Trends in Costs of Thyroid Disease Treatment in Denmark during 1995–2015

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Keywords

Iodine · Thyroid diseases · Costs and cost analysis · Health care costs · Epidemiology

Abstract

Background: Iodine fortification (IF) may contribute to changes in costs of thyroid disease treatment through changes in disease patterns. From a health economic perspective, assessment of the development in costs of thyroid disease treatment in the population is pertinent. **Objectives:** To assess the trends in annual medicine and hospital costs of thyroid disease treatment during 1995–2015 in Denmark, i.e., before and after the introduction of mandatory IF in 2000. **Methods:** Information on treatments for thyroid disease (antithyroid medication, thyroid hormone therapy, thyroid surgery, and radioiodine treatment) was obtained from nationwide registers. Costs were valued at 2015 prices using sales prices for medicines and the Danish Diagnosis-Related Group (DRG) and Danish Ambulatory Grouping System (DAGS) tariffs of surgeries/radioiodine treatments. Results were adjusted for changes in population size and age and sex distribution. **Results:** The total direct medicine and hos-

pital costs of thyroid disease treatment increased from EUR ~190,000 per 100,000 persons in 1995 to EUR ~270,000 per 100,000 persons in 2015. This was mainly due to linearly increased costs of thyroid hormone therapy and increased costs of thyroid surgery since 2008. Costs of antithyroid medication increased slightly and transiently after IF, while costs of radioiodine treatment remained constant. Costs of thyroid hormone therapy and thyroid surgery did not follow the development in the prevalence of hypothyroidism and structural thyroid diseases observed in concurrent studies. **Conclusion:** The costs of total direct medicine and hospital costs for thyroid disease treatment in Denmark increased from 1995 to 2015. This is possibly due to several factors, e.g., changes in treatment practices, and the direct effect of IF alone remains to be estimated.

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Introduction

Iodine fortification (IF) is implemented in more than 120 countries worldwide [1] to increase iodine intake, prevent thyroid diseases, and thus reduce treatment costs.

The window of adequate iodine intake is narrow [2], hence IF decreases deficiency-associated diseases (e.g., goiter) but may increase excess-associated diseases (e.g., hypothyroidism) in a population [2]. This shift in disease pattern was seen in Denmark after the implementation of mandatory IF in 2000 [3–6].

Economic assessment is relevant, but often neglected, in the evaluation of IF programs. Optimal utilization of limited health care resources requires economic evaluation of health care programs including estimates of incremental cost and health consequences. The costs for the intervention in IF are minor and thus the development in treatment costs is the primary interest. Economic assessment of medicine and hospital costs for thyroid disease is more robust and expected to be in the same direction as assessments of indirect and non-health service costs because fewer assumptions are required. Thus, we chose to estimate direct costs of treatment. Crudely, thyroid diseases present as hyperthyroidism, hypothyroidism, and/or structural changes of the thyroid gland. These are treated with antithyroid medication, thyroid hormone therapy, thyroid surgery, and/or radioiodine treatment. Vandevijvere et al. [7] estimated the potential savings in direct, indirect, medical, and nonmedical costs of thyroid nodular disease in Belgium to be EUR ≥ 14 million per year 4–5 years after the implementation of IF. However, they did not include costs of other thyroid diseases. It has not yet been evaluated how the total direct costs of thyroid disease treatment developed and whether the theoretic shift in disease pattern following IF is mirrored in the treatment costs.

Danish health registers are unique sources of complete national individual-level data on treatments [8]. Through nationwide registers, we aimed to assess the development in annual total direct medicine and hospital costs of thyroid disease treatment (medications, surgery and radioiodine treatment) during 1995–2015, i.e., before and after the introduction of IF in 2000.

Materials and Methods

Design and Study Population

This register-based study included costs of prescription medicines, and inpatient and outpatient hospital treatments for thyroid diseases in the entire Danish population during 1995–2015. Denmark has a universal tax-funded health care system [9]. Almost all patients with thyroid diseases are treated in the public health care system. Administrative registers contain individual-level information on all redeemed prescriptions, health service use, and demographics for Danish citizens. Linkage between registers is possible via the unique personal identification number assigned to all Danish citizens [8].

