

## CLINICAL STUDY

## Epidemiology of subtypes of hypothyroidism in Denmark

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### Abstract

**Objective:** Studies of hypothyroidism are often based on referred patients, and limited information is available on the incidence rates of subtypes of hypothyroidism in the general population. We therefore studied incidences of subtypes of primary, overt hypothyroidism in a Danish population cohort and compared incidences in two subcohorts with different levels of iodine intake.

**Design:** A prospective population-based study, monitoring a well-defined cohort representative of the Danish population.

**Methods:** The Danish Investigation of Iodine Intake and Thyroid Diseases registry of hyper- and hypothyroidism was established as part of the monitoring of the iodine fortification of salt in Denmark. A computer-based system linked to laboratory databases identified all patients diagnosed with new, biochemically overt hypothyroidism in populations living in Aalborg (moderate iodine deficiency,  $n = 311\,102$ ) and Copenhagen (mild iodine deficiency,  $n = 227\,632$ ). We subsequently evaluated all identified patients to verify incident thyroid disease, and subclassified hypothyroidism into nosological types.

**Results:** During a 4-year period (2 027 208 person-years) 685 new cases of overt hypothyroidism were diagnosed in the cohort; the incidence rate was 32.8 per 100 000 person-years (standardised to the Danish population). Nosological types of hypothyroidism were: spontaneous (presumably autoimmune) 84.4%, post-partum 4.7%, amiodarone-associated 4.0%, subacute thyroiditis 1.8%, previous radiation or surgery 1.8%, congenital 1.6% and lithium-associated 1.6%. Crude incidence rates were 29.0 around Aalborg and 40.6 in an area of Copenhagen. The higher incidence rate of hypothyroidism in the area with higher iodine intake was caused solely by more cases of spontaneous (presumably autoimmune) hypothyroidism, whereas the incidence of non-spontaneous hypothyroidism (all types combined) was significantly lower in the area with higher iodine intake.

**Conclusion:** In a population-based study we observed a higher incidence of hypothyroidism with higher iodine intake. This was due solely to the entity of spontaneous hypothyroidism. The occurrence of overt hypothyroidism was relatively low in Denmark.

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### Introduction

Primary hypothyroidism is a common disease in all populations (1–4), but knowledge about the epidemiology of incident cases of hypothyroidism is limited (5–11). The exact distribution of nosological subtypes of hypothyroidism has rarely been studied (6, 8), and virtually nothing is known about the importance of environmental factors for this distribution.

According to USA and UK recommendations (12, 13), cases of overt hypothyroidism referred from general practitioners to hospital will primarily include patients unresponsive to therapy, patients with concomitant disease or pregnancy and young patients.

Studies based on hospital cases may therefore be highly biased. In the few studies based on monitoring of a population (5, 8–10) large differences in incidences of overt hypothyroidism have been found. Such differences may have environmental and genetic causes (14). In particular, it has been discussed whether a higher iodine intake of a population may lead to more hypothyroidism (15).

We previously observed considerable differences in the incidence of overt hypothyroidism associated with small differences in iodine intake of the population (10), but the difference was statistically borderline. We have now studied this over a longer period with more statistical power and confirmed the results. Moreover, the higher

number of person-years observed in the present study allowed for comparison of subtypes of hypothyroidism.

## Subjects and methods

This study was part of The Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr), which monitors the Danish iodine fortification programme (16, 17). The DanThyr programme includes a number of studies among which is a prospective study of the incidence of overt thyroid dysfunction in an open population cohort before the iodine fortification of salt.

### Population cohort

We studied two regions in Denmark; an area in Copenhagen in East Denmark with 227 632 inhabitants and an area around Aalborg in West Denmark with 311 102 inhabitants. Information on population size, age and sex distribution was obtained from Statistics Denmark (18). During the study period (Aalborg: March 1997 to December 2000, Copenhagen: May 1997 to December 2000) the study population changed little. For the calculations we used the number of inhabitants on 1 January 1999. The two areas were chosen to represent the small differences in iodine intake level found in Denmark. The combined cohort ( $n = 538\,734$ ) is representative of the Danish population.

