# Acute cardiovascular events and all-cause mortality in patients with hyperthyroidism: a population-based cohort study

**Olaf M Dekkers[1,2,3], Erzsébet Horváth-Puhó[1], Suzanne C Cannegieter[3], Jan P Vandenbroucke[1,3], Henrik Toft Sørensen[1] and Jens Otto L Jørgensen[4]**

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Clinical Endocrinology and Metabolism, [3]Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands, and [4]Department of Endocrinology and Internal Medicine, Aarhus University Hospital Aarhus, Aarhus, Denmark

Correspondence should be addressed to J O L Jørgensen
**Email**
joj@clin.au.dk

## Abstract

*Objective*: Several studies have shown an increased risk for cardiovascular disease (CVD) in hyperthyroidism, but most studies have been too small to address the effect of hyperthyroidism on individual cardiovascular endpoints. Our main aim was to assess the association among hyperthyroidism, acute cardiovascular events and mortality.
*Design*: It is a nationwide population-based cohort study. Data were obtained from the Danish Civil Registration System and the Danish National Patient Registry, which covers all Danish hospitals. We compared the rate of all-cause mortality as well as venous thromboembolism (VTE), acute myocardial infarction (AMI), ischemic and non-ischemic stroke, arterial embolism, atrial fibrillation (AF) and percutaneous coronary intervention (PCI) in the two cohorts. Hazard ratios (HR) with 95% confidence intervals (95% CI) were estimated.
*Results*: The study included 85 856 hyperthyroid patients and 847 057 matched population-based controls. Mean follow-up time was 9.2 years. The HR for mortality was highest in the first 3 months after diagnosis of hyperthyroidism: 4.62, 95% CI: 4.40–4.85, and remained elevated during long-term follow-up (>3 years) (HR: 1.35, 95% CI: 1.33–1.37). The risk for all examined cardiovascular events was increased, with the highest risk in the first 3 months after hyperthyroidism diagnosis. The 3-month post-diagnosis risk was highest for atrial fibrillation (HR: 7.32, 95% CI: 6.58–8.14) and arterial embolism (HR: 6.08, 95% CI: 4.30–8.61), but the risks of VTE, AMI, ischemic and non-ischemic stroke and PCI were increased also 2- to 3-fold.
*Conclusions*: We found an increased risk for all-cause mortality and acute cardiovascular events in patients with hyperthyroidism.

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## Introduction

Hyperthyroidism, characterized by increased free thyroxin ($FT_4$) and/or free $T_3$ levels in the presence of suppressed thyroid-stimulating hormone (TSH) levels, is a common disease. Its estimated lifetime risk is 2–5% (1), occurring predominantly in women (2). Interestingly, the reported incidence of hyperthyroidism has increased annually over the last 20 years, probably as a result of increasing awareness and use of thyroid hormone tests (2). The condition is mainly caused by an autoimmune process (Graves' disease), a solitary toxic adenoma or a toxic multinodular goiter (1).

Suppressed TSH levels, as seen in hyperthyroidism, are related to a pro-coagulant state (3) and vascular dysfunction (4). Interestingly, also elevated TSH levels, as seen in hypothyroidism, are associated with risk factors for cardiovascular disease such as increased blood pressure (5), higher body mass index (BMI) (6), insulin resistance (7), higher lipid levels (8) and atherosclerosis (9).

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In subclinical hyperthyroidism (suppressed TSH with $FT_4$ levels in the normal range), an approximately 20% increased risk for all-cause mortality, coronary heart disease and death due to coronary heart disease was found (10). Clinically overt hyperthyroidism is also associated with a 20% increased mortality risk (11) and a 65% increased risk of cardiovascular events (12), including venous thromboembolism (VTE) (13). However, most studies of hyperthyroidism are not large enough to address its effect on individual cardiovascular events, such as ischemic and non-ischemic stroke or myocardial infarction. Importantly, the temporal relation between diagnosis of hyperthyroidism and CVD onset has not yet been elucidated, and it is unclear how long after the hyperthyroidism diagnosis the increased CVD risk persists. The present nationwide cohort study therefore aimed to assess in more detail the association among hyperthyroidism, acute cardiovascular events and mortality.

## Subjects and methods

### Source population

The source population for the study consisted of the entire population of Denmark (cumulative population = 7.1 million inhabitants during 1980–2012). Data were obtained from the Danish Civil Registration System (DCRS) and the Danish National Patient Registry (DNPR). The DNPR has recorded all hospital discharge diagnoses and surgical procedures nationwide since 1977 and all hospital outpatient specialty clinic and emergency room visits since 1995 (14). The DCRS has maintained electronic records on gender, age, birth date, residence, emigration date and vital status since 1968 (15). The Danish National Health Service provides universal tax-supported health care, guaranteeing free access to general practitioners and hospitals.

