RESEARCH

Hyperthyroidism incidence in a large population-based study in northeastern Italy

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Abstract

Objective: An improvement in iodine status in Veneto Region has been documented in the last decade. We aimed at estimating the incidence of hyperthyroidism in the Veneto Region (Italy) over the period 2013–2022.

Methods: Retrospective population-based study conducted in Veneto (4.9 million people) using the population registry, an administrative health database. Between 2012 and 2022, hyperthyroidism incidence was defined thank to a health-care co-payment exemption for hyperthyroidism or any hospital diagnosis of hyperthyroidism. Incident hyperthyroidism was defined from 2013 to 2022 to exclude prevalent cases. Standardized incidence rates (IRs) were reported by age, sex, and etiology of thyroid hyperfunction too.

Results: We identified 26,602 incident cases (IR of 54.38 per 100,000 person-years, 2.47-fold higher in females than in males). IR decreased from 69.87 (95% CI: 67.49, 72.25) in 2013 to 42.83 (95% CI: 40.99, 44.66) in 2022. In 2020, an out-of-trend decrease in hyperthyroidism incidence was documented, corresponding to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic outbreak, with a realignment to the trend in the subsequent years. The annual percentage change according to the cause of hyperthyroidism was as follows: −6.62% (95% CI: 8.47, 4.73) ($P < 0.0001$) in toxic multinodular goiter, −7.56% in toxic uninodular goiter (95% CI: 10.54, 4.48) ($P < 0.001$) and −4.70% (95% CI: 6.33, 3.04) in toxic diffuse goiter (Graves' disease) ($P < 0.001$).

Conclusions: We documented a decline in the incidence of hyperthyroidism in Veneto Region, paralleling the improvement of the iodine status, thanks to a long and sustained iodine prophylaxis campaign. SARS-CoV-2 pandemic and vaccination campaign did not change the declining trend of hyperthyroidism incidence in our study region.

Significance statement: An improvement in iodine status in the population residing in the Veneto region has been documented in the last decade, thanks to a nationwide voluntary iodine prophylaxis program running since 2005, but its impact on the epidemiology of thyroid disease has never been documented. This is the largest study on the incidence rates of hyperthyroidism carried out in Italy and covers the longest observation period among all regionwide population-based studies of hyperthyroidism in our country. We documented a reduction in the incidence of hyperthyroidism, which was more pronounced in nodular goiter diagnosis but involved also toxic diffuse goiter. The decline in the incidence of hyperthyroidism in Veneto Region shows the efficacy and safety of the iodine prophylaxis campaign.

Keywords

- hyperthyroidism
- incidence
- iodine

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Introduction

Hyperthyroidism is caused by an inappropriately high secretion of thyroid hormones by the thyroid (1). Hyperthyroidism has a prevalence ranging from 0.4 to 2.5% in iodine sufficient parts of the world (2, 3, 4, 5), the most common cause being Graves' disease (GD) (70–80% of cases), followed by solitary toxic adenoma and toxic multinodular goiter (TMNG) (1). In iodine-deficient areas, the prevalence of hyperthyroidism ranges from 0.4% to 2.9%, only the half of cases being caused by GD (5). GD is far more common among women than men (3% of women are expected to have a GD during lifetime vs 0.5% of men) (2, 6) and its incidence peaks among 30–60 years of age (2). TMNG has a less pronounced higher prevalence in females than in males if compared to GD and its incidence rises with age, in particular from 60 years of age (7). It is well known that iodine viability influences the epidemiology of thyroid diseases, with hypothyroidism dominating in areas of high iodine intake levels (8, 9) and hyperthyroidism being prevalent in areas of mild-to-moderate iodine deficiency (7, 10). As mentioned before, the iodine intake may also influence the epidemiology of the subtypes of hyperthyroidism (7, 11). These data are corroborated by population studies showing a reduction in overt hyperthyroidism caused by TMNG in areas in which an effective and long-standing iodine prophylaxis program is running (12, 13). It is important to stress that the association between the occurrence of thyroid disease in a population and the iodine intake is U-shaped, with a not negligible interval of optimal intake. Indeed, more than adequate and excessive iodine intakes have been associated with a higher frequency of thyroid autoimmunity (including GD), goiter, and hypothyroidism (11). Beyond influencing thyroid disease epidemiology, iodine deficiency (ID) is the world's greatest single cause of preventable brain damage (14). During the fetal life and infancy, a low iodine intake can have an influence on neurological development and growth, impacting intelligence quotient, also in case of a moderate deficit (15), thus influencing the future social and economic progress of the geographical area. The World Health Organization (WHO) recommends salt iodination as the preferred strategy to eradicate iodine deficiency disorders (IDD) (14). WHO acclaims that more than 90% of households should be using iodized salt, while the parameters consistent with an iodine-sufficiency in a population are a median iodine urinary concentration (UIC) of 100–199 µg/L, with no more than 20% with a UIC < 50 µg/L and with a goiter prevalence among school-aged children (SAC) lower than 5%. In Italy, a historically endemic goiter area (16), a nationwide voluntary iodine prophylaxis program was implemented in 2005 (Law n.55/2005). In 2009, a national monitoring program of iodine prophylaxis was created (Italian National Observatory for Monitoring Iodine Prophylaxis (OSNAMI)), with 20 regional and interregional observatories, including the observatory for Veneto/northeastern Italy. Before 2005, northeastern Italy demonstrated a non-negligible prevalence of thyroid goiter among SAC (17) (on physical examination, 7.5% of children had grade I goiter) and iodized salt was used by less than 30% of households (18). In 2012, the use of iodized salt was spread to 70% of the Veneto region's households, with a median UIC showing still a mild-to-moderate iodine deficiency (81 µg/L) (19). The last survey, carried out in in 2017–2018, documented a use of iodized salt rose to 82% of households, with a median UIC finally consistent with an iodine sufficiency, being of 111 µg/L, although still 26% of the samples showed a UIC < 50 µg/L, particularly among female subjects (20). More than fifteen years after the introduction of a sustained iodine prophylaxis program, many achievements have been made in the Veneto region, but their impact on the epidemiology of thyroid diseases has never been analyzed so far.

