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Research Article

Characteristics and Dynamics of Thyroid Dysfunction in the Bulgarian Population - Screening 2024

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Abstract

In 1994 universal iodization of salt was introduced on the whole Bulgarian territory. In 2005, an international expert group gave the country credit for solving the problem of iodine deficiency. The last screening of pregnant Bulgarian women in 2019 confirmed the presence of iodine sufficiency among the population. The current study aimed at updating the data on the prevalence of thyroid dysfunction (hypothyroidism and hyperthyroidism) in the country under conditions of iodine sufficiency in the Bulgarian population. The last population screening was conducted 12 years ago, allowing us to make a comparison with the current one in 2024, as both screenings were carried out under the conditions of systematic and continuous universal iodization of salt across the entire territory of Bulgaria. *Material and Methods:* 936 subjects were distributed into three age groups: 20-44 years - 342 (36.5%), 45-59 years - 301 (32.2%) and 60-79 years - 293 (31.3%). TSH (ECLIA-sandwich method), FT4 (competitive ECLIA method), TPOAb (ECLIA-method of the Cobas e601 analyzer) were examined. Thyroid dysfunction, which includes subclinical and clinical forms, was analysed regarding the frequency of each type and form in the studied population, as well as its distribution according to gender and among the three age groups. The data gathered in 2012 and 2024 were compared. *Results*: Hypothyroidism is the dominant disorder - 14.4% (135/936), while hyperthyroidism is 1.81% (17/936), $p < 0.05$. The highest number of patients have subclinical hypothyroidism - 13.67% (128/936). The prevalence of increased TPO antibodies is 14.4% (133/936) and as expected, it is more common in women - 71.4% (95/133) compared to men - 28.6% (38/133), $p < 0.001$. The current thyroid dysfunction in our country has significantly increased - from 6.91% (166/2402) in 2012 to 16.23% (152/936) in 2024, $p < 0.01$. The relative share of known diagnosed cases during this 12-year period shows a marked rise - from 44.51% (73/164) to 63.16% (96/152) - $p < 0.02 > 0.01$, while the relative share of newly diagnosed cases during screening has a significant drop - from 55.49% (91/164) to 36.84% (56/152) - $p < 0.02$. *Conclusion:* These favorable trends in the reduction of undiagnosed cases of thyroid dysfunction are the result of increased diagnosis of thyroid pathology, ongoing regular screening campaigns, and raised awareness among the population, which is proof of the medical community beneficial work in the country.

Keywords

Hypothyroidism, Hyperthyroidism, Diagnosed, Undiagnosed, Trends

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1. Introduction

Thyroid hormones, which affect most nuclear cells, are essential for growth and reproduction, as well as for the development of neurons and regulation of energy metabolism. Hypothyroidism and hyperthyroidism (known as thyroid dysfunction) are common conditions, which impair health and have negative effect on the population worldwide.

Normal iodine levels are a key risk factor for thyroid diseases. However, there are other factors as well, such as aging, smoking, ethnicity, genetic predisposition, endocrine influences, and the effects of some new biological agents, which may impact the epidemiology of thyroid diseases [1].

Thyroid dysfunction affects both ganders and various age groups. It is more common among women, older individuals (over 60 years), people with family history of thyroid disease, people who have had thyroid disease, as well as women after childbirth [2]. The geographical area of residence also plays a role due to variations in iodine intake [3].

Thyroid dysfunction is one of the main endocrine disorders, affecting 30-40% of the patients in the endocrine practice [4, 5]. Hypothyroidism is characterized by deficiency of thyroid hormones, defined according to biochemical parameters. Overt (clinical) hypothyroidism is combination of increased serum thyroid-stimulating hormone (TSH) levels and decreased serum free thyroxine (FT4) levels compared with the general population reference range. Subclinical hypothyroidism is defined as increased serum TSH levels combined with normal serum FT4 levels [6, 7]. Similarly, cases of clinical and subclinical hyperthyroidism are interpreted as TSH levels below the lower reference limit combined with high or normal serum FT4 levels.

The reference ranges for functional tests assessing thyroid function are based on fixed percentage of the population distribution. It is believed that there is need for precise reference intervals based on key factors such as age and gender, as well as some specific factors like pregnancy [8].

The most common cause of hypothyroidism is chronic autoimmune thyroiditis (Hashimoto's thyroiditis), although other causes, including medications (such as amiodarone, lithium, and immune checkpoint inhibitors), radioactive iodine treatment and thyroid surgery are also frequent. In areas with sufficient iodine, autoimmune thyroid disease is considered the primary cause of hypothyroidism, while in iodine-deficient regions hypothyroidism is mainly attributed to iodine deficiency [1].

As of 2009, one-third of the world's population lived in areas with iodine deficiency, which had significant impact on fetal and child neurological development [9]. A large number of countries implemented programs for iodine fortification of table salt [10]. By 2016, 110 countries were classified as having optimal iodine intake, while 19 countries continued to have insufficient iodine intake [11]. Systematic iodine fortification of household salt has become mandatory in nearly 120 countries [10].

Universal iodization of salt was introduced in Bulgaria in 1994. In 2005, a group of international experts classified Bulgaria among the countries, which successfully addressed the issue of iodine deficiency [12, 13]. According to WHO/UNICEF/ICCIDD, to eliminate iodine deficiency over 90% of the households shoud use iodized salt. Bulgaria was officially included among the countries with ≥ 90% iodized salt used in households [14].

In 2019, a national screening was conducted in the country to update the data on iodine intake in pregnant women in Bulgaria. The iodine level in urine was determined using the inductively coupled plasma mass spectrometry (ICP-MS) method. Frozen samples were transported in a special container to the accredited Limbach laboratory in Heidelberg, Germany. The median urinary iodine concentration (mUIC) for the entire group of pregnant women (n=537) was 170 μg/L (95% CI 161.00 - 177.00) [15]. The normal range for urinary iodine concentration (UIC) in pregnant women is 150 - 249 μg/L [16, 17]. That showed that there is iodine sufficiency in our country, allowing for accurate interpretation of the data obtained from thyroid hormone studies.

