

# Dietary Factors and the Risk of Thyroid Diseases: A Review

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**Background and Objectives:** Diet is one of the major risk factors for thyroid diseases. It has been shown that high or excessive iodine intake is more likely to be a health concern in iodine-sufficient regions or regions where iodine deficiency previously existed due to the emergence of iodine-induced hypothyroidism or hyperthyroidism. Therefore, this review investigates the occurrence of thyroid diseases, and particularly hypothyroidism and hyperthyroidism, in populations with different levels of iodine intake and other dietary factors in various geographic regions. **Materials and Methods:** A total of 856 articles published between January 1st, 1990 and March 31st, 2015, were identified. Epidemiological studies that showed an association between dietary factors and thyroid diseases were selected, yielding a total of 21 articles. **Results:** Due to a sudden increase in iodine supplementation (i.e., via salt iodization), regions such as Denmark and China, where insufficient iodine intake previously existed, showed a significant increase in the occurrence of hypothyroidism compared with that of hyperthyroidism. Other dietary factors, such as nitrate intake, may increase the risk of the diseases, whereas a vegan diet and alcohol intake may lower the risk. **Conclusion:** The level of iodine intake is quite variable between individuals in different geographic regions, and the risk of thyroid diseases may also vary by age and gender. Therefore, monitoring of safe levels of iodine intake should be performed to prevent iodine-induced thyroid diseases.

**Key Words:** Thyroid disease, Hypothyroidism, Hyperthyroidism, Iodine, Diet

## Introduction

In 1994, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) Joint Committee on Health Policy recommended universal salt iodization (USI) as a cost-effective strategy to ensure sufficient iodine intake for all individuals.<sup>1)</sup> Before 1990, only few countries, such as Switzerland, several Scandinavian countries, the USA, and Canada, were completely iodine sufficient.<sup>2)</sup> In the past, certain geographical locations, such as mountain ranges and al-

luvial plains at high altitudes (i.e., distant from sea), were regarded as iodine-deficient areas, but iodine deficiency has also been found in coastal areas, large cities, and highly developed countries. Currently, approximately 70% of all households have access to adequate iodized salt worldwide, and as of 2013, 111 countries had sufficient iodine intake. In the same year, moderately deficient intake was noted in 9 countries; mildly deficient intake, in 21; and severely deficient intake, in none.<sup>3)</sup>

Marine (i.e., seaweed) and dairy products are the major sources of iodine intake and highly contribute

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to the iodine supply in coastal regions<sup>4)</sup> and in certain European countries.<sup>5,6)</sup> The frequency of thyroid disorders in a population is highly influenced by the levels of iodine intake, and both low iodine intake and excess iodine intake are notable causes of thyroid diseases.<sup>7)</sup> In general, healthy adults (except lactating or pregnant women) can tolerate iodine intake greater than the daily recommendation of 150  $\mu\text{g}/\text{day}$ , but populations such as infants, pregnant and lactating women, and patients with a history of thyroid diseases are more vulnerable to iodine-induced thyroid diseases in the presence of high iodine intake.<sup>1)</sup> For instance, populations with autoimmune thyroid diseases (i.e., subacute thyroiditis) are more susceptible to iodine-induced hypothyroidism,<sup>8)</sup> whereas iodine-induced hyperthyroidism is often observed in patients with euthyroid iodine-deficient goiter in regions with suddenly increased iodine intake.<sup>9)</sup> Certain other dietary factors, such as nitrate intake, a vegan diet, and alcohol intake, also show a possible association with thyroid diseases.

Therefore, this review examines the occurrence of thyroid diseases, and particularly hypothyroidism and hyperthyroidism, in populations with different levels of iodine intake and other dietary factors in various geo-

graphical locations.

## Materials and Methods

A search was conducted in PubMed for articles published between January 1st, 1990 and March 31st, 2015. The approach to key words was searched relying on thyroid dysfunction, which mainly causes thyroid disease that comprehensively includes a term such as nodule and goiter. The key words were as follows: “(autoimmune OR thyroid disease) AND (iodine OR diet) AND (hypothyroidism OR hyperthyroidism) AND (epidemiology).” The following inclusion criteria were used: 1) epidemiological studies, including study types such as case-control, cross-sectional, and cohort studies; 2) studies investigating the association between dietary factors (i.e., iodine and others) and thyroid diseases (i.e., hypothyroidism and hyperthyroidism); and 3) studies estimating the disease risk based on the odds ratio (OR), relative risk (RR), and prevalence rate (PR) and/or incidence rate (IR).

