

## RESEARCH

# Register-based information on thyroid diseases in Europe: lessons and results from the EUthyroid collaboration

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## Abstract

**Objective:** Registers of diagnoses and treatments exist in different forms in the European countries and are potential sources to answer important research questions. Prevalence and incidence of thyroid diseases are highly dependent on iodine intake and, thus, iodine deficiency disease prevention programs. We aimed to collect European register

## Key Words

- ▶ Europe
- ▶ registries
- ▶ iodine
- ▶ thyroid diseases

data on thyroid outcomes to compare the rates between countries/regions with different iodine status and prevention programs.

*Design:* Register-based cross-sectional study.

*Methods:* National register data on thyroid diagnoses and treatments were requested from 23 European countries/regions. The provided data were critically assessed for suitability for comparison between countries/regions. Sex- and age-standardized rates were calculated.

*Results:* Register data on  $\geq 1$  thyroid diagnoses or treatments were available from 22 countries/regions. After critical assessment, data on medication, surgery, and cancer were found suitable for comparison between 9, 10, and 13 countries/regions, respectively. Higher rates of antithyroid medication and thyroid surgery for benign disease and lower rates of thyroid hormone therapy were found for countries with iodine insufficiency before approx. 2001, and no relationship was observed with recent iodine intake or prevention programs.

*Conclusions:* The collation of register data on thyroid outcomes from European countries is impeded by a high degree of heterogeneity in the availability and quality of data between countries. Nevertheless, a relationship between historic iodine intake and rates of treatments for hyper- and hypothyroid disorders is indicated. This study illustrates both the challenges and the potential for the application of register data of thyroid outcomes across Europe.

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## Introduction

Register-based data on treatments and diagnoses of thyroid disease can be used as proxies for thyroid disease frequency in a population. This has, for example, been successfully utilized in Denmark (1). In many European countries, treatments for thyroid disease and/or diagnoses of thyroid disorders are documented in nationwide or regional registers. This encompasses registers of diseases, medications and other treatments, hospital admissions, and ambulatory care, as well as registries related to health insurance. Ideally, for use in research projects, a register should cover the entire country/region or a large, well-defined sub-population whereby it is representative, and the data should be of acceptable validity (2).

European registers have previously been collated for research projects in, for example, melanoma (3), asthma (4), and cerebral palsy (5) and several initiatives to promote and improve the collaboration and utilization of registers in Europe are established (6, 7). However, the availability and applicability of register data for assessment of thyroid outcomes from the European countries have not yet been examined. After a thorough assessment of the quality and comparability of data across countries, European registers can potentially represent valuable and efficient data sources for evaluating differences in thyroid outcomes across the countries/regions.

Iodine intake in a population is a main factor behind thyroid disease epidemiology. Iodine deficiency is associated with adverse outcomes ranging from severe mental retardation and stunting to goiter/thyroid nodules and hyperthyroidism (8). However, the window of adequate iodine intake is narrow, hence, iodine excess may increase the risk of hypothyroidism and autoimmune thyroid disorders in a population (9).

Most regions of Europe will be iodine deficient without programs to prevent iodine deficiency disorders (IDD). However, the implementation and type of IDD prevention programs depend on stakeholder barriers, political prioritization (10), and cultural differences. The IDD prevention programs range from general recommendations for intake of iodine-rich foods, over recommendations for iodine supplementation especially for pregnant and lactating women, to voluntary or mandatory iodine fortification (IF), most commonly addition of iodine to table salt and salt in bread (11). An overview of IF programs and iodine intake across 23 European countries/regions are presented in Table 1. The optimal level of iodine intake and the most effective IDD prevention program remains to be established.

