Factors Influencing the Reference Interval of Thyroid Stimulating Hormone in Healthy Adults: A Systematic Review and Meta-analysis

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Abstract

Background: Thyroid stimulating hormone (TSH) is an important indicator for evaluating thyroid function. Many studies have reported that the TSH reference interval is susceptible to external factors. This paper summarizes the related studies published in recent years and comprehensively analyzes the effects of these factors on the TSH reference interval in healthy people.

Methods: Articles published from January 1980 to January 2020 were searched in PubMed, EMBASE, Cochrane, Scopus, Medline English databases and CNKI, WanFang and CQVIP Chinese databases. In total, 21 studies were ultimately included. All data were analyzed using Review Manager 5.3 software and STATA 16.0 software. Microsoft Excel 2010 was used to draw the TSH concentration curve changing with age, and GraphPad 6.0 was used to draw the TSH concentration curve with sex.

Results: The TSH reference interval was significantly influenced by sex and age. The overall trend of TSH concentration reveals that males are lower than females. The TSH reference interval is divided into 20~59-year-old, 60~69-year-old and over 70-year-old age groups for males and 20~39-year-old, 40~49-year-old, 50~69-year-old and over 70-year-old age groups for females. Regardless of sex, TSH concentrations all increase with age. In iodine-deficient areas, TSH reference intervals are generally lower than those in iodine-sufficient or iodine-excessive areas. The TSH reference interval in Asia and North American countries is generally higher than that in most European countries. Even the detection methods are consistent, different detection instruments can affect the TSH reference interval. Sample size and race are also important factors.

Conclusion: The TSH reference interval was significantly influenced by sex and age, race, region, iodine intake, sample size, detection instruments and methods, but other factors should not be ignored. Therefore, it is necessary for each laboratory to validate an appropriate TSH reference interval based on local conditions.

Background

Thyroid stimulating hormone (TSH) is a kind of glycoprotein secreted by specific basophils in the pituitary gland, which is a specific indicator for evaluating individual thyroid function [1]. Clinically common thyroid diseases include hyperthyroidism, iodine deficiency disease, thyroiditis and so on. With improvements in the understanding of thyroid diseases and health examinations, the incidence of thyroid diseases is increasing. Because many patients are asymptomatic or in a subclinical state, and some countries advocate a TSH priority strategy for the diagnosis of thyroid dysfunction [2], it is important and necessary to establish a reference interval. The reference interval is currently the most widely used tool for medical decision-making. It is usually defined as the reference value between 2.5% and 97.5%, which is the most important factor in health assessment, disease diagnosis, treatment and prognosis assessment [3]. In general, the upper limit of the TSH reference interval is an important indicator for the evaluation of thyroid disease. The International Federation of Clinical Chemistry (IFCC) and Clinical and Laboratory Standards Institute (CLSI) have recommended that each laboratory define their own reference intervals [4] so that patients with thyroid-related diseases in different countries can receive screening and diagnosis in a timely manner.

Because TSH is an important indicator for evaluating thyroid function, the preconditions that may influence the establishment of its reference interval should be considered comprehensively. Some studies based on multi-population regions have evaluated the TSH reference interval from healthy individuals according to the National Academy of Clinical Biochemistry (NACB) standards [5-8] and have noted that the TSH reference interval was influenced by age, sex, race, iodine intake and thyroid autoantibodies[9, 10]. Through comprehensive analysis, this paper mainly discusses the effect of age, sex, iodine intake and other factors, such as region, sample size, race, detection instruments and methods, on the establishment of the TSH reference interval and explains why it is necessary for different countries to establish their own TSH reference intervals.

Methods

2.1 Search Strategy and Database

Through PubMed, Medline, Embase and Cochrane English databases and WanFang, CNKI and CQVIP Chinese databases, the keywords "reference interval" or "reference value" combined with "TSH" or "thyrotrophic hormone" were used to search all relevant Chinese and English literature from January 1980 to January 2020.

2.2 Exclusion and Inclusion Criteria

Based on the selection criteria of the selected articles and the recommendations of NABC [11], the final inclusion criteria were as follows: (1) more than 120 subjects; (2) thyroid peroxidase antibody (TPOAb) or thyroglobulin antibody (TGAb) negative; (3) no family or personal history of thyroid disease; (4) no goiter and no medical history influencing thyroid function (except use of estrogens); (5) no obvious abnormalities in thyroid ultrasound; and (6) all articles grouped by age and sex.

The exclusion criteria were as follows: (1) subjects with family or personal history of thyroid disease; (2) Newcastle-Ottawa quality assessment scale (NOS) quality scores <6; (3) TPOAb or TGAb positivity; (4) subjects with enlarged thyroid at palpation or abnormal thyroid ultrasound; (5) pregnancy (including the use of oral contraceptives); and (6) subjects with organic diseases of the heart, lungs, liver, gallbladder, kidneys or endocrine system.

2.3 Quality Assessment

The NOS was selected to assess the quality of the included studies using the “star system”. Information regarding selection, comparability, and outcomes was evaluated with a maximum of 4 stars, 2 stars, and 3 stars, respectively [12]. The selected articles are defined as two classes: high-quality articles (6-9 scores) and low-quality articles (0-5 scores) [13]. If there were arguments about the scores of the studies, the third author participated in the quality assessment.