In Denmark there are regional differences in iodine intake (19), which are caused by differences in the iodine content of drinking water (20). A previous study estimated iodine concentration in drinking water to be approximately  $20\ \mu\text{g/l}$  in Copenhagen and around  $5\ \mu\text{g/l}$  in Aalborg (20). In another study of 4649 people representative of the Danish population, we measured urinary iodine excretion in inhabitants of the two regions in the period 1997–1998. Participants taking no mineral supplements had median urinary iodine excretions of  $61\ \mu\text{g/l}$  ( $93\ \mu\text{g}/24\ \text{h}$ ) in Copenhagen and  $45\ \mu\text{g/l}$  ( $62\ \mu\text{g}/24\ \text{h}$ ) in and around Aalborg (21, 22). These figures correspond to mild and moderate iodine deficiency respectively (23). Salt with low iodine content (8 p.p.m.) was introduced on a voluntary basis in 1998 (17), but the use was low with little impact on population iodine intake. Mandatory iodisation of household salt and salt in bread (13 p.p.m.) was introduced in the second half of 2000 and was considered effective from 2001, with a planned increase in population iodine intake of around  $50\ \mu\text{g}/\text{day}$  (17). Thus, the present study included the period up to effective iodisation.

### Identification of incident cases

Patients were prospectively identified using a monitoring system of clinical practice in hospitals and primary care in the study areas; no intervention or active

screening was performed. Results of all thyrotrophin (TSH) and thyroid hormone measurements in the two cohort areas were imported from laboratory databases into a registry database on a daily basis. The registry database identified cases with blood tests fulfilling the criteria of overt, biochemical hypothyroidism with high serum TSH ( $\text{TSH} > 5.0\ \text{mU/l}$ ) and low serum total thyroxine (T4) ( $\text{T4} < 60\ \text{nmol/l}$ , all four laboratories) or low serum free T4 (fT4) (Bispebjerg Hospital Laboratory,  $\text{fT4} < 9.1\ \text{pmol/l}$ ; Laboratory of General Practitioners,  $< 10.0\ \text{pmol/l}$ ). Serum tri-iodothyronine (T3) values were not used for diagnosing as T3 is not a good marker of hypothyroidism (24). The registry database automatically excluded cases previously identified in the database. All other cases were verified as new by contact with the hospital or primary care physicians who had requested the thyroid function test.

The use of this system for identification of patients, the various types of evaluation and control performed, and detailed information on participating diagnostic laboratories and biochemical tests used for evaluation of thyroid function have been described in detail previously (25, 26).

### Verification of incident cases

All patients ( $n = 863$ ) identified by the laboratory system and primarily classified as new cases were subsequently evaluated in detail. We obtained information on previous thyroid disease, history of medication, pregnancy within 1 year, symptoms and signs of subacute thyroiditis, results of subsequent thyroid testing, and initiation and results of therapy. Information was gathered from patients who accepted a comprehensive investigation programme by us, from general practitioners and from hospital records if available. The information obtained was used to verify ( $n = 685$ ) or disprove ( $n = 178$ , in the majority thyroid function tests had normalised spontaneously) new thyroid disease, and to classify causes of hypothyroidism. Subjects with no information of previous overt thyroid dysfunction were verified as new cases if they fulfilled at least one of these criteria: sustained biochemical signs of hypothyroidism after 3 weeks ( $n = 340$ ); L-T4 treatment instituted within 3 weeks (these patients had a median TSH at diagnosis of  $37.4\ \text{mU/l}$ ,  $n = 300$ ); normal thyroid function tests after 3 weeks without L-T4 treatment but with signs or history of transient hypothyroidism (post-partum hypothyroidism, lithium- or amiodarone-induced hypothyroidism, or subacute thyroiditis; total,  $n = 10$ ). The remainder of patients included ( $n = 35$ ) had no confirmative or disapproved thyroid blood test, no patient follow-up and no history or recorded signs of thyroiditis. They were old (median age, 74.6 years) and all died shortly after the blood test (all within 2 months), before a presumably confirmative test could be performed. They were considered to be true hypothyroid cases without further proof.

