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Prevalence of unknown thyroid disorders in a Sardinian cohort

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Abstract

Objective—To assess thyroid function, the presence of thyroid antibodies, as well as the presence of goiter and/or nodules in subjects without a prior diagnosis of thyroid disorders, in a region with mild to moderate iodine deficiency.

Design and methods—This cross-sectional study is based on data coming from first and third visits of participants in the SardiNIA survey. We performed two different analyses. In one we assessed the prevalence of unknown thyroid dysfunctions among 6,252 subjects who had a medical examination and blood collection for assays of thyrotropin, free thyroxine, and antibodies against thyroperoxidase (AbTPO) and against thyroglobulin (AbTG). In a second analysis, we evaluated the frequency of undiagnosed goiter and nodules among 3,377 subjects who had a thyroid ultrasound scan. Subjects were excluded if they had a previous history of thyroid disorders or presence of goiter and/or nodules, or thyroid surgery, or if they were taking drugs that could impair thyroid function.

Results—We found a low prevalence of overt thyroid dysfunction (hyperthyroidism 0.4%, hypothyroidism 0.7%). The rates of subclinical hypothyroidism and hyperthyroidism were 4.7% and 2.4%, respectively. Almost 16% of individuals were positive for at least one antibody, and 5.2% for both AbTG and AbTPO. Nodules were detected in 17.4% of the subjects, and the prevalence of goiter was 22.1%.

Conclusions—Undiagnosed biochemical thyroid dysfunctions, unknown nodules and goiter were common in subjects living in a mild to moderate iodine deficient area. In this community, thyroid disorders often go undetected and screening could be reasonable in subjects at higher risk.

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Declaration of interest

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

Keywords

Epidemiology; undiagnosed thyroid disease; unknown thyroid nodules; mild to moderate iodine deficiency area

Introduction

Thyroid disorders are one of the most frequent pathologies found in the general population, but identifying thyroid disease can be clinically challenging because subclinical thyroid dysfunction and autoimmune thyroiditis are often asymptomatic and usually diagnosed biochemically. Abnormal thyroid function has important public health consequences. Suppressed TSH levels have been associated with an increased risk of atrial fibrillation, premature atrial beats, stroke, and all cause mortality (1–3). In addition, suppressed TSH level have been associated with decreased bone density (4). Moreover, overt hypothyroidism contributes to elevated serum low-density lipoprotein cholesterol levels and is a risk factor for coronary heart disease, heart failure and atherosclerosis (5, 6). Some studies also suggest that this may also be true in patients with subclinical hypothyroidism (7). Most epidemiological surveys have reported biochemical aspects of thyroid disorders, although with different results. The difficulties for determinations and their comparison arise from the variable definitions of disease state, the heterogeneity of the populations studied, the range of normality of biochemical parameters, and the sensitivity of thyroid function tests used. For example, the introduction of assays for serum thyroid stimulating hormone (TSH) sensitive enough to distinguish between normal and low concentrations allowed the identification of subjects with subclinical hyperthyroidism. Additional variables include genetic (8, 9) and environmental factors, such as iodine intake (10, 11). Indeed, almost one-third of the world's population lives in areas of iodine deficiency (12), and the prevalence of goiter can be as high as 80%. The introduction of ultrasonography in epidemiological studies has increased the diagnostic power to assess the presence of goiter and/or nodules in comparison with studies in which goiter was assessed by physical examination (13). In the present study, a large cohort provided a unique opportunity to conduct a cross-sectional study of abnormal thyroid function and morphology. We assess both the prevalence of abnormal biochemical thyroid disease and the frequency of nodules and goiter in subjects without known thyroid abnormalities.

Materials and methods

The SardinIA study investigates more than 300 genotypic and phenotypic aging-related traits in a longitudinal survey. The main features of this project have been described detailed elsewhere (14). All residents from 4 towns (Lanusei, Arzana, Ilbono, and Elini) in a valley in Sardinia (Italy) were invited to participate. Since November 2001, participants had visit and blood tests about every three years, generating three complete surveys, and some new subjects were progressively enrolled to complete family units.