2.4 Data Extraction

Two reviewers (Dongyang Xing and Qi Zhou) extracted the following data from all eligible studies independently: first author; publication year; country; sample size; age group; mean and percentiles (2.5^{th} and 97.5^{th}) of serum TSH; detection instruments and methods. All researchers had no objection to the final results.

2.5 Statistical analysis

The random effects model was used to analyze the mean or median, standard deviation (SD), and sample size of the original data. The TSH concentration was log-transformed due to its abnormal distribution, the reference interval usually is represented by the median, mean, 2.5th percentile and 97.5th percentile. The results are presented as the standard mean difference (SMD) with a 95% confidence interval (CI). For the heterogeneity test, a p-value < 0.01 was considered a significant difference. TSH differences between different age and sex groups were analyzed using STATA 16.0 and Review Manager 5.3 software. At the same time, subgroup analyses of sample size, region, detection instruments and methods were also performed. Microsoft Excel 2010 and GraphPad Prism 8.0 were used to draw curves of the TSH concentration changes with sex and age. Microsoft Word 2010 was used by drawing flow charts and basic information tables for selected articles.

Results

4.1 Literature Search and Study Characteristics

A total of 3203 articles were retrieved according to keywords, among which 475 were duplicate articles and 2477 articles were excluded by browsing the titles and abstracts. After reading the remaining 216 articles, 195 articles were excluded. Finally, the remaining 21 [4-8, 14-29] studies were included in this meta-analysis (16 published in English and 5 in Chinese). The flow chart is as follows (Figure 1). All articles were published between 1980 and 2020 and were mainly from Korea, Japan, China, India, Thailand, France, Australia, Turkey, Sudan, Tehran and the Mediterranean. The NOS score of all studies was over 5 (basic information is shown in Table 1). There were 9 articles on age comparison and 19 articles on sex comparison (7 articles discussed sex and age at the same time). The funnel plot (Figure 2) showed that each study was distributed at the top of the funnel plot, and the left and right sides were roughly symmetrical, so there was no significant publication bias.

4.2 Age and sex distribution characteristics of TSH

The nine studies grouped by age met the following criteria: 1. The samples were healthy adults. 2. Age groups were divided into groups of 10 years old. In females, there were significant differences among the 30~39-year-old, 40~49-year-old, 50~59-year-old, 60~69-year-old and over 70-year-old age groups (P < 0.05) (Figure 3A to 3E). In males, there were significant differences between the 50-59-year-old and 60-69-year-old age groups (P < 0.05) (Figure 3F~3K). The mean value of TSH in males and females of all groups changed with age (Figure 4A and 4B). The highest mean value of TSH appeared in males aged 60-69 years old, and the lowest value appeared in females aged 40-49 years old; the lowest mean value of TSH in females appeared in females aged 30-39 years old and then increased with age. The TSH concentration increased with age in both males and females. The forest plot results showed a significant difference in the TSH concentration between males and females (P < 0.0001), in which heterogeneity was 96.1%, and the SMD was -0.17 [95% CI (-0.22, -0.11)] (Figure 5). The overall trend curve of the TSH mean value in males and females (Figure 6) showed that the TSH concentration in females was generally higher than that in males.

Discussion

Thyroid disease is a clinically common endocrine disease. TSH plays an important role in the diagnosis, treatment, prevention and control of thyroid disease. Therefore, to improve the sensitivity and specificity of the test, the TSH reference interval corresponding to the local population should be established first [30]. At present, many studies have mentioned that the establishment of the TSH reference interval is affected by

some factors. Age and sex are important independent predictors that cannot be ignored [31-33]. Iodine intake and race can also lead to significant changes in the TSH reference interval [11, 34, 35]. No articles have been found in published studies on the systematic analysis of factors affecting the TSH reference interval in healthy people. This paper is the first meta-analysis to comprehensively summarize these factors. Significant differences in sex and age were found in TSH through a sex analysis of 19 articles and an age analysis of 9 articles. Iodine intake, race, region, sample size, detection instrument and methods also had important effects on the establishment of the TSH reference interval. Therefore, this article will focus on the effects of the above factors.

4.1 Age

National Health and Nutrition Survey III (NHANES III) suggested that the serum TSH concentration increased with age in adults without thyroid disease [36]. Surks et al. [37] reported that the 97.5 percentile of TSH increased from 3.56 mIU/L in the 20~29-year-old group to 7.49 mIU/L in the over 80-year-old group. In this study, the TSH concentration also increased with age. Some researchers have suggested that the progressive increase in the TSH concentration with aging could be due to an enhancement in the prevalence of acquired autoimmune thyroid disease and an increase in anti-thyroid antibodies [36, 37]. Several changes in thyroid may also contribute to the increase in serum TSH with age, such as decreased sensitivity of TSH to the negative feedback of the thyroid hormone [38], decreased biological activity of age-related TSH[39], and abnormal free thyroxine (FT4), and the TSH feedback loop may lead to an increased TSH concentration [40]. Other studies have confirmed that the increase in TSH with age is due to the normal compensatory phenomenon in the elderly [41]. However, the TSH concentration decreased with age in a few iodine-deficient regions [20, 42] such as Italy [43] and Germany [44]. Van de Ven et al.[45] reported that the TSH concentration in iodine-deficient areas was inversely proportional to age. In conclusion, the change tendency between age and the TSH concentration is not fixed, and the TSH reference interval in different countries will be distinct due to the influence of living habits and living environment [24]. The results of this study suggest that the TSH concentration increases with age in most countries.

