Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study

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Abstract

Objective: Few population-based studies have described the epidemiology of subtypes of hyperthyroidism.

Design: A prospective population-based study, monitoring two well-defined Danish cohorts in Aalborg with moderate iodine deficiency (n = 311 102) and Copenhagen with only mild iodine deficiency (n = 227 632).

Methods: A laboratory monitoring system identified subjects with thyroid function tests suggesting overt hyperthyroidism (low s-TSH combined with high s-thyroxine or s-triiodothyronine). For all subjects, we collected information on medical history, thyroid scintigraphy and thyroid hormone receptor antibody (TRAb) measurement. Information was used to disprove or verify primary overt hyperthyroidism and to subclassify hyperthyroidism into nosological disorders.

Results: From 1997 to 2000 (2 027 208 person-years of observation), we verified 1682 new cases of overt hyperthyroidism. The overall standardized incidence rate (SIR) per 100 000 person-years was 81.6, and was higher in Aalborg compared with Copenhagen (96.7 vs 60.0, P<0.001), giving an SIR ratio (SIRR (95% confidence interval (CI))) between moderate versus mild iodine-deficient areas of 1.6 (1.4–1.8). Nosological types of hyperthyroidism (percentage/SIRR (95% CI)): multinodular toxic goitre (MNTG) 44.1%/1.9 (1.6–2.2), Graves’ disease (GD) 37.6%/1.2 (0.99–1.4), solitary toxic adenoma (STA) 5.7%/2.4 (1.3–3.5), ‘mixed type’ hyperthyroidism (TRAb-positive, scintigraphically multinodular) 5.4%/6.0 (3.0–12), subacute thyroiditis 2.3%/0.9 (0.4–1.4), postpartum thyroid dysfunction 2.3%/0.9 (0.4–1.4), amiodarone-associated hyperthyroidism 0.8%/0.9 (0.4–1.4), hyperthyroidism after thyroid radiation 0.7%/12.3 (0.8–50), lithium-associated hyperthyroidism 0.7%/0.97 (0.4–4.8) and hyperthyroidism caused by various other factors 0.7%. Lifetime risk for overt hyperthyroidism was 10.5%/6.5%/2.4% (females/all/males).

Conclusion: Hyperthyroidism was common in Denmark with MNTG and GD as dominating entities. The higher incidence of hyperthyroidism in the most iodine-deficient region was caused by higher frequency of MNTG, ‘mixed-type’, STA and amiodarone-associated hyperthyroidism.

Introduction

Primary overt hyperthyroidism is a common disease worldwide. The incidence rate of hyperthyroidism is influenced by a number of factors, of which the iodine intake in the population may be important. In areas with high iodine intake level, hypothyroidism is more common than hyperthyroidism (1, 2), whereas hyperthyroidism dominates in areas with mild and moderate iodine deficiency (3, 4). Hyperthyroidism may be divided into a number of nosological subtypes with different aetiology, clinical presentation, prognosis and outcome of therapy. The incidence of individual subtypes may also be dependent on the iodine intake level (3, 5, 6). However, the information on the epidemiology of subtypes of hyperthyroidism and the effect of environmental factors including iodine intake is limited.

Often, it is difficult to compare studies, as the criteria of inclusion, exclusion and for classification into subtypes may be different. Many studies not only included patients with biochemical overt hyperthyroidism, but also patients with subclinical hyperthyroidism (7), or may have identified patients by means of biochemical screening (2). Other studies only evaluated certain age groups (8). Most studies were based on patients referred to hospital departments (6, 9–18), potentially leading to referral bias (19).

The iodine fortification programme in Denmark was introduced rather late compared with many other countries. From year 2001, all household salt produced...
in Denmark and salt for industrial production of bread have been iodine-enriched, abiding by the law (20). We have previously published data on the incidence of primary overt hyperthyroidism in two Danish areas with different iodine intake in the period 1997–1998 (21). This study did not allow evaluation of how the various subtypes of disease contributed to the overall incidences. Now, we have expanded the study period to also include patients diagnosed with hyperthyroidism in the period 1999–2000, and to include detailed data on individual patients. This allowed us to estimate incidence rates of the nosological subtypes of hyperthyroidism and to compare various subtypes of the disease in two areas slightly different in iodine intake level.

