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Lillevang-Johansen, Mads; Abrahamsen, Bo; Jørgensen, Henrik Løvendahl; Brix, Thomas Heiberg; Hegedüs, Laszlo

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Excess Mortality in Treated and Untreated Hyperthyroidism Is Related to Cumulative Periods of Low Serum TSH

Mads Lillevang-Johansen,[1,2] Bo Abrahamsen,[2,3,4] Henrik Løvendahl Jørgensen,[5] Thomas Heiberg Brix,[1] and Laszlo Hegedüs[1]

[1]Department of Endocrinology and Metabolism, Odense University Hospital, 5000 Odense, Denmark; [2]Institute of Clinical Research, University of Southern Denmark, 5000 Odense, Denmark; [3]Odense Patient Data Explorative Network OPEN, University of Southern Denmark, 5000 Odense, Denmark; [4]Department of Medicine, Holbæk Hospital, 4300 Holbæk, Denmark; and [5]Department of Clinical Biochemistry, Bispebjerg Hospital, 2400 Copenhagen, Denmark

Introduction and Aim: Cumulative time-dependent excess mortality in hyperthyroid patients has been suggested. However, the effect of antithyroid treatment on mortality, especially in subclinical hyperthyroidism, remains unclarified. We investigated the association between hyperthyroidism and mortality in both treated and untreated hyperthyroid individuals.

Patients and Methods: Register-based cohort study of 235,547 individuals who had at least one serum thyroid-stimulating hormone (TSH) measurement in the period 1995 to 2011 (7.3 years median follow-up). Hyperthyroidism was defined as at least two measurements of low serum TSH. Mortality rates for treated and untreated hyperthyroid subjects compared with euthyroid controls were calculated using multivariate Cox regression analyses, controlling for age, sex, and comorbidities. Cumulative periods of decreased serum TSH were analyzed as a time-dependent covariate.

Results: Hazard ratio (HR) for mortality was increased in untreated [1.23; 95% confidence interval (CI), 1.12 to 1.37; $P < 0.001$], but not in treated, hyperthyroid patients. When including cumulative periods of TSH in the Cox regression analyses, HR for mortality per every 6 months of decreased TSH was 1.11 (95% CI, 1.09 to 1.13; $P < 0.0001$) in untreated hyperthyroid patients (n = 1137) and 1.13 (95% CI, 1.11 to 1.15; $P < 0.0001$) in treated patients (n = 1656). This corresponds to a 184% and 239% increase in mortality after 5 years of decreased TSH in untreated and treated hyperthyroidism, respectively.

Conclusions: Mortality is increased in hyperthyroidism. Cumulative periods of decreased TSH increased mortality in both treated and untreated hyperthyroidism, implying that excess mortality may not be driven by lack of therapy, but rather inability to keep patients euthyroid. Meticulous follow-up during treatment to maintain biochemical euthyroidism may be warranted. **(*J Clin Endocrinol Metab* 102: 2301–2309, 2017)**

Primary hyperthyroidism is a common condition with a prevalence of 0.8% to 1.3% and well-defined regarding causes and treatment (1–3). It is biochemically defined by a low concentration of serum thyroid-stimulating hormone (TSH). Based on whether serum levels of thyroxine (T4) and/or triiodothyronine (T3) are

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Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; CV, coefficient of variation; DNPR, Danish National Patient Register; DNPrR, Danish National Prescription Register; HR, hazard ratio; ICD, International Classification of Diseases; LOD, limit of detection; RAI, radioactive iodine; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone.

elevated or not, it can be subdivided into overt and subclinical hyperthyroidism, respectively. Recent studies have reported an association between hyperthyroidism and increased risk of somatic comorbidities, such as cardiovascular and pulmonary diseases (4, 5) and psychiatric diseases (6). The burden of disease is increased both prior to and after the diagnosis of hyperthyroidism (5, 6). Large-scale register-based studies (4, 7) and several meta-analyses (8–10) have supported an association between hyperthyroidism and excess mortality. Moreover, our previous studies have indicated that duration of suppressed TSH influence this increase in both mortality and risk of major osteoporotic fractures (11, 12).