4.2 Sex

In this meta-analysis, by comparing the mean values of TSH between males and females, the variation curves of the TSH concentration in diverse regions were obtained. The results showed a higher TSH concentration in females than in males in most regions. Estrogen is an important factor affecting the TSH concentration. Low estrogen may cause hypothyroidism and then lead to an increased TSH concentration [21]. Postmenopausal women were the typical group, and the TSH concentration increased significantly. This may be one of the reasons why TSH is generally higher in females than in males [46]. Although this study cannot represent the relationship of the TSH concentration between males and females in all regions, it is a general trend that the TSH concentration is higher in females than in males [36, 37, 47, 48].

4.3 Iodine intake and region

Iodine intake was an important factor that could partly explain the variation in the TSH reference interval in different studies [21, 49-51]. At the same time, the difference in TSH in different regions is also closely related to iodine intake. Park et al. [8] found that the TSH reference interval in Korea was significantly higher than that in Western countries. In their study, the mean value and upper limit of the TSH reference interval were 2.16 mIU/L and 7.03 mIU/L, respectively, while the NHANES III of the United States reported values of 1.40 mIU/L and 4.12 mIU/L, respectively. These differences may be explained by the state of iodine intake between Western and Korean countries. Other studies reported that the upper and lower limits of the TSH reference interval in regions such as North America and East Asia, where iodine is in abundant supply [7, 22], are often higher than those in iodine-deficient regions such as Europe[52, 53]. Not only different levels of iodine intake in other countries but also the levels of iodine intake vary from mild to excessive in different regions of China [54]. Guan et al. [4] suggested that it was necessary to consider iodine intake when establishing the TSH reference interval. Their study was conducted in Panshan, Zhangwu and Huanghua, regions with mildly deficient, more than adequate and excessive iodine intake, respectively, and the mean levels of TSH in Panshan, Zhangwu and Huanghua were 1.15 mIU/l, 1.28 mIU/l and 1.93 mIU/l, respectively. Therefore, iodine deficiency or excess will affect the establishment of the TSH reference interval [55]. At present, iodine intake in most European countries is deficient [53, 56], and TSH concentrations are low in these populations. However, Asia [7, 22] and North America [36] are countries with sufficient iodine intake and have populations with relatively high TSH concentrations. Therefore, iodine intake and regional distribution are important factors influencing the establishment of the TSH reference interval.

4.4 Detection instruments and methods

At present, the main methods for testing thyroid hormones employ chemiluminescence (CL). Chemiluminescence methods can be mainly divided into chemiluminescence immunoassay (CLIA), electrochemiluminescence immunoassay (ECLI) and chemiluminescence enzyme immunoassay (CLEIA) according to different markers. In this study, the TSH reference interval was mostly established by CLIA or ECLI. The main principle of CLIA is to use chemiluminescence reagents to mark antigens or antibodies. After the labeled antigens and antibodies go through a series of immune reactions and physicochemical steps with the determinand, the content of the determinand is finally expressed in

the form of luminescence intensity. ECLI is a process of chemiluminescence caused by electrochemical reactions, and its principle is similar to that of CLIA. At present, there are various detection instruments, including the Siemens ADVIA Centaur Analyzer, Abbot Architect Analyzer, Roche Cobas Analyzer, Beckman Coulter, etc. Due to the diverse range of detection instruments, even when the same detection method is used, different reagents for marking antigens or antibodies during the reaction may cause differences in the TSH reference interval. Therefore, the establishment of the TSH reference interval can be influenced by different detection instruments and methods.

4.5 Other factors

In addition to the above factors, this paper also analyzed the sample size and race factors. Based on the limited information provided by the original paper on these two sides, we provided only a brief explanation. Sample size as a possible factor should not be ignored. Chen et al. [23] proposed that the results were inconsistent with those of Wang et al. [16]. The sample size was 211 in the study of Wang and 7693 of Chen. Therefore, the difference may be related to the sample size. It is worth noting that the results of Chen et al. [23] showed that the upper limit of the TSH reference interval was higher than that of Western countries [36, 57]. Data from several recent studies showed that the median and upper limit of the TSH reference interval for both African Americans and non-Hispanic Americans were lower than those for white Americans [33-35, 58]. One possible explanation is racial differences. NHANES III [36] also proposed that the median, upper and lower limits of the reference interval for African America were lower than those for Caucasian. Boucai et al. [58] confirmed that the decrease in the African America median and the upper and lower limits of the TSH reference interval was due to the shift of the distributed population to a lower TSH reference value. Studies on genetic and environmental impacts have suggested that the negative feedback pathway of TSH is also affected by genetics [59]. Another report on gene polymorphisms in the thyroid hormone pathway also suggested that the difference in the TSH reference interval may be related to differences between African America and Caucasian [60]. Thus, the importance of race in the establishment of the TSH reference interval has been demonstrated.

