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REVIEW

The Danish investigation on iodine intake and thyroid disease (DanThyr): history and implications

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Abstract

Due to mild-to-moderate iodine deficiency in Denmark, health authorities initiated a voluntary iodine fortification (IF) program in 1998, which became mandatory in 2000. In line with recommendations from the World Health Organization, the Danish investigation on iodine intake and thyroid disease (DanThyr) was established to monitor the effect on thyroid health and disease. The program involved different study designs and followed two Danish sub-populations in the years before IF and up till 20 years after. Results showed that the IF was successfully implemented and increased the level of iodine intake from mild–moderate iodine deficiency to low adequacy. The level of thyroglobulin and thyroid volume decreased following IF, and there was an indication of fewer thyroid nodules. The incidence of hyperthyroidism increased transiently following IF but subsequently decreased below the pre-fortification level. Conversely, thyroid-stimulating hormone levels and the prevalence of thyroid autoimmunity increased along with an increase in the incidence of hypothyroidism. These trends were mirrored in the trends in treatments for thyroid disease. Most differences in thyroid health and disease between regions with different iodine intake levels before IF attenuated. This review illustrates the importance of a monitoring program to detect both beneficial and adverse effects and exemplifies how a monitoring program can be conducted when a nationwide health promotion program – as IF – is initiated.

Keywords: epidemiology; iodine; public health; thyroid disease

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Introduction: iodine fortification in Denmark

The Danish investigation on iodine intake and thyroid disease (DanThyr) was the first extensive examination of the effects of an iodine fortification (IF) program (1). IF is implemented to obtain optimal thyroid health in the population. Both iodine deficiency (ID) and iodine excess are associated with an increased risk of thyroid disease, and the optimal distribution of the population's iodine intake lies within a narrow range. Therefore, the World Health Organization (WHO), United Nations International Children's Emergency Fund, and International Council for the Control of Iodine Deficiency Disorders recommended (and still recommend) monitoring of IF programs (2).

The problem

In Denmark, ID was observed in young men in 1969 (3). Therefore, in the 1970s, a survey was initiated which found a low prevalence of goiter in school-age children (unpublished data), and thus it was concluded that the Danish population was not iodine deficient. However, later analyses of urinary iodine excretion indicated ID in adults in 1985 (4), 1987 (5), 1988 (6), and 1990–1991 (7); pregnant women in 1987 (5); and women 5 days after delivery (8) and their newborns in 1988–1990 (9). The observations of ID were accompanied by observations of a higher prevalence of enlarged thyroid or goiter (7), thyroid nodules, and subsequent hyperthyroidism (10, 11), especially in elderly women and in the most iodine-deficient areas (11). Further, observations of increased TSH in the third trimester of pregnancy indicated iodine deficiency (12).

Iodine in drinking water contributes a large proportion of the iodine intake in Denmark, but the level of iodine in the water varies due to differences in the soil (13, 14). Crudely, the western part of Denmark had moderate ID, and the eastern part of Denmark had mild ID (Fig. 1) (15).

Iodine fortification

In 1994, a working group was established to evaluate the iodine situation in Denmark and possible actions. It concluded that Denmark was iodine deficient and proposed a cautious fortification of salt (16). The Danish Food and Veterinary Administration introduced IF with the aim of increasing the iodine intake by 50–60 µg/day (17).

Initially, voluntary IF with 8 ppm in all salt (household salt and salt for food production) was implemented in June 1998, based on an estimated intake of 6–7 g iodized salt per day (1). However, after 18 months, some household salt was iodized, but practically no

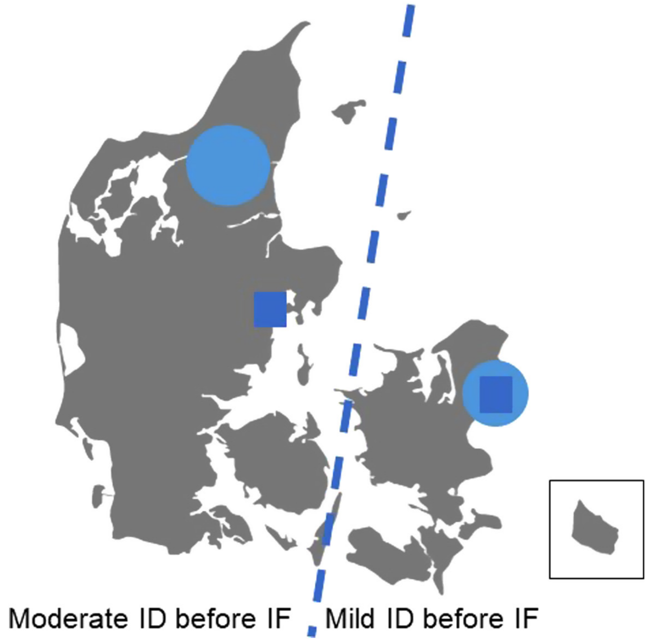

Figure 1

Map of Denmark. Crudely, western Denmark had moderate ID before IF, and eastern Denmark had mild ID before IF. Bread from bakeries was analyzed in samples from Aarhus in western Denmark and Copenhagen in eastern Denmark (squares). The cohort studies and laboratory studies were conducted in and around the city of Aalborg in western Denmark and in Copenhagen in eastern Denmark (circles). The nationwide register studies stratified the population into west and east as illustrated by the dashed line. ID, iodine deficiency; IF, iodine fortification.

salt used in food production was iodized, making this approach ineffective (17). Therefore, from July 15, 2000, fortification with 13 ppm iodine added to household salt and salt in bread and baked goods was made mandatory (18), based on an estimated intake of 4 g iodized salt per day from these sources (1). An 8-month grace period (until the end of March 2001) was allowed.