Subjects and methods

The present study is part of The Danish Investigation on Iodine Intake and Thyroid Diseases (DanThyr), which is an ongoing monitoring of the Danish iodine fortification programme (20). This study deals with the period 1997–2000 just before iodine fortification of salt became effective in Denmark.

Population cohort

We have previously published data on the iodine status of people living in the two areas under study (22), an area of mild iodine deficiency in Copenhagen in East-Denmark (227 632 inhabitants, study period May 1997 to December 2000, median urinary iodine excretion (UIE) was 61 mg/l) and an area of moderate iodine deficiency around Aalborg in West-Denmark (311 102 inhabitants, March 1997 to December 2000, median UIE was 45 mg/l (22)). The total person-years of observation were 2 027 208. Information on population size, age and sex distribution was obtained from Statistics Denmark (23). For the calculations, we used population data per January 1, 1999. The combined cohort (n = 538 734) was representative of the Danish population (24).

Identification of ‘possible new cases’ with hyperthyroidism

Patients were prospectively identified using a monitoring system of diagnostic laboratories covering all hospital and primary care institutions in the two regions studied. Thus, no intervention or active screening was performed. The use of this system for identification of ‘possible new cases’ have been described previously in detail (25, 26). In brief, results of all thyroid function tests in the two cohort areas were on a daily basis imported from laboratory databases into a register database. Four different laboratories (I: Aalborg Hospital, II: Bispebjerg Hospital, III: Frederiksberg Hospital, IV: Laboratory of General Practitioners in Copenhagen; II–IV all in Copenhagen) participated in the identification process. The register database identified ‘possible new cases’ (thus automatically excluding previously diagnosed cases) with blood tests fulfilling the criteria of overt, biochemical hyperthyroidism, i.e. with low serum TSH and either high serum thyroxine (T4) (total T4, or free T4, fT4) or high serum triiodothyronine (T3) (total T3). For the four laboratories, we used clinical cut-off values as suggested by the manufacturers: TSH <0.2 mIU/l (all four laboratories: I–IV); total T4 >140/140/160/140 nmol/l (I/II/III/IV); fT4 >23.8/22.0 pmol/l (II/IV, laboratory I and III did not use fT4); total T3 >2.7/2.1/2.5/2.5 nmol/l (I/II/III/IV). A detailed assay description including comparison between the four diagnostic laboratories has been given previously (26, 27).

A careful method evaluation (25) showed that about 98% of the population investigated was registered with and had consulted a general practitioner, who practiced within the study area, and submitted blood samples to the involved laboratories for analyses. During a 60 days test period, a manual search of abnormal thyroid function test revealed a 100% sensitivity of the automated identification system, as described in detail previously (25).

Data collection on ‘possible new cases’

In order to verify and subclassify hyperthyroidism, we collected all available data from hospital medical records, laboratory files, blood samples from subjects and thyroid scintigraphy from departments of nuclear medicine. Furthermore, we asked the general practitioners for additional medical information. In selected periods, where staff were available for a comprehensive investigative programme, a subgroup of patients (n = 587) were contacted shortly after they had been diagnosed with incident hyperthyroidism. Those who accepted an invitation (n = 554) joined a comprehensive investigation programme, including questioning of medical history, thyroid gland ultrasound investigation and measurement of TSH receptor antibody (TRAb) in serum. Non-participants were asked to answer a simple questionnaire (response, n = 206). We collected the following information in order to verify and subclassify patients with hyperthyroidism: i) thyroid function tests performed after the initial test, which suggested hyperthyroidism; ii) information on treatment with i-131, thyrostatic drugs, amiodarone, lithium, cytokines, estrogens, radiiodine and thyroid surgery; iii) thyroid TcO4 scintigraphy (performed on 1051 = 62.5% of all patients); iv) TRAb measurements (performed in 577 = 34.3% of all patients) using DYNOnet TRAK human by BRAHMS (TRAb level >1.0 IU/l was regarded as antibody-positive (TRAb +)) (28); v) supplemental information on delivery, neck pain, available erythrocyte sedimentation rate measurements and other types of neck surgery.

