Subclinical and Overt Thyroid Dysfunction and Risk of All-Cause Mortality and Cardiovascular Events: A Large Population Study

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Context: Thyroid dysfunction has been associated with both increased all-cause and cardiovascular mortality, but limited data are available on mild thyroid dysfunction and cause-specific mortality.

Objective: The objective of the study was to examine the risk of all-cause mortality, major adverse cardiovascular events (MACEs), and cause-specific events in subjects with overt and subclinical thyroid dysfunction.

Design: This was a retrospective cohort study.

Setting and Participants: Participants in the study were subjects who underwent thyroid blood tests, without prior thyroid disease, consulting their general practitioner in 2000–2009 in Copenhagen, Denmark.

Main Outcome Measure: All-cause mortality, MACEs, and cause-specific events identified in nationwide registries were measured.

Results: A total of 47 327 (8.4%) deaths occurred among 563 700 included subjects [mean age 48.6 (SD ±18.2) y; 39% males]. All-cause mortality was increased in overt and subclinical hyperthyroidism [age adjusted incidence rates of 16 and 15 per 1000 person-years, respectively; incidence rate ratios (IRRs) 1.25 [95% confidence interval (CI) 1.15–1.36] and 1.23 (95% CI 1.16–1.30)] compared with euthyroid (incidence rate of 12 per 1000 person-years). Risk of MACEs was elevated in overt and subclinical hyperthyroidism [IRRs 1.16 (95% CI 1.05–1.27) and 1.09 (95% CI 1.02–1.16)] driven by heart failure [IRRs 1.14 (95% CI 0.99–1.32) and 1.20 (95% CI 1.10–1.31)]. A reduction of all-cause mortality was observed in subclinical hypothyroidism with TSH of 5–10 mIU/L [IRR 0.92 (95% CI 0.86–0.98)].

Conclusions: Heart failure is the leading cause of an increased cardiovascular mortality in both overt and subclinical hyperthyroidism. Subclinical hypothyroidism with TSH 5–10 mIU/L might be associated with a lower risk of all-cause mortality. **(*J Clin Endocrinol Metab* 99: 2372–2382, 2014)**

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Abbreviations: AF, atrial fibrillation; CHD, coronary heart disease; CI, confidence interval; HF, heart failure; IR, incidence rate; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction; py, person-years.

It is debated whether overt and subclinical thyroid dysfunction is associated with increased mortality. Although these conditions are very common, there have been only a limited number of large studies on the effects of thyroid dysfunction on mortality and cardiovascular events (1–4). Parle et al (5) studied a cohort of 1191 individuals from primary care in Birmingham, United Kingdom, of whom 70 had subclinical hyperthyroidism, and found that the latter had an increased risk of cardiovascular and all-cause mortality. Contrary to this result, the Cardiovascular Health Study, United States, found no increased risk of coronary heart disease (CHD), cerebrovascular disease, or cardiovascular or all-cause mortality in a prospectively followed cohort of 3233 community-dwelling individuals of whom 47 had subclinical hyperthyroidism (6). Two recent registry-based studies from Denmark found that a diagnosis of hyperthyroidism was associated with both increased morbidity and mortality (7, 8).

In particular, results on mortality in overt and subclinical hypothyroidism have been discrepant: Rodondi et al (9) studied 338 individuals with subclinical hypothyroidism and found that they had an increased risk of heart failure but not of other cardiovascular events or all-cause mortality. Likewise, no association was found with cardiovascular outcomes or all-cause mortality among the 51 overt and 496 subclinical hypothyroid individuals in the Cardiovascular Health Study, and the Leiden 85-Plus Study from The Netherlands even found an increased longevity associated with increased TSH levels in the oldest (6, 10). In addition, a recent Danish study using a national database found an 50% increased risk of all-cause mortality in individuals with hypothyroidism, possibly due to prevalent comorbidity (11).

To further examine the association between thyroid dysfunction and risk of all-cause as well as cause-specific mortality, we conducted a large population-based study of a homogenous group of primary care patients that were categorized according to their thyroid status based on a first-time thyroid function testing.

Materials and Methods

Study setting

In Denmark, each resident is provided with a permanent and unique civil registration number enabling individual level-linkage between nationwide administrative registers holding information on health care usage. Since 1978 the Danish National Patient Registry has registered all hospital contacts in Denmark (12). Each admission is registered with one primary and, if appropriate, one or more secondary diagnoses according to the World Health Organization *International Classification of Diseases*, 10th revision. The Danish Register of Medicinal Product Statistics holds information regarding all claimed prescriptions (coded according to the international Anatomical Therapeutic Chemical classification) (13) in Denmark since 1995. The registry also includes information on the date of dispensation, strength, and quantity dispensed. Due to partial reimbursement of drug expenses by the Danish healthcare authorities, all pharmacies are required to provide information that ensures complete and accurate registration (14). Vital status was obtained from the Central Population Register, which records all deaths within 14 days, and specific causes of death were obtained from the Danish Register of Causes of Death (15). Annual incomes were retrieved from the Integral Database for the Danish Labor Market (16), and socioeconomic status was defined by the average yearly gross household income in a 5-year period prior to inclusion in the study.

Population

The study cohort comprised citizens of Copenhagen (the capital of Denmark) aged 18 years or older who underwent thyroid function testing at the Copenhagen General Practitioners Laboratory in the period of January 1, 2000, through December 31, 2009. Each subject entered the cohort upon first thyroid function testing and was followed up until December 31, 2009, migration, or death. The Copenhagen General Practitioners Laboratory analyses laboratory tests ordered by primary care physicians in the Copenhagen area except for the municipality of Frederiksberg. TSH, free and total T_4, and free and total T_3 were determined in serum by the commercially available ADVIA Centaur System (Bayer/Siemens) according to the instructions of the manufacturer. Thus, the same TSH assay was used throughout the study period (lower detection limit 0.01 mIU/L). Free T_4 was analyzed routinely only in patients with abnormal TSH levels or if specifically requested by the referring physician. Likewise, T_3 was measured routinely only in patients presenting with low TSH and normal T_4.

We excluded all subjects with previous thyroid dysfunction, ie, previous prescription of thyroid hormones or antithyroid drugs or any thyroid-related hospital diagnosis. Patients with previous myocardial infarction (MI), stroke, heart failure (HF), cancer, and ambiguous times of death or thyroid blood test values were also excluded. Patients where categorized according to their thyroid status at the time of first testing based on both the traditional definitions of thyroid dysfunction and using TSH level-dependent definitions of two levels of subclinical hyper- and hypothyroidism, respectively (Table 1).