Limitations

According to the 21 selected articles, we made specific explanations on the possible influencing factors. However, due to the limited data and information in original articles, we mainly summarized the following deficiencies: 1. The number of studies was limited, which did not cover the TSH reference interval in healthy people in all countries. 2. We did not perform a subgroup analysis of iodine intake and race. Due to the limited information in the original article, the number of articles for subgroup analysis was insufficient. 3. The sample size in the original article was different. These deficiencies were inevitable, as we have explained in our discussion, and this study reflects only the overall trend of the regions currently covered.

Conclusion

This study comprehensively analyzed the factors affecting the establishment of the TSH reference interval, including age, sex, iodine intake, race, region, sample size, detection instruments and methods. We suggest that TSH is significantly changed by age and sex, and our conclusions are as follows: The TSH reference interval in females was generally higher than that in males. The TSH concentration increased with age in both males and females. The establishment of the TSH reference interval was significantly influenced by iodine intake, sample size, race and other factors and should not be ignored. In addition, the instruments and reagents used in each laboratory come from diverse manufacturers, and the test results will vary to different degrees. Therefore, the reference interval provided by the manufacturer should be used selectively, and an appropriate reference interval should be established separately for special groups. As a result, to avoid incorrectly identifying TSH concentrations, we should take the above factors into full consideration when establishing the reference interval. At the same time, our meta-analysis can provide some guidance for the clinical diagnosis and treatment of thyroid-related diseases.

Abbreviations

TSH, thyroid stimulating hormone; IFCC, International Federation of Clinical Chemistry; CLSI, Clinical and Laboratory Standards Institute; NACB, National Academy of Clinical Biochemistry; NOS, Newcastle-Ottawa quality assessment scale; TPOAb, thyroid peroxidase antibody; TGAb, thyroglobulin antibody; SD, standard deviation; SMD, standard mean difference; CI, confidence interval; NHANES III, National Health and Nutrition Survey III; FT4, free thyroxine; CL, chemiluminescence; CLIA, chemiluminescence immunoassay; ECLI, electrochemiluminescence immunoassay; CLEIA, chemiluminescence enzyme immunoassay.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials: The data used to support the findings of this study are available from the PubMed (https://www.ncbi.nlm.nih.gov/), Medline (http://isiknowledge.com/medline), Embase (https://www.embase.com/login) and Cochrane (https://www.cochranelibrary.com/library) English databases and WanFang (http://www.wanfangdata.com.cn/), CNKI (https://www.cnki.net) and CQVIP (http://qikan.cqvip.com/) Chinese databases.

Competing Interest: The authors declared no conflict of interest.

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Tables

Table 1. Basic information of included studies.

First author	Year	Country	Sample size	Age	Detection instruments	Detection methods	Quality assesment
Park[8]	2018	Korea	5987	≥18	Roche Diagnostics, Mannheim	electrochemiluminescence immunoassay	8
Yoshihara[22]	2011	Japan	1388	≥20	Roche Diagnostics GmbH	electrochemiluminescence immunoassays	7
Sasso[20]	2019	Mediterranean	22602	15~105	Roche cobas e801 analyzer	electrochemiluminescence immunoassay	6
Chutintorn[5]	2014	Thailand	2545	≥14	Roche cobas e411 analyzer	electrochemiluminescence immunoassay	7
Gao[25]	2014	China	4820	15~76	Roche Cobas e601 Automatic immune analyzer	electrochemiluminescence	6
Wang[26]	2015	Urumqi	897	18~84	Roche Cobas e601 Automatic immune analyzer	chemiluminescence	6
Raman[6]	2013	Indian	1916	≥18	Roche Cobas Elecys 1010 analyzer	electrochemiluminescence	9
Amouzeger[24]	2013	Tehran	5704	≥20	Roche cobas e411 analyzer	electrochemiluminescence immunoassay	6
Tame.C[17]	2010	Turkey	55318	≥20	Roche Elecsys 2010 analyzers	electrochemiluminescence immunoassay	6
Frauk[18]	2014	Turkey	408	≥18	Roche Diagnostics GmbH, D-68298	electrochemiluminescence immunoassay	6
Nerrela[15]	2013	Australia	152261	≥18≥	Siemens ADVIA Centaur analyzer	chemiluminescent immunoassay	6
WangHao[26]	2011	China	7990	20~88	Siemens ADVIA Centaur analyzer	chemiluminescence immunoassay	6
Qiu[28]	2018	China	106335	≥18	Siemens ADVIA Centaur	chemiluminescence immunoassay	6
P. Wang[16]	2014	China	211	23~77	Siemens ADVIA Centaur XP analyzer	chemiluminescence immunoassay	6
Chen[23]	2018	China	7693	20~97	Siemens ADVLA Centaure,	chemiluminescence immunoassay	6
Jang[19]	2008	Korea	1591	18~65	Siemens IMMULITE 2000		7
Raverot[14]	2020	French	295775	≥20	Architect i2000 immunoassay analyzer	Chemiluminescence	7
Li[7]	2011	China	5639	12~85	Diagnostic Products Corporation (USA)	chemiluminescence immunoassay	6
Guan[4]	2008	China	3761	≥13	Not mentioned	Not mentioned	8
Song[29]	2012	China	390	18~65	Beckman Coulter Unicel DXI 800	chemiluminescence	6
Musa[21]	2018	Khartoum, Sudan	390	20~75	Radioimmunoassay gamma counter	Not mentioned	6