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**Verification of incident cases**

All ‘possible new cases’ (n = 2362) identified with biochemical hyperthyroidism with no previous thyroid dysfunction already known by the general practitioner were individually evaluated. This led to exclusion of a substantial number of patients (n = 680). Most of the subjects were excluded because a subsequent thyroid function test performed within 3 weeks revealed biochemical normalization without treatment, and with no medical history suggesting a transient hyperthyroid state (n = 277). Other subjects had previously suffered from hyperthyroidism (n = 76).

Patients receiving amiodarone treatment were only verified as overtly hyperthyroid if they had elevated serum T₄, as the combination of low TSH + high T₄ + normal T₃ was considered to be a normal response to medication (29) in patients being subclinically hyperthyroid (n = 72). Some patients were excluded as they had high total T₄ caused by a high thyroid hormone-binding capacity due to pregnancy or use of contraceptives (n = 71), a few others were excluded because neither a confirmative thyroid function test nor therapy could be verified (n = 73), or they had iatrogenic hyperthyroidism caused by ¹²³I treatment of hyperthyroidism, euthyroid goitre or psychiatric disease (n = 55), or the biochemical abnormality was caused by laboratory errors (n = 30). Two out of four participating laboratories used fT₄ and total T₄ in combination. To avoid epidemiological bias between the four laboratories and thus the two regions under study, the few subjects with high fT₄ but normal total T₄ were excluded from the study (n = 26). The rest of the patients were excluded due to a number of other reasons (n = 47).

As depicted in Fig. 1, patients were verified as suffering from overt hyperthyroidism, if none of the above listed criteria for exclusion were fulfilled, and they also fulfilled at least one of these criteria: i) sustained biochemical signs of overt hyperthyroidism after 3 weeks (n = 909); ii) treatment for hyperthyroidism instituted within 3 weeks after initial thyroid function test (n = 708); iii) normal thyroid function tests after 3 weeks without treatment but with signs or history suggesting transient hyperthyroidism (postpartum thyroiditis, lithium-/amiodarone-/cytokine-therapy, subacute thyroiditis (SAT), or surgical manipulation of the thyroid; total, n = 44). The remainder of patients included with biochemical signs of overt hyperthyroidism (n = 21) had no confirmative thyroid function test and had no history of thyroiditis. The primary care physicians had required thyroid function tests to evaluate possible thyroid dysfunction, but the patients died shortly (within 2 months) after the thyroid function test had been performed. They were considered to be true hyperthyroid cases without further proof.

**Classification of incident cases into nosological subtypes of hyperthyroidism**

For each patient, hyperthyroidism was nosologically classified into one of the following conditions based on medical history, thyroid scintigraphy and TRAb measurements:

i) Graves’ disease (GD): positive TRAb measurement (TRAb+, TRAb > 1.0 IU/l) or a non-suppressed homogeneous TcO₄⁻ uptake in the entire thyroid gland on scintigraphy.

ii) Multinodular toxic goitre (MNTG): thyroid scintigraphy showed a heterogeneous uptake with at least two nodules of enhanced TcO₄⁻ accumulation combined with absent or diminished uptake in the rest of the gland. If TRAb was negative or not measured, MNTG was the diagnosis.

iii) ‘Mixed type’ hyperthyroidism: patients with thyroid scintigraphy, suggesting MNTG, but with positive TRAb, suggesting GD.

iv) Solitary toxic adenoma (STA): one nodule of enhanced TcO₄⁻ uptake combined with absent or low TcO₄⁻ accumulation in rest of the thyroid gland.

