Falling threshold for treatment of raised TSH levels – balancing benefits and risks: evidence from a large community based study

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Abstract

Importance

Rates of thyroid hormone prescribing in the USA and UK have increased substantially. If a proportion of this increase is due to a lowering of the TSH threshold this may result in more marginal benefit and increased relative risk of harm.

Objective

To define trends in threshold TSH at levothyroxine initiation and the risk of developing suppressed TSH levels following treatment.

Design

Historical cohort analysis. The TSH level prior to index levothyroxine prescription, clinical background and TSH levels up to 5-years after levothyroxine initiation were studied in individuals commencing levothyroxine for primary hypothyroidism between 2001-2009.

Setting

The UK Clinical Practice Research Datalink - a primary care dataset covering approximately 5,000,000 people.

Participants

Individuals with primary hypothyroidism (N=52,298). Individuals with a history of hyperthyroidism, pituitary disease, thyroid surgery or on thyroid altering medication were excluded as were individuals with prescription related to pregnancy, or no TSH level in the 3 months prior to their index levothyroxine prescription.

Main Outcome Measures

Median TSH at index levothyroxine prescription, odds of initiating levothyroxine at TSH levels <10mU/l, age-stratified odds of developing a low/suppressed TSH post levothyroxine.

Results

The rate of new levothyroxine prescriptions increased by 181% over the period 2001-2006 and did not increase thereafter. The median TSH at index prescription fell over the whole period from 8.67mU/l to 7.88mU/l with the odds ratio of prescribing at TSH levels <10mU/l in 2009 versus 2001 after adjusting for changes in population demographics =1.30 (95%CI 1.19-1.42) p=<0.001. Older individuals and individuals with cardiac risk-factors had higher odds of levothyroxine initiated with a TSH level <10mU and a normal free thyroxine level. Five years after levothyroxine initiation, 5.8% of individuals had a TSH <0.1mU/l. Individuals with depression or tiredness at baseline had increased odds of developing a suppressed TSH whereas individuals with cardiac risk-factors including atrial fibrillation, diabetes hypertension and raised lipid levels did not.

Conclusion and Relevance

We have observed a persistent trend towards treatment of more marginal degrees of hypothyroidism. A substantial risk of developing a suppressed TSH following therapy persists. Large-scale prospective studies are required to assess the risk/benefit ratio of current practice.

Introduction

Primary hypothyroidism is one of the commonest chronic disorders in Western populations[1, 2] and largely managed in primary care[3, 4]. Levothyroxine prescriptions in the USA have increased substantially over recent years rising 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[7, 8].

Several factors are likely to have contributed to this rise. In England and Wales a proportion may be attributed to a fall in the average duration of prescriptions from 60 to 45 days[8]. Thyroid function testing has also increased substantially[9, 10] in any year 18-25% of individuals have their thyroid function tested[4, 9, 11] which is likely to have resulted in increased case-finding. However an additional factor may be a lowering of the thyroid stimulating hormone (TSH) threshold at levothyroxine initiation. This practice would be important to identify, as this might be associated with more marginal benefits and increased relative risk of patient harm. Studies before 2001 suggested that between 15-20% of individuals on levothyroxine are over-treated and develop a low TSH[12, 13], most likely due to inadequate monitoring. Over-treatment is associated with an increased risk of fractures[14] and atrial fibrillation[15].

Current American Thyroid Association (ATA) guidelines[16] only recommend consideration of levothyroxine therapy at TSH levels <10mU/l when there are clear symptoms of hypothyroidism, positive thyroid autoantibodies or evidence of atherosclerotic cardiovascular disease/heart failure (evidence level B). Data from Scotland in 2001 indicated that the majority of patients had levothyroxine initiated at

TSH levels <10mU/l, with 45-48% of patients commencing therapy with a TSH <6mU/l[10].

In the present study we used a large UK population-based database to examine trends in TSH levels pre and post levothyroxine initiation since 2001, and assess the potential for adverse outcomes from current practice.

Subjects and Methods

Cohort

Clinical data and dates of levothyroxine prescriptions and TSH levels were extracted on primary care patients from the GPRD (now called the Clinical Practice Research Datalink www.CPRD.com). The GPRD has been well described previously[17] and is the largest computerized database of anonymized medical records from primary care linked with other healthcare data. It is well validated for research on clinical diagnoses[18, 19], drug exposure and patient safety[20-22].