### Classification of incident cases

The clinical information (obtained from patients, general practitioners and hospital records) was used to classify patients into subgroups according to the cause of hypothyroidism.

- (a) Post-partum thyroid dysfunction (PPTD): overt hypothyroidism diagnosed within one year after delivery.
- (b) Subacute thyroiditis (SAT, de Quervain thyroiditis): overt hypothyroidism with absent technetium uptake on thyroid scintiscan, elevated erythrocyte sedimentation rate and anterior neck pain. As we included only patients with new thyroid dysfunction, patients initially hyperthyroid (biphasic pattern of PPTD or SAT) were excluded.
- (c) Amiodarone- and lithium-induced hypothyroidism: overt hypothyroidism in patients treated with amiodarone or lithium at any time of their life (all patients identified had received the medication within the last year).
- (d) Hypothyroidism after prior radiation or surgery: overt hypothyroidism in patients with a history of radioiodine treatment of euthyroid goitre, neck irradiation of neck tumours (e.g. lymphoma) or surgical treatment of euthyroid goitre.
- (e) Congenital hypothyroidism: information was obtained from Statens Serum Institut, which is in charge of screening for congenital hypothyroidism in Denmark (27).
- (f) Spontaneous hypothyroidism: overt hypothyroidism in patients without any of the above described conditions known to cause hypothyroidism. Spontaneous, primary hypothyroidism is normally assumed to be of autoimmune origin (28).

### Statistics

Crude incidence rates (cIRs), age-standardised incidence rates (SIRs) and standardised incidence rate ratios (SIRRs) were calculated according to standard procedures (29, 30). Confidence intervals (CIs) were calculated assuming approximation from Poisson to Gaussian distribution (30). Incidence rates of hypothyroidism, according to gender and geographical region, were compared by means of SIRRs.

We calculated age-conditional probability (risk) for hypothyroidism, which is the risk of having hypothyroidism diagnosed at various ages.

Life-time risk, defined as the probability of an inhabitant to develop hypothyroidism during an average life-time, was estimated using the calculated incidence rates applied to the Danish demographic population taking the average expected life-time (18) into account. For the calculations, we assumed that SIRs were identical in different generations, i.e. no cohort effect being

present, and that the calculated SIR was representative of the entire Danish population. We used values of SIRs in the various age strata and applied these values on the surviving population according to each age stratum.

### Ethical approval

This study was approved by the Regional Ethics Committee in Aalborg and Copenhagen. Registry permission was obtained from the Danish Data Protection Agency. There are no conflicts of interest.

### Results

In the population cohort living in Copenhagen and Aalborg we identified and verified 685 new cases of hypothyroidism.

The overall, cIR of overt hypothyroidism in the cohort was 33.8 per 100 000 person-years. A nearly similar figure (32.8 per 100 000 person-years) was obtained if the incidence rate was standardised to the age and sex composition of the entire Danish population. We found no longitudinal trend over time (1997–2000) in incidence rate in the two regions ( $P = 0.24$  for Copenhagen;  $P = 0.22$  for Aalborg).

The distribution of nosological types of hypothyroidism split by age and gender is summarised in Table 1. This table also depicts the study population. SIRs of nosological subtypes of hypothyroidism in the combined cohort are presented in Table 2. Hypothyroidism had developed spontaneously in 84.4% of cases. Spontaneous hypothyroidism is presumed to be of autoimmune origin. In accordance with this, 94.8% of the 211 patients, where results of thyroid peroxidase auto-antibody (TPOAb) measurements before therapy were available, were antibody positive. The remainder of cases (non-spontaneous hypothyroidism) developed secondarily to a number of causes, of which preceding delivery and amiodarone therapy were most frequent. Non-spontaneous hypothyroidism is a heterogeneous group of disease entities, of which some affect only one gender (post-partum hypothyroidism), whereas other entities affect only newborn infants (congenital hypothyroidism) or adults (amiodarone-induced hypothyroidism) (Table 1). The incidence rate of non-spontaneous hypothyroidism (all types combined) was roughly constant across age groups (Fig. 1). In young subjects, a preceding cause for hypothyroidism was relatively common, whereas spontaneous hypothyroidism dominated in old age. The incidence of spontaneous hypothyroidism increased nearly exponentially with age (Fig. 1). Half of the spontaneously hypothyroid patients were 67.6 years of age or older compared with 41.5 years among patients with non-spontaneous hypothyroidism, with a wide span between subtypes from zero (congenital hypothyroidism) to 71.7 years (amiodarone-induced hypothyroidism).

