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# *Changes in subtypes of overt thyrotoxicosis and hypothyroidism following iodine fortification*

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**Abstract/Summary**

Objective: To investigate the impact of mandatory iodine fortification (IF) on the incidence of nosological subtypes of overt thyrotoxicosis and hypothyroidism.

Design: We identified and scrutinized all possible new cases of overt thyrotoxicosis and hypothyroidism in an open cohort in Northern Jutland (n=309,434 January 1st, 1997) during the years 2014-16. Individual medical history was evaluated to verify and detail the incidence of overt thyroid dysfunction and for classification into nosological subtypes. A number of cases were excluded during final verification due to spontaneous normalization of thyroid function, as they had no medical history suggesting a known condition, which could transiently affect thyroid function (subacute/silent thyroiditis, PPTD and iatrogenic thyroid dysfunction). An identical survey was conducted in 1997-2000 prior to mandatory IF of salt (13 µg/g) that was in effect from year 2001.

Results: The standardized incidence rate (SIR) of verified overt thyrotoxicosis decreased markedly from 97.5/100,000/year in 1997-00 to 48.8 in 2014-16 (SIRR: 0.50 (95% CI: 0.45-0.56)). This was due to a distinct decrease in the SIR of multinodular toxic goitre (SIRR: 0.18 (0.15-0.23)), solitary toxic adenoma (SIRR: 0.26 (0.16-0.43)) and to a lesser degree Graves' disease (SIRR: 0.67 (0.56-0.79)). SIR for overt hypothyroidism was unaltered by 2014-16 (SIRR: 1.03 (0.87-1.22)). However, age distribution shifted with more young and fewer elderly cases of verified overt hypothyroidism.

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Conclusion: Mandatory IF caused a substantial reduction in SIR of verified overt thyrotoxicosis (especially of nodular origin) while avoiding an increase in SIR of verified overt hypothyroidism.

**Introduction**

Iodine deficiency (ID) has been recognized as an important health issue globally with efforts to combat iodine deficiency disorders (IDD) for more than a century. Still, the latest assessment from the World Health Organization (WHO) indicate that IDD affect 31% of the global population[1].

The population of Denmark was shown to suffer from ID during the 1990s mainly related to a low iodine content in tap water[2]. Mild ID was common in the Eastern parts of the country while moderate ID was frequent in the Western parts[3]. Thyrotoxicosis due to autonomously functioning thyroid nodules was very frequent among the elderly in the Western parts of Denmark[4], as was the occurrence of nontoxic thyroid nodules[5]. Pregnant women experienced a tendency for increased TSH during late pregnancy, possibly indicating insufficiency of thyroid hormone production[6]. Thus, a Danish iodine fortification (IF) program was initiated in July 1998 with iodization of salt at a level of 8 µg/g on a voluntary basis[7]. However, this proved to be insufficient in achieving a 50 µg increase in average daily iodine intake and was replaced by a mandatory iodization (13 µg/g) of all table salt and salt used for commercial production of bread in July 2000. Permission was granted for selling preexisting storages of uniodized salt after July 2000, thus universal salt iodization was not fully in effect before the year 2001. A multifaceted program for monitoring of the effects of salt iodization in the population was initiated before any IF was in place[8] and is still ongoing.

Results from the registration of new cases of overt thyrotoxicosis and hypothyroidism have been published for the first 20-21 years[9–12]. This registration was based on a Register Database applying a diagnostic algorithm to all thyroid function tests (TFTs) taken within the cohort areas and then excluding the cases known to the Register Database or the current general practitioner (GP) of each patient.

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The present study adds a scrutinized review of all health records for each individual case in order to clarify the distinct nosological subtype of thyroid dysfunction (thyrotoxicosis or hypothyroidism). We compared the pre-mandatory iodization period (1997-00) to a post-iodization period (2014-16).

## Methods and Materials

### *Population cohort*

The present study cohort comprised a population of 309,434 subjects (January 1st, 1997) prior to the implementation of salt iodization in Denmark. Moderate ID was widespread in the western parts of Denmark including our study cohort around Aalborg City, Northern Jutland (median UIC = 45 µg/l in 1997-98 among subjects not using iodine containing supplements; 53 µg/l if all subjects were included)[13]. After universal salt iodization, the median UIC within the study cohort increased to a level of 86 µg/l in 2004-05[14] and 74 µg/l[15] in 2008-10. The Danish municipalities were rearranged by January 2007 as a part of a national structural reform. This rearrangement slightly decreased the size of the area encompassing our study cohort. At the start of the present study period (January 1st, 2014) the study cohort comprised 272,954 subjects, while the total number of person-years covered by the present study period (2014-16) amounts to 825,842. The distribution of the nosological subtypes of thyroid dysfunction were described in detail for the cohort population during the years 1997-2000 before the mandatory iodine fortification[16,17]. Information on the composition of the cohort was provided by Statistics Denmark[18].

### *Identification of potential new cases with thyroid dysfunction*

All potential new cases of biochemically overt thyroid dysfunction were identified, manually verified and subsequently classified according to their nosological subtype of thyrotoxicosis or hypothyroidism in an open cohort located in Northern Jutland for the years 2014-16. The process of identification has been extensively described[19]. In brief:

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All TFTs sampled within the cohort area were recorded in a dedicated register database. Potential new cases of overt thyrotoxicosis were identified based on a suppressed serum TSH (<0.2mU/l) combined with an elevated serum total $T_4$ (>140nmol/l) and/or an elevated serum total $T_3$ (>2.7nmol/l). Potential new cases of hypothyroidism was identified based on an elevated serum TSH (>5.0mU/l) and a low total $T_4$ (<60nmol/l). Cases previously verified in the database as hyper- or hypothyroid were excluded.

