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ISBN: 978-0-12-374135-6
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Abstract

Until recently, Denmark was considered free of iodine deficiency disorders. It had been demonstrated that urinary iodine excretion was low, with geographical variation now known to be caused by differences in groundwater iodine content. However, goiter was not a clinical problem in children, and a national survey of more than 350,000 schoolchildren did not support the necessity of an iodine fortification program. When focus turned to other parts of the population, the consequences of iodine deficiency was clear: multinodular goiter with a high occurrence of clinical and subclinical hyperthyroidism was extraordinarily common in the elderly, and pregnant women showed signs of insufficient thyroid hormone production in late pregnancy. A program targeted to increase daily iodine intake by around 50 μg was started by the National Food Agency. The DanThyr monitoring program has shown that the population’s iodine intake has increased much as planned by adding iodine (13 ppm) to table salt and bread salt. Thyroid size and the occurrence of thyroid enlargement have diminished in all age groups. There has been a small increase in the incidence of overt hyperthyroidism, which is expected to be transient. A major concern has been the fear of an increase in the incidence of overt hypothyroidism. Until now, only a moderate increase has been observed in an area with formerly moderate iodine deficiency. National registries of the use of thyroid medication, the use of radioiodine, and surgical therapy for thyroid disorders have shown variations, in accordance with the above-mentioned developments.

Abbreviations

C1 The first population cohort investigated in the DanThyr program.
C1a The C1 cohort investigated from 1997–1998 before iodine fortification of salt
C1b The C1 cohort being reinvestigated in 2008 after iodine fortification of salt
C2 The second population cohort investigated in the DanThyr program 2004–2005.
CI Confidence interval
DanThyr The Danish investigation of iodine intake and thyroid diseases
ID Iodine deficiency
IF Iodine fortification
ns No significant difference by statistical testing
TSH Thyroid-stimulating hormone
WHO World Health Organization

Before the introduction of iodine fortification (IF) of salt, and iodine supplementation of man and domestic animals, most European countries were more or less affected by iodine deficiency (ID) disorders (Kelly and Snedden, 1960). The countries with the most severe manifestations were, in general, early to introduce preventive programs. However, some countries with only mild-to-moderate ID, such as Denmark, have only introduced programs.
more recently. The reason for the delay in recognizing and preventing the problem has primarily been the complex nature of the interaction between iodine intake and the occurrence of disease in a population. The discussions preceding the introduction of IF of salt in Denmark and the results of the monitoring of the fortification program (the Danish investigation of iodine intake and thyroid diseases, DanThyr) illustrate this complexity.

Programs aiming at increasing iodine intake to prevent disease were initiated both in the USA and in Europe (Switzerland) in the 1920s. The international focus on iodine and disease during this period led to the introduction of iodized salt on the Danish retail market (kelp table salt), with an iodine content of 10–20 ppm (microgram iodine per gram salt). Only addition of vitamins and not minerals to food was regulated at this time. No official support to the iodized product was given. In the 1970s at least three table salt products fortified with iodine were available on the Danish market (iodine content 10–40 ppm), but they only covered a few percent of the salt market. In 1974 new legislation required special permission to market food fortified with minerals in Denmark and iodized salt was subsequently withdrawn from the market.

From the late 1920s onward a number of studies on the prevalence of goiter in various areas of Denmark were performed (Dalsgaard-Nielsen, 1933, 1940; Gormsen, 1940; Rosenquist, 1943; Mathiasen, 1962; Olesen, 1966). Results varied and high prevalences were reported in a few areas. For example, Rosenquist (1943) in 1938–1940 investigated 3947 persons including 931 schoolchildren in the Gudenaa valley in Jutland and reported goiter prevalences up to 15% in some areas. However, when Mathiasen (1962) in 1961 investigated 1676 schoolchildren from some of the same areas, considerably lower prevalences were found. Thus, the general and official opinion was that ID had not been found in Denmark. In the comprehensive review of endemic goiter worldwide published by the World Health Organization in 1960, Denmark was among the relatively few countries where endemic goiter had not been described (Kelly and Snedden, 1960).