### Study population

#### *Cohort of patients with hyperthyroidism*

All patients with an initial diagnosis of hyperthyroidism between 1980 and 2012 were eligible for study inclusion. Patients with a diagnosis of thyrotoxic storm were not included as by definition, these patients have cardiovascular symptoms/disease. Patients with pregnancy-related thyroid diseases (defined as pregnancy 12 months before a hyperthyroidism diagnosis) also were excluded. Hyperthyroidism diagnosis was based on International Classification of Diseases (ICD) version 8 and version 10 diagnosis codes. (ICD8: 242 with the exception of 242.20; ICD10: E05.00, E05.01, E05.02, E05.09).

#### *Population comparison cohort*

The general population comparison cohort was sampled from the DCRS. For every patient with hyperthyroidism, ten hyperthyroidism-free persons who were alive on the date of the hyperthyroidism diagnosis (the 'index date') were sampled from the general population, matched on age and sex. Follow-up of persons in the comparison cohort was terminated if they developed hyperthyroidism, in which case they started contributing person-time to the exposed cohort.

### Start of follow-up

Follow-up started on the date of initial hyperthyroidism diagnosis for patients and on the matched index date for comparison cohort members. Follow-up was censored when an endpoint of interest occurred (only first-time events were studied), upon death or emigration or on 31 December, 2012, whichever came first. Risk estimates were stratified by time after the initial hyperthyroidism diagnosis.

### Study endpoints

We computed the mortality rates among hyperthyroid patients and comparison cohort members. We also compared the incidence of first occurrence of venous thromboembolism (VTE), acute myocardial infarction (AMI), ischemic (unspecified stroke was classified as ischemic (16)) and non-ischemic stroke (such as subarachnoid hemorrhage), arterial embolism, atrial fibrillation (AF) and percutaneous coronary intervention (PCI) in the two cohorts. Diagnoses based on ICD codes recorded in the DNPR were used to identify these endpoints. It should be noted that the ICD-10 codes used to examine AF included atrial flutter as well. Each hospital discharge or hospital outpatient visit is recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses classified according to ICD-8 until the end of 1993 and ICD-10 thereafter. Emergency room diagnoses were not included due to their low predictive value (17, 18).

**Table 1** Characteristics of patients with hyperthyroidism and members of the population comparison cohort at the time of diagnosis/index date.

| | Hyperthyroidism cohort ($n=85\,856$) | | Population comparison cohort ($n=847\,057$) | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Age | | | | |
| <51 years | 22 474 | 26.5 | 216 141 | 26.5 |
| 51–60 years | 15 865 | 18.5 | 158 678 | 18.5 |
| 61–70 years | 17 180 | 20.0 | 171 722 | 20.0 |
| >70 years | 30 064 | 35.0 | 300 516 | 35.0 |
| Gender | | | | |
| Female | 70 505 | 82.1 | 693 588 | 82.1 |
| Male | 15 351 | 17.9 | 153 469 | 17.9 |
| Year of hyperthyroidism diagnosis | | | | |
| 1980–1989 | 15 603 | 17.5 | – | – |
| 1990–1999 | 25 414 | 29.6 | – | – |
| 2000–2012 | 45 379 | 52.9 | – | – |
| Cancer history | | | | |
| No | 79 002 | 92.0 | 787 606 | 93.0 |
| Yes | 6854 | 8.0 | 59 451 | 7.0 |
| Diabetes | | | | |
| No | 81 489 | 94.9 | 820 909 | 96.9 |
| Yes | 4367 | 5.1 | 26 148 | 3.1 |
| Hypertension | | | | |
| No | 77 790 | 90.6 | 790 443 | 93.3 |
| Yes | 8066 | 9.4 | 56 614 | 6.7 |
| COPD | | | | |
| No | 80 010 | 93.2 | 812 156 | 95.9 |
| Yes | 5846 | 6.8 | 34 901 | 4.1 |

## Statistical analysis

For hyperthyroid patients and persons in the general population comparison cohort, we calculated the incidence of all-cause mortality, VTE, AMI, ischemic and non-ischemic stroke, arterial embolism, AF and PCI. Incidence rates were expressed as the number of events per 1000 person-years (py). We used Kaplan–Meier analysis to construct cumulative incidence curves and to compute risks (death was considered a competing risk for the cumulative incidence curves for cardiovascular events).

