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ORIGINAL CONTRIBUTION

Does a small difference in iodine status among children in two regions of Belgium translate into a different prevalence of thyroid nodular diseases in adults?

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Abstract
Purpose To explore whether there are regional differences in iodine status and in prevalence of thyroid diseases in the two main regions of Belgium.
Methods A national survey of iodine status among children was performed in 1998. The raw data of this survey were reanalyzed to explore regional differences. The total number of thyroidectomies, carried out for multinodular goiter or solitary nodules, was obtained from the Minimal Clinical Summary hospital discharge database. Percentage of people with thyroid diseases going to the general practitioner or the specialist was assessed by means of data about the number of adults using anti-thyroid medications. Food consumption patterns were explored using national food consumption data.
Results In Flanders, median urinary iodine concentration (UIC) was higher than in Wallonia, 84 μg/L ($n = 1{,}316$) and 78 μg/L ($n = 1{,}268$), respectively ($p < 0.001$). There were no differences in goiter prevalence and thyroid volume between the regions among children. Data from the food consumption survey showed a significant higher consumption of seafood in Flanders compared to Wallonia. Further, it was observed that the number of thyroidectomies, carried out for MNG or solitary nodules, and the use of anti-thyroid medication were significantly higher in Wallonia than in Flanders.
Conclusion Iodine status in children was found slightly different in both regions of the country. This finding is in agreement with a higher incidence of thyroidectomies and more extensive use of anti-thyroid medications in the adult population in the region with the lowest iodine excretion.

Keywords Iodine status children · Belgium · Thyroid diseases adults

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Introduction

Despite a worldwide successful implementation of iodine fortification and supplementation programs over the last four decades, iodine deficiency remains a public heath problem in Europe. In 2004, it was estimated that of the 2 billion people around the world at risk of iodine deficiency, 20% live in Europe [1]. Over the last two decades, extraordinary progress has been achieved in decreasing the prevalence of iodine deficiency disorders by increasing the number of people with access to iodized salt [2]. However, this has not been the case in Europe, where, compared to other regions in the world, iodized salt coverage is low, reaching only 27% of households [3].

Several surveys in the last 50 years have repeatedly indicated that Belgium is affected by mild iodine deficiency (MID) [4–6]. In 1998, a representative survey in Belgian school children showed a median urinary iodine concentration (UIC) of 80 μg/L [5], lower than the optimal urinary median values of 100–199 μg/L in the population [7]. Consequently, optimizing iodine intake was chosen

among several other nutritional issues as a priority by the Ministry of Health in its "National Nutrition and Health Plan for Belgium" (NNHP-B) for the period 2005–2010 [8]. The first intervention was taken in 2009: from April onwards, the bakery sector agreed to use only iodized salt (10–15 ppm) in the production of bread.

The main consequences of MID in the adult population are a high prevalence of multinodular goiter (MNG) and thyroid nodules, which may be responsible for hyperthyroidism [3, 9–13]. Consequently, MID is not only associated with morbidity but also represents an economic burden to the Belgian healthcare system [14].

The objective of the present study was to explore whether there are regional differences in iodine status and in the prevalence of thyroid diseases in the two main regions of Belgium.

Methods

A national survey of iodine status among school-aged children in Belgium was performed in winter 1998, based on the determination of thyroid volume, obtained by ultrasonography and urinary iodine concentrations (UIC). A mobile van equipped with an ultrasound instrument, a computer and a deep-freeze visited 23 schools selected from across the country [5]. The sample included 2,855 children (1,365 boys and 1,490 girls) aged 6–12 years. Thyroid volume was measured using real-time sonography (Sonoline SI400, Siemens, Erlangen, Germany) and calculated, as previously described [5]. Goiter was defined in this study as the presence of a thyroid volume above the 97th percentile for gender and for age established in the European reference population [15]. The UIC were measured by the colorimetric ceric ion arsenious acid wet-ash method based on the Sandell–Kolthoff reaction, using an auto-analyzer (Technicon, Tarrytown, NY, USA). In the present study, the raw data of this survey were reanalyzed to see whether there are regional differences in iodine status among Belgian school-aged children.