Figures

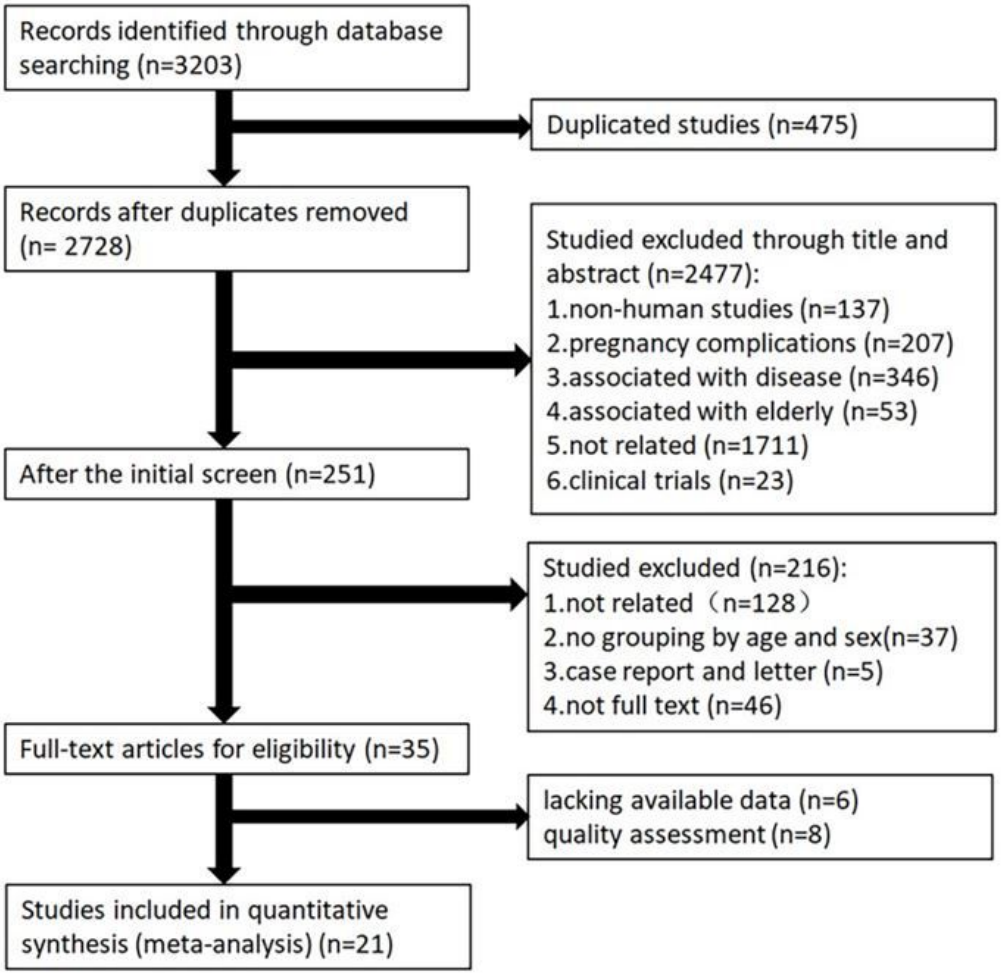

Figure 1

Flow diagram of included studies.

