Association of Iodine Fortification with Incident Use of Antithyroid Medication—A Danish Nationwide Study

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Context: Iodine-induced hyperthyroidism has been reported in the early phases of almost all iodine fortification programs, depending on prior iodine intake in the population, the amount of fortification, and the rate of change.

Objective: The aim of the study was to monitor the effect of the Danish iodine fortification program on incidence of hyperthyroidism as measured by the incident use of antithyroid medication.

Design: We conducted a register study. Using the unique identification number of all Danes, we linked data from the Register of Medicinal Product Statistics and the Civil Registration register on an individual level. All dispensing of antithyroid medication from 1995 to 2007 was studied. The place of residency was used to divide patients into mildly and moderately iodine-deficient groups.

Main Outcome Measure: We measured the incident use of antithyroid medication.

Results: In the region with moderate iodine deficiency, the number of incident users of antithyroid medication increased 46% in the first 4 yr of iodine fortification. The use increased the most among the youngest age group (younger than 40 yr) and the oldest age group (older than 75 yr). In the mildly iodine-deficient region, the number of incident users increased only 18%, and only in the youngest age groups (below 40 and 40–59 yr). After 4 yr of fortification, the incidence rates started to fall and reached baseline, for most groups, 6 yr after onset of fortification.

Conclusions: This study shows that iodine fortification induced a temporary, modest increase in the incidence of hyperthyroidism as measured by use of antithyroid medication. A new steady state has not yet evolved. **(*J Clin Endocrinol Metab* 94: 2400–2405, 2009)**

Iodine fortification programs cover billions of people in the world, including Denmark. Before fortification, Denmark was an area of mild to moderate iodine deficiency (1). No iodized salt could be purchased because legislation requested a special permission to sell fortified food in Denmark, and no license to sell iodized salt or other iodized products had been given. The Danish iodine fortification program was initiated as a voluntary program in June 1998 (adding 8 ppm KI to all salt) and altered to a mandatory fortification July 2000 (adding 13 ppm KI to household salt and salt used for commercial production of bread). The primary aims of iodine fortification in Denmark were: 1) to increase the iodine intake of the average Dane by 50 μg/d; 2) to lower the incidence of goiter; and 3) to lower the incidence of hyperthyroidism. Studies have demonstrated the program to be successful with respect to the first two aims (2, 3).

Transient iodine-induced hyperthyroidism is the most common complication of iodine fortification, and it has been reported in almost all iodine fortification programs in their early phases (4). An increase in hypothyroidism has also been reported after iodine fortification, probably as a result of iodine-induced autoimmunity (5, 6). The benefit of iodine fortification is beyond question in areas of severe iodine deficiency. The benefit of iodine fortification programs in areas of mild or moderate iodine defi-

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ciency has to be weighed against the risks, which stresses the importance to monitor its effect on the population.

The aim of this study was to analyze the nationwide effect of the Danish iodine fortification program on the incidence of hyperthyroidism by monitoring the incident use of antithyroid medication. The study is part of The Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr) (7), which is the official monitoring of the Danish iodine fortification program. A detailed description of the study has been published previously (8).

Subjects and Methods

Subjects

The study is a nationwide register study covering all inhabitants in Denmark in the period January 1, 1995, to December 31, 2007. Every person in Denmark is assigned a unique, permanent 10-digit identification number at birth or immigration. This personal registration number is used in all contacts with public services including hospitals and prescription dispensing. The identification number facilitates the use of registers and makes individual longitudinal follow-up possible. The Danish Registry of Medicinal Product Statistics provides information about all prescription drugs dispensed from Danish pharmacies since 1995. In Denmark the national health security system covers all inhabitants and partially reimburses drug expenses. Because of this, pharmacies are required by law to register all prescriptions dispensed at an individual level, which makes the registry highly valid. Coding of medicinal products is according to the Anatomic Therapeutical Chemical (ATC) classification system. The register includes information on the identification number of the patient, date of dispensing, ATC code, strength, and quantity dispensed (in defined daily doses). Both antithyroid medication and thyroid hormone are sold solely as prescription drugs in Denmark.