The time span from IF until a new steady state in thyroid disease occurrence is unclear. We decided to include data from 5 years before IF (i.e., at the start of the Danish National Prescription Registry in 1995) to 15 years after IF. Eastern and Western Denmark had mild and moderate iodine deficiency (ID), respectively, before IF and different patterns and changes in thyroid diseases after IF [4]. Therefore, changes in costs were assessed combined and by region.

Iodine Fortification

Before 1998 IF was prohibited in Denmark. From 1998 voluntary IF with 8 ppm of salt was endorsed but proved inefficient [4]. From July 2000 fortification of all household salt and salt in all bread with 13 ppm was mandatory [3]. The cost of iodization is negligible and not included in this study [7].

Costs of Thyroid Medication: Antithyroid Medication and Thyroid Hormone Therapy

Information on thyroid medication was obtained from the Danish National Prescription Registry, which contains all redeemed prescriptions. Antithyroid medication and thyroid hormone therapy were identified by the Anatomic Therapeutic Chemical (ATC) classification codes H03B (antithyroid medication) and H03A (thyroid hormone therapy) from 1995 to 2015. The defined daily doses (DDD) according to WHO (http://www.whooc.no/atc_ddd_index/) were calculated per redeemed prescription.

In Denmark, pharmacies have exclusive rights to sell prescription-only medication. Prices are set nationally through tenders every 14 days. We obtained the pharmacy retail prices per DDD, including user payments and excluding VAT, from the Danish Health Data Authority. The mean prices in 2015 were calculated per DDD for every medication type, brand, and package size. To remove the impact of fluctuation of prices and inflation we applied mean prices from 2015 in the calculation of costs for all years. The price of carbimazole (ATC H03BB01) increased approximately 250% from 2014 to 2015, and therefore the price per DDD in 2014 was applied in the cost calculations.

An association between iodine intake and thyroid cancer is unestablished, and the time span between IF and potential changes in thyroid cancer prevalence may be >20 years [10]. Therefore, costs of thyroid hormone therapy following thyroid cancer surgery were excluded, equaling 1.2–2.6% of annual thyroid hormone therapy costs.

Costs of Thyroid Surgery and Radioiodine Treatment

All thyroid surgeries are registered in the Danish National Patient Registry. Thyroid surgeries performed during 1995–2015 were identified by the Nordic Classification of Surgical Procedures (codes 08060–08200 before 1996 and BAA20–BAA60(A) after 1996). Thyroid surgeries classified with a diagnosis of thyroid cancer (ICD codes 19399 and DC739) up to 3 months after surgery were excluded, equaling 9–17% of annual surgeries.

Radioiodine treatments were not registered in the Danish National Patient Registry until 2004. Treatments from 2004 to 2015 were identified by the codes BWGGI and WT(F-L)RNJLXX for benign disease. From 1995 to 2003 doses given (600 MBq), and indication (benign/malignant) were reported from the treating hospital departments to the National Institute of Radiation Protection. We defined one dose equivalent to one treatment [11]. The

location of the treating hospital was used as a proxy for region. Trends are considered reliable within the two data sources, but not between.

The Danish Diagnosis-Related Group (DRG) and Danish Ambulatory Grouping System (DAGS) tariffs contain all hospital costs related to inpatient and outpatient treatment, respectively. DRG/DAGS tariffs are calculated nationally and express the mean costs of a treatment in the Danish health care system [12]. DRG/DAGS tariffs for 2015 were retrieved for each type of thyroid surgery and radioiodine treatment and applied to all years.

Age, Sex, and Region

Information on date of birth, sex, and region (mild or moderate ID before IF) was obtained via linkage to the Civil Registration System and linked to each redeemed prescription, surgery, and radioiodine treatment.