Comorbidity and concomitant medical therapy

From the Danish National Patient Registry comorbidities were identified using the *International Classification of Diseases*, 10th revision, codes for, eg, MI, HF, and stroke (Supplemental Table 1). These diagnoses have been validated and have high sensitivities and positive predictive values (17, 18). The Charlson comorbidity index was calculated on basis of prespecified diagnoses up to 5 years prior to cohort entry (19, 20). From the Danish Register of Medicinal Product Statistics, we identified all claimed prescriptions of thyroid hormones and antithyroid medications as well as amiodarone, lithium, and corticosteroids that are all known to affect thyroid function (21).

Table 1. Definitions of Thyroid Disease and Thyroid Dysfunction Levels

	TSH, mIU/L	Free T_4, pmol/L	Total T_4, mmol/L
Thyroid dysfunction definitions			
Overt hyperthyroidism	<0.2	>22	>140
Subclinical hyperthyroidism	<0.2	9–22	60–140
Grade I	0.1–0.2	9–22	60–140
Grade II	<0.1	9–22	60–140
Euthyroidism	0.2–5.0	9–22	60–140
Subclinical hypothyroidism	>5.0	9–22	60–140
Grade I	5.0–10.0	9–22	60–140
Grade II	>10.0	9–22	60–140
Overt hypothyroidism	>5.0	<9	<60

Outcomes

The primary outcome of interest was all-cause mortality and a combined end point of major adverse cardiovascular events (MACEs) consisting of cardiovascular death, nonfatal MI, and nonfatal stroke. Secondary outcomes included combined end points of fatal and nonfatal MI, stroke, HF, and cancer.

Statistical analysis

Baseline characteristics are presented as numbers with percentages for categorical variables and as means (±SDs) for continuous variables. Median follow-up time is reported with interquartile range. Incidence rates (IRs) were calculated as number of events per 1000 person-years (py) stratified by thyroid function.

Time-dependent Poisson regression models were constructed to estimate incidence rate ratios [IRRs; with 95% confidence intervals (CIs)] for each study outcome. The Poisson regression models were adjusted for age, sex, and calendar year and therefore included two time scales: calendar time with bands split in 1-year periods after January 1, 2000, and duration time since first thyroid function testing. Age was calculated at the beginning of each interval. Individuals were censored at the time of a fatal or nonfatal event, the end of the follow-up period (December 31, 2009) or at migration. A 5% significance level was used in all analyses including when testing for interactions.

Several sensitivity analyses were done to validate our primary findings. First, we adjusted the main model for Charlson comorbidity index and socioeconomic status at baseline. Second, we included any thyroid treatment (defined as a thyroid medication prescription or a hospital diagnosis of thyroid disease) as a time-dependent variable. Third, we adjusted for atrial fibrillation (AF) at baseline and during follow-up by splitting the risk-time at the date of AF diagnosis. Dichotomous variables were hereafter created for the diagnosis of AF (current diagnosis or no diagnosis). Fourth, we stratified on age groups below and above 65 years of age and on gender. Fifth, we stratified on 3, 6, 12, and 12 or more months of follow-up by splitting the time in these respective intervals. Sixth, we repeated all analyses using different values for the upper reference limit of TSH (2.5, 4.2, and 4.5 mIU/L).

All statistical analyses were performed with the SAS Statistical Software package version 9.2 (SAS Institute Inc) and Stata Software version 11 (StataCorp).

Results

A total of 563 700 individuals without previously recorded thyroid disease was included at first-time thyroid function testing from 2000 to 2009. Selection of the study cohort is illustrated in Figure 1, and baseline characteristics of the cohort are presented in Table 2. The study cohort comprised more females (61%) than males; the average age was 48.6 (±18.2) years, with females being 2 years younger. Men with subclinical hypo- and hyperthyroidism grade II were slightly older than those with grade I. The cohort had a low degree of comorbidity, and on average the subjects with thyroid dysfunction were older and more frequently women.

During a total follow-up time of 2 902 568 py [median follow-up 5.5 y (interquartile range 2.53–7.56 y)], a total of 47 327 subjects (8.4%) died (of these 93.0%, 4.0%, and 3.0% were in the euthyroid, hyperthyroid, and hypothyroid groups, respectively).

Hyperthyroid states: IRs and risk of MACE and death

For all outcomes, the unadjusted IRs were increased for subjects with hyperthyroidism (Table 3). Patients with overt hyperthyroidism had the highest adjusted all-cause mortality rates, ie, when estimating IRs corresponding to subjects aged 65 years. Also, adjusted IRs of all-cause mortality, MACE, and HF remained increased for subjects with hyperthyroid states. For MI, stroke, and cancer, the IRs were increased in these subjects, although these results were not statistically significant.

Results from the Poisson regression analysis adjusted for age, sex, and calendar year are illustrated in Figure 2. For all-cause mortality, a trend for increased risk with increasing degree of hyperthyroidism was observed, and likewise the risk of MACE was uniformly elevated in subclinical and overt hyperthyroidism. HF risk was significantly elevated in subclinical hyperthyroidism, and no increased risk of MI or stroke was found in either overt or subclinical hyperthyroidism.

Results investigating risks according to the two levels of subclinical hyperthyroidism are displayed in Table 3 and Figure 2. For both levels of subclinical hyperthyroidism, there was an increased risk of all-cause mortality, MACE, and HF, respectively. However, for MACE the result was not significant in patients with subclinical hyperthyroidism grade II (TSH < 0.1 mIU/L). For cancer, no risk difference was found according to level of subclinical hyperthyroidism.

Hypothyroid states: IRs and risk of MACE and death

Overall, unadjusted IRs for all outcomes were higher in the hypothyroid states compared with the euthyroid

