Systematic Review and Meta-Analysis

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A PRISMA-compliant systematic review and meta-analysis of the relationship between thyroid disease and different levels of iodine intake in mainland China

Wanwen Weng, MM, Mengjie Dong, MD*, Jun Zhan, MM, Jun Yang, MM, Bo Zhang, MB, Xingdong Zhao, MB

Abstract

Background: Low-iodine intake has historically been an issue in China, causing widespread iodine deficiency diseases (IDD). China started to introduce universal salt iodization in 1995, but reports of increased thyroid disease are a concern and appropriate levels of iodine intake must be considered.

Objective: To assess the prevalence of thyroid disease with different urinary iodine concentrations (UICs) in the general population of those residing in mainland China. Furthermore, we aimed to analyze the relationship between thyroid disease and UIC, to provide guidance in establishing effective health policies regarding iodine intake.

Methods: *PubMed*, *Cochrane*, *Embase*, *CNKI*, *Wan fang*, and *CQVIP* databases were searched for random community-based relevant studies with UIC published before January 2016 in mainland China. Two independent reviewers extracted data from eligible citations, and obtained prevalence of thyroid disease for different UICs, as well as the intergroup interaction *P* values.

Results: Forty-three articles were included. The prevalence of thyroid nodules was 22.3% (95% confidence interval [CI]: 20.6%–24.1%) for the low-iodine group, 25.4% (95% CI: 20.8%–28.8%) for the medium-iodine group, and 6.8% (95% CI: 2.8%–11.5%) for the high-iodine group. In the high-iodine group, the prevalence of thyroid nodules was lower than the other groups. The prevalence of 8.3% (95% CI: 3.8%–17.3%) for subclinical hypothyroidism in the high-iodine group was significantly higher than the low- and medium-iodine groups ($P < .01$). The prevalence of hypothyroidism in the medium-iodine group was 0.2% (95% CI: 0.1%–0.4%), and was lower than the prevalence of the other 2 groups ($P < .01$). There was no difference in prevalence of hyperthyroidism in each group.

Conclusions: Thyroid nodules are the most easily detectable thyroid disease. These have a lower prevalence in the high-iodine group. The prevalence of most thyroid diseases is lowest for a UIC ranging from 100 to 299 μg/L. This serves as a reference for health policy-making with respect to iodine levels. Further studies on this topic should be carried out according to sufficient thyroid cancer data.

Abbreviations: CIs = confidence intervals, ICCIDD = International Council for Control of IDD, IDD = iodine deficiency diseases, IIH = iodine-induced hyperthyroidism, TN = thyroid nodule(s), UIC = urinary iodine concentrations, UNICEF = United Nations International Children's Fund, USI = universal salt iodization, WHO = World Health Organization.

Keywords: mainland China, thyroid disease, urinary iodine concentration

1. Introduction

Iodine is an essential element required for normal thyroid hormone activity and regulation of thyroxine and triiodothyronine. Both insufficient and excessive iodine intake can cause thyroid hormone disorders. Low-iodine intake used to be prevalent in China, resulting in widespread iodine deficiency diseases (IDDs). Salt iodization has been widely adopted around the world since the 1990s. China started to introduce (universal salt iodization [USI]) in 1995, and salt iodization has been widely adopted since 1996. Since then, increased iodine intake has largely resulted in control of IDDs, but reports of increased thyroid disease are a public health concern and appropriate iodine-intake levels must be carefully considered. For example, what level of iodine intake will not only prevent IDD but also mitigate against thyroid diseases related to iodine excess? Therefore, we reviewed random community-based sample to perform this systematic review and meta-analysis to seek a conclusion about the relationship between iodine intake and thyroid diseases by comparing the prevalence of thyroid diseases with different UIC levels in mainland China during the last 16 years. Our study may help to identify the safe range of UIC and provide guidance on iodine intake, to reduce the prevalence of thyroid diseases.

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Department of Nuclear Medicine, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.

** Correspondence: Mengjie Dong, Department of Nuclear Medicine, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China (e-mail: dongmengjie@126.com).*

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2. Methods

2.1. Search strategy and selection criteria

The manuscripts in Chinese were collected from *CNKI* (http://www.cnki.com/), *CQVIP* (http://www.cqvip.com/), and *Wan fang*. The English manuscripts were collected from *PubMed*, *Cochrane*, and *Embase*. The search words in English database included "hyperthyroidism" or "hypothyroidism" or "thyroid cancer" or "thyroid tumor" or "thyroid tumour" or "thyriod carcinoma" or "thyroid neoplasms" or "thyroid nodule(s)" and "urine(urinary) iodine(iodides)." In Chinese database, we use Chinese words. Case reports, editorials, letters, management guidelines, studies performed in animals, and ex vivo studies were excluded. We searched the database through January 2016; although we did not limit the time when articles were published, the finally selected reports were from January 2001 to December 2015. The study is a systematic review and meta-analysis, so it does not involve the ethical issues.