In many countries, the assessment of median urinary iodine concentration in representative population samples is used to classify the iodine status and to steer IDD

**Table 1** IDD prevention and iodine intake in the European countries.

Country	Country code	Iodine fortification strategy (13, 14, 15, 16, 17, 18)	Iodine intake, Median UIC, µg/L (population, year) (18, 19, 20, 21, 22, 23)
Belgium	BE	Voluntary fortification of salt, 10–15 ppm since 2009	Insufficient, 80 (SAC, 1998) Adequate, 113 (SAC, 2010–2011)
Bulgaria	BG	Mandatory fortification of salt, 28–55 ppm since 1994/1996	Adequate, 111 (SAC, 1996) Adequate, 182 (SAC, 2008) Adequate, 176 (SAC, 2012)
Croatia	HR	Mandatory fortification of salt, 19 ppm since 2011	Adequate, 140 (SAC, 2002) Adequate, 248 (SAC, 2009)
Czech Republic	CZ	Voluntary fortification of salt, 27 ppm since 2016	Adequate, 119 (SAC, 2000) Adequate 163 (SAC, 2010)
Denmark	DK	Mandatory fortification of salt, 13 ppm since 2000	Insufficient, 61 (A, 1997–1998) Adequate, 101 (A, 2004–2005) Adequate, 145 (SAC, 2015)
Finland	FI	Voluntary fortification of salt, 25 ppm since approx. 1946	Adequate, 164 (A, 1997) Insufficient, 83 (A, 2013)
Germany	DE	Voluntary fortification of salt, 20 ppm since 1993	Adequate, 148 (SAC, 1999) Adequate, 122 (SAC, 2003–2006) Insufficient, 89 (SAC+A, 2014–2017)
United Kingdom	UK		
Northern Ireland		None	Adequate, 111 (SAC, 2014–2015)
Scotland		None	N/A
Greece	GR	Voluntary fortification of salt, 30 ppm since 1987	Adequate, 202 (2001) Adequate, 132 (A, 2017–2018)
Hungary	HU	Mandatory fortification of salt, 19 ppm since 2013	Insufficient, 80 (SAC, 1994–1997) Adequate, 228 (SAC, 2005)
Iceland	IS	None	Adequate, 150 (A, 1998) Adequate, 200 (A, 2007–2008)
Ireland	IE	None	Insufficient, 82 (A, 1999) Adequate, 111 (SAC, 2014–2015)
Israel	IL	None	Insufficient, 83 (SAC, 2016)
Latvia	LV	Voluntary fortification of salt, 20–50 (40–100) ppm since 2005	Insufficient, 59 (SAC, 2000) Adequate, 110 (SAC, 2010–2011)
North Macedonia	MK	Mandatory fortification of salt, 25 ppm since 1999	Adequate, 241 (2007) Adequate, 216 (2016)
Norway	NO	Voluntary fortification of salt, 5 ppm since 1938	Adequate, 104 (1999–2001) Insufficient, 75 (A, 2017–2018)
Poland	PL	Mandatory fortification of salt, 23 ppm since 1997	Insufficient, 84 (SAC, 1999) Adequate, 112 (SAC, 2009–2011) Adequate, 120 (SAC, 2017) Adequate, 106 (SAC, 2010)
Portugal	PT	None	Adequate, 140 (A, 2003–2005)
Slovenia	SI	Mandatory fortification of salt, 19 ppm since 1999	Adequate, 109 (SAC, 1995, 2000–2002) Adequate, 117 (2009–2010) Adequate, 173 (SAC, 2011–2012)
Spain	ES	Voluntary fortification of salt, 60 ppm since 1983	Adequate, 125 (SAC, 2006–2007)
Sweden	SE	Voluntary fortification of salt, 10 ppm since 1936, 50 ppm since 1966	
Switzerland	CH	Voluntary fortification of salt, 25 ppm since 2014	Adequate, 115 (SAC, 1999) Adequate, 120 (2009) Adequate, 137 (SAC, 2015)

A, adults; N/A, not available; SAC, school-aged children; UIC, urinary iodine concentration.

prevention programs. While this approach is relatively simple, it is not sufficient to evaluate the aim of such prevention programs, which is to reduce the prevalence and incidence of thyroid diseases and related treatments and to save expenditures in healthcare systems (12). This can potentially be achieved by analyses of register data. We hypothesized that efficient IDD prevention

programs ensuring sufficient iodine intake are robustly associated with a low burden of thyroid-related diseases in populations.