We performed two analyses. In one we analysed the frequency of biochemical thyroid disorders, including all subjects who had a medical examination at the first time in the first or third visit waves. [We did not include individuals from the second survey because TSH

was the only parameter checked at that visit.] We excluded all subjects with self-reported thyroid disease (i.e., Hashimoto's thyroiditis, hyperthyroidism or hypothyroidism) and those taking drugs impairing thyroid function (levothyroxine, thyrostatics, amiodarone, and carbolithium). The final cohort numbered 6,252 (female 54,8%) aged 14–102. A second analysis was performed to observe the prevalence of undiagnosed thyroid nodules and goiter. We assessed all subjects who performed thyroid ultrasound, which was carried out during the third visit wave. Subjects who reported thyroid nodules, goiter, or thyroid surgery were excluded, yielding a final sample of 3,377 (female 52.4%). The iodine status at the time of evaluation was not assessed. However, the urinary iodine excretion of subjects living in this area comes from a study by Martino et al., showing a mild to moderate iodine deficiency (15).

Biochemical and hormone assays

Blood venous samples were drawn between 7 and 8 a.m. after an overnight fast. Serum samples were assayed for TSH, free thyroxine (FT4), and antibodies against thyroperoxidase (AbTPO) and against thyroglobulin (AbTG) using an automated chemiluminescence assay system (Immulite 2000, Siemens, Germany). The method is a two-site, solid-phase chemiluminescent immunometric assay. Normal values are TSH, 0.4–4.0 μ IU/ml; FT4, 0.89–1.76 ng/dl; AbTPO, < 35 IU/ml; AbTG, < 40 IU/ml.

Overt hypothyroidism was defined as a serum TSH level above the upper limit of the reference range and serum FT4 level below the lower limit of reference range. Overt hyperthyroidism was defined by serum TSH levels below the lower limit of reference range and serum FT4 level above the upper limit of reference range. We defined subclinical thyroid dysfunction as serum FT4 levels in the normal reference range together with high serum TSH (subclinical hypothyroidism) or low serum TSH (subclinical hyperthyroidism).

Thyroid ultrasound

Conventional thyroid ultrasound was performed with a real-time instrument (ATL 3500 HDI machine with a linear transducer 5–12 MHz). Subjects were supine, with neck hyperextended. Nodule was defined as the presence of any distinct lesion within the thyroid gland detected with ultrasound, regardless the echoic pattern. Subjects with nodules were divided into two categories: “solitary nodule” if only one nodule was detected, and “two or more nodules” (otherwise defined “multiple”) if the ultrasound scan revealed the presence of at least two nodules. Thyroid volume was calculated according to the ellipsoid model (16). Goiter was defined as a thyroid volume exceeding 13 mL in women and 18,1 mL in men (17), regardless the presence of nodules.

Each participant signed an informed consent form. All study methods were conducted according to the principles expressed in the Declaration of Helsinki and were approved by the governing Ethics Committee, ASL4.

Statistical analysis

Results were expressed as median and interquartile range. Statistical differences in frequencies were tested by the exact Fisher test in Stata 12.0 for Macintosh. Significance was set at $P < 0.05$.

