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DOI:
10.1136/bmj.l4892

Thyroid replacement therapy, thyroid stimulating hormone concentrations, and long term health outcomes in patients with hypothyroidism: longitudinal study

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2019;366:l4892
http://dx.doi.org/10.1136/bmj.l4892

Accepted: 9 July 2019

ABSTRACT

OBJECTIVE

To explore whether thyroid stimulating hormone (TSH) concentration in patients with a diagnosis of hypothyroidism is associated with increased all cause mortality and a higher risk of cardiovascular disease and fractures.

DESIGN

Retrospective cohort study.

SETTING

The Health Improvement Network (THIN), a database of electronic patient records from UK primary care.

PARTICIPANTS

Adult patients with incident hypothyroidism from 1 January 1995 to 31 December 2017.

EXPOSURE

TSH concentration in patients with hypothyroidism.

MAIN OUTCOME MEASURES

Ischaemic heart disease, heart failure, stroke/transient ischaemic attack, atrial fibrillation, any fractures, fragility fractures, and mortality. Longitudinal TSH measurements from diagnosis to outcomes, study end, or loss to follow-up were collected. An extended Cox proportional hazards model with TSH considered as a time varying covariate was fitted for each outcome.

RESULTS

162 369 patients with hypothyroidism and 863 072 TSH measurements were included in the analysis. Compared with the reference TSH category (2-2.5 mIU/L), risk of ischaemic heart disease and heart failure increased at high TSH concentrations (>10 mIU/L) (hazard ratio 1.18 (95% confidence interval 1.02 to 1.38; P=0.03) and 1.42 (1.21 to 1.67; P<0.001), respectively). A protective effect for heart failure was seen at low TSH concentrations (hazard ratio 0.79 (0.64 to 0.99; P=0.04) for TSH <0.1 mIU/L and 0.76 (0.62 to 0.92; P=0.006) for 0.1-0.4 mIU/L). Increased mortality was observed in both the lowest and highest TSH categories (hazard ratio 1.18 (1.08 to 1.28; P<0.001), 1.29 (1.22 to 1.36; P<0.001), and 2.21 (2.07 to 2.36; P<0.001) for TSH <0.1 mIU/L, 4-10 mIU/L, and >10 mIU/L. An increase in the risk of fragility fractures was observed in patients in the highest TSH category (>10 mIU/L) (hazard ratio 1.15 (1.01 to 1.31; P=0.03)).

CONCLUSIONS

In patients with a diagnosis of hypothyroidism, no evidence was found to suggest a clinically meaningful difference in the pattern of long term health outcomes (all cause mortality, atrial fibrillation, ischaemic heart disease, heart failure, stroke/transient ischaemic attack, fractures) when TSH concentrations were within recommended normal limits. Evidence was found for adverse health outcomes when TSH concentration is outside this range, particularly above the upper reference value.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Hypothyroidism is highly prevalent and can substantially affect patients' wellbeing

No specific optimal target for thyroid stimulating hormone (TSH) concentration exists in the context of thyroid hormone replacement

Whether variation in TSH concentration within normal limits may significantly affect patients' outcomes remains unclear

WHAT THIS STUDY ADDS

No clinically meaningful difference in the pattern of long term health outcomes (mortality, cardiovascular disease, fractures) was seen when TSH concentrations were within recommended normal limits

Compared with the reference TSH category (2-2.5 mIU/L), risk of ischaemic heart disease, heart failure, and fragility fractures was increased at high TSH concentrations (>10 mIU/L)

Mortality was increased in both the lowest and highest TSH categories (<0.1 and >4 mIU/L), compared with 2-2.5 mIU/L

This study provides strong support for the current recommendations on the clinical management of hypothyroid patients and validates with hard evidence the latest guidelines

Introduction

Hypothyroidism is a highly prevalent global health problem that can substantially affect patients' wellbeing.[1] Lifelong treatment with thyroid hormone (replacement therapy) is needed when the diagnosis of persistent thyroid hormone deficiency is confirmed; consequently, levothyroxine is one of the most commonly prescribed drugs in Western countries,[2 3] and this is likely to increase further in the foreseeable future.[4]

Long term adverse health outcomes in patients with thyroid dysfunction and treatment targets to optimise these outcomes, generally monitored by serial measurements of thyroid stimulating hormone (TSH), have been extensively investigated. In particular, the cardiovascular effect of thyroid dysfunction and the negative ramifications of clinical (overt) thyroid hypofunction, mediated by changes in systemic vascular resistance, hypertension, hypercholesterolaemia, and

accelerated atherosclerosis, are well documented.[5 6] One of the targets for treatment with thyroid hormone replacement is to reverse such adverse effects. Current guidelines in Europe and the US recommend that replacement therapy should be aimed at resolving symptoms and achieving "normalisation" of TSH.[7 8] However, no specific optimal target for TSH exists in the context of thyroid hormone replacement. This uncertainty is reflected in the guidelines proposed by the American Thyroid Association Task Force and the statement issued by the British Thyroid Association Executive Committee, which suggest a wide range for TSH, 0.4-4.0 mIU/L, as an indication for optimal replacement,[7 8] after emphasising the scarcity of relevant evidence. TSH concentrations in this wide target range may be achieved by different doses of levothyroxine. However, from a physiological standpoint, a continuum of effects may plausibly occur across the spectrum of normal TSH concentrations[9]; the same human heart might behave differently at a pace dictated by a TSH concentration of 0.4 mIU/L compared with one of 4 mIU/L, both of which are considered normal. Evidence indicates that TSH and circulating thyroid hormone concentrations are quite tightly regulated on an individual basis,[10] but determining an individual's set point is not part of routine clinical practice, and replacement treatment is generally targeted in a wide reference range.