Identification of incident users

The study included all patients with a dispensing of antithyroid medication (H03B) in the period from 1995 to 2007. The year of the date of the first dispensing was used as the year in which an individual was defined an "incident user," given that the individual had not dispensed a prescription of thyroid medication [thyroid hormone (H03A) or antithyroid medication (H03B)] in the 2 preceding years. Incident users were thus defined only from 1997. Through the civil registration system, we got information about date of birth, gender, and place of residence. Place of residence is updated for every Dane on January 1 each year. Data from the different registers were compiled at the National Bureau of Statistics.

Iodine status

Denmark was divided into two regions, Eastern and Western Denmark, through the Great Belt (Fig. 1). The iodine intake is lower in the western part of the country, compared with the eastern part, primarily caused by the difference in levels of iodine in ground water (9). The median urinary iodine excretion in the city of Aalborg in the western part of the country has been shown to be 45 μg/liter, and in Copenhagen in the eastern part, 61 μg/liter before fortification (10); thus the regions were considered respectively moderately and mildly iodine deficient according to criteria outlined by the World Health Organization (11). Region of residence was used as a proxy for iodine status.

FIG. 1. Map of Denmark showing the division into Western and Eastern regions with moderate and mild iodine deficiency, respectively, before fortification.

Statistics

Data were processed using SAS 9.2 statistical software (SAS Institute Inc., Cary, NC). Incidence rates were calculated for each sex and age group (0–39, 40–59, 60–74, 75+ yr) in the two regions. To calculate the rates only within the population at risk, we subtracted individuals already using antithyroid medication (prevalent users) from the study population in all age groups, in both regions, and sexes, in a period of 2 yr before the year under investigation. To adjust for changes in the mean age within age groups, over time, incidence rates were standardized to the age composition of the Danish population in year 2000.

To calculate relative changes we used Poisson regression to model the association between the outcome (being an incident user) and the explanatory variables (calendar year and age). To account for overdispersion in the data, we estimated the scale parameter by the deviance. All analyses were stratified by sex, age group (0–39, 40–59, 60–74, 75+ yr), and region of residence. Within age groups, age was used as a continuous variable. Parameter estimates were used to obtain rate ratios and their 95% confidence intervals. Linearity of the age effect was tested, and when needed we squared the number, or raised it to the third power. The models were tested for interactions and found valid unless otherwise indicated. Patients with missing information on place of residence in the year under investigation or 5 yr earlier were censored (n = 279; 0.50% of all incident users of antithyroid medication in this time period).

Ethics

The Danish Data Protection Agency approved the present study (no. 2003-53-0865). Each personal identification number was substituted by a unique case number when data were made available to the researchers, so that individuals could not be identified.

Results

At baseline (1997), the number of incident users of antithyroid medication was 4,281, and the Danish population was 5,275,121. Female users constituted 83% of the incident users (Table 1). Of all incident users, 63% were living in the western part of Denmark with moderate iodine deficiency, giving an incidence rate of 94.4 per 100,000 person years in this area, whereas the incidence rate in the mildly iodine-deficient eastern part was 68.1 per 100,000 person years. Incidence rates varied considerably between age groups and between sexes, with the higher rates among elderly women. Within each age group, women living in the western, more iodine-deficient part of the country, had the higher rate (Fig. 2).

From the introduction of iodine fortification in 1998 to 2001, the incidence rates increased, with 46% in the moderately deficient region, compared with an increase of only 18% in the mildly deficient region (Table 1). After 2001, the incidence rate declined in the moderately iodine-deficient region to reach baseline in 2004 for women between 40 and 74 yr of age, and in 2006 for women in the oldest age group. Incidence rates showed further decline in 2006 and 2007, still not showing a tendency for a new steady state (Fig. 2). For men, the pattern was roughly the same as for women, the main difference being that the decline in

TABLE 1. Characteristics of the incident users of antithyroid medication in Denmark from 1997–2007