Results

Biochemical thyroid dysfunctions

The baseline characteristics of the subjects are shown in Table 1. Overt hypothyroidism and hyperthyroidism were diagnosed in 42 (0.7%) and 23 (0.4%) participants, respectively. Subclinical hypothyroidism was found in 293 (4.7%) individuals, whereas subclinical hyperthyroidism was detected in 152 (2.4%) subjects. The prevalence of thyroid dysfunctions progressively increased with age, to reach a maximum of 13.9% in subjects older than 80 (Table 2). The distribution of AbTPO and AbTG across age groups was shown in Figure 1. Table 3 displayed the frequency of AbTPO and AbTG across thyroid dysfunctions. The frequency of thyroid antibodies was higher in woman than in men ($p < 0.001$), as when considering the presence of at least one antibody (20.9% vs. 9.9%), as when detected both together (6.9% vs. 3.1%), as shown in Table 4. Among the whole sample studied, 1307 (20.9%) individuals had at least one biochemical thyroid disorder: 313 had hyper- or hypo-function of the gland without detectable thyroid antibodies, 797 showed only the positivity of at least one antibody, and 197 had a thyroid dysfunction associated with at least one circulating antibody.

Thyroid nodules and goiter

The second analysis included 3,377 subjects who performed thyroid ultrasound during the third survey. Among those, 588 (17.4%) showed the presence of nodularity: 232 had a solitary nodule and 356 had at least two nodules. The presence of undiagnosed thyroid nodules progressively increased with aging, with the highest prevalence in subjects aged 80 or older (31.6%, Figure 2). The presence of nodules (solitary or multiple) was associated with thyroid antibodies (AbTPO and/or AbTG) in 19% of subjects. The overall prevalence of goiter was 22.1% and progressively increased with aging, as reported in Figure 2. It was observed in 748 subjects, among which 99 (13.2%) had a solitary nodule, 106 (14.2%) had multiple nodules, and 543 (72.6%) did not show nodularity. Female had an higher frequency of nodularity than male ($p < 0.001$, Table 5), as for solitary nodule (8.0% vs. 5.6%) as for multiple (11.2% vs. 9.8%), while the prevalence of goiter was increased in male (26.1% vs. 18.5%, $p < 0.001$), as reported in Table 5.

Discussion

Although thyroid dysfunction has multiple implications for public health, the magnitude of the problem is not completely known, nor is the relationship to other thyroid alterations well delineated. Our large population-based study in an area with mild to moderate iodine deficiency provides comprehensive data on the prevalence of unknown thyroid dysfunctions, autoimmune thyroid disorders, and unknown thyroid nodularity and goiter.

Overt hyperthyroidism was found in 0.4% (23/6252) of the sample. This finding is somewhat higher than those described in Norway (18) and in the Colorado Study (19), but similar to those reported by Volzke in Germany (20). The prevalence of unknown subclinical hyperthyroidism was 2.4%. These findings were again lower than reported in some studies (17), but higher than others (20–23). Differences between studies may reflect different age ranges of cohorts and other environmental factors. Particularly important is the local iodine level. For example, a higher prevalence of hyperthyroidism due to an increased frequency of toxic nodular goiter has been documented in an iodine deficient community (17), and subclinical hyperthyroidism was also more frequent in an iodine deficient compared to an iodine replete area (17, 20, 22). Our survey showed a prevalence of hyperthyroidism which is somewhere between the prevalence reported in iodine deficient and iodine repleted areas, and consistent with the mild to moderate iodine deficiency in this area. However, we cannot differentiate the type of hyperthyroidism because we did not assess antibodies against TSH-receptor.

The prevalence of overt hypothyroidism was 0.7% (42/6252), with a higher frequency in females (71.4%) than in males (28.6%). This prevalence is similar to that reported by Volzke (20) but higher than reported by Aghini-Lombardi et al. in an another survey in Italy (17) and by Lucas et al. in Spain (21). Moreover, we found unknown subclinical hypothyroidism in 4.7% of subjects, which is substantially higher than that previously reported.