Two investigators independently checked all of the retrieved articles according to the following eligibility criteria: participants from a random community-based sample, rather than from volunteers or those receiving routine health examinations; study design were population based instead of hospital-based studies; outcome contained sufficient information (e.g., survey location, survey methodology, diagnostic criteria, sample size, number of participants, urinary iodine concentration); participants must have one of the following thyroid diseases: hyperthyroidism, subclinical hyperthyroidism, hypothyroidism, subclinical hypothyroidism, thyroid cancer, thyroid nodule(s) (TN); TN requiring ultrasound results, thyroid cancer requiring pathology results, and diagnoses of other thyroid diseases had to be based on subject's thyroid function to be included; the survey areas must be in mainland China.

The following studies were excluded: participants suffering from any related diseases, or taking medication known to affect thyroid structure or function; participants were special populations (such as pregnant women, infants, or smokers) or workers in a specific occupation; UIC data taken form historical data instead of through a survey sample; and the number of "No" or "unclear" answers exceeded 5 out of the 14 questions in the QUADAS quality assessment tool (http://links.lww.com/MD/B760).

2.2. Data extraction

Two reviewers (BZ and XZ) independently extracted information relating to the author, year of survey, urine iodine value, study design, patient characteristics, kind of disease, method of diagnosis, sample size, and outcomes. To resolve disagreement between reviewers, a third reviewer assessed all discrepant items, and decision by majority was used for the analysis. In this study, we used the median UIC to classify subjects into 3 subgroups: low-iodine group with median UIC $<100\,\mu g/L$; medium-iodine group with median UIC in the range of 100 to $299\,\mu g/L$; high-iodine group with median UIC $>300\,\mu g/L$.

2.3. Study design characteristics

We use the QUADAS quality assessment tool to extract relevant study design characteristics from each study. This tool and the definitions of the characteristics are fully described by Penny Whiting.[1] This was the first systematically developed evidence-based quality assessment tool to be used in systematic reviews of diagnostic accuracy studies. Two investigators independently assessed whether each item of QUADAS was fulfilled (yes, no, or unclear).

2.4. Statistical analysis

The Begg rank correlation method was used to assess the potential for publication bias ($P<.05$ was considered indicative of statistically significant publication bias). The prevalence and 95% confidence intervals (CIs) were used to estimate the prevalence of individual and pooled groups of hypothyroidism, subclinical hyperthyroidism, hyperthyroidism, subclinical hypothyroidism, TN, and thyroid cancer in mainland China. Heterogeneity between studies was calculated with Cochran Q test (reported as χ^2 and P values) and the I^2 statistic, which describe the percentage of variation between studies. Values of 25%, 50%, and 75% reflected low, moderate, and high degrees of heterogeneity, respectively. For a moderate or high level of heterogeneity, we adopted a random-effects meta-analysis rather than a fixed-effects model. We calculated data using the R software package (version 3.2.2). For analysis of the 3 subgroups, we reported an interaction P value.[2]

3. Results

3.1. Study selection

We identified 1368 potentially relevant publications in the electronic databases. Employing the selection criteria, we obtained quantitative data for our meta-analysis after reading all titles, abstracts, and full texts. A total of 43 studies involving 247 trials were identified for inclusion in the review. Figure 1 portrays our systematic workflow for identifying, screening, and including studies[3–45] in the systematic review.

3.2. Characteristics of papers

The total number of subjects in the selected studies was 178,995, distributed in 14 provinces of mainland China, with ages ranging from 6 to 83. Nineteen studies considered only one type of thyroid disease, and 18 studies considered 4 or more types of thyroid diseases. All studies were based on samples from the general population. The mean QUADAS score, expressed as a percentage of the maximum score, was 85.7% (range, 71.4%–92.9%). Publication bias was observed as assessed by the Begg rank correlation analysis ($P=.0016$). Table 1 provides a summary of these studies.

3.3. Pooled prevalence of thyroid diseases

Table 2 and Figures 2 and 3 show the pooled and individual group prevalence of thyroid diseases. Thyroid nodule(s) had the highest pooled prevalence among all thyroid diseases (21.2%, 95% CI: 17%–25.7%) with the second being subclinical hypothyroidism (5%, 95% CI: 3.5%–6.8%) ($P<.01$). Thyroid cancer had the lowest prevalence (0.1%, 95% CI: 0%–0.3%) for all thyroid diseases.