**Table 1** New cases of hypothyroidism according to type of disease, sex, and age.

Type of disease	Sex	Age intervals (years) <sup>k</sup>											All ages	cIR <sup>l</sup> (CI <sup>m</sup> )
		0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–90	90+			
Hypothyroidism <sup>a</sup>	Female	6	7	32	51	48	104	78	107	83	21	537	51.8 (47.5–56.2)	
	Male	6	1	2	12	11	18	27	45	21	5	148	14.9 (12.5–17.3)	
Spontaneous hypothyroidism <sup>b</sup>	Female	2	6	14	29	43	92	75	99	79	21	460	44.4 (40.4–48.5)	
	Male	0	1	2	10	7	17	20	37	20	4	118	11.9 (9.8–14.0)	
Non-spontaneous hypothyroidism <sup>c</sup>	Female	4	1	18	22	5	12	3	8	4	0	77	7.4 (5.8–9.1)	
	Male	6	0	0	2	4	1	7	8	1	1	30	3.0 (1.9–4.1)	
Post-partum <sup>d</sup>	Female	0	1	18	17	0	0	0	0	0	0	36	3.5 (2.3–4.6)	
	Male	0	0	0	0	0	0	0	0	0	0	0	0	
Amiodarone-associated <sup>e</sup>	Female	0	0	0	0	1	0	1	6	3	0	11	1.1 (0.4–1.7)	
	Male	0	0	0	0	2	1	5	7	1	0	16	1.6 (0.8–2.4)	
Subacute thyroiditis <sup>f</sup>	Female	0	0	0	3	2	4	1	0	0	0	10	1.0 (0.4–1.6)	
	Male	0	0	0	1	0	0	1	0	0	0	2	0.2 (0–0.5)	
Congenital <sup>g</sup>	Female	4	0	0	0	0	0	0	0	0	0	4	0.4 (0–0.8)	
	Male	6	0	0	0	0	0	0	0	0	0	6	0.6 (0.1–1.1)	
Lithium-associated <sup>h</sup>	Female	0	0	0	1	1	5	0	2	0	0	9	0.9 (0.3–1.4)	
	Male	0	0	0	0	1	0	0	0	0	0	1	0.1 (0–0.3)	
Radiation or surgery <sup>i</sup>	Female	0	0	0	1	1	3	1	0	1	0	7	0.7 (0.2–1.2)	
	Male	0	0	0	1	1	0	1	1	0	1	5	0.5 (0.1–0.9)	
Study population <sup>j</sup>	Female	31 043	24 162	47 901	41 506	33 092	32 420	23 355	23 506	15 257	3134	275 376		
	Male	32 759	25 325	47 726	45 655	34 664	32 615	20 706	16 014	7113	781	263 358		

<sup>a</sup> All nosological type of hypothyroidism. Only patients without previous overt thyroid dysfunction were included.  
<sup>b</sup> Cases in whom we did not find any preceding cause (see Subjects and Methods).  
<sup>c</sup> Cases in whom we did recognise a preceding case (see Subjects and Methods).  
<sup>d</sup> Post-partum thyroid dysfunction presenting with hypothyroidism within 1 year after delivery.  
<sup>e</sup> Hypothyroidism in patients treated with amiodarone (all within 1 year).  
<sup>f</sup> Subacute thyroiditis presenting with hypothyroidism.  
<sup>g</sup> Hypothyroidism diagnosed after screening for congenital hypothyroidism.  
<sup>h</sup> Hypothyroidism in patients treated with lithium (all within 1 year).  
<sup>i</sup> Hypothyroidism in patients previously treated with radioiodine, neck irradiation or thyroid surgery (euthyroid before treatment).  
<sup>j</sup> Study population on 1 January 1999 in the cohort living in Copenhagen and Aalborg.  
<sup>k</sup> Age intervals 0–9.999, 10–19.999 etc.  
<sup>l</sup> cIR = unadjusted incidence per 100 000 person-years.  
<sup>m</sup> CI = 95% CI.