The EUthyroid project was an ambitious collaborative project with participation and representatives from most EU countries funded by the European Union's Horizon 2020 research and innovation program under grant

agreement no. 634453. The overall aim of the EUthyroid project was to ‘evaluate iodine deficiency prevention and monitoring programs in European countries, to initiate capacity building for harmonized European ID prevention and monitoring programs’.

In this paper, we report lessons and results from work package 1 of the EUthyroid project. Firstly, we evaluate the availability, applicability, and comparability of the register data on thyroid outcomes in the European countries, and second, we report country-specific rates of thyroid outcomes and seek to identify patterns in the relationship with iodine supply across Europe.

## Materials and methods

### Register data

Representatives from each country participating in the EUthyroid project were requested to deliver national register data on diagnoses, medical treatments, and procedures for thyroid disorders. All data were requested for the calendar years 2011–2014 and stratified by sex and age in 5-year intervals. If this was not available, we allowed for the available data that best approximated these criteria, for example, data from 2015, data from a well-defined sub-population, or data in 10-year age intervals. Specific diagnoses and treatments requested were:

*Diagnoses:* Annual number of persons diagnosed with thyroid cancer (ICD-10: C73), congenital iodine-deficiency syndrome (ICD-10: E00), iodine-deficiency-related thyroid disorders and allied conditions (ICD-10: E01), subclinical iodine-deficiency (ICD-10: E02), other hypothyroidism (ICD-10: E03), other nontoxic goiter (ICD-10: E04), thyrotoxicosis/hyperthyroidism (ICD-10: E05), thyroiditis (ICD-10: E06), other thyroid disorders (ICD-10: E07), and one or more thyroid related diagnoses (ICD-10: E00–E07).

*Treatments:* Annual number of persons with at least one dispensed dose and total number of defined daily doses of antithyroid medication and thyroid hormone therapy. Annual number of persons with at least one procedure and the total number procedures for all thyroid surgeries, thyroid surgeries with benign indication, all radioiodine treatments, radioiodine treatments with benign indication, and fine needle biopsies.

The demographic data of the total populations (total number of individuals and stratified by sex and 5-year age

intervals) were derived from Eurostat (<http://ec.europa.eu/eurostat>) or provided from the national EUthyroid representatives for regional or sub-national populations.

Ethical and/or data handling approvals were obtained in each country according to national regulations to obtain aggregated register data. Only aggregated data were collected and, thus, no patient-level data (personal data) were handled thereby protecting the privacy of the individuals.

### Critical assessment and selection of data and variables

The national representatives were also requested to provide a description of the data sources and health care organization factors relevant to assess the completeness and validity of the data provided.

The applicability of the provided data from each country was critically assessed. For inclusion in the database and calculation of raw rates the provided data had to fulfill the criteria for the requested data. For comparison between countries and calculation of standardized rates, the data and variables had to be stratified by sex and age, collected from comparable data sources, and registered by comparable methods. The critical assessment was conducted by the senior author, BHT.

### Iodine intake

Populations’ iodine intakes were derived from published reports of urinary iodine concentrations in school-aged children or adults and summarized in [Table 1](#). Iodine intake was classified as insufficient, adequate, or excess according to current WHO epidemiological recommendations (24). Early and recent iodine intake were classified as iodine intake approximately 15–20 years before and after 2001, respectively.

### Statistical methods

Rates of medications were calculated as 1-year period prevalence per 10,000 persons. Rates of diagnoses were calculated per year per 10,000 persons. Raw rates were calculated with the treatments and diagnoses as the numerator and the demographic data of the population as the denominator in the provided sex and/or age strata where possible.