A similar identification process for cases of overt thyroid dysfunction had been performed in an open cohort in the Danish capital Copenhagen with previous mild ID from 1997-2008[9–12]. Unfortunately this registration had to be concluded in 2008 due to staff limitations.

*Data collection on the potential new cases of thyroid dysfunction*

A total of 666 patients were identified by the register database and confirmed by their GPs as potential new cases of overt thyrotoxicosis, while 403 patients were identified as potential new cases of overt hypothyroidism during the years 2014-16. In comparison, 1601 and 410 potential new cases of thyrotoxicosis and hypothyroidism were identified during the years 1997-00. All cases were individually scrutinized by examining their hospital records, medicinal databases (used by private practitioners and hospital departments), subsequent TFTs, TSH receptor antibodies (TRAb) measurements and thyroid scintigraphies performed by the department of nuclear medicine.

*Verification process of incident cases*

All patients underwent a diagnostic algorithm in order to verify or reject incident overt thyroid dysfunction, as illustrated in *figure 1.* Patients with potential new overt biochemical thyroid dysfunction, who were not previously recorded as thyrotoxic or hypothyroid patients by our Register Database or by the patients' GP, were verified if either of the following were true:

1) Sustained overt biochemical thyroid dysfunction, i.e. a confirmatory TFT at least 3 weeks later.

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2) Normalization of thyroid function due to treatment for thyrotoxicosis (anti-thyroid medication, radioiodine therapy or thyroid surgery) or hypothyroidism (levo-thyroxine (L-$T_4$) therapy).

3) Normalization of thyroid function without treatment but with a history suggesting a transient condition of thyroid dysfunction, such as: subacute thyroiditis (SAT), silent thyroiditis, postpartum thyroid dysfunction (PPTD), radiation-induced thyroid dysfunction, surgical manipulation of the thyroid gland, radioiodine-induced thyroid dysfunction, medication-induced thyroid dysfunction (amiodarone, lithium, interferons, interleukins and monoclonal antibodies).

Through use of the algorithm described above and a list of specific exclusion criteria (see appendix), we were able to verify 659 patients with overt thyroid dysfunction out of 1069 (thyrotoxicosis: 408, hypothyroidism: 251).

*Classification of incident cases into nosological subtypes of thyrotoxicosis and hypothyroidism*

Each of the verified cases of thyroid dysfunction were classified into one of the following categories based on their medical history, thyrotropine receptor antibody (TRAb) measurements and thyroid scintigraphy:

a) Graves' disease (GD) with thyrotoxicosis: positive TRAb measurement (TRAb+, TRAb > 1.0 IU/l) and/or a nonsuppressed homogeneous $TcO_4^-$ uptake within the entire thyroid gland on scintigraphy (n=181).

b) Multinodular toxic goitre (MNTG): a heterogeneous uptake on thyroid scintigraphy with at least two nodules of enhanced $TcO_4^-$ accumulation combined with absent or diminished uptake in the rest of the gland. If TRAb was negative or not measured, the diagnosis was MNTG (n=74).

c) 'Mixed type' thyrotoxicosis (Marine-Lenhart syndrome): patients with a positive TRAb measurement but a MNTG like pattern on thyroid scintigraphy (n=71).

d) Solitary toxic adenoma (STA): a single nodule with enhanced $TcO_4^-$ uptake combined with absent or low $TcO_4^-$ accumulation in rest of the thyroid gland (n=13).

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e) SAT (subacute thyroiditis/de Quervain thyroiditis): transient thyrotoxicosis and/or hypothyroidism, with no medical history which could otherwise explain the transient period of thyroid dysfunction (amiodarone, lithium, interferon, interleukin, monoclonal antibodies, radioiodine treatment, radiation or surgery) and with at least two of three SAT criteria fulfilled: anterior neck pain; absent or low $TcO_4^-$ uptake with no visible thyroid nodules on scintigraphy; or elevated erythrocyte sedimentation rate / C-reactive protein (thyrotoxicosis: n=24, hypothyroidism: n=1).

f) Silent thyroiditis: transient thyrotoxicosis with absent or low $TcO_4^-$ uptake and no presence of anterior neck pain or elevated erythrocyte sedimentation rate / C-reactive protein. Similar to SAT, no other explanation for the transient period of thyroid dysfunction should be detectable in the patient's medical history (n=6).

g) Postpartum thyroid dysfunction (PPTD): overt thyroid dysfunction presenting within one year after delivery. If TRAb was negative or not measured in the case of thyrotoxicosis, PPTD was the diagnosis. If TRAb was positive, the patient was classified as GD (thyrotoxicosis: n=15, hypothyroidism: n=23).

h) Amiodarone-associated thyroid dysfunction: overt thyrotoxicosis or hypothyroidism diagnosed during or within 12 months after amiodarone treatment (thyrotoxicosis: n=6, hypothyroidism: n=11).

i) Radioiodine-associated thyroid dysfunction: transient overt thyrotoxicosis developed within a month after radioiodine treatment of non-toxic goitre was performed, or overt hypothyroidism developed within one year (thyrotoxicosis: n=4, hypothyroidism: n=5).

j) Lithium-associated thyroid dysfunction: overt thyroid dysfunction in patients previously (<12 months) or currently treated with lithium (thyrotoxicosis: n=5, hypothyroidism: n=4).

k) 'Manipulation thyroiditis' with thyrotoxicosis: transient thyrotoxicosis developed shortly after thyroid manipulation during surgery on thyroid or parathyroid gland (n=3).