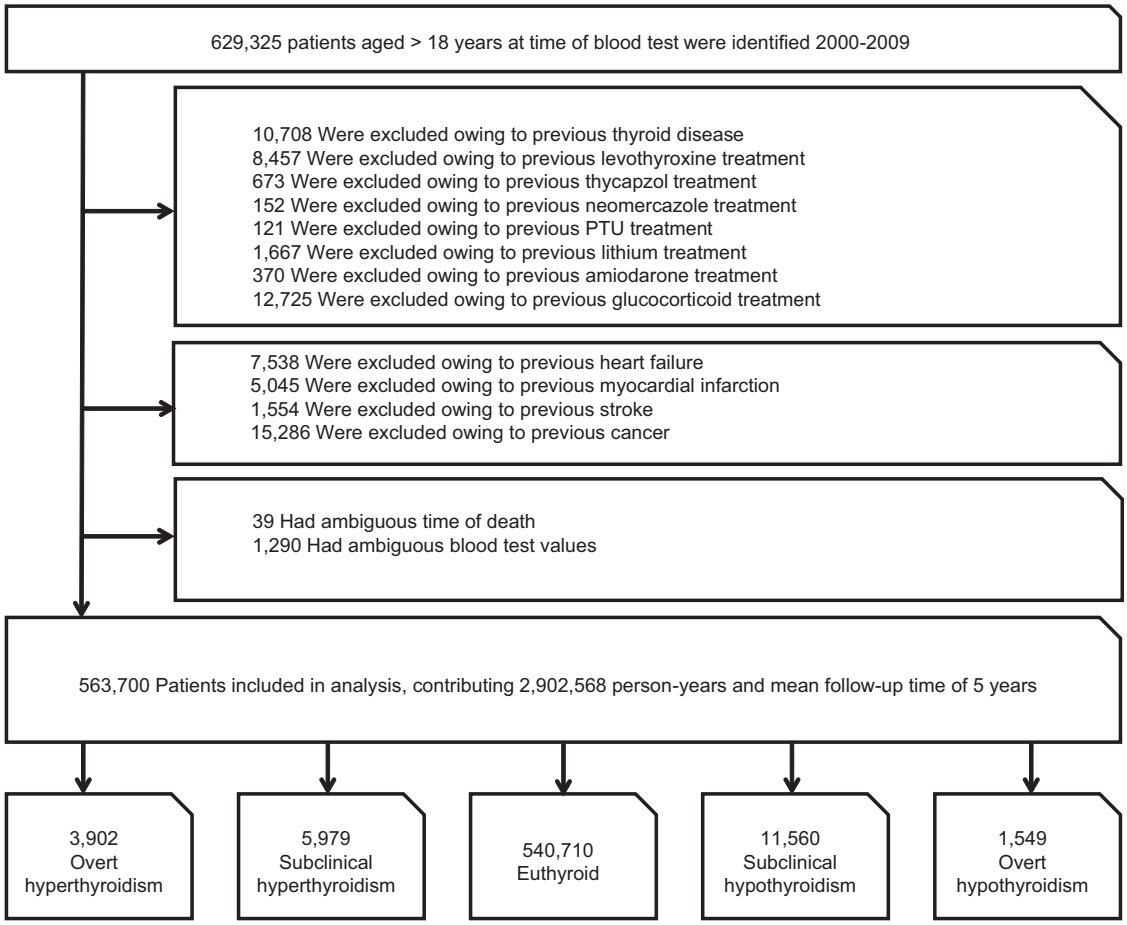

Figure 1. Flow chart of study cohort selection. PTU, propylthiouracil.

group, except for the incidence of cancer that was lower in overt hypothyroidism (Table 3). Age-adjusted incidence rates of all-cause mortality were lower in subclinical hypothyroidism, whereas the rates of MI remained high after age adjustment in both subclinical and overt hypothyroidism. Age-adjusted cancer rates were lower in both subclinical and overt hypothyroidism compared with the euthyroid state.

A lower incidence of all-cause mortality was found in subclinical hypothyroidism grade I (TSH 5.0–10.0 mIU/L) and grade II (TSH > 10.0 mIU/L), respectively (Table 3). An increased incidence of MI was found in subclinical hypothyroid grade II (TSH > 10.0 mIU/L).

Poisson regression analysis showed a significantly lower risk of all-cause mortality in subclinical hypothyroidism, as shown in Table 3 and Figure 2. Also, there was an elevated risk of MI in the subclinical hypothyroid group and a low risk of cancer in both subclinical and overt hypothyroidism.

Results from the analysis of levels of subclinical hypothyroidism showed that only those with grade I dysfunction (TSH 5.0–10.0 mIU/L) had a significantly lower risk of all-cause mortality (Table 3 and Figure 2), but the risk of MI was, on the other hand, elevated only in those with grade II dysfunction (TSH > 10.0 mIU/L). Also, the lower risk of cancer was found only in subclinical hypothyroid grade I subjects.

Supplemental sensitivity analyses

Results from the sensitivity analyses of all the end points are presented in Supplemental Tables 2–7. Adjusting for the Charlson comorbidity index, socioeconomic status, and any treatment during follow-up gave the same overall results as the main model. Likewise, adjusting for AF at baseline and during follow-up did not alter the overall findings.

The age- and gender-stratified analyses showed only a reduced risk of all-cause mortality in subclinical hypothyroid subjects older than 65 years of age and in women. No increased risk of all-cause mortality was found in overt hyperthyroid individuals younger than 65 years of age, and also in this age group, no increased risk of MACE could be demonstrated; otherwise, the overall results were the same. The analyses on 3, 6, 12, and 12 or more months of follow-up showed that overt hypo- and hyperthyroid subjects had an increased risk of all-cause mortality in the first 3 months after their first thyroid function test and that the low risk in subclinical hypothyroid subjects was ob-