	Before iodization	Initiation of voluntary iodization		Initiation of mandatory iodization		Early years of iodization			Late years of iodization		
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
No. of incident users per year (% of all inhabitants)	4281 (0.81)	4660 (0.88)	4989 (0.94)	5470 (1.03)	5966 (1.12)	5771 (1.08)	5529 (1.03)	5048 (0.94)	4764 (0.88)	4543 (0.84)	4350 (0.80)
Sex											
Women	3548 (82.9)	3877 (83.2)	4094 (82.1)	4550 (83.2)	4841 (81.1)	4695 (81.4)	4430 (80.1)	4017 (79.6)	3799 (79.7)	3643 (80.2)	3394 (78.0)
Men	733 (17.1)	783 (16.8)	895 (17.9)	920 (16.8)	1125 (18.9)	1076 (18.6)	1099 (19.9)	1031 (20.4)	965 (20.3)	900 (19.8)	956 (22.0)
Age group											
0–39 yr	731 (17.1)	766 (16.4)	859 (17.2)	965 (17.6)	1029 (17.2)	1040 (18.0)	1100 (19.9)	947 (18.8)	891 (18.7)	872 (19.2)	763 (17.5)
40–59 yr	1342 (31.3)	1416 (30.4)	1537 (30.8)	1710 (31.3)	1848 (31.0)	1915 (33.2)	1789 (32.4)	1615 (32.0)	1567 (32.9)	1519 (33.4)	1408 (32.4)
60–74 yr	1233 (28.8)	1405 (30.2)	1407 (28.2)	1481 (27.1)	1653 (27.7)	1549 (26.8)	1435 (26.0)	1424 (28.2)	1255 (26.3)	1169 (25.7)	1178 (27.1)
75+ yr	975 (22.8)	1073 (23.0)	1186 (23.8)	1314 (24.0)	1436 (24.1)	1267 (22.0)	1205 (21.8)	1062 (21.0)	1051 (22.1)	983 (21.6)	1001 (23.0)
Region of residence											
West Denmark	2696 (63.0)	2901 (62.3)	3193 (64.0)	3580 (65.4)	4037 (67.7)	3830 (66.4)	3575 (64.7)	3228 (63.9)	2997 (62.9)	2799 (61.6)	2687 (61.8)
East Denmark	1585 (37.0)	1759 (37.7)	1796 (36.0)	1890 (34.6)	1929 (32.3)	1941 (33.6)	1954 (35.3)	1820 (36.1)	1767 (37.1)	1744 (38.4)	1663 (38.2)
Incidence rate[a]											
West Denmark	94.4	101.0	110.0	122.6	137.4	129.2	119.9	106.9	98.6	91.5	86.6
East Denmark	68.1	75.0	75.8	79.2	80.3	80.2	80.5	74.4	71.7	70.1	66.4

Data are expressed as number (%), unless specified.

[a] Per 100,000 person years. Adjusted for prevalent users 2 yr before the year under investigation.

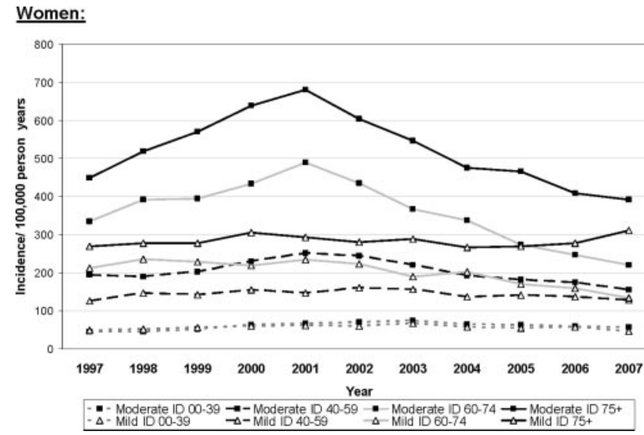

FIG. 2. The incidence rates of users of antithyroid medication for women in four age groups in Western Denmark with moderate iodine deficiency (ID) and Eastern Denmark with mild iodine deficiency. The rates are age-adjusted to the composition of the population in Denmark in year 2000. Person years from prevalent users are subtracted. ■, Moderate iodine deficiency; △, mild iodine deficiency. Incidence rates for each age group are marked with the same tone of grey and type of curve.

incidence rates did not reach baseline values for all but one group (age group 60–74 yr) (Fig. 3).