The total number of thyroidectomies, carried out for multinodular goiter (MNG) or solitary nodules, was obtained from the Minimal Clinical Summary (MCS) hospital discharge database. These are data collected by the federal health authorities between 1999 and 2006 for the entire Belgian population. MCS forms are filled in by hospital physicians upon patient discharge; they summarize the main diagnoses and medical procedures used during the hospital stay. Clinical diagnoses are coded according the International Classification of Diseases (ICD9 CM). The data for thyroidectomies were derived from patients with MNG or solitary nodules as the main diagnosis upon discharge and in whom a surgical procedure on the thyroid was performed. Demographic information to allow calculation of incidence rates was obtained from the National Institute of Statistics.

To assess the percentage of people with thyroid diseases going to the general practitioner or the specialist in the hospital, data about the number of adult persons ($\geq$18 years) using anti-thyroid medications (reimbursed medication) were exploited (FARMANET). FARMANET collects data on use of prescribed, reimbursed medicines, distributed via pharmacies, in Belgium.

The number of adult persons using not reimbursed medication (such as propylthiouracil) could not be separated by region. Following medications were included: levothyroxine, levothyroxine and liothyronine combinations and thiamazole.

Food consumption patterns were explored using the data from the national food consumption survey in Belgian adults carried out in 2004. Aims, design and methods used in this survey have been described elsewhere [16, 17]. The target population included all Belgian inhabitants of 15 years or older. The sample included 3,245 participants randomly selected from the National Register. The sampling method followed a multistage stratified procedure. Information on dietary intake was collected by a repeated non-consecutive 24-h recall in combination with a food frequency questionnaire. During the 24-h recall interviews, the respondents reported the quantity of all foods and beverages consumed during the preceding day. In order to get more information on the within-person variation, two non-consecutive 24-h recalls of each respondent were collected.

Statistical analysis

All analyses were performed with Stata 10 (Statacorp, TX, USA). Commonly used statistical methods were used to analyze the data (mean, median, percentiles and proportions).

Continuous variables were summarized by their median or mean ($\pm$SD). Means were compared using one-way analysis of variance.

Normalization did not occur after a logarithmic transformation of UIC, and therefore, medians were used rather than means.

The Scheffé multiple-comparison test was used to compare pairs of means. Mann–Whitney and chi-squared tests compared the medians of UIC and the prevalence of goiter, respectively, in both regions. All p values were two-sided.

Confidence intervals around incidence rates were computed assuming a Poisson distribution. To allow for comparison of incidence rates across regions, adjusted rates were computed by direct standardization for age and sex taking the Belgian population of 2000 as a reference.

The usual intake of fish, crustaceans and molluscs and milk and milk products was estimated with the Nusser method [18] using the C-side software [19, 20]. This method eliminates the intra-individual variance and additionally transforms the data to obtain approximately normally distributed data. The usual intake distribution was weighted and adjusted for age and sex distribution of the Belgian population and adjusted for day of the week and season.

Results

Iodine status

No schools from Brussels were represented in the sample, and the country was divided into a northern part (Flanders) with coastline and a southern part (Wallonia) to perform the analyses. Characteristics of the study sample by region can be found in Table 1. In Flanders, median UIC was higher than in Wallonia; 84 μg/L ($n = 1{,}316$) and 78 μg/L ($n = 1{,}268$), respectively ($p < 0.001$; Table 2). For boys, median UIC was higher in Flanders than in Wallonia (90 μg/L vs. 81.5 μg/L, respectively; $p < 0.001$); this was also the case for girls (78 μg/L vs. 73 μg/L, respectively; $p = 0.003$).

There were no differences in goiter prevalence (Flanders: 5.89%; Wallonia: 5.55%; $p = 0.7$) and thyroid volume ($p = 0.92$) among children between the regions (Table 3). In accordance with the UIC in children, data from the national food consumption survey among adults, carried out in 2004, showed a significant higher consumption of fish, crustaceans and molluscs in Flanders compared to Wallonia, corrected for day of the week and season. There was no difference in consumption of milk and milk products between both regions (Table 4).