Table 2. Baseline Characteristics

	Total Population (n = 563 700)	Overt Hypothyroidism (n = 1549)	Subclinical Hypothyroidism (n = 11 560)			Euthyroidism (n = 540 710)	Subclinical Hyperthyroidism (n = 5979)			Overt Hyperthyroidism (n = 3902)
			All	Grade I	Grade II		All	Grade I	Grade II	
Mean age (±SD), y	48.6 (18.2)	53.1 (18.2)	54.2 (18.6)	55.0 (17.7)	54.0 (18.8)	48.3 (18.1)	60.7 (19.6)	60.4 (19.1)	60.9 (19.8)	51.9 (19.4)
Mean age, y, women (±SD)	47.7 (19.0)	52.8 (18.5)	54.4 (18.7)	54.2 (18.9)	55.2 (17.8)	47.3 (18.9)	60.5 (20.3)	60.3 (20.1)	60.5 (20.4)	51.6 (19.8)
Mean age, y, men (±SD)	49.8 (16.8)	54.7 (16.9)	53.2 (18.1)	52.9 (18.3)	54.4 (17.1)	49.7 (16.8)	61.4 (16.8)	60.4 (16.6)	62.4 (17.0)	53.0 (17.5)
Sex, n, %										
Women	342 537 (61)	1264 (82)	9276 (80)	7221 (79)	2055 (83)	324 312 (60)	4577 (77)	1671 (71)	2906 (80)	3108 (80)
Men	221 163 (39)	285 (18)	2284 (20)	1863 (21)	421 (17)	216 398 (40)	1402 (23)	685 (29)	717 (20)	794 (20)
Thyroid function										
TSH, mIU/L (±SD)	1.86 (4.35)	63.63 (44.43)	9.27 (7.25)	6.70 (1.40)	18.72 (11.17)	1.56 (0.84)	0.08 (0.06)	0.15 (0.03)	0.04 (0.03)	0.04 (0.04)
Free T_4, pmol/L (±SD)	15.98 (8.29)	6.27 (1.91)	13.1 (2.17)	13.49 (2.09)	11.72 (1.87)	15.05 (2.28)	16.9 (2.59)	16.22 (2.40)	17.34 (2.62)	41.67 (22.41)
Comorbidity, n, %										
Peripheral vascular disease	1906 (0)	4 (0)	28 (0)	24 (0)	4 (0)	1806 (0)	43 (1)	14 (1)	29 (1)	25 (1)
Ischemic heart disease	5295 (1)	8 (1)	104 (1)	83 (1)	21 (1)	5042 (1)	109 (2)	40 (2)	69 (2)	32 (1)
COPD	2946 (1)	7 (0)	72 (1)	53 (1)	19 (1)	2756 (1)	74 (1)	35 (1)	39 (1)	37 (1)
Diabetes	4949 (1)	7 (0)	78 (1)	53 (1)	19 (1)	4728 (1)	96 (2)	35 (1)	39 (1)	40 (1)
Rheumatic disease	673 (0)	1 (0)	20 (0)	18 (0)	2 (0)	637 (0)	12 (0)	3 (0)	9 (0)	3 (0)
Chronic renal failure	476 (0)	3 (0)	16 (0)	15 (0)	1 (0)	440 (0)	13 (0)	7 (0)	6 (0)	4 (0)
Charlson comorbidity index, n, %										
0	543 672 (96)	1501 (97)	11 173 (97)	8766 (96)	2407 (97)	521 691 (96)	5,568 (93)	2,193 (93)	3375 (93)	3739 (96)
1	15 232 (3)	36 (2)	286 (2)	230 (3)	56 (2)	14 471 (3)	317 (5)	122 (5)	195 (5)	122 (3)
2	1857 (0)	8 (1)	45 (0)	35 (0)	10 (0)	1741 (0)	46 (1)	22 (1)	24 (1)	17 (0)
3+	2939 (1)	4 (0)	56 (0)	53 (1)	3 (0)	2807 (1)	48 (1)	19 (1)	29 (1)	24 (1)
Yearly family income in quintiles, n, %										
0 (lowest)	112 740 (20)	237 (15)	2115 (18)	1735 (19)	380 (15)	108 327 (20)	1308 (22)	498 (21)	810 (22)	753 (19)
1	112 740 (20)	365 (24)	2773 (24)	2163 (24)	610 (25)	106 918 (20)	1712 (29)	675 (29)	1,037 (29)	972 (25)
2	112 740 (20)	325 (21)	2368 (20)	1834 (20)	534 (22)	108 028 (20)	1225 (20)	479 (20)	746 (21)	794 (20)
3	112 739 (20)	330 (21)	2187 (19)	1702 (19)	485 (20)	108 519 (20)	955 (16)	378 (16)	577 (16)	748 (19)
4 (highest)	112 741 (20)	292 (19)	2117 (18)	165 (18)	467 (19)	108 918 (20)	779 (13)	326 (14)	453 (13)	635 (16)

Abbreviation: COPD, chronic obstructive pulmonary disease.

served only after 12 or more months of follow-up. The increased risk of MI found in subclinical hypothyroidism was present only in the first 3 months of follow-up. Using different values for the upper reference limit of TSH did not significantly affect the estimates.

Discussion

In this study on a large cohort of subjects who had their thyroid function evaluated in the primary care setting, we found that both overt and subclinical hyperthyroidism were associated with an increased risk of all-cause mortality, MACE, and HF, respectively. Furthermore, HF was the leading specific cause of increased cardiovascular mortality found in subclinical hyperthyroidism. The risk of MI, stroke, and cancer was not influenced by subclinical or overt hyperthyroidism. Subclinical hypothyroidism grade I (TSH 5.0–10.0 mIU/L) was associated with an overall lower mortality risk, and grade II (TSH > 10.0 mIU/L) was associated with an increased risk of MI.

Hyperthyroid states

Subclinical and overt hyperthyroidism were associated with 23% and 25% increased risk of all-cause mortality and 9% and 16% increased risk of MACE, respectively. This is, to our knowledge, the first time that risk has been demonstrated in a large cohort of subjects in a primary care setting, whereas previous studies mainly have comprised smaller cohorts and some of them with highly selected subjects (22). Seven previous meta-analyses have been identified and seem conflicting. Three meta-analyses found no association between subclinical hyperthyroidism and cardiovascular and all-cause mortality (2, 23, 24). In contrast, our results are essentially in agreement with more recent meta-analyses that reported up to 41% and 20% increased risk of all-cause mortality in subclinical and overt hyperthyroid subjects, respectively (1, 25, 26). Likewise, a further and large meta-analysis of 17 cohorts demonstrated the same increased risk, but a subgroup analysis revealed that cardiovascular and all-cause mortality was increased only in individuals with existing comorbidity (27). On this specific item, our analyses did not agree because excluding individuals with known comorbidity did not change our results. However, we were not able to demonstrate a clear dose-dependent relationship with decreasing levels of TSH. Also, in the age-stratified sensitivity analyses, the risk of all-cause mortality and MACE was mainly found in individuals older than 65 years of age, although a significantly increased risk of all-cause mortality was demonstrated in subclinical hyperthyroid individuals younger than 65 years. The latter finding should be interpreted with care because it is a suba-

