Trends, Determinants and Associations of Treated Hypothyroidism in the United Kingdom, 2005 – 2014

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Context: Recent reports suggest that prescriptions for thyroid hormones have increased.

Objective: To analyse recent trends in and determinants of prevalence of treated hypothyroidism across the United Kingdom (UK).

Design and setting: UK-wide data held by the National Health Service and the Office of National Statistics were examined.

Main outcome measures: Trends in prevalence of treated hypothyroidism between 2005 till 2014 were analysed. Furthermore, determinants of variation of treated hypothyroidism prevalence across health areas in the UK (n=237) in 2014 and its association with other health conditions were explored by multivariate linear regression analyses.

Results: The prevalence of treated hypothyroidism increased from 2.3% (1.4 million) to 3.5% (2.2 million) of the total UK population between the years 2005 – 2014 and is projected to rise further to 4.2% (2.9 million) by 2025. There was large geographical variation of treated hypothyroidism across the UK with London having the lowest (1.4%) and the Western Isles of Scotland having the highest (6.3%) prevalence. Prevalence of treated hypothyroidism was independently related to health areas with higher proportion of individuals who were female, White, obese, and negatively associated with prevalent cigarette smokers. Prevalence of treated hypothyroidism was significantly associated with

frequency of prevalent atrial fibrillation but not with other major health conditions including ischaemic heart disease and osteoporosis.

Conclusions: Between 2005 and 2014, prevalence of treated hypothyroidism increased across the UK, has wide geographical variation, and is likely to increase further for the foreseeable future. Clinical effects and cost-effectiveness of the trend in increasing treatment of hypothyroidism remains to be evaluated.

Introduction

Hypothyroidism is a common endocrine condition characterised by raised serum thyrotropin (TSH) and reduced circulating thyroid hormone concentrations. Hypothyroidism is more common in females and peak incidence rates occur between 40-50 years of age with autoimmune thyroid disease as the most frequent aetiology (1). Furthermore, over the last few decades there has been an increasing interest in subclinical hypothyroidism (SCH) – a milder condition characterised by a raised serum TSH and with thyroid hormones in the reference range. Current guidelines recommend treatment of SCH only in specific situations such as younger individuals with hypothyroid-symptoms (2) or pregnant women who are TPOAb (thyroid peroxidase antibody) positive (3). Data from small samples suggest that the prevalence of treated hypothyroidism (both overt and SCH) in the UK and the USA is approximately 3% (4 – 6). Levothyroxine (LT4), a synthetic isomer of the thyroid hormone thyroxine, is the recommended and ubiquitously used treatment in patients with hypothyroidism (7, 8). Poor control of treated hypothyroidism, as evidenced by abnormal serum TSH levels, is seen in 35 – 60% of patients (9, 10) and is associated with adverse bone and cardiac outcomes (11).

Several recent reports have highlighted that prescribing of LT4 has increased both in the USA and the UK (12, 13). The reasons underlying these increases in LT4 prescribing are unknown. Previous reports suggest that increased propensity to treat older individuals, those with milder

elevation in serum TSH and reduced length of LT4 prescriptions might be factors associated with increased LT4 prescribing (9, 14, 15). However, contemporary data on the trends in the prevalence of treated hypothyroidism reflective of the overall population and current clinical practice are lacking. We, therefore, interrogated UK national databases to study recent trends in the prevalence of treated hypothyroidism and to evaluate population-based determinants between the various health-areas of the UK.

Methods

The aim of this analysis was to study trends in the overall prevalence of treated hypothyroidism in the UK between 2005 and 2014 and to quantify variations in prevalence of treated hypothyroidism at local health area population level. In addition, we sought to forecast prevalence of treated hypothyroidism for the future based on recent trends. To achieve this, UK-wide data held by the National Health Service (NHS) and the Office of National Statistics (ONS) was examined.

Health areas in the United Kingdom: Information regarding prevalence of medical conditions and health-related parameters in the year 2014 was obtained from the health body for each geographical area in the UK (n=237). These local health bodies have different structures and responsibilities but collect the same information. These are the Clinical Commissioning Groups in England (n=211), Health Boards in Wales

(n=7), NHS boards in Scotland (n=14) and Health and Social Care Trusts in Northern Ireland (n=5).

Quality Outcomes Framework database: The Quality and Outcomes Framework (QOF) is a major pay-for-performance program that was introduced into UK primary care in 2004 and accounts for approximately a quarter of general practice income. The QOF is intended to reward practices for the provision of 'quality care'. QOF points are achieved based on the proportions of patients on defined disease registers who receive defined interventions. Participation by practices in the QOF is voluntary, though participation rates are very high; for example, in 2015, the QOF dataset includes data from nearly 99% of GP practices in England that were open and active at some point in the reporting period (16). Hypothyroidism was one of several clinical conditions that were covered by the QOF until 2015, when it was no longer included. Data for each individual component country of the UK was obtained separately from independent databases for that country for the period between 2005 and 2014 (the last year for when the data was available) (Online appendix). A treated hypothyroidism case was defined by a LT4 prescription for any person of any age. Prevalence of treated hypothyroidism was calculated by dividing the number of patients with hypothyroidism on the QOF register with the total number of patients registered with all of the participating practices in each health area across the UK.