In this study the prevalence of thyroid antibodies (AbTPO, AbTG or both) was 15.9% which is higher than reported in previous studies. Whether iodine intake influences the development of thyroid autoimmunity remains controversial, however. Indeed, both low and high iodine intake has been associated with an increased tendency toward thyroid autoimmune abnormalities (24–26). According to some authors, the development of goiter due to iodine deficiency might overexpose the immune system to thyroid antigens, leading to immune reactions (27, 28). Assuming that iodine intake might interfere with the thyroid autoimmune process, only genetically predisposed subjects would present the disease (29). In keeping with this hypothesis, our data are consistent with a very high incidence of autoimmune diseases such as chronic autoimmune thyroiditis, type 1 diabetes mellitus, and multiple sclerosis in the Sardinian population (30). The prevalence of thyroid dysfunctions linked to the presence of AbTPO and/or AbTG ranged from 73.8% in subjects with overt hypothyroidism to 17.1% in those with subclinical hyperthyroidism (Table 3). Moreover, 13.9% of euthyroid individuals had circulating thyroid antibodies. These data are in line with previous findings that overt and subclinical hypothyroidism generally are autoimmune, whereas subclinical hyperthyroidism is usually related to multinodular goiter, with relatively frequent detection of serum thyroid antibodies, especially in goitrous females (17, 27, 31, 32) and in older subjects, as confirmed in our analysis. The second analysis included 3377 patients who performed thyroid ultrasound. We found 588 subjects (17.4%) with unknown thyroid nodules, 232 with solitary nodules, and 356 with at least two nodules. These findings are comparable to those reported by other authors (20). The prevalence of thyroid nodules increased with age up to 80 and beyond (31.6%).

Age and sex distributions were similar to those observed in previous reports in iodine moderate-deficient area, with a progressive increased prevalence of goiter in older subjects, though the prevalence of goiter was rather lower than reported by Martino et al. in the same geographic area (15). Different methods of estimation may account for this difference.

One exclusion criterion was self-reported patient data for previous diagnosis of thyroid disease and/or medications. Hence, all the data should be analysed with some reservations about possible undercounting, but the results of our analysis are consistent previous reports.

A major finding of our study was a 20.9% (1307/6252) prevalence of undiagnosed biochemical abnormalities of the thyroid gland. In this group, 313 subjects (23.9%) had thyroid dysfunction, the positivity of thyroid antibodies was found in 797 subjects (61%), whereas thyroid dysfunction together with circulating antibodies were found in 197 participants (15.1%). Our study indicates that the prevalence of thyroid dysfunction and/or abnormal thyroid anatomy are rather frequent in an unselected population living in this mild to moderate iodine deficient region. Although the demographic characteristics of the population studied may not be completely generalizable, in this study we provide additional epidemiological data on the undiagnosed thyroid disorders confirming the magnitude of thyroid dysfunction also in this area.

The large number of patients with abnormal thyroid parameters and/or thyroid nodules, coupled with the well-established gradual progression of thyroid dysfunction, indicate potential benefit from testing for abnormal thyroid function, at least in these geographic areas.

