Prevalence, incidence and associated comorbidities of treated hypothyroidism: an update from a European population

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Abstract

Objective: Estimates of the prevalence of hypothyroidism in unselected populations date from the late 1990s.

We present an update on the prevalence and incidence of overt hypothyroidism in Piedmont, northwest Italy and examine the association between hypothyroidism and multiple chronic comorbidities.

Design and methods: Data were obtained from drug prescription and hospital discharge databases. Individuals who had received at least two levothyroxine prescriptions in 2012 were defined as having hypothyroidism; those who had undergone thyroidectomy or ¹³¹I irradiation in the previous 5 years were defined as having iatrogenic hypothyroidism and those who had either obtained exemption from treatment co-payment or had been discharged from hospital with a chronic comorbidity (diabetes and connective tissue diseases) were identified as having one of these conditions.

Results: The overall crude prevalence was 31.1/1000 (2.3/1000 for iatrogenic hypothyroidism) and the overall crude incidence was 7/1000. The average daily dose of thyroxine (122 µg) roughly corresponded to 1.7 µg/kg. There was a strong association between hypothyroidism and diabetes (type 1, type 2 or gestational) and with autoimmune diseases, with the odds ratio ranging from 1.43 (1.02–1.99) for psoriatic arthritis to 4.99 (3.06–8.15) for lupus erythematosus.

Conclusions: As compared with previous estimates, the prevalence of hypothyroidism rose by about 35%, driven mainly by non-iatrogenic forms. The increase may be due to either population aging or improved diagnostic capability or both. The frequent co-occurrence of hypothyroidism with other multiple chronic conditions characterizes it more as a comorbidity rather than an isolated chronic disease.

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Introduction

Hypothyroidism refers to any condition in which the thyroid gland fails to produce or secrete sufficient amounts of thyroxine (1, 2). Because thyroxine is an essential hormone for regulating heart rate, digestion, physical growth and brain development and functioning, an insufficient supply to cells can disrupt cellular metabolism throughout the body, leading to organ and tissue damage and result in life-threatening complications.

Iodine deficiency remains the most common cause of hypothyroidism worldwide (3). In iodine-replete areas,

however, the cause of primary hypothyroidism may be congenital or spontaneous due to chronic autoimmune disease (atrophic autoimmune thyroiditis or goitrous autoimmune thyroiditis (Hashimoto's thyroiditis)) or iatrogenic after surgery or radioiodine ablation for thyrotoxicosis. In secondary hypothyroidism, the pituitary gland fails to release thyroid-stimulating hormone (TSH). The most accurate estimates of prevalence of hypothyroidism date from the late 1990s, with percentages between 1% and 2% and predominance

among women (2). Approximately one-third of patients with newly diagnosed overt hypothyroidism have undergone ablative therapy for hyperthyroidism (iatrogenic hypothyroidism) and require thyroid hormone replacement treatment with levothyroxine continued indefinitely. Though not much can be done to prevent the occurrence of spontaneous autoimmune hypothyroidism, if identified early, benefit can be gained by monitoring its conversion to overt disease and starting levothyroxine therapy as timely as possible.

Hypothyroidism may be either subclinical or overt. Subclinical hypothyroidism, a laboratory diagnosis, is characterized by elevated serum TSH levels above the upper reference limit but normal free thyroxine levels (4). The clinical significance of TSH values remains much debated and is beyond the scope and the tools of this study. Here, we present a comprehensive update on the prevalence and incidence of hypothyroidism and the multiple chronic comorbidities associated with it in the population of a European region.

Subjects and methods

Study population and data sources

The study population was Piedmont residents (4 400 000, approximately 7.5% of the national population). Individuals were defined as having hypothyroidism if they had received at least two prescriptions, at two different times, of levothyroxine (Anatomical Therapeutic Chemical (ATC) codes: H03AA01, H03AA02 and H03AA03) between 1st January and 31st December 2012. Prescription data were retrieved from the regional drug prescription database that contains data on all drug prescriptions by general practitioners (GP) and medical specialists working in the public health system. The risk of missing incident cases occurred in the late weeks of the year can not be excluded. On the contrary, the risk out-of-pocket purchases of levothyroxine is minimal because, even in such cases, levothyroxine is mainly prescribed by GPs, who are the only medical doctors allowed to prescribe medications free of charge. The Italian Association of Clinical Endocrinologists recommends treatment for subclinical hypothyroidism only when serum TSH is >10 IU/L or when a history of cardiac disease or cardiac risk factors are present. Therefore, it is likely that the majority of patients studied had overt hypothyroidism.

