Endocrine
https://doi.org/10.1007/s12020-020-02222-7

ORIGINAL ARTICLE

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Incidence and prevalence of hyperthyroidism: a population-based study in the Piedmont Region, Italy

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Received: 22 December 2019 / Accepted: 4 February 2020
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Abstract

Purpose Unrecognized and untreated hyperthyroidism leads to serious clinical complications with adverse outcomes for patients and increasing costs for the health care system. Hence, adequate knowledge of the epidemiological features of such condition is desirable to plan effective interventions. The aim of our study was to estimate incidence and prevalence of hyperthyroidism in the mildly iodine-deficient Italian Region of Piedmont.

Methods A retrospective cohort study was conducted using Administrative Health Databases of the Piedmont Region, Italy (2012–2018). Hyperthyroidism cases were defined as the subjects who had at least one of the following claims: (i) hospital discharge records with hyperthyroidism diagnosis code; (ii) exemption from co-payment for hyperthyroidism; (iii) prescription of one of the following medications: methimazole, propylthiouracil, or potassium perchlorate.

Results The overall prevalence was 756 per 100,000 inhabitants [95% CI 748–764], and the overall incidence was 81 per 100,000-person year [95% CI 80–82]. The prevalence and incidence increased with age and were two-fold higher among women than men. Women also showed two distinct peaks in incidence at the age of 30 and 50; after the age of 60, the trend became similar between sexes. With regard to the geographic distribution, an increasing gradient of incidence was observed from the northern to the south-western areas of the Region.

Conclusion This is the first Italian study based on health databases to estimate the incidence and prevalence of hyperthyroidism in the general population. This approach can represent an inexpensive and simple method to monitor patterns of hyperthyroidism in iodine-deficient areas.

Keywords Hyperthyroidism · Incidence · Prevalence · Administrative Health Databases

Introduction

Hyperthyroidism is a condition of thyroid hormone excess and constitutes the second most frequent thyroid dysfunction after hypothyroidism, showing a five- to ten-fold lower prevalence [1]. Although hyperthyroidism can have different causes, the most common ones include Graves' disease, toxic multinodular goiter, and toxic adenoma [2]. Less common causes of hyperthyroidism encompass thyroiditis, iodine-induced and drug-induced thyroid dysfunction, and secondary hyperthyroidism of pituitary origin [3, 4].

The clinical presentation of thyroid hormone excess can vary in severity, and ranges from subclinical manifestations to thyrotoxicosis with overt hyperadrenergic symptoms. The complications of untreated or unrecognized hyperthyroidism can include weight loss, cardiovascular disorders, embolic events, psychiatric disorders and cognitive impairment, bone loss, and potential fatal events in

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Published online: 13 February 2020

case of a thyroid storm [5–7]. In hospitalized populations, adult mortality rate increases up to 10% [8]. There is evidence that the diagnosis of hyperthyroidism is often overlooked [9].

Epidemiological data on hyperthyroidism are currently sparse and mainly rely on biochemical tests of thyroid function (e.g., TSH and FT_4). Differences in diagnostic thresholds, assay sensitivities, population selection, and iodine uptake play a potential role in explaining the heterogeneity of published results [10]. In the 2002 United States National Health and Nutrition Examination Survey, subclinical and overt hyperthyroidism were detected in 0.5% and 0.7% of the general population, respectively [11]. A meta-analysis of nine European studies on previously diagnosed and undiagnosed thyroid dysfunctions estimated an overall prevalence of hyperthyroidism equal to 0.75% and an incidence rate of 51 cases per 100,000-person year [12]. These analyses also suggest that thyroid dysfunctions go undiagnosed in nearly half of the affected population [7, 8]. Noticeably, a recent review of administrative data collected between 2011 and 2017 at a tertiary referral center revealed that 67% of patients with suppressed TSH (TSH < 0.05 mU/L) failed to be appropriately evaluated, while 37% among those with at least two positive tests remained undiagnosed [13]. Given the clinical burden and financial implications of the disease, critical failures in diagnosing and timely treating hyperthyroidism can have a significant impact both for patients and for the health care system.

