

## Original Article

# Urine iodine level and multiple risks are associated with thyroid structural abnormalities among adults in Heilongjiang Province, China

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**Background and Objectives:** The prevalence of adult thyroid structural abnormalities has increased significantly worldwide. However, no study has examined the thyroid structure and urine iodine levels of adults in Heilongjiang Province in the last decade. Therefore, this study aims to investigate the rate and risk factors of thyroid structural abnormalities among the residents of this province. **Methods and Study Design:** A probability proportional sampling method was used, and a total of 3,645 individuals in Heilongjiang Province were included. The subjects were asked to complete a thyroid ultrasound and fill out a questionnaire. Furthermore, urine iodine levels and salt iodine content were determined, and multivariate logistic regression was used to identify the independent risk factors for thyroid diseases. **Results:** The prevalence of thyroid structural abnormalities in Heilongjiang Province was 56.0%. Univariate analysis showed that there were significant differences between the structural abnormalities group and the normal thyroid group in terms of sex, age, body mass index, hypertension, diabetes, smoking, alcohol consumption, frequency of seafood consumption and pickled food consumption, employment status, and urine iodine level ( $p < 0.05$ ). Multivariate analysis showed that the following were independent risk factors of thyroid disease: female, increased age, hypertension, diabetes, cigarette smoking frequent seafood consumption, employment, and urine iodine levels. **Conclusions:** The prevalence of thyroid structural abnormalities in adults in Heilongjiang Province was relatively high. Therefore, to help prevent the occurrence of thyroid disease in adults in Heilongjiang Province, the risk factors of thyroid structural abnormalities should be better understood.

**Key Words:** thyroid ultrasound, epidemiology, independent risk factor, urine iodine, universal salt iodization

## INTRODUCTION

Thyroid diseases are common in adults,<sup>1,2</sup> and the prevalence of thyroid diseases has been reported to have reached 26%–67% in recent years.<sup>3–5</sup> Thyroid diseases are closely related to lifestyle and dietary habits.<sup>6,7</sup> Iodine deficiency or excess iodine can lead to thyroid diseases because iodine is the major raw material for the synthesis of thyroid hormones.<sup>8,9</sup> China has been reported to have widespread and serious iodine deficiency diseases. Thus, China has implemented a policy of universal salt iodization since 1996,<sup>10</sup> and the salt iodine content has been adjusted several times to reduce the incidence of thyroid diseases.<sup>11,12</sup> However, no investigative report with a large sample size has been conducted on thyroid structure and urine iodine levels in adults in Heilongjiang Province in the last decade. The current study is the first study in 10 years that analyzed the prevalence and independent risk factors of thyroid structural abnormalities among adults in Heilongjiang Province in terms of their living habits, salt iodine content, and urine iodine levels.

## METHODS

### *Study participants and methods*

#### **Participants**

A probability proportional sampling method was used to sample adults from 15 cities and 15 townships in 30 research sites in Heilongjiang Province, China, from December 12, 2017, to November 10, 2018. The inclusion criteria were participants aged between 20 and 70 years old and participants residing in the region for >1 year. The exclusion criteria included pregnant women, participants with a history of neck radiotherapy, and participants who had consumed iodine-containing food within three days prior to the study examination or during the study examination period. In the end, 3,645 participants were

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included in the study. The investigation was approved by the ethics committee of Harbin Medical University, and informed consent was obtained from the participants.

### Methods

Each subject was required to finish the questionnaire, perform thyroid ultrasound examination, and collect urine and edible salt samples for iodine content determination. A thyroid ultrasound exploration was conducted with the Esaote portable ultrasound system (MyLab30cv, Italy) and a linear array high-frequency probe at a frequency of 6–15 MHz. Patients with thyroid glands that have a flat capsule, homogeneous parenchymal echoes, and normal echo areas or nodules were classified as the normal thyroid gland group, and those with a diffuse enlargement of the thyroid gland, diffuse enhancement, reduced or rough echoes, focal echo changes, and nodular lesions were classified as the thyroid structural abnormalities group.<sup>13–15</sup>

Relevant information concerning the participants was obtained using a uniformly formulated questionnaire, including gender, age, height, weight, hypertension, diabetes, cigarette smoking, drinking, seafood intake frequency, pickled food intake frequency, and employment status. The subjects were divided into 5 groups according to age: 20–29 years old (group A), 30–39 years old (group B), 40–49 years old (group C), 50–59 years old (group D), and 60–70 years old (group E). The body mass index (BMI) was calculated as the weight (kg) divided by the square of height (m<sup>2</sup>). According to BMI, the individuals were placed into four groups: underweight (<18.5), healthy weight (18.5 to ≤24.9), overweight (25 to ≤30), and obese (≥30).<sup>16</sup> Participants with hypertension (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg) were classified as a hypertension group.<sup>17</sup> For blood glucose, participants were classified as a diabetes group (fasting blood glucose level ≥6.1 mmol/L or blood glucose level ≥7.8 mmol/L at two hours after glucose load) and a non-diabetes group.<sup>18</sup>

For smoking status, there was a smoking (more than one cigarette per day for >2 years) and nonsmoking group. For alcohol consumption, men consuming >0.54 mol of alcohol per day or women consuming >0.33 mol of alcohol per day were assigned to an excessive alcohol consumption group;<sup>19</sup> otherwise, considered “non-overdose”. Frequency of seafood intake was assigned to one of two groups: frequent (regularly consumed seafood ≥3 times per week) or infrequent. Pickled food consumption, frequent (regularly consumed ≥3 times per week) and infrequent were recognised. Employment status was occupied or non-occupied.