Individuals were defined as having iatrogenic hypothyroidism if they had undergone partial or total thyroidectomy or I¹³¹ irradiation in the previous 5 years

(2007–2011). Data on surgery or irradiation were retrieved by linking (with an anonymous unique identifier) individuals with hypothyroidism with the regional hospital discharge database and the regional database of outpatient care. Individuals who had undergone a procedure coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 062*-064* (thyroidectomy) or 92.28 (irradiation) were defined as having iatrogenic hypothyroidism; all other individuals were defined as having autoimmune/iodine deficiency hypothyroidism.

Data collection

Data were collected on age, gender, geographic elevation of place of residence, educational level, levothyroxine prescriptions and chronic comorbid conditions. Age was stratified in three 10-year age groups (30–80 years, <30 and >80). Educational level for each individual was obtained by record linkage with the 2011 National Census for people aged 30 years or more and was classified according to the International Standard Classification of Education (ISCED) developed by UNESCO in five levels: level 0 (pre-primary education), level 1 (primary education, 5 years of education completed), level 2 (lower secondary education, 2–3 years duration following level 1), level 3 (upper secondary education, 2–3 years duration following level 2, vocational schools not allowing access to university; 4–5 years duration following level 2, allowing access to university) and level 5–6 (university degree or upper research qualifications). ISCED level 4 does not apply to the Italian school system. The geographic elevation of an individual's municipality of residence was classified in three categories (plain, hill and mountain) according to the 2011 National Institute of Statistics classification of Italian Municipalities (5).

To obtain the mean dosage of levothyroxine, we calculated the total amount prescribed by summing all individual levothyroxine prescriptions from 2007 to 2012 (available from the regional drug prescription database). We report the cumulative dose mean (and standard deviation), median, first and third quartiles (micrograms) for each type of hypothyroidism.

Comorbidities

In Italy, citizens are required to co-pay for drugs and outpatient visits and laboratory examinations prescribed by their GP. However, patients with certain chronic conditions can be exempt from treatment co-payment

provided they have certification of the disease confirmed by a specialist working in a public health clinic. These exemptions are collected in a regional database that we used to identify comorbidities. We used different data sources to select those comorbidities that are reportedly more likely to share a common autoimmune etiology with hypothyroidism. Furthermore, we distinguished between co-occurrence of comorbid conditions in autoimmune and in iatrogenic thyroid disease.

Type 1, type 2 and gestational diabetes mellitus

As described elsewhere (6, 7), we used three different data sources to identify individuals with diabetes: the file of all residents exempt from payment of drugs, syringes and glucose monitoring strips (Regional Register of Diabetes (RRD)) (8); the file of all prescriptions for antidiabetic drugs (ATC codes A10A and A10B) prescribed in 2012; only those individuals who had received at least two prescriptions were defined as having diabetes; the file of residents discharged from hospital with a primary or secondary diagnosis of diabetes (ICD-9-CM 250) from 2007 to 2012. These three data sources were matched by deterministic linkage using an anonymous individual identifier; individuals who were present in at least one source were defined as having diabetes. Type of diabetes was classified according to the information in the RRD. Individuals not present in the RRD were considered as having type 1 diabetes if they had been discharged from hospital with a primary or secondary diagnosis of type 1 diabetes (ICD-9-CM 250x.1 or 250x.3) in the 5 preceding years or had received at least two prescriptions of insulin in the previous 12 months and were aged 35 year or less. All other individuals were defined as having type 2 diabetes or gestational diabetes mellitus (women aged 20–45 years if this diagnosis was recorded in the RRD).

Other comorbid conditions

Celiac disease, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, psoriatic arthritis, multiple sclerosis.