Standardized rates were calculated to remove the effect of the differences in sex and age distributions between

the European countries. This was done by calculating the proportion of each sex and age-specific strata in the total European Standard Population (25) and multiplying this by the raw rate in the corresponding strata for each country before summarizing the overall standardized rate in each country. When data were provided for more than one calendar year, the rates were calculated as the average of the calendar years available.

Comparisons between countries were done using standardized rates. No formal statistical tests were applied in the comparison of rates between countries.

## Results

### Data availability and data assessment

Table 2 provides an overview of the data sources and Fig. 1 provides an overview of the flow of the data acquisition, critical assessments, and calculations.

Register data for at least one thyroid outcome was available and provided from 22 out of 23 participating countries/regions. However, the critical assessment concluded that data from three countries were considered

unsuitable to be included in the database. See an overview of data and assessments in the Supplementary Tables 1 and 2 (see section on [supplementary materials](#) given at the end of this article). Raw rates for data included in the database are presented in the Supplementary Tables 3, 4, and 5.

The outcome variables were grouped into six categories: thyroid medication, thyroid surgery, radioiodine treatment, fine needle biopsies, diagnoses of thyroid diseases, and diagnoses of incident thyroid cancer. Sex- and age-stratified data from all categories were available from four countries, whereas data from only one outcome variable were available from four countries. The critical assessment of the data included in the database found that data on the use of thyroid medication, number of thyroid surgeries, and incidence of thyroid cancer were of acceptable quality and thus appropriate for calculation of standardized rates and comparison between countries.

In contrast, data on diagnoses of thyroid diseases except for thyroid cancer were not considered suitable for comparisons across countries. In some countries, registrations included patients treated in primary care whereas only patients attending hospitals were included in other countries, and it was not possible to distinguish

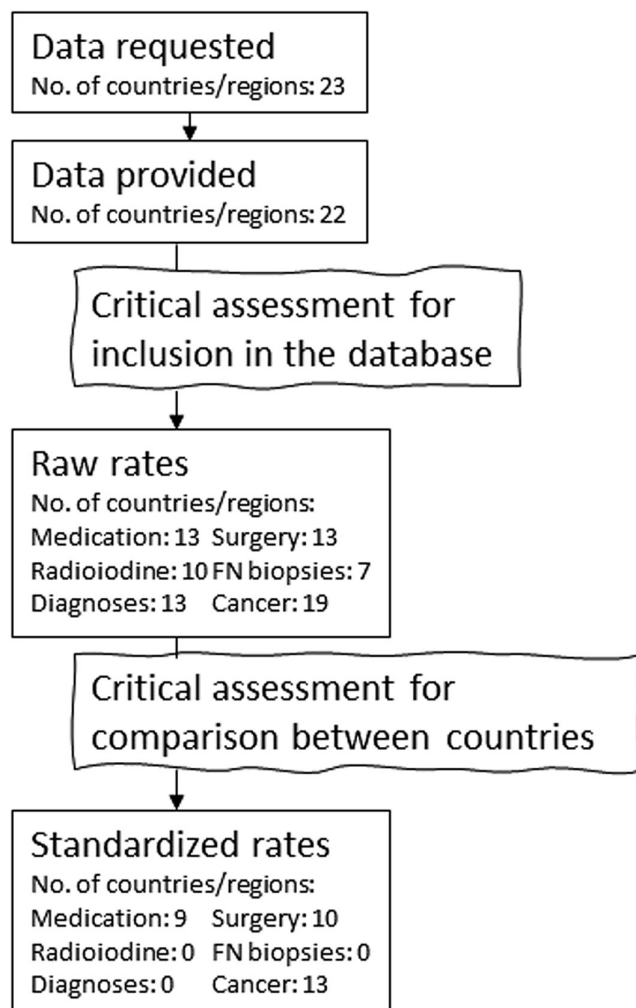
**Table 2** Data requested and provided with stratification level and area.