Monitoring iodine fortification

In accordance with national and international policies and recommendations (19), it was decided to design a program, DanThyr, aimed to monitor, analyze, and possibly adjust IF to secure optimal iodine nutrition for the Danish population. The DanThyr steering group consisted of a multidisciplinary team of experts in clinical thyroidology, nutrition, food fortification, epidemiology, and public health.

The DanThyr studies collected data before the introduction of IF and up to 20 years after. The availability of baseline data before the IF, first provided the opportunity to examine effects of long-term stable moderate and mild ID. Secondly, with data collected after the IF, it was possible to examine the effects of the

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same level of cautious IF in the two areas with different baseline iodine intake levels. Lastly, the data from the DanThyr studies provided insight into important aspects of thyroid research methodology and epidemiology. More than 90 original peer-reviewed scientific papers and reports, ten PhDs, and two doctoral dissertations have originated from the DanThyr studies.

The aim of this review is to summarize the history, the methods, and the results of the monitoring of the Danish IF program as documented through the studies conducted under the DanThyr.

Methods for monitoring iodine fortification and its effects

Four different study designs were applied to secure an optimal monitoring program (Fig. 2).

Iodine content in salt and foods

The iodine content in salt was evaluated in 2001–2002 and in 2007–2008. In the first examination, 18 types of household salt were sampled and analyzed for iodine content (17). In the second examination, 72 samples of household salt and salt for bread production were sampled and analyzed for iodine content (20).

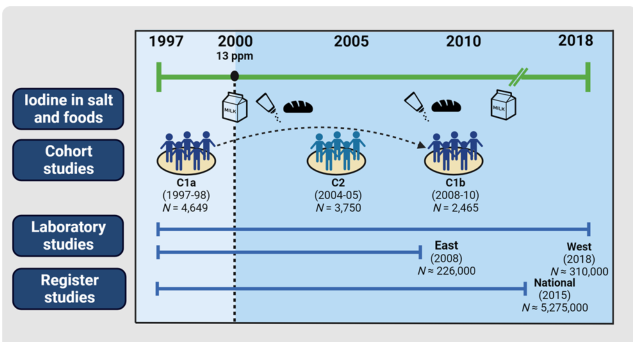

Figure 2

Overview of the four study designs and timing of these in the Danish Investigation on Iodine Intake and Thyroid Disease (DanThyr). ppm, parts per million. The DanThyr studies monitored the effects of the Danish iodine fortification through four different study designs: (1) analyses of iodine content in salt, bread, and milk monitored the implementation of IF and iodine sources, (2) two cross-sectional cohort studies in 1997–1998 and 2004–2005, with a follow-up of the first in 2008–2010, comprised questionnaires (on diseases, medication, treatments, and lifestyle), thyroid ultrasound, and blood- and urine samples. The studies were conducted simultaneously in Aalborg in western Denmark and in Copenhagen in eastern Denmark. (3) Laboratory studies collected results from all thyroid function tests ordered by general practitioners or in hospitals continuously from 1997 to 2018 in and around Aalborg in western Denmark and continuously from 1997 to 2008 in Copenhagen in eastern Denmark. (4) National register studies examined trends in treatments for thyroid disease (medication, surgery, and radioiodine) continuously from 1997 to 2015. Voluntary IF with 8 ppm was introduced in 1998, and mandatory IF with 13 ppm in 2000. Western Denmark had moderate iodine deficiency before iodine fortification, and eastern Denmark had mild iodine deficiency before iodine fortification.

In 2001–2002, 125 rye bread and 187 wheat bread industrially manufactured and baked at retail shops were sampled and analyzed for iodine content (17). In 2009, 59 bread (39 wheat, 20 rye) from bakeries and 121 bread (66 wheat, 55 rye) industrially produced in Denmark were sampled in the two largest cities in Denmark. Iodine content was analyzed (21).

Iodine content was evaluated in milk sampled every month for one year in 2000–2001 and in April and July/August 2013 from conventional and organic dairies covering all of Denmark (22).

Population-based cohort studies in two parts of Denmark

Two cross-sectional population-based studies were conducted from March 1997 to June 1998 (C1a) (23) and from January 2004 to July 2005 (C2) (24). From February 2008 to February 2010, a follow-up (C1b) of the first cohort was conducted. Each study consisted of data collection in two geographical areas: Aalborg in western Denmark with moderate ID and Copenhagen in eastern Denmark with mild ID (Fig. 1). Participants were randomly selected from the civil registration system in prespecified age and sex strata (women aged 19–22, 26–30, 41–45, 61–65 years, and men aged 61–65 years) and invited to participate in the studies. Participation rates in the west and east were as follows: C1a: 54.6% (2220/4065) and 46.6% (2429/5209), total $n = 4649$; C2: 49.0% (1785/3644) and 44.5% (1785/4014), total $n = 3570$ (24); and C1b: 60.3% (1229/2039) and 57.9% (1236/2135), total $n = 2465$, respectively.