The use of claim data represents a novel and inexpensive method to estimate the burden of endocrine disorders in large population databases. This approach allows us to evaluate the prevalence and the incidence of the disease, its morbidity and their general impact on health care systems [14–16].

The present study used administrative health data to identify incident and prevalent cases of hyperthyroidism in the Piedmont Region (Italy), an area that has been traditionally considered at mild iodine deficiency [17].

Methods

Data source

A retrospective cohort study was conducted using the Administrative Health Databases (AHDs) of Piedmont, an Italian Region covering a population of around 4,400,000 inhabitants (corresponding to 7.5% of the national Italian population), from January 1st, 2012 to December 31st, 2018. Data concerning only individuals residing in Piedmont during the aforementioned period were considered, adopting a record linkage from different sources: (a) inhabitant registry (containing demographic information such as gender, date of birth, date of death, etc.); (b) hospital information system, including hospital discharge records (HDRs) from public or private hospitals; (c) co-payment exemption registry; (d) Drug Claims Registry, including records of all outpatient drug prescriptions reimbursable by the Italian National Health Service.

Selection of cases

Potential cases of primary hyperthyroidism were defined as the subjects with at least one of the following claims during the study period:

(1) HDRs with hyperthyroidism diagnosis code (ICD-9-CM: 242.XX);
(2) Exemption from co-payment for hyperthyroidism (code: 035);
(3) Prescription for one of the following medications, in accordance with guidelines for management of hyperthyroidism (1): methimazole (ATC: H03BB02), propylthiouracil (ATC: H03BA02) and potassium perchlorate (ATC: H03BC01).

To exclude cases of iatrogenic hyperthyroidism, patients treated with amiodarone (ATC: C01BD01), lithium (ATC: N05AN01), or levothyroxine sodium (ATC: H03AA01) before the index claim were not taken into account in the present analysis.

All procedures conducted in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the local ethical committee of the "Maggiore della Carità" Hospital, Novara (CE 60/19). The study was conducted using data routinely collected in the aforementioned regional administrative health care databases in which authors had access to anonymized data only, hence informed consent was not required.

Statistical analysis

The prevalence of hyperthyroidism in 2018 was calculated by dividing the number of prevalent cases (i.e., those having hyperthyroidism-related claims at any time during the period 2012–2018 and alive in 2018) by the total number of residents in Piedmont. The incidence of hyperthyroidism in 2015–2018 was calculated by dividing the number of new cases of hyperthyroidism (i.e., no evidence of hyperthyroidism during 3 years prior to the index claim) by the total person time at risk during the same period. The period 2012–2014 was thus used to eliminate prevalent cases (look-back time). Incidence and prevalence estimates were

stratified by age, gender, and local health authority (LHA) of residence.

Clopper–Pearson and Byar methods were used to estimate the 95% confidence intervals (CI) for prevalence and incidence, respectively. Comparisons of incidence and prevalence between the two sexes were carried out estimating rate ratios and prevalence ratios. All statistical analyses were performed using STATA software 12 (StataCorp, College Station, TX, USA).

Results

In the period 2012–2018, 33,257 cases of hyperthyroidism, consisting of 9,165 men and 24,092 women, were identified in the Piedmont population, with an overall prevalence of 756 per 100,000 inhabitants [95% CI 748–764]. Incident cases in the period 2015–2018 were 14,259, of whom were 4,286 men and 9,973 women, accounting for an overall incidence of 81 per 100,000-person year [95% CI 80–82] (Table 1).

About 90% of the identified cases had at least one prescription for hyperthyroidism treatment; in particular, methimazole accounted for 98% of all prescriptions. Thirteen percent of cases had a record of hospital admission for hyperthyroidism, and about 25% of them were surgically treated. Exemption from co-payment for hyperthyroidism was recorded in 29% of cases.