### Urine iodine and salt iodine

A morning urine sample was collected from each participant. And the urine iodine level was determined using As<sup>3+</sup>-Ce<sup>4+</sup> catalytic spectrophotometry.<sup>20</sup> The urine iodine levels were assessed in six groups: <20 µg/L (group I), 20–49 µg/L (group II), 50–99 µg/L (group III), 100–199 µg/L (group IV), 200–299 µg/L (group V), and ≥300 µg/L (group VI).<sup>21</sup>

Each participant brought a sample of salt from home and the salt iodine content was determined using the di-

rect titration method.<sup>22</sup> Salt iodine content was grouped into four: noniodized salt (<5 mg/kg), low iodized salt (5 mg/kg to <18 mg/kg), appropriately iodized salt (18–33 mg/kg), and highly iodized salt (>33 mg/kg).<sup>12</sup> Internal quality control samples of salt iodine and urinary iodine were provided by the Reference Center of Iodine Deficiency Disorders of the China CDC.

### Statistical analysis

Data were entered in Excel 2019 by specialized personnel and were independently checked to ensure objectivity and accuracy. The statistical analyses were performed using R version v1.2.1335. Data that conformed to normal distributions were expressed as mean ± standard deviation. Data that did not conform were expressed as medians. Enumerations were expressed using frequency or percentage, and chi-squared tests were used to compare groups. Univariate analyses and multivariate logistic regression analysis were used to assess factor relationships to disease incidence. Statistical significance was set at  $p < 0.05$ .

## RESULTS

### Epidemiological characteristics of thyroid structural abnormalities

The total number of study participants was 3,645 (average age: 48.7±12.4 years; males: 48.1±13.0 y; females: 48.9±12.1 y). The prevalence of thyroid structural abnormalities was 56.0% (females: 61.4%; males: 44.0%). The prevalence in females was significantly higher than in males ( $\chi^2=56.9$ ,  $p < 0.05$ ). Significant differences were observed in thyroid structural abnormalities among the different age groups. In groups A, B, C, D, and E, the prevalences of thyroid structural abnormalities were 34.8%, 42.2%, 54.6%, 60.3%, and 70.1%, respectively. Among these groups, the highest prevalence of thyroid structural abnormalities was found in the 60–70 years age group. The prevalence rate of thyroid structural abnormalities increased with age ( $\chi^2=176$ ,  $p=0.00$ ). (Table 1 and Figure 1).

### Univariate analysis on risk factors influencing thyroid structural abnormalities

Univariate analysis was performed for sex, age, BMI, hypertension, diabetes, cigarette smoking, alcohol consumption, seafood consumption frequency, pickled food consumption frequency, employment status, urine iodine levels, place of residence and salt iodine content. Differences between the thyroid structural abnormalities and normal group were found for sex ( $\chi^2=94.4$ ,  $p < 0.001$ ), age ( $\chi^2=176$ ,  $p < 0.001$ ), BMI ( $\chi^2=15.3$ ,  $p < 0.01$ ), hypertension ( $\chi^2=141$ ,  $p < 0.001$ ), diabetes ( $\chi^2=88.4$ ,  $p < 0.001$ ), cigarette smoking ( $\chi^2=37.3$ ,  $p < 0.001$ ), alcohol consumption ( $\chi^2=14.8$ ,  $p < 0.001$ ), seafood consumption frequency ( $\chi^2=131$ ,  $p < 0.001$ ), pickled food consumption frequency ( $\chi^2=69.2$ ,  $p < 0.001$ ), employment status ( $\chi^2=779$ ,  $p < 0.01$ ), and urine iodine level ( $\chi^2=26.7$ ,  $p < 0.001$ ). However, there were no differences between the urban and rural groups or among the different salt iodine level groups ( $p > 0.05$ ) (Table 1).

**Table 1.** Prevalence of thyroid structural abnormalities in different groups

Factor	Normal	Structural abnormalities	Prevalence rate (%)	$\chi^2$	<i>p</i> -value
Sex					
Female	974	1549	61.4	94.4	<0.001
Male	628	494	44.0		
Age				176	<0.001
Group A	202	108	34.8		
Group B	338	247	42.2		
Group C	402	483	54.6		
Group D	416	633	60.3		
Group E	244	572	70.1		
BMI				15.3	<0.01
Low body weight	90	67	42.7		
Normal body weight	984	1241	55.8		
Overweight	448	641	58.9		
Obesity	80	94	54.0		
Hypertension				141	<0.001
Non-hypertension	1469	1571	51.7		
hypertension	133	472	78.0		
Diabetes				88.4	<0.001
Non-diabetes	1569	1843	54.0		
diabetes	33	200	85.8		
Cigarette smoking status				37.3	<0.001
Non-smoking	1342	1541	53.5		
Smoking	260	502	65.9		
Alcohol consumption				14.8	<0.001
Non-excess	1443	1753	54.8		
Excess	159	290	64.6		
Seafood consumption				131	<0.001
Occasionally	1461	1570	51.8		
Often	141	473	77.0		
Pickled food consumption				69.2	<0.001
Occasionally	1127	1162	50.8		
Often	475	881	65.0		
Employment status				779	<0.01
Occupation	811	185	18.6		
Nonoccupation	791	1858	70.1		
Urine iodine				26.7	<0.001
Group I	21	40	65.6		
Group II	94	152	61.8		
Group III	260	330	55.9		
Group IV	668	721	51.9		
Group V	362	460	56.0		
Group VI	197	340	63.3		
Place of residence				0.0	0.83
Urban	877	1110	55.9		
Rural	725	933	56.3		
Salt iodine				1.6	0.67
Non-iodized salt	194	269	58.1		
Lowly iodized salt	41	46	52.9		
Appropriately iodized salt	1336	1683	55.7		
Highly iodized salt	31	45	59.2		
Total	1602	2043	56.0		