Table 3. Rates and IRRs of All-Cause Mortality, MACE, MI, HF, Stroke, and Cancer

	Total (n)	Events (n)	Time at Risk (1000 py)	Incidence Rate (n/1000 py)	Adjusted Incidence Rate (n/1000 py)	IRR (95% CI)
All-cause mortality						
Overt hyperthyroidism	3902	528	22.0	24.0	15.5	1.25 (1.15–1.36)
Subclinical hyperthyroidism	5979	1352	31.4	43.1	15.3	1.23 (1.16–1.30)
Grade I	2356	514	12.4	41.4	15.2	1.22 (1.12–1.33)
Grade II	3623	838	19.0	44.1	15.4	1.23 (1.15–1.32)
Euthyroidism (referent)	540 710	44 032	2727.5	16.1	12.4	1.00 (referent)
Subclinical hypothyroidism	11 560	1246	58.8	21.2	11.4	0.92 (0.87–0.97)
Grade I	9084	980	46.0	21.3	11.4	0.92 (0.86–0.98)
Grade II	2476	266	12.8	20.8	11.3	0.91 (0.81–1.03)
Overt hypothyroidism	1549	169	8.3	20.4	12.4	0.99 (0.86–1.16)
MACE						
Overt hyperthyroidism	3902	402	21.5	18.7	15.1	1.16 (1.05–1.27)
Subclinical hyperthyroidism	5979	942	30.5	30.9	14.3	1.09 (1.02–1.16)
Grade I	2356	373	12.0	31.0	14.6	1.12 (1.01–1.24)
Grade II	3623	569	18.5	30.8	14.1	1.07 (0.99–1.16)
Euthyroidism (referent)	540 710	38 606	2677.4	14.4	13.1	1.00 (referent)
Subclinical hypothyroidism	11 560	1099	57.4	19.2	13.1	0.99 (0.94–1.06)
Grade I	9084	863	45.0	19.2	13.1	0.99 (0.93–1.06)
Grade II	2476	236	12.4	19.0	13.1	1.00 (0.88–1.14)
Overt hypothyroidism	1549	137	8.1	16.9	12.7	0.96 (0.82–1.14)
MI						
Overt hyperthyroidism	3902	86	21.9	3.9	3.3	1.03 (0.83–1.27)
Subclinical hyperthyroidism	5979	202	31.1	6.5	3.3	1.02 (0.89–1.18)
Grade I	2356	89	12.3	7.3	3.6	1.13 (0.92–1.39)
Grade II	3623	113	18.8	6.0	3.1	0.95 (0.79–1.15)
Euthyroidism (referent)	540 710	10 417	2709.3	3.8	3.3	1.00 (referent)
Subclinical hypothyroidism	11 560	297	58.3	5.1	3.7	1.13 (1.01–1.27)
Grade I	9084	223	45.6	4.9	3.5	1.08 (0.95–1.24)
Grade II	2476	74	12.7	5.8	4.3	1.33 (1.06–1.67)
Overt hypothyroidism	1549	41	8.2	5.0	3.9	1.21 (0.89–1.65)
HF						
Overt hyperthyroidism	3902	192	21.7	8.9	6.5	1.14 (0.99–1.32)
Subclinical hyperthyroidism	5979	505	30.6	16.5	6.8	1.20 (1.10–1.31)
Grade I	2356	197	12.1	16.3	6.8	1.20 (1.04–1.38)
Grade II	3623	308	18.5	16.6	6.8	1.20 (1.07–1.34)
Euthyroidism (referent)	540 710	18 908	2695.9	7.0	5.7	1.00 (referent)
Subclinical hypothyroidism	11 560	558	57.9	9.6	5.9	1.03 (0.94–1.12)
Grade I	9084	435	45.3	9.6	5.9	1.02 (0.93–1.12)
Grade II	2476	123	12.6	9.8	6.1	1.07 (0.89–1.27)
Overt hypothyroidism	1549	69	8.2	8.5	5.8	1.01 (0.8–1.28)
Stroke						
Overt hyperthyroidism	3902	177	21.6	8.2	7.3	1.04 (0.89–1.20)
Subclinical hyperthyroidism	5979	419	30.8	13.6	7.2	1.02 (0.93–1.12)
Grade I	2356	168	12.1	13.8	7.4	1.06 (0.91–1.23)
Grade II	3623	251	18.6	13.5	7.0	1.00 (0.88–1.13)
Euthyroidism (referent)	540 710	18 867	2694.3	7.0	7.1	1.00 (referent)
Subclinical hypothyroidism	11 560	515	57.9	8.9	6.7	0.94 (0.86–1.03)
Grade I	9084	399	45.3	8.8	6.6	0.93 (0.84–1.02)
Grade II	2476	116	12.5	9.2	7.0	0.99 (0.83–1.19)
Overt hypothyroidism	1549	59	8.2	7.2	6.0	0.85 (0.66–1.10)
Cancer						
Overt hyperthyroidism	3902	356	21.5	16.6	17.9	1.03 (0.93–1.15)
Subclinical hyperthyroidism	5979	742	30.2	24.5	17.5	1.02 (0.95–1.10)
Grade I	2356	300	12.0	25.1	18.0	1.05 (0.94–1.17)
Grade II	3623	442	18.3	24.2	17.1	1.00 (0.91–1.10)
Euthyroidism (referent)	540 710	40 118	2662.1	15.1	17.6	1.00 (referent)
Subclinical hypothyroidism	11 560	979	57.2	17.1	16.0	0.91 (0.85–0.97)
Grade I	9084	772	44.7	17.3	16.1	0.91 (0.85–0.98)
Grade II	2476	207	12.5	16.6	15.5	0.88 (0.77–1.01)
Overt hypothyroidism	1549	108	8.1	13.3	13.4	0.77 (0.63–0.92)

Risk estimates are adjusted for sex, age, and calendar year. Age-adjusted incidence rates are adjusted to an age of 65 years.

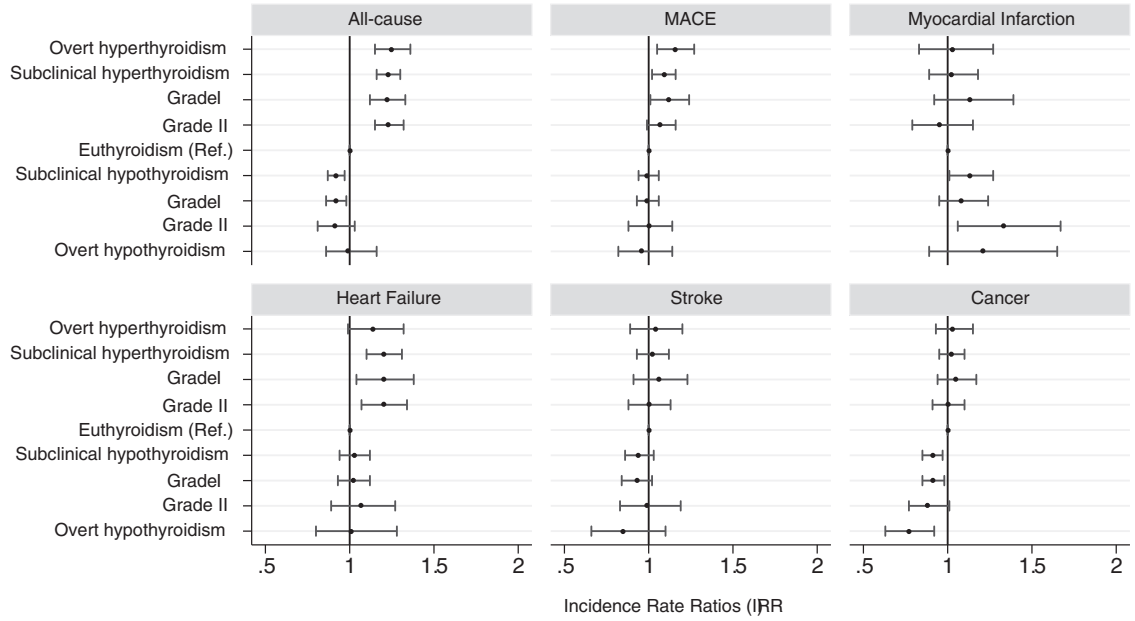

Figure 2. Incidence rate ratios of all-cause mortality, MACEs, MI, heart failure, stroke, and cancer in overt and subclinical thyroid dysfunction adjusted for age, sex, and calendar year.

nalysis, and the question whether individuals younger than 65 years of age have an increased risk remains open, also in view of previous findings (28).