Cox regression was used for time-to-event analysis, and hazard ratios (HRs) were computed with accompanying 95% confidence intervals (CIs). We performed Cox regression to adjust for potential baseline imbalances (cancer, diabetes recorded in the DNPR, hypertension, chronic obstructive pulmonary disease (COPD) as a proxy for smoking, obesity, liver disease, chronic pancreatitis and alcoholism-related diseases other than those affecting the liver or pancreas). We stratified our analyses by age (≤50 years, 50–≤60, 60≤70 and >70 years) and gender.

We performed four sensitivity analyses: (1) an analysis restricted to ICD codes congruent with Graves' disease; (2) an analysis restricted to patients without a cardiovascular diagnosis at baseline to avoid potential confounding by Amiodarone use; (3) an analysis excluding the first month after diagnosis

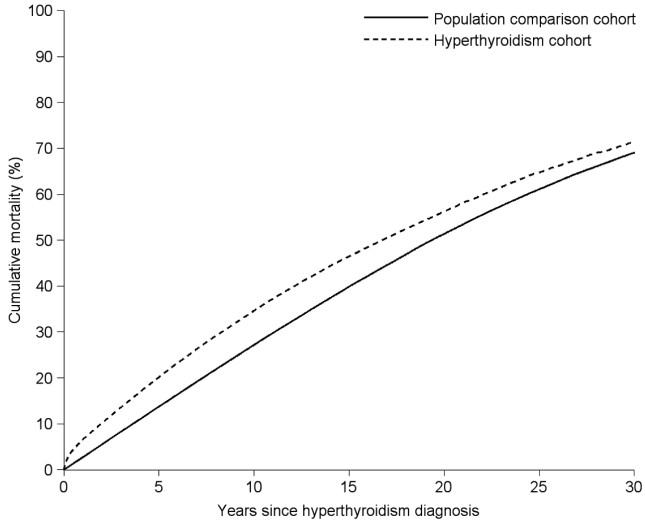


**Figure 1**
Cumulative mortality in hyperthyroidism patients and an age- and sex-matched population comparison cohort.

to circumvent potential diagnostic work-up bias and (4) an analysis restricted to patients with an ICD code for hyperthyroidism combined with either prescribed antithyroid drugs within 3 months before up to 1 year after diagnosis of hyperthyroidism (codes used codes H03BB01, H03BA02, H03BB02, V03AB21) or treatment with radioactive iodine up to 1 year (follow-up time accounting for immortal time bias) after this diagnosis (BWGG and BWGG1). Because the fourth sensitivity analysis depended on linkage with the Danish National Health Service Prescription Database, it could cover only patients diagnosed starting on 1 January 2004 (19).

Analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC, USA). The study was approved by the Danish Data Protection Agency (record no. 1-16-02-1-08).

## Results

### Patient characteristics

The study included a total of 85 856 patients with hyperthyroidism. The majority (82%) was female, and 27% of patients were younger than age 50 at the time of diagnosis. We observed an increasing incidence of hyperthyroidism since 1980. Total follow-up time in the hyperthyroidism cohort was 791 574 years, with a mean follow-up of 9.2 years. Among patients diagnosed after 2004, 70% were treated with antithyroid drugs and 4% were treated with radioactive iodine in the first year after diagnosis; the proportion of patients treated with antithyroid drugs within 5 years after diagnosis increased to 72% (Table 1).

### Mortality

A total of 33 941 patients with hyperthyroidism died during follow-up. Cumulative mortality risks are shown in Fig. 1. The mortality rate was higher in the first year after diagnosis (69/1000 py), compared with years 1–3 after diagnosis (39/1000 py). The highest mortality rate was observed in the first 3 months after diagnosis (123/1000 py) (Table 2).

Mortality was higher in patients with hyperthyroidism than in the general population comparison cohort. The hazard ratio (HR) for mortality was highest in the first 3 months after diagnosis (HR: 4.62, 95% CI: 4.40–4.85). Although the HR decreased thereafter, it remained elevated even during long-term follow-up (>3 years after diagnosis of hyperthyroidism) (HR: 1.35, 95% CI: 1.33–1.37).