### **Multivariate logistic regression analysis of risk factors influencing thyroid structural abnormalities**

Factors were included in the multivariate analysis on the basis of the univariate analyses. Multivariate logistic regression analysis showed that being female (odds ratio [OR]=2.07 [1.74–2.48],  $p<0.001$ ), increased age (OR=1.03 [1.02–1.04],  $p<0.001$ ), hypertension (OR=2.55 [1.97–3.33],  $p<0.001$ ), diabetes (OR=2.39 [1.54–3.81],  $p<0.001$ ), cigarette smoking (OR=2.01 [1.55–2.60],  $p<0.001$ ), frequent seafood consumption (OR=1.75 [1.37–2.25],  $p<0.001$ ), employment (OR=10.1 [8.34–

12.3],  $p<0.001$ ), and urinary iodine (OR=1.001 [1.0006–1.0016],  $p<0.001$ ) were independent risk factors for thyroid structural abnormalities ( $p<0.001$ ). By contrast, BMI, excessive alcohol consumption, and pickled food consumption frequency were not ( $p>0.05$ ) (Table 2).

### **Risk factors for thyroid structural abnormalities in urban residents**

The univariate analyses showed differences in prevalences for 9 univariate groupings, namely, sex, age, hypertension, diabetes, cigarette smoking, seafood consumption

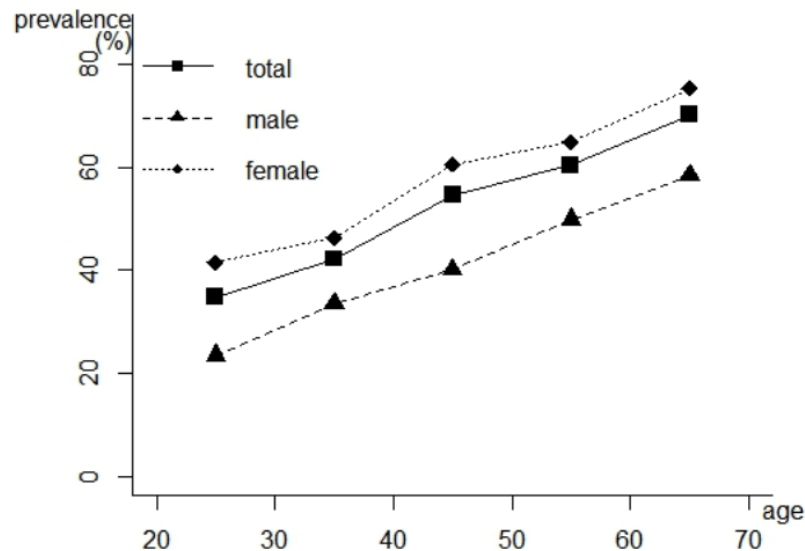


Figure 1. Prevalence of thyroid structural abnormalities in different sexes and ages.

Table 2. Logistic regression analysis for risk factors of thyroid structural abnormalities

Influencing factor	OR	95% CI	p-value
Female	2.07	1.74-2.48	<0.001
Age	1.03	1.02-1.04	<0.001
BMI	1.000	NA-1.00	0.846
Hypertension	2.55	1.97-3.33	<0.001
Diabetes	2.39	1.54-3.81	<0.001
Smoking	2.01	1.55-2.60	<0.001
Excessive alcohol consumption	0.925	0.679-1.26	0.620
Frequent seafood consumption	1.75	1.37-2.25	<0.001
Frequent pickled food consumption	1.19	1.00-1.41	0.053
Occupation group	10.1	8.34-12.3	<0.001
Urine iodine	1.001	1.0006-1.0016	<0.001

CI: confidence interval; OR: odds ratio.

frequency, pickled food consumption frequency, employment status, and urinary iodine (Supplementary table 1). The multivariate logistic regression revealed eight independent risk factors for thyroid structural abnormalities among urban residents: female sex (OR=2.11 [1.64–2.73],  $p<0.001$ ), increased age (OR=1.03 [1.02–1.04],  $p<0.001$ ), hypertension (OR=2.38 [1.63–3.53],  $p<0.001$ ), diabetes (OR=2.27 [1.14–4.82],  $p<0.05$ ), cigarette smoking (OR=2.36 [1.68–3.33],  $p<0.001$ ), seafood consumption frequency (OR=2.00 [1.42–2.86],  $p<0.001$ ), employment (OR=12.7 [9.75–16.6],  $p<0.001$ ), and urinary iodine (OR=1.0007 [1.000–1.001],  $p<0.05$ ) (Table 3).

#### Risk factors for thyroid structural abnormalities in rural residents

Univariate analyses revealed differences in prevalences for 11 univariate groupings, namely, sex, age, BMI, hypertension, diabetes, cigarette smoking, excessive alcohol consumption, seafood consumption frequency, pickled food consumption frequency, employment status, and urine iodine levels (Supplementary table 2). The multivariate logistic regression analyses revealed independent risk factors for thyroid structural abnormalities in rural residents to be female sex (OR=1.98 [1.54–2.55],  $p<0.001$ ), age (OR=1.03 [1.01–1.04],  $p<0.001$ ), hypertension (OR=2.70 [1.90–3.90],  $p<0.001$ ), diabetes (OR=2.52

[1.44–4.60],  $p<0.001$ ), cigarette smoking (OR=1.66 [1.15–2.413],  $p<0.001$ ), frequent seafood consumption (OR=1.51 [1.06–2.17],  $p<0.05$ ), employment (OR=8.16 [6.09–11.1],  $p<0.001$ ), and urine iodine levels (OR=1.002 [1.0008–1.0023],  $p<0.001$ ) (Table 4). The risk factors for thyroid structural abnormalities in urban and rural residents were the same.