Country	Country code	Thyroid medication	Thyroid surgery	Radio-iodine	Fine needle biopsies	Diagnoses of thyroid disease	Diagnoses of thyroid cancer
Belgium	BE	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	N/A	<b>Sex/age</b>
Bulgaria	BG	<b>Sex</b>	<b>Sex</b>	<b>Total</b>	<b>Sex</b>	<b>Sex</b>	<b>Sex/age</b>
Croatia	HR	N/A	N/A	N/A	N/A	N/A	<b>Sex</b>
Czech Republic	CZ	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<b>Sex</b>
Denmark	DK	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>
Finland	FI	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>
Germany	DE	<i>Sex/age<sup>a</sup></i>	N/A	N/A	N/A	<i>Sex/age<sup>a</sup></i>	N/A
United Kingdom	UK						
Northern Ireland		N/A	N/A	N/A	N/A	N/A	<b>Sex/age</b>
Scotland		N/A	N/A	N/A	N/A	N/A	<b>Sex/age</b>
Greece	GR	<b>Total<sup>a</sup></b>	N/A	<b>Total<sup>a</sup></b>	N/A	<b>Total<sup>a</sup></b>	<b>Total<sup>a</sup></b>
Hungary	HU	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	N/A	<b>Age</b>	<b>Age</b>
Iceland	IS	<b>Sex</b>	N/A	N/A	N/A	N/A	<b>Sex</b>
Ireland	IE	N/A	N/A	N/A	N/A	N/A	<b>Sex/age</b>
Israel	IL	<i>Sex/age</i>	N/A	N/A	N/A	<i>Sex/age</i>	<i>Sex/age</i>
Latvia	LV	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>	<b>Sex/age</b>
North Macedonia	MK	<b>Total<sup>a</sup></b>	N/A	N/A	N/A	N/A	N/A
Norway	NO	<b>Sex/age</b>	<b>Sex/age</b>	N/A	N/A	<b>Sex/age</b>	<b>Sex/age</b>
Poland	PL	<b>Total<sup>a</sup></b>	<b>Total</b>	N/A	N/A	<b>Total</b>	<b>Sex/age</b>
Portugal	PT	<b>Total<sup>a</sup></b>	<b>Sex/age</b>	<b>Sex/age<sup>a</sup></b>	N/A	<b>Sex/age</b>	<b>Sex/age</b>
Slovenia	SI	<b>Total</b>	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<b>Sex/age</b>
Spain	ES	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>	<i>Sex/age</i>
Sweden	SE	<b>Sex/age</b>	<b>Sex/age</b>	<b>Total</b>	N/A	<b>Sex/age</b>	<b>Sex/age</b>
Switzerland	CH	N/A	N/A	N/A	N/A	N/A	N/A

Bold indicates National data; Italics indicate regional data or data from less defined sub-populations.

<sup>a</sup>Data not suitable for inclusion in the database and calculation of raw rates.

N/A, not available.



**Figure 1** Overview of data availability, critical assessments, and calculation of rates.

between incidence and prevalence data. Furthermore, in some countries registration of diagnoses was based on the ICD-9 system whereas the ICD-10 system was used in other countries and the conversion of data from ICD-9 to

ICD-10 caused some misclassification. Data on radioiodine and fine-needle biopsies were only available from a few countries and were generally considered unreliable.

### Thyroid medication

Data from nine countries were found to be appropriate for comparison of standardized rates of thyroid medication between countries. Hereby we found that the use of antithyroid medication was lowest for Sweden, Finland, Norway, and Spain (8.6–13.7 users/10,000 persons) and highest for Denmark, Latvia, and Hungary (34.8–43.2 users/10,000 persons). Conversely, the use of thyroid hormone therapy was lowest for Latvia, Denmark, and Hungary (192.4–253.1 users/10,000 persons) and highest for the Czech Republic, Belgium, Finland, Sweden, and Norway (424.8–612.8 users/10,000 persons) (Table 3).

There was a clear indication of higher use of antithyroid medication relative to thyroid hormone therapy for countries with early iodine insufficiency. However, there was no apparent pattern in the association between recent iodine intake and use of thyroid medications.