Another event claimed to impact GD incidence is thought to be the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Certainly, following the widespread use of SARS-CoV-2 vaccines, many cases of thyroid dysfunction, mainly GD and subacute thyroiditis have been described. GD has been reported to occur more frequently with mRNA-based vaccines than with the adenovirus-vectored (while inactivated vaccines seem to be not associated), after the first or second dose and both as a new diagnosis of GD, in absence of a previous thyroid disease, or as a relapse in a previously controlled/remittent GD (21, 22). Although the vaccination seems to have a 'precipitative' rather than a 'causative' role in GD (22), mechanistic solid data are not available in this issue and the eventual modification in hyperthyroidism incidence following large-scale SARS-CoV-2 vaccination has never been analyzed, to the best of our knowledge.

Our aim was to estimate variations of hyperthyroidism trend incidence between 2013 and 2021 in the northeastern area of Italy, to analyze temporal trends after a long, effective, and sustained iodine prophylaxis campaign and in a population with a high coverage of full-regimen SARS-CoV-2 vaccination.

Materials and methods

This is a retrospective population-based study conducted in the Veneto Region, northeastern Italy, with a population of about 4.9 million residents. In Veneto, health-care services are provided by nine local social and health-care units, two university hospitals, two hospitals for scientific research and private accredited providers, based on a hub-and-spoke hospital model. Hospital care in Italy is free of charge for all residents and covered by general taxation. The Veneto Region is also one of the most crowded regions of the country, accounting for 8% of the entire Italian population (it is the fourth most populous Italian region) and contributing to 9.2% of the Italian gross domestic product.

All inhabitants in the Veneto Region between January 2012 and December 2022 were identified by means of a population registry, which has virtually full coverage of all residents of this region. Residents were then linked with the hospital discharge records and health-care co-payments exemptions database. The health-care co-payment exemption database includes information on all individuals with a diagnosis performed by a medical specialist with specific conditions for which the national health service provides specific outpatient free of charge services.

Hospital discharge records contain data on all inpatient episodes, including (i) sociodemographic characteristics (sex, age, city of residence, educational level); (ii) clinical information (primary and secondary diagnoses, any surgical or medical procedure performed on the patient, and the mode of discharge); and (iii) data on the hospital (hospitalization ward, admission and discharge date).

All diagnoses are coded according to the International Classification of Diseases Revision, Ninth Revision, Clinical Modification (ICD-9-CM) coding system, currently used in Italy.

All inhabitants in the Veneto Region between January 1, 2012, and December 31, 2022, were included in the analyses. This time window was chosen according to the availability of data required for hyperthyroidism case identification in the registry, as the health-care co-payments exemptions database was available since January 2012. Any resident with a health-care co-payment exemption for hyperthyroidism (code 035) or at least one hospitalization with a primary or secondary diagnosis of hyperthyroidism (ICD-9-CM 242) was defined as affected by hyperthyroidism. Since the electronic health record database for health-care co-payment exemption was established in 2012, to minimize the risk of prevalent cases with hyperthyroidism being identified as incident cases, analyses on incident hyperthyroidism started after January 1, 2013. The incidence date was defined as the earliest date between health-care co-payment exemptions and hospital discharge records.

Details on the selection of the cohort are reported in Supplementary Fig. 1 (see section on supplementary materials given at the end of this article).

