Epidemiology of hyperthyroidism in Iran: a systematic review and meta-analysis

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Abstract

Background Hyperthyroidism is a systemic disorder that causes severe morbidity and is even fatal. Several studies have been performed in Iran to determine the epidemiologic properties of hyperthyroidism; however, they did not use a systematic approach or meta-analysis to evaluate the results. Therefore, this systematic review and meta-analysis aimed to evaluate the epidemiologic data on hyperthyroidism in Iran.

Methods In order to find all relevant papers published by October 2017, we searched both international (Web of Science, Scopus, PubMed, Embase, and Cochrane library) and Persian databases (Scientific Information Database, Magiran, and Barekat Knowledge Network System). Meta-analysis was performed using metaprop random effects analysis for prevalence and metaprop fix effect analysis for incidence by Stata statistical software. I^2 was used for the demonstration of heterogeneity.

Results Of 7667 published papers or conference proceeding, 7448 studies were removed after eliminating duplicates and reviewing titles/abstracts. Finally, after reviewing 219 full texts, 18 papers met the inclusion and exclusion criteria. The pooled prevalence of total, overt, and subclinical hyperthyroidism in general population were 2.43% (95% CI: 0.23–4.63%), 0.69% (95% CI: 0.21–1.18%), and 1.52% (95% CI: 0.14–2.89%), respectively. The pooled annual incidence of total hyperthyroidism was 2.2 (95% CI: 1.1–3.3) per 1000 population: 0.8 (0.1–1.4) and 1.3 (0.4–2.2) per 1000 population for overt and subclinical hyperthyroidism, respectively.

Conclusions This is the first systematic review and meta-analysis, which investigated the epidemiology of hyperthyroidism in Iran. It seems that the prevalence and incidence of hyperthyroidism among the general population in Iran is similar to that in other parts of the world.

Keywords Prevalence · Incidence · Epidemiology · Iran · Hyperthyroidism

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Abbreviations

CI	Confidence Interval
NHANES III	The third National Health and Nutrition Examination Survey
TSH	Thyroid Stimulating Hormone
T4	Thyroxine
T3	Thriiodothyronine
ISI	Web of Science
SID	Scientific Information Database
MeSH	Medical Subject Headings
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
GBD	Global Burden of Diseases
TTS	Tehran Thyroid Study
EMRI	Endocrinology and Metabolism Research Institute

Introduction

Hyperthyroidism is a systemic disorder that causes severe morbidity and is even fatal [1, 2]. Timely diagnosis of hyperthyroidism could prevent most of the complications [1, 2]. The three most common causes of hyperthyroidism are Graves' disease, toxic multinodular goiter, and autonomously functioning thyroid adenoma [3].

To estimate the burden of this disease and make public health policies, it is necessary to have enough knowledge about the epidemiology of hyperthyroidism. The prevalence of thyroid disease widely varies by age, sex, geographic area, ethnicity, and iodine status of populations [1, 3–5]. As a result, it is necessary to determine the epidemiology of thyroid disease in each community. In addition, to design an appropriate plan for thyroid disease screening, it is necessary to properly estimate the magnitude of total thyroid dysfunction and its rate of diagnosis.

The third National Health and Nutrition Examination Survey (NHANES III) showed that the prevalence of hyperthyroidism in the United States was 1.3% (0.5% overt and 0.7% subclinical) [6]. It is estimated that approximately half of the patients with thyroid disorders remain undiagnosed in the United States [7, 8]. A meta-analysis of studies conducted in Europe showed that the estimated prevalence and incidence of overt hyperthyroidism were 0.68% and 0.51/1000/year, respectively [9]. Moreover, most studies demonstrated higher prevalence and incidence rates among females [3, 9].

After more than 20 years (since 1994) of mandatory iodination of all salts for household usage, Iran is now considered as an iodine-replete area [10]. Studies that performed since 1996 and thereafter in Iran showed that more than 90% of households consumes iodized salts and had adequate urine iodine level [10, 11]. Several studies have been performed in Iran to determine the epidemiologic properties of

hyperthyroidism; however, there has been no systematic approach or meta-analysis to evaluate the results. Therefore, the main aim of this systematic review and meta-analysis was to evaluate the prevalence and incidence of hyperthyroidism in Iran. In addition, it was aimed to determine the diagnostic rate of hyperthyroidism based on the available data.