In the late 1960s new focus came on iodine intake in Denmark. Around 1967 Munkner (1969) organized a nationwide collection of 24 h urine from 4585 high school boys aged 17–20 years. The average urinary iodine excretion was 64 µg/24 h. There were considerable geographical differences with higher values in the east (Sealand 74 µg/24 h, \( n = 2088 \)) than in the west (Jutland 49 µg/24 h, \( n = 2084 \)). These figures were subsequently confirmed in several smaller investigations (Pedersen et al., 1997).

The study led the Danish National Board of Health in 1970 to appoint an expert working group to evaluate whether ID was a health problem in Denmark (Sundhedsstyrelsen, 1975). The group organized a large survey of Danish schoolchildren according to the WHO recommendation. A total of 364395 children were investigated for goiter by their local school physician. Some results of the study are shown in Figure 119.1. It is well-known that clinical evaluation of small goiters is difficult, with low reproducibility of results. This was also found in this study, with very different prevalence of goiter reported by physicians from the same areas. Finally, it was decided by the working group that only goiter of clinical significance was considered to be the clinically important goiter. The age at first year at school was 6–7 years. Data by courtesy of the now late Dr Sigurd Eskjaer Jensen, who was a member of the 1970–1975 expert committee on iodine deficiency in Denmark. Sundhedsstyrelsen, (1975).

**Figure 119.1** Goiter prevalence in the national Danish schoolchildren survey performed in 1972–1973. Clinical examination for goiter was performed by local school doctors. The participation rate was 51% (girls, \( n = 172505 \); boys, \( n = 177596 \)). Goiter was graded according to: 1, palpable but not visible; 2, visible and palpable; 3, neck altered, “thick”; 4, large goiter. The expert group compared results obtained by different investigators in the same areas and concluded that goiter grade 1 was unreliable. Results are shown for grades 2–4 combined. As grade 2 was also found to be of considerable uncertainty, results are also shown for combined grades 3–4, which was considered to be the clinically important goiter. The age at first year at school was 6–7 years. Data by courtesy of the now late Dr Sigurd Eskjaer Jensen, who was a member of the 1970–1975 expert committee on iodine deficiency in Denmark. Sundhedsstyrelsen, (1975).
importance (goiter with change of shape of the neck) was reliable, and this was not common (Figure 119.1). There was some correlation between goiter prevalence and the urinary iodine values published by Munkner (1969), but no pockets of high goiter prevalence were identified, and overall the prevalence of clinically important goiter was well below 5%. The study confirmed the opinion among the experts that goiter in children was not a problem in Denmark. The reports published during this period on the side-effects of the IF program, e.g., with an increase in the incidence of hyperthyroidism in Tasmania (Connolly et al., 1970; Stewart et al., 1971; Vidor et al., 1973) were also taken into account by the group. In 1975 the working group recommended that there should be no iodization program in Denmark (Sundhedsstyrelsen, 1975).

In 1982 an application was received by the National Board of Health for an authorization to place table salt fortified with iodine on the market. As food policies were that vitamins and minerals should not be added to food without documentation of a need for this, no authorization was given. However, it was legal to add iodine (mostly 150 μg) to vitamin-plus-mineral tablets, and such supplements were (and are) taken by a considerable part of the population (Knudsen et al., 2002d).

In the 1980s and early 1990s more and more data accumulated on low-iodine intake in Denmark and on the consequences for health. In particular, it was shown that even if goiter was not a clinical problem in children, it was a major problem in elderly subjects, and this was accompanied by a high incidence of hyperthyroidism caused by multinodular toxic goiter. In a study of subjects 68 years of age living in the commune of Randers in Jutland, 1 out of 8 of the women had either been operated on for goiter (8%) or had a clearly visible and palpable goiter (4%), 10% of the women had subclinical hyperthyroidism with low serum thyroid-stimulating hormone (TSH), and 1 out of 30 had undiagnosed (mostly mild) overt hyperthyroidism as judged from biochemical testing (Laurberg et al., 1998). Elderly women in Sealand also had a high prevalence of goiter (Nyggaard et al., 1993).

Another area of focus was pregnant women and their newborn (Pedersen et al., 1990, 1993; Nøhr et al., 1993, 1994). Women not receiving iodine supplements had a gradual increase in serum TSH during pregnancy (Weeke et al., 1982) that was prevented by iodine supplements (Pedersen et al., 1993).