v) SAT (de Quervain thyroiditis): transient hyperthyroidism, with no history of excessive iodine intake (amiodarone or contrast media), no medication which could explain the transient thyrotoxic period (amiodarone, lithium and cytokines) and with at least two of three SAT criteria fulfilled (absent or low TcO₄⁻ uptake with no visible thyroid nodules on scintigraphic picture; elevated erythrocyte sedimentation rate; or neck pain).

vi) Postpartum thyroid dysfunction (PPTD): overt hyperthyroidism diagnosed within 1 year after delivery. If TRAb was negative or not measured, PPTD was the diagnosis. If TRAb was positive, the patient was classified as GD.

vii) Amiodarone-associated hyperthyroidism: overt hyperthyroidism diagnosed during or within 12 months after amiodarone treatment.

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**Figure 1** Number of patients with hyperthyroidism fulfilling the criteria used for verification (n = 1682) in the DanThyr study in the period 1997–2000. A total of 909 patients had sustained hyperthyroidism after 3 weeks, 1313 patients had received treatment within 3 weeks and 138 had a history suggesting transient hyperthyroidism.
viii) Radioiodine-associated hyperthyroidism: transient overt hyperthyroidism developed within a month after radioiodine treatment of euthyroid goitre was performed.

ix) Lithium-associated hyperthyroidism: overt hyperthyroidism in patients previously (<12 months) or currently treated with lithium.

x) ‘Manipulation thyroiditis’ with hyperthyroidism: transient hyperthyroidism developed shortly after thyroid manipulation during surgery on thyroid or parathyroid gland.

xi) Hyperthyroidism associated with previous (<12 months) or current cytokine therapy: we carefully scrutinized all available information, but found no patients with this disorder. Neither did we identify any history of prior contrast media or other types of excessive iodine exposure as the course for hyperthyroidism.

By means of the above-mentioned criteria, we were able to classify hyperthyroidism for most of the patients (n=1147). However, no TRAb measurements or thyroid scintigraphy were available on a large fraction of the patients (n=535), but a complete medical history indicated that they could not suffer from subtype e to k. In other words, they suffered from MNTG, GD, ‘mixed type’, or STA (a to d). In order to classify these patients, we employed hot-deck imputation of missing values using the principle of ‘nearest neighbour imputation’ (30). This was done after stratification according to region and sex, and subsequent sorting according to age.

Statistical analysis

Age-standardized incidence rates (SIRs) and SIR ratios (SIRR) were calculated according to standard procedures (31, 32). For SIR and SIRR, we calculated 95% confidence intervals (CIs) or z values for the t-test assuming approximation from Poisson to Gaussian distribution (32), or calculated s.e.m. in case of few patients in part studies.

Lifetime risk, defined as the probability of an inhabitant to have diagnosed overt hyperthyroidism during an average lifetime, was estimated using the calculated incidence rates applied to the Danish demographic population (23). For the calculations, we assumed that SIRs were identical in different generations, i.e. no cohort effect being present, and that the combined study population was representative of the entire Danish population.

Ethical approval

This study was approved by Regional Ethics Committees in Aalborg and Copenhagen. Registry permission was obtained from the Danish Data Protection Agency. No conflicts of interest were present.

Results

Total incidence of hyperthyroidism

In the combined cohort, we identified and verified 1682 new cases of overt hyperthyroidism. Thus, the incidence rate of hyperthyroidism in the combined Danish cohort was 81.6 per 100 000 person-years. Hyperthyroidism was more frequent in the area of moderate versus mild iodine deficiency (Aalborg versus Copenhagen; 96.7 vs 60.0 per 100 000 person-years: SIRR = 1.6 (95% CI: 1.4–1.8)).