At the time of this study the GPRD contained computerized medical records of over 5,000,000 people from 508 primary care practices throughout the UK. Details of our dataset, including participants' eligibility criteria, are provided in the **supplementary online material**.

Identification of TSH and free thyroxine results generating first levothyroxine prescription

We studied incident (first) levothyroxine prescriptions. A TSH/free thyroxine (FT_4) was regarded as relevant if it occurred in the 90 days prior to levothyroxine initiation. If more than one result was available, then the one closest to date of levothyroxine initiation was used. Prescribing rates were calculated using baseline GPRD denominator data and adjusted after removing from the denominator the person-time of individuals prescribed levothyroxine after 2001, from the date of their levothyroxine prescription until either the end of the study period or their exit from GPRD. Individuals we excluded such as those prescribed levothyroxine relating to pregnancy were also removed from the person-years at risk.

Identification of factors potentially relevant to prescribing levothyroxine at the time of initiating treatment

Medical codes were studied for each patient in the 60 days prior to the relevant TSH test. Codes regarding symptoms, examination findings, diagnoses, clinic appointments and investigations were grouped into categories specified *a priori* (**Supplementary Table 5**). For example the atrial fibrillation/tachycardia category had several medical codes including "atrial fibrillation" "AF" "paroxysmal AF" pertaining to it. Individuals could appear in more than one category, but would only be counted once within a category.

TSH levels post-levothyroxine

Using the date of index levothyroxine as time zero, the TSH levels post-levothyroxine therapy were studied for up to 5 years. Time bands were split into 6-month intervals. Individuals could only appear once in each time-band. If 2 or more TSH values were available for a patient in the same 6-month period, the later TSH level was used. We studied TSH values 30-36 months and 54-60 months after levothyroxine initiation. TSH levels below 0.5mU/l were regarded as low and values below 0.1mU/l were regarded as suppressed in keeping with previous regional UK studies[10, 15]. Univariable logistic regression was used to study the odds of developing a suppressed TSH at 5 years post levothyroxine for sex, age, year, TSH at index levothyroxine prescription and key clinical characteristics prior to levothyroxine therapy. Multivariable logistic regression was then undertaken adjusting for sex, age, year, and TSH at index levothyroxine prescription.

All statistical analysis was undertaken using STATA version 12 (STATACORP, College Station, TX, USA).

Regulatory approval

Access to the GPRD dataset 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.

Results

Characteristics of individuals prescribed levothyroxine

The flow of patients in our dataset is shown in **Supplementary Figure 1**. 57,318 individuals matching our inclusion criteria were identified of whom 53,333 (93.0%) had a prescription within 90 days after a documented TSH level. 1,035 individuals had a levothyroxine prescription related to pregnancy and were excluded. The median age at index levothyroxine was 59 years (IQR 47-72) with a Male:Female ratio of 1:3.74.

Prescribing patterns in initiating levothyroxine therapy

Overall the median TSH prior to index levothyroxine between 2001-2009 was 8.20mU/l (IQR 5.91–13.9) (**Figure 1**). The annual median TSH level fell over the study period, from 8.67mU/l to 7.88mU/l (**Figure 2)**. This fall reflected a reduction in individuals with an initial TSH level greater than 10mU/l (42.1% to 35.9%) and a rise in those treated for a TSH in the range 4-10mU/l (49.8% to 58.1%) (**Table 1, Supplementary Table 1)**. The odds ratio of having an index levothyroxine prescription with a TSH level less than 10mU/l at the end of the study period, compared to the beginning after adjusting for age at prescription, sex, presence of diabetes/hypertension/raised lipids, and presenting symptom was 1.30 (95%CI 1.19, 1.42) p=<0.001.Free thyroxine (FT_4) levels were available in 66.6% of subjects at index prescription see **Supplementary Online Material**. The odds of starting levothyroxine with a TSH of <10mU/l at the end of the study in the subgroup of subjects with a TSH <10mU/l and a FT_4 in the reference range was slightly lower compared to those with a TSH <10mU/l alone OR=1.17 (95%CI 1.00, 1.36) p=0.05.