To assess variation in prevalence of hypothyroidism across the UK additional data on demographics (total population size, proportion aged more than 65 years, race and gender), mean index of multiple deprivation scores, percentage of tobacco smokers, percentage of population with obesity, and proportion of the population with concomitant potentially related medical conditions (ischaemic heart disease, heart failure, atrial fibrillation, hypertension, stroke/transient ischaemic attack, diabetes mellitus, depression, dementia, osteoporosis, and chronic kidney disease) were obtained for each health area from the QOF and/or the ONS database registrations in 2014. Details in Appendix Table 1 (online only).

Statistics

The association of demographic, social and lifestyle-related potential determinants (as independent covariates) with treated hypothyroidism prevalence (as the dependent variable) was analysed using multiple linear regression models. First, univariate regression models were fitted to identify relevant determinants and final models were built using a stepwise approach. Non-linearity was assessed by adding quadratic terms with subsequent visual inspection of regression plots and assessment of changes in the effect estimates and/or explained variance of the model (relevant non-linear effects were identified for percentage aged >65 years). Variables that were associated with treated hypothyroidism prevalence in univariate analyses were then combined into a multivariate analysis. Adjusted R-squared values were used to examine degree of variation in hypothyroidism prevalence that is explained by the model.

In addition, to assess the association of prevalence of treated hypothyroidism with other major health conditions, similar multivariate models were created with prevalence of these diseases as dependent variables and associated demographic, social, lifestyle-related, and prevalence of treated hypothyroidism as independent variables were combined in multivariate regression analyses. Furthermore, for each individual dependent variable other health conditions that could be causally linked were added to the final model. For example, prevalence of atrial fibrillation was added to the model assessing the association between stroke disease and hypothyroidism, and so on. Moreover, due to the number of diseases being evaluated (n=10), a p value of less than 0.005 was used to denote significance for this particular analysis. We calculated the variance inflation factor (VIF) to assess collinearity. To fulfil model assumptions, variables that had a high VIF (>2.5) were centred and standardised. Assumption of normal distribution of residuals of the model were assessed and confirmed by visual inspection of standardised residuals and Q-Q plots.

Linear trend forecasting was performed to estimate the projected estimate of the prevalence of treated hypothyroidism in the UK taking into account previous trends and the predicted changes in total population. Observed and fitted values were calculated using ARIMA (autoregressive integrated moving average) modelling adjusted for the projected total UK population until 2025. These population projections take into account population demographic change estimates (migration,

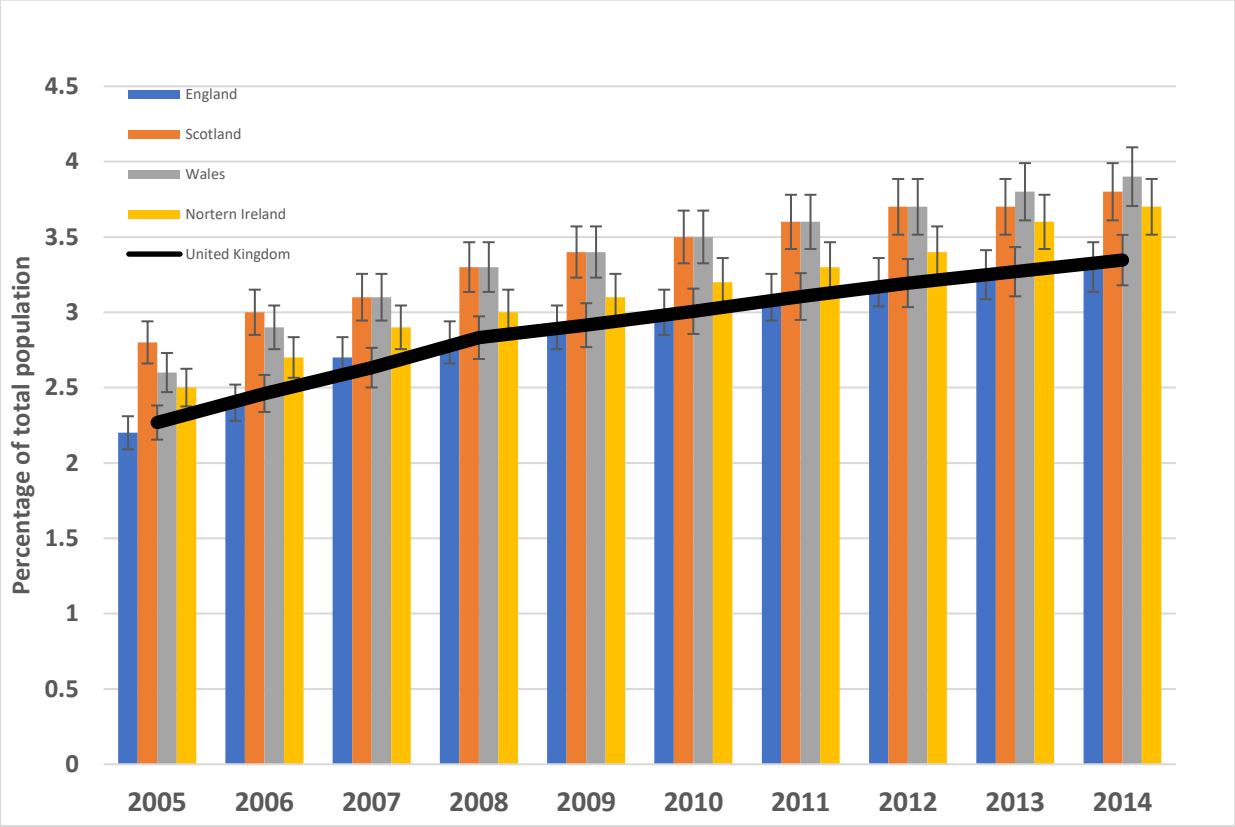
deaths, births and longevity) (17). From these forecasting models a stationary R-squared value (a measure that compares the stationary part of the model to a simple mean model, is preferable to ordinary r^2 when there is a trend or seasonal pattern and can range from negative infinity to 1) was calculated. The statistical software Minitab version 17.0 and SPSS version 22.0 (SPSS Inc., Chic, Ill, USA) were utilised for all analyses. Geo-mapping was undertaken using Tableau® version 10.3.