Therefore, the Danish National Food Agency in 1994 took the initiative to re-evaluate the need for an iodine enrichment program in Denmark (Rasmussen et al., 1996).

**Report on Iodine Deficiency in Denmark**

A working group was established including representatives of the National Food Agency and the National Board of Health, and external experts in the fields of nutrition and toxicology, as well as specialists in thyroid diseases and iodine. The conclusions of the report were:

1. The majority of the Danish population of all ages suffered from mild-to-moderate ID.
2. This resulted in excessive rates of nontoxic and multinodular toxic goiter in adults, with the highest rates in elderly women.
3. Thyroid function was slightly impaired in pregnant women.
4. The benefits of iodine supplementation were expected to clearly outweigh the risks.
5. The optimal level of iodine intake to prevent thyroid disorders in a population may be within a relatively narrow range, with both lower and higher intake levels leading to a higher incidence of disease.
6. Therefore, the iodine-supplementation program should be cautious.
7. A program of monitoring was mandatory. In addition to regular measurement of the iodine content of iodized salt and checking the market share of iodized salt in Denmark, monitoring should include investigations of iodine intake and the occurrence of thyroid diseases in areas of both mild and moderate ID before and after fortification.

The report was published in detail in Danish (Rasmussen et al., 1995), with a short version in English (Rasmussen et al., 1996).

The monitoring program of iodine intake and thyroid diseases (DanThyr) was designed to secure optimal iodine nutrition of the Danish population, and also to improve knowledge on how to evaluate the iodine status of a population. Moreover, the design would give information on the epidemiology of thyroid disorders in areas with different levels of iodine intake, and the effects of an increase in iodine intake. An additional aim was to clarify the role of various environmental factors for the development of thyroid disease in the population, and in particular to study how these factors may interact with iodine intake.

**Fortification of Salt with Iodine in Denmark**

Starting from June 1998 a program of voluntary use of iodized salt was launched by the Danish National Food Agency in cooperation with salt manufacturers and the food industry (Figure 119.2). The public was informed in several ways about the state of ID in Denmark and the beneficial effects of using iodized salt. The target of the program was to increase the iodine intake of the average Dane by around 50 μg/day, and it was expected that 80% of household salt and salt used by the food industry would be iodized. This corresponds to an average intake of iodized salt of around 6–7 g/day, and the amount of iodide added to salt was therefore, set to 8 ppm.
After 2 years, it turned out that only around half of household salt and practically no salt used by the food industry were iodized. The estimated average increase in daily iodine intake was well below 10 g. Therefore, a mandatory program was introduced during the period July 2000–April 2001 (Figure 119.2). Household salt and salt used for the production of bread were to be iodized (Fødevareministeriet, 2000).

The intake of iodized salt by this program was estimated to be around 4 g/day, and the iodization level was set to 13 ppm. Bread is a staple food in Denmark, and simulation studies performed by the Danish National Food Agency based on Danish food surveys had shown that iodized salt in bread, in combination with iodized table salt, would distribute the iodine nearly as evenly in the population as iodization of all salt used by the food industry.

Monitoring of Iodine Intake and Thyroid Disorders: The DanThyr Study

The basic monitoring of iodine in salt and the use of iodized salt in Denmark was used to guide an early revision of the program as described above. This monitoring has also been the basis for the reinforcement of regulations for manufacturers of household salt. Measurements of the iodine content of samples of salt and bread collected from supermarkets and retail stores nationwide in 2002 showed that regulations were followed; 98% of rye bread and 90% of other breads sold in Denmark were iodized. Based on Danish food composition tables and investigations of intake of bread in Denmark, it was estimated that the medium iodine intake from bread had increased by 25 g/day, and the medium total iodine intake had increased by 63 g/day (Rasmussen et al., 2007).