Individuals were defined as having celiac disease if they had either obtained an exemption from treatment co-payment (all patients with celiac disease can obtain clinical tests and gluten-free food free of charge provided they have a biopsy-verified diagnosis of the disease) or been discharged from hospital with a primary or secondary diagnosis of celiac disease (ICD-9-CM 579.0)

between 2007 and 2012 (9); rheumatoid arthritis if they had either obtained an exemption from treatment co-payment or been discharged from hospital with a primary or secondary diagnosis of rheumatoid arthritis (ICD-9-CM 714.0) between 2007 and 2012 (10); ankylosing spondylitis if they had either obtained an exemption from treatment co-payment or been discharged from hospital with a primary or secondary diagnosis of ankylosing spondylitis (ICD-9-CM 720.0) between 2007 and 2012; systemic lupus erythematosus if they had either obtained an exemption from treatment co-payment or been discharged from hospital with a primary or secondary diagnosis of systemic lupus erythematosus (ICD-9-CM 710.0) between 2007 and 2012; psoriatic arthritis if they had either obtained an exemption from treatment co-payment or been discharged from hospital with a primary or secondary diagnosis of psoriatic arthritis (ICD-9-CM 696.0) between 2007 and 2012; multiple sclerosis if they had either obtained an exemption from treatment co-payment or been discharged from hospital with a primary or secondary diagnosis of multiple sclerosis (ICD-9-CM 340.0) between 2007 and 2012 or had received at least two drug prescriptions for specific drugs (ATC codes: L03AX13, L03AB07, L03AB08, L04AA27 and L04AA23) in the preceding 12 months (11).

Because this automated system is anonymous, ethical committee approval and informed consent for this study were not required.

Statistical analysis

The overall crude prevalence of hypothyroidism was calculated by dividing the total number of patients with hypothyroidism who were resident in Piedmont and alive on 31st December 2012 by the total number of residents alive on 31st December 2012. The number of the resident population was retrieved from the Unique Regional Archive of residents covered by the regional health system. The overall crude (cumulative) incidence of hypothyroidism was calculated by dividing the number of residents who had received their first prescription of levothyroxine between 1st January and 31st December 2013 and had not received any levothyroxine prescription in the previous 12 months (in 2012), by the total number of residents alive on 31st December 2013. Both prevalence and incidence were also calculated by gender, age, geographic elevation of the municipality of residence and educational level (individuals ≥ 30 years). Prevalence and incidence were standardized by age using the age

Table 1 Prevalence ($\times 1000$) of hypothyroidism in Piedmont; 31 December 2012.

Total	Autoimmune/iodine deficiency			Post-surgery/post-irradiation			Total		
	n	Crude (95% CI)	Age adj. (95% CI)	n	Crude (95% CI)	Age adj. (95% CI)	n	Crude (95% CI)	Age adj. (95% CI)
Age (years)	125972	28.8 (28.6–29.0)		10064	2.30 (2.26–2.35)		136036	31.1 (30.9–31.3)	
0–29	3980	3.43 (3.33–3.54)		193	0.17 (0.14–0.19)		4173	3.60 (3.49–3.71)	
30–39	8378	14.6 (14.3–14.9)		659	1.15 (1.07–1.24)		9037	15.8 (15.5–16.1)	
40–49	16767	23.6 (23.2–23.9)		1614	2.27 (2.16–2.38)		18381	25.9 (25.5–26.2)	
50–59	23985	39.6 (39.1–40.1)		2299	3.80 (3.65–3.96)		26284	43.4 (42.9–43.9)	
60–69	29994	55.2 (54.6–55.9)		2678	4.93 (4.75–5.12)		32672	60.2 (59.5–60.8)	
70–79	27728	59.0 (58.4–59.7)		2125	4.52 (4.34–4.72)		29853	63.6 (62.9–64.3)	
≥ 80	15140	48.6 (47.8–49.3)		496	1.59 (1.46–1.74)		15636	50.2 (49.4–50.9)	
Gender									
Men	17982	8.52 (8.40–8.64)	8.41 (8.29–8.53)	2185	1.04 (0.99–1.08)	1.02 (0.98–1.07)	20167	9.56 (9.42–9.69)	9.76 (9.62–9.07)
Women	107990	47.7 (47.4–48.0)	46.2 (45.9–46.5)	7879	3.48 (3.41–3.56)	3.43 (3.35–3.50)	115869	51.2 (50.9–51.5)	49.6 (49.4–49.9)
Elevation ^a									
Plain	73605	29.1 (28.9–29.3)	29.6 (29.4–29.8)	6168	2.44 (2.38–2.50)	2.47 (2.41–2.53)	79773	31.6 (31.4–31.8)	32.1 (31.9–32.3)
Hill	39412	29.1 (28.9–29.4)	29.3 (29.0–29.6)	2960	2.19 (2.11–2.27)	2.20 (2.13–2.28)	42372	31.3 (31.0–31.6)	31.47 (31.2–31.8)
Mountain	12680	25.7 (25.2–26.1)	25.9 (25.4–26.3)	922	1.87 (1.75–1.99)	1.90 (1.78–2.02)	13602	27.5 (27.1–28.0)	27.8 (27.3–28.2)
Educational level ^b									
Level 0	5378	56.3 (54.9–57.8)	42.0 (40.4–43.7)	307	3.22 (2.88–3.59)	3.44 (2.96–3.99)	5731	60.0 (58.5–61.5)	45.5 (43.7–47.2)
Level 1	38316	57.8 (57.3–58.4)	40.8 (40.0–41.6)	2740	4.14 (3.98–4.29)	3.82 (3.57–4.09)	41394	62.5 (61.9–63.1)	44.6 (43.8–45.4)
Level 2	45535	39.4 (39.1–39.8)	41.0 (40.6–41.4)	3517	3.05 (2.95–3.15)	3.29 (3.19–3.40)	49506	42.9 (42.5–43.3)	44.3 (43.9–44.7)
Level 3	21555	31.3 (30.9–31.7)	36.7 (36.1–37.2)	1479	2.15 (2.04–2.26)	2.58 (2.45–2.72)	23256	33.8 (33.4–34.2)	39.3 (38.7–39.8)
Level 5–6	8962	28.5 (28.0–29.1)	33.8 (33.0–34.6)	555	1.77 (1.63–1.92)	2.19 (2.01–2.40)	9601	30.6 (30.0–31.2)	36.0 (35.2–36.9)
Levothyroxine (mg)									
Mean (s.d.)		108.75 (47.5–175)			132.5 (80–195)			110 (50–177.5)	
Median (1Q–3Q)*		119.99 (84.82)			143.02 (80.93)			121.7 (84.75)	