Methods

Study design

The present study was conducted as a systematic review and meta-analysis of published literature on the prevalence and incidence of hyperthyroidism in Iran.

Definitions

Overt hyperthyroidism was defined as patients with known history of overt hyperthyroidism (history of medical or surgical treatment for hyperthyroidism) or subjects with a suppressed Thyroid Stimulating Hormone (TSH) and elevated thyroxine (T4), thriiodothyronine (T3), or both [1].

Subclinical hyperthyroidism was considered when there was a suppressed TSH with normal T3 and T4 [1].

Diagnostic rate of overt hyperthyroidism was defined as the proportion of subjects with known history of overt hyperthyroidism (history of medical or surgical treatment for hyperthyroidism) to the total number of overt hyperthyroid patients (known by history plus discovered by thyroid function tests).

The medical treatment rate of overt hyperthyroidism was defined as the proportion of subjects who have or had been receiving a type of the anti-thyroid medications or had history of radioiodine ablation to the total number of overt hyperthyroid patients (known by history plus discovered by thyroid function tests).

The drug-prescription rate of overt hyperthyroidism was defined as proportion of subjects who have or had been receiving a type of the anti-thyroid medications to the total number of overt hyperthyroid patients (known by history plus discovered by thyroid function tests).

Search strategy

Searched databases: International databases including Web of Science (ISI), Scopus, PubMed, Embase, and Cochrane library were considered for searching. Moreover, Persian databases including Scientific Information Database (SID), Magiran, and Barekat Knowledge Network System were searched for papers published up to October 2017. The main search keywords were “hyperthyroidism,” “thyrotoxicosis,” “thyroid,” “epidemiology,” “incidence,” “prevalence,” “frequency,” “Diagnosis,” and “Iran” in human and their

synonyms, related words, Medical Subject Headings (MeSH) terms, and Emtree terms. The search was done without language restriction. We also considered conference proceedings. The search flowchart using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method is demonstrated in Fig. 1.

Inclusion and Exclusion Criteria: Studies which fulfilled all the following criteria were included: 1) general population sampling (i.e. population based cross-sectional, or baseline data of population-based cohort studies), or subjects with goiter; 2) reported hyperthyroidism based on thyroid function tests; 3) studies conducted on Iranian population. Since there was not a systematic approach to access the reports of studies that did not published (gray literatures); we did not considered them for inclusion. The exclusion criteria were thesis, studies published before 1994 (before mandatory iodination of all salts for household usage), studies, which included only individuals with co-morbidities or specific conditions (such as diabetes, underlying autoimmune disease, pregnancy, grade specific goiter [i.e. grade 2 only], adequate urine iodine level, positive antibodies), and studies which omitted known cases of hyperthyroidism (but not mentioned the number). In addition, studies that reported the prevalence as zero were

excluded for meta-analysis of diagnostic, medical treatment or drug-prescription rate of overt hyperthyroidism.

An endocrinologist carefully reviewed the titles and abstracts of the articles. Finally, the full texts of the selected studies were re-evaluated to ensure they meet the inclusion and exclusion criteria.

Data extraction

A standardized Excel spreadsheet that was accepted by the Global Burden of Diseases (GBD) investigators was used for extracting various variables including the name of the first authors, subjects' sex and age, year of publications and conducting studies, thyroid function tests profile, province of Iran (a political and geographic division) of the studies, sampling method, total sample size, response rate, number of subjects with overt and subclinical hyperthyroidism, diagnostic rate, medical treatment rate, drug-prescription rate, and the prevalence of hyperthyroidism in subjects with goiter. Extracted data were double-checked by two trained researchers to ensure accuracy. When, there were several reports from a study, we only considered the most comprehensive results for prevalence meta-analyses.

Fig. 1 Flowchart of the systematic review and meta-analysis

Study quality assessment

The quality of the included studies was assessed based on GBD quality assessment checklist, which is used in other meta-analysis studies as well [12, 13]. The final quality assessment score for each paper was obtained through summing up the scores of sample size (0–3), the sampling method (1–4 score), and the response rate (0–6).