Notably, HF risk was increased by 20% in subjects with subclinical hyperthyroidism and 14% in overt hyperthyroid states. Similar results were found in all levels of subclinical hyperthyroidism. Our estimates were slightly lower than reported in a meta-analysis by Gencer et al (29), who found a 46% increased risk of HF in subclinical hyperthyroidism and also an increased risk of HF in the subclinical hypothyroid subjects. However, this meta-analysis included only six studies, raising the risk of selection bias, and it is unclear whether the included studies were confounded by the use of amiodarone (30).

Hyperthyroidism has been associated with a range of conditions such as AF (31), increased cardiac output, and increased left ventricular mass that could contribute to an excess cardiovascular mortality and HF in this group (32, 33). Also, increased cell turnover and radioiodine treatment as well as genetic factors have been speculated to contribute to the increased mortality in hyperthyroid states (34). However, in this study, HF appeared to be the only cause-specific cardiovascular event that could explain the clear association between the hyperthyroid states and MACE, even after adjusting for AF at baseline and during follow-up. This novel finding is in accordance with current evidence from the Nord-Trøndelag Health Study from Norway that found an increased mortality from CHD but no increased risk of MI (35) and with a recent large cohort study from Sweden that excluded hyperthyroidism as an independent risk factor for stroke (36).

Hypothyroid states

Hypothyroidism is a disease that has been associated with a number of known risk factors for early death such as dyslipidemia, diastolic hypertension, atherosclerosis, decreased heart rate variability, and increased risk of MI (37). Interestingly, we found reduced all-cause mortality in subclinical hypothyroidism with no increase in MACE, but a slightly elevated risk of MI in those with subclinical hypothyroidism grade II (TSH > 10 mIU/L). The protective effect of subclinical hypothyroidism could be found only in subjects older than 65 years in the sensitivity analysis, possibly due to few events in the younger population. Likewise, the increased risk of MI was found only in the first 3 months of follow-up in the sensitivity analysis and thus could be due to selection bias. Isolated increased risk of CHD for those with high TSH has previously been reported (38), whereas others found no association (6, 39), and some found an increased risks of both CHD and all-cause mortality (40, 41). A large meta-analysis of 11 prospective cohorts also found no overall association between subclinical hypothyroidism and all-cause mortality and cardiovascular events. However, individuals with TSH greater than 10 mIU/L did have an increased risk of cardiovascular events (38).

Reduced mortality in subclinical hypothyroidism has previously been reported (10, 42), and recently Boelaert et al (43) even found reduced mortality among hyper-

thyroid patients with radioiodine-induced hypothyroidism compared with radioiodine treatment not resulting in hypothyroidism. Subclinical hypothyroidism has been associated with lower risk of both AF and bone fractures, and beneficial effects of this condition in certain individuals are therefore possible (31, 44).

In overt hypothyroid patients, we found no effect on all-cause mortality or cardiovascular events, which is in line with a recent meta-review (3). However, we found a decreased risk of cancer, which was also observed in the subjects with subclinical hypothyroidism, and in line with this finding, it has been suggested that hypothyroidism could delay the onset of cancer (45). Indeed, a low incidence of breast cancer in women and prostate cancer in men has previously been reported among hypothyroid subjects (46, 47).

International guidelines recommend considering treatment of subclinical hypothyroidism when TSH greater than 10 mIU/L (except in the oldest individuals) and a more individually tailored approach to patients with a TSH less than 10 mIU/L (48, 49). Therefore, a large number of patients with subclinical hypothyroidism may experience spontaneous normalization of TSH values without treatment or periods with untreated low thyroid function, which again can influence the examined study end point. Other such subjects might progress to more severe hypothyroidism with the associated potential adverse effects if left untreated (50). This could also explain that the elevated risk of MI was significant only in the individuals with subclinical hypothyroidism grade II and the reduced all-cause mortality and cancer risk only in those with grade I dysfunction.

Strengths and limitations

This study's main strength is the large sample size including a cohort of subjects from primary care who had thyroid function testing performed and that complete follow-up data were available. The total population in the capital region of Denmark comprised 1.17 million individuals in 2009, and we had access to thyroid function tests from approximately half of these individuals. Furthermore, although the current study was not a population prevalence study, the distribution of thyroid dysfunction in the cohort was comparable with the findings of the National Health and Nutrition Examination Survey Study (51). This indicates that the distribution of thyroid dysfunction in the cohort is probably representative. The slightly higher number of overt hyperthyroid subjects compared with the overt hypothyroid patients in our cohort could be due to the iodine fortification program in Denmark (52).

We categorized patients based on the results of their first thyroid function testing and did not take into account the possibility that subjects could have had nonspecific changes in TSH due to, eg, nonthyroid illness. However, in the sensitivity analyses (Supplementary Tables 2–7) in which we stratified on follow-up and adjusted for any thyroid-related treatment during follow-up (defined as hospital diagnosis of thyroid disease or prescription of thyroid medication), the overall findings were similar. To examine the possibility of misclassification, we assessed the subsequent thyroid treatment of subjects included at baseline (Supplemental Figure 1). This analysis showed that only a small percentage of patients were misclassified based on the baseline evaluation of thyroid function.

Of the 540 710 euthyroid individuals in the reference population, it is possible that some might have had low T_3 syndrome (normal TSH and T_4 but isolated low T_3) due to concomitant, nonthyroid illness, which is known to be associated with increased morbidity and mortality (53). Having these individuals in the reference population could potentially bias our results against the null hypothesis. However, low T_3 syndrome has primarily been described in severely ill, typically hospitalized patients, whereas our cohort comprised solely individuals from primary care. Furthermore, adjusting for important comorbidities using the Charlson comorbidity index did not change our overall findings.