The AIM of the current study is to update the data on the prevalence of thyroid dysfunction in Bulgaria under conditions of iodine sufficiency. The last screening was conducted 12 years ago, enabling comparisons, especially since both screenings were carried out under the systematic and continuous universal iodization of salt across the entire territory of Bulgaria.

2. Material and Methods

Precise criteria for the selection of the study participants had been set in advance. The participants in the study were divided into groups by their age, gender and place of residence. This distribution was made according to the data from the population census in Bulgaria by the National Statistical Institute (NSI), documented in December 2022. Non-institutionalized individuals from the population were studied as advised in the Recommendations of National Health and Nutrition Examination Survey (NHANES'2022) [18].

The study was carried out from 25-th March to 16-th May 2024 in 16 regions with 51 nests. 1352 individuals aged from 20 to 79, randomly selected from regional population registers according to age and gender were invited. A total of 936 people (69.2%) agreed to participate, signed an informed consent, and were included in the study - 479 women (51.2%) and 457 men (48.8%). The avarage age of the participants was 50.5 ± 13.6 years (from 20 to 79). The distribution of the subjects who were studied was made not only by gender, but also in three age groups according to the last population census of 2022 - 20-44 years - 342 (36.5%), 45-59 years - 301 (32.2%), 60-79 years - 293 (31.3%), Table 1 [19].

Table 1. *Distribution of 936 subjects by gender and age.*

Gender, age	20-44 years	45-59 years	60-79 years	Total
Women - number (%)	159 (46.5%)	148 (49.2%)	172 (58.7%)	479 (51.2%)
Men - number (%)	183 (53.5%)	153 (50.8%)	121 (41.3%)	457 (48.8%)
Total	342 (100%)	301 (100%)	293 (100%)	936 (100%)

All the data came from cross-sectional population-based multicenter study of the Bulgarian Society of Endocrinology. After thorough statistical analysis, the regions for the study were preselected and the optimal representative number of subjects from each region was estimated.

The sample size was calculated with the expectation of at least 6% prevalence of the studied variable among the target population, 95% confidence level and 5% absolute precision. The geographic regions, the nests, the gender and age distribution of the sample were planned to represent the adult population (from 20 to 79 years). All participants signed informed consent approved by the local ethics committee at the University Hospital, and the research was conducted in accordance with the Declaration of Helsinki. The participants filled in a questionnaire containing demographic data, current and past health status, medical history, family history for cardiovascular, thyroid disorders and diabetes, past history and therapies, menstrual status for the females, and current smoking. Height, body weight and arterial pressure on the arm in sitting position were measured. The body mass index (BMI - kg / m^2) was calculated. Hypertension was defined according to the recommendation for arterial pressure levels up to 130 / 80 mmHg in the latest Guideline of European Society of Hypertension (ESH) 2023 [20].

1. Methodology

The lack of consensus regarding the reference ranges for thyroid hormone levels used for diagnosis, as well as the sensitivity analysis, has led to some differences in the assessment of the prevalence of thyroid dysfunction. The number of participants in a given sample also played a role. With a smaller number, higher estimates of frequency are provided, and such a trend has been noted in analyses from Southern and especially Eastern Europe [21].

In countries with iodine sufficiency, the prevalence of hypothyroidism varies from 1-2%, increasing to 7% in individuals aged between 85-89 years. In the absence of age-specific reference ranges for TSH, population aging is likely to lead to higher prevalence of hypothyroidism [22].

Regarding reference ranges for serum thyroid hormones, the variation in the upper limit of the reference range for TSH concentration in most studies is significant (ranging from 3.4 to 5.5 mIU/L) [23].

The most commonly cited reference range for TSH concentration in the clinical literature has set the upper limit at 4.0 mIU/L and the lower limit at 0.4 mIU/L [24].

TSH was determined using an electrochemiluminescence immunoassay (ECLIA) for the *in vitro* quantitative determination in human serum, with measuring range of 0.005-100 μIU/mL > 20 years TSH - 0.27 - 4.20 mIU/L. The conceptual definition of subclinical hypothyroidism (increased TSH and normal free thyroid hormone) and clinical hypothyroidism (high TSH and low free thyroid hormone) is currently in effect [23]. Some authors arbitrarily classify subclinical hypothyroidism as grade 1 (mild) if the initial TSH is < 10 mIU/L and grade 2 (severe) if the initial TSH is ≥ 10 mIU/L [25, 26].

Our criteria for assessing thyroid function are as follows: subjects with TSH values below 0.27 mIU/L were considered hyperthyroid, and those with values above 4.20 mIU/L - hypothyroid. Subclinical hypothyroidism was defined as TSH > 4.20 mIU/L with normal FT4 levels (11.9 - 21.6 pmol/L) and overt hypothyroidism - as TSH > 4.20 mIU/L with FT4 < 11.9 pmol/L. Subclinical hyperthyroidism was defined as TSH < 0.27 mIU/L with normal FT4 levels (11.9 - 21.6 pmol/L) and overt hyperthyroidism - as TSH < 0.27 mIU/L with FT4 > 21.6 pmol/L; TPOAb: 0 - 34 IU/mL.

2. Laboratory analysis

After a 12-hour overnight fast, cubitalis venipuncture blood samples were taken to determine TSH (Thyroid-Stimulating Hormone), FT4 (free thyroxine), TPOAb (thyroid peroxidase antibody).

The laboratory analysis of all blood samples was performed in a Central laboratory on the day of taking morning blood sample on an empty stomach. Thyroid-Stimulating Hormone (TSH) - reference limits 0.27 - 4.2 mIU/L was quantified using the ECLIA-sandwich method of the Cobas e601 analyzer; free thyroxine (FT4) with a competitive ECLIA method (reference limits 11.9 - 21.6 pmol/L), as well as thyroid peroxidase antibody (TPOAb) - reference limits < 34 IU/mL by the ECLIA-method of the Cobas e601 analyzer.

3. Ultrasound examination

To determine the volume and structural characteristic of the thyroid gland, an ultrasound examination was performed with a Digital Color Doppler Diagnostic Scanner, C5 Ex (Shenzhen Landwind Medical Industry, China). The volume of the thyroid gland in mL was calculated according to a standard formula, [27].