Statistical analysis

The collected data were entered into Stata statistical software version 12 and metaprop random effects analysis was used for calculating the prevalence of hyperthyroidism, drug-prescription rate, medical treatment rate, and diagnostic rate of overt hyperthyroidism and metaprop fix effect analysis was used for incidence of hyperthyroidism. [14]. Amount of heterogeneity of the selected studies was demonstrated by I-squared. Subgroup analyses were carried out by type of hyperthyroidism (total, overt, and subclinical) for prevalence and incidence and by sex for incidence. Moreover, pooled and individual data of the included surveys were depicted by Forest Plots. Causes of heterogeneity was assessed by univariate and multivariate meta-regression analysis.

Results

Characteristic of the studies included

In the primary search, we identified 7667 published papers or conference proceedings, including 713 papers in ISI, 1300 in Scopus, 1024 in PubMed, 2138 in Embase, and 39 in Cochrane Library in international databases and 435 in SID, 500 in Magiran, and 1518 in Barekat Knowledge Network System in Persian databases. Of all, 3720 papers were removed after eliminating duplicated articles. Of 3947 remaining papers, 3728 were excluded because of irrelevancy by reviewing the titles and abstracts. After full text review of 219 articles, 18 papers with a sample size of 42,793 subjects were found to be eligible for systematic review according to inclusion and exclusion criteria [4, 15–31] (Fig. 1); based on the results of systematic review, six studies were related to the prevalence of hyperthyroidism in general population without age restriction (category 1) [4, 16, 18, 19, 27, 28], four studies assessed the prevalence of hyperthyroidism in <20 years old population (category 2) [17, 20, 21, 30], five studies reported the prevalence of hyperthyroidism in subjects with goiter (category 3) [4, 17, 23, 28, 29], three studies reported the incidence rate of hyperthyroidism (category 4) [16, 22, 31], and seven studies reported the diagnostic, medical treatment, or drug-prescription rate of overt hyperthyroidism (category 5) [4, 15, 16, 18, 24–26]. Meta-analysis was performed only on

categories with sufficient data. Finally, 12 studies [4, 15, 16, 18, 19, 22, 24–28, 31] with a sample size of 37,883 subjects were entered into the meta-analyses (Fig. 1). The characteristics of included studies is summarized in Table 1.

Epidemiology of hyperthyroidism

The prevalence of total hyperthyroidism (overt and subclinical) in general population was 2.43% (95% Confidence Interval (CI): 0.23–4.63%) (Fig. 2 & Table 2). Pooled prevalence of overt hyperthyroidism was 0.69% (95% CI: 0.21–1.18%) (Fig. 3 & Table 2).

The prevalence of hyperthyroidism among subjects <20 years old and subjects with goiter were not included in meta-analysis and reported individually (Table 2).

The incidence of hyperthyroidism was reported by three studies [16, 22, 31], two of which used data collected by Tehran Thyroid Study (TTS) (Table 2). The pooled annual incidence rates of total, overt and subclinical hyperthyroidism per 1000 females were 2.6 (95% CI: 1.0–4.2), 1.0 (95% CI: 0.0–2.0) and 1.5 (95% CI: 0.3–2.7), respectively. For males, the pooled annual incidence rates of total, overt and subclinical hyperthyroidism were 1.6 (95% CI: 0.1–3.0), 0.2 (95% CI: 0.0–0.6) and 1.0 (95% CI: 0.0–2.2) per 1000 population, respectively.

Furthermore, the data about diagnostic rate of overt hyperthyroidism were found in three studies [4, 18, 24]. The pooled result was 67.40% (95% CI: 23.67–100%). Moreover, pooled medical treatment and drug-prescription rate of overt hyperthyroidism, calculated based on the results of six studies [4, 15, 16, 24–26] were 43.06% (95% CI: 0–86.69%) and 42.92% (95% CI: 0–86.65%), respectively.

In subclinical hyperthyroidism, only three studies [4, 18, 24] reported the drug-prescription rate; two of them reported zero and one reported 4%.

Meta-regression

Meta-Regression analysis was utilized to detect the source of heterogeneity.