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l) Thyroid dysfunction associated with previous (<12months) or current treatment with interferon (IFN), interleukin (IL) or monoclonal antibodies (thyrotoxicosis: n=4, hypothyroidism: n=5).

m) Radiation-associated thyroid dysfunction: overt thyrotoxicosis within 3 months after any radiation therapy against the neck region or overt hypothyroidism within one year (thyrotoxicosis: n=2, hypothyroidism: n=7).

n) Surgically induced hypothyroidism: overt hypothyroidism within one year after hemithyrodectomi or total thyrodectomi (n=12). Patients who underwent sufficient L-$T_4$ substitution immediately after surgery would logically not emerge as hypothyroid.

o) Congenital hypothyroidism: identified through the Danish neonatal screening program (n=3).

p) Spontaneous hypothyroidism: overt hypothyroidism in patients without any of the above described conditions (n=180). We have previously shown that this combined group of patients with hypothyroidism due to Hashimoto's or Ort's disease almost exclusively (>99%) harbored TPO-Ab and/or Tg-Ab[20].

Of the 408 verified cases of thyrotoxicosis, we were able to classify 380 using the criteria described above. However, a small number of patients (n=28) had no TRAb measurement or thyroid scintigraphy performed. From their medical history, we knew they did not suffer from the entities e-m. In accordance with our previous study, we used nearest neighbor hot deck-imputation[21] to classify this small group of patients (6.9%) into the subgroups a-d (GD/MNTG/mixed-type/STA: n=10/9/8/1). Nearest neighbor hot deck-imputation did not alter any of the results of the present study.

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*Statistical methods*

The standardized incidence rate (SIR) of each nosological subtype was calculated according to the principle of direct standardization[22]. The Danish population as of January 1st, 1999 was used as the standard population to allow for comparison with data from the same cohort during the years before initiation of effective IF (1997-2000). The 95% confidence intervals of the standardized incidence rate ratios (SIRR) were used to determine any significant differences.

The study was approved by the National Committee on Health Research Ethics in Denmark and by The Danish Data Protection Agency.

**Results**

*Incidence of verified thyrotoxicosis and its subtypes*

The overall SIR of verified thyrotoxicosis decreased markedly from 97.5 during the pre-iodine fortification years 1997-00 to 48.8/100,000/year in 2014-16, with a SIRR of 0.50 (95% CI: 0.45-0.56), (figure 2). The SIR of MNTG decreased from 44.5 to 8.2 (SIRR: 0.18 (0.15-0.23)), GD from 33.2 to 22.2 (SIRR: 0.67 (0.56-0.79)) and STA from 6.1 to 1.6 (SIRR: 0.26 (0.16-0.43)). No changes were observed in mixed-type thyrotoxicosis (SIRR: 1.14 (0.83-1.58)), post partum thyrotoxicosis (SIRR: 1.03 (0.53-1.99)) and thyrotoxicosis due to iatrogenic causes (SIRR: 1.09 (0.64-1.86)). Only the SIR of SAT increased significantly among the subtypes of thyrotoxicosis during the study period from 1.8 to 3.7 (SIRR: 2.07 (1.15-3.72)). The SIR of thyrotoxicosis among both men and women decreased significantly from 1997-00 to 2014-16; SIR for men from 33.0 to 21.3 (SIRR: 0.65 (0.51-0.82)) and SIR for women from 160.4 to 75.6 (SIRR: 0.47 (0.42-0.53)).

When divided into three age groups (young, middle-aged and elderly: 20-39, 40-59 and 60+ years) a decrease in SIR of thyrotoxicosis was evident in all three groups, though only statistically significant

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among the middle-aged (40-59 y) and elderly (60+ y). Young: (SIRR: 0.80 (0.63-1.02)), middle-aged (SIRR: 0.67 (0.56-0.80)) and elderly (SIRR: 0.30 (0.25-0.35)), (figure 3).

*Incidence of verified hypothyroidism and its subtypes*

No significant change in the overall SIR of verified hypothyroidism was evident from the years 1997-00 (29.4/100.000/year) to 2014-16 (30.3; SIRR: 1.03 (0.87-1.22)), (figure 4). The SIR of spontaneous presumably autoimmune hypothyroidism decreased non-significantly from 23.3 to 21.6 (SIRR: 0.93 (0.77-1.12)). The SIR of post partum hypothyroidism increased from 1.8 to 3.3 (SIRR: 1.83 (0.97-3.44)), hypothyroidism due to iatrogenic causes from 3.1 to 4.8 (SIRR: 1.58 (1.00-2.50)), while hypothyroidism due to other causes (SAT, congenital, sarcoidosis etc.) experienced a non-significant decline from 1.3 to 0.6 (SIRR: 0.44 (0.17-1.16)). The SIR of hypothyroidism did not change significantly among either men or women in the present study; SIR for men from 12.6 to 16.9 (SIRR: 1.34 (0.96-1.86)) and among women from 45.8 to 43.4 (SIRR: 0.95 (0.78-1.15)).