The methods used for data collection were similar in the two geographical sites and in the three studies. The participants answered self-administered questionnaires on diseases, medication and treatments, lifestyle, and food frequency (25). Information on thyroid disease and treatment was further evaluated in an interview by a medical doctor, and all participants underwent a clinical examination for goiter, height, weight, and blood pressure. A thyroid ultrasound was performed (26). Non-fasting blood samples were analyzed for TSH, fT4, fT3, Tg, TPO antibodies (TPOAb), and Tg antibodies (TgAb), and in a subsample also for selenium and selenoprotein P (27, 28). Spot-urine samples were analyzed for iodine and creatinine (23), and in a subsample for cotinine too (29). Efforts were made to ensure the validity and reliability of the methods between the geographical sites and over time. For example, sonographers performed blinded confirmatory inter-observational studies (24), and a subsample of blood samples from C1a was reanalyzed with blood samples from C2 (30) and C1b to confirm reproducibility.

Laboratory studies in two parts of Denmark

An automated system was established collecting results from all thyroid function tests ordered by general practitioners or in hospitals. Laboratory data were collected in two well-defined open sub-cohorts: western Denmark in the city of Aalborg and surrounding municipalities serviced by one laboratory (Aalborg Hospital Laboratory) and eastern Denmark in the area around Bispebjerg Hospital in Copenhagen serviced by three laboratories (Bispebjerg Hospital Laboratory, Frederiksberg Hospital Laboratory, and Laboratory of General Practitioners in Copenhagen) (n = 310,125 and n = 225,734, respectively, January 1, 1997) (31). The results of thyroid function tests were run through a diagnostic algorithm identifying all possible incident patients fulfilling the diagnostic criteria for biochemically overt hyper- or hypothyroidism, and a database of incident patients was established (31). Data were collected from 1997 until 2018 in western Denmark and until the end of September 2008 in eastern Denmark (32). The medical history of all possible new cases was scrutinized and verified by contact with the responsible physician/hospital department, and the specific nosological subtype was determined in the study periods 1997–2000 in both sub-cohorts (33) and in 2014–2016 in the western Denmark sub-cohort (34).

National register studies

Danish nationwide registers, with individual-level health care and basic information on the entire Danish population, were utilized to evaluate the use of treatments for thyroid disease from 1997 to 2007/2009 (35, 36, 37), and updated until 2015 (38). Individual-level linkage between data sources is possible via the unique personal identification number assigned at birth to every Dane. Information on incident use of antithyroid medication and thyroid hormone therapy was retrieved from the Danish National Prescription Registry (39), and information on thyroid surgery and radioiodine (available from 2004) for benign thyroid disease was retrieved from the Danish National Patient Register (40). Treatments were individually linked with information on age, sex, and municipality of residence (divided into western and eastern Denmark) from The Danish Civil Registration System (41). Costs were applied to the medications and procedures from central lists of prices (42).

The individual scientific papers of DanThyr applied different designs, statistical methods, and exclusions and adjustments depending on the aim of each paper. In Table 1 the unadjusted results are presented, and primarily the results of the main adjusted analyses are presented in the following sections. We refer to the individual publications for details.

The DanThyr studies followed the ethical requirements that were applied over the study period. Where relevant, the studies were approved by the Ethics Committees and the Data Protection Agency. Informed written consent was obtained prior to participation in the cohort studies.

Results

Effect on iodine content in salt and foods

Evaluations of IF of household salt in 2001–2002 found three types of salt out of 18 different types that were not fortified, and 5 out of 18 types exceeded 20 ppm (17). In 2007–2008, the iodine content in household salt and salt for bread production was within the acceptable range of 80–150% of the fortification level of 13 ppm (10.4–19.5 ppm) in 93% (65/72) of the samples. The iodine concentration was above and below limits in four and three samples, respectively (20).

For bread analyzed in 2001–2002, approximately 3% of the rye bread and approximately 10% of the wheat bread were not fortified with iodine (17). In 2009, 14% (8/59) of breads from bakeries were not fortified, and in 36% (21/59), the iodine content was outside the acceptable range (10.4–19.5 ppm). All 121 industrially produced breads were fortified, but in 8% (10/121), the iodine content was outside the acceptable range (21).

The overall mean iodine concentration in milk was 16 µg/100 g (SD 6) in 2000–2001 and 12 µg/100 g (SD 3) in 2013 (test for difference: $P < 0.001$) (22).

Effects on iodine intake

Median urinary iodine concentration (UIC) is the recommended indicator of current population-level iodine intake, and adequate iodine nutrition is defined as a median UIC of 100–199 µg/L in children above 6 years and adults, and 150–249 µg/L in pregnant women (43).

In the first cross-sectional study (C1a), the median UIC of 53 µg/L in western Denmark and 68 µg/L in eastern Denmark confirmed the previously observed moderate and mild ID, respectively (44, 45, 46). After IF, in C2, a low-adequate intake was achieved with a median UIC of 93 and 108 µg/L in western and eastern Denmark, respectively (24). In C1b, the 11-year follow-up of C1a, the UIC was 83 µg/L and 84 µg/L in western and eastern Denmark, respectively (47, 48) (Table 1). Between C2 and C1b, a decline in the iodine intake was observed for women but not for men (22).