^a289 missing; ^bmissing: 1859; *1Q–3Q, 1st quartile – 3rd quartile.

Table 2 Incidence ($\times 1000$) of hypothyroidism in Piedmont; 31 December 2012–31 December 2013.

Total	Autoimmune/iodine deficiency			Post-surgery/post-irradiation			Total		
	n	Crude (95% CI)	Age adj. (95% CI)	n	Crude (95% CI)	Age adj. (95% CI)	n	Crude (95% CI)	Age adj. (95% CI)
Age (years)									
0–29	29426	6.62 (6.55–6.70)		1643	0.37 (0.35–0.39)		31069	6.99 (6.91–7.07)	
30–39	1890	1.61 (1.53–1.68)		52	0.04 (0.03–0.06)		1942	1.65 (1.58–1.72)	
40–49	3209	5.71 (5.51–5.91)		172	0.31 (0.26–0.36)		3381	6.01 (5.81–6.22)	
50–59	4715	6.53 (6.35–6.72)		299	0.41 (0.37–0.46)		5014	6.95 (6.76–7.14)	
60–69	5566	8.89 (8.66–9.13)		393	0.63 (0.57–0.69)		5959	9.52 (9.28–9.76)	
70–79	5629	10.2 (9.92–10.5)		362	0.65 (0.59–0.73)		5991	10.8 (10.6–11.1)	
≥ 80	4785	10.1 (9.81–10.4)		282	0.59 (0.53–0.67)		5067	10.7 (10.4–11.0)	
Gender	3632	11.3 (10.9–11.6)		94	0.29 (0.24–0.36)		3726	11.6 (11.2–11.9)	
Men	4706	2.19 (2.13–2.26)	2.28 (2.22–2.35)	315	0.15 (0.13–0.16)	0.15 (0.13–0.17)	5021	2.34 (2.28–2.40)	2.43 (2.36–2.50)
Women	24720	10.8 (10.7–10.9)	10.7 (10.5–10.8)	1328	0.58 (0.55–0.61)	0.58 (0.55–0.61)	26048	11.4 (11.2–11.5)	11.3 (11.1–11.4)
Elevation ^a									
Plain	16635	6.45 (6.35–6.55)	6.70 (6.60–6.81)	990	0.38 (0.36–0.41)	0.40 (0.37–0.42)	17625	6.83 (6.73–6.93)	7.10 (7.00–7.21)
Hill	8594	6.31 (6.18–6.45)	6.43 (6.30–6.57)	441	0.32 (0.30–0.36)	0.33 (0.30–0.36)	9035	6.64 (6.50–6.77)	6.76 (6.62–6.90)
Mountain	3290	6.63 (6.41–6.86)	6.79 (6.56–7.02)	170	0.34 (0.29–0.40)	0.35 (0.30–0.41)	3460	6.97 (6.75–7.21)	7.14 (6.90–7.38)
Educational level ^b									
Level 0	1022	10.7 (10.1–11.4)	9.55 (8.69–10.5)	45	0.47 (0.35–0.63)	0.61 (0.43–0.88)	1073	11.2 (10.6–11.9)	10.2 (9.28–11.2)
Level 1	6724	10.2 (9.91–10.4)	8.25 (7.83–8.69)	321	0.48 (0.43–0.54)	0.53 (0.44–0.65)	7115	10.7 (10.5–10.9)	8.8 (8.35–9.24)
Level 2	9846	8.53 (8.36–8.70)	8.83 (8.65–9.02)	495	0.43 (0.39–0.47)	0.50 (0.46–0.54)	10456	9.06 (8.88–9.23)	9.33 (9.14–9.52)
Level 3	5247	7.63 (7.42–7.83)	8.48 (8.21–8.75)	260	0.38 (0.33–0.43)	0.45 (0.40–0.50)	5569	8.09 (7.89–8.31)	8.92 (8.65–9.20)
Level 5–6	2597	8.27 (7.96–8.59)	8.84 (8.45–9.25)	99	0.32 (0.26–0.38)	0.43 (0.35–0.53)	2720	8.66 (8.34–8.99)	9.27 (8.87–9.69)