### Cardiovascular endpoints

The risk of all acute cardiovascular endpoints studied (VTE, AMI, ischemic and non-ischemic stroke, arterial embolism, AF and PCI) was higher in patients with hyperthyroidism than in the general population cohort, with the highest risk observed in the first 3 months after diagnosis. The hazard ratios were highest for atrial fibrillation (HR: 7.32, 95% CI: 6.58–8.14) and arterial embolism (HR: 6.08, 95% CI: 4.30–8.61), but the risks of VTE, AMI, ischemic and non-ischemic stroke and PCI were also increased 2- to 3-fold in patients with hyperthyroidism compared with those in the general population. Between 3 and 6 months after diagnosis of hyperthyroidism, the increased risk for all cardiovascular endpoints dropped by half, but remained increased, especially for new-onset atrial fibrillation (HR: 3.02, 95% CI: 2.62–3.47), arterial embolism (HR: 1.93, 95% CI: 1.22–3.07) and non-ischemic stroke (HR: 2.15, 95% CI: 1.42–3.25). During long-term follow-up (>3 years after diagnosis of hyperthyroidism), the risk of AMI and VTE almost normalized, whereas the risks of arterial embolism (HR: 1.64, 95% CI: 1.48–1.82), non-ischemic stroke (HR: 1.20, 95% CI: 1.10–1.32) and AF (HR: 1.46, 95% CI: 1.42–1.51) remained slightly elevated. Cumulative incidences for the cardiovascular events are shown in Table 2.

### Stratified and sensitivity analyses

Subgroup analyses were performed according to age and gender. Female and male hyperthyroidism patients had similarly increased risks of mortality and cardiovascular morbidity during the first year after diagnosis. Mortality risk remained approximately 30% increased during long-term follow-up for both genders. In the first year of follow-up, increased risks were more pronounced in patients age ≤50 years compared with those in patients aged >50 years. Especially in patients >70 years relative risk for mortality and cardiovascular morbidity were lower (Table 3).

To assess the robustness of our results, we performed four sensitivity analyses, including one restricted to patients with a Graves' disease-compatible ICD code, one restricted to patients without cardiovascular disease at baseline and one restricted to patients with an ICD code of hyperthyroidism in addition to a hyperthyroidism-defining treatment (i.e., antithyroid drugs or radioactive iodine). For all follow-up windows, risk estimates were similar to those obtained in the main analysis (data not shown). Risks for acute cardiovascular endpoints remained

**Table 2** Rates and hazard ratios with 95% confidence intervals (95% CIs) for risk of mortality, venous thromboembolism (VTE), acute myocardial infarction (AMI), ischemic and non-ischemic stroke, arterial embolism, atrial fibrillation (AF) and percutaneous coronary intervention (PCI) in patients with hyperthyroidism, stratified by time since diagnosis.