Results

Trends in Prevalence of treated hypothyroidism, 2005 - 2014

Overall, in the UK, the total number of individuals treated for hypothyroidism has increased by 57%: from 1.43 million (2.3%) to 2.24 million (3.5%) between 2005 and 2014. All the constituent countries in the UK have seen an increase in the prevalence of treated hypothyroidism over this period. However, there are consistent differences in prevalence between the constituent countries with England having the lowest and Scotland and Wales having the highest prevalence (Figure 1).

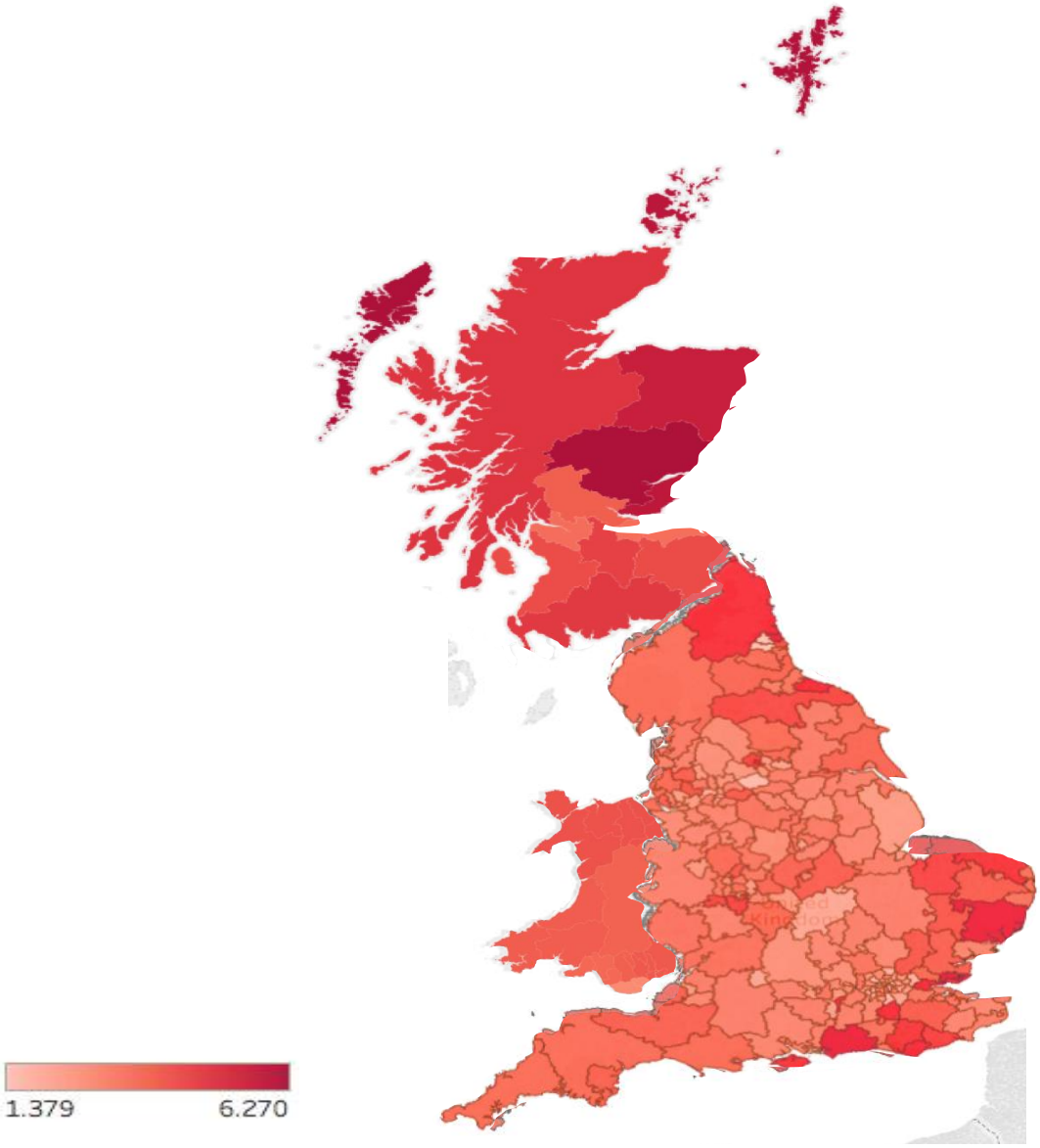
Figure 1. Prevalence of hypothyroidism in UK and constituent countries between 2005 and 2014.