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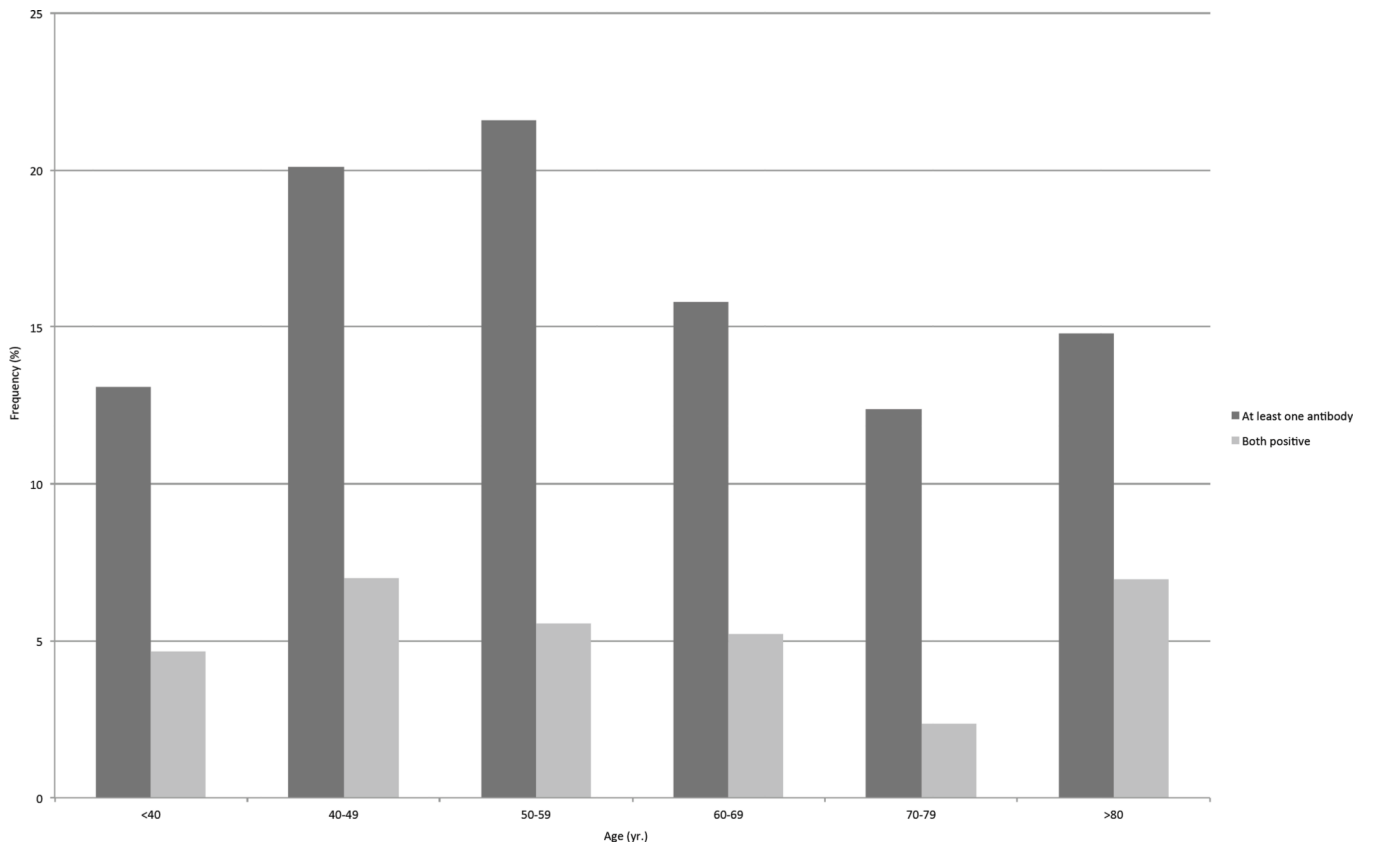


Figure 1. Frequency of antibodies against thyroglobulin and thyroperoxidase across different age groups.