#### DISCUSSION

In recent years, the prevalence of adult thyroid structural abnormalities has increased.<sup>23</sup> Ultrasonography is recognized as the preferred method for screening the thyroid gland, and with its advances the detection of the microscopic lesions of the thyroid gland has increased.<sup>24,25</sup> Iodine is essential for thyroid hormone synthesis and involved in thyroid function and morphology. Epidemiologically, a “U” curve relationship exists between urinary iodine and the prevalence of thyroid diseases (i.e., excess iodine and iodine deficiency can both lead to an increased rate of thyroid structural abnormalities).<sup>26–29</sup> In addition to its consumption by the thyroid gland, about 80%–85% of iodine intake is excreted via the urine. Therefore, urinary iodine is often used as an index of iodine intake. Universal salt iodization has been implemented in China since 1996, enabling iodine deficiency-related diseases as well as goiter to be controlled.<sup>30</sup> However, excessive iodine

**Table 3.** Logistic regression analysis for thyroid structural abnormalities in urban residents

Influencing factor	OR	95% CI	p-value
Sex	2.11	1.64-2.73	<0.001
Age	1.03	1.02-1.04	<0.001
BMI	1.00	NA-1.00	0.887
Hypertension	2.38	1.63-3.53	<0.001
Diabetes	2.27	1.14-4.82	0.025
Cigarette smoking	2.36	1.68-3.33	<0.001
Seafood consumption	2.00	1.42-2.86	<0.001
Pickled food consumption	1.19	0.935-1.51	0.160
Occupation group	12.7	9.75-16.6	<0.001
Urine iodine	1.0007	1.000-1.001	0.028

BMI, body mass index; CI, confidence interval; OR, odds ratio.

**Table 4.** Logistic regression analysis for thyroid structural abnormalities in rural residents

Influencing factor	OR	95% CI	p-value
Sex	1.98	1.54-2.55	<0.001
Age	1.03	1.01-1.04	<0.001
BMI	1.00	0.978-1.03	0.83
Hypertension	2.70	1.90-3.90	<0.001
Diabetes	2.52	1.44-4.60	<0.01
Cigarette smoking	1.66	1.15-2.41	0.01
Excessive alcohol consumption	1.08	0.711-1.64	0.72
Seafood consumption	1.51	1.06-2.17	0.03
Pickled food consumption	1.16	0.901-1.50	0.25
Occupation group	8.16	6.09-11.1	<0.001
Urine iodine	1.002	1.0008-1.0023	<0.001

CI: confidence interval; OR: odds ratio.

status has appeared in some regions, with an increased prevalence of thyroid diseases.<sup>31-32</sup> The salt iodine content has been adjusted several times, and the average standard downregulated to 20–30 mg/kg in 2012.<sup>11-12</sup>

We investigated 3,645 adults in 15 cities and 15 rural townships in Heilongjiang Province. The prevalence of thyroid structural abnormalities in adults in Heilongjiang Province is now 56.05%, higher than Beijing (49.0%),<sup>7</sup> Shanghai (27.76%),<sup>29</sup> Tianjin (26.7%),<sup>33</sup> and Zhejiang (21.78%).<sup>34</sup> This might be related to factors such as the environment, iodine nutrition status, and lifestyle.<sup>35-37</sup> Heilongjiang Province has been a serious selenium deficiency.<sup>38</sup> Wu et al<sup>39,40</sup> found that a low Se increased the risk of thyroid diseases. Heilongjiang Province is a long distance away from the ocean, so that the iodine content in the food consumed by residents is low. Widespread unhealthy personal behaviours and the high incidence of chronic disease such as hypertension and diabetes may also increase the prevalence of thyroid disease.<sup>41-43</sup>

The multivariate logistic regression analyses showed that female sex and increased age were independent risk factors for thyroid structural abnormalities, which is consistent with the findings of Kang et al<sup>42,44</sup> In our study, the prevalence in females (61.40%) was higher than in males (44.03%). As reported, sex differences in the prevalence of thyroid structural abnormalities in adults may be estrogen related.<sup>6</sup> Estrogen binds to receptors on the thyroid gland, causing the thyroid to produce thyroid stimulating hormone (TSH), which enhances the proliferation of thyroid cells and leading to structural change in the thyroid gland.<sup>45-47</sup> In the present study, thyroid structural abnor-

mality prevalence increased from 34.8% to 70.1% for young to older age groups. A possible cause for this age-related finding may be degeneration of the thyroid gland and the subsequent decrease in thyroid function. The ability to regulate iodine status would be impaired and the prevalence of thyroid nodules increased when iodine absorption decreases.<sup>48-49</sup>

The logistic regression analyses showed that urinary iodine and seafood consumption frequency were independent risk factors for thyroid structural abnormalities. When urinary iodine levels were in the ranges of <20, 20–49, 50–99, 100–199, 200–299, and >300 µg/L, the corresponding prevalence rates for thyroid structural abnormalities were significantly different: 65.6%, 61.8%, 55.9%, 51.9%, 56.0%, and 63.3%. This is consistent with the previously reported “U”-shaped relationship between thyroid diseases and urinary iodine content.<sup>26,27</sup> When the body lacks iodine, thyroid hormone synthesis decreases; this affects the thyroid gland via feedback from the hypothalamus–pituitary–thyroid axis and promotes thyroid structural abnormalities. Excess iodine has been shown to lead to changes in thyroid structure via genetic and cell injury mechanisms.<sup>28,29,50,51</sup> The prevalence of thyroid structural abnormalities in participants who frequently consume seafood is high, perhaps because of the relatively high iodine content of seafood. The frequent consumption of pickled food was not an independent risk factor, probably because Heilongjiang residents use large-grain iodine-free salt for pickling; therefore, this would not have increased their iodine intake.