4. Statistical analysis

A. Descriptive and evaluation methods Variance analysis of quantitative variables - mean, median, standard deviation,

standard error of the mean, 95% confidence interval of the mean and median, minimum, maximum.

Frequency analysis of qualitative variables (nominal and rank), which includes absolute frequencies, relative frequencies (in percentages), cumulative relative frequencies (in percentages).

B. Hypothesis Testing Methods Chi-square test or Fisher's exact test - search for a relationship between two qualitative variables.

Logistic regression analysis for odds ratios (OR). The statistical analysis was performed using IBM SPSS Statistics 25. The critical significance level we used was $\alpha = 0.05$. The corresponding null hypothesis is rejected when the P-value is less than α.

3. Results

The average levels of TSH, FT4, and TPO for the entire studied group and for both genders are shownd in Table 2.

Table 2. *Average levels of TSH, FT4, and TPO in both genders and overall for the entire group.*

Group	Mean	Standard deviation	Median	95% Confidence Interval for Median
TSH				
Women (n-479)	3.04	5.73	2.20	2.04 - 2.32
Men (n-457)	2.27	1.52	1.95	1.84 - 2.05
Total (n-936)	2.39	4.25	2.05	1.97 - 2.16
FT4				
Women (n-479)	15.80	2.47	15.70	15.40 - 15.92
Men (n-457)	16.01	2.17	15.99	15.68 - 16.20
Total (n-936)	15.90	2.33	15.80	15.60 - 16.00
TPO				
Women (n-479)	52.77	111.81	11.50	10.80 - 12.00
Men (n-457)	27.13	68.20	10.50	10.20 - 11.20
Total (n-936)	40.25	93.93	10.90	10.60 - 11.40

There is a significant difference in the level of TSH between the two genders in favor of women in the middle (45-59 years) and older (60-79 years) age groups - 2.27 (95% CI: 1.99-2.60) versus 1.91 (95% CI: 1.73-2.16), $p < 0.025$, and respectively 2.30 (95% CI: 1.96-2.61) versus 1.87 (95% CI: 1.60-2.09), $p = 0.047$ (Chi-Square test). In the younger age group (20-44 years) no such difference was found ($p = 0.422$), see Supplementary material Table S1.

At the same time, a significant difference in the FT4 level was observed between the two genders only in the younger age group (20-44 years) - 15.79 ±2.22 pmol/L versus 16.44 ± 2.26 pmol/L, $p < 0.013$, see Supplementary material Table S2.

A statistically significant difference was found between the two genders regarding TPOAb - 52.77 ± 111.81 IU/mL, median 11.50 (95% CI: 10.8-12.0) for women versus 27.13 ± 68.20 IU/mL, median 10.50 (95% CI: 10.2-11.2) for men, $p < 0.006$ (Mann-Whitney Test). The average level of TPOAb is higher in women compared to men in every age group, but the difference is significant only in the younger age group (20-44 years) - 50.06 ±107.6 IU/mL versus 22.8 ±55.78 IU/mL, $p < 0.02$. In the other two age groups, the ratios favoring women are maintained, but there is no significant difference, see Supplementary material Table S3.

Table 3 presents the current prevalence of the two main functional disorders (hypothyroidism and hyperthyroidism in both clinical and subclinical forms) overall and by gender. The prevalence of functional thyroid disorders is 16.23% (152/936), with hypothyroidism being significantly more common compared to hyperthyroidism - 14.4% (135/936) vs. 1.8% (17/936), $p < 0.05$.

Table 3. *Types of thyroid dysfunction in the studied group - overall and by gender (current summarized data).*

Disorder	Total number (%)	Women-number (%)	Men- number (%)
Clinical hypothyroidism	7 (0.74%)	5 (1.04%)	2 (0.44%)
Subclinical hypothyroidism	128 (13.67%)	98 (20.45%)	30 (6.56%)
Hypothyroidism - total	135 (14.4%)	103 (21.5%)	32 (7.0%)
Clinical hyperthyroidism	3 (0.32%)	2 (0.41%)	1 (0.22%)
Subclinical hyperthyroidism	14 (1.49%)	8 (1.67%)	6 (1.31%)
Hyperthyroidism - total	17 (1.81%)	10 (2.1%)	7 (1.53%)
Euthyroid state	784 (83.79%)	366 (76.4%)	418 (91.47%)
Total	936 (100%)	479 (100%)	457 (100%)

In the pre-conducted survey among the participants, current and past illnesses, current treatments, and surgeries related not only to the thyroid gland but to all diseases were declared in the Questionnaire. Information about any known thyroid disease was obtained from 19.76% (185/936) of the examined individuals. In 8.86% (83/936) of the cases, individuals reported a nodular goiter—women 7.58% (71/936) and men 1.28% (12/936), NS. Autoimmune thyroid disease (AITD) was reported by 10.89% (102/936) of the examined individuals—women 9.6% (90/936) and men 1.28% (12/936), NS. Based on the participants' data, two separate analyses have been prepared—one for known thyroid diseases and one for newly diagnosed thyroid diseases, which are presented in two separate tables (Tables 4 and 5).

It should be noted that 79 of the examined individuals reported being on treatment for thyroid disease. 7.26% (68/936) have been taking Levothyroxine, 1.17% (11/936) - thionamide, or a total of 8.44% (79/936). Additionally, another 1.8% (17/936) of the participants have undergone surgery for thyroid pathology, meaning that a total of 10.25% (96/936) have received some therapeutic intervention for previously known thyroid disease. After surgery, only 35.3% (6/17) had functional thyroid disorders, and all of them were included in the group of patients with known functional thyroid disorders, as shown in Table 4.