The prevalence of TN in the high-iodine group was 6.8% (95% CI: 2.8%–11.5%) and the prevalence was significantly lower compared with the low- and medium-iodine groups ($P<.01$). Figures 4 to 6 are the forest plots that show the prevalence of TN with different urinary iodine concentration. The prevalence of subclinical hypothyroidism was 2.7% (95% CI: 1.8%–4.1%) for the medium-iodine group and 8.3% (95% CI: 3.8%–17.3%) for

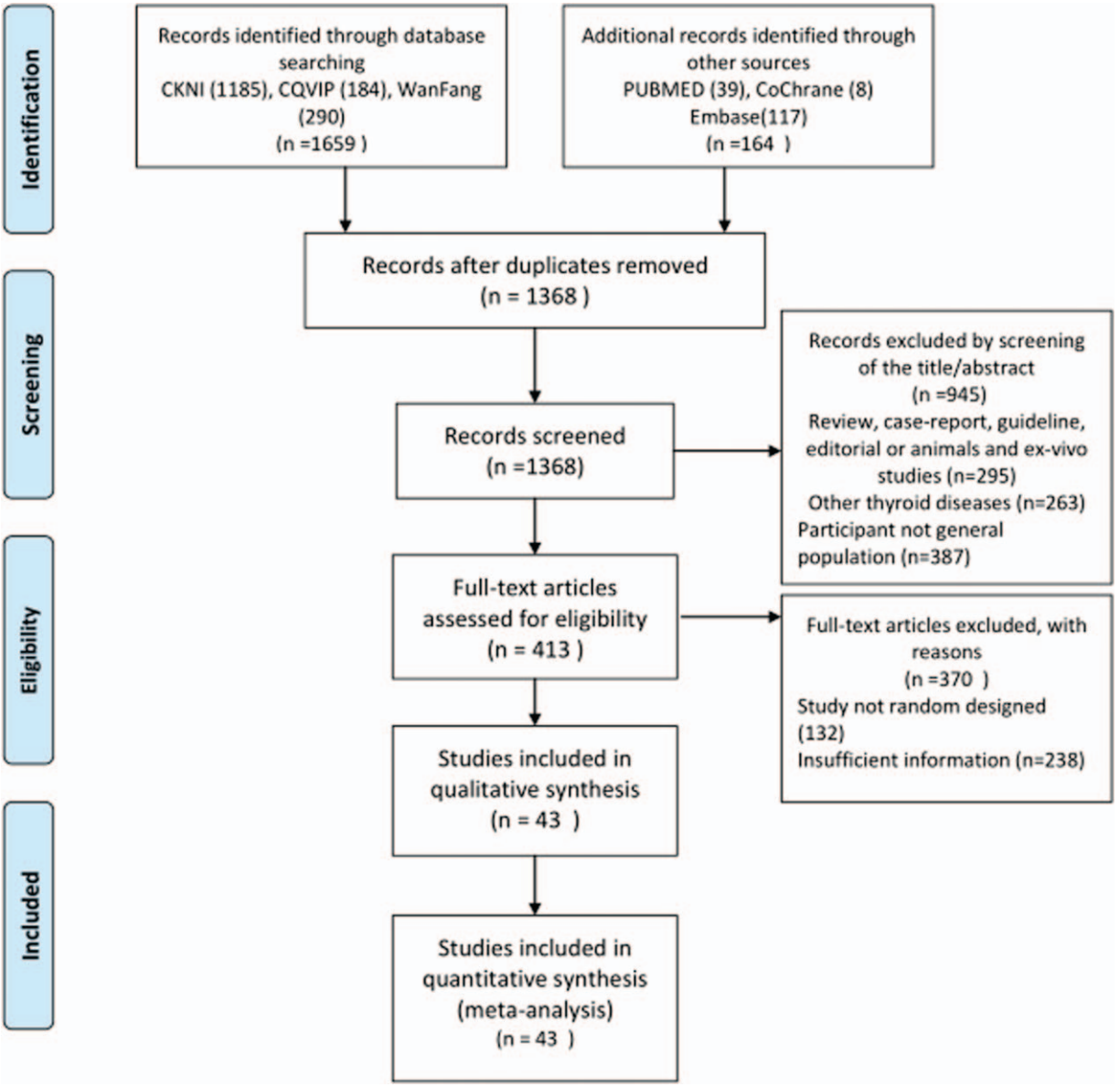

Figure 1. The systematic review workflow.

the high-iodine group. The prevalence of the high-iodine group was significantly higher than the low- and medium-iodine groups ($P < .01$). The prevalence of hypothyroidism in the medium-iodine group was 0.2% (95% CI: 0.1%–0.4%) and it was lower than the prevalence of the other 2 groups ($P < .01$). The prevalence of hyperthyroidism in each group was not significantly different.