The multivariate analyses showed that employment,

hypertension, diabetes, and cigarette smoking were independent risk factors for thyroid structural abnormalities. The rate of thyroid structural abnormalities in employed participants was 70.1%, which was higher than that in unemployed participants (18.6%). We hypothesise that employed participants may have experienced prolonged periods of mental stress, affecting their immune function and contributing to a high rate of thyroid disease.<sup>52,53</sup> The prevalence of hypertension was high (78.0% vs 51.7%), perhaps attributed to the increased level of TSH.<sup>54,55</sup> The prevalence in diabetes, was also high (85.8% vs 54.0%). The increased leptin found in diabetic patients may increase TSH, or its gene expression affected in diabetes,<sup>56</sup> resulting in abnormal thyroid structure.<sup>57</sup> For smokers and nonsmokers, thyroid structural abnormality prevalence was different (65.9% vs 53.5%). We consider that this may be related to thiocyanate, a product of cyanide degradation in tobacco smoke and which simulates iodine deficiency by competitively inhibiting iodine intake.<sup>58</sup> Vejbjerg et al<sup>59</sup> reported that cigarette smoking stimulated the secretion of thyroid hormones, leading to abnormal thyroid structure.

Heilongjiang is a large agricultural province, and the rural population accounts for some 40% of its total.<sup>60</sup> However, we found no difference in prevalence of thyroid structural abnormalities between urban and rural areas (55.86% vs 56.27%), and the independent risk factors for urban and rural were comparable. There may have been a narrowing gap between urban and rural ways of life, food habits and environmental exposures during the past 30 years, making differences in thyroid abnormalities less likely.

This study has certain limitations. First, urine iodine concentration is not part of the routine physical examination, thus limiting its value as a screening factor. Second, there is a lack of tests of thyroid function tests are in this study which must be addressed in future studies.

### Conclusion

The prevalence of thyroid structural abnormalities in Heilongjiang Province is higher than in other regions of China. Being female, of increased age, hypertensive, having diabetes, being a cigarette smoker, having frequent seafood consumption, employment status, and abnormal urinary iodine are independent risk factors for thyroid structural abnormalities. But there are no differences in the independent risk factors between urban and rural areas. Understanding the independent risk factors for abnormal thyroid structure in adults in Heilongjiang Province will help popularize thyroid-related health knowledge, change unhealthy lifestyles, and further provide a theoretical basis for preventing thyroid disease.

### AUTHOR DISCLOSURES

The authors have no conflicts of interest to declare.

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### REFERENCES

1. Wong R, Farrell SG, Grossmann M. Thyroid nodules: diagnosis and management. *Med J Aust.* 2018;209:92-8. doi: 10.5694/mja17.01204.
2. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P. American association of clinical endocrinologists, American college of endocrinology, and associazione medici endocrinologi medical guidelines for clinical Practice for the diagnosis and management of thyroid nodules-2016 update. *Endocr Pract.* 2016;22:622-39. doi: 10.4158/EP161208.GL.
3. Hegedus L. The thyroid nodule. *N Engl J Med.* 2004;351:1764-71. doi: 10.1056/nejmcp031436.
4. Acar T, Ozbek SS, Acar S. Incidentally discovered thyroid nodules: frequency in an adult population during Doppler ultrasonographic evaluation of cervical vessels. *Endocrine.* 2014;45:73-8. doi: 10.1007/s12020-013-9949-3.
5. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. *Eur J Clin Invest.* 2009;39:699-706. doi: 10.1111/j.1365-2362.2009.02162.x.
6. Huan Q, Wang K, Lou F, Zhang L, Huang Q, Han Y et al. Epidemiological characteristics of thyroid nodules and risk factors for malignant nodules: a retrospective study from 6,304 surgical cases. *Chin Med J (Engl).* 2014;127:2286-92. doi: 10.3760/cma.j.issn.0366-6999.20140246.
7. Jiang H, Tian Y, Yan W, Kong Y, Wang H, Wang A, Wang A, Liang P, Mu Y. The prevalence of thyroid nodules and an analysis of related lifestyle factors in Beijing communities. *Int J Environ Res Public Health.* 2016;13:442. doi: 10.3390/ijerph13040442.
8. Zhao W, Han C, Shi X, Xiong C, Sun J, Shan Z, Teng W. Prevalence of goiter and thyroid nodules before and after implementation of the universal salt iodization program in mainland China from 1985 to 2014: a systematic review and meta-analysis. *PLoS One.* 2014;9:e109549. doi: 10.1371/journal.pone.0109549.
9. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: A comprehensive review of animal and human studies. *Thyroid Res.* 2015;8:8. doi: 10.1186/s13044-015-0020-8.
10. Ministry of Health of the People's Republic of China. GB14880-94, Hygienic Standard for Use of Food Nutrition Enhancers. Beijing: Standards Press of China; 1996. (In Chinese)
11. Ministry of Health of the People's Republic of China. GB 5461-2000, National Standard for Edible Salt. Beijing: Standards Press of China; 2000. (In Chinese)
12. Ministry of Health of the People's Republic of China. GB 26878-2011 National Food Safety Standard "Iodine Content of Edible Salt". Beijing: Standards Press of China; 2011. (In Chinese)
13. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. *N Engl J Med.* 2003;348:2646-55. doi: 10.1056/NEJMra021194.
14. Yeh HC, Futterweit W, Gilbert P. Micronodulation: ultrasonographic sign of Hashimoto thyroiditis. *J Ultrasound Med.* 1996;15:813-9. doi: 10.7863/jum.1996.15.12.813.
15. Tessler FN, Middleton WD, Grant EG. Thyroid imaging reporting and data system (TI-RADS): a user's guide. *Radiology.* 2018;287:29-36. doi: 10.1148/radiol.2017171240.
16. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser.* 2000;894:i-xii, 1-253. doi: 10.1002/jps.3080150106.
17. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection,

- Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71:e13-e115. doi: 10.1161/HYP.0000000000000065.
18. Chamberlain JJ, Rhinehart AS, Shaefer CF, Neuman A. Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. *Ann Intern Med*. 2016;164:542-52. doi: 10.7326/M15-3016.
  19. Dietary Guidelines for Chinese Residents (2016). National Health and Family Planning Commission of China. *Swine Raising*; 2016. p. 8. (In Chinese)
  20. Health Industry Standard of the People's Republic of China WS/T 107.1-2016 "Determination of iodine in urine—Part 1: As<sup>3+</sup>-Ce<sup>4+</sup> catalytic spectrophotometry". National Health and Family Planning Commission of the People's Republic of China. 2016. (In Chinese)
  21. World Health Organization, UNCEF, ICCID. Assessment of iodine deficiency disorders and monitoring their elimination. [cited 2020/01/17]; Available from: [https://www.who.int/nutrition/publications/micronutrients/iodine\\_deficiency/9789241595827/en/](https://www.who.int/nutrition/publications/micronutrients/iodine_deficiency/9789241595827/en/).
  22. National Standard of the People's Republic of China GB/T 13025.7-2012 "General test method in salt industry—Determination of iodine". General Administration of Quality Supervision, Inspection and Quarantine of the People's Republic of China. 2012. (In Chinese)
  23. Chen Z, Xu W, Huang Y, Jin X, Deng J, Zhu S, Liu H, Zhang S, Yu Y. Associations of noniodized salt and thyroid nodule among the Chinese population: a large cross-sectional study. *Am J Clin Nutr*. 2013;98:684-92. doi: 10.3945/ajcn.112.054353.
  24. Xie C, Cox P, Taylor N, LaPorte S. Ultrasonography of thyroid nodules: a Pictorial review. *Insights Imaging*. 2015; 7:77-86. doi: 10.1007/s13244-015-0446-5.
  25. Moon WJ, Baek JH, Jung SL, Kim DW, Kim EK, Kim JY et al. Ultrasonography and the ultrasound-based management of thyroid nodules: consensus statement and recommendations. *Korean J Radiol*. 2011;12:1-14. doi: 10.3348/kjr.2011.12.1.1.
  26. Du Y, Gao Y, Meng F, Liu S, Fan Z, Wu J, Sun D. Iodine deficiency and excess coexist in china and induce thyroid dysfunction and disease: a cross-sectional study. *PLoS One*. 2014;9:e111937. doi: 10.1371/journal.pone.0111937.
  27. Song J, Zou SR, Guo CY, Zang JJ, Zhu ZN, Mi M et al. Prevalence of thyroid nodules and its relationship with iodine status in Shanghai: a population-based study. *Biomed Environ Sci*. 2016;29:398-407. doi: 10.3967/bes2016.052.
  28. Laurberg P, Bülow Pedersen I, Knudsen N, Ovesen L, Andersen S. Environmental iodine intake affects the type of nonmalignant thyroid disease. *Thyroid*. 2001;11:457-69. doi: 10.1089/105072501300176417.
  29. Teng X, Shan Z, Chen Y, Lai Y, Yu J, Shan L et al. More than adequate iodine intake may increase subclinical hypothyroidism and autoimmune thyroiditis: a cross-sectional study based on two Chinese communities with different iodine intake levels. *Eur J Endocrinol*. 2011;164: 943-50. doi: 10.1530/EJE-10-1041.
  30. Codling K, Chen Z, Hongmei S, Li M, Gu Y, Lu ZX. China: Leading the way in sustained IDD elimination: The international council for control of iodine deficiency disorders (ICCIDD) global network. *IDD Newsl*. 2014;42:1-5.
  31. Song R, Xu D, Yao JH, Li BX. Analysis on monitoring results of the intake of iodized salt of the residents in Xuhui District of Shanghai from 2012 to 2015. *Shanghai Journal of Preventive Medicine*. 2017;29:382-5. doi: 10.3969/j.issn.1004-9231.2017.05.016. (In Chinese)
  32. Teng XC, Teng WP. Iodine excess and thyroid diseases. *Practical Journal of Clinical Medicine*, 2007;4:5-7. doi: 10.3969/j.issn.1672-6170.2007.05.003. (In Chinese)
  33. Fan L, Tan L, Chen Y, Du C, Zhu M, Wang K, Wei H et al. Investigation on the factors that influence the prevalence of thyroid nodules in adults in Tianjin, China. *J Trace Elem Med Biol*. 2018;50:537-42. doi: 10.1016/j.jtemb.2018.03.004.
  34. Mo Z, Mao GM, Zhu WM, Lou XM, Ding GX. Effect factors of the prevalence of thyroid nodules in Zhejiang Province in 2010. *Wei Sheng Yan Jiu*. 2017;46:875-87. doi: 10.19813/j.cnki.weishengyanjiu.2017.06.003. (In Chinese)
  35. Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D et al. Effect of iodine intake on thyroid diseases in China. *N Engl J Med*. 2006;354:2783-93. doi: 10.1056/NEJMoa054022.
  36. Akarsu E, Akcay G, Capoglu I, Unuvar N. Iodine deficiency and goiter prevalence of the adult population in Erzurum. *Acta Medica Hradec Kralove*. 2005;48:39-42. doi: 10.14712/18059694.2018.27.
  37. Knudsen N, Laurberg P, Perrild H, Bülow I, Ovesen L, Jørgensen T. Risk factors for goiter and thyroid nodules. *Thyroid*. 2002;12:879-88. doi: 10.1089/105072502761016502.
  38. Yang GQ, Wang SZ, Zhou RH, Sun SZ. Endemic selenium intoxication of humans in China. *Am J Clin Nutr*. 1983; 37:872-81. doi: 10.1093/ajcn/37.5.872.
  39. Wu Q, Rayman MP, Lv H, Schomburg L, Cui B, Gao C et al. Low population selenium status is associated with increased prevalence of thyroid disease. *J Clin Endocrinol Metab*. 2015;100:4037-47. doi: 10.1210/jc.2015-2222.
  40. Rasmussen LB, Schomburg L, Köhrle J, Pedersen IB, Hollenbach B, Hög A, Ovesen L, Perrild H, Laurberg P. Selenium status, thyroid volume, and multiple nodule formation in an area with mild iodine deficiency. *Eur J Endocrinol*. 2011;164:585-90. doi: 10.1530/EJE-10-1026.
  41. Aydin LY, Aydin Y, Besir FH, Demirin H, Yildirim H, Önder E, Dumlu T, Celbek G. Effect of smoking intensity on thyroid volume, thyroid nodularity and thyroid function: the Melen study. *Minerva Endocrinol*. 2011;36:273-80. doi: 10.1530/ERC-10-0283e.
  42. Guo H, Sun M, He W, Chen H, Li W, Tang J et al. The prevalence of thyroid nodules and its relationship with metabolic parameters in a Chinese community-based population aged over 40 years. *Endocrine*. 2014;45:230-35. doi: 10.1007/s12020-013-9968-0.
  43. Anil C, Akkurt A, Ayturk S, Kut A, Gursoy A. Impaired glucose metabolism is a risk factor for increased thyroid volume and nodule prevalence in a mild-to-moderate iodine deficient area. *Metabolism*. 2013;62:970-5. doi: 10.1016/j.metabol.2013.01.009.
  44. Kwong N, Medici M, Angell TE, Liu X, Marqusee E, Cibas ES et al. The influence of patient age on thyroid nodule formation, multinodularity, and thyroid cancer risk. *J Clin Endocrinol Metab*. 2015;100:4434-40. doi: 10.1210/jc.2015-3100.
  45. Rajoria S, Suriano R, George AL, Kamat A, Schantz SP, Geliebter J, Tiwari RK. Molecular target based combinational therapeutic approaches in thyroid cancer. *J Transl Med*. 2012;10:81. doi: 10.1186/1479-5876-10-81.
  46. Fiore E, Rago T, Latrofa F, Provenzale MA, Piaggi P, Delitala A et al. Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. *Endocr Relat Cancer*. 2011;18:429-37. doi: 10.1530/ERC-11-002.