Table 4. *Distribution of known thyroid functional disorders—overall and by gender.*

Disorder	Total-number (%)	Women- number (%)	Men -number (%)
Clinical hypothyroidism	4 (0.42%)	4 (0.83%)	0
Subclinical hypothyroidism	76 (8.11%)	68 (14.2%)	8 (1.75%)
Hypothyroidism - total	80 (8.53%)	72 (15.03%)	8 (1.75%)
Clinical hyperthyroidism	2 (0.21%)	2 (0.41%)	0
Subclinical hyperthyroidism	14 (1.5%)	7 (1.46%)	7 (1.53%)
Hyperthyroidism - total	16 (1.7%)	9 (1.87%)	7 (1.53%)
Euthyroid state	840 (89.76%)	398 (83.1%)	442 (96.7%)
Total	936 (100%)	479 (100%)	457 (100%)

(1) total - hypothyroidism-80/8.53% + hyperthyroidism-16/1.7% - 96/936 = 10.23%.
(2) women - hypothyroidism-72/15.03% + hyperthyroidism-9/1.87% - 81/936 = 8.65% or 81/479 = 16.9%.
(3) men - hypothyroidism-8/1.75% + hyperthyroidism-7/1.53% - 15/936 = 1.6% or 15/457 = 3.28%.

The summary shows that some thyroid dysfunction is present in 10.24% (96/936) of the examined

individuals—hypothyroidism in 8.53% (80/936) and hyperthyroidism in 1.7% (16/936), $p < 0.02$. Functional disorders are about 5 times more common in women compared to men: 16.9% (81/479) vs. 3.28% (15/457), NS. This ratio is due to higher prevalence of hypothyroidism in women compared to men: 15.03% (72/479) vs. 1.75% (8/457), NS.

Functional thyroid disorders in individuals with newly diagnosed thyroid dysfunction were analyzed separately, with the corresponding frequencies presented in Table 5. Subclinical hypothyroidism is present in 5.5% (52/936), clinical hypothyroidism in 0.32% (3/936) of the examined individuals, resulting in overall hypothyroidism frequency of 5.8% (55/936). Subclinical hyperthyroidism was present in 0.1% (1/936), while no cases of clinical hyperthyroidism were identified, making the overall hyperthyroidism frequency 0.1% (1/936). Overall, newly diagnosed thyroid dysfunction is present in 5.98% (56/936) of the examined group.

Table 5. *Distribution of newly diagnosed thyroid functional disorders - overall and by gender.*

	Total- number (%)	**women - number (%)**	**men -number (%)**
Clinical hypothyroidism	3 (0.32%)	1 (0.21%)	2 (0.43%)
Subclinical Hypothyroidism	52 (5.55%)	30 (6.26%)	22 (4.81%)
Hypothyroidism - total	55 (5.8%)	31 (6.47%)	24 (5.25%)
Clinical hyperthyroidism	0	0	0
Subclinical Hyperthyroidism	1 (0.1%)	1 (0.1%)	0
Hypetthyroidism - total	1 (0.1%)	1 (0.1%)	0
Euthyroid state	880 (94.1%)	447 (93.43%)	433 (94.75%)
Total	936 (100%)	479 (100%)	457 (100%)

Distribution of functional thyroid disorders was made according to type in the three age groups (20-44 years, 45-59 years, 60-79 years) - overall and by gender, Table 6. No significant difference was found in the frequency of each type of thyroid dysfunction between the three age groups.

Table 6. *Thyroid functional disorders by type - in the three age groups and for both genders.*

Gender, number, percent	**Type of functional disorder**	**Number, per cent**	**Functional disorder for each group - number (%)**
20-44 years women- 159 (46.5%) men - 183 (53.5%) total - 342 (100%)	Total Hypothyroidism 20-44 years	women - 22 (71%) men - 9 (29%) total - 31 (100%)	9.06% (31/342)
	Subclinical hypothyroidism	women - 20 (69%) men - 9 (31%) total - 29 (100%)	
	Clinical hypothyroidism	women - 2 (100%) men - 0 total - 2 (100%)	
45-59 years women- 148 (49.2%) men - 153 (50.8%)	Total Hypothyroidism 45-59 years	women - 39 (73.6%) men - 14 (26.4%) total - 53 (100%)	17.6% (53/301)

Gender, number, percent	Type of functional disorder	Number, per cent	Functional disorder for each group - number (%)
total - 301 (100%)			
	Subclinical hypothyroidism	women - 37 (74%) men - 13 (26%) total - 50 (100%)	
	Clinical hypothyroidism	women - 2 (66.7%) men - 1 (33.3%) total - 3 (100%)	
60-79 years women-172 (58.7%) men - 121 (41.3%) total - 293 (100%)	Total Hypothyroidism 60-79 years	women - 40 (78.4%) men - 11 (21.6%) total - 51 (100%)	17.4% (51/293)
	Subclinical hypothyroidism	women - 39 (%) men - 10 (%) total - 49 (100%)	
	Clinical hypothyroidism	women - 1 (%) men - 1 (%) total - 2 (100%)	
20-44 years women- 159 (46.5%) men - 183 (53.5%) total - 342 (100%)	Total hyperthyroidism 20-44 years	women - 3 (75%) men - 1 (25%) total - 4 (100%)	1.16% (4/342)
	Subclinical hyperthyroidism	women - 3 (75%) men - 1 (25%) total - 4 (100%)	
	Clinical hyperthyroidism	women - 0 men - 0 total - 0	
45-59 years women - 148 (49.2%) men - 153 (50.8%) total - 301 (100%)	Total hyperthyroidism 45-59 years	women - 3 (75%) men - 1 (25%) total - 4 (100%)	1.3% (4/301)
	Subclinical hyperthyroidism	women - 2 (66.7%) men - 1 (33.3%) total - 3 (100%)	
	Clinical hyperthyroidism	women - 1 (100%) men - 0 total - 1 (100%)	
60-79 years women - 172 (58.7%) men - 121 (41.3%) total - 293 (100%)	Total hyperthyroidism 60-79 years	women - 7 (77.8%) men - 2 (22.2%) total- 9 (100%)	3.07% (9/293)
	Subclinical hyperthyroidism	women - 6 (85.7%) men - 1 (14.3%)	

Gender, number, percent	Type of functional disorder	Number, per cent	Functional disorder for each group - number (%)
		total - 7 (100%)	
		women - 1 (50%)	
	Clinical hyperthyroidism	men - 1 50 (%)	
		total - 2 (100%)	

The distribution of TPO antibodies (TPOAb) frequency among individuals of both genders in euthyroid, hypothyroid, and hyperthyroid states is presented in Table 7.