Monitoring the iodine intake and the occurrence of thyroid disorders in the population (the DanThyr program) consisted of three main parts, all of which were started before the iodination of salt, so as to include a control period (Figure 119.2). Several considerations were taken into account when planning the monitoring. Excessive IF may lead to an early large surge of hyperthyroidism in a previously iodine-deficient population (Stanbury et al., 1998). To be able to detect and counteract such a development, a system of continuous monitoring of the incidence of overt hyperthyroidism was developed. To evaluate the long-term effects and benefits of iodine supplementation, this monitoring is planned to continue for a prolonged period of time, because it may take many years after a change in population iodine intake before a new steady state in the occurrence of thyroid diseases is reached (Barker and Phillips, 1984; Phillips et al., 1985).
A high iodine intake may be associated with a higher incidence of hypothyroidism in the population (Laurberg et al., 2001), but the level at which this occurs is unknown. Therefore, monitoring included the incidences of both overt hyper- and hypothyroidism (the DanThyr registry of overt hyper- and hypothyroidism).

It was neither necessary nor feasible to monitor goiter incidence continuously. This was to be evaluated by repeated investigations of cohorts (the DanThyr Cohort Study), including the iodine status of the population as to intake of an iodine-rich diet and supplements, the prevalence rate of subclinical thyroid disease, and possible confounding factors that might influence the occurrence of thyroid abnormalities independent of iodine intake.

Prospective detailed epidemiological studies of the effects of iodine supplementation on a population are scarce, even though several billion people in the world are more or less covered by some public iodine-supplementation program. Denmark presented a unique opportunity to monitor the epidemiology of thyroid diseases when changing to iodine sufficiency after a long history of mild-to-moderate deficiency. Accordingly, we planned for the monitoring to be detailed and scientific, and obtained supplementary funding for it. The studies compared the eastern part of the country, with only mild ID (the city of Copenhagen), to the western part, with moderate deficiency (the city of Aalborg) (Figure 119.3).

Finally, large amounts of data on disease therapy are continuously collected in various Danish national registries. The third part of DanThyr consists of using these data to compare the use of antithyroid drugs, levothyroxine, the number of patients treated with radiiodine, and the number of thyroid operations in areas of Denmark with different iodine intake levels before and after IF of salt.

The DanThyr Cohort Study

The first cohort study (C1a, n = 4649) took place from March 1997 to June 1998 in and around the city of Aalborg in Jutland, and in Copenhagen on Zealand (Figure 119.3). Details on the random selection of cohorts from the population, participation rates, and analysis of potential bias caused by nonparticipation have been published (Knudsen et al., 2000a).

We chose to investigate women in four age intervals (young women, 18–22 years; women in the main reproductive age, 25–30 years; premenopausal women, 40–45 years; and postmenopausal women, 60–65 years) and men in the oldest age group. This was done to obtain maximum information from the investment of time and money. Participants filled out an extensive questionnaire on lifestyle, diseases, medication and food frequency (Rasmussen et al., 2001), including intake of dietary supplements (Knudsen et al., 2002d). A clinical investigation for goiter was performed, and weight, height and blood pressure were measured. Subsequently, thyroid ultrasonography was performed (Knudsen et al., 1999), and spot urine and blood samples were collected. Investigation took place in two centers at Aalborg and Bispebjerg Hospitals. A program of training and control of ultrasonography performance (Knudsen et al., 1999), and evaluation of clinical investigation for goiter were used to coordinate centers.

Status before Salt Iodization

In the C1 cohort median urinary iodine concentration was 53 µg/l in participants from Aalborg and 68 µg/l in Copenhagen (Rasmussen et al., 2002a), corresponding to the difference in groundwater iodine content (around 5 µg/l in Aalborg, 20 µg/l in Copenhagen; Pedersen et al., 1999; Rasmussen et al., 2000). Participants who did not take iodine supplements had median urinary iodine concentrations of 45 µg/l (Aalborg) and 61 µg/l (Copenhagen). Thus, it was confirmed that participants from Copenhagen
had mild ID, and those from Aalborg had moderate ID (World Health Organization, 2001). Even the subgroup with the highest intake of fish and dairy products (rich in iodine) had ID if they lived in Aalborg (Rasmussen et al., 2002a). Milk and milk products alone contributed about 44% of iodine intake, and ID was more severe in the group with low intake of milk products.