47. del Senno L, degli Uberti E, Hanau S, Piva R, Rossi R, Trasforini G. In vitro effects of estrogen on tgb and c-myc gene expression in normal and neoplastic human thyroids. *Mol Cell Endocrinol.* 1989;63: 67-74. doi: 10.1016/0303-7207(89)90082-8.
48. Zimmermann, MB. Thyroid gland: Iodine deficiency and thyroid nodules. *Nat Rev Endocrinol.* 2014;10:707-8. doi: 10.1038/nrendo.2014.187.
49. Camargo RY, Tomimori EK, Neves SC, Rubio IGS, Galvão AL, Knobel M, Medeiros-Neto G. Thyroid and the environment: exposure to excessive nutritional iodine increases the prevalence of thyroid disorders in Sao Paulo, Brazil. *Eur J Endocrinol.* 2008;159:293-9. doi: 10.1530/EJE-08-0192.
50. Słowińska-Klencka D, Klencki M, Sporny S, Lewiński A. Fine-needle aspiration biopsy of the thyroid in an area of endemic goitre: influence of restored sufficient iodine supplementation on the clinical significance of cytological results. *Eur J Endocrinol.* 2002;146:19-26. doi: 10.1530/eje.0.1460019.
51. Zois C, Stavrou I, Kalogera C, Svarna E, Dimoliatis I, Seferiadis K, Tsatsoulis A. High prevalence of autoimmune thyroiditis in schoolchildren after elimination of iodine deficiency in northwestern Greece. *Thyroid.* 2003;13:485-9. doi: 10.1089/105072503322021151.
52. Sonino N, Tomba E, Fava GA. Psychosocial approach to endocrine disease. *Adv Psychosom Med.* 2007;28:21-33. doi:10.1159/000106795.
53. Sonino N, Girelli ME, Boscaro M, Fallo F, Busnardo B, Fava GA. Life events in the pathogenesis of Graves' disease. A controlled study. *Acta Endocrinol (Copenh).* 1993;128: 293-6. doi: 10.1530/acta.0.1280293.
54. Gumieniak O, Perlstein TS, Hopkins PN, Brown NJ, Murphey LJ, Jeunemaitre X, Hollenberg NK, Williams GH. Thyroid function and blood pressure homeostasis in euthyroid subjects. *J Clin Endocrinol Metab.* 2004;89:3455-61. doi: 10.1210/jc.2003-032143.
55. Chen H, Xi Q, Zhang H, Song B, Liu X, Mao X, Li J, Shen H, Tang W, Zhang J. Investigation of thyroid function and blood pressure in school-aged subjects without overt thyroid disease. *Endocrine.* 2012;41:122-9. doi: 10.1007/s12020-011-9517-7.
56. Lewandowski K, Randeva HS, O'Callaghan CJ, Horn R, Medley GF, Hillhouse EW, Brabant G, O'Hare P. Effects of insulin and glucocorticoids on the leptin system are mediated through free leptin. *Clin Endocrinol (Oxf).* 2001; 54:533-9. doi: 10.1046/j.1365-2265.2001.01243.x.
57. Morshed SA, Ma R, Latif R, Davies TF. Biased signaling by thyroid-stimulating hormone receptor-specific antibodies determines thyrocyte survival in autoimmunity. *Sci Signal.* 2018;11. doi: 10.1126/scisignal.aah4120.
58. Aydin LY, Aydin Y, Besir FH, Demirin H, Yildirim H, Önder E, Dumlu T, Celbek G. Effect of smoking intensity on thyroid volume, thyroid nodularity and thyroid function: The Melen study. *Minerva Endocrinol.* 2011;36:273-80. doi: 10.1530/ERC-10-0283e.
59. Vejbjerg P, Knudsen N, Perrild H, Carlé A, Laurberg P, Pedersen IB, Rasmussen LB, Ovesen L, Jørgensen T. The impact of smoking on thyroid volume and function in relation to a shift towards iodine sufficiency. *Eur J Epidemiol.* 2008;23:423-9. doi: 10.1007/s10654-008-9255-1.
60. National Bureau of Statistics of China. [cited 2020/03/06]; Available from: <http://data.stats.gov.cn/easyquery.htm?cn=C01>.