The DanThyr studies did not include examinations of iodine intake in children and pregnant women. However, two separate studies have evaluated iodine

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Table 1 Main results from the DanThyr cohort studies. Levels of biomarkers and clinical markers in the three DanThyr cohort studies. All values given are unadjusted. Voluntary IF with 8 ppm introduced in 1998, and mandatory IF with 13 ppm in 2000. Western Denmark had moderate iodine deficiency before iodine fortification, and eastern Denmark had mild iodine deficiency before iodine fortification.

			1997–1998		2004–2005	2008–2010
	Reference	**Region**	C1a	C1a + C1b	C2	C1a + C1b
UIC, µg/L	22, 24, 45, 46, 47					
Median		West	53/45[a]	53	93/86[a]	83/76[a]
Median		East	68/61[a]	68	108/99[a]	84/73[a]
TSH, mU/l	48, 55					
Median (95% CI)		West	1.28	1.24 (1.19–1.29)	1.47	1.28 (1.23–1.34)
Median (95% CI)		East	1.33	1.30 (1.25–1.35)	1.56	1.49 (1.43–1.55)
Tg, µg/L	53, 54					
Median		West	14.6	11.4	8.9	9.0
Median		East	10.9	9.1	8.7	9.1
TPOAb and/or TgAb positivity	30					
%		West	20.6	22.7	34.2	42.2
%		East	19.3	22.0	30.1	37.2
Solitary nodules	24, 44, 57					
%		West	6.3	6.3	5.9	6.2
%		East	5.6	4.9	5.4	4.0
Multinodality	24, 44, 58					
%		West	11.0	9.1	10.8	15.4
%		East	11.5	10.5	9.8	12.4
Thyroid volume, mL	24, 44, 58					
Median (IQR)		West	13.6	13.3 (10.3–18.0)	11.6	13.1 (10.0–18.3)
Median (IQR)		East	11.9	11.8 (9.0–15.9)	11.2	12.2 (9.6–15.8)

[a]Not taking dietary supplements containing iodine.
C1a + C1b indicates results for persons participating in both C1a and C1b; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; TPOAb, thyroid peroxidase autoantibodies; TgAb, thyroglobulin autoantibodies; UIC, urinary iodine concentration.

intake in children in Denmark, but none of these had data on iodine intake before IF. In 2012, a median UIC of 126 µg/L was measured in 51 children aged 1–14 years in western Denmark (49). In 2015, a median UIC of 129 µg/L in girls and 145 µg/L in boys was measured in 244 children aged 7–8 and 11–12 years in eastern Denmark (50). Additionally, in 2012, 245 pregnant women in western Denmark had a median UIC of 68 and 109 µg/L for those not taking and taking iodine supplements, respectively (51). In 2014, the median UIC was 82 and 118 µg/L for those not taking and taking iodine supplements, respectively, in 240 pregnant women in eastern Denmark (52).

Effects on thyroid biomarkers and clinical markers

Thyroglobulin

Thyroglobulin (Tg) levels reflect iodine nutrition over a period of months to years and correlate with UIC and thyroid volume at the population level. Elevated Tg levels are found both in iodine deficiency and excess (43).

In C1a, the median Tg level was 14.6 µg/L and 10.9 µg/L in western and eastern Denmark, respectively. In the second cross-sectional study, C2, this difference had attenuated to a median of 8.9 and 8.7 µg/L (53). The follow-up, C1b, confirmed the attenuation: within-person Tg had decreased (median: 11.4–9.0 µg/L (P < 0.001)) in western Denmark, while there was no statistically significant change in eastern Denmark (median: 9.1–9.1 µg/L (P = 0.67)) (54) (Table 1).

Thyroid-stimulating hormone

TSH is a sensitive marker of thyroid function because it responds inversely and with amplification to alterations in thyroid hormone levels.

Between C1a and C2, TSH increased in both regions: from a median of 1.28–1.47 mIU/L in western and from 1.33–1.56 mIU/L in eastern Denmark (55). Within persons participating in both C1a and C1b, after adjustment, TSH had increased from 1.21 mIU/L (95% CI: 1.15–1.27) to 1.25 mIU/L (1.18–1.31) in western Denmark (P = 0.14) and from 1.28 mIU/L (95% CI: 1.22–1.34) to 1.45 mIU/L (95% CI: 1.38–1.52) in eastern Denmark (P < 0.01) (48).

Thyroid autoantibodies

The presence of thyroid autoantibodies is associated with an increased risk of autoimmune thyroid disease, and alterations in the prevalence of thyroid autoantibody positivity may thus be clinically important.

Before IF, in C1a, the prevalence of thyroid autoantibodies (TPOAb >30 U/l and/or TgAb >20 U/l) was 20.6% and 19.3% in western and eastern Denmark, respectively, and this had increased to 34.2% and 30.1% in C2. This equaled an increase in odds ratio (OR) 1.80 (95% CI: 1.61–2.01) for TPOAb and/or TgAb; OR 1.80 (95% CI: 1.59–2.04) for TPOAb; and OR 1.49 (95% CI: 1.31–1.69) for TgAb (30, 56). The increase in thyroid autoantibodies was most pronounced at low serum concentrations (TPOAb <1032 U/l and/or TgAb <60 U/l) and in young women (30). The changes in thyroid autoantibodies within persons participating in both C1a and C1b were analyzed for this publication (Supplementary materials, see section on supplementary materials given at the end of this article). The prevalence of TPOAb and/or TgAb increased from 22.7% to 42.2% in western Denmark and from 22.0% to 37.2% in eastern Denmark, corresponding to OR 1.98 (95% CI: 1.76–2.22) in an adjusted model. The largest increase was observed in the youngest age groups at baseline. When women aged 40–43 years in C1a and in C1b were treated as independent cohorts, the increase in the prevalence of TPOAb and/or TgAb was smaller, yet still apparent.