After stratification by gender, both incidence and prevalence were higher among women. Compared with men, rate ratio in women was 2.18 [95% CI 2.10–2.26], while the prevalence ratio was 2.77 [95% CI 2.71–2.82].

Mean age at hyperthyroidism diagnosis was 62 years [IQR 48–77], and it was lower in women (61 [IQR 46–77]) than in men (65 [IQR 54–78]). Age-specific prevalence and incidence were generally higher in women than in men and exhibited different trends between the two sexes (Figs 1 and 2). In particular, women displayed two peaks in incidence and prevalence rates around their 30s and 50s, which were not present among men. The incidence trend became similar in the two sexes after their 60s. The highest incidence rates were observed in the early 80s, followed by a sharp decrease. A similar reduction was also observed in prevalence, which started from the late 70s.

We also found a north–south gradient in the incidence of hyperthyroidism in the Region for both sexes. Incidence rates were almost twofold higher in southern compared with Northern LHAs (Fig. 3).

Discussion

In this study, we used administrative health databases to estimate incidence and prevalence of hyperthyroidism in a large mildly iodine-deficient Italian Region.

We estimated an incidence of hyperthyroidism of 81 cases per 100,000-person years [95% CI 80–82], and a

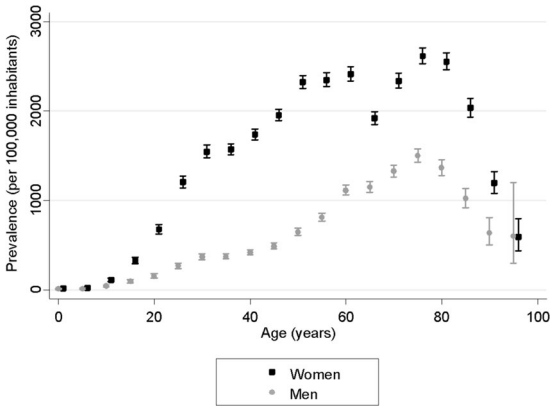

Fig. 1 Prevalence of hyperthyroidism in the Piedmont Region (Italy) in 2018, stratified by sex and age groups

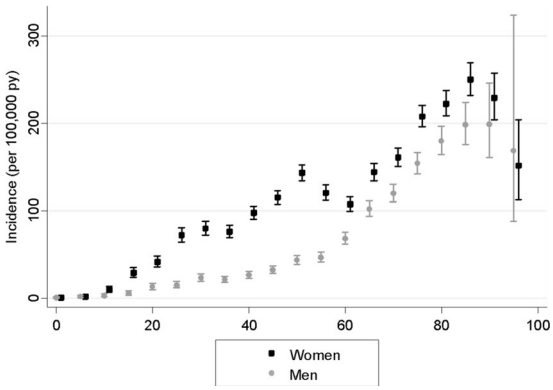

Fig. 2 Incidence of hyperthyroidism in the Piedmont Region (Italy) in the period 2015–2018, stratified by sex and age groups

Table 1 Prevalence (year 2018) and incidence (period 2015–2018) of hyperthyroidism in the Piedmont Region (Italy), stratified by sex

	Men		Women		Total	
	N	Estimate (95% CI)	*N*	Estimate (95% CI)	*N*	Estimate (95% CI)
Incidence	4,286	49 (47–50)	9,973	113 (111–116)	14,259	81 (80–82)
Prevalence	9,165	417 (408–425)	24,092	1,095 (1,081–1,109)	33,257	756 (748–764)

Results expressed as cases per 100,000-person years (incidence) and cases per 100,000 inhabitants (prevalence)