Subtypes of hyperthyroidism

In all the 1682 patients newly diagnosed with overt hyperthyroidism, we were able to classify subtype of disease directly in 1147 patients suffering from MNTG (n=405), GD (n=484), ‘mixed type’ (n=65), STA (n=71), SAT (n=38), PPTD (n=37), amiodarone thyrotoxicosis (n=14), radioiodine thyrotoxicosis (n=12), lithium thyrotoxicosis (n=11) and due to other causes (n=10; nine patients had no uptake on the thyroid scintigram and no history suggesting specific type of disease; one patient had thyrotoxicosis shortly after removal of parathyroid hormone excreting adenoma). Hot-deck imputation was performed on the remaining 535 patients with no definite subtype of hyperthyroidism and gave subtype classification into MNTG (n=336), GD (n=149), ‘mixed type’ (n=25) and STA (n=25).

Data on nosological type of disease, age and sex of the 1682 patients newly diagnosed with hyperthyroidism are depicted in Table 1, which also includes the age and sex composition of the background population.

The SIRs of the nosological subtypes of hyperthyroidism are shown in Table 2. MNTG and GD were the dominating types of hyperthyroidism, accounting for more than 80% of all cases. STA and SAT were also common types of hyperthyroidism.

The median age of patients classified with various subtypes of hyperthyroidism is shown in Table 2. Patients were on average 61.8 years old with a span from 30.7 years among women diagnosed with PPTD to 75.2 years in patients suffering from MNTG.

The age-specific incidence rates of the three most common nosological subtypes of hyperthyroidism (GD, MNTG and STA) are depicted in Fig. 2. The age-specific incidence rate of GD was quite constant in subjects aged 30–80 years, whereas an almost exponential rise with age was observed for MNTG. GD was the dominating type of hyperthyroidism in patients up to 45 years of age. Because of the age composition of the population, the highest number of patients with GD was observed within the age interval 30–39 years (Table 1). With advancing age above 45 years, MNTG increasingly outnumbered GD. The incidence rate for STA also rose with age and peaked in the sixth decade, but without the profound rise with advancing age as observed for MNTG.
Regional difference in incidence of hyperthyroidism

The age-specific incidence rates of hyperthyroidism (all types combined) in four groups stratified according to region and gender are depicted in Table 1. The overall incidence of overt hyperthyroidism rose almost linearly with age, and female sex was a strong risk factor throughout the entire span of ages. In both gender and at all ages above 20 years, a higher incidence was observed in Aalborg (moderate ID) compared with Copenhagen (mild ID).

The regional difference in incidence of overt hyperthyroidism was further studied for the various subtypes. The higher incidence of hyperthyroidism in Aalborg compared with Copenhagen was caused by more cases with MNTG (SIRR 95% CI = 1.9 (1.6–2.2)), STA (SIRR = 2.4 (1.3–3.5)), ‘mixed type’ hyperthyroidism (SIRR = 6.0 (3.0–12)) and amiodarone-associated hyperthyroidism (SIRR = 7.1 (1.1–65)). No statistical significant regional difference was observed with regards to GD (SIRR = 1.2 (0.99–1.4)), SAT (SIRR = 0.9 (0.4–1.4)), PPTD (SIRR = 1.6 (0.8–30)), post-radiation thyrotoxicosis (SIRR = 12.3 (0.8–50)), or Li-thyrotoxicosis (SIRR = 0.97 (0.4–4.8)).

Sex distribution among subtypes of hyperthyroidism

In the combined cohort, the lifetime risk for development of overt hyperthyroidism was calculated to be 6.5% (Table 1), with more than four times predominance in women (10.5 vs 2.4% in men). The pronounced female preponderance was present for all subtypes (ratio between 4.4 and 6.4) except for STA (ratio was 1.4) and amiodarone-associated hyperthyroidism (ratio was 0.27).

Discussion

We provide data on the incidence rates of subtypes of overt, primary hyperthyroidism in two Danish subcohorts with mild and moderate iodine deficiency.

Total incidence of hyperthyroidism

Hyperthyroidism was common in Denmark with an SIR of 81.6 per 100 000 person-years. The sensitive design used in the present study may be responsible for the high incidence compared with previous Danish studies.