For each patient, hyperthyroidism was classified into one of the following conditions based on ICD-9-CM diagnosis reported in health-care copayment exemption or hospital discharge records: toxic diffuse goiter (242.0), toxic uninodular goiter (242.1), toxic multinodular goiter (242.2), other hyperthyroidism (242.3–242.9). Toxic diffuse goiter is the code used for autoimmune forms of hyperthyroidism, corresponding thus to GD. Thereafter, we will refer to GD and toxic diffuse goiter as the same entity, throughout the article.

Measurements

The study was conducted using anonymized records of data routinely collected by health-care services. All regional health records undergo a standardized anonymization process that assigns a unique anonymous code to each individual, allowing record linkage between electronic health records without any possibility of back retrieving the subject's identity.

All data in the Local Health Authority registries are recorded with the patient's consent and can be used as aggregate data for scientific studies without further authorization (Garante per la protezione dei dati personali, Resolution n.85 of March 1, 2012). This study complies with the Declaration of Helsinki and the Italian Decree n.196/2003 on personal data protection.

Patient and public involvement

There were no funds or time allocated for patient and public involvement, so no patients were involved in the study.

Statistical analysis

Univariate and bivariate analyses were performed to summarize data with respect to the patient demographic characteristics. Continuous variables were reported with descriptive statistics (mean, S.D., median and interquartile range (IQR)). For categorical variables, frequencies and percentages were calculated. The difference between groups was examined by Student's *t*-test or Mann–Whitney *U* test for continuous variables, Pearson's chi-square test or Fisher's exact test for categorical variables, as appropriate. $P < 0.05$ was considered statistically significant. The yearly incidence rates were estimated by dividing the number of new patients diagnosed with hyperthyroidism each year by the number of residents in the Veneto Region in that year. Incidence per 100,000 people, along with the 95% CI, were presented for each year and stratified by age and sex and subtypes of hyperthyroidism. Direct standardization by age was performed using the resident population of Veneto Region in 2017 as a reference. The average annual percentage change in age-standardized rates (APC) and the relative 95% confidence interval (CI) were obtained from linear regression models with the logarithm of age-standardized rates weighted by the inverse of their variance as the dependent variable and the corresponding year as the regressor. All statistical analyses were conducted using Statistical Analysis Software (SAS) software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

During the study period, we identified 26,602 incident hyperthyroidism cases, corresponding to a standardized incidence rate (IR) of 54.38 per 100,000 person-years (95% confidence interval, CI: 53.73, 55.04). The median age at diagnosis was 56 years (IQR 43–71), slightly lower among females than males (54, IQR 41–70 vs 61, IQR 48–73; $P < 0.0001$).

Overall, there was a sustained decline of the incidence of hyperthyroidism from 2013 to 2022, from a standardized IR of 69.87 (95% CI: 67.49, 72.25) in 2013 to a standardized IR of 42.83 (95% CI: 40.99, 44.66) in 2022, with a comparable trend in females and in males (Fig. 1A). Table 1 shows the yearly hyperthyroidism IR trend. In 2020, an out-of-trend decrease in hyperthyroidism incidence was documented, corresponding to the SARS-CoV-2 pandemic outbreak (standardize IR of 37.92; 95% CI: 36.20, 39.64), with a realignment to the trend in the subsequent years (Fig. 1A and Table 1), with a nadir in hyperthyroidism new diagnosis between March and April 2020 and between December 2020 and January 2021, corresponding to Italian stricter lockdown periods. IR in females was 2.47-fold higher than in males (76.75 per 100,000 person-years and 31.13 per 100,000 person-years, respectively; $P < 0.0001$) (Table 2). The female-to-male incidence ratio reached a peak in the 30–34 years age group (female-to-male ratio 4.61) and a nadir in the 80–84 years age group (female-to-male ratio 1.35) (Table 2 and Fig. 1B). Figure 2 shows the IR of hyperthyroidism according to the cause (toxic diffuse goiter, toxic multinodular goiter, and toxic uninodular goiter) from 2013 to 2022. Overall, there was a decrease in the incidence of hyperthyroidism, with an APC of 5.78% (95% CI: 7.36, 4.18) ($P < 0.0001$), with a sharper decrease in males than in women, 6.42% (95% CI: 8.47, 4.32) and 5.51% (95% CI: 7.03, 3.97), respectively ($P < 0.001$). In particular, according to the type of hyperthyroidism, we documented a decline of 6.62% (95% CI: 8.47, 4.73) ($P < 0.0001$) in toxic multinodular goiter, of 7.56% in toxic uninodular goiter (95% CI: 10.54, 4.48) ($P < 0.001$) and of 4.70% (95% CI: 6.33, 3.04) in toxic diffuse goiter ($P < 0.001$), without significant differences between females and males. Table 3 shows the APC of hyperthyroidism incidence by type during 2013–2022 according to sex. Figure 3 reports the annual standardized IR of hyperthyroidism disorders by provinces (more detailed data are provided in supplemental materials): we can notice a decrease in hyperthyroidism incidence in all Veneto provinces, but with different extent of the phenomenon. Among the entire observation period (2013–2022), Belluno showed the highest decline in IR (–8.60%; 95% CI, –13.14%, –3.82%), followed by Padova (–6.35%; 95% CI: –7.96, –4.72), Verona (–6.14%, 95% CI, –8.16%, –4.09%), Treviso (–5.51%; 95% CI: –8.18%, –2.76%), Vicenza (–6.18%, 95% CI: –8.45%, –3.85%), Rovigo (–3.64%, 95% CI: –6.01, –1.22), and Venezia (–4.59%; 95% CI: –6.30%, –2.84%).