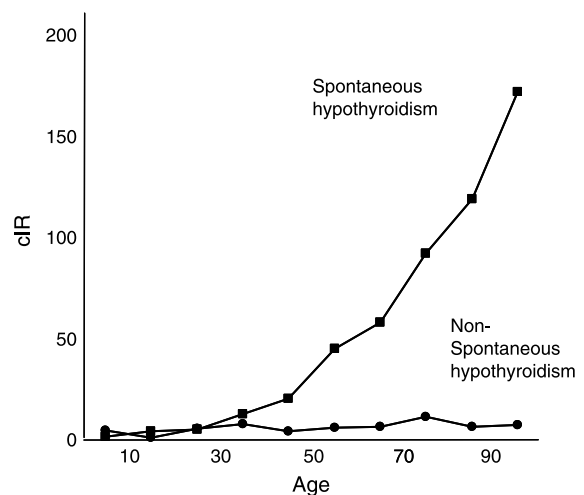
Figure 2, showing the age-conditional probability (risk) for hypothyroidism, illustrates the preponderance of hypothyroidism among females and depicts that a steep increase in the incidence of hypothyroidism in females took place around 40–50 years of age. Among males, the increase seemed to occur two or three decades later in life. The life-time risk for all

types of hypothyroidism was 2.7% with a three times predominance in women (4.1 vs 1.3% in men). The sex dependency became even more evident when looking at the entity of spontaneous hypothyroidism; the

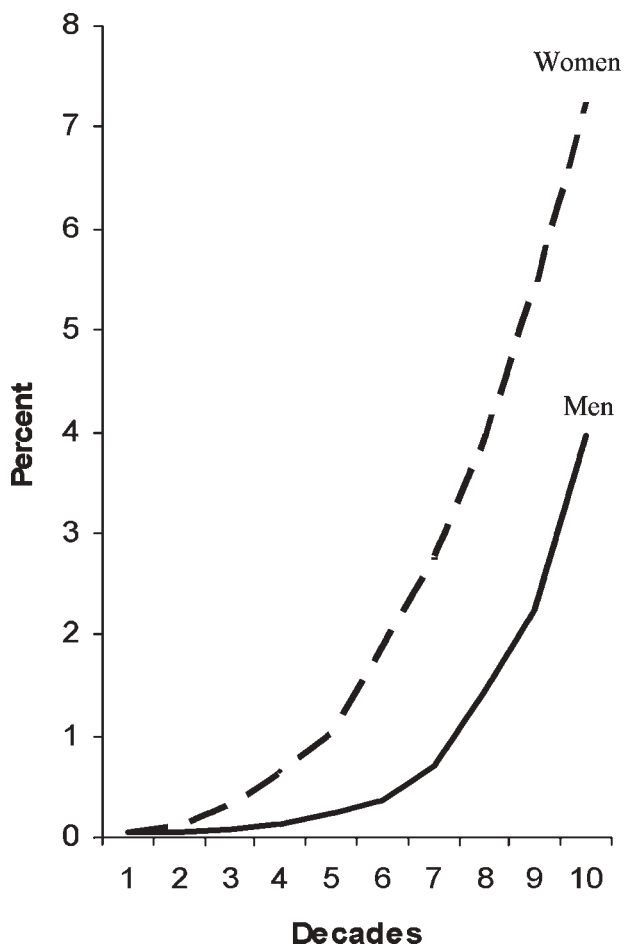
**Table 2** Standardized incidence rates (SIRs) of nosological subtypes of hypothyroidism in Denmark.