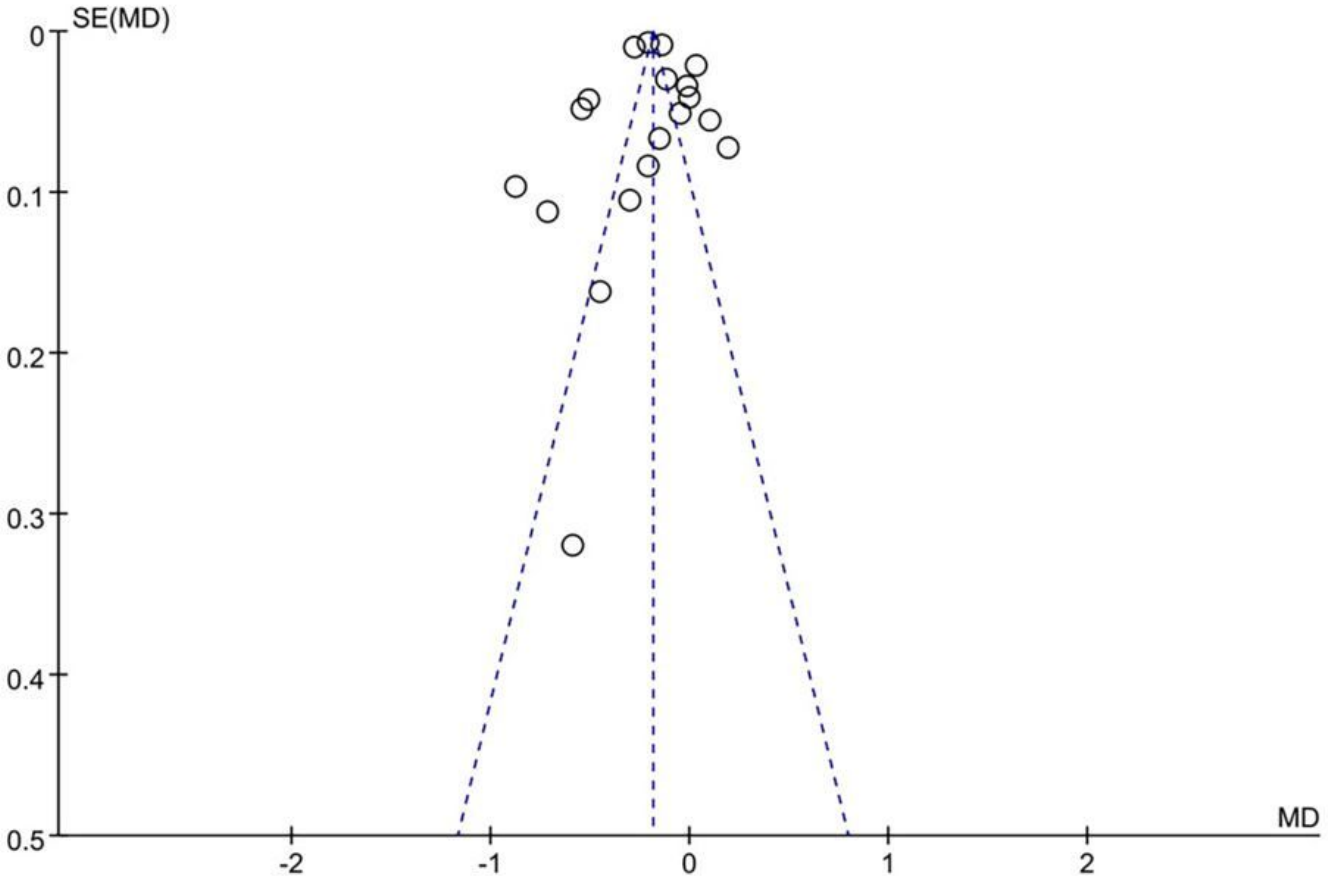

Figure 2

Funnel plot.

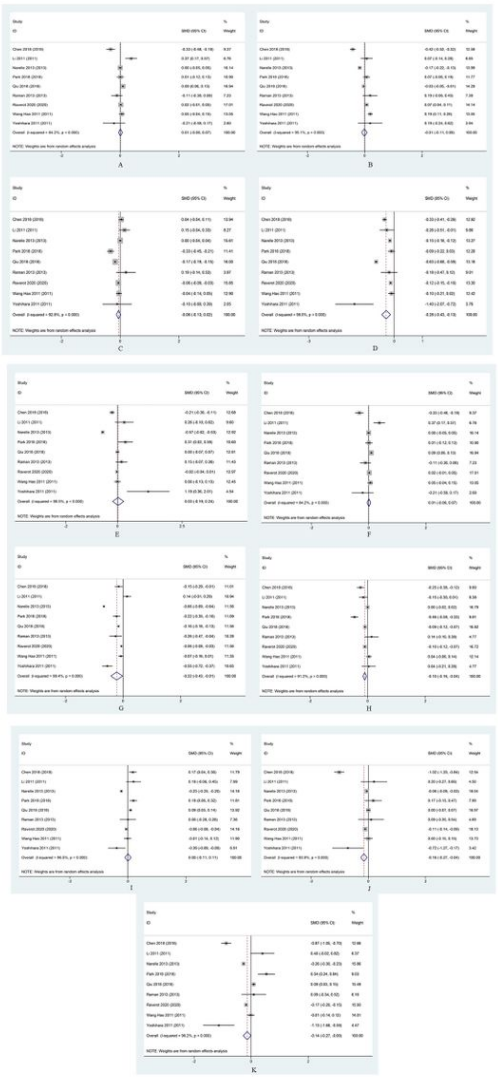

Figure 3

A~E showed the comparison between 20~29 and 30~39 years old (A, p=0.916), 30~39 and 40~49 years old (B, p=0.036), 40~49 and 50~59 years old (C, p=0.002), 50~59 and 60~69 years old (D, p=0.965) and 60~69 and ≥70 years old (E, p=0.006) in females. F~K showed the comparison between 20~29 and 30~39 years old (F, p=0.83), 30~39 and 40~49 years old (G, p=0.845), 20~29 and 40~49 years old (H, p=0.868), 40~49 and 50~59 years old (I, p=0.143), 50~59 and 60~69 years old (J, p≤0.001) and 60~69 and ≥70 years old (K, p=0.814) in males.