Discussion

This is the largest study on the incidence rates of hyperthyroidism carried out in Italy and covers the longest observation period among all regionwide population-based studies of hyperthyroidism in our country, to the best of our knowledge. The incidence of hyperthyroidism has declined in the observation period, mainly due to a decrease in the incidence of toxic nodular goiter and to a lesser degree in GD. This change is attributable to the implementation of an

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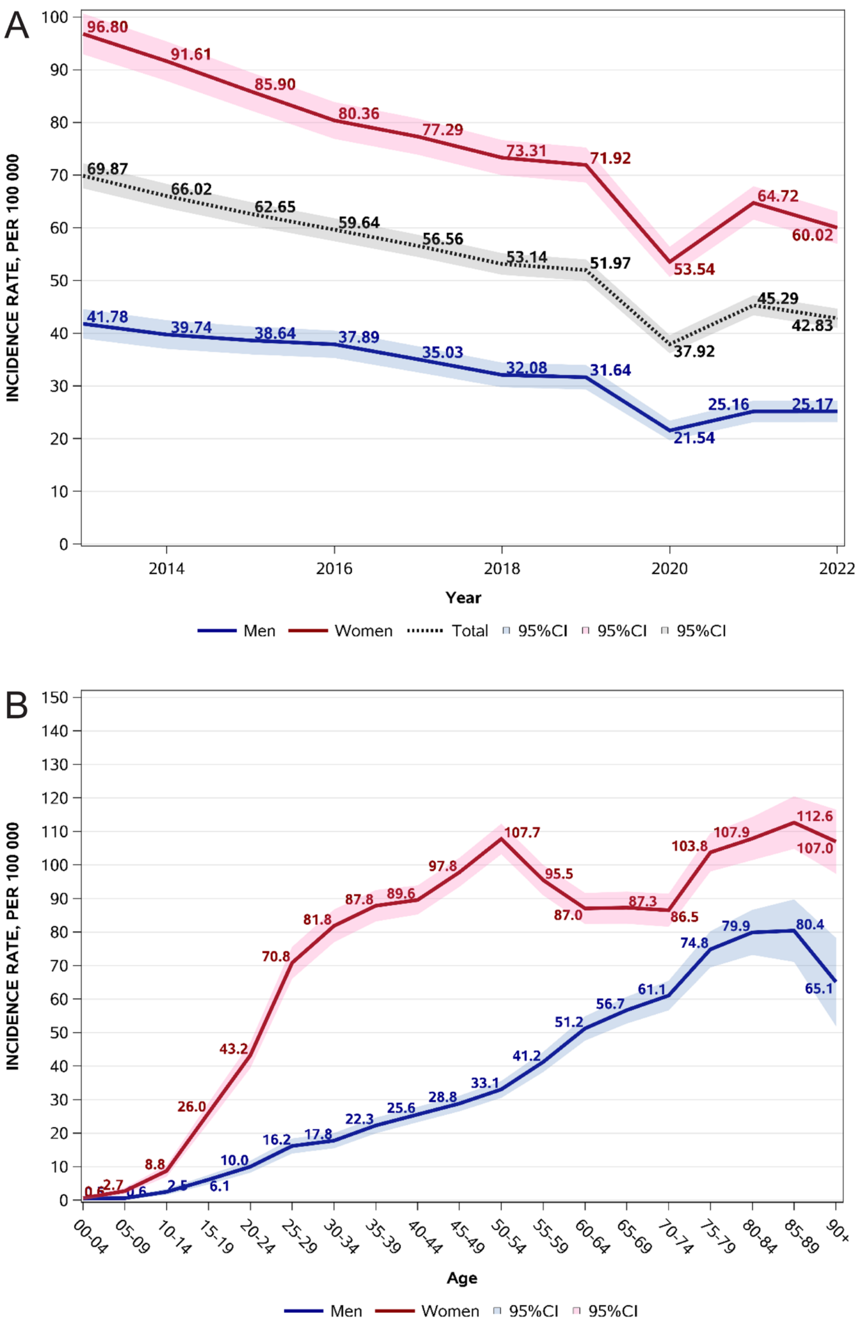

Figure 1
Standardized incidence rate by year (A) and age- and sex-specific incidence rate (B).

iodine prophylaxis program in our study region, that in the observation period has passed from being an area of mild-to-moderate iodine deficiency to an area of adequate iodine intake (19, 20).