	SIR <sup>a</sup> (CI <sup>b</sup> )	% <sup>c</sup>
Spontaneous	27.7 (23.3–32.2)	84.4
PPTD	1.5 (0.6–2.5)	4.7
Amiodarone-associated	1.3 (0.4–2.3)	4.0
SAT	0.6 (0–1.3)	1.9
Radiation/surgery	0.6 (0–1.3)	1.8
Lithium associated	0.5 (0–1.2)	1.6
Congenital	0.5 (0–1.2)	1.6
All types	32.8 (28.0–37.7)	100

<sup>a</sup> Standardized incidence rates per 100 000 person-years (age-adjusted to the Danish population, 1 January 1999).  
<sup>b</sup> 95% CI of SIRs.  
<sup>c</sup> Distribution of subtypes (%).



**Figure 1** cIRs (per 100 000 person-years) of spontaneous and non-spontaneous hypothyroidism according to age.



**Figure 2** Age-conditional risk for having diagnosed hypothyroidism in women and men. This is the probability (risk) of having developed hypothyroidism under the condition that the subject will attain the specific age.

**Table 3** Regional differences in standardized incidence rates of the various subtypes of hypothyroidism.

	SIR <sup>a</sup>		SIRR <sup>b</sup> (CI <sup>c</sup> )
	Copenhagen	Aalborg	
Hypothyroidism	38.9	29.2	1.33 (1.15–1.55)*
Spontaneous	35.0	23.1	1.53 (1.29–1.80)*
Non-spontaneous	3.9	6.1	0.64 (0.43–0.96)*
PPTD	1.4	1.8	0.77 (0.40–1.50)
Amiodarone	0.8	1.6	0.60 (0.26–1.37)
SAT	0.3	0.9	0.30 (0.06–1.35)
Radiation/surgery	0.3	0.9	0.26 (0.06–1.20)
Lithium	0.4	0.6	0.69 (0.18–2.66)
Congenital	0.7	0.4	1.72 (0.50–5.95)

<sup>a</sup>Incidence rates per 100 000 person-years (age-adjusted to the Danish population 1 January 1999).

<sup>b</sup>SIRR, standardized incidence rate ratio; An SIRR value above 1.0 indicates a higher frequency of hypothyroidism in Copenhagen compared with Aalborg. The difference is statistically significant if 1.0 is not included in the CI of SIRR.

<sup>c</sup>95% CIs of SIRRs.

\* Statistically significant ( $P < 0.05$ ).

female–male ratio was 3.5 and the life-time risk was 2.3% (3.5% in women and 1.0% in men). In non-spontaneous hypothyroidism, the female–male ratio was only 2.1. The reason for monitoring two regions in Denmark is that they represent the minor systematic difference in level of iodine intake in Denmark caused by the different iodine contents of ground water (19). Table 3 depicts the SIRs observed in the two regions. Further, the ratios of the two regional SIRs are listed. Hypothyroidism was 33% more common in the Copenhagen cohort with higher iodine intake. This difference was caused by a 53% higher occurrence of spontaneously developed hypothyroidism. On the other hand, we found a higher incidence of non-spontaneous hypothyroidism in the population cohort around Aalborg with a lower iodine intake (moderate iodine deficiency). When cases of non-spontaneous hypothyroidism were split into subtypes, the statistical power became low and there were no significant regional differences in any of the subgroups (Table 3).

Incidence rates of spontaneous hypothyroidism in the regions according to sex and age are shown in Fig. 3. It illustrates that the higher incidence of hypothyroidism with increasing age, in women and in the Copenhagen cohort (mild vs moderate iodine deficiency) was observed even after stratification at several levels.