We confirmed that moderate and mild ID in a population cause a high goiter prevalence in adults (Knudsen et al., 2000a). This is illustrated in Figure 119.4, showing the occurrence of goiter by clinical examination and by ultrasonography in the various groups investigated. The highest rates occurred in 60–65 year-old women from Aalborg, where 13.3% knew they had goiter, 33.4% had enlarged thyroids by ultrasonography, 23.9% had goiter by clinical examination and 5.7% had a history of previous goiter surgery. All values were higher in moderate (Aalborg) than in mild (Copenhagen) ID. In the women, thyroid size and the prevalence of goiter increased with age up to the 40–45 year-old group, but not much thereafter. However, the prevalence of multiple thyroid nodules ≥1 cm increased with age from 15% in 40–45 year-old women to 25–30% in women aged 60–65 years. Around 10% of the elderly women had a solitary ≥1 cm thyroid nodule by ultrasonography. Median thyroid volume was larger in the elderly men than in the women, but all thyroid abnormalities were considerably more common in the women.

Subsequent analysis of the data revealed high prevalences of subclinical hyperthyroidism, especially in Aalborg and in the elderly (Knudsen et al., 2000b). Serum thyroglobulin was a very sensitive marker of thyroid abnormalities and of ID (Knudsen et al., 2001a; Rasmussen et al., 2002b). Tobacco smoking severely heightened the clinical consequences of low-iodine intake (Knudsen et al., 2002a), and previous pregnancy also tended to increase the risk of goiter if iodine intake was low (Knudsen et al., 2002b). A family history of goiter, social class and level of education all increased the risk of goiter (Knudsen et al., 2003), whereas alcohol intake (Knudsen et al., 2001b) and oral estrogen use (Knudsen et al., 2002c) decreased the risk. Thus, a number of factors should be taken into account when evaluating the occurrence of goiter in a population.

### Status after Salt Iodization

The C2 cohort (n = 3570) examined from April 2004 to July 2005 was similar to the C1a cohort examined in 1997–1998 with respect to age, sex and place of residence. Again, a random sample of people living in the two defined areas (but born 7 years later) was drawn from the Civil Registration System (excluding people who participated in C1). The participation rate was 50.1% in C1 and 46.6% in C2. The investigational programs were identical,
using identical equipment for ultrasonography of the thyroid gland and the same people performing the ultrasound investigations.

The median iodine excretion in a nonfasting spot urine in the combined C2 cohort was 101 μg/l. It was 108 μg/l in Copenhagen and 93 μg/l in Aalborg. After the exclusion of subjects taking individual iodine supplementation the figures were 99 and 86 μg/l, respectively. This corresponds to an increase in median values of 38 μg/l (Copenhagen) and 41 μg/l (Aalborg), compared to values before iodization of salt (Vejbjerg et al., 2007).

If it is assumed that 90% of iodine intake is excreted in urine, and that 24 h urinary iodine excretion (μg/24 h) roughly corresponds to spot urine concentration (microgram/liter) multiplied by 1.5 (Laurberg et al., 2007), an increase of 39 μg/l in spot urine iodine concentration would correspond to an increase in daily iodine intake of approximately 64 μg/24 h, which is close to the value estimated from food analyzes (Rasmussen et al., 2007). Before the iodization program, the plan for IF of table salt and salt in bread was to increase iodine intake in the average Dane with around 50 μg/day. Thus, the models used by the Danish National Food Agency (now the National Food Institute) to predict changes in iodine intake from databases on the use of salt have been quite successful. Detailed studies on iodine intake in subgroups of the population with, e.g., different dietary habits are currently being performed to see if the program gives universal coverage.

Median thyroid volume was lower in all age groups after IF (C2 cohort) compared to before (C1 cohort) (Vejbjerg et al., 2007). The largest differences were found in the area with previous, moderate ID (Aalborg) where thyroid volume was on average 14.1% lower. After iodization, there were no regional differences in thyroid volume in the age group less than 45 years of age. Before iodization, 17.6% had thyroid enlargement; after iodization, 10.9% of the people examined had thyroid enlargement.

Thus, this prospective study demonstrated a rather rapid and effective lowering of thyroid volume in all age groups after iodization of salt. As might be anticipated, the decline was largest in the area with former, moderate ID. The equal thyroid volumes in the two regions among the younger age groups indicate approximation to an optimal iodine intake — even if intake is still at the lower edge of the recommended level (Vejbjerg et al., 2007).