Variation in prevalence of treated Hypothyroidism across the UK in 2014

Data was available from all 237 health areas of the UK comprising 9711 participating General Practices. The smallest area by population was Orkney (population of 20,803) whereas the largest was Greater Glasgow and Clyde (population of 1,316,735). There were striking differences in the prevalence of treated hypothyroidism across the various geographical areas of the UK, with the lowest prevalence in the Central London area (1.4%) and the highest in the Western Isles of Scotland (6.3%). (Figure 2)

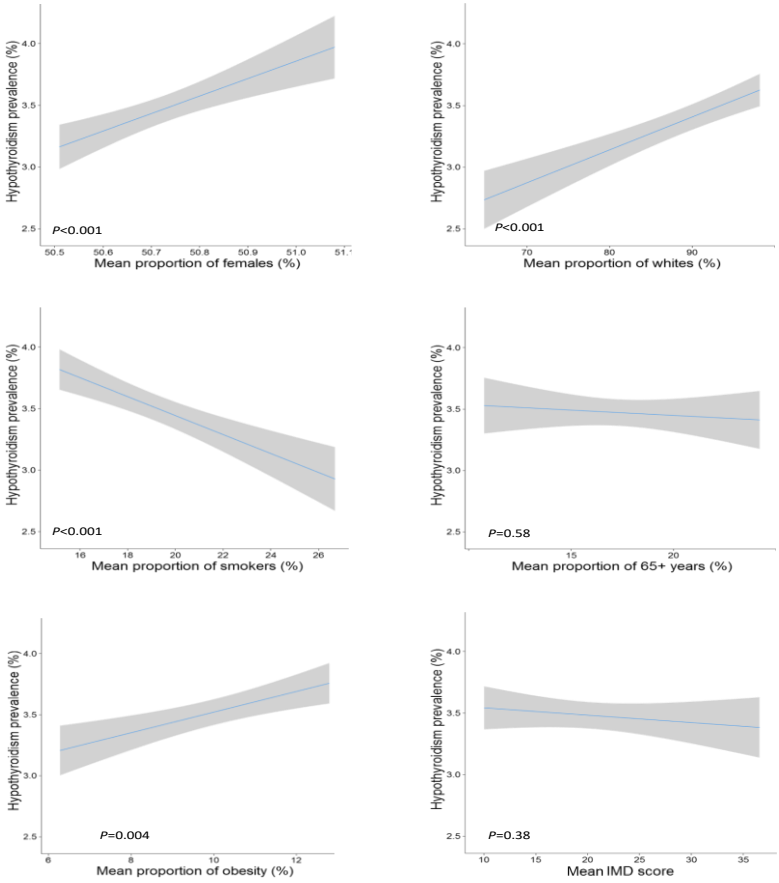
Figure 2. Variation in prevalence of hypothyroidism (as percentage of total local population) in 2014 by CCG area in England.



Determinants of prevalence of treated hypothyroidism across health areas

In univariate analysis, a number of variables were associated with the prevalence of treated hypothyroidism in each health area in the UK (Table 2, Appendix). In the multivariate analysis, prevalence of treated hypothyroidism was positively associated with the population health area percentage of females, percentage of White individuals, percentage prevalence of obesity, and negatively associated with percentage of smokers (Supplementary Table 3) (Figure 3). The proportion of individuals aged more than 65 years and the index of multiple deprivation score of each health area were no longer significantly related to prevalence of treated hypothyroidism after multivariate adjustment. The final model explained 52% of the variation in prevalence of treated hypothyroidism between the different health areas.