In univariate meta-regression analysis for prevalence only the years of publications was related to heterogeneity which was remained significant after adjustment for other probable sources with multivariate analysis (Table 3).

There was not heterogeneity ($I^2 = 0$) in terms of incidence and none of mentioned variables were significant in meta-regression analysis.

Discussion

While several population-based studies reported the prevalence of hyperthyroidism in different provinces of Iran,

Table 1 Characteristics of included studies

Study	Applied for	Years of sampling	Publication year	Province	Age	Quality score
Shakeri et al. [30]	6 ^a , & 7 ^a	2011	2016	North Khorasan	7–18	7
Amouzegar et al. [16]	1 ^{a,b,&c} , 3, 4, 5, & 8	1997–2004	2017	Tehran	>= 20	10
Dabbaghmanesh et al. [21]	7 ^{a,b,&c}	2005	2009	Fars	8–13	9
Aminorroaya et al. [4]	1 ^{a,b,&c} , 2, 3, 4, 5, & 6 ^c	2006	2008	Isfahan	20–86	10
Azizi et al. [18]	1 ^{a,b,&c} , 2, & 5	1996	2005	Tehran, Mazandaran, Gilan, Ilam	>= 6	10
Asadi Karam et al. [17]	6 ^{a,b,&c} , & 7 ^{a,b,&c}	2000	2004	Kerman	6–18	7
Azizi et al. [20]	7 ^a	1996	2000	National (26 province)	8–10	4
Azizi et al. [19]	1 ^a	1995	2002	Tehran	3–70	10
Salarkia et al. [28]	1 ^{a,b,&c}	1996	2000	Tehran	>= 10	8
Fani et al. [23]	6 ^{a,b,&c}	2000–2001	2002	Markazi	0–70	10
Rahmani et al. [27]	1 ^a	1999	2000	Ilam	>= 20	8
Mehran et al. [26]	3, 4, & 5	1997–2004	2014	Tehran	>= 20	10
Amouzegar et al. [15]	3, 4, & 5	1999–2001	2016	Tehran	>= 20	10
Heydarian et al. [24]	2, 3, 4, & 5	1999–2000	2002	Tehran	>= 20	10
Mehran et al. [25]	3, 4, & 5	1997–2004	2017	Tehran	>= 20	10
Seyfhashemi et al. [29]	6 ^a	2006	2007	Semnan	6–12	12
Delshad et al. [22]	8	1999–2006	2012	Tehran	>= 20	10
Aminorroaya et al. [31]	8	2006–2011	2017	Isfahan	25–82	8

1- Meta-analysis for Prevalence

a. Overt

b. Subclinical

c. Total

2- Diagnostic rate

3- Drug-Prescription rate

4- Medical treatment rate

5- Diagnostic/medical treatment rate

6- Systematic review for prevalence in subjects with goiter

a. Overt

b. Subclinical

c. Total

7- Systematic review for prevalence in subjects <20 years

a. Overt

b. Subclinical

c. Total

8- Meta-analysis for incidence

because of the variations in the results it is necessary to adopt a systematic approach to investigate the prevalence of hyperthyroidism in Iran. This is the first study which adopted a systematic approach to conduct a meta-analysis of the prevalence of hyperthyroidism in Iran. Six studies were considered for meta-analysis of the prevalence (category one). After pooling the data, it was found that the prevalence of total (overt and subclinical) hyperthyroidism was higher than 2% in general population. The prevalence of overt and subclinical hyperthyroidism was about 0.7% and 1.5% in general population respectively. Our results are consistent with the results of other studies

conducted in other regions. A systematic review and meta-analysis in 2014 which was performed on the studies conducted in European countries showed that the prevalence of overt and subclinical hyperthyroidism were 0.68% (95% CI: 0.54–0.84%) and 2.91% (95% CI: 2.63–3.21%) respectively, but the prevalence widely varied by different European countries, ranging from 0.42% to 2.92% for overt and 0.81 to 6.49 for subclinical hyperthyroidism [9]. A large study in the United State population showed that the prevalence of total hyperthyroidism was 1.3% (0.5% overt and 0.7% subclinical) [6]. The Colorado Thyroid Disease Prevalence Survey showed that