Although the available evidence points toward excess mortality in hyperthyroidism, the studies are very inhomogeneous in terms of study design, age and sex of the subjects, use of confounder control, definition of hyperthyroidism, and exclusion of transient thyrotoxicosis. Most importantly, none of these studies investigated whether treatment of hyperthyroidism influenced mortality risk. Previous studies (13–18) have found improvement of cardiovascular parameters after treatment of hyperthyroidism (whether by antithyroid drugs, radioiodine, and/or surgery), but these studies are either hampered by one or more shortcomings, such as limited study populations ($N < 50$) (13–16), inadequate confounder control (13–18), or lack of mortality data (13–16, 18). The results of the few studies which have investigated mortality in treated hyperthyroid patients show diverging results, with some showing increased mortality (19, 20), and some not (21). As an example, increased mortality in hyperthyroid patients treated with radioactive iodine (RAI) doses insufficient to induce hypothyroidism has been reported (19).

The current large-scale long-term cohort study aimed at investigating the hitherto unclarified mortality risk in both untreated and treated individuals with well-defined hyperthyroidism. Additional focus was on the influence of age, comorbidities, degree of hyperthyroidism, and its duration.

Patients and Methods

Data sources

The Danish National Patient Register (DNPR) includes admissions to Danish hospitals since 1 January 1977 and outpatient visits since 1 January 1995 (22). All records are based on the International Classification of Diseases (ICD)-8 and ICD-10 codes. The Department of Clinical Biochemistry and Pharmacology at Odense University Hospital maintains databases recording blood biochemistry ordered by hospitals and practitioners, including all general physicians, on the Island of Funen (population of 476,580 in January 2005). The Danish National Prescription Register (DNPrR) contains data on all medications dispensed by pharmacies in Denmark since 1995 (23). The Danish Register of Causes of Death contains data regarding mortality (24). Crosslinking data between the registers is made possible through a unique 10-digit personal identifier.

Study design and participants

This is an observational register-based cohort study including all individuals on the Island of Funen with a TSH measurement in the period 1 January 1995 to 1 January 2011. The participants were followed from their first-ever TSH determination until death or end of study (30 November 2012). In this period, 275,467 individuals had at least one serum TSH measurement. Danish health datasets become accessible to researchers via Statistics Denmark only after a delay because of the quality assurance and integrity checks undertaken by the National Board of Health before database lock and release. The inclusion process is described in additional detail in the first analyses based on this dataset, published in 2014 (12). Taking into account as exclusion criteria prior pituitary disease, age <18 years, prior treatment with antithyroid medication, thyroid hormones, RAI or thyroid surgery, loss to follow-up and emigration, and a 1-year washout period, 239,768 eligible individuals with at least one TSH measurement remained. In this study, thyroid function was defined from the first-ever TSH determination. Hyperthyroidism was defined as having a minimum of two decreased TSH values within a period of 6 months, with at least 14 days between measurements. This was done to ensure the hyperthyroid status of the individuals, and to reduce the likelihood of nonthyroidal illness or transient thyrotoxicosis as the cause of low TSH. Because of the minimum of 14 days between TSH measurements, we left-truncated the data and started follow-up 2 weeks after the first TSH measurement. Individuals who either died or reached end of study (30 November 2012) prior to the start of follow-up were excluded (n = 1807), as were individuals who were hypothyroid at the first TSH determination, using the same criteria as for hyperthyroid cases, albeit with an elevated TSH (n = 2414). This left 235,547 participants, including 232,754 euthyroid controls and 2793 hyperthyroid cases. Because being hyperthyroid (exposed) and euthyroid (unexposed) was defined by the first-ever measured TSH and the nature of repeat blood measurements, it was possible for controls to become hyper- and hypothyroid during follow-up. During follow-up, 3687 unexposed controls became hyperthyroid, whereas 4119 became hypothyroid. Because these individuals did not fulfill our initial case definition, they were censored and exited the study at the time of development of thyroid dysfunction.

Thyroid function

Euthyroidism was defined as TSH between 0.3 and 4.0 mIU/L, and overt hyperthyroidism was defined as TSH <0.3 mIU/L and T4 >135.0 nmol/L and/or T3 >2.2 nmol/L. Subclinical hyperthyroidism was characterized as TSH <0.3 mIU/L and T4 <135.0 nmol/L and T3 <2.2 nmol/L. A TSH >4.0 mIU/L constituted hypothyroidism.