The SIR of hypothyroidism behaved differently across the three aforementioned age groups. A significant increase in SIR was evident among the young (20-39 y) from 14.7 to 26.5 (SIRR: 1.81 (1.20-2.72)), while a non-significant increase was present among the middle-aged from 33.0 to 43.8 (SIRR: 1.33 (1.00-1.77)), (figure 3). However, significant decrease in SIR was evident among the elderly (60+ y) from 76.5 to 48.1 (SIRR: 0.63 (0.49-0.80)), thus preventing an increase in the overall SIR of hypothyroidism for the whole population.

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## Discussion

### *Principal findings*

In Denmark, the overall SIR of overt thyrotoxicosis decreased 50% after 14-16 years of mandatory IF, while the overall SIR of overt hypothyroidism remained constant. This remarkable reduction in thyrotoxicosis incidence was primarily due to lower incidence of MNTG, STA and secondarily a smaller reduction in the GD incidence.

### *Comparison with other studies*

Our finding of a lower incidence of thyrotoxicosis many years after IF is in accordance with several other studies[23–25]. After increasing the salt iodization in Switzerland from 7.5 to 15 ppm in 1980, decreases in incidence rates of MNTG and GD were observed with strong similarities to those observed in the present study[23]. The overall incidence rate of thyrotoxicosis was reduced by 56% in 1988-89 compared to 50 % in the present study. The incidences of MNTG and GD were reduced by 73% and 33% respectively compared to 82% and 33% in the present study. The study from Switzerland however, differs from the current study in its design, as only patients referred to one specific hospital were included. Furthermore, it differs in the preexisting ID level of the study population (changed from mild ID to recommended iodine intake in Switzerland while our cohort population changed from moderate to mild ID).

Similarly to Switzerland the salt iodization in Austria was doubled from 7.5 to 15 ppm in 1990. Recording the incidence rate of thyrotoxicosis from 14 departments of nuclear medicine from 1987-1995 revealed an initial peak and a subsequent decline in incidence rates of both GD and thyroid autonomy[24]. This study had only five years of follow-up after the increase in salt iodization, which may explain why the incidence at the end of the study did not reach below baseline level.

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In Slovenia salt iodization was increased from 10 to 25 ppm of potassium iodide in 1999. The incidence rate of GD, thyroid autonomy and Hashimoto's thyroiditis were determined by referrals to the Thyroid Department at the University Medical Centre Ljubljana[25]. From 1999 to 2009 the incidence rate of thyrotoxicosis due to thyroid autonomy (MNTG and STA) decreased by 27%, while no difference to baseline level was observed for GD. The incidence rate of Hashimoto's thyroiditis increased markedly during the study period to a level 127% above baseline in 2009. This discrepancy with the findings of the current study likely results from the fact that both overt and subclinical hypothyroidism were compiled in the Slovenian study.

The Pescopagano-study in Italy examined the prevalence of nodular thyrotoxicosis (MNTG and STA), GD and hypothyroidism in an iodine deficient rural community in Northern Italy in 1995 and again in 2010 after voluntary iodization of salt at a national level was instituted at a level of 30 ppm in 2005[26]. Neither the prevalence of nodular thyrotoxicosis nor GD changed significantly. The prevalence of Hashimoto's thyroiditis increased significantly from 2.8% in 1995 to 5.0% in 2010. The diagnosis was based on compound criteria of thyroid antibodies (Abs), hypoechoic pattern on ultrasound and TFTs suggesting thyroid failure. Thus, many of the included patients were euthyroid or subclinically hypothyroid.

As a part of the DanThyr studies, two cross-sectional studies and a follow-up study of the initial cross-sectional study were performed before and after introduction of IF in Denmark (1st: 1997-98, 2nd: 2004-05 and follow-up to the first study: 2008-10). Ultrasonographic examination of the participants in the baseline cross-sectional study in 1997-98 and at follow-up in 2008-10 showed a lower frequency of both multiple and solitary thyroid nodules during follow-up when participants of similar age at the time of examination were compared. Thus, the diminished development of thyroid nodules among participants of the same age group after introduction of IF and the disappearance of existing nodules may explain the decreased development of MNTG and STA in the present study. This would be in accordance with the current conception of how autonomous thyroid nodules

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develop under conditions of iodine deficiency[27]. It has been suggested that iodine deficiency may cause nodular transformation of the thyroid gland through the following sequence of events: TSH induced hyperplasia and increased functional activity may cause increased mutagenesis through $H_2O_2$ and reactive oxygen species (ROS) formation, and thus allow for gain of function mutations in genes involved with thyrocyte growth leading to emergence of autonomous thyrocyte clones[27].

Data from national registers in Denmark confirm many of the findings of the present study. A 23% decrease in the use of anti-thyroid medication below pre-fortification level on a national scale was observed between 1997 and 2014[28]. Unsurprisingly, radioiodine treatment was much more frequent in Denmark before and during the time of IF initiation than during the present study period (47.7/100,000/year in 1997 vs 33.1 in 2015)[28]. The substantial reduction in MNTG and STA development seems the likely explanation for this decrease in frequency of radioiodine treatment.