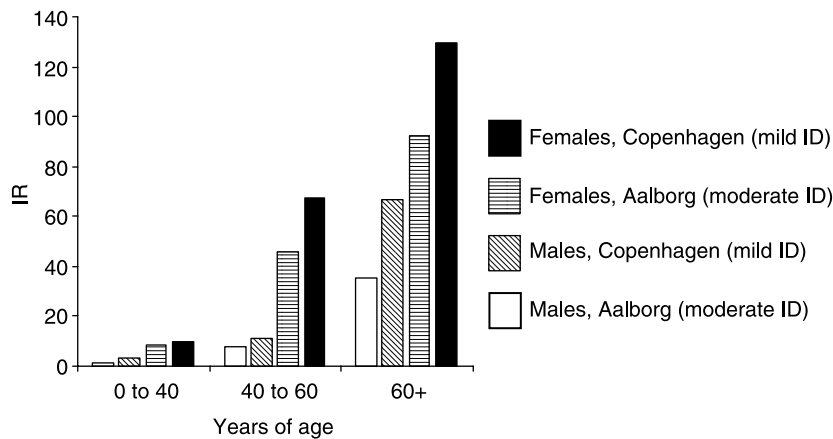
**Discussion**

We have provided data on overall incidence rate and incidence rates of subtypes of overt, primary hypothyroidism in a cohort representative of the Danish population. We found that overt hypothyroidism is relatively uncommon in Denmark compared with the few other areas where this has been studied.

In addition, we compared two regions with different levels of iodine intake using identical criteria of case identification, verification and sub-classification. Our results confirmed and extended previous studies showing that even small differences in iodine intake, in a population with moderate to mild iodine deficiency, may be of major importance for the development of overt hypothyroidism. Moreover, the higher incidence of overt hypothyroidism with higher iodine intake was entirely caused by more cases of spontaneous autoimmune hypothyroidism.

**Overall incidence rate of overt hypothyroidism**

The overall SIR of hypothyroidism in Denmark was 32.8 per 100 000 person-years. This was higher than in a previous Danish study, where cases were identified retrospectively from records in hospitals, general practitioners or internists in practice (8). The difference may be due to a more sensitive method of case identification in the present study (prospective identification by linkage to diagnostic laboratories) and omission of transient hypothyroid cases in the previous study.



**Figure 3** Incidence rates (IR; per 100 000 person-years) of overt hypothyroidism in two regions with mild and moderate iodine deficiency (ID) according to sex and age.

Furthermore, the previous study was exclusively performed in East Jutland with relatively low iodine intake, and diagnostic activity may have increased over time.

On the other hand, much higher values were found in two independent epidemiological studies performed in the UK (5, 9). The Whickham study (5), including approximately 40 000 person-years of follow-up, used a combination of retrospective case finding and cross-sectional screening for identification of patients. The study only included people aged 18 years and above, and elderly subjects (more than 45 years old) were over-represented. The cIR of hypothyroidism (among subjects aged 18 or above) was 350/60 per 100 000 person-years (women/men) in the Whickham study compared with 62/18 (women/men) in this age group in our study. The Tayside study (9), a large study of 1.2 million person-years, identified cases retrospectively by combining data from six different registries. cIRs were 498 per 100 000 person-years among women and 88 per 100 000 person-years among men. The corresponding figures from our study were 51.8 and 14.9 respectively. Even if there were differences in methods between these studies, it is unlikely that this would be the sole cause for the large difference in incidences. Other possibilities are differences in genes and environment; among the latter, the iodine intake level may play an important role (31). The level of iodine intake in the UK (urinary iodine excretion around 140  $\mu\text{g}/\text{l}$  (9)) is not excessive but clearly higher than in Denmark (21, 22).

Two studies performed in Sweden (7, 11), a country of iodine sufficiency (32), found higher incidence rates of spontaneous hypothyroidism compared with our study. In women aged 38–66 years (11) the incidence rate was 156 per 100 000 person-years. We found incidence rates of 68.6 per 100 000 person-years among women aged 40–69 years. A second Swedish study (7) estimated incidence rates of 243 per 100 000 person-years among women aged 70–79 years. In this subgroup we calculated an incidence rate of 121 per 100 000 person-years. In the Swedish studies, thyroid function was investigated in all participants. Furthermore, both studies

were relatively small and only seven cases with hypothyroidism were identified in each study.