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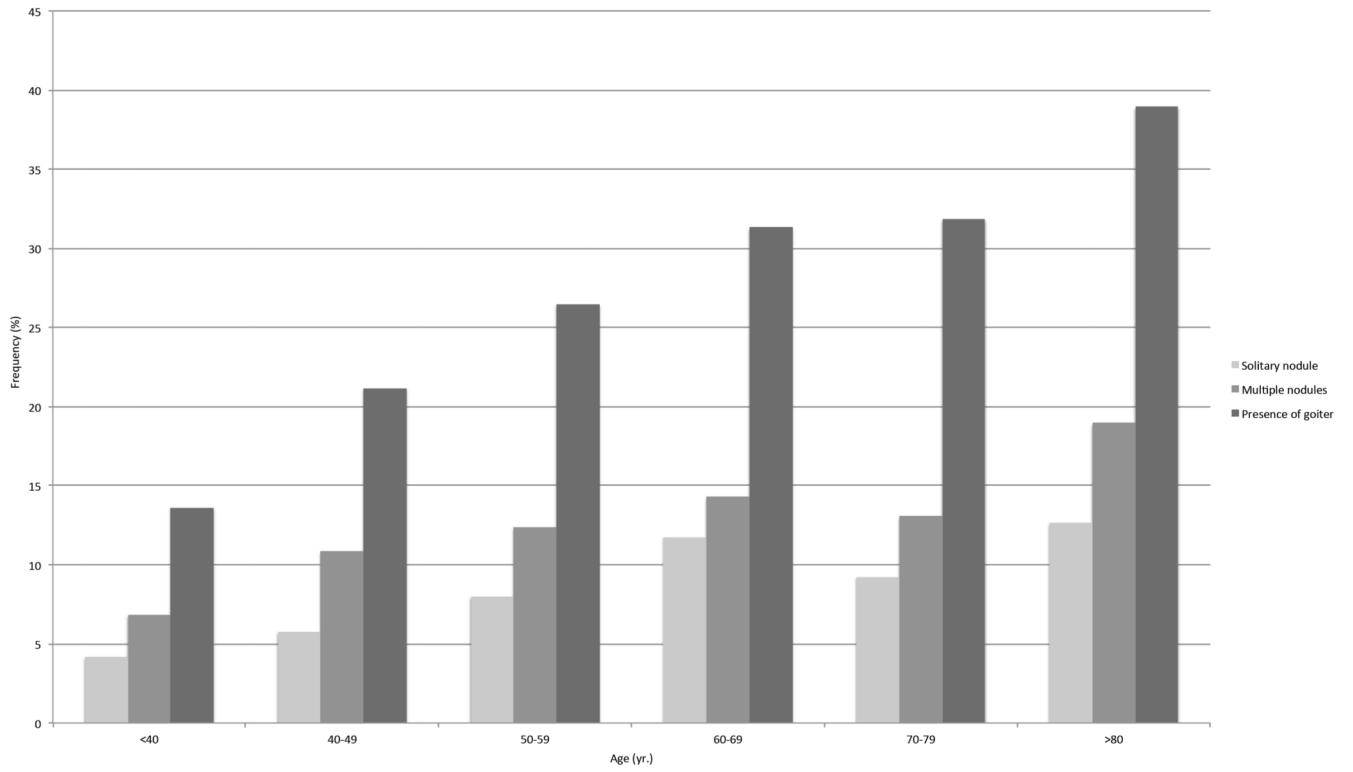


Figure 2.
Prevalence of nodules and goiter across age groups.

Table 1

Characteristics of subjects in the analyses.

	Biochemical analysis	Ultrasound analysis
Subjects (n)	6252	3377
Sex (M/F)	2826/3426	1608/1769
Age (yr.)	41.7 (28.8 – 57)	45.8 (34.4 – 59.4)
TSH (μ IU/ml)	1.61 (1.05 – 2.32)	2.37 (1.12 – 2.37)
FT4 (ng/dl)	1.27 (1.14 – 1.4)	1.39 (1.12 – 1.39)

n, absolute number. Data are expressed as median (interquartile range).

Abbreviations: thyrotropin, TSH; free thyroxine, FT4.

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Table 2

Distribution of thyroid status across different age groups.

Thyroid status	Age (yr.)						
	< 40	40–49	50–59	60–69	70–79	80	
Overt hypothyroidism	n	10	11	9	7	4	1
	%	0.3	1.0	1.0	0.9	0.9	0.9
Subclinical hypothyroidism	n	161	51	30	26	16	9
	%	5.5	4.6	3.3	3.5	3.8	7.8
Euthyroidism	n	2721	1027	845	671	379	99
	%	92.9	92.2	91.9	89.6	89.0	86.1
Subclinical hyperthyroidism	n	27	22	33	41	24	5
	%	0.9	2.0	3.6	5.5	5.6	4.3
Overt hyperthyroidism	n	9	3	3	4	3	1
	%	0.3	0.3	0.3	0.5	0.7	0.9
Total	n	2928	1114	920	749	426	115
	%	100	100	100	100	100	100
Any dysfunction*	n	207	87	75	78	47	16
	%	7.0	7.9	8.2	10.4	11.0	13.9

* Presence of any biochemical thyroid dysfunction (subclinical and overt).