^aMissing: 949; ^bmissing: 2030.

Clinical Study	C B Giorda and others	Update of epidemiology of overt hypothyroidism	176:5	538
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Table 3 Prevalence of comorbidities in individuals with autoimmune/iodine deficiency (non-iatrogenic hypothyroidism), age-adjusted odds ratios (OR) and 95% confidence intervals (CI); 31 December 2012.

	Men		Women	
	Prevalence × 1000 (95% CI)	OR (95% CI)	Prevalence × 1000 (95% CI)	OR (95% CI)
Type 2 diabetes	145.92 (140.84–151.16)	1.52 (1.46–1.59)	95.74 (94.00–97.51)	1.49 (1.46–1.52)
Type 1 diabetes	10.18 (8.81–11.75)	4.14 (3.56–4.80)	5.93 (5.49–6.40)	3.29 (3.02–3.59)
Gestational diabetes (20–45 years)				1.69 (1.71–2.02)
Celiac disease	3.67 (2.88–4.67)	5.80 (4.52–7.44)	5.35 (4.93–5.81)	3.10 (2.84–3.39)
Rheumatoid arthritis	4.34 (3.48–5.41)	1.74 (1.39–2.19)	12.54 (11.89–13.22)	2.08 (1.96–2.20)
Ankylosing spondylitis	0.78 (0.46–1.31)	1.99 (1.17–3.38)	0.53 (0.41–0.68)	1.94 (1.47–2.56)
Lupus erythematosus	0.94 (0.59–1.52)	4.99 (3.06–8.15)	2.60 (2.31–2.92)	2.23 (1.96–2.53)
Psoriatic arthritis	1.95 (1.40–2.71)	1.43 (1.02–1.99)	1.95 (1.71–2.24)	1.56 (1.35–1.80)
Multiple sclerosis	1.39 (0.28–2.06)	2.07 (1.39–3.08)	2.71 (2.42–3.04)	1.71 (1.52–1.93)

distribution of the 2012 Piedmont population (direct standardization).

The overall crude prevalence of comorbidities was calculated by dividing the total number of individuals with hypothyroidism and a comorbidity by the total number of individuals with hypothyroidism (both autoimmune and iatrogenic). Logistic regression, adjusted for age, was used to compare the prevalence of comorbidities between individuals with hypothyroidism and all Piedmont residents after excluding those affected with hypothyroidism. Odds ratios (OR) and 95% confidence intervals (95% CI) were differently calculated according to sex. The SAS System (version 9.3) and STATA 13 were the software used.