Our data on the temporal trends of hyperthyroidism following the implementation of an iodine prophylaxis program are comparable with those of a similar population-based study, carried out in Denmark. Similarity, as expected, the sharper decrease in incidence rates involved TMNG and toxic adenoma, but fewer incident cases of GD were also observed (13).

These results are in line with those obtained also in other less numerous series, conducted on hospital-based data in Switzerland and Austria, in which a decrease in the incidence of TMNG and GD were observed, following salt iodination (23, 24).

Our results confirm in a population-based scale previous reports obtained in our country in less numerous series. The Pescopagano study, conducted in a rural community in Northern Italy, in which the prevalence of thyroid disorders was examined in 1995 and then again in 2010, documented a substantial

Table 1 Trends in standardized IR of hyperthyroidism by sex in the Veneto Region between 2013 and 2022.

Year	Incident cases (*n*)	Population	Standardized IR (95% CI) per 100,000	Male		Female	
				Incident cases (*n*)	Standardized IR (95% CI) per 100,000	Incident cases (*n*)	Standardized IR (95% CI) per 100,000
2013	3.340	4,901,415	69.87 (67.49, 72.25)	901	41.78 (38.99, 44.58)	2.439	96.80 (92.94, 100.66)
2014	3.186	4,905,712	66.02 (63.72, 68.32)	864	39.74 (37.03, 42.46)	2.322	91.61 (87.86, 95.35)
2015	3.040	4,902,694	62.65 (60.42, 64.88)	854	38.64 (36.00, 41.27)	2.186	85.90 (82.29, 89.51)
2016	2.896	4,890,648	59.64 (57.46, 61.81)	844	37.89 (35.30, 40.48)	2.052	80.36 (76.87, 83.85)
2017	2.762	4,883,373	56.56 (54.45, 58.67)	791	35.03 (32.56, 37.50)	1.971	77.29 (73.86, 80.71)
2018	2.608	4,880,936	53.14 (51.10, 55.18)	738	32.08 (29.74, 34.42)	1.870	73.31 (69.97, 76.64)
2019	2.558	4,884,590	51.97 (49.95, 53.99)	731	31.64 (29.32, 33.96)	1.827	71.92 (68.61, 75.24)
2020	1.871	4,879,133	37.92 (36.20, 39.64)	513	21.54 (19.67, 23.41)	1.358	53.54 (50.67, 56.41)
2021	2.230	4,869,830	45.29 (43.40, 47.18)	596	25.16 (23.13, 27.20)	1.634	64.72 (61.56, 67.89)
2022	2.111	4,847,745	42.83 (40.99, 44.66)	598	25.17 (23.14, 27.21)	1.513	60.02 (56.97, 63.08)
TOTAL	26.602	48,846,076	54.38 (53.73, 55.04)	7.430	32.52 (31.78, 33.27)	19.172	75.45 (74.38, 76.53)

The resident population of Veneto Region in 2017 was used as a reference.
IR, incidence rate.

reduction of hyperthyroidism, mostly due to a nodular origin (12). The mechanism by which iodine deficiency leads to hyperthyroidism associated with nodular goiter is quite well understood and thus the decrease in nodular goiter incidence with the improvement of iodine status is expected. The mechanism is slow and could take decades to go from euthyroidism to subclinical hyperthyroidism finally to overt hyperthyroidism. Low iodine intake may lead to an upregulation of many thyroidal processes and promote thyroid hyperplasia, in the attempt to increase thyroid hormone production. The increased thyroid growth, together with H_2O_2 excess may lead to an increased mutagenesis, with the appearance of somatic mutations promoting nodular transformation and autonomous hormone production (1, 11). However, it is worth noting that the reduction in TMNG and GD has not been observed in all the series analyzing the epidemiology of thyroid diseases with the improvement of iodine status. In Slovenia, iodine increased from 10 to 25 mg of potassium iodide per kg of salt in 1999. Thyroid epidemiology was observed over the successive years, up to 2014: although diffuse goiter and hyperthyroidism incidence decreased (the latter with a higher proportion of subclinical cases than in the past), no long-term changes were observed for GD, while the incidence of

Table 2 IR and female-to-male IR ratio by age and sex for hyperthyroidism in the Veneto Region.