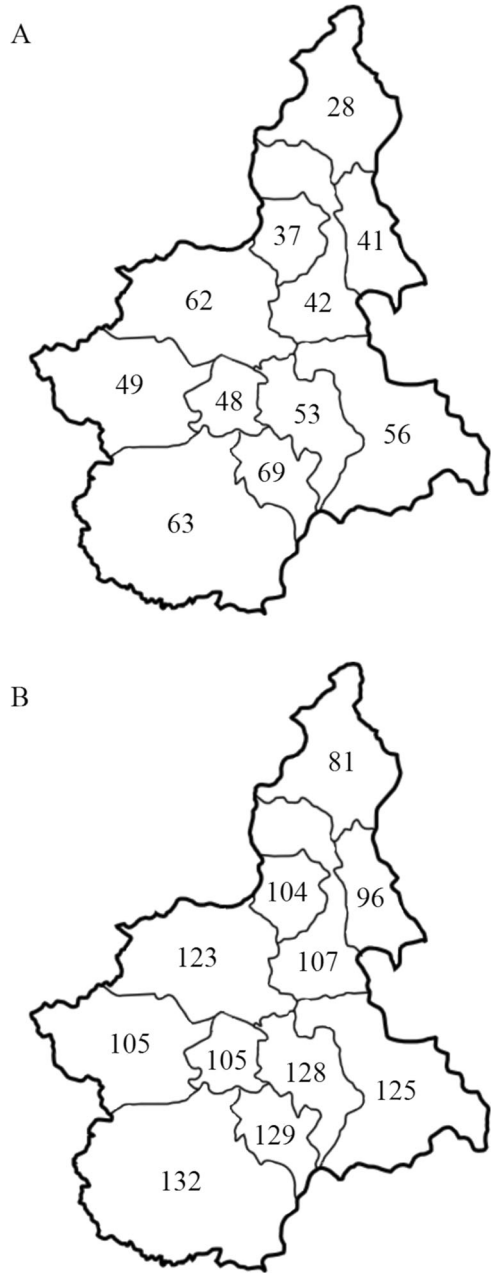

Fig. 3 Incidence of hyperthyroidism in the Piedmont Region (Italy) in the period 2015–2018, stratified by Local Health Authority in men (**a**) and women (**b**)

prevalence of 756 cases per 100,000 inhabitants [95% CI 748–764]. These figures are in line with published research. In fact, studies conducted in USA, Australia, Asia, and Europe reported incidence rates for overt hyperthyroidism between 25 and 93 cases per 100,000-person years and prevalence between 200 and 1,300 cases per 100,000 inhabitants [10, 12].

However, it should be also considered that, because of the different iodine status of the populations, a direct comparison of prevalence and incidence of hyperthyroidism in different countries is not straightforward. In fact, depending on iodine availability, the thyroid gland has sensitive mechanisms for up- or downregulating thyroid hormone production that makes it vulnerable to a wide spectrum of diseases. Long-standing mild and moderate iodine deficiency increases the risk of developing autonomously functioning nodules in the thyroid gland, especially among the middle aged and elderlies [18].

In Italy, iodine fortification has been implemented since the 1970s with an empowerment in 2005, but according to recent data, our country is still characterized by a mild iodine deficiency, with a substantial regional heterogeneity [19]. A survey conducted in Pescopagano, an iodine-deficient village of Southern Italy showed in 1995 a prevalence of hyperthyroidism of 2,100 cases per 100,000 inhabitants [20]. A second survey conducted 15 years later in the same area after a iodine prophylaxis intervention, showed a declining prevalence of 1,600 cases per 100,000 inhabitants [21], demonstrating the key role of iodine supplementation in the prevention of thyroid diseases.

In Piedmont Region, epidemiological data on the incidence and prevalence of endemic goiter were made first available in 1974 by Costa et al. [22], who classified this region as mildly iodine deficient. According to a recent survey, this status has remained unchanged since then, despite the iodine fortification campaign conducted in the last decades [17]. This finding is similar to that documented in other Northern Regions of Italy, such as Lombardy and Veneto, that are still considered as mild iodine deficiency [19]. Interestingly, Bartalena et al. [23] recently showed in the Northern Italian Region of Lombardy that the phenotype of patients with newly diagnosed Graves's disease was milder than reported in past, possibly due both to earlier diagnosis/treatment and to improved iodine intake. Because Lombardy and Piedmont border each other and share a similar iodine status [19], this observation could imply the beneficial effects of iodized salt prophylaxis on goiter prevalence, the severity of hyperthyroidism, and the prevalence of Graves' orbitopathy.