Assays

All TSH determinations were done in the same laboratory. In brief, until 2006, TSH was measured using a time-resolved fluoroimmunoassay based on a direct sandwich technique with three mouse antihuman monoclonal antibodies, and

concentrations of T3 and T4 were analyzed using time-resolved fluoroimmunoassays based on competitive binding to T3- or T4-specific antibodies, respectively. Analyses were performed using the AutoDELFIA equipment (Wallac, Turku, Finland). For TSH, the limit of detection (LOD) was 0.005 mIU/L, whereas within-run imprecision had a coefficient of variation (CV) of 2.7% at 0.89 mIU/L and 1.3% at 17.6 mIU/L. For T3 and T4, LOD was 0.3 and 5.0 nmol/L, respectively, and CV was 3.2% at 1.37 nmol/L and 2.8% at 79.0 nmol/L, respectively.

From 2006, TSH was determined with a solid-phase, two-site chemiluminescent immunometric assay on Immulite 2000 equipment (Siemens, Erlangen, Germany). The analytical LOD was 0.004 mIU/L. Within-run CV was 5.3% at 0.32 mIU/L and 3.9% at 3.3 mIU/L. To assure compatibility between the two analyses, method comparison was performed in 120 patient samples showing comparable means (range, 0.008 to 49 mIU/L) and a regression coefficient of 0.991. Furthermore, an external quality control program assured comparability (Ringversuche, RfB, Bonn, Germany).

Treatment

Treatment was defined as having redeemed at least one prescription of antithyroid drugs as registered in the DNPrR, or having had thyroid surgery or RAI treatment as registered in the DNPR, during follow-up. In the case of a participant having received both antithyroid drugs and surgery/RAI, treatment date was defined as whichever treatment was initiated first.

Outcome

The outcome was mortality. Data on time of death was extracted from the Danish Register of Causes of Death.

Morbidity

The Charlson Comorbidity Index (CCI) is based on 19 disease groups (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, ulcer disease, diabetes mellitus with or without complications, hemiplegia, moderate or severe renal disease, cancer with or without metastases, leukemia, lymphoma, mild liver disease, moderate or severe liver disease, and AIDS) (25). All disease categories were identified from ICD-8 and ICD-10 codes in the DNPR (26). The score reflects the time period from 1 January 1977 (establishment of DNPR) until the date of the first-ever TSH determination, for both cases and controls.

Approvals

The project is approved by the Danish Data Protection Agency and by Statistics Denmark to access health records. Approval from the ethics committee was not needed. Odense Patient data Explorative Network is an approved research institution permitted to access data hosted by Statistics Denmark (project no. 704047).

Statistical analyses

Data processing was done in Stata V14.1 (StataCorp, College Station, TX) and SAS version 9.4 (SAS Institute Inc., Cary, NC) through virtual private network access to Statistics Denmark.

Differences in baseline values of the outcome groups were analyzed using nonparametric, parametric, or categorical statistical methods where appropriate. Multivariate Cox proportional hazards models were used to calculate hazard ratios (HRs) for all-cause mortality in treated and untreated hyperthyroid individuals compared with controls. HRs were adjusted for age, sex, and CCI. The validity of the proportional hazards assumption was evaluated by inspection of Schoenfeld residuals vs time, and Cox-Snell residuals. In large data sets one would expect small deviations from the linear association between the observed data points and the fitted value. No substantial deviations from the proportional hazards assumptions were present.

Analyses using TSH level as a time-dependent covariate were performed. Thus, the number of 6-month periods of decreased TSH was incorporated as a cumulative covariate in the Cox regression. This allowed analyzing the effect of decreased TSH during follow-up rather than depending on the baseline classification alone, hence incorporating changes to thyroid status over time rather than carrying the initial TSH value forward. Any 6-month periods in which no further TSH measurement had been performed were considered periods of normal TSH.

Sensitivity analyses were performed to analyze the influence of immortal time bias regarding treatment, to adjust for possible influence of postpartum thyroiditis and pregnancy on TSH levels, and age stratification.

A significance level of 0.05 in two-tailed tests was used in all analyses.