Although age specific TSH targets may be considered, especially in the context of high cardiovascular risk,[7] this strategy is based on the findings of studies in euthyroid or subclinically hypothyroid people. However, patients with hypothyroidism need a higher concentration of serum free thyroxine to achieve a normal TSH concentration compared with euthyroid controls.[11] Consequently, a hypothyroid patient receiving thyroid replacement therapy and a euthyroid patient with comparable TSH concentrations are not expected to have comparable circulating free thyroxine concentrations. The same is true of free triiodothyronine concentrations in patients who have had total thyroidectomy.[12] Therefore, any extrapolations on the association between optimal TSH concentrations and cardiovascular outcomes in patients receiving thyroid replacement therapy based on studies in euthyroid patients should be treated with caution, as serum free thyroxine and free triiodothyronine concentrations (relevant to cardiovascular physiology) may differ significantly between the two groups.

Moreover, in primary studies in euthyroid or subclinically hypothyroid patients,[13] and in the related meta-analyses and reviews,[14-20] thyroid function testing was done only at baseline. The potential therefore exists for misclassification bias in all estimates to date as a result of established and anticipated changes in thyroid hormone production over the life course of a patient, as well as instances of transient thyroid dysfunction (such as non-thyroidal illness or following the hyperthyroid phase of a painless thyroiditis). A person classified as euthyroid at baseline might go on to develop hypothyroidism, overt or subclinical, whereas those classified as subclinically hypothyroid might be found to be euthyroid on follow-up thyroid function testing.

Similar limitations affect studies assessing the association between thyroid dysfunction and risk of fracture,[21 22] and whether variation in TSH concentration within normal limits may significantly affect the skeleton or whether any effect is insignificant in clinical terms (fracture risk remains unaffected) remains unclear. This is further challenged by evidence suggesting that free thyroxine concentrations are the main driver of the above clinical outcomes.[23 24]

The aim of this study was to explore whether TSH concentration is associated with an increased risk of cardiovascular diseases, mortality, and fractures in patients with a diagnosis of hypothyroidism. We treated TSH as a time varying covariate to account for variation in TSH concentration over time within individuals.

Methods

Data source

We extracted data from The Health Improvement Network (THIN) database, an unobtrusive medical data collection scheme that collects anonymised information on patients from UK general practices that use Vision electronic medical records software. THIN contains data for approximately 15 million patients registered with 787 practices. The database consists of coded information on patients' characteristics, drug prescriptions, diagnoses, consultations, and diagnostic test results.[25]

Study design

This was a retrospective cohort study. The study period was 1 January 1995 to 31 December 2017.

Study population

To ensure high data quality, general practices were eligible for inclusion in the study from 12 months after the latest of the practice acceptable mortality reporting date (a measure of data quality)[26] and the date on which the practice began using electronic medical records. We included adults aged 18 years or above with a diagnosis of hypothyroidism; diagnosis was ascertained by a record of a clinical (Read) code. For each of the outcomes, we excluded patients with a record of that outcome at baseline. We also excluded patients without at least one measurement of TSH concentration after the diagnosis of hypothyroidism.

Patients were eligible for inclusion one year after joining the practice. To mitigate immortal time bias, we included only patients with an incident (new) record of hypothyroidism after the patient became eligible to join the study. The index date was the date of an incident record of a diagnosis of hypothyroidism. For each outcome, we followed patients from the index date until the earliest of the following events (exit date): patient died, last data collection from the practice, patient left the practice, patient diagnosed as having outcome, or study end date.

Exposure, outcomes, and covariates

The exposure was TSH concentration in patients with hypothyroidism. The primary outcomes were incidences of cardiovascular diseases, including ischaemic heart disease, heart failure, and stroke/transient ischaemic attack. Secondary outcomes were incidences of mortality, atrial fibrillation, all fractures, and fragility fractures. We considered fractures of the spine, hip, distal radius, and humerus to be fragility fractures. We used relevant clinical (Read) codes to define outcomes; these codes have been validated in several studies. In the UK, GPs are required to maintain a mandatory register of patients with ischaemic heart disease, heart failure, stroke/transient ischaemic attack, and atrial fibrillation as part of the Quality and Outcomes Framework; these diagnoses are therefore well recorded in primary care. Mortality data and clinical codes for cardiovascular diseases in THIN have been previously validated.[27-29]

Covariates included in the models were sex, age, socioeconomic status (measured using fifths of Townsend deprivation),[30] smoking status (smoker/non-smoker), body mass index, prescription for lipid lowering drug, diabetes, hypertension, and prescription for thyroxine as recorded at baseline. We categorised body mass index (kg/m^2) as less than 25 (normal weight), 25-30 (overweight), and above 30 (obese).

We treated TSH as a time varying covariate measured annually. For patients with multiple TSH values recorded within a single year, we used the mean value. We treated TSH concentration as a categorical variable to explore clinically meaningful thresholds: below 0.1, 0.1-0.4, 0.4-1, 1-1.5, increasing increments of 0.5 up to 4, and then 4-10 and >10 mIU/L. We defined TSH categories after reviewing the literature and consulting clinical experts. To explore variation within the usual normal limits, we selected increments of 0.5 mIU/L so that resulting TSH categories did not cross the reported individual reference range for TSH.[31] We selected TSH concentrations above 10 mIU/L and below 0.1 mIU/L as the thresholds for unequivocal diagnosis of overt hypothyroidism and hyperthyroidism respectively. We assumed the remaining categories (TSH 0.1-0.4 and 4-10 mIU/L) to include subclinical thyroid dysfunction, serving both ease of interpretation and biological plausibility.