Table 7. *Frequency of increased TPOAb among women and men according to the type of functional thyroid disorder.*

Functional thyroid status	Women	Men	Total
Clinical hypothyroidism	6 (66.7%)	3 (33.3%)	9 (100%)
Subclinical hypothyroidism	44 (86.3%)	7 (13.7%)	51 (100%)
Clinical hyperthyroidism	2 (66.7%)	1 (33.3%)	3 (100%)
Subclinical hyperthyroidism	0	0	0
Euthyroid state	43 (61.4%)	27 (38.6%)	70 (100%)
Total	95 (71.4%) *	38 (28.6%) *	133 (100%)

*$p < 0.001$

The frequency of TPOAb (TPOAb/+/) in women is significantly higher than that in men - 71.4% (95/133) compared to 28.6% (38/133), $p < 0.001$. In the group of women, the frequency of TPOAb/+/ is almost two times higher at 19.8% (95/479) than that in men - 8.31% (38/457), NS.

In 47.4% (63/133) of cases, increased TPOAb/+/ is associated with functional thyroid disorders, while in 52.6% (70/133) it is present in an euthyroid condition. The highest frequency of TPOAb/+/ is found in hypothyroidism - 95.2% (60/63), whereas in hyperthyroidism, it is only 4.76% (3/63), $p < 0.001$, Table 8.

Table 8. *Frequency of TPOAb/+/ in impaired thyroid function and in euthyroid status.*

TPO	Total number	Hypothyroidism number (%)	Hyperthyroidism - number (%)	Euthyroid state - number (%)
TPO/+/	133	45.11% (60/133)*	2.25% (3/133)	52.63% (70/133)**
TPO/-/	803	9.33% (75/803)*	1.74% (14/803)	88.91% (714/803)**
Total number	936	135	17	784
p		< 0.001*	NS	< 0.001**

Additionally, a comparative analysis of thyroid functional disorders in our country over the past 12 years was conducted based on the current screening and the analysis from 2012, as seen in Table 9.

Table 9. *Comparison of the frequency of functional thyroid disorders (hypothyroid and hyperthyroid variants) in 2012 and 2024.*

	2024 y	**2012 y**	
Thyroid function	Total number (%)	Total number (%)	p
Hypothyroidism- clinical	0.75% (7/936)	0.9% (22/2402)	NS
Hypothyroidism - subclinical	13.67% (128/936)	3.2% (76/2402)	< 0.01
Known hypothyroidism	8.55% (80/936)	2.2% (53/2402)	NS
Euthyroid condition	73.51% (688/936)	90% (2163/2402)	< 0.001
Hyperthyroidism -clinical	0.32% (3/936)	0.4% (9/2402)	NS
Hyperthyroidism - subclinical	1.49% (14/936)	2.5% (59/2402)	NS
Known hyperthyroidism	1.71% (16/936)	0.8% (20/2402)	NS
Total	936 (100%)	2402 (100%)	
Impaired thyroid function	16.23% (152/936)	6.91% (166/2402)	< 0.01

4. Discussion

There is an increasing trend in the prevalence of thyroid diseases worldwide, with numerous demographic and geographic factors influencing their epidemiology [28]. Variations in the prevalence of thyroid diseases across different countries may be due to several factors—differences in testing locations (in-clinic or outside), age, gender, race/ethnicity, geographic variations in iodine dietary intake, certain medications, and the method used for assessment. Additionally, the particular case of the included individuals is not always clear—whether they have known thyroid disease or are being treated with thyroid hormones or other medications, which may influence thyroid function [29].

Diogo Mendes et al. (2019) presented a very important analysis, emphasizing the role of numerous factors in assessing the prevalence of thyroid dysfunction, particularly the most common disorder, hypothyroidism - gender, age, number of participants in specific studies, and geographic area. Obviously, hypothyroidism is more common in women compared to men [women - 4.83% (2.74-7.46), F=99.06% versus men - 2.67% (1.62-3.96%), F=96.08%]. The prevalence of hypothyroidism below and above the age of 65 is as follows: under 65 - 4.16% (2.34-6.48), F=99.54% versus over 65 - 6.60% (2.54-12.35%), F=NR.

The number of individuals included in the study plays a significant role. The prevalence of hypothyroidism with less than 1000 participants is 6.72% (2.11-13.60%), F=NR; with a number between 1000 and 10,000 - 4.54% (3.73-5.42%), F=81.41%; and with more than 10,000 - 3.54% (0.87-7.93%), F=NR.

Geographic location also plays a significant role in assessing hypothyroidism prevalence. In Europe, the northern and western parts have the same prevalence of hypothyroidism, the south has a slightly higher prevalence, while the eastern part of the continent shows the highest prevalence of this thyroid disorder. In Western Europe, the prevalence is 4.08% (3.12-5.31%), F=NR, while in Eastern Europe, it is 6.43% (4.36-9.40%), F=NR.

All of the above factors should be considered in the analyses, so it will not be correct if we compare mechanically population studies which may differ regarding gender, age, number, and geographic locations. The same analysis emphasizes that subclinical hypothyroidism is the dominant form in Europe, more common among women and individuals over 65 years, with higher prevalence in Southern and especially Eastern Europe [21].

Our data demonstrated that among the two functional thyroid disorders, hypothyroidism is more common—88.8% (135/152), while hyperthyroidism accounts for only 11.2% (17/152), $p < 0.001$.

In both disorders, subclinical forms are significantly more common, which is typical for Europe. For hypothyroidism, subclinical forms are present in 94.8% (128/135), whereas clinical hypothyroidism is present in 5.2% (7/135), $p<0.001$. In hyperthyroidism, 82.3% (14/17) were subclinical, and 17.7% (3/17) were clinical, $p<0.01$ (Table 3).