Analyses

Each DDD, thyroid surgery, and radioiodine treatment was multiplied by the corresponding cost per DDD or DRG/DAGS tariff. The total sum of costs and the sum of costs for each type of treatment were calculated per year and region. To adjust for changes in population size and age and sex distribution the yearly costs were standardized to the distribution in 2000 by region by multiplying the relative difference in population strata. By comparing the unstandardized costs to the standardized costs the proportion of change attributable to change in the population size and demographic distribution was calculated. Results are presented as costs per 100,000 persons. For medications, mean and 95% confidence intervals (CI) of costs per person per year are reported. All costs were calculated in Danish kroner (DKK) and converted to euro (EUR) by the exchange rate DKK/EUR of 7.46.

Ethics

According to Danish legislation approval from the Danish Health Research Ethics Committee System is not required for studies based solely on registers. Approval from the Danish Data Protection Agency was obtained for handling the data (journal No. 2003-53-0865).

Results

Per January 1, 2000 there were 5,330,119 persons with a Danish personal registration number. A total of 2,394,963 and 2,935,156 persons lived in the regions with mild and moderate ID, respectively, before IF. During 1995–2015, 100 million DDDs of antithyroid treatment, 404 million DDDs of thyroid hormone therapy, 33,773 thyroid surgeries, and 42,091 radioiodine treatments were identified. The unit costs in Table 1 were applied.

Total Direct Medicine and Hospital Costs

The total direct medicine and hospital costs for thyroid disease treatment increased by EUR ~80,000 per 100,000 persons from 1995 to 2015 (Fig. 1; Table 2).

Table 1. Direct costs per thyroid disease treatment unit

Treatment	Cost per unit, EUR
Antithyroid medication (per DDD)	0.22–0.46
Thyroid hormone therapy (per DDD)	0.13–0.39
Thyroid surgery	3,216–4,747
Radioiodine treatment	572–2,053

The range specifies the lowest and highest price per treatment unit. 2015 prices applied. DDD, defined daily dose.

Antithyroid Medication

Costs of antithyroid medication increased before IF and continued to increase until 2003/2004 followed by a decrease. In 2009 the costs were below the costs at IF (Table 2). This development was primarily driven by changes in the region with moderate ID before IF (Fig. 2a). The decrease in costs from 2000 to 2015 was 19.5% when standardized for changes in population size and age and sex distribution, and 8.1% in the unstandardized costs (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000485973). During 2001–2008 the cumulated additional costs compared to 2000 were EUR 30,000 per 100,000 persons. During 2009–2015 the cumulated savings compared to 2000 were EUR 28,000 per 100,000 persons (Table 2). The mean cost of antithyroid medication was EUR 75.1/user/year (95% CI 74.9–75.2).

Thyroid Hormone Therapy

Costs of thyroid hormone therapy increased almost linearly from 1995 to 2015 (Table 2). The costs and development in costs per 100,000 persons were almost equal in the regions with moderate and mild ID before IF (Fig. 2b). Changes in population size and age and sex distribution accounted for 19.4% of the increase in unstandardized costs from 2000 to 2015 (online suppl. Table 1). The mean cost of thyroid hormone therapy was EUR 35.5/user/year (95% CI 35.4–35.5).

Thyroid Surgery

Costs of thyroid surgeries were relatively constant during 1995–2008 followed by a fluctuating overall increase (Table 2). The tendencies were roughly similar in the two regions but the costs per 100,000 persons were higher in the region with moderate ID before IF (Fig. 2c). Changes in population size and age and sex distribution accounted for 35.5% of the increase in unstandardized costs from

Fig. 1. Total costs for thyroid disease treatments per 100,000 persons in Denmark. Costs were standardized for changes in population size and age and sex distribution. 2015 prices applied. The vertical line marks the implementation of mandatory iodine fortification in 2000.

2000 to 2015 (online suppl. Table 1). Less than 3.5% of the patients had more than one surgery.