Fig. 2 Forest plot of the prevalence of total hyperthyroidism

the prevalence of total hyperthyroidism was 1% (0.1% overt and 0.9% subclinical) in subjects not taking thyroid hormone [32]. The prevalence of total hyperthyroidism in a study in China varies between 2.3% (1.2% overt and 1.1% subclinical) and 5.9% (2% overt and 3.9% subclinical) according to regions the study conducted. [33]. The prevalence of total hyperthyroidism in a study in Japan was 2.8% (0.7% overt and 2.1% subclinical) [34]. A study which was performed in Libya showed that the prevalence of total hyperthyroidism was 1.68% (0.84% overt and 0.84% subclinical) [35]. As, it was shown above, our results are similar to the results of other mentioned studies (the uncertainty of our estimation covered the rates that reported by most studies). The differences observed between our study and the studies in China and different European countries may be due to diversity in genetic backgrounds of the subjects, environmental factors, iodination status, or the time passed from the implementation of universal salt iodination [3, 5, 36, 37].

We found that the prevalence of overt hyperthyroidism in studies investigating participants aged less than 20 years old was significantly lower than those without age restriction. Our result is consistent with this approved fact that the incidence of hyperthyroidism is rare before puberty and the peak incidence of hyperthyroidism is observed after the age of 20 [3, 38]. Furthermore, we observed that the prevalence of hyperthyroidism in subjects with goiter was generally higher than that in the general population; this finding is consistent with the results of other studies since goitre is one of the presentations

of graves' disease, toxic multi nodular goiter and toxic adenoma [39, 40].

Although the gender of hyperthyroid patients was not reported in most of the reviewed studies for prevalence, in those studies that reported gender, most of them showed a female preponderance.

This study showed that the pooled annual incidence of overt hyperthyroidism was about 0.8 per 1000 persons. As it was expected, the incidence of subclinical hyperthyroidism was higher than overt hyperthyroidism.

According to Garmendia Madariaga et al. meta-analysis which was reporting an annual incidence rate of 0.51 per 1000 persons [9], the incidence rate of overt hyperthyroidism in European population is a little lower than Iran. However, European meta-analysis incidence rate was covered by the uncertainty of our estimation.

Similar to other reports, our results were consistent with higher incidence of hyperthyroidism among females. For example in Whickham study, the annual incidence of overt hyperthyroidism was 0.8 per 1000 in females with no new cases were identified in males [41]. In another study, which performed in Tayside, Scotland, the annual incidence rate of overt hyperthyroidism was 0.77/1000 in females and 0.14/1000 in males [42].

Because of scarcity of data we were not able to compare the prevalence or incidence of hyperthyroidism before and after salt iodination in Iran. There was only one report that compared the number of hyperthyroid patients in 1989 (before salt iodination) and 1995 (after salt iodination) in the same area in