4. Discussion

Iodine is mainly derived from the diet and the most absorbed iodine is excreted in the urine. According to the World Health Organization (WHO), the United Nations International Children's Fund (UNICEF), and the International Council for Control of IDD (ICCIDD) recommended standards, a UIC normal range is 100 to 199 μg/L, UIC <100 μg/L determines iodine deficiency, a UIC between 200 and 299 μg/L is exceeding appropriate scope, and a UIC ≥300 μg/L is an excess of iodine nutrition. As USI policy was established, public health authorities have been committed to eliminating IDD and have obtained satisfactory results. For example, China reached its goal of eliminating IDD in 1999. However, the change in iodine intake and its influence on thyroid diseases, especially when UIC ≥300 μg/L, has not been systematically researched.

Our study reveals that TN had the highest prevalence among all thyroid diseases. Other research also shows that TN are one of the commonest types of thyroid disease. The US Marshall Islands has a moderate level of iodine deficiency and has a TN prevalence of 28%.[46] Völzke et al[47] reported an area, which was historically mildly iodine deficient, but now the population consumes more than what is considered normal iodine intake and has a TN prevalence of 20.2%. The prevalence of TN in China is similar to other countries and regions. For example, a recent study in Zhejiang province revealed a TN prevalence of 20.9% for a median UIC of 163 μg/L.[48] These data are consistent with our results.

Table 1

Characteristics of studies.

First author	Location	Publication year	Sample size	Age	UIC (μg/L)	Type of thyroid diseases
Guo XW[3]	Shandong	2013	103	7–12	319.3	D
Teng W[4]	Liaoning	2006	1103	36±13	103	A; B; C; D; E; F
			1584	39±13	375	
			1074	37±13	615	
Xiong RQ[5]	Fujian	2015	89	26–69	173.2	F
			100		243	
			97		128.3	
Zhou GF[6]	Zhejiang	2014	1124	>6	152	F
Zhu WY[7]	Zhejiang	2012	1389	>20	320.7	E
			502		188.9	
			737		122.2	
			294		271.7	
			362		193.6	
Wang J[8]	Jilin	2002	7799	16–72	283.43	A
			9370		213.69	
			7218		267.83	
Zhu WY[9]	Zhejiang	2009	230	>20	185	A; D; F
			230		286.8	
Zhang KZ[10]	Fujian	2002	10,454	Residents	57	A
			1032		25	
			3473		210	
			2394		409	
Ding GQ[11]	Zhejiang	2012	689	8–10	180.5	A; F
Gao TS[12]	Liaonin	2001	116	6–10	99	A; B; C; D
			110	7–10	338	
			112	6–11	631	
Xu QH[13]	Zhejiang	2013	890	Residents	192.3	F
Huan YM[14]	Zhejiang	2011	770	>18	120	A; B; C; D
			705		188.73	
Dou YG[15]	Gansu	2014	104	18–45	189	A; B; C; D
Jiao LS[16]	Shandong	2015	482	6–15	437.7	F
Liao M[17]	Guangxi	2015	637	52.07±15.02	62.5	A; B; C; D; F
Wu HY[18]	Hannan	2013	330	8–10	195.4	B; D
			330	Childbearing age	171.1	
Meng H[19]	Zhejiang	2015	827	45.12±18.32	162.74	F
Shen Y[20]	Shanghai	2013	695	>14	122.8	F
Hou CC[21]	Tianjin	2015	506	18–69	168.1	F
Weng CX[22]	Zhejiang	2008	1045	18–23	249	A; C; F
			1112	25–50	509	
			1215	25–50	512	
			1021	25–50	238	
Ye Z[23]	Zhejiang	2014	226	3–89	163	G
			223		125	
			334		161	
			297		140	
			1277		138.6	
Wang CW[24]	Zhejiang	2013	707	>8	117.06	A; B; C; D; F
			117		182.57	
Mo Z[25]	Zhejiang	2011	18,956	45.23±18.88	160.74	F
Yang NZ[26]	Zhejiang	2012	793	>6	178.25	F
Zhu WY[27]	Zhejiang	2011	1389	46±13	320.7	C; D
			502		188.9	
			737		122.2	
			362		193.6	
			294		271.7	
Zhao CY[28]	Zhejiang	2012	1389	46±13	320.7	A; B
			502		188.9	
			737		122.2	
			362		193.6	
			294		271.7	

(*continued*)

Table 1

(continued).