Finally, a Spanish study from Vigo City (6) found an incidence rate of 18.4 per 100 000 person-years with a broad margin of precision, since only 19 patients were identified with overt hypothyroidism.

### **Incidence rates of subtypes of hypothyroidism**

The higher overall incidence rate of hypothyroidism with higher iodine intake was entirely caused by more cases of spontaneous hypothyroidism. The level of iodine intake has considerable effects on the occurrence of thyroid disorders in a population (15). Our findings support the idea that higher iodine intake may lead to more autoimmune hypothyroidism (33) and this is already observed at the level of mild to moderate iodine deficiency. Iodine has multiple, mostly inhibitory effects, on the thyroid gland, and the precise mechanisms leading to more hypothyroidism with higher iodine intake remain to be elucidated.

Non-spontaneous hypothyroidism was more frequent in the area with the lowest iodine intake level (Aalborg). Subgroup analyses could not be performed because of low statistical power. However, subjects in this area are known to have more multinodular euthyroid goitres than subjects in Copenhagen (22). This condition is often treated with radioiodine or surgically with a risk of later development of overt hypothyroidism.

We have found no other population-based study of overt hypothyroid patients that contains enough cases to allow for incidence rate estimation of subtypes of the disease.

### **Incidence of hypothyroidism according to age and gender**

We found a nearly constant incidence of non-spontaneous hypothyroidism regardless of age. This finding was caused by the heterogeneity of the disease entity comprising disorders dominating in different ages.

The nearly exponentially rising incidence of spontaneous hypothyroidism with age is in accordance

with other studies (34, 35). In populations, the prevalence of thyroid auto-antibodies in serum increases with age, but subsequently may level off in elderly people (4, 36, 37). The continued rise in the incidence of hypothyroidism in old people suggests that duration of thyroid autoimmunity is important for the development of thyroid insufficiency.

Hypothyroidism was more common among females with a female/male incidence rate ratio of 3.5; the ratio was 3.7 for spontaneous hypothyroidism. This was lower than ratios (up to 7) found in other studies (5, 6, 8, 9).

### Study strengths and limitations

We prospectively identified overt hypothyroidism diagnosed in hospitals and primary care. We prospectively identified overt hypothyroidism diagnosed in hospitals and primary care without altering daily routine. It appears that no major surveillance bias was introduced, since the yearly incidence rate did not rise during the study period.

Our case identification system had a high sensitivity (25) and identified primarily also a number of patients not having true, incident hypothyroidism. The majority of these had transient conditions biochemically mimicking thyroid disease, and normalised spontaneously. They were subsequently excluded from the study.

Patients were subclassified according to preceding conditions known to cause hypothyroidism. If a trigger was found, it was assumed to be the cause of hypothyroidism. Even though this biologically plausible assumption is often made (28), a causal relationship is only suggestive.

Patients with elevated serum TSH and normal serum T4 were not identified in the present study. If such patients with subclinical hypothyroidism are treated, they never become overtly hypothyroid and therefore will not be diagnosed with overt hypothyroidism. However, our previous cross-sectional study gave no indication that this phenomenon could introduce a major bias in the present study (38).

Only patients with new overt thyroid dysfunction were identified in the DanThyr registry. The present study describes patients who had not previously been identified with overt hyper- or hypothyroidism. Patients who developed hypothyroidism after previous radioiodine or surgical therapy of overt hyperthyroidism were therefore not included. Furthermore, patients with post-partum hypothyroidism or SAT initially presenting with hyperthyroidism were not included.

Finally, since hypothyroidism is often associated with few or even no symptoms and signs, some patients might have the disease undiagnosed. The magnitude of this problem could not be quantified in this study.

### Conclusion

A substantial difference in the occurrence of hypothyroidism was found between two areas of different iodine

intake levels. The higher incidence of hypothyroidism with higher iodine intake level was entirely due to spontaneous hypothyroidism, which is presumably of autoimmune origin (95% of patients were positive for TPOAb). Similarly, the increase in incidence of hypothyroidism with age was caused by spontaneous hypothyroidism.

### Acknowledgements

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