Results

As of December 31, 2012, we identified 125972 people with autoimmune or iodine deficiency hypothyroidism and 10064 with iatrogenic hypothyroidism (1181 after irradiation). The crude prevalence was 28.8×1000 and 2.3×1000 (overall 31.1×1000) respectively. The overall

prevalence was fivefold higher in women than that in men, rose steadily with increasing age and then started to decline in the very old. The prevalence was slightly lower in those living in a municipality at high geographic elevation and was inversely related to educational attainment, being lower in individuals with a higher educational level. After adjusting for age, the fivefold difference by gender was confirmed, as was the lower risk for those living in mountainous areas, whereas the social gradient was attenuated to a 25% higher prevalence among individuals with a lower educational level (Table 1). The six-year cumulative prescription of levothyroxine was slightly higher among individuals with non-iatrogenic hypothyroidism than those with iatrogenic hypothyroidism (median cumulative dose 143 mg and 120 mg respectively).

As for incidence, we identified 31069 new cases of hypothyroidism in 2013, 94% of which were due to autoimmune/iodine deficiency. The overall crude incidence rate was 7×1000 . Age and gender distribution was rather similar to prevalence, being higher among women (fivefold higher) and

Table 4 Prevalence of comorbidities in individuals with non-hypothyroidism, age-adjusted odds ratios (OR) and 95% confidence intervals (CI); 31 December 2012.

	Men		Women	
	Prevalence × 1000 (95% CI)	OR (95% CI)	Prevalence × 1000 (95% CI)	OR (95% CI)
Type 2 diabetes	135.93 (122.18–150.95)	1.54 (1.36–1.74)	88.72 (82.64–95.20)	1.47 (1.36–1.60)
Type 1 diabetes	3.66 (1.83–7.30)	1.40 (0.70–2.80)	2.79 (1.84–4.24)	1.38 (0.91–2.10)
Gestational diabetes (20–45 years)				1.17 (0.83–1.66)
Celiac disease	2.29 (0.95–5.49)	3.30 (1.37–7.95)	4.06 (2.87–5.74)	2.01 (1.42–2.86)
Rheumatoid arthritis	5.95 (3.46–10.22)	2.49 (1.44–4.30)	12.18 (9.99–14.86)	1.88 (1.54–2.30)
Ankylosing spondylitis	0	0	0.38 (0.13–1.18)	1.22 (0.39–3.79)
Lupus erythematosus	0	0	2.28 (1.44–3.62)	1.67 (1.05–2.65)
Psoriatic arthritis	0.46 (0.06–3.24)	0.30* (0.04–2.14)	2.16 (1.34–3.47)	1.51 (0.94–2.44)
Multiple sclerosis	0.91 (0.23–3.65)	1.14 (0.28–4.59)	1.90 (1.15–3.15)	1.02 (0.61–1.69)

*Only one individual.

Clinical Study	C B Giorda and others	Update of epidemiology of overt hypothyroidism	176:5	539
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Table 5 Prevalence of comorbidities in individuals with iatrogenic hypothyroidism, age-adjusted odds ratios (OR) and 95% confidence intervals (CI); 31 December 2012.

	Men		Women	
	Prevalence × 1000 (95% CI)	OR (95% CI)	Prevalence × 1000 (95% CI)	OR (95% CI)
Type 2 diabetes	135.93 (122.18–150.95)	1.54 (1.36–1.74)	88.72 (82.64–95.20)	1.47 (1.36–1.60)
Type 1 diabetes	3.66 (1.83–7.30)	1.40 (0.70–2.80)	2.79 (1.84–4.24)	1.38 (0.91–2.10)
Gestational diabetes (20–45 years)				1.17 (0.83–1.66)
Celiac disease	2.29 (0.95–5.49)	3.30 (1.37–7.95)	4.06 (2.87–5.74)	2.01 (1.42–2.86)
Rheumatoid arthritis	5.95 (3.46–10.22)	2.49 (1.44–4.30)	12.18 (9.99–14.86)	1.88 (1.54–2.30)
Ankylosing spondylitis	0	0	0.38 (0.13–1.18)	1.22 (0.39–3.79)
Lupus erythematosus	0	0	2.28 (1.44–3.62)	1.67 (1.05–2.65)
Psoriatic arthritis	0.46 (0.06–3.24)	0.30* (0.04–2.14)	2.16 (1.34–3.47)	1.51 (0.94–2.44)
Multiple sclerosis	0.91 (0.23–3.65)	1.14 (0.28–4.59)	1.90 (1.15–3.15)	1.02 (0.61–1.69)

*Only one individual.

progressively increasing with age. No differences in incidence were noted when the data were stratified by geographic elevation of place of residence, whereas there was a direct relationship with educational level, with a lower incidence the higher the educational level. However, this difference disappeared after adjusting for age (Table 2).