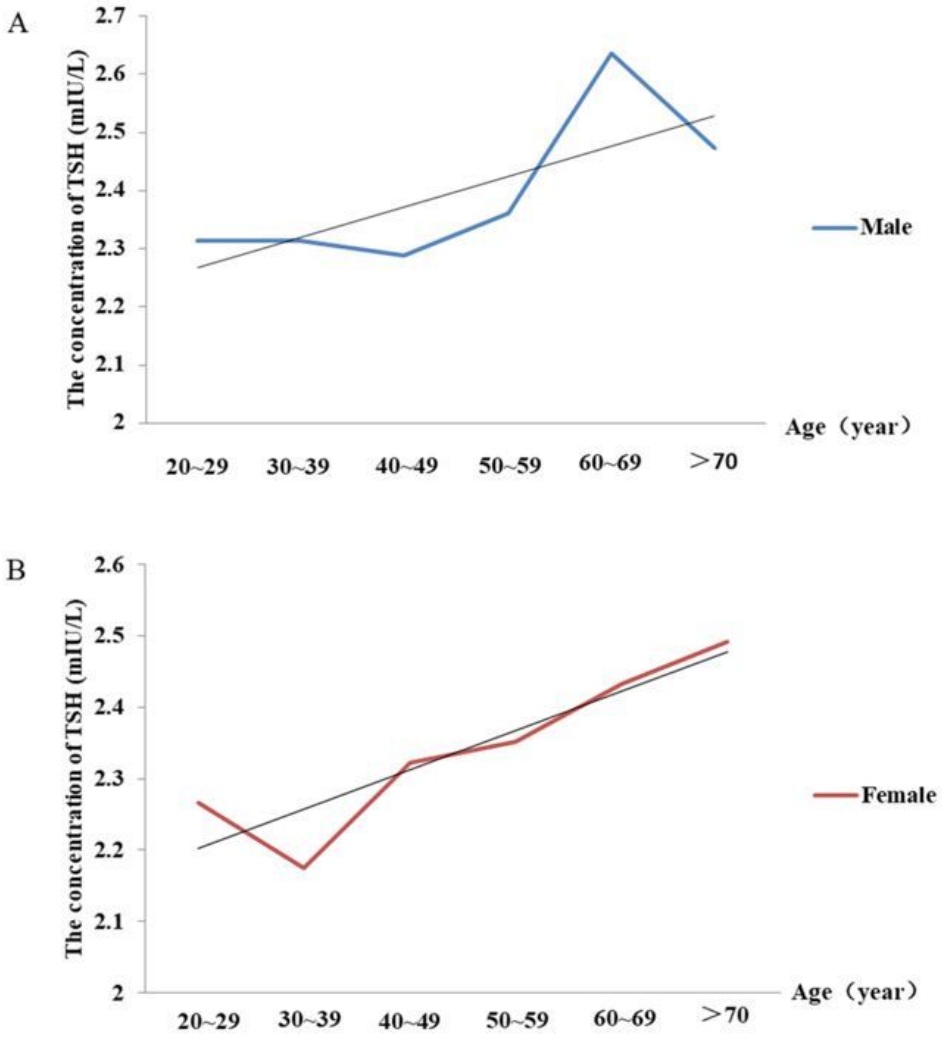

Figure 4

A and B respectively showed the changes of the overall mean value of TSH with age in different age groups in males and females in seven studies.