Thyroid nodules

Thyroid nodules are prevalent and clinically relevant because of possible compressive and cosmetic complaints, fear of cancer in the nodules, subsequent investigations for cancer, and they may become autonomous and induce hyperthyroidism.

Before IF, in C1a, the prevalence of thyroid nodules (diameter ≥ 10 mm) was similar between regions with solitary nodules in 6.3% in western and 5.6% in eastern Denmark, and multinodularity in 11.0% in western and 11.5% in eastern Denmark. However, the nodules were often larger and more often palpable in western Denmark (44). The prevalence of thyroid nodules did not change between C1a and C2 (24). Between C1a and C1b, where participants had aged 11 years, follow-up examinations found no change in the prevalence of solitary nodules (from 6.3% to 6.2% in western and from 4.9% to 4.0% in eastern Denmark) and an overall increase in the prevalence of multinodularity, primarily driven by a rise in western Denmark (from 9.1% to 15.4% in western and from 10.5% to 12.4% in eastern Denmark). When comparing women aged 40 in C1a and women aged 40 in C1b, the prevalence of both types of nodules was lower in C1b (57).

Thyroid volume and goiter

Determination of enlarged thyroid, i.e. goiter, was the traditional indicator of ID in populations. Thyroid hyperplasia is a response to iodine insufficiency, and thyroid volume reflects years or decades of iodine levels and can thus be applied as an indicator of long-term effects of IF.

Before IF, in C1a, median thyroid volume was 13.6 mL and 11.9 mL in western and eastern Denmark, respectively, and the prevalence of thyroid enlargement (defined as >18 mL in women and >25 mL in men) was 14.6% and 9.8%. Both measures were strongly correlated with age (44). In C2, thyroid volume had decreased in all age groups and both regions, to 11.6 mL and 11.2 mL in western and eastern Demark, respectively, along with an overall decrease in the prevalence of thyroid enlargement (24). Within-person analyses, from C1a to C1b, found no change in median thyroid volume in western Denmark (13.3–13.1 mL, P = 0.07) and a small increase eastern Denmark (11.8–12.2 mL, P < 0.001) (58).

Effects on thyroid disorders

Hyperthyroidism

The laboratory studies found that before IF, in 1997–1998, the incidence of overt hyperthyroidism was 128.5 and 80.1 per 100,000 person-years (PY) in western (moderate ID before IF) and eastern (mild ID before IF) Denmark, respectively. A transient increase was observed in both regions. In western Denmark, the incidence peaked in 2000–2001 at 39% above the level before IF and fell gradually. From approximately 2010, the incidence rate plateaued at 33% below the rate before IF. In eastern Denmark, the incidence of hyperthyroidism peaked in 2004–2005 at 52% above the level before IF, and thereafter declined to the same level as before IF in 2008 (Fig. 3A). Incident overt hyperthyroidism was consistently three to four times more frequent in women compared with men throughout the study period. The initial rise in incidence was observed in all three age groups, and the subsequent decrease in incident cases was primarily driven by the two oldest age groups, while the incidence of overt hyperthyroidism remained elevated in the youngest age group (59, 60). This is supported in the cohort studies where the prevalence of subclinical and overt hyperthyroidism decreased between C1a and C2 in both regions (55).

Subtype of hyperthyroidism

Multinodular toxic goiter and Graves' disease constituted over 80% of incident hyperthyroid cases, while solitary toxic adenoma, 'mixed type' (scintiscan suggesting multinodularity but with positive TRAb), subacute, and postpartum thyroiditis made up a minor part, and hyperthyroidism from external causes was rare (61). In 1997–2000, the incidence of Graves' disease was similar in the two regions, while multinodular toxic goiter was 87% more frequent in western Denmark. Graves' disease predominated in patients under 45 years, and multinodular toxic goiter was the most common cause of hyperthyroidism in patients over 45 years (61).

Between 1997–2000 and 2014–2016 in western Denmark, the decrease in incident hyperthyroidism was due to an 82% decrease in multinodular toxic goiter and a 33% decrease in Graves' disease (34).

Hypothyroidism

In the laboratory studies, the incidences of overt hypothyroidism were 32.9 and 47.3 per 100,000 PY in 1997–1998 in western and eastern Denmark, respectively. This had increased by 150% in 2014–2016 in western Denmark and by approximately 130% in 2004–2009 in eastern Denmark (Fig. 3B). The rise in incident overt hypothyroidism was driven by a rise in the two youngest out of three age groups in both regions (32, 62). The cohort studies found that between C1a and C2, the prevalence of subclinical hypothyroidism had increased in both regions, while the prevalence of overt hypothyroidism was largely unchanged in western Denmark and had increased markedly in eastern Denmark (55).