Results

We identified 2793 individuals who fulfilled our operational criteria for hyperthyroidism, 486 of whom only had data on TSH. There were 232,754 individuals with at least one TSH measurement within the normal range who constituted the control group. There were 1656 (59.3%) hyperthyroid individuals who received treatment during follow-up, whereas 1137 (40.7%) did not (Fig. 1).

Subdivision by degree of hyperthyroidism identified 1909 individuals with overt hyperthyroidism and 498 with subclinical hyperthyroidism. There were 1309 (68.6%) overtly hyperthyroid individuals and 140 (28.1%) subclinically hyperthyroid individuals who subsequently received treatment during follow-up.

Baseline characteristics are summarized in Table 1. The control group was significantly younger and contained fewer women than the hyperthyroid groups. The controls had a significantly lower burden of comorbidity than the untreated hyperthyroid individuals, but not compared with the treated ones. Median follow-up time was nominally shorter in the control group compared with all the hyperthyroid groups, with exception of the untreated subclinically hyperthyroid individuals. Median follow-up in the entire study population was 7.3 years (range, 0 to 16.9 years).

At baseline, overtly hyperthyroid individuals who subsequently received treatment during follow-up had significantly higher levels of T4 and T3 than the untreated individuals ($P < 0.0001$). Significantly higher baseline

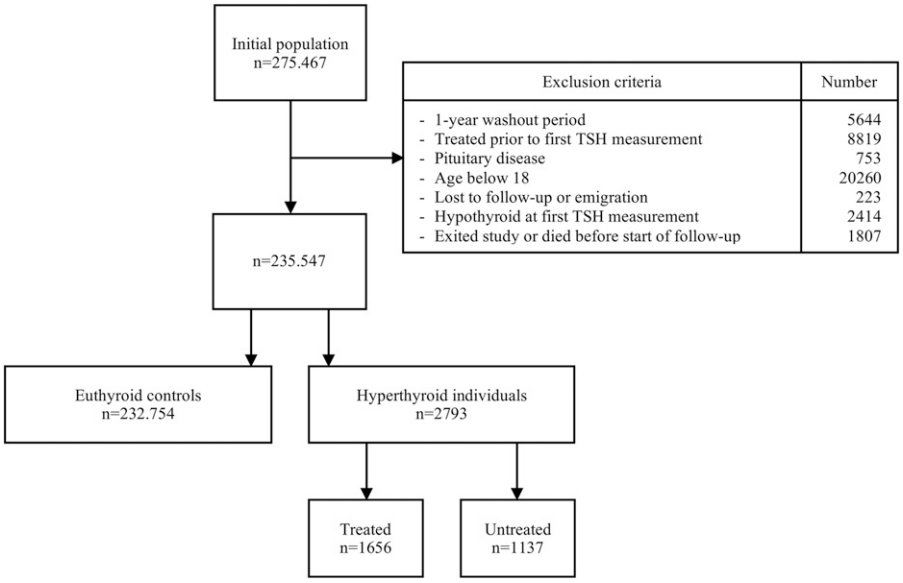

Figure 1. Flowchart describing the inclusion process.

levels of T3 were observed in the treated subclinically hyperthyroid individuals than in the untreated individuals (P = 0.0071) (Table 2).

Mortality in the entire hyperthyroid group

During a median follow-up of 9.4 years (range, 0 to 16.9 years), 476 treated individuals died (28.7%), which was significantly fewer than in the untreated group where, during a median follow-up time of 7.8 years (range, 0 to 16.7), 389 died (34.2%) ($P < 0.005$). The HR for all-cause mortality in the treated hyperthyroid individuals was 1.49 [95% confidence interval (CI), 1.36 to 1.73; $P < 0.001$], and 2.06 (95% CI, 1.86 to 2.28; $P < 0.001$) in the untreated hyperthyroid individuals. When adjusting for age, sex, and comorbidities, the HR in the treated group was 1.01 (95% CI, 0.92 to 1.10; P value is not significant), but still significantly increased in the untreated group (HR, 1.24; 95% CI, 1.12 to 1.37; $P < 0.001$) (Table 3). Due to power reasons, we did not find it meaningful to evaluate the effect of different treatment modalities because only 173 treated hyperthyroid patients received either RAI or surgery at some point during follow-up, and only 68 of these were first-line treatments.