Figure 3. Determinants of treated hypothyroidism with population characteristics across different health areas of the United Kingdom.



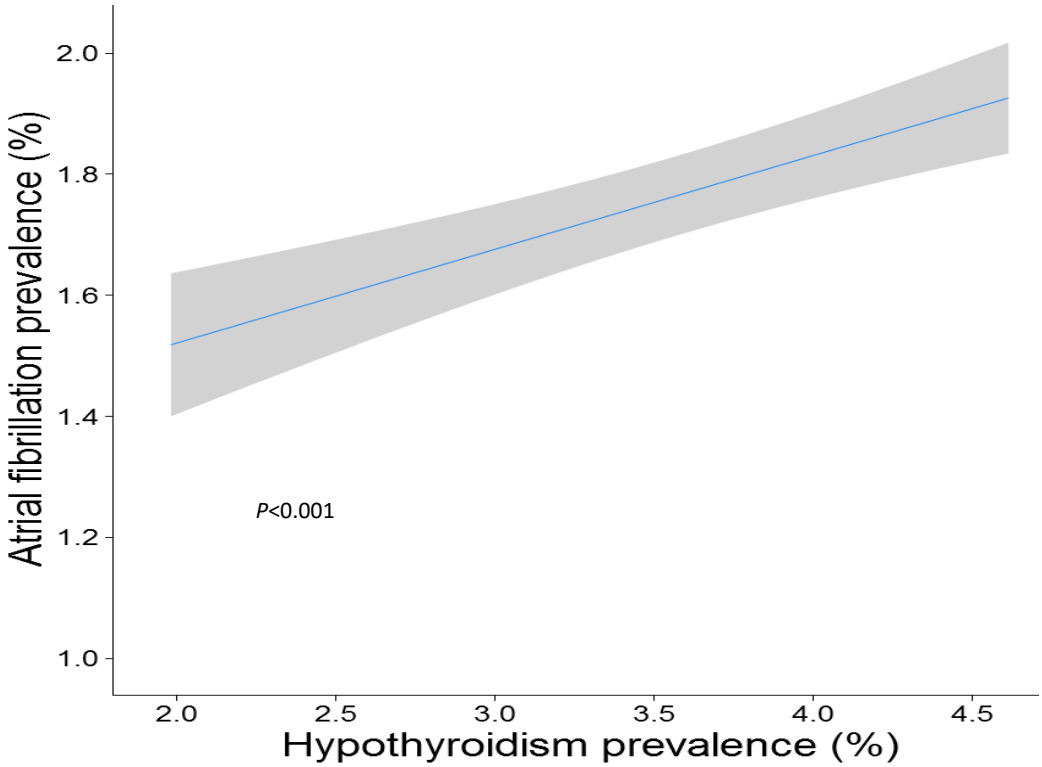
Plots show the association of population characteristics for studied areas with hypothyroidism prevalence as the predicted mean (blue lines) with 95% confidence interval (grey area). All y-axes show the range of the 10th percentile (lower limit) to 90th percentile (highest limit) for hypothyroidism prevalence. All analyses are from a multivariate linear regression including all displayed variables.

Associations of treated hypothyroidism with major health conditions across health areas

The prevalence of treated hypothyroidism in each health area was significantly associated with the prevalence of atrial fibrillation (β co-efficient 0.20, 95% confidence intervals 0.14 – 0.26, p< 0.001); this association attenuated after further addition of prevalent ischaemic heart disease (β co-efficient 0.10, 95% confidence intervals 0.04 – 0.15, p<

0.001) (Figure 4). All other major health conditions evaluated however showed no significant association with prevalent hypothyroidism. Specifically, there was no statistically significant association between prevalence of ischaemic heart disease, heart failure or osteoporosis with the prevalence of treated hypothyroidism across each of the health areas studied. The only exception was for the prevalence of hypertension, which remained significantly associated with prevalence of treated hypothyroidism even after additional adjustment for multiple analyses. However, the VIF was high suggesting high level of multicollinearity. This association therefore needs to be interpreted with caution (Table 4 in Appendix).

Figure 4. The association of prevalent treated hypothyroidism with prevalent atrial fibrillation.