Between 2001-2006 there was a 1.81 fold increase in the rate of index levothyroxine prescriptions. After this time the rate of new prescriptions did not substantially change despite a continuing decline in the median TSH at index levothyroxine (**Figure 2**). Age-standardized rates comparing 2001 prescribing to 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 dataset was taken into account. Age-stratified rates are shown in **Supplementary Table 2.**

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

Clinical data in subjects prescribed levothyroxine

The symptoms and signs recorded in the 60-day period prior to initiating levothyroxine are shown in **Supplementary Table 5.** The commonest symptoms were tiredness (19.3%), weight gain/obesity (14.0%) and depression (5.8%). Individuals with recorded sleep apnea (23.1mU/l), or peri-orbital edema (32.7mU/l), had median TSH levels substantially greater than 10mU/l consistent with their presence in more profound hypothyroidism. Individuals starting levothyroxine with a TSH in the range 4-10mU/l and a normal FT_4 rather than a low FT_4 were more likely to be older, have cardio-vascular risk-factors, but not to have tiredness obesity or depression at baseline (Supplementary Table 4). Whereas individuals prescribed levothyroxine with a TSH between 4-10mU/l rather than a TSH >10mU/l were more likely to be female, older, prescribed levothyroxine after 2004, or have cardiovascular

risk factors, with trends also observed for depression/tiredness (**Supplementary Table 4B**).

TSH levels post-initiation of levothyroxine

Trends are shown in (**Fig 3A+3B**). Not all individuals had TSH levels repeated regularly. The dataset was created in 2010, at which time we had TSH levels at 3 year follow-up in 17,154 individuals (51.5% of those with 3 year follow-up) and 5 year follow-up in 9,252 individuals (39.7% of those with 5 years follow-up) During the period, 6 month–5 years post levothyroxine initiation the percentage of those with a TSH less than 0.1mU/l increased from 2.7%–5.8% and those with a TSH between 0.1-0.5mU/l increased from 6.3-10.2%; this was accompanied by a fall in those with a TSH between 5-10 mU/l from 29.8% to 18.8% (**Fig 3B**). 2.7% of individuals still had a TSH greater than 10mU/l even 5 years after starting levothyroxine.

Individuals' baseline characteristics appeared to substantially influence the odds of developing a suppressed TSH 5 years post-levothyroxine (**Table 2**): these included being female (OR=1.57, 95%CI 1.18, 2.08 p=0.002), presenting with tiredness (OR=1.51, 95%CI 1.13, 2.01, p=0.005), or depression (OR=1.63, 95%CI 1.02, 2.60, p=0.04) having a TSH value less than 4mU/l (OR=1.83 95%CI 1.35, 2.47 p=<0.001) or greater than 10mU/l (OR= 2.68, 95%CI 2.07, 3.44, p=<0.001). Having cardiovascular risk-factors at baseline was generally associated with reduced odds of a low TSH at 5 year follow-up, although the presence of atrial fibrillation or diabetes had wide confidence intervals that included equality (**Table 2)**.

Discussion Our results show that the annual rate of new levothyroxine prescriptions increased 1.74 fold over our study period. During this time there was a fall in median TSH threshold at index levothyroxine prescription from 8.67mU/l to 7.88mU/l with a 30% increase in odds of having levothyroxine initiated at a TSH level <10mU/l.

This increase in rate was not simply due to an ageing population as age-adjusted and age-stratified rates also demonstrated a rise (**Supplementary Table 1+2**). Furthermore, it was not due to shorter prescriptions as 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 TSH threshold for initiating treatment could explain this increase. Since our dataset does not contain information on individuals that never received levothyroxine, we cannot calculate the relative contribution of these two factors.

Even though it may only partly account for the overall increase in the number of people being started on levothyroxine, the reduction in TSH threshold is important as it implies the net benefits of levothyroxine therapy are becoming more marginal. For example, the highest age-adjusted and age- stratified rates of new levothyroxine prescribing (even with a normal FT_4) were observed in the elderly (**Supplementary Table 2**) and the elderly had the highest odds of being prescribed levothyroxine with a TSH between 4-10mU/l (Supplementary Table 4B). A substantial number of these prescriptions may be unwarranted as mild TSH elevations may be a normal manifestation of ageing[24]. Furthermore, there is evidence that treatment of subclinical hypothyroidism in subjects over the age of 70 has less cardiovascular benefit than in younger subjects[25] and over-treatment in the elderly may cause net harm[14, 26].