Radioiodine Treatment

From 1995 to 2003 the total national costs for radioiodine treatment was constant (Table 2), but decreased in the region with former mild ID and increased in the region with former moderate ID. From 2004 to 2015 costs of radioiodine treatments were constant, but marginally higher and fluctuating in the region with moderate ID before IF (Fig. 2d). Less than 4% of the patients received more than one treatment.

Discussion

The total direct medicine and hospital costs for thyroid disease treatment increased continuously during 1995–2015. This was mainly due to costs for thyroid hormone therapy, which increased during the whole period, and costs for thyroid surgery, which increased during recent

years. Costs for antithyroid treatment increased transiently after IF and fell below prefortification level. Total costs for radioiodine treatment remained fairly constant throughout the study period.

We expected the development in treatment costs to reflect the development in disease prevalence. This was true for costs of antithyroid medication that followed the curve of incident hyperthyroidism observed in previous studies: a transient increase after IF followed by a decrease below the level before IF [13, 14]. Contrarily, thyroid hormone therapy costs did not follow the expected curve: a Danish study of laboratory results found a 23% higher risk of incident overt hypothyroidism in 2003–2005 compared to 1997–1998 driven by an increase only in the region with moderate ID before IF [5]. During the same period we found a 42% increase in thyroid hormone therapy costs in both regions. Likewise, thyroid surgery costs did not reflect the decrease in thyroid volume and enlargement after IF found in Danish clinical cohort studies [15, 16]. It is unlikely that the increase in thyroid surgery costs from 2008 is associated with IF. Due to

Table 2. Costs for thyroid disease treatments (EUR) per 100,000 persons in Denmark

Year	Antithyroid medication	Thyroid hormone therapy	Thyroid surgeries	Radioiodine treatment ³	Total cost for treatments
1995	25,496	31,915	100,012	31,743	189,165
1996	27,251	33,270	99,797	35,721	196,039
1997	26,041	34,425	101,328	36,392	198,187
1998 ¹	27,674	36,095	103,158	36,691	203,617
1999	29,393	37,590	103,182	37,076	207,241
2000 ²	30,867	39,647	107,636	36,796	214,947
2001	34,143	42,165	101,630	38,202	216,140
2002	35,912	44,793	100,150	37,201	218,057
2003	36,707	47,592	100,869	35,190	220,358
2004	36,602	50,505	98,820	21,116	207,043
2005	35,400	52,519	104,955	22,380	215,255
2006	33,721	55,397	103,812	23,678	216,609
2007	32,771	58,487	105,150	26,135	222,543
2008	31,486	62,104	99,311	16,981	209,882
2009	29,819	64,334	118,628	19,174	231,955
2010	28,624	69,147	118,856	24,546	241,173
2011	27,518	73,722	118,496	25,943	245,679
2012	26,624	76,456	109,828	25,536	238,445
2013	25,513	79,692	119,930	23,416	248,552
2014	24,723	82,679	126,761	23,441	257,604
2015	24,856	86,203	132,158	25,273	268,490

Standardized for changes in population size and age and sex distribution. 2015 prices applied. ¹ Implementation of voluntary iodine fortification. ² Implementation of mandatory iodine fortification. ³ Number of radioiodine treatments was obtained from the National Institute of Radiation Protection in 1995–2003 and from the Danish National Patient Registry in 2004–2015.

changes in data sources it was difficult to assert whether the development in radioiodine treatment costs changed in accordance with hyperthyroidism and structural thyroid changes, but the results do not indicate this. Thus, changes in disease pattern after IF do not fully explain the changes in costs of thyroid disease treatment.