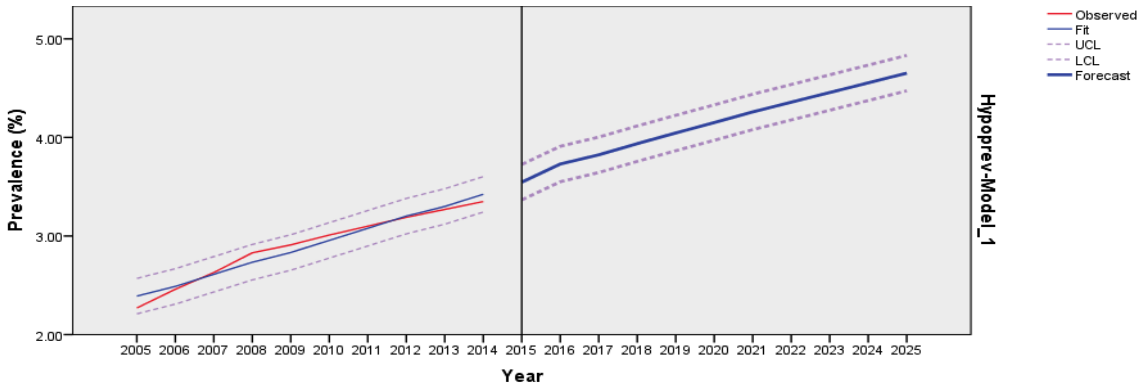


Plot shows the association of hypothyroidism prevalence per studied area with the mean prevalence of atrial fibrillation as the predicted mean (blue lines) with 95% confidence interval (grey area). All y-axes are show at the range of the 10th percentile (lower limit) to 90th percentile (highest limit). The analysis is adjusted for the proportion of age above 65 years, females, smoking, whites and obesity.

Projected trends in prevalence of treated hypothyroidism between 2015 and 2025

Forecasting trend modelling (stationary R-squared=0.965) suggests that the prevalence of treated hypothyroidism will increase further to 4.65% (95% CI 4.47 – 4.83) of the total population in the year 2025, taking into account UK population projected changes (figure 5). In 2025, the population of the UK is estimated to be just over 69 million and based on these models the number of people with treated hypothyroidism is therefore projected at 3.23 (95% CI 3.10 – 3.35) million.

Figure 5. Observed and forecasted prevalence of treated hypothyroidism in the United Kingdom up to the year 2025.



UCL – upper confidence limit, LCL – lower confidence limit

Discussion

The prevalence of treated hypothyroidism has increased in the UK in the last ten years (between 2005 and 2014) from 2.3 to 3.5%, thereby affecting 0.8 million more individuals. The reasons behind this increase are unclear but likely to be multifactorial and include a growing population with changes in demographic features and lifestyle. The results of our analysis do not provide any data on whether there is an increase in the incidence of hypothyroidism or if there is an increased propensity to detect and treat milder (subclinical) forms of the condition. There is wide geographic variation within the UK in the prevalence of treated hypothyroidism, which is partly explained by population demographics and lifestyle habits in that area such as proportion of women, white population, obesity levels and smoking habits. In 2014, two and quarter million individuals were being treated for hypothyroidism in the UK. If the current trend continues then it is likely that the prevalence of treated hypothyroidism will rise further to 4.65% of the total population (affecting just over 3.2 million individuals).

There is limited data available on trends in the prevalence of treated hypothyroidism at a national level. Analysis from several NHANES cycles in US adults (aged 20 years or older) showed that prevalence of thyroid hormone use increased from 5.1% in 1999-2000 to 6.4% in 2011-12 ($p=0.007$ for trend) (5). There were increases observed in both men and women (from 2 to 3.2% and 8 to 9.3%, respectively) as well as in younger (40 – 64-year olds: 5.9 to 6.9% and >65-year olds: 13 to 15%)

over this time-period. However, this data was obtained from a relatively small group (approximately 5000 participants per each NHANES cycle), although data were weighted to be nationally representative.

Interestingly, the biggest increase in thyroid hormone use was seen in non-Hispanic Whites. An interrogation of a large population-based health database in Tayside, Scotland found that the prevalence of treated hypothyroidism increased in both men and women, from 0.5 to 0.9% and 3.1 to 5.1%, respectively, between 1994 to 2001, which they attributed to increasing incidence and earlier diagnosis and treatment (18). Analysis of community prescription data from England showed that the number of prescriptions for thyroid hormones and the ingredient costs increased between 1998 and 2007 whilst the average length of prescriptions reduced (15). The data provided in the current analysis not only confirms these earlier results but also provides a more accurate and contemporary representation of treated hypothyroidism prevalence and variation across the entire population of the UK. Furthermore, as treated hypothyroidism is no longer on the QOF list of conditions for which data is gathered, it is unlikely that updates for the results of this analysis will be possible in the future using similar methodology.

There are several possible explanations for the increased trend observed in the prevalence of treated hypothyroidism. The total population of the UK has increased from 60.4 million to 64.6 million (an increase of 6.9%) between 2005 and 2014 (19); partly due to the increase in longevity (average lifespan has increased from 79.1 to 81.1 years between 2005

and 2015 - an increase of 2.5%) (20). These small increases however do not fully explain the large relative increase in the prevalence of treated hypothyroidism. Other possible reasons could be an increase in TFT checking leading to higher case-finding and treatment (21), increased propensity to treat milder forms of hypothyroidism particularly in older individuals (9), and a decline in cigarette smoking (22) leading to a rise in TSH and TPOAb levels (23). A raised serum TSH – a diagnostic hallmark of hypothyroidism – is influenced by increases with age but age-specific reference ranges are not utilised (24, 25). Our analysis however does not confirm that areas with higher proportion of older individuals (>65 years) have greater prevalence of treated hypothyroidism once other factors are taken into account. Other possible explanations for the increase in the prevalence of treated hypothyroidism could be due to the increasing use of ablative radioiodine and surgical therapies for both benign and cancerous thyroid diseases (26, 27) as well as increasing use of thyroid hormones during pregnancy (28) may be contributing to the apparent increase in the prevalence of treated hypothyroidism. Finally, increase in body mass index leads to an increase in serum TSH levels (29) and our analysis suggests that areas with higher prevalence of obesity are associated with higher prevalence of treated hypothyroidism.