Tables 3 and 4 show the crude prevalence and the age-adjusted ORs for selected comorbidities in individuals with non-iatrogenic hypothyroidism (Tables 3 and 4) and in those with iatrogenic hypothyroidism (Table 5). In both men and women, the prevalence of type 2 diabetes was about 50% higher in individuals with hypothyroidism, both autoimmune and iatrogenic. Type 1 diabetes showed a very strong association (OR 4.14 in men and 3.29 in women) with autoimmune but not with iatrogenic hypothyroidism; similarly, gestational diabetes was 70% more prevalent among women with autoimmune hypothyroidism, whereas no association emerged with iatrogenic disease. There was a statistically significant association between comorbid conditions and autoimmune hypothyroidism in both men and women; the association with celiac disease, rheumatoid arthritis and systemic lupus erythematosus (only for women) was also confirmed among individuals with iatrogenic hypothyroidism. However, these cases could be autoimmune hyperthyroidism becoming hypothyroidism after operation or irradiation.

Conclusions

As hypothyroidism can be readily diagnosed by laboratory testing and easily treated, efforts to update the epidemiology of the disease are largely justified (12). The prevalence of clinical hypothyroidism in the

Western general population was estimated to be around 1–2% and considered as a major health problem. In 1977, Tunbridge and coworkers (Whickham Survey) (13) found a prevalence of 1.9 in females and 0.23% in males in the community in northeast England and followed up the cohort for 18 years. In 1995, the mean incidence was 3.5/1000 survivors/year (2.8–4.5) in women and 0.6/1000 survivors/year (0.3–1.2) in men (14). In a selected population of elderly (over age 60 years) American men and women in the original cohort of the Framingham Study, the prevalence of overt hypothyroidism was 4.4% (15). It should be noted, however, that the most recent epidemiology surveys have the limitation that they consider only the elderly population and date from the early years of this century (16). Our study fills this gap to better understand trends in the prevalence and incidence of hypothyroidism in the general population in the last 15 years.

Our data show an unexpectedly high prevalence of hypothyroidism in the study population, with an increase of about 35% over previous levels. This could be due to the rise in the rate of thyroid disease driven by the general increase in autoimmune diseases and the aging population. Another possible explanation is that awareness campaigns may have helped boost physicians' attention to the condition. Also, greater access to medical facilities and more sensitive diagnostic assays may have increased the detection of hypothyroidism. However, given that in the Piedmont Region, median urinary iodine excretion dropped from 115.8 µg/L in 2002 to 98 µg/L in 2011 and iodized salt is used only by 47% of the population, iodine deficiency should also be considered (17). The increase also involves the proportion of individuals with iatrogenic hypothyroidism, especially those in the age groups between 50 and 80 years,

Clinical Study	C B Giorda and others	Update of epidemiology of overt hypothyroidism	176:5	540
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confirming the not negligible role of ablative therapies. Hypothyroidism, both iatrogenic and not iatrogenic, continues to be far more common in women than that in men, consistent with the well-known characteristic of all thyroid disorders.

The total average dose of levothyroxine 122 mg corresponds roughly to 1.7 µg/kg, not far from the 1.6 µg/kg considered the correct dosage for safe replacement therapy (1).

There is scanty information on the incidence of hypothyroidism. Our findings indicate that it is remarkably higher than that in the previously mentioned Whickham study (3) and that the pressure of new cases is meaningful for health care decision making. We found no difference in incidence when the study population was stratified by educational level, which we used as a proxy of deprivation; however, it appears that the lower the educational level, the higher the prevalence of the disease. Our data seem to be discordant with the patterns seen in other autoimmune diseases, where people in lower educational and income levels are reported to be less prone to develop immune-mediated diseases (18, 19) due to the effect on immune regulation of decreased early-life exposure to infectious diseases: the so-called 'hygiene hypothesis' (20). However, because the hygiene hypothesis operates in the younger but not in the older age groups, they might have been exposed to other determinant factors. For the latter, exposure to iodine deficiency in childhood (a more frequent condition in the past than nowadays) could have caused cognitive impairment and hampered attaining higher levels of educational achievement ('reverse causation').