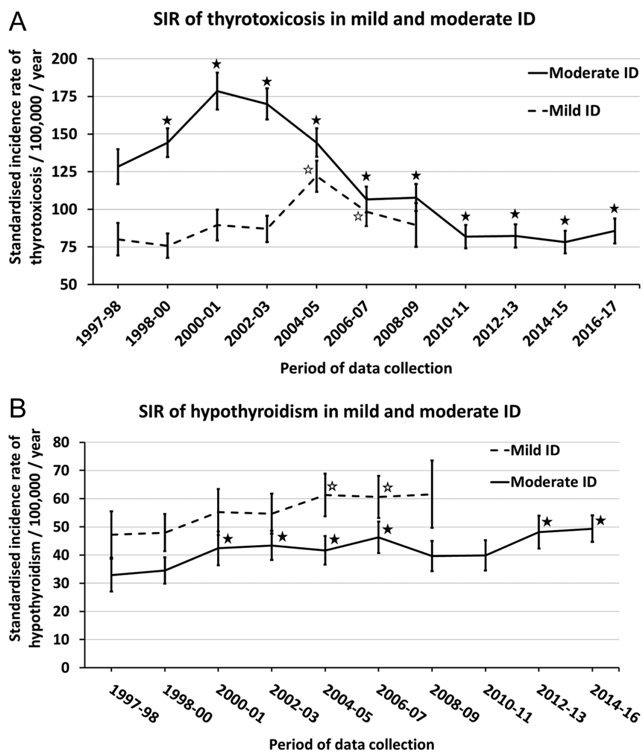

Figure 3

Main results from the DanThyr laboratory studies (32, 59). SIR, standardized incidence rates; ID, iodine deficiency; PY person-years. Development in standardized incidence rates of thyrotoxicosis (A) and hypothyroidism (B) in the laboratory studies. Error bars indicate the 95% CI. Asterix (*) indicates SIRs are statistically significantly different from the SIRs in 1997–mid 1998. Voluntary IF with 8 ppm was introduced in 1998, and mandatory IF with 13 ppm in 2000. Western Denmark had moderate iodine deficiency before iodine fortification, and eastern Denmark had mild iodine deficiency before iodine fortification. Originally published in refs. (59) and (32).

Subtype of hypothyroidism

In 1997–2000, the most frequent cause of incident overt hypothyroidism was spontaneous (presumably autoimmune, 99.3% had positive TPOAb and/or TgAb), constituting 84.4% of cases. The remaining cases were caused by amiodarone, lithium, subacute thyroiditis, previous radiation or surgery, or congenital or postpartum hypothyroidism. The risk of spontaneous autoimmune hypothyroidism was 53% higher in eastern Denmark, explaining the overall higher risk of overt hypothyroidism. Spontaneous autoimmune hypothyroidism was predominant in the oldest age groups in both regions (33). Between 1997–2000 and 2014–2016 in western Denmark, no overall change was observed in the distribution of nosological subtypes of hypothyroidism (34).

Effects on treatments of thyroid disorders

Antithyroid medication

The studies utilizing data from the Danish nationwide registers found that standardized incident use of antithyroid medication was 85.9 and 61.3 per 100,000 PY in 1997 in western and eastern Denmark, respectively (37, 38). Incident use increased transiently in both regions but only statistically significantly above the level before IF in western Denmark. From approximately 2010, the incident use of antithyroid medication plateaued around 65 per 100,000 PY, with a relative risk (RR) of 0.66 (95% CI: 0.60–0.73) in western and 50 per 100,000 PY, RR 0.80 (95% CI: 0.71–0.89) in eastern Denmark compared with the use in 2000. The decrease in incident use was driven by a decrease in the two oldest out of three age groups in women in both regions (38).

Thyroid hormone therapy

Standardized incident use of thyroid hormone therapy was 74.9 and 86.8 per 100,000 PY in 1997 in western and eastern Denmark (36), respectively, and increased in both regions to a plateau from approximately 2010 at 135 per 100,000 PY, with a RR of 1.65 (95% CI: 1.48–1.84) in western Denmark and 180 per 100,000 PY, with a RR of 1.86 (95% CI: 1.66–2.08) in eastern Denmark compared with 2000. The increase was observed in both men and women and was strongest in the two youngest age groups (38).

Thyroid surgery and radioiodine treatment

The number of thyroid surgeries was roughly constant at around 30 and 25 per 100,000 persons every year in western and eastern Denmark (35), respectively,

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from 1997 until 2009, whereafter it increased slightly in eastern Denmark (38). The number of radioiodine treatments fluctuated around 30 per 100,000 persons every year throughout the study period, with slightly higher levels in western than eastern Denmark (38).

Costs of treatments

The development in treatments described above yielded a total increase in national costs of treatment of thyroid disease from EUR ~190,000 per 100,000 PY in 1995 to EUR ~270,000 per 100,000 PY in 2015 (2015 prices). This was primarily due to the large number of additional low-cost thyroid hormone therapy treatments and a minor increase in high-cost surgeries (42). Additional unpublished analyses indicate that if there had been no changes in tests and treatment threshold for thyroid hormone therapy, the costs would have increased minimally.