Missing data

We replaced missing values for the annual (time varying) TSH concentration by carrying forward the last recorded observation.[32-34] To assess the accuracy of this approach in reproducing missing data, we validated imputed/carried forward values against observed values by using the following method: for each year, we calculated the mean of all observed TSH values and the mean of all imputed TSH values; we then plotted observed mean yearly TSH and imputed mean yearly TSH (with upper and lower confidence limits) against follow-up year to check that observed mean values fell within the confidence interval for imputed mean values, thereby ensuring that the imputed data were representative of the original study dataset. In addition, we did a sensitivity analysis for the mortality outcome by using multiple imputation to impute missing TSH values; covariates used in the imputation were sex, age, body mass index, fifth of Townsend deprivation, smoking status, diabetes, hypertension, and levothyroxine prescription (supplementary methods 1). We treated missing values for other covariates (body mass index, smoking status, and fifth of Townsend deprivation) as a separate missing category for each variable.[35]

Analysis

We used extended Cox proportional hazards models to estimate hazard ratios and their corresponding 95% confidence intervals for each outcome (supplementary methods 2).[36] For each of the seven outcomes (ischaemic heart disease, heart failure, stroke/transient ischaemic attack, atrial fibrillation, all fractures, fragility fractures, and mortality), the Cox proportional hazards model was adjusted for the following baseline covariates: age, sex, body mass index, smoking status, fifth of Townsend deprivation, prescription for lipid lowering drug, diabetes, hypertension, and prescription for levothyroxine. For mortality, the model was also adjusted for Charlson comorbidity index. We considered TSH as a categorical time varying covariate. We calculated hazard ratios for each TSH category compared with the reference category (2-2.5 mIU/L) to investigate the incremental change in risk of cardiovascular diseases or fractures. We did subgroup analyses by age group (≤65 years and >65 years) and sex. We used R 3.4.1 for all analyses.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for dsign or implementation of the study. No patients were asked to advise on interpretation or writing up of results. Dissemination of the findings to participants is not possible owing to the use of an anonymised dataset.

Results

The study population included 162 369 patients with hypothyroidism; we excluded 1930 patients with a baseline TSH measurement only and no subsequent measurement. The remaining 160 439 included patients contributed a total of 1 073 038 person years, with a median follow-up of 6 years (supplementary table A); 23.2% (n=37 226) of patients were men, and 76.8% (n=123 213) were women. The mean age of patients at the time of diagnosis of hypothyroidism was 58.43 (SD 17.15) years. A total of 863 072 TSH measurements were collected for the analysis.

Table 1 shows baseline characteristics of patients with hypothyroidism for each of the seven outcomes (ischaemic heart disease, heart failure, stroke/transient ischaemic attack, atrial fibrillation, all

fractures, fragility fractures, and mortality). The number of patients included in the analysis for each of the outcomes varies slightly, as patients with a record of the outcome at baseline were excluded.

Cardiovascular diseases

Table 2 shows the number of patients who developed each of the outcomes. Incidence rates were higher in men than in women.

After adjusting for potential confounders, we found a statistically significant increase in risk of ischaemic heart disease and heart failure at high TSH concentrations (>10 mIU/L) compared with the reference category (2-2.5 mIU/L) (hazard ratio 1.18 (95% confidence interval 1.02 to 1.38; P=0.03) and 1.42 (1.21 to 1.67; P<0.001), respectively (fig 1 and supplementary tables B and C). This was not the case for stroke/transient ischaemic attack; however, the risk was marginally reduced at TSH concentrations of 3-3.5 mIU/L (hazard ratio 0.86 (0.75 to 0.99; P=0.04) and 4-10 mIU/L (0.90 (0.80 to 1.00; P=0.05)) (fig 1 and supplementary table D). At low TSH concentrations (<0.4 mIU/L), no association with ischaemic heart disease or stroke/transient ischaemic attack was present, but we observed a protective effect for heart failure (hazard ratio 0.79 (0.64 to 0.99; P=0.04) for TSH <0.1 mIU/L and 0.76 (0.62 to 0.92; P=0.006) for 0.1-0.4 mIU/L).

In the adjusted model, we observed no association between risk of atrial fibrillation and the lowest or highest TSH categories. However, we found a marginal protective effect at TSH concentrations of 0.1-0.4 mIU/L (hazard ratio 0.86 (0.74 to 1.00; P=0.05) (fig 1 and supplementary table E).

We obtained similar results in age (≤65 and >65 years) and sex stratified analyses (supplementary tables B-E). The association between the highest TSH concentration and increased risk of heart failure persisted in all subgroups, whereas the association with increased risk of ischaemic heart disease remained significant only in patients aged 65 years or under. The association between the lowest TSH categories and reduced risk of heart failure remained significant only in women and patients aged over 65 years. The protective effect on stroke/transient ischaemic attack of TSH concentrations of 3-10 mIU/L was evident only in women and patients aged over 65 years. TSH below 0.4 mIU/L was protective for atrial fibrillation

Table 1 | Baseline characteristics of patients with hypothyroidism included in each of the seven analyses. Values are numbers (percentages) unless stated otherwise