A significant increase in the prevalence of thyroid peroxidase antibodies (TPO-Abs) and thyroglobulin antibodies (Tg-Abs) was evident in the Danish cross-sectional studies from 1997-98 to 2004-05 (TPO-Ab: 14.3 vs 23.8%; Tg-Ab: 13.7 vs 19.9%; P<0.001)[29]. From the latest study we have a clear indication of the association between the level of TPO-Ab and TSH above the reference range[29,30]. The increase in prevalence of TPO-Ab positivity was most pronounced in the younger age groups and least among the elderly[29], which corresponds well with the findings of the present study where an increased incidence rate of hypothyroidism was observed only among the young.  This may also explain the borderline increase in post partum hypothyroidism observed in the present study.

In the DanThyr cross-sectional studies, the frequency of thyroid autoantibodies was negatively associated with smoking, which might explain some of the increased TPO-Ab positivity discovered after initiation of IF, as smoking has become significantly less frequent during the last two decades in Denmark[31].

Similarly, smoking might be an important factor in explaining the decreased incidence of GD

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observed in the present study as smoking is positively associated with the onset and severity of GD[32].

The number of new patients with TFT results compatible with overt hypothyroidism (TSH>5.0 and total $T_4$<60) increased 50% between 1997-98 and 2014-16 in the cohort area utilized in the present study[12]. However, when patients with spontaneous normalization of thyroid function (not requiring treatment) and no signs or history of a condition known to cause transitory thyroid dysfunction (e.g. SAT, PPTD and iatrogenic causes) were excluded from the analysis, this increase in incidence rate of overt hypothyroidism disappeared entirely. Thus, the cause of the previously observed increased incidence rate was mild, transitory cases with no need for treatment.

*Strengths and limitations*

The present study utilizes a well-established surveillance program and includes a period with no mandatory iodization of salt (4 years), followed by the currently longest follow-up study period of mandatory IF (14 years). The study also deals with 13 different nosological entities of overt thyrotoxicosis and 10 nosological entities of hypothyroidism. Furthermore, the present study includes all possible new cases of overt thyroid dysfunction identified by general practitioners, hospital departments and specialists with private practice, thus avoiding the referral bias often seen among studies exclusively utilizing data from the secondary healthcare sector[23–25]. We used identical algorithms and criteria (1997-00 vs. 2014-16) for identification, verification and subtype classification.

From 1997-2014 the incident use of thyroid hormone therapy almost doubled on a national scale[28]. This could seem contrary to our results though an increase in treatment of subclinical hypothyroidism seems the more likely explanation. Evidence exists to suggest a lower s-TSH threshold for initiating L-$T_4$ treatment among hypothyroid patients in Copenhagen between 2001 and 2015[33]. The median s-TSH upon initiation of L-$T_4$ treatment was 10 mU/l in 2001 and 6.8 in

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2015[33]. Treating subclinical cases of hypothyroidism could ensure that patients never become overtly hypothyroid, thus remaining undetected by our surveillance program.

It seems highly probable that the diagnostic activity for thyroid dysfunction have increased since the initiation of IF in Denmark. This could however, lead to an underestimation of the substantial reduction in SIR of overt verified thyrotoxicosis and the absent increase in SIR of overt verified hypothyroidism. In Copenhagen the annual number of s-TSH measurement increased 164% from 2001 to 2015[33].

*Perspectives and clinical implications*

A small increase in daily iodine intake (<50 µg) among a population with moderate iodine deficiency did not increase the incidence rate of sustained verified overt hypothyroidism, but markedly decreased the incidence rate of overt thyrotoxicosis with 50 %. Thus, a cautious iodization of salt will manage to substantially reduce the burden of overt thyrotoxicosis among an iodine deficient population without increasing the incidence of overt hypothyroidism (when mild temporary cases with spontaneous normalization of TFTs are excluded). The incidence rates of MNTG and STA in particular should be expected to substantially diminish after introduction of IF while the effect on GD occurrence remains less obvious. Furthermore, an altered age distribution among both overt thyrotoxicosis and hypothyroidism should be expected, with more cases among the young relatively to the elderly.

*Conclusion*

Cautious iodine fortification causes a substantial reduction in the incidence rate of overt thyrotoxicosis (MNTG and STA especially), without increasing the overall incidence of sustained overt hypothyroidism. Development of overt thyroid dysfunction after introduction of IF differs significantly among age groups.

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**Data Availability Statement**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions

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**Legends**

Figure 1:

Flowchart showing the process of verification for cases of overt thyroid dysfunction. Cases identified by the diagnostic algorithms within the cohort area who have not been registered with overt thyroid dysfunction prior by either the patients current general practitioner or by the Register Database constitute the pool of cases for further evaluation. Cases were first evaluated with respect to normalization of thyroid function tests, and then according to whether normalization was the result of treatment or a case of spontaneous normalization. Cases of spontaneous normalization were verified as true hypothyroid or thyrotoxic patients if their medical history suggested a known condition of transient thyroid dysfunction (e.g. subacute thyroiditis, post partum thyroid dysfunction or one of several iatrogenic causes). All verified cases were further scrutinized to determine their nosological subtype.