Mortality in overt hyperthyroidism

When compared with the control population, mortality was significantly increased in both treated and untreated overtly hyperthyroid individuals (HR, 1.36; 95% CI, 1.22 to 1.51; $P < 0.001$ and HR, 1.49; 95% CI, 1.27 to 1.74; $P < 0.001$, respectively). Irrespective of

Table 1. Baseline Characteristics of the Study Population According to Thyroid Status, Treatment, and Number of Deaths

	Entire Hyperthyroid Group		Subclinical Hyperthyroidism		Overt Hyperthyroidism		
Characteristic	**Treatment (n = 1656)**	**No Treatment (n = 1137)**	**Treatment (n = 140)**	**No Treatment (n = 358)**	**Treatment (n = 1309)**	**No Treatment (n = 600)**	**Controls (n = 232,754)**
Age at first TSH ± standard deviation	59.9 ± 17.7[a]	62.5 ± 16.8[a,b]	65.9 ± 15.8[a]	66.4 ± 15.7[a]	58.4 ± 17.7[a]	59.6 ± 16.9[a]	51.0 ± 18.2
Females (%)	81.2[a]	72.8[a,b]	75.0[a]	69.6[a]	81.4[a]	74.0[a,b]	55.8
CCI (%) 0	79.1	70.8[a,b]	70.7	67.0[a]	80.8	74.8[a,b]	79.6
1	13.9	18.8[a,b]	18.6	20.7[a]	12.8	16.7[a,b]	13.9
2	4.4	6.0[a,b]	5.7	7.8[a]	4.3	4.8[a,b]	3.6
≥3	2.6	4.4[a,b]	5.0	4.5[a]	2.1	3.7[a,b]	2.9
Median follow-up years (range)	9.4 (0–16.9)[a]	7.8 (0–16.7)[a,b]	8.6 (0.2–16.8)[a]	7.3 (0.1–16.5)[b]	9.2 (0–16.9)[a]	8.1 (0.1–16.7)[a]	7.2 (0–16.9)
Deaths, n (%)	476 (28.7)[a]	389 (34.2)[a,b]	50 (35.7)[a]	151 (42.2)[a]	337 (25.7)[a]	152 (25.3)[a]	36,487 (15.7)

[a]Significantly different compared with controls.

[b]Significantly different than treated within the same group.

Table 2. Baseline Serum T4 and T3 Levels at Inclusion in Subsequently Treated and Untreated Hyperthyroid Individuals

	Subclinical Hyperthyroidism		Overt Hyperthyroidism	
	Treatment	No Treatment	Treatment	No Treatment
n	140	358	995	526
T3 (nmol/L)	1.87 ± 0.28	1.79 ± 0.30[a]	4.05 ± 2.45	2.61 ± 0.70[b]
n	140	358	1306	599
T4 (nmol/L)	110.8 ± 16.6	108.2 ± 17.6	193.7 ± 61.4	147.2 ± 33.2[b]

Data are presented as mean ± standard deviation or as otherwise indicated. Data are compared within group.

[a] $P = 0.0071$.

[b] $P < 0.0001$.

treatment status, this excess mortality attenuated and was no longer significantly increased when adjusting for age, sex, and comorbidities (Table 3).

Mortality in subclinical hyperthyroidism

Subclinically hyperthyroid individuals who received treatment had significantly increased mortality compared with euthyroid controls (HR, 1.95; 95% CI, 1.48 to 2.58; $P < 0.001$). This was also the case for the untreated individuals (HR, 2.70; 95% CI, 2.30 to 3.17; $P < 0.001$). When adjusted for age, sex, and comorbidities, the mortality in the treated group was not significantly different from that in the control population, whereas the HR for mortality in the untreated individuals attenuated, but remained significantly higher than in the controls (HR, 1.36; 95% CI, 1.16 to 1.60; $P < 0.001$) (Table 3).