The regional incidence rates cover big differences between age groups and sexes as illustrated in Figs. 4 and 5. Among women, in the western region, the highest incidence rate relative to the baseline was seen in the oldest and the youngest age groups with increases of 55 and 60%, respectively. In the eastern region, on the other hand, the relative incidence rate declined in the oldest age group in this period, whereas it increased markedly in the youngest age group (41%). Among men, the trends are roughly the same, although the relative changes are even steeper: an increase of 110% in the oldest age group and 51% in the youngest age group in the previously moderately iodine-deficient area, and an increase of 107% in the youngest age group in the previously mildly iodine-deficient area and only nonsignificant changes among the oldest age group.

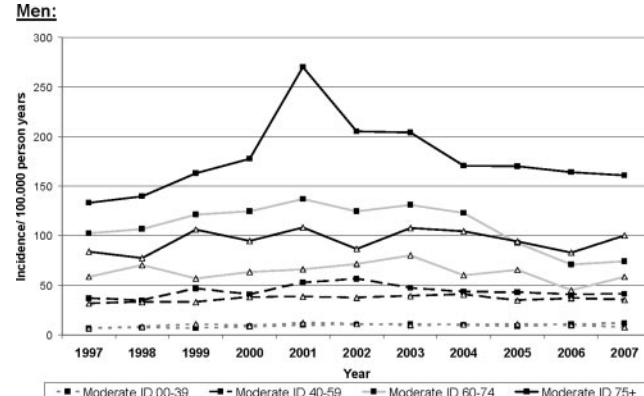

FIG. 3. The incidence rates of users of antithyroid medication for men in four age groups in Western Denmark with moderate iodine deficiency (ID) and Eastern Denmark with mild iodine deficiency. The rates are age-adjusted to the composition of the population in Denmark in year 2000. Person years from prevalent users are subtracted. ■, Moderate iodine deficiency; △, mild iodine deficiency. Incidence rates for each age group are marked with the same tone of grey and type of curve.

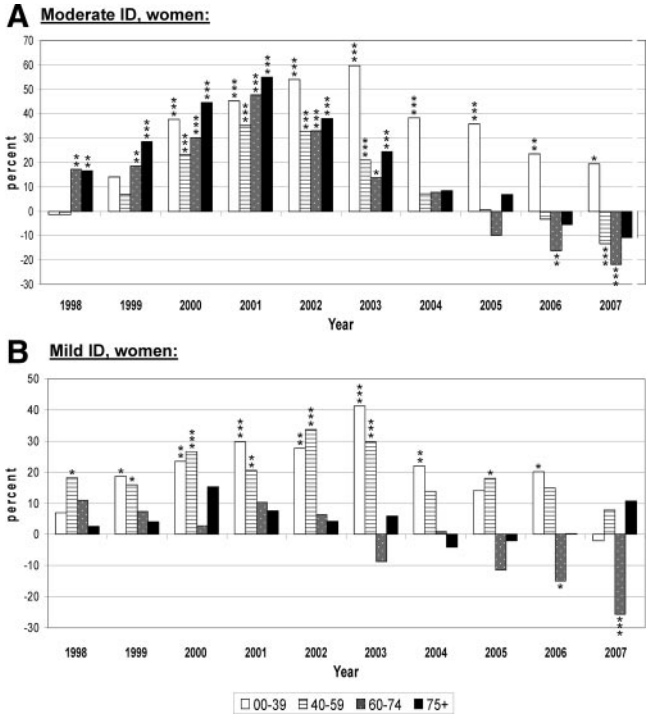

FIG. 4. The relative changes in incidence rates of female users of antithyroid medication (percentage change in incidence rate compared with incidence rate at baseline, 1997) in Western Denmark with moderate iodine deficiency (A) and Eastern Denmark with mild iodine deficiency (B). *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. ID, Iodine deficiency.

