90 (0.61-1.32)	.58	0.66 (0.34-1.29)	.23	0.79 (0.40-1.56)	.50
General screening	1.15 (0.85-1.58)	.36	1.08 (0.78-1.51)	.63	0.96 (0.56-1.66)	.90	0.99 (0.57-1.72)	.99

Abbreviations: ellipsis, not applicable; OR, odds ratio.

[a] Calculated using the Wald test.

[b] Adjusted for sex, year of the index levothyroxine prescription, age group at the index prescription, and thyrotropin level at the time of the index prescription among 9252 individuals with 5 follow-up years.

having these cardiovascular risk factors or documented symptoms, consistent with hypothyroidism before levothyroxine therapy (eTables 3 and 4A in the Supplement). Although some data may be unrecorded, up to 50% of individuals with subclinical hypothyroidism may be treated inconsistently with guidelines. It is somewhat reassuring that in individuals having cardiovascular risk factors, levothyroxine was preferentially initiated among those with thyrotropin levels in the range of 4.0 to 10.0 mIU/L compared with those not having cardiovascular comorbidities (eTable 4A and B in the Supplement). Contrary to American Thyroid Association guidelines,[16,28] another concern is that 34.6% of individuals prescribed levothyroxine with a thyrotropin level between 4.0 and 10.0 mIU/L had only one abnormal thyrotropin reading before initiation of therapy (eTable 5 in the Supplement). Greater use of confirmatory testing might reduce unnecessary prescriptions given

that 46% of individuals with a thyrotropin level between 4.5 and 7.0 mIU/L reverted to normal levels within 2 years without treatment.[29] This is especially relevant because the indication for levothyroxine therapy is rarely reviewed once initiated. In our data set, more than 90% of individuals were still being prescribed levothyroxine at the end of the study.

Set against the uncertain potential for benefit in a large proportion of patients with initiation of levothyroxine therapy, it is important to examine the potential for harm. At 5 years after levothyroxine initiation, 10.2% of patients had a low thyrotropin level, and 5.8% had a suppressed thyrotropin level. Individuals with a suppressed thyrotropin level are at potentially increased risk of developing osteoporotic fractures[15] and atrial fibrillation,[30] and data for the increased risk of harm from subclinical hyperthyroidism are stronger than the data for potential benefit from treatment of subclinical hypothyroidism. Individuals with cardiac risk factors had reduced odds of developing a suppressed thyrotropin level, suggesting that prescribers were aware of this risk, but 10.6% of individuals treated for subclinical hypothyroidism who had cardiovascular risk factors ultimately manifested a low thyrotropin level, which may have actually increased their risk. The results of a recent meta-analysis[31] also suggested that the risk of osteoporosis is increased in individuals with a thyrotropin level in the low to normal range, even if not suppressed, highlighting the potential for net harm with marginal overtreatment. Individuals with tiredness or depression at baseline but not those with diabetes mellitus or weight gain or obesity were more likely to be overtreated at 5 years (Table 2), raising the possibility that there may be an element of intentional increased dosing with levothyroxine rather than a lack of careful monitoring in these individuals.

In the United Kingdom, 1.6 million individuals are on long-term levothyroxine regimens, most of whom have been prescribed it for primary hypothyroidism.[3] If current practice continues, up to 30% of persons receiving levothyroxine therapy may have been prescribed it without an accepted indication and with the potential for net harm if they develop even a low thyrotropin level (as occurred in 12.2% of individuals prescribed levothyroxine for subclinical hypothyroidism in our data set). In the United States, the prevalence of hypothyroidism is similar to that in the United Kingdom,[12] and one might expect approximately 5 million individuals in the United States to be on long-term levothyroxine regimens for primary hypothyroidism; if prescribing patterns in the United States are similar, more than 1.6 million individuals may be taking levothyroxine with limited evidence of benefit.

The strengths of our study include the use of a large population-based data set from many different practitioners collected during a long period. Detailed clinical data allowed us to ascertain cases of primary hypothyroidism and to exclude individuals who had levothyroxine prescribed as a result of pregnancy or following treatment of hyperthyroidism or pituitary disease. In addition, the use of electronic medical records by UK primary care physicians to issue prescriptions makes it unlikely that prescriptions of levothyroxine were missed. Similarly, almost all laboratories sent biochemical data electronically by 2000, so few thyrotropin results were unavailable, and transcription errors were eliminated. We also had substantial data on cardiovascular risk factors and symptoms before initiation of levothyroxine therapy to enable us to investigate the appropriateness of levothyroxine prescriptions.

The limitations of our study include the lack of data about individuals who did not receive a levothyroxine prescription and the absence of reliable data about thyroid peroxidase antibody titers. Furthermore, data on FT_4 measurements were unavailable in all patients because this estimation is not always routine practice, and follow-up thyrotropin values were only available in 39.7% of the cohort at 5 years. Hence, the potential for bias exists in the subgroups of individuals analyzed; however, no differences were observed in sex or age group between those with FT_4 levels available and those without (eTable 4A in the Supplement). The thyrotropin assay used varied between laboratories, and we were unable to account for this, although most assays have similar thresholds for defining low or suppressed thyrotropin levels. Finally, we were unable to identify and exclude from our denominator data individuals who were prescribed levothyroxine before 2001 (and hence, not at risk of receiving another first levothyroxine prescription). We were also unable to remove from the denominator person-years for individuals excluded by the GPRD in the creation of our data set. However, we consider that the influence of this factor on the accuracy of our results is likely to be small, particularly with regard to the relative rate.

In summary, our results suggest that there is widespread prescribing of levothyroxine for borderline thyrotropin levels among individuals with limited evidence of benefit. This practice may be harmful given the high risk of developing a suppressed thyrotropin level after treatment. While thyroidologists are still debating whether subclinical hypothyroidism should be more widely treated, it is increasingly apparent that this is already happening in primary care. Randomized controlled trials with sufficient power to assess the health consequences of borderline or subclinical hypothyroidism and its treatment are urgently needed to refine current levothyroxine prescribing and to indicate the balance of risks and benefits of current practice.

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Author Affiliations: Thyroid Research Group, Institute of Molecular and Experimental Medicine, Cardiff University School of Medicine, Cardiff, United Kingdom (Taylor, Draman, Okosieme, Dayan); Department of Social and Community Based Medicine, University of Bristol, Bristol, United Kingdom (Taylor, Sayers); Henry Wellcome Laboratories for Integrative Neurosciences and Endocrinology, University of Bristol, Bristol, United Kingdom (Iqbal, Dayan); Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom (Minassian, Thomas); University Hospitals Bristol National Health Service Foundation Trust, Bristol, United Kingdom (Greenwood); University of Exeter Medical School, Exeter, United Kingdom (Hamilton); Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, Australia (Panicker).

Author Contributions: *Study concept and design:* Taylor, Iqbal, Dayan.
Acquisition of data: Taylor, Iqbal, Minassian.
Analysis and interpretation of data: Taylor, Iqbal, Minassian, Sayers, Greenwood, Hamilton, Okosieme, Panicker, Thomas.

Drafting of the manuscript: Taylor, Iqbal, Minassian, Sayers, Draman, Okosieme, Panicker.
Critical revision of the manuscript for important intellectual content: Taylor, Minassian, Greenwood, Hamilton, Okosieme, Panicker, Thomas, Dayan.
Statistical analysis: Taylor, Iqbal, Minassian, Sayers, Greenwood, Thomas.

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