The distribution between the two genders showed that thyroid dysfunction is present in 12.07% (113/936) of the women and 4.16% (39/936) of he men, NS. The distribution of the two types of functional thyroid disorders among women and men is as follows:

(1) *In women,* thyroid dysfunction is present in 12.07% (113/936) - with 11% hypothyroidism (103/936) and 1.06% hyperthyroidism (10/936). However, the distribution within the female group (n=479) shows that overall thyroid dysfunction is present in 23.59% (113/479) - with hypothyroidism 21.5% (103/479) and hyperthyroidism - 2.1% (10/479).

(2) *In men*, thyroid dysfunction is present in 4.16% (39/936) - with 3.4% hypothyroidism (32/936) and 0.75% hyperthyroidism (7/936). However, the distribution only within the male group (n=457) shows that overall thyroid dysfunction is present in 8.53% (39/457) - with 7% hypothyroidism (32/457) and 1.53% hyperthyroidism (7/457).

It can be summarized that functional thyroid disorders are about three times more common in women compared to men, 23.59% (113/479) versus 8.53% (39/457), $p < 0.05$ - > 0.02. This ratio is due to the high prevalence of hypothyroidism in women compared to men, 21.5% (103/479) versus 7.0% (32/457), $p < 0.05$ (Table 3).

In the young age group (20-44 years), the prevalence of hypothyroidism is 9.06% (31/342), with the prevalence doubling in the next two age groups - 17.6% (53/301) for the middle group (45-59 years) and 17.4% (51/293) for the third age group (60-79 years), NS.

The prevalence of hyperthyroidism in the young age group (20-44 years) and the middle age group (44-59 years) is 1.16% (4/342) and 1.3% (4/301), respectively, and it nearly triples in the older age group (60-79 years) to 3.1% (9/293), which is not statistically significant (NS). Summarizing thyroid dysfunction across the three age groups, the distribution is as follows: 20-44 years - 10.23% (35/342); 45-59 years - 18.93% (57/301); 60-79 years - 20.47% (60/293), NS. Therefore, the frequency of thyroid dysfunction doubles with advancing age, Table 6.

In all age groups, hypothyroidism predominates among women, who comprise about two-thirds of the cases: 20-44 years - 71% (22/31); 45-59 years - 73.6% (39/53); 60-79 years - 78.4% (40/51). The same ratio between the two genders is maintained across the three age groups for hyperthyroidism - 20-44 years - 75% (3/4); 45-59 years - 75% (3/4); 60-79 years - 77.8% (7/9), Table 6. All these facts strongly emphasize the powerful role of gender in the development of thyroid disorders.

The role of age is well illustrated in the study by Nermin Diab et al. (2019), which examined 5 392 participants over the age of 65 and found that nearly 25% of them had thyroid dysfunction, with subclinical forms predominating. In our study, a very similar result was found in the older age group (60-79 years) where thyroid dysfunction was present in 20.47% (60/293) of the screened individuals. Notably, in the study of Nermin Diab et al., while only 0.11% (6/5392) were on thyroid suppressive treatment, 16.9% (911/5392) were on replacement therapy with Levothyroxine. Thus, individuals with hypothyroidism made up 23.78%, and those with hyperthyroidism 1.25%, leading to prevalence of thyroid dysfunction of 25.03% among individuals over 65. It should be noted that the participants in this study included two races (white and black), which is important for the interpretation of the data [30].

The analysis by Nermin Diab et al. provides indisputable evidence for the importance of age in the increasing prevalence of thyroid dysfunction, which we also indicated in our material. On the other hand, a comparison of data from the two analyses showed that lower percentage of individuals in our material were on replacement therapy with Levothyroxine - 7.26% (68/936) compared to 16.9% (911/5392) in the study by Nermin Diab et al., while at the same time, our data showed thyroid suppressive treatment to be more frequent with 1.17% (11/936) compared to 0.11% (6/5392). These significant differences do not allow for direct comparison of our findings with the results obtained by Nermin Diab et al. regarding thyroid dysfunction.

It is also important to discuss the inclusion of individuals in our screening who were under treatment for thyroid dysfunction, accounting for 8.44% (79/936) of those screened - with 7.26% (68/936) taking Levothyroxine and 1.17% (11/936) on antithyroid medication. Moreover, 1.8% (17/936) of screening participants had undergone surgery for thyroid pathology, with only 35.3% (6/17) having functional thyroid disorders post-surgery. These 6 individuals were also included in the group of patients with known functional thyroid disorder.

In the analysis by Wouters, H. J. C. M. et al. (2020), involving 152 180 participants with an average age of 44.6 ± 13.1 years, 58.5% were women. Thyroid medication was used by 4790 participants (3.1%), primarily Levothyroxine in 98.2% of cases. 88% of the participants were women. Among those on Levothyroxine, 59.3% had normal TSH levels. TSH levels outside the reference range in individuals not taking thyroid medications were found in 10.8% - with 9.4% having slightly higher levels (4.01-10.0 mIU/L), 0.7% with moderately high levels (>10.0 mIU/L), and another 0.7% who had suppressed TSH levels (<0.40 mIU/L). More than 98% of patients with TSH levels between 4 and 10 mIU/L had normal FT4 levels [31]. These researchers report a much lower percentage of participants included in screening who were on thyroid treatment - 3.1% compared to 7.26% in our screening. The most significant difference between these two screenings was the number of participants included and the geographic location, which made direct comparison difficult.

The significant role of habitat and the sufficiency or deficiency of iodine in the studied region were demonsrated by the data from Shiva Kargar et al. (2016) meta-analysis showing the prevalence of thyroid dysfunction at 19.2% (95% CI: 11.0-33.2) among adults in some Middle Eastern countries. The analysis highlighted the great difference in the frequency of thyroid dysfunction among different countries in the Middle East, ranging from 31.3% in Saudi Arabia to 12.7% in Iran. The high prevalence of thyroid diseases in Saudi Arabia may be due to proven iodine deficiency and poor nutrition [32]. Another notable finding in the analysis of Shiva Kargar et al. is the distribution of forms of thyroid dysfunction - clinical hypothyroidism at 7.2% (95% CI: 3.6-4.3), subclinical hypothyroidism at 8.3% (95% CI: 5.3-13.0), clinical hyperthyroidism at 2.4% (95% CI: 1.4-3.9), and subclinical hyperthyroidism at 3.2% (95% CI: 2.1-4.7). The

higher frequency of clinical forms of thyroid dysfunction is noteworthy, which is not typical for the European population where subclinical forms predominate. There are several reasons for this discrepancy - methods of investigation, inclusion of different population groups by age/sex/ethnicity, various environmental factors, iodine sufficiency or deficiency in the country or region, accepted cut-off for determining the presence of thyroid dysfunction, frequency of screening studies, public awareness, and healthcare structure [33].