Further studies of thyroid research methodology and epidemiology

This review focuses on the primary aim of the DanThyr studies: the effects of IF on thyroid health and disease. In addition, the DanThyr studies evaluated methodologies for thyroid research, such as urinary sampling for iodine intake measurement (63), validation of ultrasonography (26), and food frequency questionnaires (25), and evaluated biomarkers (64, 65). Finally, numerous studies were conducted within DanThyr examining the epidemiology of thyroid health and disease, focusing on risk factors (smoking (29, 66, 67, 68, 69), alcohol intake (70, 71, 72), pregnancy (73, 74, 75), selenium status (27), and socioeconomic status (76)), body weight (77, 78), symptoms (79, 80, 81, 82), clinical features of thyroid disease (83, 84, 85, 86, 87), and referral bias (88, 89).

Discussion

Summation of the findings

After mandatory IF with 13 ppm of household salt and salt in bread and baked goods, the correct level of fortification was found in most tested samples of vehicles. The fortification increased the level of iodine intake from mild–moderate ID to low adequacy. Most markers of thyroid function and thyroid disease were affected: the level of Tg and thyroid volume fell, and there was an indication of a decrease in thyroid nodules. The incidence of hyperthyroidism increased transiently after IF and subsequently decreased below the pre-fortification level. Conversely, TSH and the prevalence of thyroid autoimmunity increased along with an increase in the incidence of hypothyroidism. These trends were mirrored by the trends in treatment with antithyroid medication and thyroid hormone therapy. The improvements in thyroid diseases were primarily driven by the oldest age groups, while thyroid autoimmunity and hyperthyroidism and hypothyroidism increased in the youngest age groups. Before IF, western Denmark (moderate ID before IF) had overall more indicators of thyroid dysfunction compared with eastern Denmark (mild ID before IF). The trends in changes in thyroid function and thyroid disease after IF were largely similar in western and eastern Denmark, and most differences between the regions attenuated.

Other studies of the effects of IF

Universal mandatory IF was in 2023 implemented in 126 countries worldwide (90). However, in only a few countries, this has been accompanied by systematic monitoring programs and none preplanned and as comprehensive as the DanThyr studies. Switzerland was one of the first countries to implement universal IF and hereby corroborates the early findings of the prevention of enlarged thyroid and goiter through IF (91), as also seen decades later in the DanThyr studies. Switzerland (92), Austria (93), and Tasmania (94) also observed an increase in hyperthyroidism after the introduction of IF, but the degree, duration, and subsequent decrease in incidence varied widely with the baseline iodine intake and level of fortification, indicating fewer detrimental effects with a cautious stepwise introduction of IF. In China, a comprehensive population study of thyroid disease was performed in 1999 and 2004 and followed up in 2019 after ID had been corrected to adequacy in one of three regions. In this region, they found a marked reduction in cases of goiter but a non-significant increase in thyroid nodules. In contrast to the DanThyr studies, they observed a reduction in the prevalence of thyroid autoantibodies. Hyper- and hypothyroidism trends were in the same directions as in the DanThyr studies, but only subclinical hyperthyroidism was statistically significantly decreased after the correction of iodine intake (95). The pre-fortification iodine level was closest to the level in eastern Denmark where also the smallest changes in thyroid markers were observed.

Mechanisms

The aim of the Danish IF program was a cautious increase in iodine intake of 50–60 µg/day, which was achieved between 1997–1998 (C1) and 2004–2005 (C2) through the fortified vehicles, while the iodine intake from other sources did not change during this period (46). However, a minor decrease in iodine intake was observed between C2 and C1b in women. This may be explained by the decreased iodine content in milk, but attrition may also affect the results because this limits the comparability between a cross-sectional (C2) and a follow-up study (C1b). Factors that may also contribute to unforeseen changes in iodine intake in a population

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or sub-population include, for e.g., changed intake of the primary sources of iodine (milk, fish/shellfish, salt) or products with high iodine content (seaweed, kelp). This underlines the importance of continued monitoring of iodine intake even after IF has been successfully implemented. Furthermore, despite low-adequate iodine intake in the general population, the iodine intake in pregnant women is still markedly below the recommended level in Denmark and many other countries, which is a major concern.

Hypertrophy and hyperplasia of the thyroid gland are well-known compensatory mechanisms in ID (96), and reversion of this may explain the reduced thyroid volume after IF. It has previously been observed that after IF, diffuse goiter and goiter in younger persons decreases in volume more readily than nodules and in older persons (97), supporting the finding in DanThyr that within-person correction of thyroid nodules is not prominent after IF, but fewer thyroid nodules may be observed in younger cohorts. A large decline in nodule prevalence was probably not to be expected, as comparisons across population studies, or cross-sectional studies with areas of different iodine intake (95), did not indicate a strong correlation between iodine intake and nodule prevalence. This contrasts with the strong association between iodine intake and thyroid volume. Increased Tg is an indicator of thyroid stress and is closely correlated with ID (64), thus the fall in Tg in western Denmark confirms the correction of ID. The increase in TSH at population level after IF mirrors the underlying decrease in hyperthyroidism and increase in hypothyroidism. The initial transient increase in hyperthyroidism may have been caused by failure of the Wolff-Chaikoff effect (98), and the sustained long-term decrease in hyperthyroidism was caused by a marked decrease in toxic nodules. Thus, although there was no apparent decrease in thyroid nodules after IF, fewer nodules may become toxic and induce hyperthyroidism after IF. Furthermore, there was a decrease in Graves' disease despite the overall increase in thyroid autoantibodies. The increase in thyroid autoantibodies was most pronounced in young women matching the sustained increase in hyperthyroidism in this group. Also, hypothyroidism, which was primarily of autoimmune origin, increased driven by the youngest age groups. This tendency should be studied further, as autoimmune thyroid disease can have adverse long-term consequences. Notably, the difference in iodine intake between the regions before IF had not resulted in large differences in thyroid autoimmunity, but the implementation of IF prompted a marked increase in thyroid autoimmunity in both regions.