Age group (years)	Incident cases (*n*)		IR (95% CI) per 100,000		Ratio F/M (95% CI)	*P*
	Male	Female	Male	Female		
00–19	115	425	2.51 (2.05, 2.97)	9.84 (8.91, 10.78)	3.92 (3.19, 4.81)	<0.0001
20–24	121	490	9.99 (8.21, 11.77)	43.21 (39.38, 47.04)	4.33 (3.55, 5.28)	<0.0001
25–29	200	851	16.17 (13.93, 18.42)	70.83 (66.07, 75.59)	4.38 (3.75, 5.11)	<0.0001
30–34	236	1082	17.76 (15.5, 20.03)	81.83 (76.96, 86.71)	4.61 (4.00, 5.30)	<0.0001
35–39	348	1360	22.29 (19.95, 24.63)	87.85 (83.18, 92.51)	3.94 (3.50, 4.43)	<0.0001
40–44	479	1648	25.57 (23.28, 27.86)	89.56 (85.24, 93.89)	3.50 (3.16, 3.88)	<0.0001
45–49	594	1981	28.84 (26.52, 31.16)	97.82 (93.51, 102.13)	3.39 (3.09, 3.72)	<0.0001
50–54	663	2156	33.06 (30.54, 35.57)	107.75 (103.2, 112.3)	3.26 (2.99, 3.56)	<0.0001
55–59	724	1712	41.21 (38.21, 44.22)	95.49 (90.97, 100.02)	2.32 (2.12, 2.53)	<0.0001
60–64	771	1368	51.23 (47.62, 54.85)	87.03 (82.42, 91.65)	1.70 (1.56, 1.86)	<0.0001
65–69	776	1283	56.70 (52.71, 60.69)	87.26 (82.49, 92.04)	1.54 (1.41, 1.68)	<0.0001
70–74	740	1186	61.05 (56.65, 65.45)	86.50 (81.58, 91.42)	1.42 (1.29, 1.55)	<0.0001
75–79	737	1268	74.84 (69.44, 80.24)	103.75 (98.04, 109.46)	1.39 (1.27, 1.52)	<0.0001
80–84	546	1086	79.89 (73.19, 86.59)	107.86 (101.44, 114.27)	1.35 (1.22, 1.50)	<0.0001
85–89	286	795	80.4 (71.08, 89.72)	112.62 (104.79, 120.45)	1.40 (1.22, 1.60)	<0.0001
90+	94	481	65.11 (51.95, 78.27)	106.95 (97.4, 116.51)	1.64 (1.32, 2.05)	<0.0001
Total[a]	7430	19,172	31.13 (30.43, 31.84)	76.75 (75.66, 77.83)	2.47 (2.40, 2.53)	<0.0001

The study period was 2013–2022.
[a]Sex-specific and overall crude incidence rate.
IR, incidence rate.

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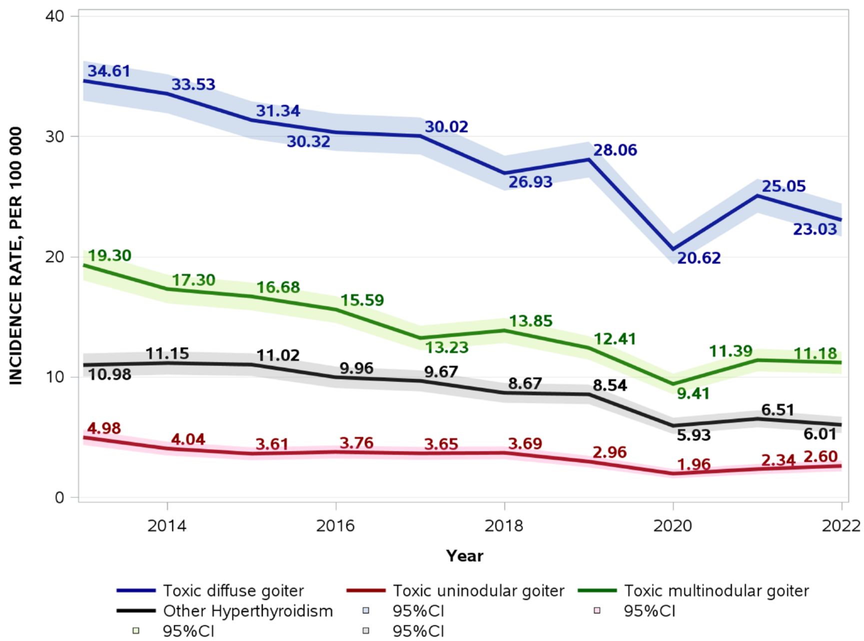

Figure 2
Annual standardized incidence rate of hyperthyroidism disorders by type.