Several other factors may have influenced the treatment costs. Firstly, changes in treatment practices (i.e., diagnostic activity and indication for treatment) over 20 years can be expected and clinically warranted but will unavoidably influence total treatment costs. Thus, a recent Danish study found that the annual number of TSH measurements in general practices in the Copenhagen area increased by 164% and the median TSH at initiation of thyroid hormone treatment decreased from 13 to 7.3 mU/L during 2001–2015 [17]. This may explain a substantial part of the increase in prescriptions and thereby costs of thyroid hormone therapy. The same pattern was observed by Taylor et al. [18] who found that a larger proportion of British patients with subclinical hypothyroidism were treated from 2001 to 2009, and more guidelines

recommend treatment of subclinical hypothyroidism [19, 20] despite continued discussion of best practice [21]. Likewise, the annual number of fine needle biopsies (procedure code: KTBA10) in our data approximately doubled from the start of 2000 to the start of 2010, and may indicate an increased diagnostic activity in structural thyroid diseases. Secondly, iodine intake may have fluctuated beyond the effect of IF. Following IF, median urinary iodine concentration increased from 61 µg/L in 1997/1998 to 97–114 µg/L in 2004/2005 [22] in cross-sectional studies, but a follow-up of the first study in 2008/2010 found a urinary iodine concentration of 83 µg/L [23]. The intake of the main sources of iodine in Denmark, salt and milk [24], remained constant [25, 26] but the iodine content in milk decreased, which may explain the decreased iodine excretion from 2004 to 2010 [22]. Thirdly, both smoking and alcohol consumption decreased during the study period [27, 28]. This may affect the pattern of thyroid diseases as smoking is associated with increased risk of goiter [29] while alcohol intake may be associated with a decreased risk of goiter, thyroid nodules [30] and Graves

Fig. 2. Costs for antithyroid medication (a), thyroid hormone therapy (b), thyroid surgery (c), and radioiodine treatment (d) per 100,000 persons stratified by region. Costs were standardized for changes in population size and age and sex distribution. 2015 prices applied. The vertical line marks the implementation of mandatory iodine fortification in 2000. ID, iodine deficiency.

(Figure continued on next page.)

hyperthyroidism [31]. Both smoking and alcohol intake are associated with lower risk of autoimmune hypothyroidism [32] but not to an extent that explains the steep increase in thyroid hormone therapy.

Vandevijvere et al. [7] applied the development in thyroid nodular disease prevalence observed in the Danish cohort studies to the Belgian population and thus found theoretical projected savings provided that all other factor remained stable. However, over 20 years it is unlikely that other factors remain constant, and evaluation in real life settings must consider the changing factors.

It is a strength that 2015 prices were applied to treatments in all years and results were standardized to the demographic composition of 2000, so changes in these did not affect the results. The validity and completeness of the Danish registers is high and has increased over the past 20 years [33]. Thyroid hormone therapy and thyroid surgeries were excluded if the patient was diagnosed with thyroid cancer between 1990 and the treatment. Thus there is risk of truncation as treatments in recent years had longer follow-up. The proportion of surgeries ex-

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cluded was constant during 1995–2015, but excluded thyroid hormone therapies increased from 1.2 to 2.6%. This may also be explained by improved survival in thyroid cancer patients [34].

Estimation of only direct medicine and hospital costs produces reliable but conservative estimates likely in the same direction as all direct, indirect, medical, and non-medical costs. We chose not to include costs of diagnosis, follow-up, and primary health care, e.g., monitoring visits with the general practitioner, which is expected to be sub-

stantial. Furthermore, we did not include secondary costs such as consequences of changes in cognitive function and sick days on productivity, and changes in risk of coronary heart disease secondary to thyroid disease. Inclusion of these costs would require more assumptions and render the estimates less reliable. However, future health-economic evaluations including this array of variables are warranted. This will further strengthen the basis for decision making in IF programs.

In conclusion, the costs of total direct medicine and hospital costs for thyroid disease treatment in Denmark increased from 1995 to 2015. This is possibly due to several factors, e.g., changes in diagnostic activity, treatment practices, and incidence of thyroid diseases. Thus, although the incidence of thyroid diseases is monitored closely, the impact from other factors makes a reliable estimation of the specific economic impact of IF difficult.

Acknowledgments

The authors acknowledge support from Helsefonden, DanThyr, and EUthyroid.

Disclosure Statement

The authors declare no conflict of interest.

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