Overall, although the iodine intake increased by approximately the same amount in the two regions, beneficial effects were stronger in western Denmark with previous moderate ID compared with eastern Denmark with previous mild ID. The approximation to the same levels of thyroid markers and thyroid disease despite continued differences in iodine intake suggests that differences in iodine intake are more problematic outside the WHO recommended range, but variations near or within the recommended intake range are possibly of less significance.

In addition to biological mechanisms, the results may also be influenced by external sources of bias. For example, the annual number of TSH measurements increased by 164% and the median TSH before initiation of thyroid hormone therapy fell markedly between 2001 and 2015 in eastern Denmark, in line with tendencies in other countries (99, 100). This may partly explain why thyroid hormone therapy in the register studies, and consequently the costs of thyroid hormone therapy, increased more than incident overt hypothyroidism observed in the laboratory studies. Furthermore, at the beginning of the DanThyr studies, subclinical biochemical thyroid disease was rarely treated, but at the end of the study period, many patients underwent treatment for subclinical hypothyroidism or even without a confirmatory thyroid function test (99). Thus, it is highly plausible that fewer patients at the end of the study period would progress to develop overt biochemical disease, thus lowering the incidence of overt hypothyroidism in the DanThyr laboratory studies.

Overall, the Danish IF program has had consequential impact on public health: a marked reduction in cases of hyperthyroidism was achieved, while conversely, the increase in the incidence of hypothyroidism ascribed to IF was more moderate. However, while most beneficial clinical effects of IF were observed in the oldest age groups, the outcomes may be more mixed in the younger age groups who will grow up in iodine sufficiency and thus probably have a lower risk of thyroid dysfunction, but conversely also had a higher rise in thyroid autoimmunity after IF. Thus, the full impact of IF on public health will probably not be known for decades.

The data indicate that iodine intake levels at the lower end of the recommended range might constitute an optimal level for the prevention of thyroid disease, and it can be questioned whether additional clinical benefits can be achieved by further increasing the iodine intake. However, this does not consider the effects on fetal neurological development during pregnancy, where the optimal iodine intake level may differ.

The DanThyr studies were extensive in design and resource consumption, and although the WHO recommends monitoring of IF programs, such extensive designs are not always feasible. We suggest that the minimum monitoring program includes: (a) iodine content in the primary iodine sources (both natural and the fortified iodine sources) and iodine intake from these sources, (b) median UIC in the overall population and relevant sub-populations, and (c) if possible, indicators of thyroid disease in line with the quote by Peter Laurberg, 1994: 'The efforts [of IF] should be used to prevent measurable disease, not to make laboratory values conform to arbitrary limits' (101).

Primary strengths and limitations

The primary strengths of the DanThyr studies are, first, the preplanned collection of baseline data before the implementation of IF. Secondly, the DanThyr studies evaluated the effect of baseline iodine levels and IF on several central parameters in the process from iodine in the vehicles, iodine intake, thyroid biomarkers and signs and symptoms, and incident overt thyroid disease, to treatment. Additionally, the populations were well described with many relevant covariables. This has improved the possibility of elucidating the mechanisms behind the observed effects of IF. Thirdly, triangulation via the application of four different study designs and different methods is a major strength because the specific strengths and limitations of the different methods complement each other and strengthen the confidence in the findings.

The primary limitation of the DanThyr studies is the omission of children and pregnant women from the study populations. Children and pregnant women are especially vulnerable to ID, and the effects of IF should also be monitored in these groups.

In establishing and leading the DanThyr monitoring program, the steering group has been a key strength in ensuring overview, continuity, and have close communications with and support from the authorities (102). Based on the iodine intake observed in C1b and in pregnant women, the DanThyr group recommended an increase in the level of IF, and from July 2019, the level of iodine added to household salt and salt in bread and baked goods in Denmark was increased from 13 ppm to 20 ppm (103). The implications of this increase will be followed by the current DanThyr group. Thus, a thorough monitoring program such as DanThyr has the power to influence and improve strategic public health prevention initiatives.

Conclusion and perspectives

Through a well-planned monitoring program applying four different designs and assessing key parameters of iodine intake and thyroid health and disease, the DanThyr studies provided new knowledge of the effects of IF. The Danish IF was successfully implemented and increased the population's iodine intake from mild–moderate ID to low adequacy. This caused an overall improvement of thyroid health, with fewer cases of hyperthyroidism and lower thyroid volume. However, an increase in cases of hypothyroidism and thyroid autoimmunity, especially in the youngest age groups, should be recognized.

Worldwide ID is pervasive without preventive strategies, and IF is the recommended method for securing optimal iodine nutrition (19). We hope that the DanThyr studies can inform clinicians and policymakers of the effects of IF and that DanThyr can inspire the monitoring of future public health initiatives aiming at influencing large population groups.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-23-0230.

Declaration of interest
The authors declare no conflicts of interest that may be perceived as prejudicing the impartiality of the study reported.

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