In our main analyses, we used an upper reference limit of TSH of 5.0 mIU/L because the Copenhagen General Practitioners Laboratory used this during the period of 2000–2009. Lower cutoff limits for TSH have since been recommended, ranging from 2.5 to 4.5 mIU/L (54–56). Therefore, we performed additional analyses using 2.5, 4.2, and 4.5 mIU/L, respectively, as the upper cutoff limits of TSH, but we did not find any change in the overall results.

In observational studies one should not draw direct conclusions on causal relationships. Importantly, we had no knowledge of the reasons for thyroid function testing in each subject. Thus, we cannot exclude that the results were influenced by selection bias, ie, that the selection of subjects for thyroid function testing by the physician could in itself be associated with the outcomes of interest. Also, we did not have access to a number of important clinical parameters, eg, information on body weight, blood pressure, serum lipid, glucose levels, echocardiographic or electrocardiographic findings, thyroid autoantibody levels, smoking status, or the specific cause of thyroid dysfunction. With regard to the latter, previous studies have found that the specific cause of thyroid dysfunction (nodular or autoim-

mune disease) could have an impact on the cause-specific mortality found in hyperthyroidism (57). However, this remains an open question.

Smoking has previously been associated with an increased risk of hyperthyroidism, protection against hypothyroidism, and lower levels of TSH, respectively (58, 59). However, if smoking was an important confounder in the hyperthyroid patients, an increased risk of MI, stroke, and cancer would be expected in these groups, which was not the case. Also, adjustment for socioeconomic status (a recognized proxy for smoking status) and the Charlson comorbidity index that includes chronic obstructive pulmonary disease did not alter the overall results.

The Danish population comprises mainly Caucasians, and extrapolation of the results to other ethnic groups should be done with care. Likewise, because the study included individuals in the primary care setting, extrapolation of our results to patients from in- or outpatient clinics also should be performed with caution. Furthermore, it should be acknowledged that the study has a relatively short mean follow-up period of 5.5 years and that some of the outcomes studied might occur only after longer periods of thyroid dysfunction.

Conclusion

In a large cohort of subjects from primary care, we found an increased risk of all-cause mortality and MACE in both subclinical and overt hyperthyroidism, with HF being the leading specific cause of MACE. Subclinical hypothyroidism grade I (TSH 5–10 mIU/L) seemed to be associated with a decreased risk of all-cause mortality. These findings support increased awareness of the importance of subclinical thyroid dysfunction in clinical practice and underline the increased risk of cardiovascular events in hyperthyroid patients, together with the potential health benefits of subclinical hypothyroidism with discrete TSH elevation.

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This study was approved by The Danish Data Protection Agency (reference 2007-41-1667). Retrospective register studies do not require ethical approval in Denmark. C.S. and G.H.G had full access to the data and take full responsibility for their integrity.

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References

1. **Brandt F, Green A, Hegedus L, Brix TH.** A critical review and meta-analysis of the association between overt hyperthyroidism and mortality. *Eur J Endocrinol*. 2011;165:491–497.
2. **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;148:832–845.
3. **Thvilum M, Brandt F, Brix TH, Hegedus L.** A review of the evidence for and against increased mortality in hypothyroidism. *Nat Rev Endocrinol*. 2012;8:417–424.
4. **Cooper DS, Biondi B.** Subclinical thyroid disease. *Lancet*. 2012; 379:1142–1154.
5. **Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA.** Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. *Lancet*. 2001;358:861–865.
6. **Cappola AR, Fried LP, Arnold AM, et al.** Thyroid status, cardiovascular risk, and mortality in older adults. *JAMA*. 2006;295:1033–1041.
7. **Brandt F, Almind D, Christensen K, Green A, Brix TH, Hegedüs L.** Excess mortality in hyperthyroidism: the influence of preexisting comorbidity and genetic confounding: a Danish nationwide register-based cohort study of twins and singletons. *J Clin Endocrinol Metab*. 2012;97:4123–4129.
8. **Brandt F, Thvilum M, Almind D, et al.** Morbidity before and after the diagnosis of hyperthyroidism: a nationwide register-based study. *PloS One*. 2013;8:e66711.
9. **Rodondi N, Newman AB, Vittinghoff E, et al.** Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. *Arch Intern Med*. 2005;165:2460–2466.
10. **Gussekloo J, van Exel E, de Craen AJ, Meinders AE, Frolich M, Westendorp RG.** Thyroid status, disability and cognitive function, and survival in old age. *JAMA*. 2004;292:2591–2599.
11. **Thvilum M, Brandt F, Almind D, Christensen K, Hegedüs L, Brix TH.** Excess mortality in patients diagnosed with hypothyroidism: a nationwide cohort study of singletons and twins. *J Clin Endocrinol Metab*. 2013;98:1069–1075.
12. **Lynge E, Sandegaard JL, Rebolj M.** The Danish National Patient Register. *Scand J Public Health*. 2011;39:30–33.