Mortality and cumulative exposure to low TSH

In untreated hyperthyroid individuals, the HR for mortality per every 6 months of decreased TSH was 1.11 (95% CI, 1.09 to 1.13; $P < 0.0001$). In the treated hyperthyroid individuals, the HR for mortality per every 6 months of decreased TSH was 1.13 (95% CI, 1.11 to 1.15; $P < 0.0001$). This corresponds to a 184% and 239% increase in mortality, respectively, after 5 years of low TSH. When subdividing into degree of hyperthyroidism, the HR for mortality per every 6 months of decreased TSH was 1.16 (95% CI, 1.13 to 1.18; $P < 0.0001$) in the untreated overtly hyperthyroid individuals and 1.14 (95% CI, 1.12 to 1.17; $P < 0.0001$) in treated individuals. In the untreated subclinically hyperthyroid individuals, the HR for mortality per every 6 months of decreased TSH was 1.15 (95% CI, 1.12 to 1.18; $P < 0.0001$) and 1.18 (95% CI, 1.16 to 1.21; $P < 0.0001$) in treated subjects. Only 73 individuals received T4 replacement after RAI or surgery, which did not allow for any meaningful statistical evaluation of excess treatment on mortality.

Sensitivity analyses

Excluding hyperthyroid patients who were registered with a diagnosis of postpartum thyroiditis or had contact to hospitals regarding pregnancy in a 9-month period before and after first-ever measured TSH did not alter our findings. We also stratified age into <65 and ≥65 years. In this analysis, mortality was increased in the entire group of untreated hyperthyroid individuals ≥65 years, and in the untreated subclinically hyperthyroid individuals ≥65 years, but not those below (data not shown).

Because 292 of the 1656 treated hyperthyroid individuals (17.6%) did not start treatment within the first year of becoming hyperthyroid, there was a risk of introducing immortal time bias, also known as guarantee-time

Table 3. Mortality in Individuals With Hyperthyroidism Compared With Controls

	Entire Hyperthyroid Group (n = 2793)		Subclinical Hyperthyroidism (n = 498)		Overt Hyperthyroidism (n = 1909)	
	Treated vs Controls	Untreated vs Controls	Treated vs Controls	Untreated vs Controls	Treated vs Controls	Untreated vs Controls
Unadjusted HR	1.49 (1.36–1.63)[a]	2.06 (1.86–2.28)[a]	1.95 (1.48–2.58)[a]	2.70 (2.30–3.17)[a]	1.36 (1.22–1.51)[a]	1.49 (1.27–1.74)[a]
Adjusted HR[b]	1.01 (0.92–1.10)	1.24 (1.12–1.37)[a]	0.87 (0.66–1.15)	1.36 (1.16–1.60)[a]	1.03 (0.93–1.15)	1.03 (0.88–1.20)

Values are expressed as HR (95% CI).

[a] $P < 0.001$.

[b] Adjusted for age, sex, and CCI.

bias (27). This bias arises when allocation into a certain study group is defined by an incident during follow-up, in this case, treatment. As an example, a hyperthyroid patient who starts treatment at some point during follow-up is effectively immortal until this point in time. This may lead to an overestimation of survival in this group. We performed a sensitivity analysis where follow-up started 1 year after the date of the first TSH measurement; therefore, hyperthyroid individuals who started treatment after this date were classified as untreated for the remainder of the follow-up (28). This did not affect our results significantly (Table 4).

Discussion

Using a large-scale, register-based, long-term cohort study of biochemically verified treated and untreated hyperthyroid individuals, we demonstrate excess mortality in the individuals who did not receive antithyroid treatment, as compared with euthyroid controls. One of the major strengths in our study lies in the utilization of two TSH measurements when defining hyperthyroidism. Previous studies also reported increased mortality in hyperthyroid patients, but relied on either diagnosis codes (7) or only a single measurement of TSH (4, 11). Clearly, a case definition based on a single TSH measurement is hampered by a high risk of misclassification of hyperthyroidism because of transient thyrotoxicosis. In fact, approximately 50% of patients with a decreased TSH will have normal levels at repeat investigation (29). If only using one TSH measurement in this cohort, 6424 individuals would have been included in the case group rather than the control group, highlighting the pitfalls regarding case definition. Using a single measurement of TSH as a case definition also carries a risk of introducing selection bias. Thus, the fact that a person admitted to hospital, who happens to have a low TSH measurement, may die immediately after because of reasons unrelated to hyperthyroidism, introduces higher mortality in this group. By requiring two TSH values, we reduced the risk of this bias.