| Outcome | Time since diagnosis | Rate (95% CI) per 1000 person-years in hyperthyroidism cohort ($n = 85\,856$) | Rate (95% CI) per 1000 person-years in comparison cohort ($n = 847\,057$) | Hazard ratio (95% CI), age and sex-adjusted model | Hazard ratio (95% CI), fully adjusted model* |
|---|---|---|---|---|---|
| All-cause mortality | 0–3 months | 122.66 (117.9, 127.4) | 27.42 (26.71, 28.14) | 4.66 (4.45, 4.89) | 4.62 (4.40, 4.85) |
| | >3–6 months | 61.02 (57.59, 64.46) | 27.89 (27.16, 28.62) | 2.32 (2.18, 2.47) | 2.20 (2.06, 2.34) |
| | >6–12 months | 46.13 (44.02, 48.24) | 28.06 (27.55, 28.58) | 1.76 (1.67, 1.85) | 1.68 (1.59, 1.76) |
| | >1–3 years | 38.86 (37.84, 39.89) | 29.34 (29.07, 29.62) | 1.44 (1.40, 1.48) | 1.37 (1.33, 1.41) |
| | >3–30 years | 40.16 (39.64, 40.69) | 35.80 (35.65, 35.95) | 1.40 (1.38, 1.42) | 1.35 (1.33, 1.37) |
| VTE | 0–3 months | 6.97 (5.82, 8.11) | 2.15 (1.94, 2.35) | 3.28 (2.71, 3.97) | 3.11 (2.56, 3.77) |
| | >3–6 months | 2.88 (2.13, 3.63) | 1.93 (1.73, 2.12) | 1.50 (1.13, 1.99) | 1.46 (1.10, 1.95) |
| | >6–12 months | 2.62 (2.11, 3.13) | 1.91 (1.77, 2.05) | 1.43 (1.16, 1.76) | 1.36 (1.10, 1.69) |
| | >1–3 years | 2.39 (2.13, 2.65) | 1.98 (1.91, 2.05) | 1.25 (1.11, 1.40) | 1.20 (1.07, 1.35) |
| | >3–30 years | 2.46 (2.33, 2.59) | 2.35 (2.31, 2.39) | 1.16 (1.09, 1.23) | 1.13 (1.06, 1.20) |
| AMI | 0–3 months | 9.08 (7.75, 10.40) | 3.79 (3.52, 4.07) | 2.42 (2.06, 2.85) | 2.24 (1.90, 2.65) |
| | >3–6 months | 4.93 (3.94, 5.93) | 3.76 (3.48, 4.04) | 1.34 (1.08, 1.67) | 1.25 (1.00, 1.56) |
| | >6–12 months | 4.48 (3.81, 5.15) | 3.71 (3.52, 3.91) | 1.24 (1.05, 1.45) | 1.12 (0.95, 1.32) |
| | >1–3 years | 3.88 (3.55, 4.21) | 3.82 (3.72, 3.92) | 1.05 (0.96, 1.15) | 1.00 (0.91, 1.10) |
| | >3–30 years | 4.28 (4.11, 4.45) | 4.12 (4.07, 4.17) | 1.17 (1.12, 1.23) | 1.13 (1.08, 1.18) |
| Ischemic stroke | 0–3 months | 11.02 (9.56, 12.48) | 3.95 (3.67, 4.23) | 2.77 (2.38, 3.22) | 2.70 (2.31, 3.14) |
| | >3–6 months | 5.03 (4.02, 6.03) | 4.32 (4.02, 4.61) | 1.18 (0.95, 1.46) | 1.11 (0.90, 1.38) |
| | >6–12 months | 5.75 (4.99, 6.51) | 4.43 (4.22, 4.64) | 1.34 (1.16, 1.55) | 1.29 (1.11, 1.48) |
| | >1–3 years | 5.81 (5.41, 6.21) | 4.48 (4.37, 4.59) | 1.35 (1.25, 1.45) | 1.31 (1.21, 1.41) |
| | >3–30 years | 6.43 (6.22, 6.64) | 5.83 (5.77, 5.89) | 1.27 (1.22, 1.31) | 1.24 (1.19, 1.29) |
| Non-ischemic stroke | 0–3 months | 1.81 (1.22, 2.40) | 0.74 (0.62, 0.86) | 2.51 (1.74, 3.63) | 2.47 (1.70, 3.58) |
| | >3–6 months | 1.52 (0.96, 2.07) | 0.75 (0.62, 0.87) | 2.11 (1.41, 3.15) | 2.15 (1.42, 3.25) |
| | >6–12 months | 0.91 (0.61, 1.21) | 0.70 (0.61, 0.78) | 1.34 (0.94, 1.91) | 1.30 (0.91, 1.86) |
| | >1–3 years | 0.99 (0.83, 1.16) | 0.77 (0.72, 0.81) | 1.35 (1.13, 1.62) | 1.30 (1.08, 1.55) |
| | >3–30 years | 0.98 (0.90, 1.06) | 0.90 (0.87, 0.92) | 1.22 (1.11, 1.34) | 1.20 (1.10, 1.32) |
| Arterial embolism | 0–3 months | 2.62 (1.92, 3.32) | 0.45 (0.36, 0.54) | 6.08 (4.33, 8.53) | 6.08 (4.30, 8.61) |
| | >3–6 months | 1.16 (0.69, 1.64) | 0.59 (0.48, 0.69) | 2.05 (1.31, 3.22) | 1.93 (1.22, 3.07) |
| | >6–12 months | 0.88 (0.59, 1.18) | 0.50 (0.43, 0.56) | 1.96 (1.36, 2.82) | 1.93 (1.33, 2.79) |
| | >1–3 years | 0.87 (0.72, 1.03) | 0.54 (0.50, 0.58) | 1.73 (1.43, 2.10) | 1.66 (1.37, 2.02) |
| | >3–30 years | 0.82 (0.75, 0.90) | 0.55 (0.53, 0.57) | 1.69 (1.52, 1.87) | 1.64 (1.48, 1.82) |
| AF | 0–3 months | 34.93 (32.19, 37.67) | 4.89 (4.56, 5.22) | 7.27 (6.55, 8.07) | 7.32 (6.58, 8.14) |
| | >3–6 months | 15.49 (13.62, 17.35) | 5.08 (4.75, 5.42) | 3.11 (2.71, 3.58) | 3.02 (2.62, 3.47) |
| | >6–12 months | 11.92 (10.77, 13.07) | 4.94 (4.71, 5.18) | 2.43 (2.18, 2.71) | 2.36 (2.11, 2.63) |
| | >1–3 years | 8.68 (8.16, 9.20) | 5.24 (5.12, 5.37) | 1.75 (1.63, 1.86) | 1.69 (1.58, 1.81) |
| | >3–30 years | 9.29 (9.02, 9.56) | 7.26 (7.19, 7.33) | 1.49 (1.45, 1.54) | 1.46 (1.42, 1.51) |
| PCI | 0–3 months | 7.53 (6.09, 8.97) | 2.15 (1.91, 2.40) | 3.60 (2.88, 4.51) | 3.47 (2.75, 4.37) |
| | >3–6 months | 3.00 (2.07, 3.93) | 1.90 (1.67, 2.14) | 1.63 (1.17, 2.28) | 1.51 (1.08, 2.12) |
| | >6–12 months | 2.45 (1.85, 3.04) | 1.75 (1.60, 1.91) | 1.42 (1.10, 1.84) | 1.35 (1.03, 1.75) |
| | >1–3 years | 1.88 (1.60, 2.16) | 2.06 (1.97, 2.15) | 0.94 (0.81, 1.10) | 0.89 (0.76, 1.04) |
| | >3–30 years | 2.16 (1.98, 2.35) | 2.13 (2.08, 2.19) | 1.08 (0.99, 1.18) | 1.04 (0.95, 1.14) |