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Figure 2:

Standardized incidence rates of overt thyrotoxicosis and nosological subtypes per 100,000 per year between 1997-00 (pre-iodine fortification period) and 2014-16 (after iodization of salt). Grey columns represent data from 1997-00 and white columns data from 2014-16. Stars indicate significant change from baseline value (1997-00).

Figure 3:

Relative change in standardized incidence rate of overt thyrotoxicosis and hypothyroidism between 1997-00 and 2014-16 among three age groups (20-39, 40-59 and 60+ years). Black arrows represent overt thyrotoxicosis and grey arrows represent overt hypothyroidism. Stars indicate significant change from baseline value (1997-00).

Figure 4:

Standardized incidence rates of overt hypothyroidism and nosological subtypes per 100,000 per year between 1997-00 (pre-iodine fortification period) and 2014-16 (after iodization of salt). Grey columns represent data from 1997-00 and white columns data from 2014-16.

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**Appendix**

*Exclusion criteria for potential new cases of overt thyroid dysfunction*

Patients were excluded from the group of verified cases of overt thyroid dysfunction if any of the following were present:

i) Spontaneous normalization without treatment with no signs or history suggesting at transitory thyrotoxic or hypothyroid condition (n=201). ii) Patients had previously suffered from overt thyroid dysfunction (n=9). iii) Patients were receiving levothyroxine or anti-thyroid medication at the time of diagnosis (n=115).

iv) Presence of gestational transient thyrotoxicosis (n=22). v) An elevated TBG present due to either pregnancy or estrogen therapy (n=11). vi) No confirmative blood test result in a patient who survived beyond 2 months (n=6). vii) Amiodarone treatment where the thyrotoxic patients did not have an elevated total $T_3$ (n=19) (elevated total $T_4$ should be expected in a patient with subclinical thyrotoxicosis receiving amiodarone). viii) Treatment was initiated after the patient had shifted from overt to subclinical thyroid dysfunction (n=14). ix) Other reasons (n=13), these included cases with pituitary disease, children having different reference intervals of total $T_4$ and erroneously being included as cases of overt thyrotoxicosis, cases where overt thyroid dysfunction occurred several years after spontaneous normalization, one case where the thyroid gland was surgically removed before any confirmatory TFT could be performed.

Thus, the total number of patients excluded was 410 out of 1069. Patients who had no confirmatory blood test preformed and died within 2 months were considered true cases whether or not a trigger of transient thyroid dysfunction was present or treatment was initiated.

*Patients with possible new overt thyroid dysfunction invited for examination in our center*

A selected number of patients were furthermore contacted by our research group shortly after their diagnostic blood sample and invited for a thorough investigation at our research center including: several comprehensive questionnaires about their medical history, blood tests for TRAb, anti-TPO

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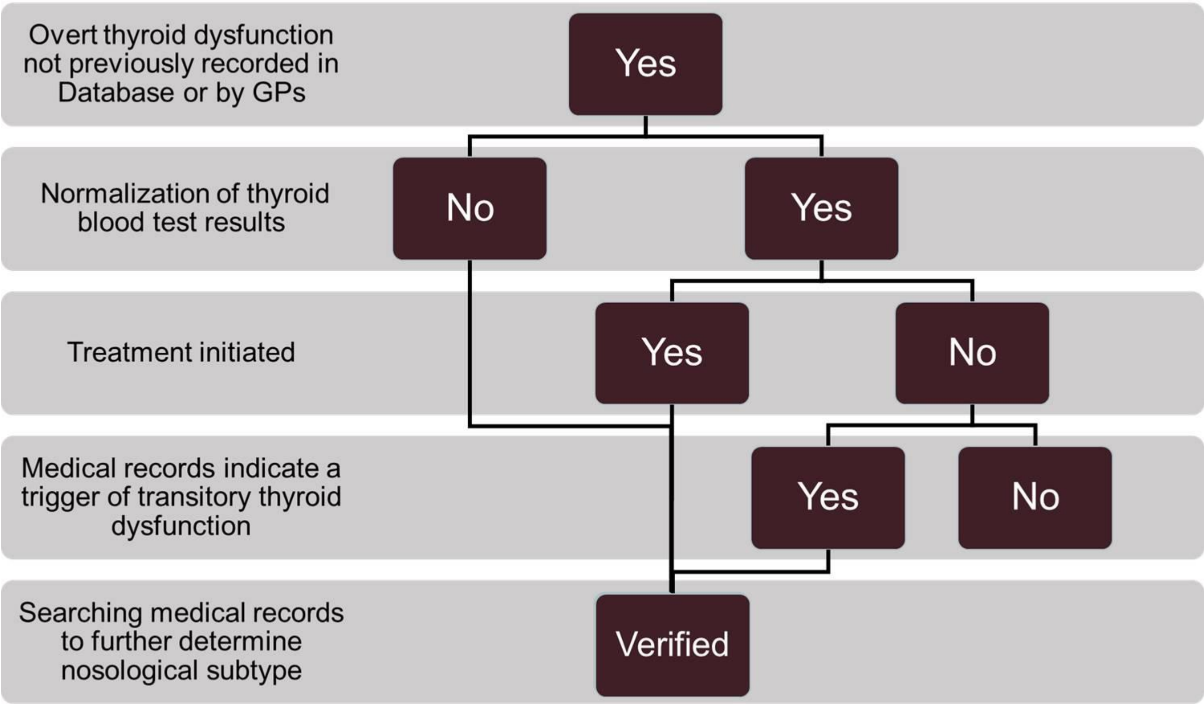
Ab, anti-Tg Ab, TBG and thyroglobulin, ultrasonographic examination of the thyroid gland and thyroid scintigraphy. Of the 1069 potential new cases in 2014-16, we examined 511 patients at our research center (48%). Similarly, 38% of all new cases of overt thyroid dysfunction were examined in 1997-00. Consent has been obtained from each patient or subject after full explanation of the purpose and nature of all procedures used.