First author	Location	Publication year	Sample size	Age	UIC (μg/L)	Type of thyroid diseases
Yan SL[29]	Shandong	2004	554	7–14	316.03	A
			543		302.6	
			437		264.74	
			610		277.28	
			330		328.44	
			570		289.52	
			562		232.51	
Zhang GQ[30]	Hebei	2015	506	Adult	1152.01	A; B; C; D
			348		185.2	
Miao HH[31]	Fujian	2015	6098	38.77 ± 20.74	161.6	A; C; E
			8387		156.8	
			3108		146.8	
			3592		206.9	
Li HQ[32]	Hebei	2012	300	46.71 ± 10.77	1094.92	A;B;C;D
Bao CH[33]	Zhejiang	2014	2463	8–70	140.12	F
Zhao XF[34]	Zhejiang	2015	1131	6–80	112.54	F
Zhou YL[35]	Jiangsu	2008	17,471	Residents	1961	A; B; C; D; E
			12,765		255.1	
Chen ZX[36]	Zhejiang	2013	9412	>6	172.55	F
Liu L[37]	Hebei	2011	1575	>20	439	E
			1258		198	
Liu LX[38]	Guangxi/Shanxi	2015	106	26.59 ± 4.88	51.3	A; B; C; D; F
			104	25.53 ± 3.60	282.42	
			133	25.49 ± 3.30	822.51	
Peng NC[39]	Guizhou	2013	1509	20–78	198	A; B; C; D
Zou SR[40]	Shanghai	2012	5168	5–69	146.7	A; B; C; D; F
Chen W[41]	Hebei	2012	371	7–13	1032.8	A; B; C; D
Teng XC[42]	Liaoning	2011	1905	47.26 ± 15.96	145	A; B; C; D
			1908	46.32 ± 15.85	261	
Teng XC[43]	Liaoning	2008	213	>13	78.1	A; B; C; D
			354		113.8	
			211		233.3	
Gu XL[44]	Liaoning	2013	1004	>20	224.96	A; B; C; D
Yang D[45]	Shanxi/Shandong	2014	861	>18	750.18	A; B; C; D; F
			509		228.70	
			667		62.03	

A = hyperthyroidism, B = subclinical hyperthyroidism, C = hypothyroidism, D = subclinical hypothyroidism, E = thyroid cancer, F = thyroid nodule, UIC = urinary iodine concentrations.

It is well known that excessive intake of iodine may induce thyroid disease, but we found the prevalence of TN was 6.8% (95% CI: 2.8%–11.5%) for the high-iodine group, which was lower than the other 2 groups. There are few studies that have explored the associations between excessive iodine intake and TN in adult populations. Szabolcs et al[49] reported the prevalence of TN as being 20.2%, 16.2%, and 3.3% for iodine deficiency, iodine prophylaxis, and abundant iodine intake, respectively. One study of company employees found that the prevalence of multiple TN decreased from 25.51% to 12.99% with increasing UIC, with a clear downward trend ($P < .01$).[50] However, the author of that study concluded that there were no associations between iodine intake and TN based on multivariate logistic regression analysis. In previous studies, the prevalence of TN has depended on sex, age, and head-and-neck radiation exposure history.[51,52] There is no direct evidence to prove that excessive iodine intake can increase the incidence of TN. Whether high-iodine urine levels decrease the risk of TN warrants further research.

In our study, the prevalence of subclinical hypothyroidism was the second most common type of thyroid disease for low-,

Table 2

Prevalence of thyroid disease by different group.

	Pooled	95% CI	Low	95% CI	Medium	95% CI	High	95% CI
Hyperthyroidism	0.007	0.005–0.009	0.008	0.005–0.015	0.006	0.004–0.008	0.009	0.005–0.015
Subclinical hyperthyroidism	0.012	0.007–0.017	0.023	0.011–0.047	0.009	0.006–0.014	0.016	0.009–0.027
Hypothyroidism	0.005	0.003–0.007	0.013	0.004–0.037	0.002	0.001–0.004	0.011	0.006–0.021
Subclinical hypothyroidism	0.050	0.035–0.068	0.023	0.015–0.036	0.027	0.018–0.041	0.083	0.038–0.173
Thyroid nodule(s)	0.212	0.170–0.257	0.223	0.206–0.241	0.254	0.208–0.288	0.068	0.028–0.115
Thyroid cancer	0.001	0.000–0.003	—*	—	0.001	0–0.03	0.002	0.001–0.01

CI = confidence interval.

* There are no statistics on the prevalence of thyroid cancer in the low-iodine group due to lack of data.

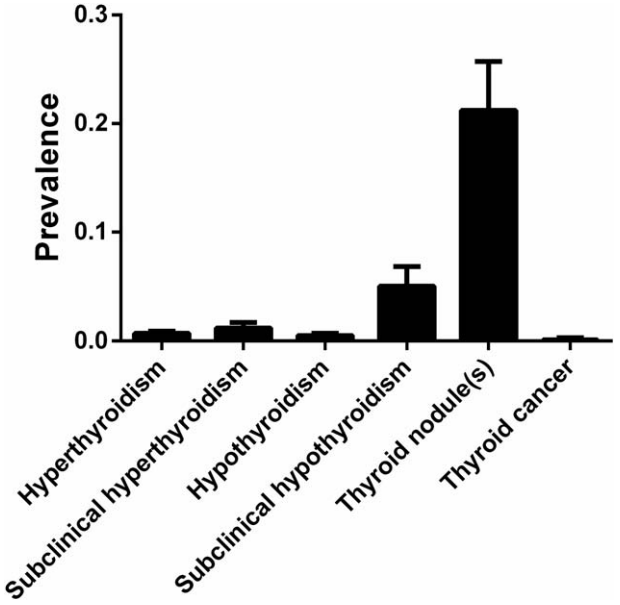

Figure 2. Pooled prevalence of thyroid disease.