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

The majority of patients (61%) in our dataset were initiated on levothyroxine with a TSH level of less than 10mU/l (**Figure 1**). FT_4 values were available in 68.3% individuals prescribed levothyroxine with a TSH between 4-10mU/l and 82.7% of this group had FT_4 values within the reference range, consistent with a diagnosis of subclinical hypothyroidism (**Supplementary Table 4A**). The evidence for clinical benefit of treatment in this range outside of pregnancy is weak and as a result recent ATA guidelines only recommend treatment here if there are clear symptoms of hypothyroidism, positive thyroid autoantibodies or evidence of atherosclerotic cardiovascular disease/heart failure[16]. 39.4% of individuals prescribed levothyroxine for subclinical hypothyroidism had a history of hypertension, raised lipids, atrial fibrillation or diabetes before levothyroxine initiation with 46.9 % having either these cardiovascular risk-factors or documented symptoms consistent with hypothyroidism prior to levothyroxine (Supplementary Table 4A/Supplementary Table 5). Although some data may be unrecorded, it suggests that up to 50% of individuals with subclinical hypothyroidism are treated outside of guidelines. However it is somewhat

reassuring that individuals with cardiovascular risk-factors were preferentially initiated on levothyroxine in the TSH 4-10mU/l group compared to those without these comorbidities (**Supplementary Tables 4 A+B**). Another concern is that 34.6% of individuals prescribed levothyroxine with a TSH level between 4-10mU/l only had one abnormal TSH measured before initiating therapy contrary to ATA guidelines[16, 28](**Supplementary Table 3**). Greater use of confirmatory testing might reduce unnecessary prescriptions given that 46% of individuals with a TSH between 4.5-7.0mU/l reverted to normal within 2 years without treatment[29]; especially as the indication for levothyroxine is rarely reviewed once started; in our dataset over 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 initiated on levothyroxine, it is important to examine the potential for harm. 5 years after levothyroxine initiation 10.2% of patients had a low TSH and 5.8% had a suppressed TSH. Individuals with a suppressed TSH are at a 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 of potential benefit from treatment of subclinical hypothyroidism. Individuals with cardiac risk factors had reduced odds of developing a suppressed TSH, suggesting that prescribers were aware of this risk, but 10.6% of individuals treated for subclinical hypothyroidism who had cardiovascular risk factors ended up with a low TSH level which may have actually increased their risk.. A recent meta-analysis also suggested that the risk of osteoporosis is increased in individuals with a TSH in the low-normal range, even if not suppressed[31] highlighting the potential for net harm even with marginal over-treatment. Individuals with tiredness or depression at baseline but not those with

diabetes or obesity were more likely to be over-replaced 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.

There are now 1.6 million individuals in the UK on long-term levothyroxine most of whom have been prescribed it for primary hypothyroidism[3]. If current practice continues, up to 50% of people on levothyroxine may have been prescribed it without an accepted indication, and with potential for net harm if they develop even a low TSH (as occurred in12.2% of individuals prescribed levothyroxine for subclinical hypothyroidism in our dataset). In the USA the prevalence of hypothyroidism is similar to the UK[12] and one might therefore expect approximately 5 million individuals to be on long-term levothyroxine for primary hypothyroidism; if prescribing patterns in the USA are similar over 2 million individuals may be on levothyroxine with limited evidence of benefit.

The strengths of our study include the use of a large population-based dataset from many different practitioners collected over a long period. Detailed clinical data allowed us to ascertain cases of primary hypothyroidism and 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 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 TSH results were unavailable and transcription errors were eliminated. We also had substantial data on cardiovascular risk-factors and

symptoms pre levothyroxine to enable us to investigate the appropriateness of levothyroxine prescriptions.

The limitations include the lack of data on individuals who did not receive a levothyroxine prescription and the lack of reliable data on thyroid peroxidase antibody titres. Furthermore data on FT_4 measurements were not available in all subjects, as this estimation is not always routine practice and follow-up TSH values were only available in 40% of the cohort at 5 years. Hence there is the potential for bias in the subsection of subjects analysed however there was no observed difference in sex or age-group between those with FT_4 levels available and those without see Supplementary Online Material Table 4A. The TSH assay used varied between individuals, and we were unable to account for this, although the majority of assays have similar thresholds for defining low or suppressed TSH. Finally, we were unable to identify and exclude from our denominator data individuals who were prescribed levothyroxine prior to 2001 (and hence not at risk of receiving another first thyroxine prescription) We were also not able to adjust for individuals excluded by GPRD in the creation of our dataset. However we consider that the impact of this on the accuracy of our results is likely to be small, particularly with regard to the relative rate.

In summary, our results suggest there is widespread prescribing of levothyroxine for borderline TSH levels where there is limited evidence of benefit. This practice may even be harmful, given the relatively high risk of developing a suppressed TSH after treatment. Whilst thyroidologists are still debating whether subclinical hypothyroidism should be more widely treated, it is increasingly apparent that this is already happening in primary care. Randomised controlled trials with sufficient power

to assess the health consequences of borderline/subclinical hypothyroidism and its treatment are urgently needed to refine current levothyroxine prescribing and indicate the balance of risks and benefits of current practice.