Table 1 Number of hyperthyroid patients according to nosological subtype of disease, sex and age.

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<th>20–29</th>
<th>30–39</th>
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<th>50–59</th>
<th>60–69</th>
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aAge intervals 0–9.99, 10–19.99 etc.
bAll nosological types of hyperthyroidism.
cMultinodular Tc-99 uptake pattern on thyroid scintigraphy with positive TRAb measured.
dPostpartum thyroid dysfunction (PPTD) presenting with hyperthyroidism within 1 year after delivery.
eSubacute thyroiditis (SAT) presenting with hyperthyroidism.
fHyperthyroidism in patients treated with amiodarone (within 12 months).
gHyperthyroidism in patients treated with lithium (within 12 months).
hHyperthyroidism developed after thyroid radiiodine treatment (within 1 month).
iHyperthyroidism associated with a mixture of disorders (see text). One patient had ‘manipulation thyroiditis’ with hyperthyroidism developed 2 days after surgery for parathyroid adenoma.
jStudy population on January 1, 1999 in the combined cohort (Copenhagen and Aalborg).
reporting incidence rates (per 100 000 person-years) of 22.0 (17), 27.6 (33), 38.7 (4), 44.0 (11) and 60.5 (34). Interestingly, during World War II, the incidence rate in Denmark increased from 24.6 to 81.5 (35) – the reason for this still remains unknown. The total incidence rate of hyperthyroidism was quite high in Denmark compared with other countries reporting figures of 22.7 in UK (36), 23.6 in Iceland (37), 25.8 in New Zealand (38), 25.8 rising to 43.0 in a Swedish region before and after salt iodization (14, 39), 32.0 in Spain (7), 32.7 in another Swedish region studying adults only (8), 34.7 also in Sweden (40), 36.9 in China after iodine fortification of salt (41), 46.0 in Scotland (42), around 50 in two Austrian studies (6, 43) and above 100 after excessive iodine exposure in Tasmania (44). A comparison between these studies and the present study is difficult, as they differ with regards to the design. In our study, all subjects with biochemical hyperthyroidism were quite high in Denmark compared with other countries reporting figures of 22.7 in UK (36), 23.6 in Iceland (37), 25.8 in New Zealand (38), 25.8 rising to 43.0 in a Swedish region before and after salt iodization (14, 39), 32.0 in Spain (7), 32.7 in another Swedish region studying adults only (8), 34.7 also in Sweden (40), 36.9 in China after iodine fortification of salt (41), 46.0 in Scotland (42), around 50 in two Austrian studies (6, 43) and above 100 after excessive iodine exposure in Tasmania (44). A comparison between these studies and the present study is difficult, as they differ with regards to the design. In our study, all subjects with biochemical hyperthyroidism were individually scrutinized. No active screening was performed, and the patients who were not referred to hospital were included as well as referred patients. However, the most likely cause for the higher incidence of hyperthyroidism in our study is the magnitude of iodine deficiency. In Denmark, the incidence of hyperthyroidism was more than twice the incidence of hypothyroidism, 81.6 vs 32.8 per 100 000 person-years of observation (27). Even comparing the two regions (Aalborg versus Copenhagen) only slightly differing in iodine deficiency, the ratio of hyperthyroidism to hypothyroidism was highest in the region of moderate versus mild iodine deficiency (3.3 vs 1.6).

Subtypes of hyperthyroidism

The incidence of MNTG in Denmark (34.6 per 100 000 person-years) is higher than in most other countries studied, where the calculated SIRs spanned from 3.3 to 30.5 per 100 000 person-years (6, 8). All these studies were performed in regions with a higher iodine intake in the population compared with Denmark. This supports that MNTG is an important complication to long-standing low iodine intake. Thus, constitutively activating TSH receptor mutations have been demonstrated in hot microscopic areas of euthyroid iodine-deficient goitres (45).