### Thyroid surgeries

For thyroid surgeries, data from 10 countries were found to be appropriate for comparison between countries. We found that the standardized rates of thyroid surgeries for benign indications were lowest for the Czech Republic, Slovenia, Norway, Sweden, and Spain (1.4–2.0 patients/10,000 persons), all with early iodine adequacy, and highest for Belgium, Latvia, and Hungary (4.3–5.1 patients/10,000 persons), all with early iodine insufficiency (Table 4). However, no clear pattern was indicated for thyroid surgeries for all indications or when compared with recent iodine intake.

**Table 3** Thyroid medication use per 10,000 persons, sex- and age-standardized.

Country	Country code	Thyroid medication			
		Antithyroid medication, users	Antithyroid medication, DDD	Thyroid hormone therapy, users	Thyroid hormone therapy, DDD
Belgium	BE	19.28		481.46	
Czech Republic	CZ	26.60		612.83	
Denmark	DK	43.19	8825	241.76	58,356
Finland	FI	9.94		513.95	
Hungary	HU	34.78	4386	253.09	39,040
Latvia	LV	41.51	5372	192.36	30,901
Norway	NO	13.12		424.78	
Spain	ES	13.71	1672	308.24	55,989
Sweden	SE	8.59	3235	432.84	91,269

DDD, defined daily dose.

**Table 4** Thyroid surgeries per 10,000 persons, sex- and age-standardized.

Country	Country code	Thyroid surgery			
		All indications, number of persons	All indications, number of procedures	Benign indications, number of persons	Benign indications, number of procedures
Belgium	BE	5.67		5.05	
Czech Republic	CZ	5.94	6.11	1.42	1.55
Denmark	DK	3.77	4.10	3.37	3.51
Finland	FI	4.12	4.38	3.68	3.79
Hungary	HU	4.57	5.27	4.29	4.83
Latvia	LV	5.20	5.31	4.73	4.76
Norway	NO	3.20	3.28	1.99	2.00
Slovenia	SI			1.57	1.57
Spain	ES	2.77		2.27	
Sweden	SE	5.35	5.53	2.20	2.22

### Thyroid cancer

Data on standardized rates of thyroid cancer diagnoses were assessed to be appropriate for comparison between 13 countries/regions. The lowest rates were found in Bulgaria, Northern Ireland, and Scotland (0.4–0.5 patients/10,000 persons) and the highest rates in Denmark, Latvia, and Hungary (0.9–1.4 patients/10,000 persons) (Table 5), with no clear pattern in the association between early or recent iodine intake and cancer rates.

### Discussion

In this first collation of register data on thyroid outcomes from European countries, we found a high degree of heterogeneity in the availability and quality of register data between countries. Data for thyroid medication, thyroid surgery, and thyroid cancer were suitable for comparison between 9, 10, and 13 countries, respectively. These data indicated higher rates of antithyroid medication and thyroid surgery for benign disease and lower rates of

thyroid hormone therapy in countries with early iodine insufficiency. There was no apparent pattern in the association between thyroid cancer and iodine intake.

### Registers, data availability, and data quality

All but one of the 23 participating countries had data on at least one thyroid outcome. However, the data sources, the number of variables, and the quality of register data varied widely due to differences in the organization of the healthcare systems, digitization, history/culture, and political decisions. This is also recognized in previous papers acknowledging the vast potential of the European registers but also addressing the challenges (6, 7, 26).

Nationwide health registries were established in the Scandinavian countries, Latvia, Hungary, and in the Region of Catalonia in Spain. In contrast, Croatia, Germany, Greece, Great Britain, North Macedonia, and Switzerland provided no data from registers fulfilling the requested criteria. Register data from the Czech Republic, Belgium, and Bulgaria were derived from health insurance companies covering the majority of the population or a well-defined sub-population. These encompass both public and private health insurance companies. Information on thyroid cancer was available from most countries.