### The DanThyr Registry of Overt Hypo- and Hyperthyroidism

We developed a computer-based system to register new cases of overt hyper- and hypothyroidism in a well-defined population cohort by linkage to diagnostic laboratory databases. It automatically identifies previously unknown cases of hyper- and hypothyroidism, and records diagnostic activity in two geographical cohorts which cover a total of 535,859 inhabitants (Aalborg, n = 310,124; Copenhagen, n = 225,707, as of January 1998). During the initial phase of monitoring, the system was carefully evaluated, as has been described in detail (Pedersen et al., 2002b).

In 1997–1998, before salt iodization, the incidence rate of overt hyperthyroidism (diagnosis verified in each individual patient) was high in the area with the lowest iodine intake (Aalborg, 92.9/100,000 per year) compared with the area with only mild ID (Copenhagen, 65.4/100,000 per year). Standardized rate ratio in Aalborg vs. Copenhagen was 1.49 (95% confidence interval, CI 1.22–1.81). Hypothyroidism was in general less common, but with the opposite pattern in the two areas [moderate ID 26.5 and mild ID 40.1 per 100,000 per year, standardized rate ratio 0.73 (0.55–0.97)] (Pedersen et al., 2002a). The difference in incidence of spontaneous autoimmune hypothyroidism in Copenhagen (Carlé et al., 2006).

The pattern in Aalborg is similar to previous findings in another part of Jutland (Laurberg et al., 1999), and the differences between Aalborg and Copenhagen are qualitatively similar to the previously observed differences between Jutland, with a low-iodine intake, and Iceland, with a much higher iodine intake (Laurberg et al., 1998).

### Incidence of Overt Hyperthyroidism after Iodine Fortification of Salt

The registry has enabled us to prospectively follow the incidence of overt hyperthyroidism in the two population cohorts after IF of salt. At baseline, the crude incidence rate of hyperthyroidism (without follow-up verification of diagnosis in individual patients) in the entire Aalborg + Copenhagen cohort was 102.8/100,000/year. The incidence rate increased during IF, but became stable at a level about 35% above baseline (Pedersen et al., 2006).

The increase in occurrence of hyperthyroidism developed somewhat differently in the two subcohorts (Figure 119.5), although it was statistically significant in both areas (P for trend ≤0.001). In Aalborg, with moderate ID, the increase in hyperthyroidism was more pronounced, and evident before the increase in Copenhagen, with mild ID. Hyperthyroidism was much more common in the elderly than in young subjects, which is the pattern in populations with low-iodine intake (Laurberg et al., 1991), but the increase in the number of new cases had mainly occurred in younger subjects (Pedersen et al., 2006). It is to be expected that the incidence of hyperthyroidism will decrease (Stanbury et al., 1998) and become lower than before the iodization program, because there will be fewer cases of multinodular toxic goiter among the elderly. However, there may be relatively more cases of hyperthyroidism caused by Graves’ disease in younger
The few studies of incidence of overt hypothyroidism have shown tremendous differences between areas. It is at present unknown if this is caused by genetic or environmental differences, and methodological differences between studies may also play a role (Laurberg, 2005). A high iodine intake has been shown to correlate to more subclinical hypothyroidism in a population (Laurberg et al., 1998; Szabolcs et al., 1997; Teng et al., 2006), and it is very important to obtain reliable figures on variations in overt hypothyroidism in a population after an increase in iodine intake.

The DanThyr registry has shown a moderate increase in the incidence of overt hypothyroidism (Figure 119.6). During the same period there has been a similar increase in the use of thyroid function tests in the population (Pedersen et al., 2007). This is to be expected, because there has been an increase in number of both hyper- and hypothyroid patients to treat and control. However, it cannot be ignored that there has been an increase in diagnostic activity, and that this may be one reason for the increase in number of patients. Further data from a more prolonged follow-up are necessary before a conclusion can be drawn on the association between the iodization program and the incidence of overt hypothyroidism.