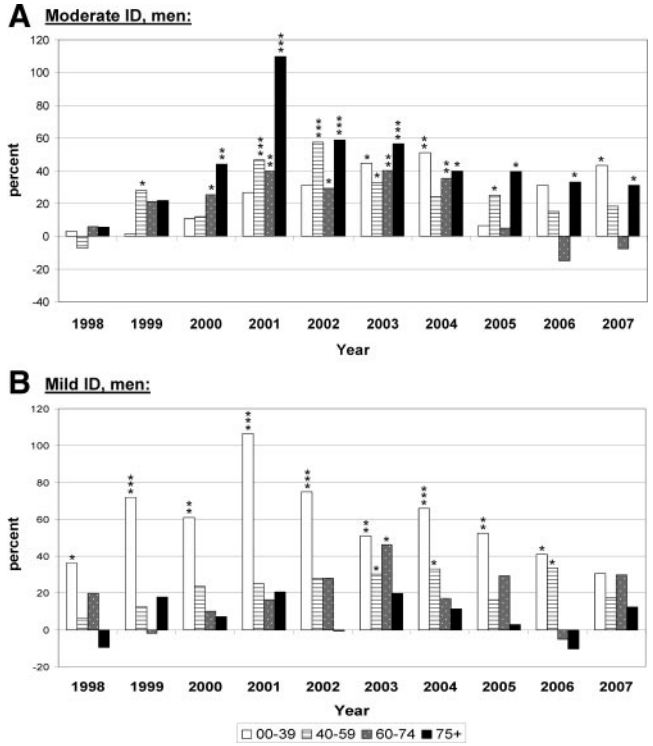

FIG. 5. The relative changes in incidence rates of male users of antithyroid medication (percentage change in incidence rate compared with incidence rate at baseline, 1997) in Western Denmark with moderate iodine deficiency (A) and Eastern Denmark with mild iodine deficiency (B). Interaction was found between the age- and year-effect among men resident in Eastern Denmark, in the age group 60 to 74 yr of age. Because this was the only situation of this interaction, its significance was neglected. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$. ID, Iodine deficiency.

Discussion

This register study shows that after a temporary increase, the number of incident users of antithyroid medication is now lower than before iodine fortification. We have no knowledge of similar prospective studies of the use of medication to monitor the effects of iodine fortification on thyroid diseases.

Although the Danish iodine fortification program was carefully and cautiously planned, aiming at a median increase in iodine intake of only 50 μg iodine/day, the incidence rate of hyperthyroidism increased, especially in the area that was more iodine deficient before fortification. This transient increase lasted about 6 yr. In the previously moderate iodine-deficient area, the temporary increase was seen among the oldest people, probably because of a higher prevalence of autonomous thyroid nodules in enlarged thyroid glands (12). This effect has been reported from many iodine supplementation programs all over the world (13–16). However, an even larger relative change was seen among the youngest age group in the previously moderately iodine-deficient area. In the area of previous mild iodine deficiency, the rate ratio increased markedly in the youngest age group, whereas it actually decreased in the oldest age group. These findings suggest that there might be different mechanisms for triggering hyperthyroidism in young people compared with older people when increasing the intake of iodine. This finding supports the findings of an earlier study of the DanThyr group, using diagnostic laboratory registers of new cases of overt hyper- and hypothyroidism, in two regions in Denmark (17) where it was found that the increase in incidence of hyperthyroidism relative to baseline values predominantly occurred in young people (20–39 yr of age) (18). In this study in the more iodine-deficient area, we observed a transient increase among the oldest people as expected because of a higher percentage of thyroid enlargement (19). In the less iodine-deficient area, with a lower percentage of enlarged thyroid glands, no significant increase was seen among the oldest. A high iodine intake has been shown to be associated with a high incidence of Graves' disease in earlier studies, especially among young people (20, 21). This may be the mechanism by which the increased iodine intake induced hyperthyroidism among the youngest age group as seen in this study.