The incidence of GD was quite high in Denmark, but this may be due to the sensitive design of our study. In order to compare the relative frequency of GD versus MNTG, we calculated a ratio between SIRs of GD and MNTG of 0.9 (31.2/35.0), which was comparable to the

<table>
<thead>
<tr>
<th>SIRa (CI)b</th>
<th>%c</th>
<th>Median age^d</th>
<th>F/M-ratioe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multinodular toxic goitre</td>
<td>35.0 (30.1–40.0)</td>
<td>44.1</td>
<td>75.2</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>31.2 (26.4–35.9)</td>
<td>37.6</td>
<td>46.0</td>
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<tr>
<td>Solitary toxic adenoma</td>
<td>4.8 (2.9–6.7)</td>
<td>5.7</td>
<td>66.5</td>
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<td><em>Mixed type</em>f</td>
<td>4.7 (2.8–6.6)</td>
<td>5.4</td>
<td>56.3</td>
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<td>Subacute thyroiditis</td>
<td>2.0 (0.8–3.2)</td>
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<td>44.5</td>
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<tr>
<td>Postpartum thyroid dysfunctiong</td>
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<td>2.2</td>
<td>30.7</td>
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<tr>
<td>Amiodarone-associated</td>
<td>0.72 (0–1.5)</td>
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<td>56.1</td>
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<tr>
<td>Radiation-induced</td>
<td>0.63 (0–1.3)</td>
<td>0.7</td>
<td>64.0</td>
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<tr>
<td>Lithium-associated</td>
<td>0.54 (0–1.2)</td>
<td>0.7</td>
<td>56.6</td>
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<tr>
<td>Various typesh</td>
<td>0.47 (0–1.0)</td>
<td>0.6</td>
<td>46.4</td>
</tr>
<tr>
<td>All types combined</td>
<td>81.6 (73.9–89.2)</td>
<td>100</td>
<td>61.8</td>
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</table>

*aSIR per 100 000 person-years (age-adjusted to the Danish population, January 1, 1999). 
*b95% CI of SIRs. 
*cNumber of patients/1682 (in percentage). 
^Median age at diagnosis for all 1682 hyperthyroid patients, including those who were classified by means of ‘hot-deck imputation’. 
*SIRR between SIR for females and males. 
*fTRAb+ (suggesting GD) and with a heterogeneous uptake pattern on thyroid scintigraphy (suggesting MNTG). 
*gSIR was 3.3 per 100 000 female-years, and IR was 11.0 per 100 000 female years in the ages 20–40 years. 
*hMixture of not proven painless thyroiditis (n=9), and thyroid gland manipulation during neck surgery (n=1).
ratio of 0.8 in another Danish study (3). Other iodine-deficient countries have also reported low incidence rate ratios of GD/MNTG (6, 46). However, from other studies reporting GD to be more frequent than MNTG, we have calculated ratios of 1.4 in a Swedish study (39), 1.9 in a Danish study of patients referred to hospital (47), 2.1 in Spain (7), 2.3 in New Zealand (38), 3.3 from another Swedish study (14), 7.4 in a Swedish study from 2008 (8), 13.5 in Iceland (37) and 16 in a South African study on the Black population (15).

The three most common types of hyperthyroidism had very different age distribution, with GD dominating in young people, and MNTG dominating in the old. This is similar to a previous finding in an iodine-deficient Denmark population (3). STA was also more prominent in patients being > 50 years of age. However, the peak incidence of this subtype of disease was seen around 60 years of age, whereas the MNTG incidence continued to increase with age. We previously found a similar difference (48), but have no good explanation for this difference in age association.

**Regional difference in incidence of hyperthyroidism**

In both genders and at all ages, we found a higher incidence of hyperthyroidism in Aalborg (moderate ID) compared with Copenhagen (mild ID). The small difference in iodine intake, mostly caused by differences in ground water iodine content (49), had a large impact on the incidence of subtypes of hyperthyroidism. While the incidence of GD was similar, MNTG was 87% more frequent in the most iodine-deficient region.