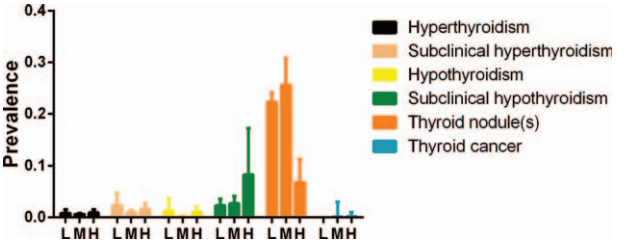

Figure 3. Prevalence of thyroid disease with different urinary iodine concentration.

medium-, and high-iodine groups. The prevalence was higher than in the low- and medium-iodine groups. Szabolcs et al[49] conducted an investigation of 346 senior subjects, and found that the prevalence of subclinical hypothyroidism was 4.2%, 10.4%, and 23.9%, respectively, for regions with UIC of 72, 100, and 513 μg/L, that is, the prevalence increased with increasing iodine intake. The previous conclusion was that subclinical hypothyroidism was related to thyroid antibodies, TPOAb and TgAb. However, a recent study[53] revealed that subjects with subclinical hypothyroidism had only a 20.6% TPOAb seropositivity rate and a 21.2% TgAb seropositivity rate, indicating that autoimmune factors might not be the most important factors in the mechanism of subclinical hypothyrodism. In an animal model,[54] it was shown that prolonged high-iodine intake inhibited pituitary type 2 deiodinase activities and increased the serum TSH level.

The prevalence of hypothyroidism is also related to iodine intake. UIC <100 μg/L indicates iodine deficiency, and iodine-deficiency disorders include hypothyroidism.[55] It is widely reported that high-iodine intake causes an increase in the prevalence of hypothyroidism,[49,53,56] and it is an independent risk factor in precipitating hypothyroidism.[57] This trend is true for children as well as for adults. There is a higher prevalence rate of hypothyroidism among subjects in high-iodine regions compared with other regions. In vitro experiments have proven that excessive iodine intake may cause thyroid follicle apoptosis.[58] Our study reveals that the prevalence of hypothyroidism was 0.2% in the medium-iodine group, 1.3% in the low-iodine group, and 1.1% in the high-iodine group. As hypothyroidism is closely related to hyperlipidemia, heart disease, and neurological diseases, iodine and its correlation with health defects must be taken seriously.

The most common complication of iodine intervention is iodine-induced hyperthyroidism (IIH). When too much iodine is ingested, the thyroid can develop a high tolerance to iodine, with possible regulation mechanisms, including lowering of TSH level; reduction in activity level and amount of sodium–iodine symporter; and the Wolff–Chaikoff effect of short-term blockage of iodine intake.[59] However, individual subjects have very different levels of tolerance to high-iodine intake. After approximately 100 years of iodized salt being ingested around the world, the prevalence of IIH is almost inevitable. There have been multiple reports of IIH in China since the adoption of the policy of iodized salt was introduced in 1995. Since the Netherlands adopted mandatory iodized bread, the prevalence of IIH has increased 20-fold.[60] Delange et al[61] believe that IIH typically occurs after a general increase in increased iodine intake or if medication containing iodine is ingested, and is more common among adults aged >40 with nodular goiter in very low-iodine regions. It is commonly accepted that the increase in IIH is an inevitable consequence of a salt iodization policy, but eventually the prevalence of IIH drops back to levels before salt iodization intervention.[62] Our study indicates that the prevalence of hyperthyroidism was not significantly different among different groups, possibly because the data were gathered