Characteristic	IHD (n=145 161)	Heart failure (n=155 210)	Stroke/TIA (n=152 624)	Atrial fibrillation (n=151 651)	All fractures (n=129 778)	Fragility fractures (n=146 775)	Mortality (n=160 439)
Age (years):							
Mean (SD)	56.8 (16.8)	57.7 (16.9)	57.5 (16.9)	57.3 (16.8)	57.8 (16.8)	57.8 (16.8)	58.4 (17.1)
Median (IQR)	56.4 (44.5-69.2)	57.7 (45.4-70.6)	57.4 (45.2-70.4)	57.2 (45.1-69.9)	57.7 (45.5-70.6)	57.7 (45.5-70.6)	58.4 (45 9-71.6)
Male sex	30 273 (20.9)	34 861 (22.5)	34 354 (22.5)	33 222 (21.9)	28 862 (22.2)	34 429 (23.5)	37 226 (23.2)
Follow-up period (years):							
Mean (SD)	6.6 (4.4)	6.7 (4.4)	6.6 (4.4)	6.6 (4.4)	6.5 (4.4)	6.6 (4.4)	6.7 (4.4)
Median (IQR)	6 (-10)	6 (3-10)	6 (3-10)	6 (3-10)	6 (3-9)	6 (3-10)	6 (3-10)
Townsend fifth:							
1	31 853 (21.9)	33 758 (21.8)	33 197 (21.8)	32 814 (21.6)	28 417 (21.9)	31 941 (21.8)	34 741 (21.7)
2	28 315 (19.5)	30 207 (19.5)	29 710 (19.5)	29 444 (19.4)	25 197 19.4)	28 533 (19.4)	31 185 (19.4)
3	27 481 (18.9)	29 414 (19.0)	28 956 (19.0)	28 715 (18.9)	24 589 (18.9)	27 839 (19.0)	30 446 (19.0)
4	23 118 (15.9)	24 903 (16.0)	24 526 (16.1)	24 459 (16.1)	20 729 (16.0)	23 559 (16.1)	25 882 (16.1)
5	15 723 (10.8)	17 067 (11.0)	16 660 (10.9)	16 769 (11.1)	13 996 (10.8)	16 022 (10.9)	17 740 (11.1)
Missing	18 671 (12.9)	19 861 (12.8)	19 575 (12.8)	19 450 (12.8)	16 850 (13.0)	18 881 (12.9)	20 445 (12.7)
Body mass index:							
<25	46 076 (31.7)	48 831 (31.)	47 736 (31.3)	47 484 (31.3)	40 848 (31.5)	45 697 (31.1)	50 309 (31.4)
25-30	43 055 (29.7)	46 819 (30.2)	45 924 (30.1)	45 652 (30.1)	39 061 (30.1)	44 347 (30.2)	48 476 (30.2)
>30	38 029 (26.2)	40 971 (26.4)	40 660 (26.6)	40 241 (26.5)	34 015 (26.2)	39 160 (26.7)	42 414 (26.4)
Missing	18 001(12.4)	18 589 (12.0)	18 304 (12.0)	18 274 (12.1)	15 854 (12.2)	17 571 (12.0)	19 240 (12.0)
Smoking:							
Non-smokers	116 590 (80.3)	125 160 (80.6)	123 215 (80.7)	121 872 (80.4)	104 872 (80.8)	118 486 (0.7)	129 774 (80.9)
Smokers	22 934 (15.8)	24 217 (15.6)	23 621 (15.5)	24 038 (15.9)	19 738 (15.2)	22 684 (15.5)	24 638 (15.4)
Missing	5637 (3.9)	5833 (3.8)	5788 (3.8)	5741 (3.8)	5168 (4.0)	5605 (3.8)	6027 (3.8)
Drugs:							
Baseline levothy oxine	118 597 (81.7)	126 926 (81.8)	124 760 (81.7)	124 205 (81.9)	106 226 (81.9)	120 046 (81.8)	130 856 (81.6)
Levothyroxine during follow-up	140 449 (96.8)	150 189 (96.8)	147 720 (96.8)	146 828 (96.8)	125 649 (96.8)	142 053 (96.8)	155 191 (96.7)
Base ine lipid lowering drug	26 854 (18.5)	35 827 (23.1)	33 650 (22.0)	34 225 (22.6)	30 388 (23.4)	34 824 (23.7)	38 887 (24.2)
Medical conditions at baseline:							
Hypertension	37 269 (25.7)	42 879 (27.6)	41 149 (27.0)	40 842 (26.9)	36 042 (27.8)	40 870 (2.8)	45 736 (28.5)
Diabetes	11 846 (8.2)	13 959 (9.0)	13 772 (9.0)	13 633 (9.0)	12 030 (9.3)	13 822 (9.4)	15 255 (9.5)
Charlson comorbidity index:							
0	97 753 (67.3)	101 230 (65.2)	101 234 (66.3)	98 739 (65.1)	83 952 (64.7)	93 934 (64.)	101 234 (63.1)
1	34 379 (23.7)	37 857 (24.4)	36 080 (23.6)	36 416 (24.0)	30 833 (23.8)	35 318 (24.1)	39 088 (24.4)
2	7723 (5.3)	9503 (6.1)	8658 (5.7)	9424 (6.2)	8350 (6.4)	9725 (6.6)	11 092 (6.9)
3	3449 (2.4)	4229 (2.7)	4158 (2.7)	4376 (2.9)	4025 3.1)	4675 (3.2)	5367 (3.3)
≥4	1857 (1.3)	2391 (1.5)	2494 (1.6)	2696 (1.8)	2618 (2.0)	3123 (2.1)	3658 (2.3)

IHD=ischaemic heart disease; IQR=interquartile range; TIA=transient ischaemic attack.

in women, and TSH 0.1-0.4 mIU/L was protective for atrial fibrillation in patients aged 65 years or under.

All cause mortality

In the adjusted model, both the lowest and highest TSH concentrations were associated with increased mortality compared with the reference TSH category (hazard ratio 1.18 (1.08 to 1.28; P<0.001), 1.29 (1.22 to 1.36; P<0.001), and 2.21 (2.07 to 2.36; P<0.001) for TSH <0.1 mIU/L, 4-10 mIU/L, and >10 mIU/L (fig 1 and supplementary table F).

In sex stratified subgroup analysis, the associations between the lowest and highest TSH concentrations and increased mortality remained significant in both men and women. We observed some evidence of reduced mortality in men with TSH 3-3.5 mIU/L (hazard ratio 0.88 (0.77 to 0.99). In age stratified analysis, the association between increased mortality and highest TSH remained in both the younger and older subgroups, but the association with lowest TSH became non-significant.