The major novelty of our study lies in the evaluation of untreated and treated hyperthyroid patients. The hyperthyroid individuals receiving treatment had mortality similar to that of the controls, whereas those left untreated had an increased mortality. Although some previous studies found increased mortality in treated hyperthyroid individuals (19, 20), others did not (21, 30). Interestingly, and in line with our results, Boelaert *et al.* (19) found that patients who developed hypothyroidism after RAI treatment had mortality similar to that of the background population. However, the aforementioned studies are very inconsistent in controlling for comorbidities, which constitutes a challenge in interpretation of the results because the burden of comorbidities influences mortality (7). The CCI, as used in this paper, is a highly valid method for controlling for comorbidities known to impact strongly on mortality, allowing examination of a direct association between hyperthyroidism and mortality. With this approach, the mortality risk in treated hyperthyroid individuals was attenuated when controlling for comorbidities, stressing the paramount importance of confounder control. Importantly, and a limitation, previous studies examining the effect of antithyroid treatment in hyperthyroid subjects only investigated patients with overt hyperthyroidism. In our study, we subdivided according to severity of thyroid dysfunction, and demonstrate that treated patients with subclinical hyperthyroidism have a mortality risk similar to the euthyroid controls, whereas mortality is increased in the untreated. A number of previous studies have shown increased mortality in subclinically hyperthyroid

Table 4. Sensitivity Analysis—Mortality

	Entire Hyperthyroid Group (n = 2665)		Subclinical Hyperthyroidism (n = 464)		Overt Hyperthyroidism (n = 1849)	
	Treated vs Controls	Untreated vs Controls	Treated vs Controls	Untreated vs Controls	Treated vs Controls	Untreated vs Controls
Unadjusted HR	1.44 (1.29–1.61)[a]	2.02 (1.84–2.23)[a]	1.71 (1.48–2.58)[b]	2.62 (2.23–3.07)[a]	1.33 (1.17–1.51)[a]	1.64 (1.42–1.89)[a]
Adjusted HR[c]	1.10 (0.99–1.23)	1.12 (1.02–1.23)[b]	0.90 (0.57–1.43)	1.27 (1.08–1.50)[d]	1.10 (0.97–1.25)	1.02 (0.88–1.18)

Values are expressed as HR (95% CI). Follow-up started 1 year after the date of the first TSH measurement, implying that hyperthyroid individuals who started treatment after this date were classified as untreated for the remainder of the follow-up. There were 8373 subjects who exited the study or died before the start of follow-up, and 292 subsequently treated hyperthyroid individuals were regarded as untreated.

[a] $P < 0.001$.

[b] $P = 0.022$.

[c] Adjusted for age, sex, and CCI.

[d] $P = 0.003$.

individuals (4, 9, 11, 31, 32), but only one study had information regarding treatment (4). However, that study did not differentiate between treated and untreated individuals.

Accepting that there seems to be increased mortality and increased risk of cardiovascular events in subclinically hyperthyroid patients, disagreement on whether such patients should receive antithyroid treatment persists (33, 34). In the 2015 guidelines of the European Thyroid Association, treatment of patients >65 years of age with grade 2 (TSH <0.1 mIU/L) subclinical hyperthyroidism is recommended, whereas the recommendation for patients <65 years is weak with low-quality evidence (35). When stratifying by age, we showed an increased mortality in untreated subclinically hyperthyroid patients above but not below 65 years. It is important to accept that the latter finding may rely on lack of power because only 155 patients with subclinical hyperthyroidism age <65 years did not receive treatment. Although earlier attempts have been unsuccessful, the current findings reinforce the need for randomized interventional studies in this condition.