The results of our analysis have several implications. It is increasingly becoming apparent that a mildly raised serum TSH (subclinical hypothyroidism) is not associated with adverse outcomes, particularly in

older individuals (30, 31, 32). Importantly, short-term trials of treatment of subclinical hypothyroidism in older individuals have not shown any improvement in symptoms or quality of life (33, 34). In addition, several observational studies in older individuals have a shown that higher serum thyroxine levels and/or lower circulating TSH concentrations are associated with worse outcomes (35 – 37). There are economic implications of increased LT4 prescribing as well with sparse evidence of cost-effectiveness particularly in the elderly. In the UK, a diagnosis of hypothyroidism leads to exemption from payment of prescription charges in people who would otherwise have to pay (38). Poor control of hypothyroidism whilst on treatment, as evidenced by abnormal serum TSH levels, is common (9, 10) and has been associated with increased risk of cardiovascular disease, atrial fibrillation and osteoporotic fractures (11). It is concerning that our data suggests that areas with higher prevalence of treated hypothyroidism have a higher frequency of atrial fibrillation, independent of other risk factors. However, it is unclear from our data whether there is a causal link between the two conditions. Reassuringly, the current analysis does not suggest that areas with higher prevalence of treated hypothyroidism are associated with higher occurrence of other major diseases such as ischaemic heart disease, heart failure, osteoporosis, depression or dementia.

Our data has several strengths. This is the first report, as far as we are aware, outlining the prevalence of treated hypothyroidism using a national-level database. The data obtained from the QOF has been shown

to be reliable and accurate in other conditions (39). In addition, we were able to analyse geographical variation across the entire country and study population-level factors that may be associated with the variation in prevalence. This analysis has some weaknesses too. The results obtained may not be generalised to other countries as the health care model and data collection methodology may be different. In addition, data was collected at population level and therefore several important individual-level factors such as demographic details (age, gender and smoking status), underlying aetiology of hypothyroidism, serum TSH and thyroid hormone level at diagnosis, control of hypothyroidism based on serum TSH levels on treatment, and symptoms and quality of life could not be assessed. Finally, our projections for the future are based on previous years' data on prevalence and changes in population numbers and/or demographics as well as clinical practice may affect actual observations. In conclusion, this analysis has shown that the diagnosis of treated hypothyroidism has increased in the UK between 2005 and 2014. There is wide geographical variation in the prevalence of the condition, partly related to population demographics in each area and, therefore, could change as a result of demographic or lifestyle changes. There appears to be an association between the prevalence of treated hypothyroidism and atrial fibrillation that requires further evaluation. The clinical outcomes and cost-effectiveness of increased treatment of hypothyroidism across various age and racial groups – mostly for marginally elevated serum TSH levels – needs to be studied in a prospective manner.

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Appendix

References for prevalence of hypothyroidism

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Table 1. Description of variables across each health area

Condition	Inclusion criteria	Description	Source
Age >65 years (%)		Percentage of individuals aged more than 65 years	ONS
Female (%)	All age groups	Percentage of women	ONS
White population (%)	All age groups	Percent of people who describe themselves as White	ONS
Smoking* (%)	Aged ≥ 15 years	Percentage of patients whose notes record current smoking status in preceding 24 months	QOF
Obesity* (%)	Aged ≥ 16 years	Percentage of patients with a BMI ≥ 30 kg/m^2 in preceding 12 months	QOF
Index of multiple deprivation	For each health area	Mean measure of relative deprivation	ONS
Hypothyroidism (%)	All age groups	Percentage of patients diagnosed with hypothyroidism and are currently treated with levothyroxine	QOF
Ischaemic heart disease (%)	All age groups	Patients diagnosed with coronary heart disease	QOF