Fractures

In the adjusted model, we found no association between low or high TSH and risk of all fractures; however, we observed an increase in risk of fragility fractures at TSH concentrations above 10 mIU/L compared with the reference category (hazard ratio 1.15 (1.01 to 1.31; P=0.03)) (fig 1 and supplementary table G and H). This was predominantly driven by women and older patients (hazard ratio 1.18 (1.02 to 1.35) and 1.37 (1.17 to 1.61), respectively); the association was non-significant in men and patients aged 65 years or under. In age stratified analysis, we also found some evidence of a reduction in risk of fragility fractures in patients aged 65 years or under at TSH 3-3.5 mIU/L (hazard ratio 0.82 (0.68 to 0.99)).

Discussion

In this analysis using repeated measures of TSH concentration over time, we investigated whether maintaining TSH at different concentrations across the "normal" and "abnormal" range in hypothyroid patients was associated with long term adverse outcomes. We found no difference in mortality rates within the recommended normal TSH range of 0.4-4 mIU/L; however, mortality was higher in the lowest TSH category (<0.1 mIU/L) and for concentrations above 4 mIU/L. Similarly, we observed no increase in risk of ischaemic heart disease, heart failure, stroke/transient ischaemic attack, atrial fibrillation, and fractures in patients with hypothyroidism across TSH concentrations within the specified normal range. The risk of heart failure was elevated when TSH was above 10 mIU/L and lower when TSH was below 0.4 mIU/L. Interestingly, we found a higher risk of fragility fractures for TSH above 10 mIU/L, driven predominantly by women and patients aged over 65 years.

We explored whether the findings were robust in sex and age specific analyses. The cardiovascular effects of subclinical hyperthyroidism and hypothyroidism have been studied in great detail,[37 38] and evidence suggests that these may be age related,[39 40] although this has not been universally confirmed.[41] Age seems to have a rather neutral effect when variation of thyroid function within the reference range is studied.[42 43] We found little evidence to suggest a differential pattern of response on the basis of sex or age within the recommended normal range. Some evidence existed of reduced risk of stroke/transient ischaemic attack in women and patients aged over 65 years when TSH concentrations were within 3-4 mIU/L, but this was offset by a higher risk of atrial fibrillation in those aged over 65 years. At TSH 3-3.5 mIU/L, we also found some evidence of a decrease in mortality in men and a decrease in risk of fracture in patients aged 65 years or under. These findings may be the result of multiple testing, although each result occurs within the 3-4 mIU/L concentration range.

In clinical terms, these findings corroborate the current recommendations for management of hypothyroid patients. However, by showing effects on all cause mortality when hypothyroidism is suboptimally treated, our findings challenge the notion of a "benign" disease and underline the need for diligent monitoring, which is sometimes overlooked during the long course of the disease in real life scenarios. In the study dataset, 11.6% and 32.4% of the annual TSH measures were below (<0.4 mIU/L) or above (>4 mIU/L) the recommended optimal range, respectively, which is largely in line with previous relevant reports.[44]

Strengths and limitations of study

To our knowledge, this is the first study that has taken variation of TSH concentrations over time (years) into account in the design. An earlier study by Flynn et al included multiple TSH measures for each patient but

Table 2 | Sex specific incidence rates of cardiovascular diseases, atrial fibrillation, fractures, and mortality

	No of patients (person years)		No of outcomes		Incidence rate per 10 000 person years		
Outcomes	Men	Women	Men	Women	Men	Women	All
IHD	30 273 (178 000)	114 888 (779 059)	1500	3024	84.27	38.82	47.27
Heart failure	34 861 (209 124)	120 349 (825 738)	1338	2424	63.98	29.36	36.35
Stroke/TIA	34 354 (203 721)	118 270 (804 929)	1395	3827	68.48	47.54	51.77
Atrial fibrillation	33 222 (197 964)	118 429 (808 058)	1674	3836	84.56	47.47	54.77
All fractures	28 862 (169 788)	100 916 (672 025)	1528	8857	89.99	131.79	123.36
Fragility fractures	34 429 (204 920)	112 346 (759 068)	1007	6121	49.14	80.64	73.94
Mortality	37 226 (222 792)	123 213 (846 323)	7555	14 488	339.11	171.19	206.18

IHD=ischaemic heart disease; TIA=transient ischaemic attack.