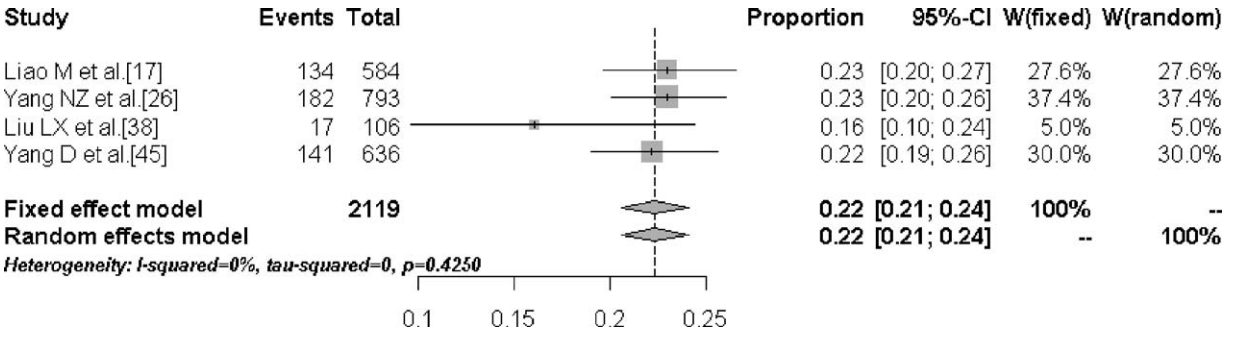

Figure 4. Forest plot displaying the prevalence of thyroid nodules with low urinary iodine concentration.

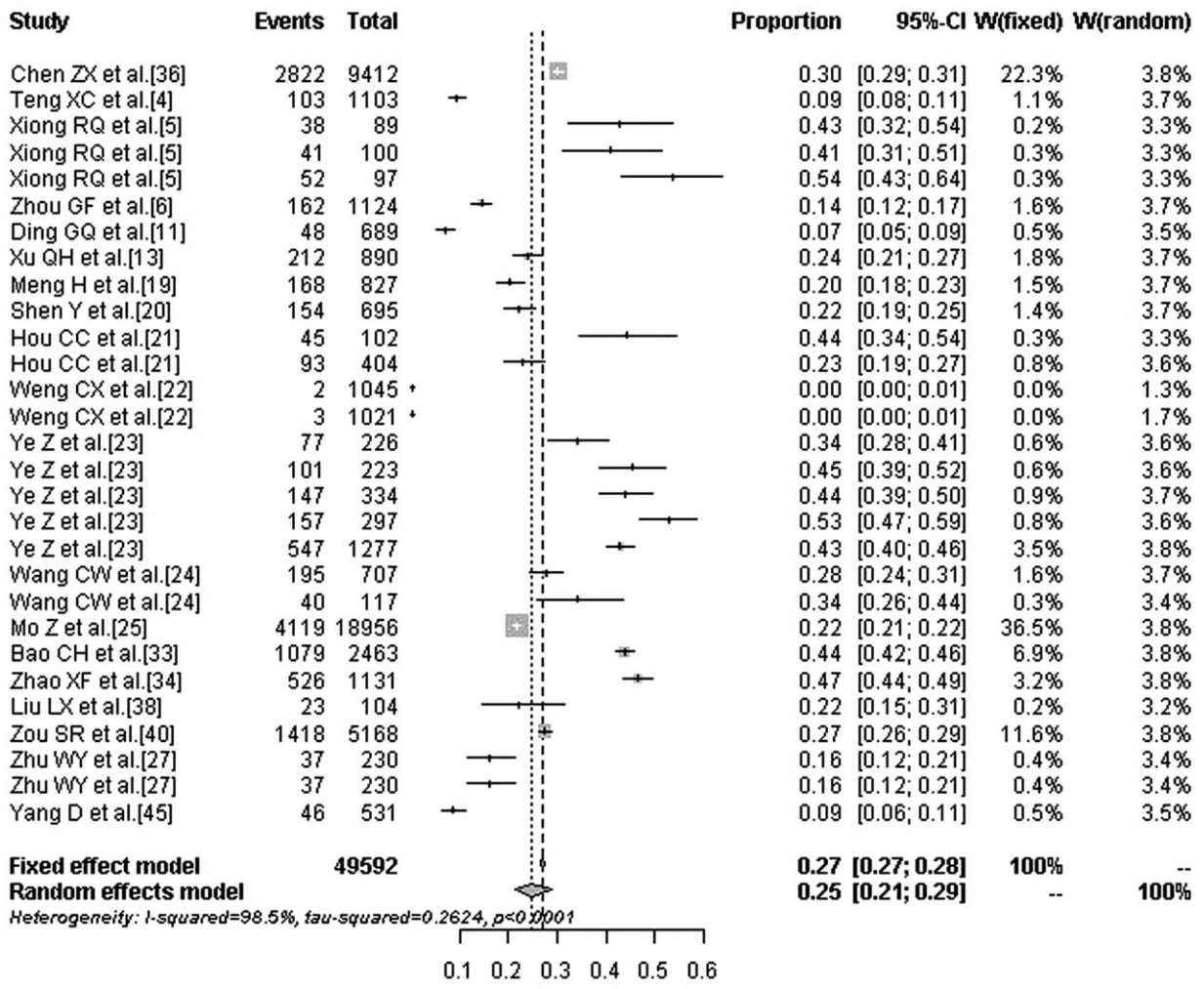

Figure 5. Forest plot displaying the prevalence of thyroid nodules with medium urinary iodine concentration.