*Model adjusted for age, sex, calendar time (by study design), cancer, diabetes, hypertension, obesity, chronic obstructive pulmonary disease, liver disease and alcoholism-related diseases.

**Table 3** Stratified analyses for risk of mortality, venous thromboembolism (VTE), acute myocardial infarction (AMI), ischemic and non-ischemic stroke, arterial embolism, atrial fibrillation (AF) and percutaneous coronary intervention (PCI) in patients with hyperthyroidism. The table presents hazard ratios (adjusted) with 95% confidence intervals.

| Outcome | Time since diagnosis | Males ($n = 15\,351$) | Females ($n = 70\,505$) | Patients ≤50 years ($n = 22\,747$) | Patients >50 and ≤60 years ($n = 15\,635$) | Patients >60 and ≤70 years ($n = 16\,798$) | Patients >70 years ($n = 28\,929$) |
|---|---|---|---|---|---|---|---|
| All-cause mortality | 0–1 year | 2.47 (2.32, 2.64) | 2.57 (2.49, 2.66) | 3.37 (2.60, 4.36) | 2.81 (2.40, 3.28) | 3.03 (2.78, 3.31) | 2.46 (2.38, 2.54) |
| | >1–3 years | 1.31 (1.23, 1.40) | 1.39 (1.35, 1.44) | 1.19 (0.94, 1.50) | 1.52 (1.34, 1.73) | 1.58 (1.47, 1.71) | 1.33 (1.28, 1.37) |
| | >3–30 years | 1.29 (1.24, 1.33) | 1.37 (1.35, 1.39) | 1.15 (1.09, 1.28) | 1.29 (1.24, 1.34) | 1.38 (1.34, 1.42) | 1.38 (1.35, 1.40) |
| VTE | 0–1 year | 2.07 (1.58, 2.70) | 1.84 (1.59, 2.12) | 2.18 (1.38, 3.42) | 2.21 (1.48, 3.30) | 2.32 (1.75, 3.07) | 1.70 (1.45, 2.00) |
| | >1–3 years | 1.01 (0.76, 1.36) | 1.25 (1.10, 1.41) | 1.06 (0.70, 1.61) | 1.50 (1.07, 2.08) | 1.32 (1.04, 1.68) | 1.11 (0.95, 1.30) |
| | >3–30 years | 1.13 (0.98, 1.31) | 1.13 (1.06, 1.20) | 1.07 (0.93, 1.24) | 1.18 (1.04, 1.33) | 1.19 (1.07, 1.33) | 1.06 (0.96, 1.18) |
| AMI | 0–1 year | 1.15 (0.93, 1.41) | 1.58 (1.40, 1.78) | 2.49 (1.31, 4.71) | 1.67 (1.19, 2.34) | 1.59 (1.27, 1.98) | 1.34 (1.18, 1.52) |
| | >1–3 years | 0.93 (0.78, 1.12) | 1.03 (0.93, 1.14) | 0.87 (0.51, 1.50) | 1.23 (0.94, 1.61) | 1.03 (0.85, 1.25) | 0.95 (0.85, 1.07) |
| | >3–30 years | 1.00 (0.91, 1.10) | 1.17 (1.12, 1.24) | 1.31 (1.16, 1.49) | 1.23 (1.11, 1.35) | 1.14 (1.05, 1.24) | 1.01 (0.94, 1.09) |
| Ischemic stroke | 0–1 year | 1.33 (1.08, 1.63) | 1.67 (1.50, 1.85) | 1.82 (1.04, 3.19) | 2.20 (1.56, 3.12) | 1.76 (1.41, 2.21) | 1.50 (1.34, 1.67) |
| | >1–3 years | 1.23 (1.04, 1.45) | 1.33 (1.22, 1.44) | 1.50 (1.01, 2.24) | 1.54 (1.18, 2.01) | 1.53 (1.29, 1.81) | 1.22 (1.11, 1.34) |
| | >3–30 years | 1.06 (0.97, 1.16) | 1.28 (1.23, 1.33) | 1.27 (1.13, 1.42) | 1.31 (1.20, 1.43) | 1.23 (1.15, 1.32) | 1.19 (1.13, 1.27) |
| Non-ischemic stroke | 0–1 year | 1.30 (0.79, 2.16) | 1.96 (1.54, 2.49) | 1.58 (0.46, 5.40) | 2.46 (1.20, 5.04) | 2.18 (1.32, 3.61) | 1.68 (1.29, 2.19) |
| | >1–3 years | 1.33 (0.89, 1.97) | 1.29 (1.05, 1.59) | 0.55 (0.17, 1.81) | 1.37 (0.78, 2.41) | 2.21 (1.56, 3.12) | 1.10 (0.86, 1.39) |