In our study, we also observed a substantial intraregional heterogeneity in the incidence of hyperthyroidism, with an almost two-fold increase in the southern compared with the Northern part of the Region. Whether this distribution pattern might depend on different levels of iodine intake across the Region remains unclear, although it is generally acknowledged that the consumption of iodized table salt remains low in Italy [17, 24]. On the other hand, the Piedmont Region sits by the Northwestern Alps and comprises a complex geographical combination of plains (25%), mountains (48%), hills (25%), and rivers/lakes (2%) [25]. Although there is no obvious explanation for the north–south gradient in hyperthyroidism incidence rates, this trend parallels the gradual geographical decline from

mountain to plain territories in the Region. Interestingly, the plains of Piedmont show an increasing soil concentration of phytoavailable arsenic, likely due to postglacial geological transformations [26]. Because arsenic is a recognized goitrogen [27, 28], we cannot exclude a relationship between dietary arsenic and the risk of hyperthyroidism, although this link is speculative and remains to be demonstrated in a specifically designed study.

With regards to gender- and age-related distribution of hyperthyroidism, its prevalence and incidence in females were twice as high as those observed in males. Other studies reported an even larger difference between sexes, ranging between 4 and 10 times [29–31]. It is plausible that sex differences are particularly large in iodine-sufficient populations, where most of the cases of hyperthyroidism are due to Graves's disease, a condition that is much more common in women than men. On the opposite, in iodine-deficient populations like ours, where a relevant proportion of cases is expected to be due to toxic multinodular goiter and toxic adenoma, which are evenly distributed among sexes, the differences between sexes will be smaller. Among women, we also observed a dichotomic age-related pattern in hyperthyroidism rates, peaking at around 30 and 50 years of age. This pattern did not occur in the male counterpart and likely reflects the natural occurrence of Graves' disease at earlier adult ages and multinodular toxic goiter at older ages [29].

The strengths of our study are the completeness of the sample, which is represented by the entire population of the region, and the use of reliable administrative health data, which are commonly used for epidemiological research in Italy and elsewhere [32]. Hence, results are more generalizable than estimates derived from single-institution studies or case series [33]. Moreover, the use of the Drug Claims Registry allowed to exclude iatrogenic cases of hyperthyroidism. A known limitation of using these databases is the lack of clinical information, as well as the results of laboratory tests.

Another possible bias due to the intrinsic limitation of AHDs is the inability to check for the consumption of iodine-rich nutrients in diet (e.g. milk, cheese, yogurt, egg, fish, and seaweeds) [34] that could influence thyroid diseases pattern, especially in women with a low socioeconomic status or with linguistic or cultural barriers, in which a low-frequency intake of iodine-rich-foods is reported [35].

Finally, but more important, our algorithm requires a thorough validation to constitute an effective tool.

In conclusion, we provide a reliable method to estimate the incidence and prevalence of hyperthyroidism offering a complete view of the epidemiology of this condition in the Piedmont Region. Our results are in agreement with other studies on the same topic available in the literature. This approach can represent an inexpensive and simple method to monitor patterns of hyperthyroidism in iodine-deficient areas. Considering the public health concern of the disease and its morbidity, we hope that our study could be useful to health authorities to improve strategies and educative program to ameliorate iodine nutritional status, stressing the importance of iodine supplementation and salt fortification.

Funding This work was supported by PRIN (Progetti di ricerca di Rilevante Interesse Nazionale) 2015 (2015ZHKFTA_001).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (ethical committee of the "Maggiore della Carità" Hospital, Novara, CE number 60/19) and with the 1964 Helsinki declaration and its later amendments.

Informed consent The study was conducted using data routinely collected in the regional administrative health care databases in which authors had access to anonymized data only, hence informed consent was not required.

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