Table 2 The prevalence and incidence of hyperthyroidism

Study	Years of sampling	N	Age range, yr	Tests	Hyperthyroidism		
					Total %	Subclinical %	Overt%
Prevalence of hyperthyroidism without age restriction (category 1)							
Amouzegar et al. [16]	1997–2004	5783 (59% F)	>= 20	TSH, FT4	5.88	3.68	2.20
Aminorroaya et al. [4]	2006	2523 (49% F)	20–86	TSH, TT4, TT3, T3RU, FT4I	1.82 (70% F)	0.99 (64% F)	0.83 (76% F)
Aziz et al. [18]	1996	6048	>= 6	TSH, TT4, TT3, T3RU, FT4I, FT3I	0.76	0.41	0.35
Aziz et al. [19]	1995	3146 (59% F)	3–70	TSH, TT4, TT3	–	–	0.19*
Salarkia et al. [28]	1996	707 (62% F)	>= 10	TSH, TT4, TT3	1.27	0.99**	0.28
Rahmani et al. [27]	1999	301	>= 20	TSH, TT4, TT3, T3RU	–	–	0.33 (0% F)***
Present meta-analysis	2017	18,508			2.43	1.52	0.69
95% CI					0.23–4.63	0.14–2.89	0.21–1.18
Prevalence of hyperthyroidism in <20 years old (category 2)							
Shakeri et al. [30]	2011	176 (44% F)	7–18	TSH, FT4, FT3	–	–	0.00
Dabbaghmanesh et al. [21]	2005	500 (50% F)	8–13	TSH, FT4, FT3	0.20	0.20 [§]	0.00
Asadi Karam et al. [17]	2000	201	6–18	TSH, TT4, T3RU	0.00	0.00	0.00
Aziz et al. [20]	1996	1553	8–10	TSH, TT4, TT3, T3RU, FT4I, FT3I	–	–	0.06
Prevalence of hyperthyroidism in subjects with goiter (category 3)							
Shakeri et al. [30]	2011	50 (54%)	7–18	TSH, FT4, FT3	–	–	0.00
Aminorroaya et al. [4]	2006	478 (75% F) [†]	20–86	TSH, TT4, TT3, T3RU, FT4I	6.07	–	–
Asadi Karam et al. [17]	2000	129 (40% F)	6–18	TSH, TT4, T3RU	0.00	0.00	0.00
Fani et al. [23]	2000–2001	2138 (72% F)	0–70	TSH, TT4, TT3	5.99	1.17	4.82
Seyfhashemi et al. [29]	2006	342 (56% F)	6–12	TSH, TT4	–	–	9.06 (55% F)
Incidence of hyperthyroidism /year (category 4)							
Amouzegar et al. [16]	1997–2004	4204 (55% F)	>= 20	TSH, FT4	0.16 (63% F)	0.09 (61% F)	0.07 (65% F)
Delshad et al. [22]	1999–2006	1999 (61% F)	>= 20	TSH, TT4, T3RU, FT4I	0.58 (74% F)	0.48 (71%F)	0.09 (91% F)
Aminorroaya et al. [31]	2006–2011	618 (49% F)	25–82	TSH, TT4, TT3	0.46 (88% F)	0.27 (80% F)	0.19 (100% F)
Present meta-analysis	2017	6821 (56% F)			0.22	0.13	0.08
95% CI					0.11–0.33	0.04–0.22	0.01–0.14

F, female; TSH, Thyroid Stimulating Hormone; T4, thyroxine; T3, triiodothyronine; TT3/4, Total T3/T4; FT3/4, free T3/T4; FT3/4I, free T3/T4 index; T3RU, T3 resin uptake

*As the type of hyperthyroidism is not determined, we considered overt

**As the number of subclinical hyperthyroidism is not determined in the article obviously, we considered subclinical hyperthyroidism in those with TSH < 0.3

***As the type of hyperthyroidism is not determined, we considered overt (only one hyperthyroid male reported)

§As the type of hyperthyroidism was not determined in this article we use the result of another article that performed in the same population (51)

† As the type of female percentage was not determined in this article we use the result of another article that performed in the same population (52)

Iran that showed an increase in hyperthyroid patients, but this finding was not statistically significant [19].

Although the pooled diagnostic rate of overt hyperthyroidism in our study was about 65%, if we included those studies that reported the medical treatment rate (these studies not reported the number of surgical treatment for hyperthyroidism) of overt hyperthyroidism, the pooled diagnostic/medical treatment rate would have become about 41% (data is not shown).

Most of the patients with overt hyperthyroidism in the world and Iran are treated by anti-thyroid drugs and radioiodine ablation therapy; on the other hand, surgical

therapy is rarely performed for treatment of this problem [39, 43–46]. As a result it seems logical to merge these studies to calculate the diagnostic rate of overt hyperthyroidism (diagnostic/medical treatment rate).

In NHANES III study, the estimated diagnostic rate of overt hyperthyroidism was about 70% [6]. According to Knudasan et al.'s study which was performed in a European population, the diagnostic rate of overt hyperthyroidism was about 70% [47]. The diagnostic rate of chronic disease is related to physician densities in communities and socioeconomic status of population [48, 49]. With improving the

Fig. 3 Forest plot of the prevalence of overt hyperthyroidism

socioeconomic status, the diagnostic rate gets closer to 100%. The discrepancy between the results of the studies may be due to differences in socioeconomic status and lower density of endocrinologists and internists in Iran, as compared with the United States and European countries. However, because of significant improvement in healthcare indices in Iran in recent years, further studies are needed to reevaluate these rates.