13. **World Health Organization Collaborating Centre for Drug Statistics Methodology.** Guidelines for ATC classification and DDD assignment, 2012. http://www.whocc.no/atc_ddd_publications/guidelines/. Accessed November 20, 2013.
14. **Kildemoes HW, Sorensen HT, Hallas J.** The Danish National Prescription Registry. *Scand J Public Health*. 2011;39:38–41.
15. **Helweg-Larsen K.** The Danish Register of Causes of Death. *Scand J Public Health*. 2011;39:26–29.
16. **Baadsgaard M, Quitzau J.** Danish registers on personal income and transfer payments. *Scand J Public Health*. 2011;39:103–105.
17. **Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M.** The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol*. 2003;56:124–130.
18. **Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T.** Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology*. 2007;28:150–154.
19. **Nuttall M, van der Meulen J, Emberton M.** Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. *J Clin Epidemiol*. 2006;59:265–273.
20. **Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT.** The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83.
21. **Barbesino G.** Drugs affecting thyroid function. *Thyroid*. 2010;20:763–770.
22. **Sgarbi JA, Matsumura LK, Kasamatsu TS, Ferreira SR, Maciel RM.** Subclinical thyroid dysfunctions are independent risk factors for mortality in a 7.5-year follow-up: the Japanese-Brazilian thyroid study. *Eur J Endocrinol*. 2010;162:569–577.
23. **Singh S, Duggal J, Molnar J, Maldonado F, Barsano CP, Arora R.** Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis. *Int J Cardiol*. 2008;125:41–48.
24. **Völzke H, Schwahn C, Wallaschofski H, Dörr M.** Review: the association of thyroid dysfunction with all-cause and circulatory mortality: is there a causal relationship? *J Clin Endocrinol Metab*. 2007;92:2421–2429.
25. **Haentjens P, Van Meerhaeghe A, Poppe K, Velkeniers B.** Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies. *EurJ Endocrinol*. 2008;159:329–341.
26. **Collet TH, Gussekloo J, Bauer DC, et al.** Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med*. 2012;172:799–809.
27. **Yang LB, Jiang DQ, Qi WB, et al.** Subclinical hyperthyroidism and the risk of cardiovascular events and all-cause mortality: an updated meta-analysis of cohort studies. *Eur J Endocrinol*. 2012;167:75–84.
28. **Bahn RS, Burch HB, Cooper DS, et al.** Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. *Endocr Pract*. 2011;17:456–520.
29. **Gencer B, Collet TH, Virgini V, et al.** Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation*. 2012;126:1040–1049.
30. **Cohen-Lehman J, Dahl P, Danzi S, Klein I.** Effects of amiodarone therapy on thyroid function. *Nat Rev Endocrinol*. 2010;6:34–41.
31. **Selmer C, Olesen JB, Hansen ML, et al.** The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. *BMJ*. 2012;345:e7895.
32. **Biondi B, Palmieri EA, Fazio S, et al.** Endogenous subclinical hyperthyroidism affects quality of life and cardiac morphology and function in young and middle-aged patients. *J Clin Endocrinol Metab*. 2000;85:4701–4705.
33. **Faber J, Wiinberg N, Schifter S, Mehlsen J.** Haemodynamic changes following treatment of subclinical and overt hyperthyroidism. *Eur J Endocrinol*. 2001;145:391–396.
34. **Biondi B.** How could we improve the increased cardiovascular mortality in patients with overt and subclinical hyperthyroidism? *Eur J Endocrinol*. 2012;167:295–299.
35. **Asvold BO, Bjoro T, Platou C, Vatten LJ.** Thyroid function and the risk of coronary heart disease: 12-year follow-up of the HUNT study in Norway. *Clin Endocrinol (Oxf)*. 2012;77:911–917.
36. **Friberg L, Rosenqvist M, Lip GY.** Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33:1500–1510.
37. **Kahaly GJ.** Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid*. 2000;10:665–679.
38. **Rodondi N, den Elzen WP, Bauer DC, et al.** Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304:1365–1374.
39. **LeGrys VA, Funk MJ, Lorenz CE, et al.** Subclinical hypothyroidism and risk for incident myocardial infarction among postmenopausal women. *J Clin Endocrinol Metab*. 2013;98:2308–2317.
40. **Iervasi G, Molinaro S, Landi P, et al.** Association between increased mortality and mild thyroid dysfunction in cardiac patients. *Arch Intern Med*. 2007;167:1526–1532.
41. **McQuade C, Skugor M, Brennan DM, Hoar B, Stevenson C, Hoogwerf BJ.** Hypothyroidism and moderate subclinical hypothyroidism are associated with increased all-cause mortality independent of coronary heart disease risk factors: a PreCIS database study. *Thyroid*. 2011;21:837–843.
42. **Atzmon G, Barzilai N, Hollowell JG, Surks MI, Gabriely I.** Extreme longevity is associated with increased serum thyrotropin. *J Clin Endocrinol Metab*. 2009;94:1251–1254.
43. **Boelaert K, Maisonneuve P, Torlinska B, Franklyn JA.** Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. *J Clin Endocrinol Metab*. 2013;98:1869–1882.
44. **Taylor PN, Razvi S, Pearce SH, Dayan C.** A review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab*. 2013;98(9):3562–3571.
45. **Hercbergs AH, Ashur-Fabian O, Garfield D.** Thyroid hormones and cancer: clinical studies of hypothyroidism in oncology. *Curr Opin Endocrinol Diabetes Obes*. 2010;17:432–436.
46. **Cristofanilli M, Yamamura Y, Kau SW, et al.** Thyroid hormone and breast carcinoma. Primary hypothyroidism is associated with a reduced incidence of primary breast carcinoma. *Cancer*. 2005;103:1122–1128.
47. **Mondul AM, Weinstein SJ, Bosworth T, Remaley AT, Virtamo J, Albanes D.** Circulating thyroxine, thyroid-stimulating hormone, and hypothyroid status and the risk of prostate cancer. *PloS One*. 2012;7:e47730.
48. **Pearce SHS, Brabant G, Duntas LH, et al.** ETA guideline: management of subclinical hypothyroidism. *Eur Thyroid J*. 2013;2:215–228.
49. **Garber JR, Cobin RH, Gharib H, et al.** Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012;18:988–1028.
50. **Somwaru LL, Rariy CM, Arnold AM, Cappola AR.** The natural history of subclinical hypothyroidism in the elderly: the cardiovascular health study. *J Clin Endocrinol Metab*. 2012;97:1962–1969.
51. **Hollowell JG, Staehling NW, Flanders WD, et al.** Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab*. 2002;87:489–499.
52. **Cerqueira C, Knudsen N, Ovesen L, et al.** Association of iodine fortification with incident use of antithyroid medication—a Danish nationwide study. *J Clin Endocrinol Metab*. 2009;94:2400–2405.
53. **Burger A, Nicod P, Suter P, Vallotton MB, Vagenakis P, Braverman**

L. Reduced active thyroid hormone levels in acute illness. *Lancet*. 1976;1:653–655.
54. **Jensen E, Hyltoft Petersen P, Blaabjerg O, et al.** Establishment of a serum thyroid stimulating hormone (TSH) reference interval in healthy adults. The importance of environmental factors, including thyroid antibodies. *Clin Chem Lab Med*. 2004;42:824–832.
55. **Surks MI, Ortiz E, Daniels GH, et al.** Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004;291(2):228–238.
56. **Biondi B, Cooper DS.** The clinical significance of subclinical thyroid dysfunction. *Endocr Rev*. 2008;29:76–131.
57. **Brandt F, Thvilum M, Almind D, et al.** Graves' disease and toxic nodular goiter are both associated with increased mortality but differ with respect to the cause of death. A Danish population-based register study. *Thyroid*. 2013;23(4):408–413.
58. **Asvold BO, Bjoro T, Nilsen TI, Vatten LJ.** Tobacco smoking and thyroid function: a population-based study. *Arch Intern Med*. 2007; 167:1428–1432.
59. **Knudsen N, Bulow I, Laurberg P, Perrild H, Ovesen L, Jorgensen T.** High occurrence of thyroid multinodularity and low occurrence of subclinical hypothyroidism among tobacco smokers in a large population study. *J Endocrinol*. 2002;175:571–576.