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Disclaimer: This study is based in part on data from the full feature GPRD obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. However, the interpretation and conclusions contained in this study are those of the authors alone.

Table and Figure Legends

Table 1 TSH levels prior to index levothyroxine prescription by year and the odds of an index prescription of levothyroxine arising from a TSH greater than 10mU/l by year, using prescribing data of levothyroxine in 2001 as baseline.

Table 2 The odds of developing a suppressed TSH 5 years post levothyroxine therapy by sex, age-group, index TSH level, presence of cardiovascular risk-factors and motivation for prescribing levothyroxine

Figure 1 Histogram of TSH levels at index prescription of levothyroxine

Figure 2 Median TSH at index prescription and rate of index levothyroxine prescription by year

Figure 3A TSH levels post initiation of levothyroxine – under-replaced

Figure 3B TSH levels post initiation of levothyroxine – over-treated

Table 1 TSH levels prior to index levothyroxine prescription by year and the odds of an index prescription of levothyroxine arising from a TSH less than 10mU/l by year, using prescribing data of levothyroxine in 2001 as baseline.

Year	% TSH	% TSH	% TSH	Model 1#			Model 2#			Model 3#		
	< 4.0mU/l	4 -10mU/l	> 10 mU/l	Odds Ratio	95%CI	p value*	Odds Ratio	95%CI	p value*	Odds Ratio	95%CI	p value*
2001	8.08	49.8	42.1	1			1			1		
2002	5.57	53.1	41.3	1.03	0.94 - 1.12	0.49	1.02	0.94 – 1.12	0.59	1.02	0.93 - 1.11	0.68
2003	5.51	53.3	41.2	1.04	0.95- 1.12	0.41	1.04	0.95 – 1.13	0.45	1.03	0.94 – 1.12	0.53
2004	6.63	54.3	39.1	1.14	1.04 – 1.23	0.003	1.14	1.05 – 1.24	0.002	1.13	1.04 – 1.22	0.005
2005	5.44	56.0	38.5	1.16	1.04 – 1.25	<0.001	1.17	1.08 – 1.27	<0.001	1.14	1.05 – 1.24	0.001
2006	5.84	57.4	36.7	1.27	1.15– 1.35	<0.001	1.27	1.17 – 1.38	<0.001	1.24	1.14 – 1.34	<0.001
2007	5.22	57.3	37.4	1.22	1.11 – 1.32	<0.001	1.23	1.13 – 1.34	<0.001	1.19	1.10 – 1.31	<0.001
2008	6.67	55.8	37.5	1.18	1.11 – 1.32	<0.001	1.24	1.14 – 1.35	<0.001	1.20	1.10 – 1.31	<0.001
2009	6.28	58.1	35.6	1.32	1.20 – 1.43	<0.001	1.34	1.23 – 1.46	<0.001	1.30	1.19 – 1.42	<0.001

52,298 individuals in model
* Calculated using the Wald test
Model 1 Crude
Model 2 Adjusted for age at levothyroxine initiation, and sex,
Model 3 Adjusted for age at levothyroxine initiation, and sex, diabetes prior to levothyroxine initiation, hypertension or raised lipid levels prior to levothyroxine initiation presenting symptom,

Table 2 The odds of developing a suppressed TSH 5 years post levothyroxine therapy by sex, age-group, index TSH level, presence of cardiovascular risk-factors and motivation for prescribing levothyroxine