At variance with a number of recent studies showing an increase in mortality among hyperthyroid individuals (4, 7, 11), we found no excess mortality in the overtly hyperthyroid group, whether treated or not. One possible explanation for the diverging results is that we may in fact be underestimating the effect of hyperthyroidism, and that of treatment, on mortality. As evident from our baseline characteristics, the treated overtly hyperthyroid individuals had significantly more pronounced thyroid dysfunction than the untreated. Thus, a potential increase in mortality may have been offset because of treatment. The consensus is to treat overt hyperthyroidism, and why treatment was withheld or declined in the untreated individuals remains unanswered. This hardly indicates possible errors in the database system for recording treatment because the DNPrR is a highly valid national database that electronically records any prescription dispensed to any individual in any pharmacy. A study investigating primary nonadherence with prescribed medication has shown that 31.3% of incident prescriptions are not redeemed, which could help explain why >30% of overtly hyperthyroid patients do not receive treatment (36). Another possibility could be that a patient dies or reaches the end of study before being able to initiate treatment. This scenario seems implausible when taking into account the results of our sensitivity analysis where we essentially find similar results. More likely, these untreated patients may have mild and oligosymptomatic disease, possibly with spontaneous remission (37), or may be among the 7% of hyperthyroid cases caused by reversible causes, such as subacute thyroiditis, and treatment with amiodarone or lithium (2). These are factors that may explain the lack of excess mortality in this group. It is also important to emphasize that these results are based on the first thyroid function tests and do not take into account changing thyroid status. Our cumulated dose-dependent mortality analysis, adjusted for age, sex, and comorbidities, demonstrated an 11% and 13% increase in mortality per 6 months of decreased TSH in untreated and treated hyperthyroid patients, respectively. This corresponds to a 184% and 239% increase in mortality after 5 years of decreased TSH, respectively, in the two groups. Essentially similar results were found when subdividing into overt and subclinical hyperthyroidism. Our findings in the multivariate Cox regression together with the results from the cumulative analysis indicate a beneficial effect of treatment of hyperthyroidism with lowering of excess mortality. Close monitoring of therapy and maintaining euthyroidism may be equally important.

We lack information on clinical covariates such as smoking status and alcohol consumption, both of which influence the risk of hyperthyroidism and mortality (38, 39). However, adjusting for a number of somatic disorders, including chronic pulmonary disease, cancer, and liver disease, disorders very firmly linked to smoking and alcohol consumption and mortality, our findings are at least in part adjusted for the possible effect of smoking and alcohol. We had no information on the clinicians' decision of either initiating or withholding treatment, neither do we know the reason for TSH being measured in the first place. The TSH determination presumably has been performed because of suspicion of thyroid disease, or in the context of general testing, and it is important to emphasize that the control population is not a random population sample, and thus does not necessarily represent a healthy background population. Therefore, even when controlling for comorbidities, we may have underestimated the mortality displayed in our analyses.

There are two inherent limitations in investigating TSH as a time-varying covariate. First, we classified any 6-month period with no TSH measurement as a euthyroid period. This implies that a study participant may *de facto* remain hyperthyroid, although considered euthyroid in the analysis. Hypothetically, this would lead to an underestimation of the effect of hyperthyroidism and lowering of the risk estimate of mortality because actual hyperthyroid individuals remain part of the control group. The register-based approach does not allow us to quantify this. Second, shorter survival irrespective of cause will reduce the number of 6-month periods in which a patient could be flagged as biochemically hyperthyroid. This would conservatively bias our risk estimates in the cumulative analysis rather than inflate the importance of achieving euthyroidism. Neither were we

able to differentiate between the two major causes of hyperthyroidism: Graves disease and toxic nodular goiter. Theoretically, because of differences in age distribution, burden of comorbidity, and cause of death between the two phenotypes, treatment effect on mortality may also differ (2, 40). Because of the nature of our data, we were not able to distinguish between the two. Ideally, treatment should be analyzed as a time-varying covariate to reduce the risk of immortal time bias, considering that treated hyperthyroid individuals are by design immortal in the period from first TSH determination until start of treatment. In our study cohort, 292 patients did not start treatment until ≥1 year after the first measured TSH value. In view of the first TSH in these cases logically not being the deciding factor for treatment initiation, we found it acceptable to consider these patients as untreated in the sensitivity analysis, to reduce the risk of bias. This method did not change our results significantly, indicating that this bias is of little importance.

In conclusion, cumulative periods of decreased TSH increased mortality in both treated and untreated hyperthyroidism. This suggests that excess mortality may not be driven by lack of therapy, but rather inability to keep patients euthyroid. Meticulous follow-up during treatment to maintain biochemical euthyroidism may be warranted. Qualifying these statements further will need carrying out of prospective randomized interventional studies, especially in subclinical hyperthyroidism.

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Address all correspondence and requests for reprints to: Mads Lillevang-Johansen, MD, Kløvervænget 10, 6th floor, 5000 Odense C, Denmark. E-mail: mads.lillevang-johansen2@rsyd.dk.

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