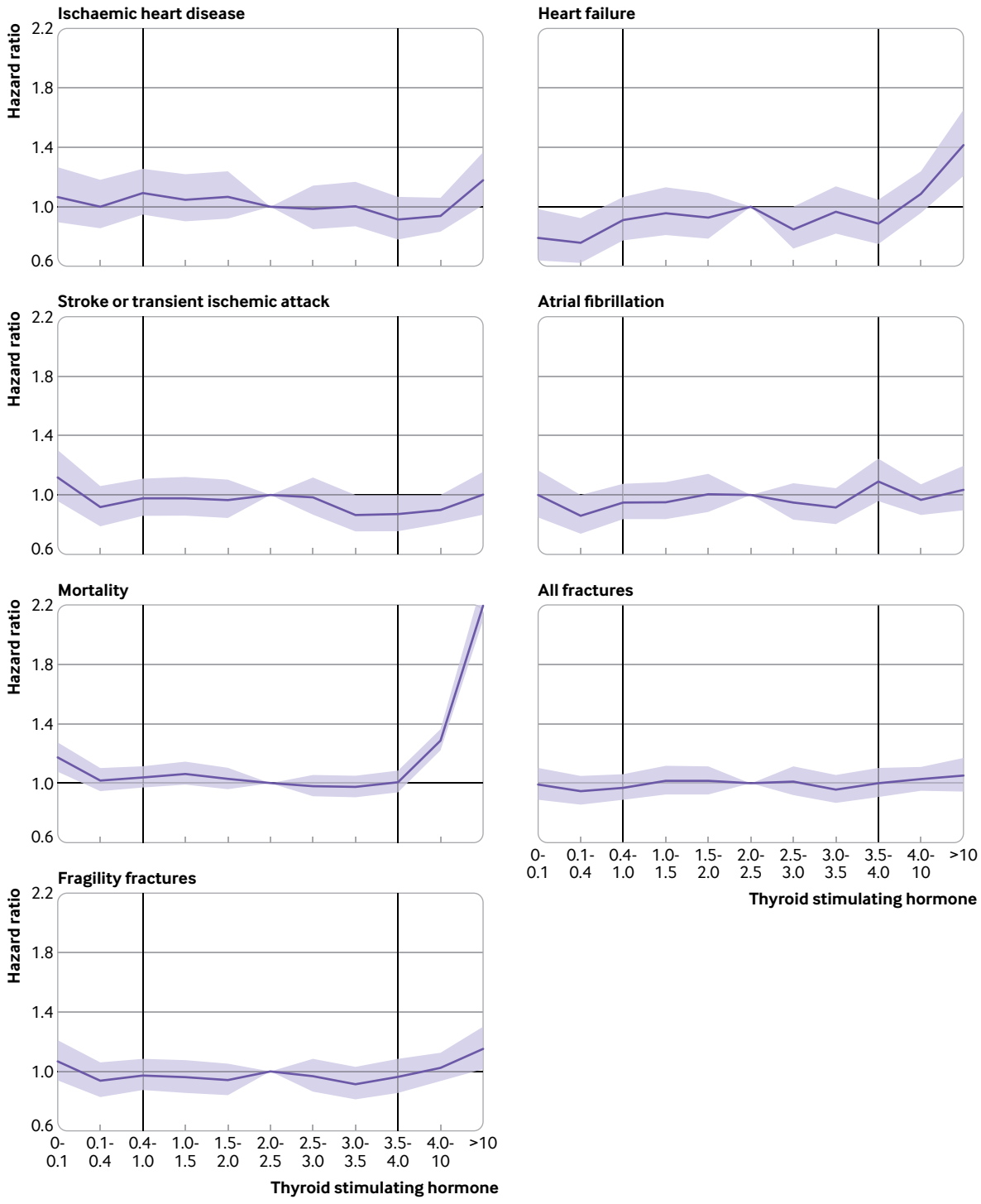

Fig 1 | Hazard ratios with 95% CIs for each of seven outcomes for different thyroid stimulating hormone (TSH) categories relative to 2-2.5 mIU/L reference category. TIA=transient ischaemic attack

used these to create a single weighted mean value that was used to assign patients to one of four categories (suppressed, low, normal, and high TSH)[6]; the method did not account for changes in TSH concentration or category during the follow-up period. The results obtained using our methods are reassuring and suggest that misclassification bias, resulting from different TSH concentrations during the course of life in any individual, had a minimal effect on the outcomes studied. This, combined with the rigorous selection of covariates and a large and well powered study population, enabled us to explore a comprehensive list of relevant outcomes reflecting the full spectrum of cardiovascular disease.

However, the findings should be interpreted in the context of the limitations of the study. Firstly, we did not differentiate the cause of hypothyroidism (for exam ple, autoimmune, post-radioiodine or thyroidectomy,

doi: 10.1136/bmj.l4892 | BMJ 2019;366:l4892 | the bmj

and thyroiditis). Furthermore, assay variability, potential interference with rheumatoid factors or heterophilic antibodies, occasional cases of macro-TSH, the observed age related shift towards higher TSH concentrations in older iodine sufficient patients, and obesity may affect this population based sample to an extent.[45-48] As we could not confirm diagnoses, a small proportion of patients with subclinical hypothyroidism may have been miscoded as having hypothyroidism in general practice. We treated TSH as a time varying covariate; for other variables, we included baseline values in the model, but these too (for example, smoking status, body mass index, and drugs) may have varied over time. The median follow-up period was six years; this may not be sufficient to observe all long term outcomes. However, observing that the detrimental effects become apparent when TSH concentrations dissociate from normal limits, we can be relatively confident that the results reflect a true effect (type I error is minimal). Cause specific mortality is not recorded in THIN, so we could not ascertain cause of death. The increase in mortality observed at high TSH concentrations could be the result of cardiovascular disease resulting in sudden death that is not captured in the database (cause specific mortality). The possibility of reverse causality also exists, whereby the last TSH measurement close to death may have been aberrant. In the primary analysis, we did not exclude patients with pituitary disease, in whom TSH concentrations may not accurately reflect circulating thyroid hormone concentrations owing to TSH deficiency being caused by inadequate secretion of TSH. However, we did a sensitivity analysis for the mortality outcome in which we excluded the 1416 (0.9%) patients with a record of pituitary disease; this had no effect on the findings. Osteoporosis is poorly recorded in primary care, so we could not include osteoporosis as an outcome; we used fragility fracture as an alternative.

Implications of findings

Our findings may have important implications for research and clinical practice. The finding that long term outcomes remain similar across a wide range of "normal" TSH concentrations supports flexibility in the levothyroxine dosing schemes to preserve TSH within the normal range. Extrapolating, this is also supportive of the not uncommonly overlooked importance of an individual's set point in thyroid homoeostasis, as opposed to the laboratory reference.[7] Related to the above, the local, tissue level activation or inactivation of thyroid hormones by deiodination (D2 and D3 deiodinases, which are critical determinants of the cytoplasmic triiodothyronine pool[49]) may provide the individual with the necessary buffering capacity to control the activation of thyroid receptors at the tissue level according to the individual's needs, provided that this buffering capacity is not overwhelmed by high or low hormone concentrations. From a clinical perspective, this study provides strong support for the current recommendations on the clinical management of hypothyroid patients and validates with hard evidence the latest American Thyroid Association and British Thyroid Association guidelines.[7 8]

Conclusions

Using repeated measures of TSH concentration over time in a well balanced and highly powered study population, we observed no clinically meaningful difference in the pattern of long term health outcomes, including all cause mortality, heart failure, ischaemic heart disease, stroke/transient ischaemic attack, atrial fibrillation, all fractures, and fragility fractures, in patients with a diagnosis of hypothyroidism when TSH concentrations lie within normal limits. However, targets for individual patients should be considered in line with their clinical needs.