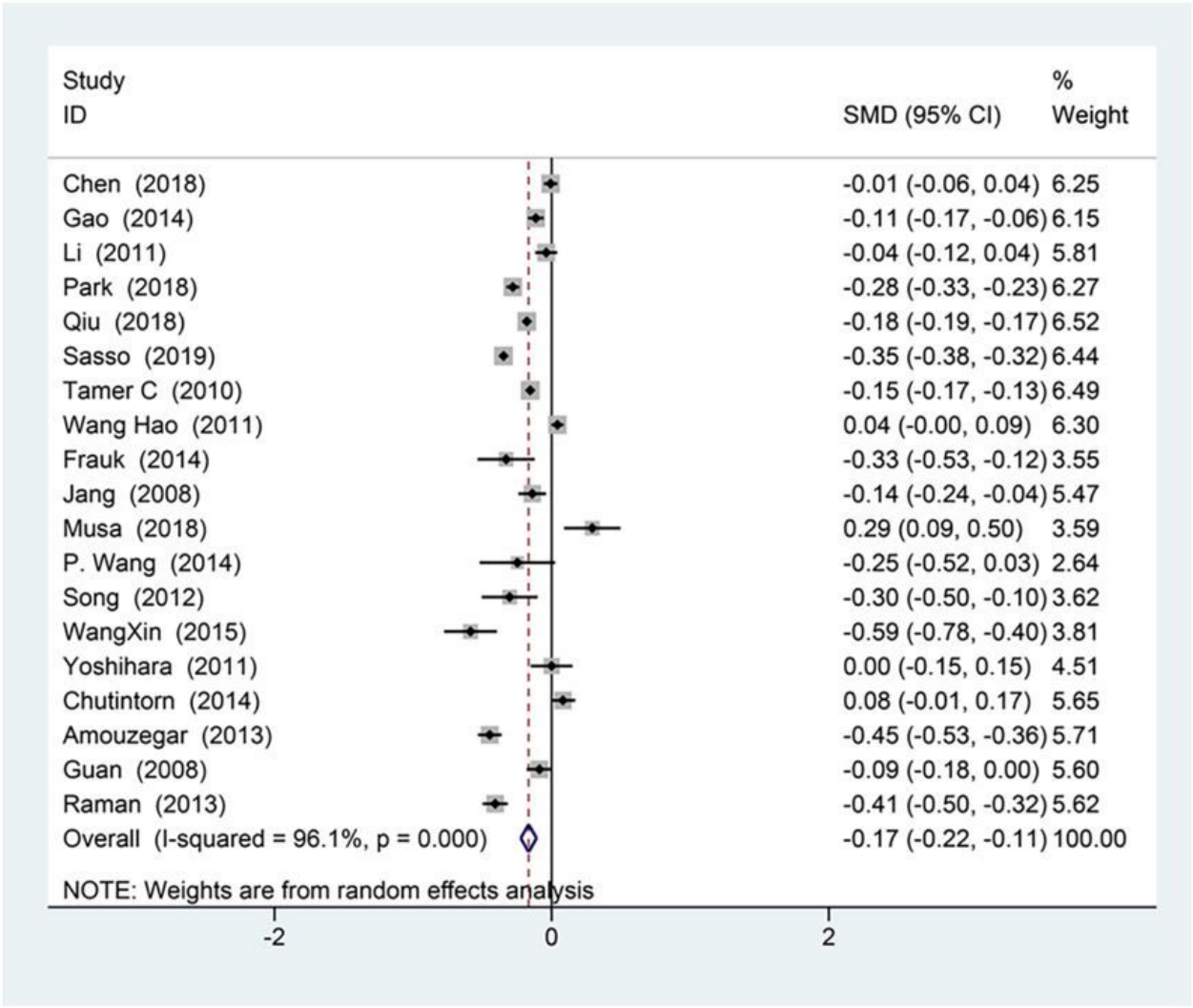

Figure 5

Forest plot for the comparison of sex in 19 articles.

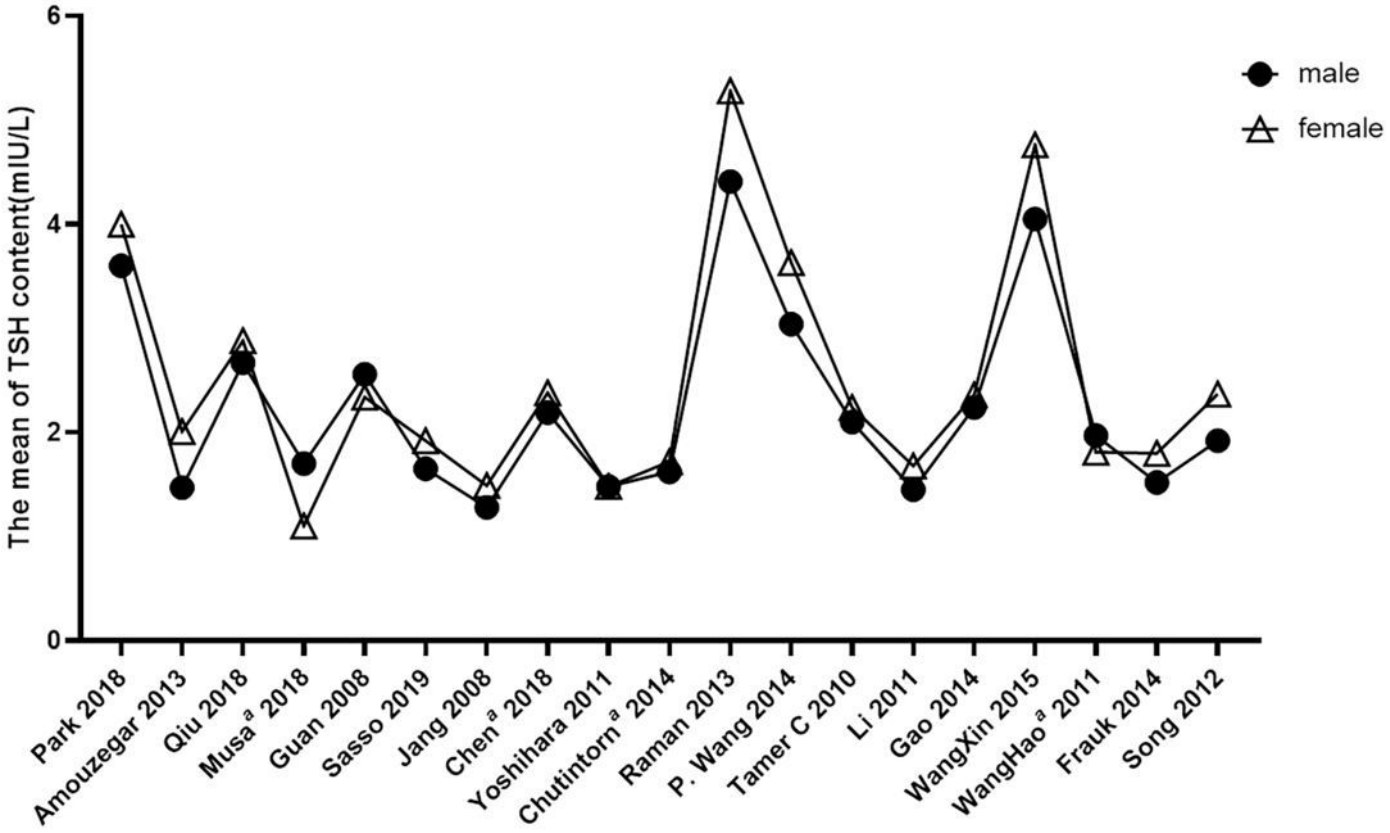

Figure 6

showed the relationship between the TSH concentration of males and females in 19 studies. a Musa et al., Chutintorn et al., Wanghao et al. and Chen et al. did not use log-transformed of TSH and used median instead of mean to represent TSH concentration directly. Other studies used mean to represent TSH concentration.

Supplementary Files

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