Heart failure (%)	All age groups	Percentage of patients with a diagnosis of heart failure (diagnosed on or after 1 April 2006) which has been confirmed by an echocardiogram or by specialist assessment 3 months before or 12 months after entering on to the register	QOF
Atrial fibrillation (%)	All age groups	Percentage of patients diagnosed with atrial fibrillation	QOF
Hypertension (%)	All age groups	Percentage of patients diagnosed with established hypertension	QOF
Stroke/transient ischaemic attack (%)	All age groups	Percentage of patients diagnosed with a stroke or a transient ischaemic attack	QOF
Diabetes mellitus (%)	Aged ≥ 17 years	Percentage of patients	QOF
Depression* (%)	Aged ≥ 18 years	Percentage of patients with a new diagnosis of depression in the preceding year and who have had a bio-psychosocial assessment	QOF
Dementia (%)	All age groups	Percentage of patients diagnosed with dementia	QOF
Osteoporosis* (%)	Aged ≥ 50 years	Aged ≥ 50 and < 75 years with a record of a fragility fracture in the preceding year and a diagnosis of osteoporosis confirmed on DXA scan, or aged ≥ 75 years with a record of a fragility fracture in the preceding year	QOF
Chronic kidney disease (CKD)* (%)	Aged ≥ 18 years	Percentage of patients with CKD stages 3 – 5	QOF

*The prevalence rates for these conditions that are reported for specific age groups are based on appropriate age-banded list size information. For example, diabetes registers were expressed as a percentage of patients on practices lists who are aged 17 and over.

The Indices of Multiple Deprivation (IMD) provide a set of relative measures of deprivation for areas across England, based on seven domains of deprivation: Income Deprivation, Employment Deprivation, Education, Skills and Training Deprivation, Health Deprivation and Disability, Crime, Barriers to Housing and Services, Living Environment Deprivation.

QOF – Quality Outcomes Framework, ONS – Office of National Statistics

Table 2. Univariate relationship between percentage prevalence of treated hypothyroidism and population health area variables

	R value	**P value**
Age > 65 years (%)	0.47	<0.001
(Age > 65 years)^2	0.42	<0.001
Females (%)	0.49	<0.001
(Females)^2	0.49	<0.001
White population (%)	0.65	<0.001
(White population)^2	0.66	<0.001
Ischaemic Heart Disease (%)	0.66	<0.001
Diabetes mellitus (%)	0.14	0.03
Atrial fibrillation (%)	0.74	<0.001
Osteoporosis (%)	0.33	<0.001
Index of multiple deprivation score	-0.18	0.006
Obesity (%)	0.30	<0.001
Depression (%)	0.30	<0.001
Current Cigarette Smokers (%)	-0.13	0.03
Hypertension (%)	0.74	<0.001
Chronic kidney disease (%)	0.58	<0.001

Table 3. Variables associated with health area-wise percentage prevalence of hypothyroidism in the UK in 2014

	Beta-coefficient (95% CI)	**p value**
Age >65 years (%)	0.09 (-0.09 to 0.27)	0.31
Female population (%)	0.12 (0.01 to 0.02)	<0.001
White race (%)	0.01 (0.001 to 0.02)	<0.001
Current smokers (%)	-0.07 (-0.11 to -0.04)	<0.001
Obesity (%)	0.07 (0.02 to 0.12)	0.004
Index of multiple deprivation scores	-0.01 (-0.02 to 0.00)	0.14

Table 4. The association of the prevalence of major health conditions with health area-wise percentage prevalence of hypothyroidism independent of socio-demographic and lifestyle factors (and other relevant health conditions) in the UK in 2014

Major health conditions	**Beta-coefficient (95% CI)**	**P value[$]**	**Further adjusted P value***
Ischaemic heart disease	0.36 (0.26 to 0.47)	<0.001	0.27
Heart failure	0.11 (0.08 to 0.14)	<0.001	0.88
Atrial fibrillation	0.2 (0.14 to 0.26)	<0.001	<0.001
Hypertension	1.25 (1.01 to 1.49)	<0.001	<0.001[±]
Stroke/TIA	0.17 (0.12 to 0.22)	<0.001	0.92
Diabetes mellitus	0.09 (-0.06 to 0.24)	0.25	
Depression	-0.02 (-0.31 to 0.26)	0.87	
Dementia	-0.02 (-0.31 to 0.27)	0.88	
Osteoporosis	0.02 (-0.01 to 0.05)	0.18	
Chronic kidney disease	0.1 (0.07 to 0.49)	<0.001	0.47

$Adjusted for percentage aged > 65 years, squared term of percentage aged > 65 years, percentage of white, percentage of smokers, percentage of obesity, index of multiple deprivation and percentage prevalence of treated hypothyroidism.

*After further adjustment for additional relevant prevalent health conditions and/or number of dependent variables assessed (p<0.005 as significant); performed only for conditions that were significant at initial analysis

Ischaemic heart disease: further adjusted for prevalence of hypertension; Heart Failure: further adjusted for prevalence of hypertension and ischaemic heart disease; Stroke/TIA: further adjusted for prevalence of atrial fibrillation; Hypertension: further adjusted for multiple analyses; Atrial fibrillation: further adjusted for prevalence of ischaemic heart disease; Chronic kidney disease: further adjusted for prevalence of hypertension.

[±] High variance inflation factor (VIF = 6.5) suggesting moderate multicollinearity