Characteristic	TSH 0.1 -0.5 mU/l						TSH < 0.1 mU/l					
	Odds ratio	(95%CI)	p value*	Odds ratio#	(95%CI)#	p value#*	Odds ratio	(95%CI)	p value*	Odds ratio#	(95%CI)#	p value#*
Sex												
Male	1			1			1			1		
Female	1.40	(1.19- 1.64)	<0.001	1.45	(1.23 – 1.73)	<0.001	1.55	(1.17 – 2.04)	0.002	1.57	(1.18 -2.08)	0.002
Age group												
18 – 45	1						1			1		
45 – 70	0.81	(0.70 – 0.93)	0.003	0.82	(0.70 – 0.95)	0.009	0.71	(0.58 – 0.89)	0.002	0.76	(0.61 – 0.94)	0.01
70 – 99	0.52	(0.44 – 0.62)	<0.001	0.54	(0.45 – 0.65)	<0.001	0.38	(0.28 – 0.51)	<0.001	0.41	(0.30 - 0.55)	<0.001
Year of index prescription												
2001	1			1			1			1		
2002	0.95	(0.80-1.14)	0.64	0.97	(0.80 -1.18)	0.78	1.03	(0.75 – 1.39)	0.87	1.06	(0.78 – 1.45)	0.70
2003	0.97	(0.82 -1.16)	0.79	0.98	(0.82 – 1.18)	0.86	1.30	(0.98 – 1.72)	0.07	1.37	(1.03 – 1.82)	0.03
2004	0.75	(0.63 -0.90)	0.002	0.78	(0.65 – 0.94)	0.009	0.91	(0.68 – 1.22)	0.53	0.97	(0.72 – 1.30)	0.83
TSH at index prescription												
< 4.0 mU/l	1.49	(1.24 – 1.79)	<0.001	1.44	(1.20 – 1.72)	<0.001	1.96	(1.46 – 2.64)	<0.001	1.83	(1.35 – 2.47)	<0.001
4.0 - 7.0 mU/l	1			1			1			1		
7.0 – 10.0 mU/l	1.18	(0.98 – 1.42)	0.08	1.19	(0.99 – 1.41)	0.002	1.21	(0.87 – 1.69)	0.24	1.22	(0.88 - 1.71)	0.21
10 + mU/l	2.54	(2.19 – 2.94)	<0.001	2.82	(2.22– 2.99)	<0.001	2.64	(2.05 – 3.39)	<0.001	2.68	(2.07 – 3.44)	<0.001
Presence of AF												
No	1						1			1		
Yes	0.72	(0.53 – 0.98)	0.04	0.87	(0.63 – 1.20)	0.40	0.32	(0.15 – 0.68)	0.003	0.42	(0.20 – 0.90)	0.03
Raised blood pressure/lipids												
No	1						1			1		
Yes	0.70	(0.61 – 0.80)	<0.001	0.81	(0.71- 0.94)	0.004	0.55	(0.44 – 0.71)	<0.001	0.68	(0.53 – 0.87)	0.002
Presence of Diabetes												
No	1			1			1			1		
Yes	0.63	(0.48, 0.83)	0.001	0.81	(0.61 – 1.07)	0.15	0.59	(0.37, 0.95)	0.03	0.78	(0.48 - 1.27)	0.32
T4 at levothyroxine initiation												
Normal	1			1			1			1		
Low	2.02	(1.73, 2.36)	<0.001	1.60	1.36 – 1.89	<0.001	1.81	(1.41 – 2.34)	0.001	1.37	(1.04 - 1.81)	0.02
Clinical reasons for TSH measurement												
Depression	1.91	(1.41 – 2.58)	<0.001	1.64	(1.19 - 2.27)	0.003	1.86	(1.18 – 2.95)	0.008	1.63	(1.02 – 2.60)	0.04
Tired	1.51	(1.25 – 1.82)	<0.001	1.56	(1.28 – 1.89)	<0.001	1.69	(1.27 – 2.24)	<0.001	1.51	(1.13 – 2.01)	0.005
Weight gain/obesity	1.31	(1.05 – 1.63)	0.02	1.26	(1.00 -1.59)	0.05	1.10	(0.75 – 1.62)	0.61	1.03	(0.70 – 1.51)	0.89
Peripheral Oedema	0.78	(0.52 -1.17)	0.23	0.86	(0.57 -1.30)	0.49	0.50	(0.22 – 1.14)	0.10	0.57	(0.25 – 1.29)	0.18
Menstrual irregularities	1.29	(0.90 – 1.83)	0.16	0.99	(0.68 – 1.42)	0.94	1.68	(1.01 – 2.80)	0.04	1.11	(0.66 – 1.87)	0.69
Diabetes review	0.79	(0.55 -1.15)	0.23	0.90	(0.61 -1.32)	0.58	0.66	(0.34 – 1.29)	0.23	0.79	(0.40 – 1.56)	0.50
General Screening	1.15	(0.85 – 1.58)	0.36	1.08	(0.78 – 1.51)	0.63	0.96	(0.56 – 1.66)	0.90	0.99	(0.57 – 1.72)	0.99

*Calculated using the Wald test

Adjusted for sex, age group, year of index prescription, TSH at index prescription 9,252 individuals with 5 year follow-up

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