| | >3–30 years | 1.13 (0.90, 1.41) | 1.22 (1.10, 1.35) | 0.72 (0.52, 1.01) | 1.28 (1.05, 1.56) | 1.21 (1.02, 1.43) | 1.32 (1.14, 1.52) |
| Arterial embolism | 0–1 year | 1.52 (1.46, 1.58) | 2.95 (2.31, 3.77) | 4.07 (1.41, 11.77) | 2.88 (1.08, 7.64) | 3.47 (2.15, 5.61) | 2.73 (2.11, 3.54) |
| | >1–3 years | 1.65 (1.03, 2.63) | 1.69 (1.37, 2.10) | 1.52 (0.52, 4.44) | 1.45 (0.73, 2.86) | 1.37 (0.83, 2.25) | 1.75 (1.39, 2.21) |
| | >3–30 years | 1.64 (1.27, 2.13) | 1.69 (1.37, 2.10) | 1.76 (1.32, 2.36) | 1.49 (1.17, 1.91) | 1.66 (1.36, 2.01) | 1.65 (1.40, 1.94) |
| AF | 0–1 year | 4.47 (3.91, 5.12) | 3.56 (3.30, 3.84) | 8.47 (5.65, 12.7) | 7.13 (5.64, 9.02) | 5.36 (4.63, 6.19) | 3.09 (2.85, 3.35) |
| | >1–3 years | 1.74 (1.51, 2.01) | 1.67 (1.55, 1.81) | 2.60 (1.76, 3.84) | 2.66 (2.14, 3.30) | 1.80 (1.55, 2.09) | 1.54 (1.42, 1.67) |
| | >3–30 years | 1.41 (1.31, 1.53) | 1.47 (1.42, 1.53) | 1.73 (1.57, 1.91) | 1.53 (1.42, 1.65) | 1.44 (1.36, 1.53) | 1.37 (1.30, 1.44) |
| PCI | 0–1 year | 1.86 (1.47, 2.36) | 2.19 (1.80, 2.66) | 3.56 (1.93, 6.56) | 1.89 (1.28, 2.81) | 2.27 (1.74, 2.96) | 1.64 (1.30, 2.07) |
| | >1–3 years | 0.97 (0.76, 1.23) | 0.89 (0.72, 1.09) | 0.67 (0.32, 1.39) | 0.88 (0.59, 1.30) | 1.00 (0.76, 1.31) | 0.85 (0.68, 1.08) |
| | >3–30 years | 1.05 (0.90, 1.22) | 1.07 (0.95, 1.20) | 1.34 (1.05, 1.71) | 1.16 (0.97, 1.39) | 0.99 (0.85, 1.17) | 0.87 (0.73, 1.04) |

increased when we excluded the first month of follow-up to avoid diagnostic work-up bias (data not shown).

## Discussion

Our nationwide cohort study showed an increased risk of mortality, VTE, AMI, ischemic and non-ischemic stroke, AF, arterial emboli and PCI in patients with hyperthyroidism compared with a matched general population cohort. Our findings emphasize that hyperthyroidism is a serious condition, with increased cardiovascular morbidity beyond atrial fibrillation and heart failure. The marked risk increase in the initial months after diagnosis suggests a direct contribution of elevated $FT_4$ levels.

Our study data were obtained from databases with nationwide coverage in Denmark. The diagnosis of hyperthyroidism in these databases has been shown previously to have high validity, with a misclassification rate of only 2% (20). Major cardiovascular events such as AMI, VTE and AF also have shown high validity in Danish registries (17, 18, 21). To assess the robustness of our results, we performed a sensitivity analysis restricted to patients treated with antithyroid drugs (These are disease-defining drugs, as they are not prescribed for any conditions other than hyperthyroidism). The results of this sensitivity analysis were similar to those for the whole patient cohort. As well, our results are in line with those of a cohort study that used validated hyperthyroidism diagnoses, also based on Danish registries (12).