The issue of undiagnosed cases of thyroid dysfunction is always the subject of analysis when conducting population screening. Garmendia Madariaga A. et al. (2014) in meta-analyses focused specifically on undiagnosed forms and reported that the prevalence of undiagnosed hyperthyroidism was 1.7% (95% CI: 1.66-1.88), with subclinical forms of thyroid dysfunction predominating; clinical hyperthyroidism at 0.35% (95% CI: 0.29-0.41) and subclinical hyperthyroidism at 0.50% (95% CI: 0.57-1.43) [4]. Bulgarian data show only 56 cases of newly diagnosed thyroid dysfunction - 5.98% (56/936), of which 93% (52/56) have subclinical hypothyroidism. No cases of newly diagnosed clinical hyperthyroidism were found, and only one case of subclinical hyperthyroidism at 1.7% (1/56). Garmendia Madariaga A. et al. also utilized an empirical Bayesian random-effects model to estimate the prevalence of undiagnosed thyroid dysfunction in 7 studies with an overall average of 6.71% (95% CI: 6.49%-6.93%), while in our material, undiagnosed thyroid dysfunction is 5.98% (56/936).

It is important to emphasize the fact that in the group of patients with newly diagnosed hypothyroidism, the percentage of men is higher - 5.25% (24/457) compared to that of women - 6.47% (31/479). In comparison, in the group with known hypothyroidism, men had a frequency of 1.75% (8/457) versus 15.03% (72/479) of women, which is 8 times lower. It can be concluded that in the screening for thyroid functional disorders, attention should be directed toward both genders without ignoring men.

Increased TPO antibodies (TPOAb/+/) are present in our material in 14.2% (133/936) of the examined individuals - 10.15% (95/936) women and 4.06% (38/936) men, NS. The frequency of TPOAb/+/ in the female group is 19.8% (95/479) and 8.3% (38/457) in the male group, NS, Table 7. The current results are very similar to those from our screening in 2012 - overall 16.5% (women - 23%, 219/953 and men - 10%, 93/934, $p < 0.001$) [34].

It should be noted that in individuals with TPOAb/+/, the frequency of hypothyroidism is significantly higher at 45.1% (60/133) compared to individuals with TPOAb/-/ - 9.33% (75/803), $p < 0.001$. Hyperthyroidism is present in only 2.25% (3/133) of individuals with TPOAb/+/ compared to 1.74% (14/803) in individuals with TPOAb/-/, NS, Table 8. Among euthyroid individuals (n=784), only 70 have TPOAb/+/ - 8.9% (70/784), while the remaining 714 are TPOAb/-/ - 91.1% (714/784), $p < 0.001$. It can be summarized that among 133 individuals with TPOAb/+/, 45.1% (60/133) have hypothyroidism, 2.25% (3/133) have hyperthyroidism, and the remaining 52.65% (70/133) are euthyroid.

In epidemiological data from Croatia, Ivana Striki ć Đula et al. (2022) found TPO/+/ in 23.7% (1044/4402) of the examined individuals. Of these, 1/4 (227/1044) were in individuals with thyroid dysfunction, and the remaining 3/4 (773/1044) - in euthyroid individuals [35]. Therefore, they found higher frequency of TPOAb/+/ among euthyroid individuals compared to our data - 74.2% (773/1044) versus 52.6% (70/133). Similar results were reported by Kamel M. Ajlouni et al. (2022), who found 14.9% frequency of TPOAb/+/ in a group of 3753 examined individuals. However, in their euthyroid group, the frequency of TPOAb/+/ was 10.3%, which was about two-thirds of the cases. The frequency was significantly higher in women compared to men - 15.79% versus 8.3%, $p < 0.001$ [36].

An important aspect for us is the comparison of the dynamics in the frequency of thyroid dysfunction established in our two studies from 2012 and 2024 [37]. The analysis showed that subclinical hypothyroidism increased four times from 3.2% (76/2402) to 13.67% (128/936), $p < 0.01$. At the same time, the frequency of subclinical hyperthyroidism decreased insignificantly - from 2.5% (59/2402) to 1.49% (14/936), NS. The frequency of the two clinical forms (hypothyroidism / hyperthyroidism) remained stable, Table 9. The relative share of known cases with thyroid functional disorders when comparing the data from the two screenings increased almost four times - 3.04% (73/2402) for 2012 compared to 10.25% (96/936) for 2024, $p < 0.05$. Therefore, the possibility of diagnosing and treating thyroid functional disorders significantly increased over the 12-year period. Very important are the data from the analysis by Arulmani Thiyagarajan et al. (2024), who use the German database for pharmacoepidemiological studies (GePaRD - data from ~ 20% of health insurance covering about 25 million of the German population). The authors examine trends in Germany for the period 2008-2019 after the implementation of a national program for disease prevention related to iodine deficiency in 1993. For the 12-year period (2008-2019), after stratification by gender and age, the assessment was that the frequency of TSH testing increased by 44% in men (from 165 to 238 per 1000 individuals) and by 31% in women (from 134 to 176 per 1000). At the same time, the prevalence in the use of Levothyroxine increased by ~ 31%, both in men (from 36 to 47 per 1000) and in women (from 134 to 175 per 1000). It should be noted that the prevalence in the use of thionamide, iodine, thyroidectomy, and treatment with radioactive iodine decreased [38].

A study from Denmark using data from the National Registry reported that after the implementation of the iodine enrichment program, the prevalence of Levothyroxine use increased. It become stable in 10 years but remained above the level at the start of the program [39].

It is very important to study the Gonzalo J Acosta et al.