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Contributors: RT and NJA are joint first authors and contributed equally. KAT and KN are joint senior authors. KN, KAT, and CS developed the research question. RT, NJA, and KN designed the study and analysis, interpreted the results, and drafted the manuscript. NT and DS provided input on the study design. MP supervised the analysis. All authors reviewed and revised the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. RT is the guarantor.

Funding: None.

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; KN has received funding from AstraZeneca and fees from Sanofi, MSD, and Boehringer Ingelheim outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The THIN data collection scheme and research carried out using THIN data were approved by the NHS South-East Multicentre Research Ethics Committee in 2003; under the terms of this approval, studies must undergo independent scientific review. The study protocol was approved by the Scientific Review Committee in August 2018 (SRC reference number: 18THIN068).

Transparency declaration: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

1 Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol* 2018;14:301-16. doi:10.1038/nrendo.2018.18

2 Biondi B, Wartofsky L. Treatment with thyroid hormone. *Endocr Rev* 2014;35:433-512. doi:10.1210/er.2013-1083
3 Mitchell AL, Hickey B, Hickey JL, Pearce SH. Trends in thyroid hormone prescribing and consumption in the UK. *BMC Public Health* 2009;9:132. doi:10.1186/1471-2458-9-132
4 Razvi S, Korevaar TIM, Taylor P. Trends, Determinants, and Associations of Treated Hypothyroidism in the United Kingdom, 2005-2014. *Thyroid* 2019;29:174-82. doi:10.1089/thy.2018.0251
5 Grais IM, Sowers JR. Thyroid and the heart. *Am J Med* 2014;127:691-8. doi:10.1016/j.amjmed.2014.03.009
6 Flynn RW, Bonellie SR, Jung RT, MacDonald TM, Morris AD, Leese GP. Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy. *J Clin Endocrinol Metab* 2010;95:186-93. doi:10.1210/jc.2009-1625
7 Jonklaas J, Bianco AC, Bauer AJ, et al, American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid* 2014;24:1670-751. doi:10.1089/thy.2014.0028
8 Okosieme O, Gilbert J, Abraham P, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. *Clin Endocrinol (Oxf)* 2016;84:799-808. doi:10.1111/cen.12824
9 Cappola AR, Arnold AM, Wulczyn K, Carlson M, Robbins J, Psaty BM. Thyroid function in the euthyroid range and adverse outcomes in older adults. *J Clin Endocrinol Metab* 2015;100:1088-96. doi:10.1210/jc.2014-3586
10 Hoermann R, Midgley JE, Larisch R, Dietrich JW. Relational Stability in the Expression of Normality, Variation, and Control of Thyroid Function. *Front Endocrinol (Lausanne)* 2016;7:142. doi:10.3389/fendo.2016.00142
11 Iverson JF, Mariash CN. Optimal free thyroxine levels for thyroid hormone replacement in hypothyroidism. *Endocr Pract* 2008;14:550-5. doi:10.4158/EP.14.5.550
12 Ito M, Miyauchi A, Morita S, et al. TSH-suppressive doses of levothyroxine are required to achieve preoperative native serum triiodothyronine levels in patients who have undergone total thyroidectomy. *Eur J Endocrinol* 2012;167:373-8. doi:10.1530/EJE-11-1029
13 Tseng FY, Lin WY, Lin CC, et al. Subclinical hypothyroidism is associated with increased risk for all-cause and cardiovascular mortality in adults. *J Am Coll Cardiol* 2012;60:730-7. doi:10.1016/j.jacc.2012.03.047
14 Chaker L, Baumgartner C, den Elzen WP, et al, Thyroid Studies Collaboration. Subclinical Hypothyroidism and the Risk of Stroke Events and Fatal Stroke: An Individual Participant Data Analysis. *J Clin Endocrinol Metab* 2015;100:2181-91. doi:10.1210/jc.2015-1438
15 Ochs N, Auer R, Bauer DC, et al. Meta-analysis: subclinical thyroid dysfunction and the risk for coronary heart disease and mortality. *Ann Intern Med* 2008;148:832-45. doi:10.7326/0003-4819-148-11-200806030-00225
16 Rotondi M, Magri F, Chiovato L. Risk of coronary heart disease and mortality for adults with subclinical hypothyroidism. *JAMA* 2010;304:2481, author reply 2482. doi:10.1001/jama.2010.1786
17 Collet TH, Gussekloo J, Bauer DC, et al, Thyroid Studies Collaboration. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med* 2012;172:799-809. doi:10.1001/archinternmed.2012.402
18 Suh S, Kim DK. Subclinical Hypothyroidism and Cardiovascular Disease. *Endocrinol Metab (Seoul)* 2015;30:246-51. doi:10.3803/EnM.2015.30.3.246
19 Peeters RP. Subclinical Hypothyroidism. *N Engl J Med* 2017;377:1404. doi:10.1056/NEJMc1709853
20 Biondi B, Cooper DS. Subclinical Hyperthyroidism. *N Engl J Med* 2018;379:1485-6.
21 Vestergaard P, Mosekilde L. Fractures in patients with hyperthyroidism and hypothyroidism: a nationwide follow-up study in 16,249 patients. *Thyroid* 2002;12:411-9. doi:10.1089/105072502760043503