**Supplementary table 1.** Prevalence of thyroid structural abnormalities in urban residents

Factor	Normal	Structural abnormalities	Prevalence rate (%)	$\chi^2$	<i>p</i> -value
Sex					
Female	551	858	60.9	49.0	<0.001
Male	326	252	43.6		
Age					
Group A	106	58	35.4	94.3	<0.001
Group B	192	134	41.1		
Group C	216	271	55.6		
Group D	236	352	59.9		
Group E	127	295	69.9		
BMI					
Low body weight	53	38	41.8	8.03	0.05
Normal body weight	534	686	56.2		
Overweight	249	336	57.4		
Obesity	41	50	54.9		
Hypertension					
Non-hypertension	815	907	52.7	52.4	<0.001
Hypertension	62	203	76.6		
Diabetes					
Non-diabetes	864	1039	54.6	28.0	<0.001
Diabetes	13	71	84.5		
Cigarette smoking status					
Non-smoking	765	897	54.0	14.3	<0.001
Smoking	112	213	65.5		
Alcohol consumption					
Non-excess	832	1035	55.4	2.00	0.16
Excess	45	75	62.5		
Seafood consumption					
Occasionally	804	851	51.4	78.2	<0.001
Often	73	259	78.0		
Pickled food consumption					
Occasionally	624	626	50.1	45.1	<0.001
Often	253	484	65.7		
Employment status					
occupation	490	96	16.4	523.2	<0.001
nonoccupation	387	1014	72.4		
Urine iodine					
Group I	11	27	71.1	18.8	<0.01
Group II	51	92	64.3		
Group III	155	186	54.5		
Group IV	376	392	51.0		
Group V	177	248	58.4		
Group VI	107	165	60.7		
Salt iodine					
Non-iodized salt	133	187	58.4	1.50	0.68
Lowly iodized salt	18	24	57.1		
Appropriately iodized salt	708	881	55.4		
Highly iodized salt	18	18	50.0		

**Supplementary table 2.** Prevalence of thyroid structural abnormalities in rural residents

Factor	Normal	Structural abnormalities	Prevalence rate (%)	$\chi^2$	<i>p</i> -value
Sex					
Female	423	691	62.0	45.0	<0.001
Male	302	242	44.5		
Age				82.7	<0.001
Group A	96	50	34.2		
Group B	146	113	43.6		
Group C	186	212	53.3		
Group D	180	281	61.0		
Group E	117	277	70.3		
BMI				8.58	0.04
Low body weight	37	29	43.9		
Normal body weight	450	555	55.2		
Overweight	199	305	60.5		
Obesity	39	44	53.0		
hypertension				89.6	<0.001
Non-hypertension	654	664	50.4		
hypertension	71	269	79.1		
diabetes				59.8	<0.001
Non-diabetes	705	804	53.3		
diabetes	20	129	86.6		
Cigarette smoking status				22.9	<0.001
Non-smoking	577	644	52.7		
Smoking	148	289	66.1		
Alcohol consumption				13.3	<0.001
Non-excess	611	718	54.0		
Excess	114	215	65.3		
Seafood consumption				52.2	<0.001
Occasionally	657	719	52.3		
Often	68	214	75.9		
Pickled food consumption				24.3	<0.001
Occasionally	503	536	51.6		
Often	222	397	64.1		
Employment status				262.6	<0.001
occupation	321	89	21.7		
nonoccupation	404	844	67.6		
Urine iodine				14.7	0.01
Group I	10	13	56.5		
Group II	43	60	58.3		
Group III	105	144	57.8		
Group IV	292	329	53.0		
Group V	185	212	53.4		
Group VI	90	175	66.0		
Salt iodine				3.13	0.37
Non-iodized salt	61	82	57.3		
Lowly iodized salt	23	22	48.9		
Appropriately iodized salt	628	802	56.1		
Highly iodized salt	13	27	67.5		