(2024), who pointed out cases of inappropriate inclusion of Levothyroxine, which occured due to the disregard for the physiological changes in TSH levels and the higher frequency of hypothyroidism with age, which may create the impression of increased use of Levothyroxine [40].

In our 2012 data compared to that from 2024, there is a noticeable difference in newly discovered thyroid functional disorders, with their relative share increasing by about 60% - from 91 cases (43 hypothyroidism and 48 hyperthyroidism) in 2012 or 3.78% (91/2402), they became 56 cases (55 hypothyroidism and 1 hyperthyroidism) in 2024 or 5.98% (56/936). In 2012, the number of newly diagnosed cases of the two functional disorders was similar, and there was even a slight predominance of hyperthyroid cases, whereas in 2024, there was only one case with increased function and all the others had hypothyroidism.

When comparing individuals with proven thyroid dysfunction, it turned out that the relative share of known cases in 2024 was significantly higher than in 2012 - 63.16% (96/152) versus 44.51% (73/164), $p < 0.02$ - > 0.01. At the same time, the share of newly diagnosed cases during the screening itself (2024 vs. 2012) decreased significantly - 36.84% (56/152) versus 55.49% (91/164), $p < 0.02$.

Regarding the frequency of undiagnosed i.e., newly discovered cases of thyroid dysfunction, a comparison was made with data from an epidemiological study in Croatia published in 2022 [35]. It should be noted that among participants in our screening with proven thyroid dysfunction, only 36.8% (56/152) were discovered during the screening, that is, undiagnosed up to that point. That was the indicator with which we compared our data with the data from the national study carried out in Croatia, where there was sufficient iodine among their population, similar to ours, and very similar habitat - the Balkan Peninsula. The only difference was in the number of individuals examined - for Croatia 4402 and for Bulgaria - 936, which slightly reflected on the frequency, i.e., in a tested population of up to 1000 individuals, the frequency is slightly higher [21]. The frequency of hypothyroidism reported by Ivana Striki ć Đula et al. (2022) was 10.5% and hyperthyroidism - 1.3%, which is very close to our data. The large difference is in the share of undiagnosed cases with thyroid dysfunction in Croatia. The authors reported a high percentage of undiagnosed individuals - the frequency of undiagnosed subclinical and clinical hypothyroidism was 6.9% and 2.8% respectively, and undiagnosed subclinical and clinical hyperthyroidism - 0.9% and 0.1% respectively [35]. In comparison, in the Bulgarian data, undiagnosed individuals with hypothyroidism are 5.82% (subclinical 5.5% and clinical 0.32%), and with hyperthyroidism - 0.1% - only subclinical, Table 5. In fact, only cases of subclinical hypothyroidism, with the exception of four cases of clinical thyroid dysfunction (three with hypothyroidism and one with hyperthyroidism) were newly discovered.

Similar data came from an epidemiological study conducted in Jordan by Kamel M. Ajlouni et al. (2022), which reported an overall prevalence of thyroid dysfunction in 11.9% of the screened individuals, with about 76% newly discovered i.e., previously undiagnosed [36]. In Jordan, iodine sufficiency was achieved following the introduction of special program whereby 96% of households have used iodized salt (≥15 ppm) since 2010 [41]. However, there are two differences from our study - different geographical area and larger number of screened participants - 3753 compared to 936 in our screening. The percentage of newly diagnosed individuals with thyroid dysfunction was twice as high as in their case - 76% (2852/3753) versus 36.8% (56/152). The data presented in the last two studies showed that the relative share of undiagnosed cases was much higher than our data, which was only 36.8% (56/152).

5. Conclusion

The dynamic changes in the prevalence of thyroid dysfunction in our country over the last 12 years (2012-2024) showed significant increase in the proportion of known diagnosed cases - 63.16% (96/152) compared to 44.51% (73/164) - $p < 0.02 > 0.01$, which can be explained with the increased diagnosis of thyroid pathology, the screening campaigns, and raised public awareness. At the same time, there was marked reduction in the proportion of undiagnosed cases of thyroid dysfunction during the time of screening - 36.84% (56/152) compared to 55.49% (91/164) - $p < 0.02$, which is evidence of the medical community useful work in the country - good training of medical specialists, active participation of cardiologists and general practitioners, mass screening of pregnant women and increasing the health culture of the population.

Both screenings were conducted under conditions of iodine sufficiency, allowing for a comparative analysis. Thus, the current prevalence of thyroid dysfunction in our country has significantly increased from 6.91% (166/2402) in 2012 to 16.23% (152/936) in 2024, $p < 0.01$, primarily due to the number of diagnosed cases. Therefore, screening for thyroid function in the presence of risk factors for thyroid disease, along with screening by gynecologists, cardiologists, and internal medicine specialists, can help the early detection of thyroid dysfunction and its timely treatment.

Abbreviations

TSH	Thyroid Stimulating Hormone
FT4	Free Thyroxine
TPO	Thyroid Specific Peroxidase
WHO	World Hwalth Organization
UNICEF	United Nation Children's Fund
ICCIDD	International Council for Control of Iodine Deficiency Disorders
ICP-MC	Inductively Coipled Plasma Mass Spectrometry

mIUC	Median Urinary Iodine Concentration
UIC	Urinary Iodine Concentration
NSI	National Statistical Institute
NHANES	National Health and Nutrition Examination Survey
BMI	Body Mass Index
ESH	European Society of Hypertension
ECLIA	Electrohemiluminescence Immunoassay
TPOAb	Thyroid Peroxidase Antibody
AITD	Autoimmune Thyroid Disease
GEPARD	German Pharmacoepidemiological Research Database

Supplementary Material

The supplementary material can be accessed at https://doi.org/10.11648/j.cmr.20251403.13

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Author Contributions

Anna-Maria Borisova: Conceptualization, Resources, Formal Analysis, Funding acquisition, Project administration, Supervision, Writing - original draft, Methodology

Boyana Trifonova: Investigation, Project administration, Supervision, Writing - review & editing

Lilia Dakovska: Data curation, Investigation

Mircho Vukov: Software, Formal Analysis, Validation

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Conflicts of Interest

The authors declare no conflicts of interest.

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