Table 1 Characteristics by region of the 2,855 school children of the study population (n Flanders = 1,518, n Wallonia = 1,336) (n = number of individuals)

Age (years)	Flanders ($n = 1{,}518$)		Wallonia ($n = 1{,}336$)	
	Boys	Girls	Boys	Girls
6	89	96	112	97
7	112	131	84	86
8	126	159	115	90
9	109	182	121	104
10	115	141	123	125
11	87	148	133	92
12	7	16	32	22
Total	645	873	720	616

Table 2 Percentiles of urinary iodine concentration (μg/L) by region

Percentiles (%)	Flanders ($n = 1{,}316$)	Wallonia ($n = 1{,}268$)
1	18	17
5	30	29
10	39	38
25	60	54
50	84	78
75	114	106
90	160	143
95	196	173
99	282	258

270 missing values for urinary iodine concentration

p value for difference in urinary iodine concentration Flanders versus Wallonia was <0.001

Table 3 Percentiles of thyroid volume (mL) by region

Percentiles (%)	Flanders ($n = 1{,}517$)	Wallonia ($n = 1{,}332$)
Percentiles of thyroid volume (mL)		
1	1.9	1.9
5	2.3	2.2
10	2.7	2.5
25	3.3	3.3
50	4.3	4.3
75	5.6	5.6
90	7.1	7.3
95	8.2	8.5
99	11.5	12.0

p value for difference in thyroid volume Flanders versus Wallonia was 0.92

Epidemiology of thyroid diseases

When data about the total number of thyroidectomies, carried out for multinodular goiter (MNG) or solitary nodules in the adult population between 1999 and 2006, were compared between the regions, it was observed that this number was significantly higher in Wallonia than in Flanders (Table 5).

The prevalence of goiter and MNG was significantly higher in Wallonia than in Flanders, and a similar trend was observed concerning thyroidectomies for MNG and solitary nodules (Table 5). In Wallonia, the frequency of thyroidectomies for MNG and solitary nodules was fourfold and fivefold higher, respectively, than in Flanders. The prevalence of hyperthyroidism was also higher in Wallonia than in Flanders. By contrast, the prevalence of Graves' disease was slightly higher in Flanders than in Wallonia.

Table 4 Usual intake (g/day) of milk and milk products (without cheese), fish, crustaceans and molluscs among the Belgian adult population (food consumption survey 2004)

Product	Region	Mean	SD	P25	P50	P75	P97.5	*n*	*N*
Fish, crustaceans and molluscs	Flanders	26.6	15.4	15.0	25.0	36.0	61.0	727	1,923
	Wallonia	19.7	10.0	12.5	18.4	25.5	43.1	437	1,160
Milk and milk products	Flanders	156.8	125.3	64	131	215	480	1,605	1,923
	Wallonia	156.9	111.5	76	135	213	433	977	1,160

The mean is corrected for interview day, season, sex and age of the Belgian population

n = number of persons who consumed out of this food group at least once during both recall days

N = total number of participants in the survey

p value for difference in consumption of fish, crustaceans and molluscs in Flanders versus Wallonia was <0.001

p value for difference in consumption of milk and milk products in Flanders versus Wallonia was 0.97

Table 5 Frequency of therapy (per 100,000 person-years) and incidence of thyroid diseases

Characteristics	Flanders		Wallonia		Total	*p* value
	Observed	Adjusted[a]	Observed	Adjusted[a]	Observed	
Goiter	35.3 (34.8–35.9)	34.6 (34.2–34.9)	79.9 (78.9–81.0)	79.7 (79.1–80.3)	51.1 (50.7–51.6)	<0.001
MNG	12.1 (11.8–12.4)	11.8 (11.5–12.0)	41.7 (40.9–42.5)	41.5 (41.1–41.9)	22.7 (22.4–23.0)	<0.001
Thyroidectomy for MNG	11.1 (10.8–11.4)	10.8 (10.6–11.0)	40.6 (39.8–41.4)	40.5 (40.0–40.9)	21.7 (21.4–22.0)	<0.001
Thyroidectomy for SN	2.5 (2.4–2.7)	2.5 (2.4–2.6)	10.3 (9.9–10.7)	10.3 (10.1–10.5)	5.3 (5.2–5.5)	<0.001
Hyperthyroidism	17.8 (17.4–18.2)	17.43 (17.2–17.7)	21.4 (20.9–220)	21.4 (21.0–21.7)	17.7 (18.5–19.1)	<0.001
Graves' disease	6.3 (6.1–6.5)	6.2 (6.0–6.3)	5.9 (5.6–6.2)	5.9 (5.7–6.1)	6.1 (5.9–6.2)	0.025

MNG multinodular goiter, *SN* solitary nodule

[a] By direct standardization for age group and sex; Belgium 2000 population taken as reference population

[b] p value of difference Flanders vs. Wallonia, based on Poisson regression

In addition, the use of anti-thyroid medication by adults was also significantly higher in Wallonia than in Flanders. In 2008, 6.9% of the inhabitants of Wallonia took this type of medication, while only 2.9% of inhabitants of Flanders. In 2009, these figures were 6.5 and 3.0%, respectively. This medication includes levothyroxine, levothyroxine and liothyronine combinations and thiamazole.