22 Yang R, Yao L, Fang Y, et al. The relationship between subclinical thyroid dysfunction and the risk of fracture or low bone mineral density: a systematic review and meta-analysis of cohort studies. *J Bone Miner Metab* 2018;36:209-20. doi:10.1007/s00774-017-0828-5
23 Murphy E, Glüer CC, Reid DM, et al. Thyroid function within the upper normal range is associated with reduced bone mineral density and an increased risk of nonvertebral fractures in healthy euthyroid postmenopausal women. *J Clin Endocrinol Metab* 2010;95:3173-81. doi:10.1210/jc.2009-2630
24 Gammage MD, Parle JV, Holder RL, et al. Association between serum free thyroxine concentration and atrial fibrillation. *Arch Intern Med* 2007;167:928-34. doi:10.1001/archinte.167.9.928
25 Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011;19:251-5.
26 Maguire A, Blak BT, Thompson M. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol Drug Saf* 2009;18:76-83. doi:10.1002/pds.1688
27 Hall GC. Validation of death and suicide recording on the THIN UK primary care database. *Pharmacoepidemiol Drug Saf* 2009;18:120-31. doi:10.1002/pds.1686
28 Doran T, Fullwood C, Gravelle H, et al. Pay-for-performance programs in family practices in the United Kingdom. *N Engl J Med* 2006;355:375-84. doi:10.1056/NEJMsa055505
29 Hall GC, Sauer B, Bourke A, Brown JS, Reynolds MW, LoCasale R. Guidelines for good database selection and use in pharmacoepidemiology research. *Pharmacoepidemiol Drug Saf* 2012;21:1-10. doi:10.1002/pds.2229
30 Adams J, Ryan V, White M. How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data. *J Public Health (Oxf)* 2005;27:101-6. doi:10.1093/pubmed/fdh193
31 Andersen S, Bruun NH, Pedersen KM, Laurberg P. Biologic variation is important for interpretation of thyroid function tests. *Thyroid* 2003;13:1069-78. doi:10.1089/105072503770867237
32 Mallinckrodt CH, Watkin JG, Molenberghs G, Carroll RJ. Choice of the primary analysis in longitudinal clinical trials. *Pharm Stat* 2004;3:161-9. doi:10.1002/pst.124
33 Molenberghs G, Thijs H, Jansen I, et al. Analyzing incomplete longitudinal clinical trial data. *Biostatistics* 2004;5:445-64. doi:10.1093/biostatistics/kxh001
34 Hamer RM, Simpson PM. Last observation carried forward versus mixed models in the analysis of psychiatric clinical trials. *Am J Psychiatry* 2009;166:639-41. doi:10.1176/appi.ajp.2009.09040458
35 Nur U, Shack LG, Rachet B, Carpenter JR, Coleman MP. Modelling relative survival in the presence of incomplete data: a tutorial. *Int J Epidemiol* 2010;39:118-28. doi:10.1093/ije/dyp309
36 Therneau T, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the cox model. 2019. https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf.
37 Boelaert K. Thyroid dysfunction in the elderly. *Nat Rev Endocrinol* 2013;9:194-204. doi:10.1038/nrendo.2013.30
38 Jones CM, Boelaert K. The Endocrinology of Ageing: A Mini-Review. *Gerontology* 2015;61:291-300. doi:10.1159/000367692
39 Hyland KA, Arnold AM, Lee JS, Cappola AR. Persistent subclinical hypothyroidism and cardiovascular risk in the elderly: the cardiovascular health study. *J Clin Endocrinol Metab* 2013;98:533-40. doi:10.1210/jc.2012-2180
40 Jasim S, Gharib H. Thyroid and Aging. *Endocr Pract* 2018;24:369-74. doi:10.4158/EP171796.RA
41 Pearce SH, Razvi S, Yadegarfar ME, et al. Serum Thyroid Function, Mortality and Disability in Advanced Old Age: The Newcastle 85+ Study. *J Clin Endocrinol Metab* 2016;101:4385-94. doi:10.1210/jc.2016-1935
42 Razvi S, Jabbar A, Pingitore A, et al. Thyroid Hormones and Cardiovascular Function and Diseases. *J Am Coll Cardiol* 2018;71:1781-96. doi:10.1016/j.jacc.2018.02.045
43 Åsvold BO, Vatten LJ, Bjøro T, et al, Thyroid Studies Collaboration. Thyroid function within the normal range and risk of coronary heart disease: an individual participant data analysis of 14 cohorts. *JAMA Intern Med* 2015;175:1037-47. doi:10.1001/jamainternmed.2015.0930
44 Okosieme OE, Belludi G, Spittle K, Kadiyala R, Richards J. Adequacy of thyroid hormone replacement in a general population. *QJM* 2011;104:395-401. doi:10.1093/qjmed/hcq222
45 Favresse J, Burlacu MC, Maiter D, Gruson D. Interferences With Thyroid Function Immunoassays: Clinical Implications and Detection Algorithm. *Endocr Rev* 2018;39:830-50. doi:10.1210/er.2018-00119
46 Loh TP, Kao SL, Halsall DJ, et al. Macro-thyrotropin: a case report and review of literature. *J Clin Endocrinol Metab* 2012;97:1823-8. doi:10.1210/jc.2011-3490
47 Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. *Lancet Diabetes Endocrinol* 2015;3:286-95. doi:10.1016/S2213-8587(14)70225-6
48 Tiller D, Ittermann T, Greiser KH, et al. Association of Serum Thyrotropin with Anthropometric Markers of Obesity in the General Population. *Thyroid* 2016;26:1205-14. doi:10.1089/thy.2015.0410
49 Bianco AC, Kim BW. Deiodinases: implications of the local control of thyroid hormone action. *J Clin Invest* 2006;116:2571-9. doi:10.1172/JCI29812

Supplementary materials