Table 3
Frequency of antibodies against thyroperoxidase and against thyroglobulin across thyroid status.

Thyroid status		Only AbTPO	Only AbTG	AbTPO and/or AbTG	AbTPO and AbTG	No antibodies
Overt hypothyroidism	n	29/42	13/42	31/42	11/42	11/42
	%	69.1	31.0	73.8	26.2	26.2
Subclinical hypothyroidism	n	117/293	81/293	129/293	69/293	164/293
	%	39.9	27.7	44.0	23.5	56.0
Euthyroidism	n	533/5742	489/5742	797/5742	225/5742	4945/5742
	%	9.3	8.5	13.9	3.9	86.1
Subclinical hyperthyroidism	n	14/152	21/152	26/152	9/152	126/152
	%	9.2	13.8	17.1	5.9	82.9
Overt Hyperthyroidism	n	8/23	11/23	11/23	8/23	12/23
	%	34.8	47.8	47.8	34.8	52.2
Total	n	701/6252	615/6252	994/6252	322/6252	5258/6252
	%	11.2	9.8	15.9	5.2	84.1

Abbreviations: antibodies against thyroperoxidase, AbTPO; antibodies against thyroglobulin, AbTG

Table 4

Frequency of thyroid disorders stratified by sex.

Biochemical analysis	Female (n= 3426)	Male (n=2826)	Total (n=6252)	P value[¶]
<i>Thyroid dysfunction</i>	335 (9.8%)	175 (6.2%)	510 (8.2%)	< 0.001
Overt hypothyroidism	30 (0.9%)	12 (0.4%)	42 (0.7%)	0.016 [#]
Subclinical hypothyroidism	198 (5.8%)	95 (3.4%)	293 (4.7%)	< 0.001 [§]
Subclinical hyperthyroidism	92 (2.7%)	60 (2.1%)	152 (2.4%)	ns
Overt hyperthyroidism	15 (0.4%)	8 (0.3%)	23 (0.4%)	ns
<i>Antibodies</i>				
Only AbTPO	494 (14.4%)	207 (7.3%)	701 (11.2%)	< 0.001
Only AbTG	456 (13.3%)	159 (5.6%)	615 (9.8%)	< 0.001
AbTPO and/or AbTG	715 (20.9%)	279 (9.9%)	994 (15.9%)	< 0.001
AbTPO and AbTG	235 (6.9%)	87 (3.1%)	332 (5.2%)	< 0.001
<i>Any biochemical thyroid disorders[*]</i>	895 (26.1%)	412 (14.6%)	1307 (20.9%)	< 0.001

Data show the number of patients in each group, with percentages in parentheses.

Abbreviation: antibodies against thyroperoxidase, AbTPO; antibodies against thyroglobulin, AbTG.

[¶]Female vs. men (Fisher's exact test).

[#]Overt hypothyroidism vs. euthyroid

[§]Subclinical hypothyroidism vs. euthyroid

^{*}Presence of thyroid dysfunction and/or presence of at least one thyroid antibody

Table 5

Frequency of goiter and nodules stratified by sex.

Ultrasound analysis	Female (n=1769)	Male (n=1608)	Total (n=3377)	P value [¶]
<i>Goiter</i>	328 (18.5%)	420 (26.1%)	748 (22.1%)	< 0.001
<i>Nodules</i>	341 (19.2%)	247 (15.4%)	588 (17.4%)	0.002
Solitary nodule	142 (8.0%)	90 (5.6%)	232 (6.9%)	0.002
Two or more nodules	199 (11.2%)	157 (9.8%)	356 (10.5%)	ns

Data show the number of patients in each group, with percentages in parentheses

[¶]Female vs. men (Fisher's exact test).

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