For all data sources, the representativity and validity were assessed. There was little concern regarding the representativity in the Nordic registers (27), but some health insurance registers may carry a risk of social stratification hampering the representativity. European cancer registries have a long history and the coverage is generally high (6). The validity of registers could be compromised by over-, under-, or misreporting. Thyroid medications require prescriptions in most European countries and are rarely prescribed in hospitals. This increases the probability of correct reporting as most registers are based on redeemed prescriptions (26). However, for example, in the Latvian

**Table 5** Incident thyroid cancer per 10,000 persons, sex- and age-standardized.

Country	Country code	Diagnoses of thyroid cancer
Belgium	BE	0.87
Bulgaria	BG	0.40
Denmark	DK	1.38
Finland	FI	0.90
Great Britain	UK	
Northern Ireland		0.46
Scotland		0.49
Hungary	HU	0.91
Ireland	IE	0.65
Latvia	LV	1.12
Norway	NO	0.73
Slovenia	SI	0.72
Spain	ES	0.89
Sweden	SE	0.62

National Health Service register, only reimbursed prescriptions were registered. Some patients may have private insurance or choose to pay fully out-of-pocket and are thus not registered. The validity of thyroid surgeries was also assessed to be appropriate for the included countries. In cancer registries, the data are generally reliable but comparability is still somewhat influenced by diverse methods between countries (6). In contrast, diagnoses other than cancer were considered to be unreliable. Registration of thyroid diagnoses varies both between countries and can also vary within countries between health care providers and specialists; for example, the rates of congenital iodine-deficiency syndrome were far higher in some countries than what national experts regard as plausible. Validation studies are rarely available for any of the registers (26).

In addition, between-country differences in other risk factors for thyroid outcomes (e.g. alcohol (28, 29), smoking (30), and other micronutrient deficiencies (31)) and between-country differences in diagnostic activity and treatment practices may also influence the rates of thyroid outcomes independently of iodine intake. Especially differences in ultrasound utilization can impact the detection and thus diagnoses and treatment for thyroid nodules and cancer. Despite clinical practice guidelines developed by recognized professional associations, surveys among clinicians find some variability and divergence from guidelines in the clinical management of Grave's disease, hypothyroidism, and thyroid nodules (32, 33, 34). Furthermore, during 2001–2009/2015 a fall in threshold for treatment initiation of thyroid hormone therapy was observed in both Great Britain and in Denmark leading to more prescriptions of thyroid hormone therapy, but the fall in treatment threshold was markedly steeper in Denmark (35, 36). It is a limitation that we were unable to adjust for these between-country differences.

Overall, collection and comparisons of register-based data from European countries are time-consuming and complicated. When it comes to the burden of thyroid diseases, the potential consequences of differences in iodine intake status and IDD prevention programs may be overshadowed by within- and between-country sources of bias and confounding.

### Differences in thyroid medication, surgery, and cancer rates

Despite the potential biases in comparisons, we still found fairly consistent rates of thyroid outcomes in line with

previous research both when comparing the Scandinavian countries who have rather similar registers, healthcare systems, and health behaviors, but also when including data from quite different countries.

Thus, the findings of the highest rates of treatments most frequently applied for hyperthyroidism and/or structural thyroid diseases in countries with early iodine insufficiency and, conversely, the highest rates of treatment for hypothyroidism in countries with early iodine adequacy correspond with previous studies within countries comparing areas with high and low iodine intake (37, 38, 39) and over time when iodine adequacy was achieved after introduction of IDD prevention programs (40, 41, 42, 43). However, it is a limitation that the specific indication for treatment is not known.

We also found that rates of thyroid cancer did not correlate with early or recent iodine intake, for which previous results are not fully consistent (44). Previous studies have indicated that increased iodine intake is associated with an increase in the ratio between papillary and follicular thyroid cancer (45), which was not measured in our study. Nevertheless, whether the overall incidence of thyroid cancer is influenced by the population level iodine intake is still not clear (44).