TMNG and solitary nodule transiently increased or remained unchanged (25, 26, 27). Study design, population's characteristics (the most important being age), observation periods, and the combination between the entity of the iodine deficiency and the strategy of iodine prophylaxis campaign could all play a role in the heterogeneity of these results. The reduction in the incidence of GD in our series, registered also in Danish, Swiss and Austrian data (13, 23, 24) is less straightforward, since the pathogenesis of GD is autoimmune. A recent Italian study, carried out on a series of 283 subjects newly diagnosed of GD documented a greater proportion of milder phenotypes (subclinical hyperthyroidism, lower proportion of goiter and orbitopathy) than that observed in past series, also possibly due to an earlier diagnosis, but also an improved iodine nutrition (28). The reduction in the prescription of methimazole (–13.5%) from the introduction of a nationwide program of iodine prophylaxis corroborates this trend. The physiopathogenesis of this phenomenon is to be clarified, but it is at least interesting to note that the iodine prophylaxis program on a voluntary basis based on salt iodination is safe. Indeed, many authors advocate an increase in thyroid autoimmunity as a consequence of an increase in iodine intake in a population (29, 30), while others do not confirm a modification in thyroid autoimmunity following iodine salt fortification (31, 32, 33). According to the conclusions of a recent review on this debate, it could be drawn that a relevant long-term alteration of thyroid function due to autoimmune diseases is more frequently observed in the presence of long-standing relatively high UIC (i.e. 200 µg/L or more) (34), confirming the U-shaped relationship between thyroid autoimmune disease and the population iodine intake (35). In Italy, the content of iodine is 30 mg per kg salt, with an allowed range of 24–42 mg, that is higher than in other European countries. Nonetheless, according to our data, the program has been shown to be effective in decreasing the incidence

Table 3 Trend analysis: estimated annual percentage change (APC) of hyperthyroidism incidence by type during 2013–2022.

Type of hyperthyroidism	APC (95% CI)	P	Male		Female	
			APC (95% CI)	P	APC (95% CI)	P
242.0 – Toxic diffuse goiter	–4.70 (–6.33, –3.04)	0.0002	–5.35 (–6.89, –3.78)	0.0001	–4.43 (–6.29, –2.53)	0.0007
242.1 – Toxic uninodular goiter	–7.56 (–10.54, –4.48)	0.0005	–7.15 (–10.77, –3.39)	0.0026	–7.82 (–10.96, -4.56)	0.0006
242.2 – Toxic multinodular goiter	–6.62 (–8.47, –4.73)	<0.0001	–6.58 (–8.98, –4.12)	0.0003	–6.6 (–8.51, –4.66)	0.0001
Other hyperthyroidism	–7.22 (–9.30, –5.09)	0.0001	–8.08 (–11.47, -4.56)	0.0008	–6.79 (–8.42, –5.12)	<0.0001
Total	–5.78 (–7.36, –4.18)	<0.0001	–6.42 (–8.47, –4.32)	0.0001	–5.51 (–7.03, –3.97)	<0.0001

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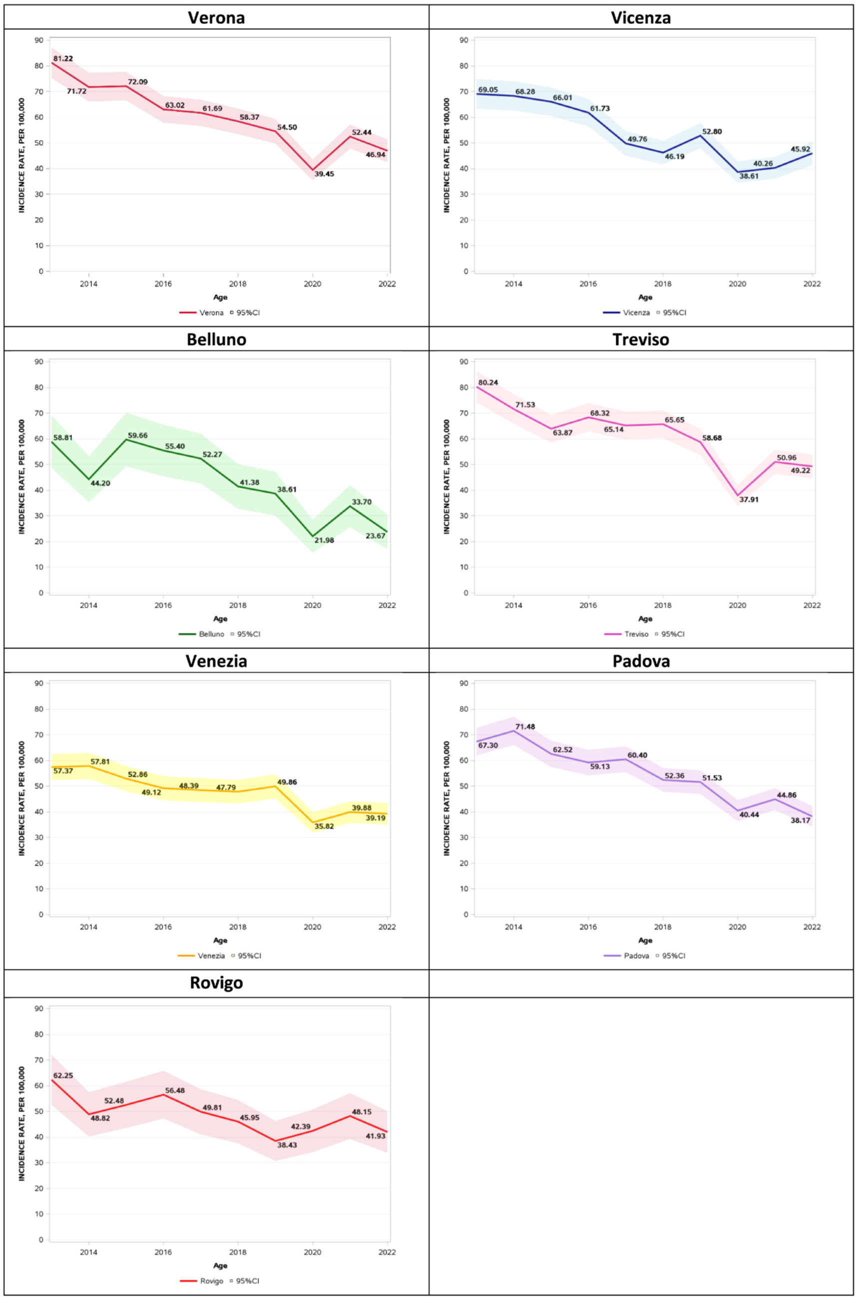