6 to 10 years after USI adoption, hence the prevalence rate of IIH had dropped.

It is commonly accepted that the prevalence of thyroid cancer is related to multiple fractionizing radiation, genetic susceptibility, benign TN, and other determinants. There is no clear correlation between iodine intake and thyroid cancer. A case-control study in Sweden[63] indicated that the prevalence of follicular thyroid carcinoma was closely related to iodine deficiency. An epidemiological study in Greece[64] indicated that papillary carcinoma of the thyroid accounted for 84% of all thyroid diseases among

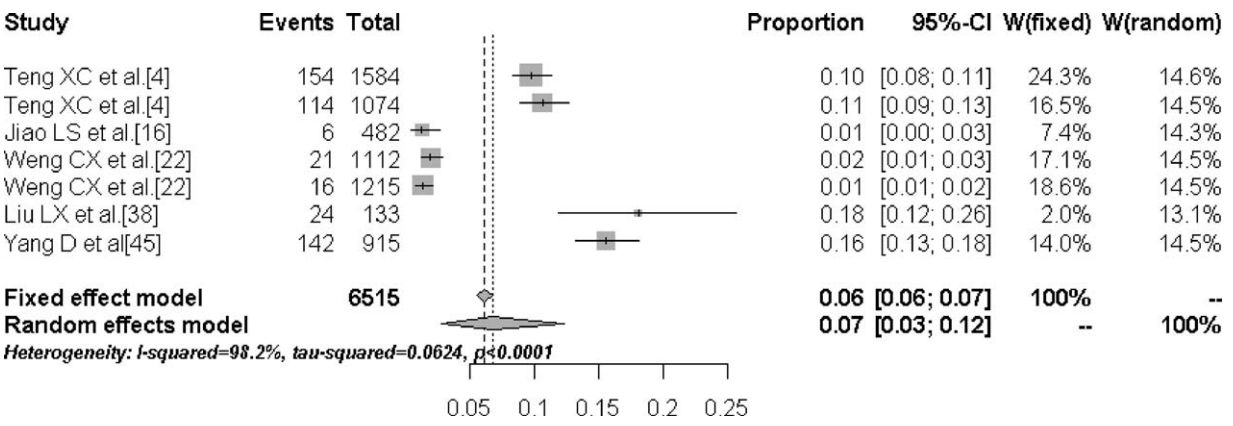

Figure 6. Forest plot displaying the prevalence of thyroid nodules with high urinary iodine concentration.

subjects in high-iodine regions, which was much higher than subjects in low-iodine regions. Some other studies have also indicated that the prevalence of thyroid cancer is not very different between subjects in high-iodine regions and low-iodine regions. However, the types of thyroid diseases were different: follicular carcinoma was more common in low-iodine regions, whereas papillary carcinoma was more common in high-iodine regions.[65,66] In this study, there were only 5 papers[4,7,31,35,37] based on random population surveys, and supported by pathology. There were no statistics on the prevalence of thyroid cancer in the low-iodine group due to lack of data, whereas the prevalence of thyroid cancer was 0.1% (95% CI: 0%–3%) in the medium-iodine group and 0.2% (95% CI: 0.1%–1%) in the high-iodine group.

The relationship between the iodine intake level of a population and the occurrence of thyroid diseases is U-shaped with an increase in risk from both low- and high-iodine intake levels.[67] There is a relatively narrow range for optimal intake; disease is more likely to develop in the populations with iodine intake above and below this range. In our study, the prevalence of thyroid diseases was lowest when the UIC was in the range of 100 to 299 μg/L. An individual's iodine intake is determined by multiple factors, including the environmental iodine concentration levels, dietary habits, and absorptive capacity. The environmental iodine concentration level varies widely among different regions in China. A study of IDD in 2005 indicated that the average UIC was 246 μg/L, and >5 provinces had a UIC exceeding 300 μg/L.[68] In our study, different subjects in the same region may have widely varying iodine levels, therefore it may not be sufficient to adopt a unified standard of iodine intake. If possible, UIC measurements and dietary evaluation should be conducted to determine if it is necessary to ingest iodinated salt, and keep a UIC in the recommended range of 100 to 299 μg/L, to prevent thyroid diseases.

There are several limitations to our study. First, the studies were limited to 14 provinces, among a total of 34 administrative regions in China. Second, no definitive conclusions can be drawn on thyroid cancer due to lack of data. Our future work includes collecting more data on thyroid cancer to explore the relationship between thyroid cancer and iodine intake.

5. Conclusions

Thyroid nodules are the most easily detectable thyroid disease. These have a lower prevalence in the high-iodine group. Subclinical hypothyroidism was the second most common type of thyroid disease. The prevalence of most thyroid diseases is lowest for UIC range of 100 to 299 μg/L. This serves as a reference for health policy-making with respect to iodine levels.

Acknowledgments

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