Our study is limited by the inability to present data with certainty according to underlying cause of diagnosed hyperthyroidism (Graves' disease, toxic adenoma or toxic multinodular goiter), mainly because the ICD-8 and ICD-10 classification systems are not completely uniform regarding causes of hyperthyroidism. This could be important, as cardiovascular risk likely depends on the degree of hyperthyroidism, and Graves' disease is accompanied by higher $FT_4$ levels (10). Another shortcoming is the lack of laboratory data to relate cardiovascular risk to $FT_4$ levels in patients with hyperthyroidism. Also, reasons for not treating (mild or transient hyperthyroidism for example) a substantial subset of the cohort (~25%) could not be obtained from the database.

It is interesting that both hyperthyroidism and hypothyroidism are associated with increased cardiovascular morbidity. A meta-analysis showed almost two-fold increased CVD risk in patients with subclinical hypothyroidism whose TSH levels were >10 U/L (22). Our study found increased cardiovascular morbidity in patients with hyperthyroidism, in line with an earlier cohort study (12). It is likely that different pathways lead to CVD in hypo- and hyperthyroidism. Increased prothrombotic tendency (3) and vascular dysfunction (4) are possible mechanisms leading to cardiovascular disease in hyperthyroidism. What is also striking is the full spectrum of increased cardiovascular risk associated with hyperthyroidism, ranging from arterial to venous events and from ischemic to non-ischemic events. It seems clear that no single pathway associated with hyperthyroidism could explain such a broad association. Importantly, the increased risk was also found in patients without known cardiovascular disease and were not restricted to atrial fibrillation and heart failure. It should also be emphasized that hyperthyroidism and hypothyroidism are not mutually exclusive conditions, as hypothyroidism can occur in the course of treated hyperthyroidism.

The increased mortality risk in hyperthyroidism was shown before in a large cohort of patients in whom TSH was measured (23). Our mortality estimates were higher, probably due to differences in control selection. Although our study used the general population, the study by Laulund *et al*., selected on TSH being measured, may have sampled controls with higher morbidity and mortality risk.

However, two non-causal interpretations of our finding should also be considered. Firstly, diagnostic work-up bias (a patient having a higher probability of being detected with other diseases during hyperthyroidism-related doctor visit) might play a role. However, diagnostic work-up bias cannot fully explain the results because some endpoints like mortality or arterial embolism or stroke are not likely to be detected as part of a routine medical care for hyperthyroidism. Also, results did not change materially when the first month of follow-up was excluded from the analysis. A second non-causal interpretation of the results that should be considered is confounding, as the Danish registries lack detailed information on, for example, smoking and socio-economic status. In agreement, it might be that despite our extensive adjustment for comorbidities, residual confounding still remains to a certain degree. It should be noticed that despite this being true, our results are clearly in line with studies that show an increased risk for death or cardiovascular disease even after more detailed statistical adjustments (10, 12). Besides, as age is an important determinant of mortality in the context of thyroid disease (24), age was adjusted for by matching it to a population comparison cohort. Interestingly, relative risks for mortality and cardiovascular morbidity were

lowest in patients >70, which might be due to a milder form of hyperthyroidism in this subgroup, differences in underlying diagnosis, postponing of treatment and can also be a reflection of higher baseline risks in this group.

As smoking is related to hyperthyroidism, especially in Graves' disease, unmeasured confounding might be considered (25). However, there are two reasons why this is unlikely to explain our results completely. Firstly, there is a clear peak in risk in the first months following a hyperthyroidism diagnosis, a pattern compatible with a direct effect of elevated FT4 levels, and not with smoking (3). Second, smoking is not considered a strong risk factor for one important outcome of our study, i.e., venous thrombosis (26). In addition, the risk estimates were similar in the analyses restricted to the population with Graves' disease and in the total cohort.

In conclusion, our study showed a clear association between hyperthyroidism and mortality as well as acute cardiovascular events. This should be taken into account when considering and discussing the necessity of treatment for this condition, especially in patients with lack of symptoms. Future studies are needed to investigate whether treatment at an earlier stage of the hyperthyroidism will lower the cardiovascular risks.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Author contribution statement**

O D, H S and J O J contributed to the conception of the study; O D, E P, S C, J V, H S and J O J drafted the protocol; E P contributed to analysis and O D, E P, S C, J V, H S and J O J drafted the manuscript.

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