A highly relevant finding of our study is the magnitude of the association between hypothyroidism and other metabolic and immune conditions such as diabetes, including gestational diabetes. The association with type 1 diabetes and celiac disease is well known and can be easily dismissed as a common genetic predisposition to autoimmune disease. Unclear, though not entirely new, is the association with type 2 diabetes. The rate of primary hypothyroidism in people with diabetes is known to be greater than that in the non-diabetic population (21, 22, 23) and a possible synergic negative impact on complications has been suggested (24). Metformin, the most widely used medication for treating type 2 diabetes, interferes with TSH levels; it may reduce the incidence of hypothyroidism but also mask detection of established disease (21, 25). Much controversy surrounds the effect of metformin (21) and no conclusions can be drawn. The association between hypothyroidism and gestational

diabetes, a potentially serious combination of risk factors for negative pregnancy outcomes, can be regarded as a relevant new finding by our study. It provides additional evidence supporting minor observations from not-purposely designed studies (26, 27).

The association with other autoimmune diseases showed higher than expected odd ratios. A number of thyroid dysfunctions leading to either hyperthyroidism or hypothyroidism are mediated by autoimmune mechanisms (28). Thyroid abnormalities may be an isolated alteration or may precede incipient disorders, as occurs in polyendocrine syndromes. In patients with connective tissue diseases or rheumatoid arthritis, thyroid dysfunction may precede or follow the appearance of rheumatic manifestations (28). The mechanisms by which the autoimmune thyroid disorders may be linked to systemic autoimmune diseases have not been fully explained; however, alterations in common pathways are suggested by shared genetic variants affecting autoantigen presentation and regulation of immune response. In our findings, however, the strong association of rheumatoid arthritis with thyroid deficiency, involving both autoimmune and iatrogenic types, suggests a direct causal relationship in the same patient. Arguably, the chance exists that patients with autoimmune diseases are better screened for other coexisting autoimmune conditions such as hypothyroidism, even in the absence of symptoms.

Thyroid disorders often co-exist in patients with multiple sclerosis (29, 30). We found that hypothyroidism was at least three times more common in women with multiple sclerosis than that in female controls. Because hypothyroidism is usually due to Hashimoto's thyroiditis, its association with multiple sclerosis may support the hypothesis for an autoimmune pathogenesis of the disease. However, as interferon treatment can induce antithyroid antibodies (31) and possibly thyroid hormone deficiency, our findings might have therapeutic implications because some of these cases could be secondary to interferon treatment.

This study has several limitations. First, our definition of hypothyroidism based on levothyroxine prescriptions included only diagnosed and treated cases, thus excluding subclinical conditions that are rather common, particularly in the elderly (16). As already mentioned, there may have been misclassification based on hypothyroidism diagnosed late in the calendar year. No clinical data (TSH, antithyroid peroxidase antibody (TPO) antibodies) were available, and Hashimoto's thyroiditis was captured indirectly. Surgery or I¹³¹ irradiation was only sought in the previous 5 years,

with a possible underestimation of postsurgical cases and inclusion of some iatrogenic cases of hypothyroidism in the autoimmune/iodine deficiency group. The cross-sectional design precluded making inferences about causal associations: cohort studies are needed to disentangle the complex web of relations between thyroid disorders and other autoimmune conditions.

The strengths of our study are the completeness of the sample; namely, the entire population of a region and the reliable algorithm for retrieving treated patients. This update on hypothyroidism prevalence and incidence signals a growing burden of thyroid disease in parallel with the general increase in rates reported for immune diseases. The strong links with other chronic conditions characterize hypothyroidism as an important comorbidity rather than an isolated chronic disease and suggest that individuals with either overt hypothyroidism or an autoimmune disease should be followed up for the possible coexistence of other chronic conditions.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

C B G and R G: literature search, study design, data collection, data interpretation, writing; P C: data analysis and interpretation; F R: literature search, data interpretation; G C data interpretation, writing; B T: literature search and data interpretation.

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Clinical Study	C B Giorda and others	Update of epidemiology of overt hypothyroidism	176:5	542
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