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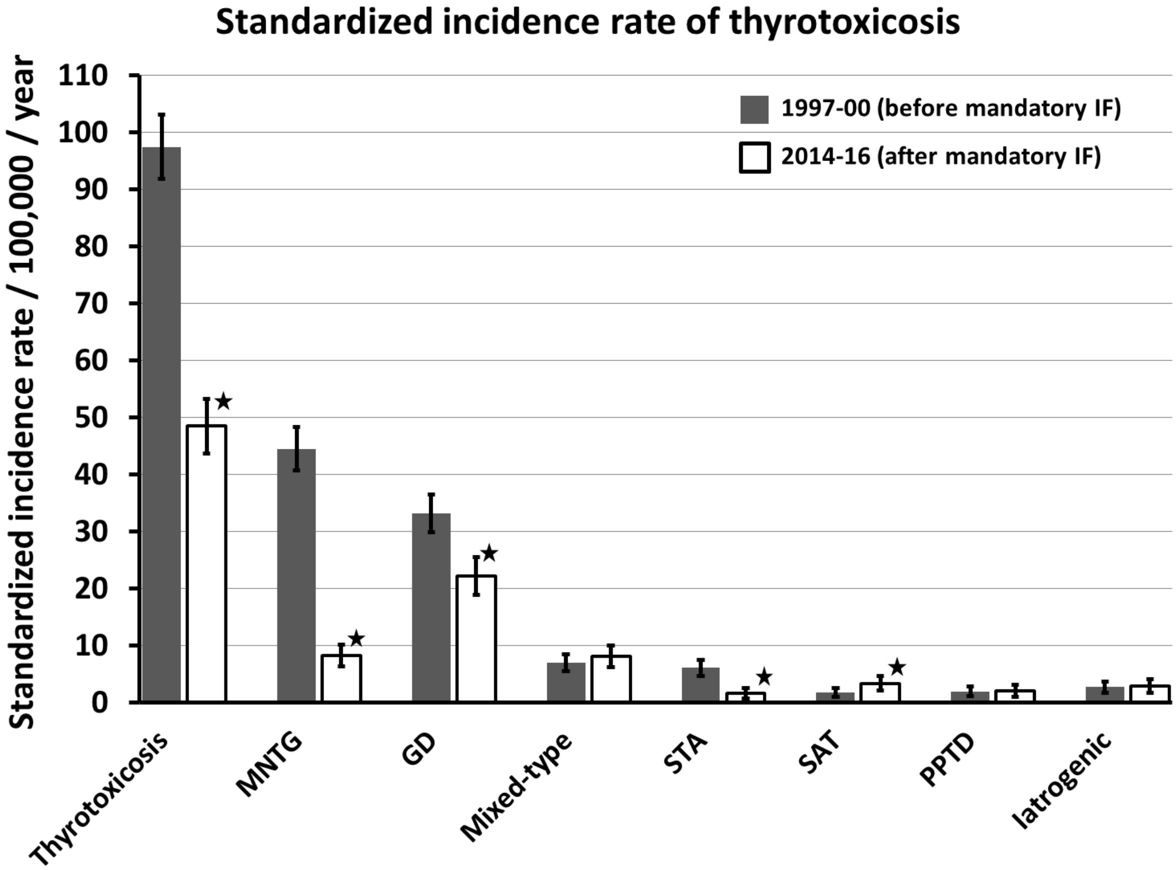