Discussion

The small difference in iodine excretion during childhood between the two regions of Belgium reflected important regional differences in the prevalence of nodular thyroid diseases. This is the first study showing a different iodine status between the northern (Flanders) and the southern (Wallonia) part of Belgium, although previous data indicated a higher prevalence of visible goiter in adults in the southern part of the country [21]. In addition, the neonatal T4 was reported to be significantly lower and TSH higher in the southern part of the country [22]. Finally, the consumption of seafood, as shown in the national food consumption survey, is significantly lower in Wallonia than in Flanders [23]. Wallonia is also more distant to the sea than Flanders possibly resulting in a lower iodine load of local food. Collectively, these data suggest a difference in the iodine intake between the northern and the southern part of Belgium. The existence of marginal lower iodine supply in Wallonia (southern part of the country) is the most plausible explanation for the difference in the prevalence of thyroid nodular diseases although a follow-up study would have strengthened our findings.

It is important to note that in the national study fewer girls and more boys were included in Wallonia than in Flanders. This probably leads to an underestimation of the difference in UIC found between the regions because girls were found to have a lower UIC than boys, as previously reported [5]. Despite the differences in iodine excretion between the regions, we did not find differences in childhood goiter or thyroid volume between both regions. The lack of difference in thyroid volume in children may be explained by the small difference in iodine excretion, precluding the detection of volume change at that age. It is likely that volume determination at later age would have shown regional differences. Alternatively, the absence of difference could be due to the design of the study. In fact,

the survey performed in 1998 was a national but not regional representative survey. Consequently, it may have lacked of power to detect small differences.

The lower iodine status in children in Wallonia was associated with higher prevalence of thyroid nodular diseases in the adult population.

The prevalence of goiter and MNG was higher in hospitalized patients in Wallonia. The frequency of thyroidectomies was fourfold more frequent than in Flanders.

Moreover, the use of anti-thyroid medication by the adult population was also higher in Wallonia.

In addition to a higher frequency of benign nodular thyroid diseases suggested by our study, it has been reported also that the incidence of thyroid cancer is higher in Wallonia (Belgian register of cancer, cancer incidence in Belgium reports 2004–2005 and 2008). The majority of these cases are microcarcinoma, a very low risk thyroid cancer, which are most likely discovered incidentally after thyroidectomy for benign conditions such as multinodular goiter. The higher frequency of thyroidectomy for thyroid nodular disease in Wallonia may lead to a higher diagnosis rate of thyroid cancer mainly microcarcinoma. Because most microcarcinoma do not require specific treatment and follow-up, a higher detection of microcarcinoma may unnecessarily cause concern to the patients and health authorities as is the case in Belgium.

This study has several limitations. The data for the frequency of thyroidectomies and the incidence of thyroid diseases were obtained using the ICD9 CM classification system, which has not been validated for epidemiological studies on thyroid diseases. In addition, the incidences of thyroid diseases which do not require hospitalizations like goiter or hyperthyroidism are underestimated. Consequently, the data do not represent the prevalence of thyroid diseases in the population accurately.

The present study corroborates a previous report indicating that small variations in the daily iodine intake are sufficient to modify the epidemiological profile of thyroid disease in the population [24].

Nevertheless, the magnitude of differences in iodine excretion in Belgian children is even smaller than that reported in adults in Denmark [25]. Our results indicate that in areas of mild iodine deficiency, slight differences in iodine intake may have measurable impact on the frequency of nodular thyroid diseases.

It is also possible that in some iodine-deficient regions, the inadequately low iodine intake may be more pronounced in adults than in children as previously shown in other countries [26].

In conclusion, iodine status in children was found to be slightly different in both regions of the country. This finding is in agreement with a higher incidence of thyroidectomies and more extensive use of anti-thyroid medications in the adult population in the region with the lowest iodine excretion.

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