Heterogeneity in data and our approach

Heterogeneity in meta-analysis approach was demonstrated by $I^2 > 50\%$ [50]. In meta-regression analysis of prevalence, the only factor that was significantly associated with heterogeneity was articles publication years. Probably, some sources of heterogeneity could not be addressed by our analyses.

Some of these sources could be a little different in terms of the definition of hyperthyroidism, or they might have utilized different assay kits or even instruments to measure the thyroid function.

Sensitivity analysis

Several published articles have been extracted from TTS study. Although, these articles have different sample sizes and differently analyzed the data obtained from a unique population, one article from TTS that had more comprehensive results was included in our prevalence meta-analysis. We also analyzed results with the data of omitted articles (i.e. Delshad et al. [22], Heydarian et al. [24] studies) in order to detect its effect. The pooled prevalence of total hyperthyroidism

Table 3 Univariable and multivariable meta-regression analysis for detecting source of heterogeneity in prevalence

Variables	Univariable			Multivariable		
	Coefficient	95% CI Coefficient	P value	Coefficient	95% CI Coefficient	P value
Years of publications	0.0012319	0.0006363–0.0018275	0.005	0.0014074	0.0007928–0.0020219	0.010
Provinces	−0.0020539	−0.0101746 - 0.0060668	0.521	−0.0011416	−0.0032445 - 0.0009612	0.145
Sample size	1.61e-06	−2.23e-06 - 5.45e-06	0.310	—	—	—
Years of conducting	0.0002868	−0.0022927 - 0.0028663	0.773	—	—	—
Quality score	0.0028483	−0.006901 - 0.0125975	0.463	−0.002494	−0.0065915 - 0.0016035	0.120

changed to 1.73% [0.52% overt and 1.09% subclinical (the numbers are not add up because the articles considered for data extraction in each subgroup were not exactly the same)] that was within the uncertainty of our previous reported results (data not shown).

On the contrary, since we found a few articles on diagnostic rate of hyperthyroidism, data of all articles from TTS study that reported diagnostic/medical treatment rate were considered for meta-analysis. In order to detect the effect of this multi-publication from unique population on pooled data of diagnostic/medical treatment rate, we also analyzed the results without these articles (three studies of Aminorroaya et al. [4], Amouzegar et al. [16], Azizi et al. [18] remained). The diagnostic/medical treatment rate changed only about 1% (data not shown).

Limitations and advantages of our study

Our study suffered from some limitations. Because of the scarcity of data, we could not address the frequency of different treatment modalities prescribed for hyperthyroid patients or the etiology of hyperthyroidism in Iran. Moreover, we could not analyze the trend, sex, and geographic distribution of the hyperthyroidism prevalence in all parts of Iran. However, because of universal salt iodine enrichment in Iran, it seems that the iodine intake as one of the important predictors of hyperthyroidism [1, 3] became homogenous in Iran [10, 11]. Hence, it is not now expected to observe a large difference in the prevalence of the hyperthyroidism.

To the best of our knowledge, this is the first systematic review of the prevalence of hyperthyroidism in Iran. Our searches were very comprehensive as we searched the most important international and all national medical databases for the prevalence of hyperthyroidism in Iran. Furthermore, it may be the first meta-analysis in Middle East and north of Africa that reported the diagnostic rate of overt hyperthyroidism and prescription rate of anti-thyroid agents.

Conclusion

In conclusion, it seems that the prevalence and incidence of hyperthyroidism among the general population in Iran is similar to other regions of the world. We recommend conducting well-designed surveys with enough geographic disparity about the epidemiologic characteristic of thyroid dysfunction in Iran that could provide a better picture of age, sex, trend, and geographic distribution of hyperthyroidism. The diagnostic and drug-prescription rates of the overt hyperthyroidism were less than 50% of affected patients and were lower than the rates observed in developed countries. Whereas, the healthcare indices in Iran were improved in recent years and

further studies to reevaluate these rates are needed, the policy makers' attention is essential to improved diagnostic rate of thyroid dysfunctions.

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Compliance with ethical standards

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