Figure 3
Annual standardized incidence rate of hyperthyroidism disorders by provinces.

of hyperthyroidism associated with thyroid nodular disease and at the same time safe: not only we did not observe an increase in hyperthyroidism associated with GD, but we also documented a decrease in its incidence. Unfortunately, data on the temporal trends of thyroid autoantibodies positivity or on the incidence of autoimmune hypothyroidism were not available, to draw a complete picture.

Considering the various Veneto provinces, it is interesting to note how the decline in hyperthyroidism IR reflects the efficacy of the iodine prophylaxis program, evaluated through the median UIC among SACs. According to the data collected in 2012 on 1375 SACs residing in Veneto Region, the median UIC was higher in the mountainous zone (median UIC = 94 µg/L), corresponding to the Belluno province, followed by the plane zone (median UIC = 77 µg/L) (Padova) and the hilly zone (median UIC = 54 µg/L) (Vicenza) (19). In the present study, the sharper reduction in hyperthyroidism IR was documented in Belluno provinces, followed by Padova, while Vicenza registered a less pronounced reduction. According to the last survey of the OSNAMI, based on data collected between 2015 and 2019, the median UIC improved, reaching iodine

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sufficiency in all the three zones (36), but it will take many years to see the effects on thyroid disease incidence.

Regarding hyperthyroidism epidemiology according to sex, we confirm the female-to-male prevalence in the gender distribution, in particular in younger ages, corresponding to the peak of GD incidence and realigning in the older ages, with the increasing incidence of the nodular disease.

Finally, SARS-CoV-2 vaccines have been claimed to cause or precipitate thyroid autoimmune diseases (37). If it is true, an increase in the IR of hyperthyroidism due to GD would have been documented, after the massive vaccination campaign carried out in the Veneto Region. The vaccination coverage was wide, with 85% of Veneto residents covered with the full vaccination schedule, mostly with mRNA-based vaccines (38). Our data suggest that SARS-CoV-2 vaccination campaign did not have an impact on the epidemiology of hyperthyroidism. Indeed, during the periods of stricter restrictions we registered a reduction in the hyperthyroidism IR due to declined access to health-care services associated with lockdown periods, fear of the contagion and other barriers. However, when the restrictions have been loosened, the IR of hyperthyroidism realigned to the decreasing trend registered before the lockdown, without any peak nor inversion in the trend. This is the first report, on a large population-based scale, analyzing the impact of the pandemic and of massive SARS-CoV-2 vaccination on the incidence of hyperthyroidism and we can conclude that the mass vaccination did not change the preexisting long-term declining trend.

Our study has strengths and limitations. Among the strengths there is the wide population-based dataset, covering a long period of observation, spanning over more than a decade. The main limitation is the absence of clinical and laboratory data, so that we do not have information about the severity of hyperthyroidism.

In conclusion, in the last decade there was a decline in the incidence of hyperthyroidism in Veneto Region, paralleling the improvement of the iodine status, thanks to a long and sustained iodine prophylaxis campaign. SARS-CoV-2 vaccination did not have a significant impact on the IR of hyperthyroidism in our Region.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-23-0292.

Declaration of interest

The authors have no competing financial interests to disclose. Filippo Ceccato is a senior editor of *Endocrine Connections*. Filippo Ceccato was not involved in the review or editorial process for this paper, on which he is listed as an author.

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Data availability

The data that support the findings of this study are available on request from the corresponding author, Simona Censi.

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