**Incidence of Overt Hypothyroidism after Iodine Fortification of Salt**

![Figure 119.5](image1.png)  
**Figure 119.5** Incidence rates of overt hyperthyroidism before and after iodine fortification (IF) of salt. The incidence rate of hyperthyroidism in Aalborg (moderate ID) and Copenhagen (mild ID) before and after the first 6 years of IF of salt. Basic is the time before IF of salt (1997–1998), 1999–2000 is the period of voluntary IF, 2001–2002 is the early, and 2003–2004 is the late period of mandatory IF. The incidence of hyperthyroidism increased significantly in both subcohorts during the study period. In Aalborg, the increase was more pronounced and came before the increase in Copenhagen. Aalborg: baseline vs. voluntary IF, \( P < 0.001 \); voluntary IF vs. early mandatory IF, \( P = 0.001 \); early vs. late mandatory IF, \( P = 0.001 \); voluntary IF vs. early mandatory IF, \( P < 0.001 \); early vs. late mandatory IF, \( P = 0.001 \). Statistical significance compared with baseline, \(^* P < 0.05; ^{**} P = 0.01; ^{***} P = 0.001 \). Data from Pedersen et al., (2006).

![Figure 119.6](image2.png)  
**Figure 119.6** Incidence rates of overt hypothyroidism before and after iodine fortification of salt. The incidence of hypothyroidism in Aalborg with previous moderate ID and Copenhagen with previous mild ID in three periods with different iodine intake compared to baseline, which is the preiodine incidence. The vertical bars indicate the 95% CI to the rate. In Copenhagen the incidence of hypothyroidism was stable. In Aalborg, however, the incidence rates of hypothyroidism were significantly higher in both periods with mandatory ID compared to baseline, as one was not included in the 95% CI. Data from Pedersen et al., (2007).

Central Registry for Surgical and Medical Treatment

Data from a number of central registries are currently being used to compare the use of antithyroid drugs and levothyroxine, the number of patients treated with radiiodine and the number of thyroid operations in areas of Denmark with different iodine intake levels. Before IF of salt, the use of antithyroid drugs was higher in the west than in the east part of Denmark, more people were treated with radiiodide, and thyroid surgery was more common (Jorgensen et al., 2002). This corresponds to the higher incidence of hyperthyroidism and high prevalence of goiter in Jutland, with the lowest iodine intake.

From 1999 to 2003, the quantity of antithyroid drugs sold increased in north Jutland and the number of patients treated increased. Little change occurred in Copenhagen (Perrild et al., 2005). This difference corresponds to the...
more severe increase in incidence of hyperthyroidism in Aalborg than in Copenhagen after iodide fortification of salt (Pedersen et al., 2006).

**Conclusion**

The monitoring of the Danish IF program has given considerable information on the importance of small systemic differences in iodine intake for the occurrence of thyroid diseases in a population. Some other risk factors, such as smoking and pregnancy, seem to act via interaction with iodine intake, whereas others, such as alcohol consumption and use of estrogen, are independent of iodine. Information on risk factors is useful for the guidance of individual patients, and it gives a basis for studying pathogenic mechanisms. Moreover, they should be corrected for when studying the effect of iodine intake. DanThyr has verified the high occurrence of multinodular thyroid disease and hyperthyroidism in low-iodine intake areas. The program will allow a comprehensive description of the changes occurring in thyroid diseases in a population when the iodine intake is increased to a low recommended level from being clearly insufficient.

So far, the program has shown that it is possible to direct population iodine intake to be within a predicted interval by use of targeted iodization of food. Furthermore, it has illustrated the rapid and beneficial effects of even a relatively small increase in population iodine intake on thyroid size and frequency of thyroid enlargement in the Danish population. The program will allow a comprehensive description of the changes occurring in thyroid diseases in a population when the iodine intake is increased to a low recommended level from being clearly insufficient.

**Summary Points**

- Mild-to-moderate ID in a well-nourished population leads to a frequent occurrence of goiter and hyperthyroidism in the elderly.
- There may be impairment of thyroid function in pregnant women.
- A mandatory iodization of household salt and bread salt has led to a well-distributed increase in iodine intake in the Danish population.
- The Danish iodization program has led to a decrease in thyroid size and frequency of thyroid enlargement in practically all groups investigated.
- The expected early increase in hyperthyroidism has been low.
- Hypothyroidism has become slightly more common.

**References**