We chose to only examine overall patterns in the relationship between iodine intake and rates of thyroid outcomes because the available data on iodine intake were collected by different methods, timepoints, and populations across the European countries and thus not sufficiently comparable. If valid data on early and recent iodine intake in Europe are harmonized it will be possible to perform more advanced statistical analyses of associations between the burden of thyroid diseases and iodine intake (46, 47).

Of note, our results indicate a higher correlation between early iodine intake and thyroid outcomes than recent iodine intake. Many of the included countries have introduced IDD prevention programs and achieved iodine sufficiency during the past two decades, and thus the adult population may still be affected by the exposure to decades of iodine insufficiency. Biologically it is plausible that thyroid function and thereby thyroid disease are influenced by the lifetime iodine intake level (48). Furthermore, the introduction of IF can cause a temporary rise in incident hyperthyroidism in countries with previous ID (8) or may induce thyroid dysfunction due to excessive iodine intake (49). This could affect the rates of treatment in several included countries. In Denmark, steady states were achieved for rates of thyrotoxicosis but not for hypothyroidism approximately



10 years after the implementation of mandatory IF (42, 43). Our study indicates that it may take even longer before the difference between former iodine adequacy and iodine insufficiency is negated between countries. Despite overall iodine adequacy, iodine deficiency can still be present in vulnerable groups, for example, pregnant women, which is observed in several countries (46).

The results show no differences between countries characterized by different IDD prevention strategies. Thus, a best-practice model of IDD prevention cannot be identified through this study. This may be explained, firstly, by the difference in coverage and impact of especially voluntary IF. Second, IDD prevention programs are optimally designed to compensate for the level of iodine deficiency in the target population, thus, similar iodine intakes may be achieved from different IDD prevention strategies.

### Strengths and limitations

The main strengths of this study are, firstly, the strong collaboration between representatives from thyroid research and clinical environments from the European countries. The national EUthyroid representatives had or obtained knowledge of the availability and documentation of data that would not be possible for one researcher from one country. Second, the acquisition of several thyroid outcomes enabled us to evaluate different aspects of thyroid disease and the relationship with iodine intake. Third, the critical assessment of data secured that only data of appropriate quality was included. However, the critical assessment was based on evaluations of the available documentation, and thorough validation of most of the variables was not possible. Raw rates were calculated for all provided data included in the database, however, it is important to note that these should be interpreted with caution because the validity of some data is uncertain and comparison of the raw rates will be confounded by differences in sex- and age distributions. Only few variables met the criteria for comparison between countries and these variables were only available for few countries, which is a major limitation. This in combination with the heterogeneity of iodine intake data and lack of confounding factors limited the generalizability and our ability to draw more firm conclusions on the effect of iodine intake and IDD prevention programs.

This study elucidates the limitations of the registers and points out the need for greater participation and more uniformity in reporting in the future to optimally utilize

the valuable registry information. The current increase in digitization and awareness of the possibilities within register research may lead to more valid register data sources on thyroid diagnoses and treatment with easy access and utilization in the European countries in the future. This will be of great value to thyroid research.

### Conclusion and perspectives

The availability and quality of register data on thyroid diagnoses and treatments are highly heterogeneous between European countries. Thus, comparison of rates of thyroid outcomes is currently only possible between a limited number of countries. The available data indicate lower rates of antithyroid medication and thyroid surgery for benign disease and higher rates of thyroid hormone therapy in countries with early iodine intake adequacy, and no difference for thyroid cancer or according to recent iodine intake.

As stated in the Krakow Declaration, evaluation of primary thyroid outcomes is essential in the control of IDD prevention programs (50). Registers may be an effective tool for this evaluation. Thus, the present project serves as initial exploration of the availability and quality of register data of thyroid outcomes across Europe, while more in-depth examination of the validity and comparability of registers is still needed to fully utilize the potential of the registers.

#### Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EC-21-0525>.

#### Declaration of interest

The authors have no conflicts of interest to declare. The author Alicja Hubalewska-Dydejczyk is an editor of the journal.

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