There was a higher incidence of amiodarone-associated hyperthyroidism in the area with the highest degree of iodine deficiency. It is well established that amiodarone-induced hyperthyroidism is common in iodine-deficient populations (50). We further studied the amiodarone intake in the two study regions. The use of amiodarone in Denmark is registered by Danish Medicines Agency (www.laegemiddelstyrelsen.dk) as defined daily doses (DDD). In the years 1997–2000, the average DDD in Aalborg was 0.90 (span from 0.67 to 1.17), which was more than twice the DDD in Copenhagen reported to be 0.44 (span from 0.37 to 0.48). Thus, the high incidence of amiodarone-associated hyperthyroidism in Aalborg was at least partly caused by a more frequent prescription of amiodarone.

**Study strengths and limitations**

We identified patients with overt hyperthyroidism as they are diagnosed in the population, in hospitals and in primary care institutions. Inclusion in the present study would require that a physician took initiative to diagnose thyroid dysfunction by requesting thyroid function tests.

Patients were subclassified according to the scintigraphic picture, but a proportion of the hyperthyroid patients had no scintiscan performed. Age differed between those who had scintiscan performed and those who had not (median age 56.8 vs 74.0 years). In a logistic multivariate regression model, we tested if sex, age, region of inhabitancy and degree of hyperthyroidism could predict whether a scintiscan was performed or not. Only age ($P < 0.001$) and region ($P < 0.001$) were significant predictors. To avoid bias from the age-/region-dependent ability to subclassify hyperthyroidism, we used hot-deck imputation. This was done to minimize selection bias to a minimum. However, this mathematical procedure would make CIs around incidence rates to widen, and therefore less reliable. As 31.8% of all patients newly diagnosed with hyperthyroidism were classified by means of imputation, we reanalyzed data after down-regulation of

**Table 3** Life time risk (in percentage) for having diagnosed overt hyperthyroidism in Denmark.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Women</th>
<th>Men</th>
</tr>
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<tbody>
<tr>
<td>Multinodular toxic goitre</td>
<td>3.0</td>
<td>5.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>2.3</td>
<td>3.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Solitary toxic adenoma</td>
<td>0.5</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>All types combined</td>
<td>6.5</td>
<td>10.5</td>
<td>2.4</td>
</tr>
</tbody>
</table>

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person-years of observation by the same fraction to obtain broader CIs and higher \( z \) values for the t-test. This conservative handling of data did not alter any of our conclusions: we still found a statistically significant difference in incidence ratio between Aalborg and Copenhagen with regards to MNTG (\( P < 0.001 \)), ‘mixed-type’ (\( P < 0.001 \)), STA (\( P = 0.003 \)), and no regional difference in occurrence of GD (\( P = 0.10 \)).

We previously reported that up to 15–20% of hyperthyroid patients with a multinodular scintigraphic pattern are TRAb positive (28). Even higher frequencies of TRAb positivity have been reported in clinic-based studies from Germany (51). The difference may be caused by differences in iodine intake and study design. Most likely, this is GD on top of a nodular goitre (28). We have labelled this entity ‘mixed type’ hyperthyroidism, as the scintigraphic picture suggested MNTG, whereas the measurable TRAb indicated GD.

Conclusion

Hyperthyroidism was very common in Denmark with a lifetime risk of 10.5% in women. This was due to a high frequency of MNTG probably caused by iodine deficiency. Even a slight difference in iodine deficient state between two study areas resulted in a large difference in the incidence of MNTG. The study highlights the need for an increase in iodine intake in Denmark (20).

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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This study was part of The Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr), which is supported by grants from the Danish Medical Foundation, the 1991 Pharmacy Foundation, North Jutland County Research Foundation. Tommerhandel Wilhelm Bangs Foundation and Copenhagen Hospital Corporation Research Foundation. We are indebted to the general practitioners in Copenhagen and Northern Jutland for their collaboration.

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Deep thanks should also be addressed to the laboratories involved. Finally, we thank staff of the hospital record offices in Aalborg, Bispebjerg and Frederiksborg for their collaborative support.

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