As shown in Fig. 2, the rise in incidence rates in the two oldest age groups started in 1998. Given that only table salt was actually fortified after the voluntary fortification and that the market share of iodized salt was low, this increase was unexpected. Assuming an average intake of table salt of 2.5 g/d (range, 1–4 g/d) and 60% of table salt fortified with iodine (information from Danish salt suppliers who cover almost 100% of the market) at a level of 8 μg/g, the average intake of iodine from fortification would be 12 μg/d (range, 7.2–19.2 μg/d). However, because the market share of iodized salt was low, those who actually bought the iodized salt would have had a higher intake than the estimated value (20 μg/d), whereas those who did not buy iodized salt would get no extra iodine at all. This could have affected an early response among those who got the extra iodine and a later response among those who only got extra iodine when adding

iodine was made mandatory. Yet, no distinct additional effect in the rate of incident use of antithyroid medication was observed when the program was changed from a voluntary to a mandatory program in 2000 (fully implemented in 2001). It seems that even a slight average increase in iodine intake may trigger iodine-induced hyperthyroidism among susceptible older persons. Among young people, the rates only peaked in 2003, which may reflect that more iodine is needed to provoke hyperthyroidism in the younger age group, or that it takes longer to induce hyperthyroidism by this mechanism. Relative changes in the incidence rates were found in this study to be higher among men than among women, a finding also observed by Hartsock (22) in the United States in the 1920s. Often men are not included in the study population because of the female dominance among patients with thyroid diseases, but it could be speculated that men are even more susceptible to react to increments of iodine intake.

By the definition of an incident user used in this study, we included persons not using thyroid medication for a period of at least 2 yr as incident users. It is known, that an increase of iodine intake of patients in remission after previous medical therapy may induce relapse (23), which could result in an overestimation of the "true" incidence rates in the years following the iodine fortification in this study if the "true" incidence rate is thought of as new patients among persons formerly without thyroid disease.

Other explanations could be a change in treatment pattern, changes in diagnostic activity and other confounders. During the 11 yr covered by this study, there has been a certain focus on thyroid diseases in Denmark, and concern about the effect of the Danish iodine supplementation has been raised. This has resulted in an increase in the number of blood tests made for detection of thyroid dysfunction (18). The higher level of diagnostic activity may explain some of the increases in the incidence rates of hyperthyroidism. Yet, the increase in diagnostic procedures has been steady throughout the years and thus cannot explain the return of the incidence rates to and beyond baseline values or the falling incidence rates for the older age group throughout the period in the mildly iodine-deficient area.

During the time covered by the study, there have been no shifts in the medical indication of the use of antithyroid medication, which could explain the changes. Neither have there been any shifts in favor of or against alternative treatments (surgery or radioactive treatment). The use of radioiodine therapy has followed almost the same pattern as for antithyroid medication: an increase in the usage, reaching maximum in 2001, followed by a decline (24). Surgery rates have remained almost constant during this period. Thus the changes in the use of antithyroid medication, seen over time, do not seem to be the result of changes in preferred treatment method for hyperthyroidism. As in other studies from the DanThyr group, it is surprising to find that even a small difference in iodine intake has influence on the incidence rates of thyroid diseases and on the effect of iodine supplementation on the pattern of iodine-induced thyrotoxicosis, even despite the fact that there are still local differences within regions.

As for other register studies, there are limitations to the data accessible to us. We are not able to get information about possible confounders such as smoking status, intake of nonprescribed dietary supplements, family history of thyroid diseases, etc. However, it appears unlikely that these confounders changed at exactly the same time periods as the introduction of iodine fortification; therefore it is unlikely to explain the changes over time, but this may explain some of the differences between the two regions in a given year. No attempt was made to link information to the use of other drugs, *e.g.* amiodarone; however, the number of patients with drug-induced thyrotoxicosis is thought to be small.

In conclusion, this study shows that iodine fortification induced a temporary, modest increase in the incidence of hyperthyroidism as measured by use of antithyroid medication. A new steady state has not yet evolved.

Acknowledgments

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