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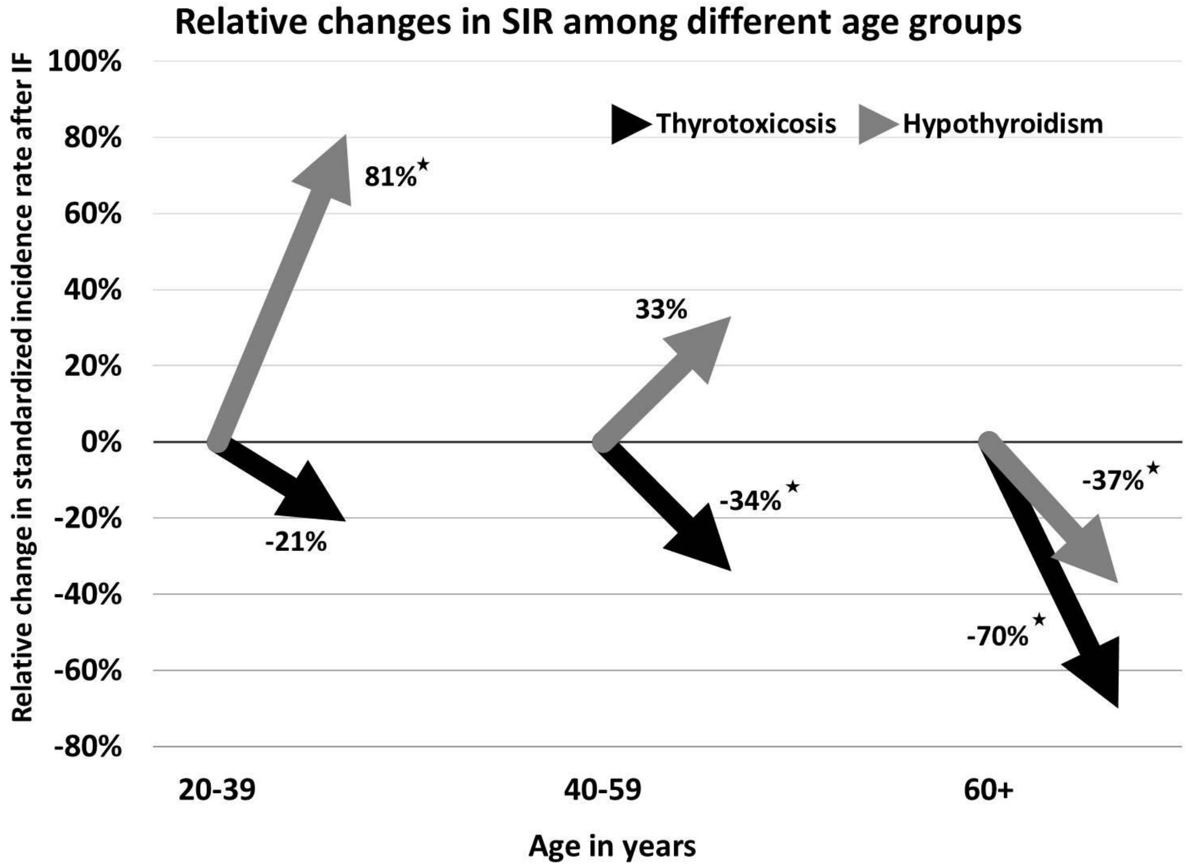


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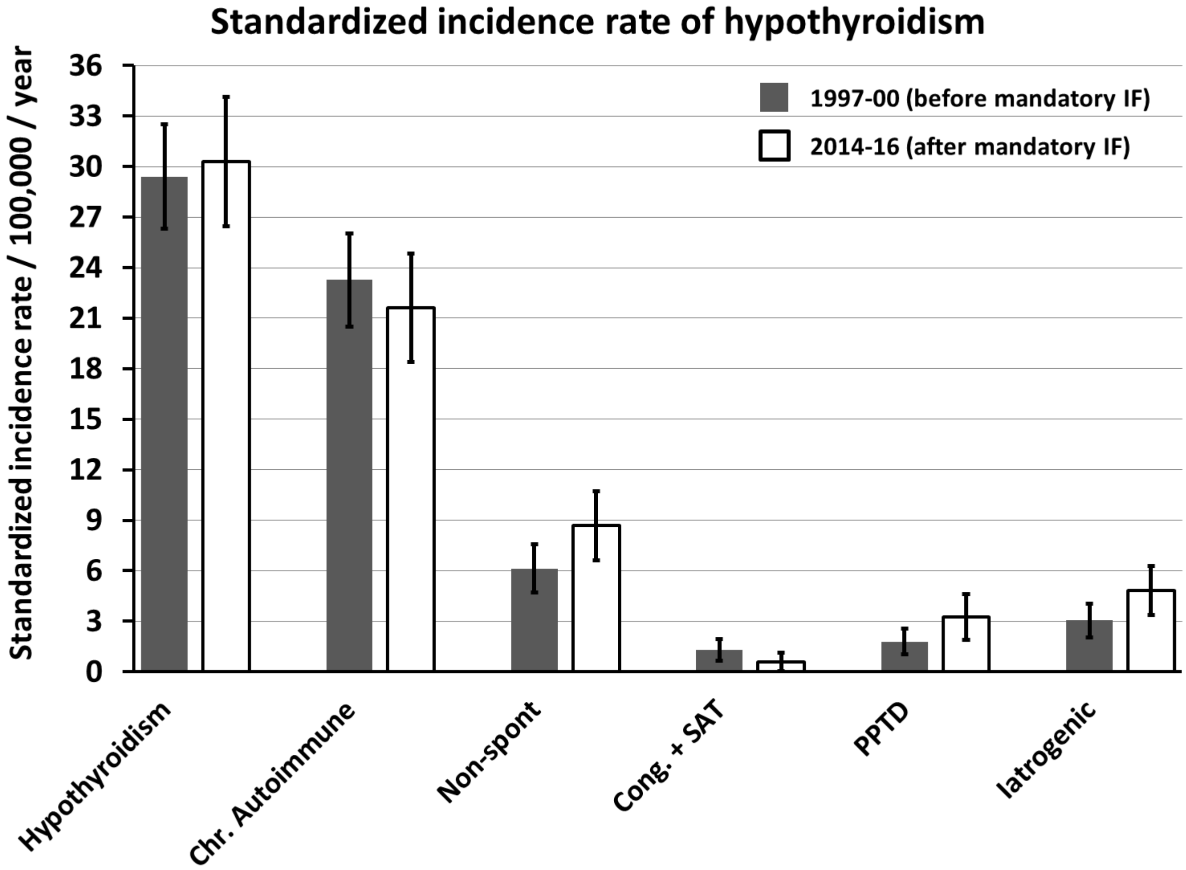


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