A total of 856 articles were identified as containing the major key words. Firstly, by screening the title and abstract, articles focused on diseases other than thyroid diseases were excluded (n=191). Of the 665

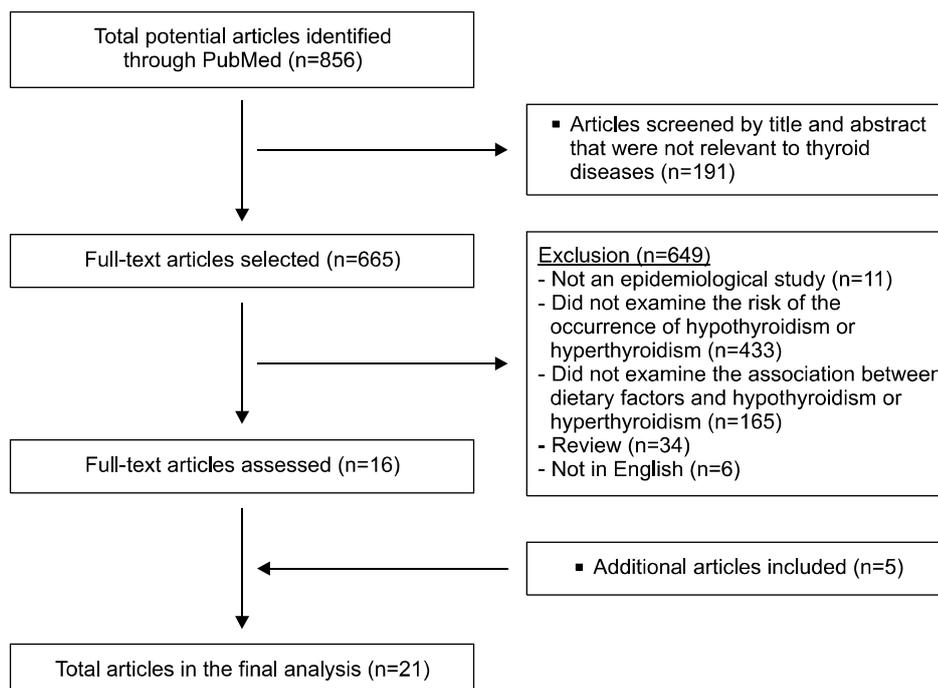


Fig. 1. Flow chart for selection of eligible studies.

full-text articles, additional articles were excluded for the following reasons: 1) the study was not epidemiological ( $n=11$ ), 2) the results did not depict the risk of the occurrence of hypothyroidism or hyperthyroidism ( $n=433$ ), 3) the study did not examine dietary factors associated with hypothyroidism or hyperthyroidism ( $n=165$ ), 4) the study was a review ( $n=34$ ), and 5) the study was not in English (i.e., it was in Spanish, Italian, or Chinese) ( $n=6$ ). Sixteen studies remained and 5 additional studies were included based on references in other articles, and a total of 21 relevant articles were identified. Considering geographical locations, 10 studies were from Europe; 9 studies, from Asia; and 2 studies, from the USA. The flow chart of the literature search and study selection is presented in Fig. 1.

### Results

Table 1 shows the association between iodine intake and thyroid diseases in Europe. In the Danish Investigation on Iodine Intake and Thyroid Disease (DanThyr) cohort study, populations living in regions with moderate or mild iodine deficiency (i.e., in Aalborg and Copenhagen) were selected. In a study by Laurberg et al.,<sup>10</sup> elderly individuals with iodine deficiency who had lived in Jutland for many years showed a high prevalence of non-toxic goiter (i.e., hyperfunction), whereas those with long-term high iodine intake in Iceland showed impaired thyroid function (i.e., hypofunction). Cases of subclinical hypothyroidism were more prevalent in Iceland; the incidence of hyperthyroidism was quite low. Before mandatory iodine fortification (IF) in 2000, the incidence of hypothyroidism was more pronounced in mildly iodine-deficient regions (i.e., Copenhagen, OR=1.33 [1.15–1.55];  $p < 0.05$ ) due to a high occurrence of spontaneous hypothyroidism (that is, a subtype) in 1999 (OR=1.53 [1.29–1.80];  $p < 0.05$ ).<sup>11</sup> In the first 2 years after IF, the incidence of hypothyroidism in Copenhagen was higher than in Aalborg (Aalborg/Copenhagen, standardized rate ratio [SRR]=0.73 [0.55–0.97]), whereas the incidence of hyperthyroidism was higher in Aalborg than in Copenhagen (Aalborg/Copenhagen, SRR=1.49 [1.22–1.81]).<sup>12</sup> When the baseline (1997–1998) and

late mandatory IF (2003–2004<sup>13</sup>; 2003–2005<sup>14</sup>) periods were compared, the incidence of hyperthyroidism and hypothyroidism was significantly increased in young and middle-aged individuals between 20 and 39 years of age. Additionally, when the periods before (1997–1998) and after IF were compared, mild hypothyroidism was most pronounced in young women ( $p=0.01$ ).<sup>15</sup> In Almería, Spain, a region where the major iodine supply is dairy products, children and adolescents aged between 1 and 16 years had an optimal level of iodine intake.<sup>16</sup> Of those children aged between 12 and 16 years with excess iodine intake, thyroid autoimmunity was more prevalent than among those with iodine deficiency.

Table 2 shows the association between iodine intake and thyroid diseases in Asia. The majority of studies were conducted in China, where the USI was introduced in 1996. Similar to studies in Denmark, three different regions, or Panshan, Zhangwu, and Huanghua, were selected in a large cohort study with follow-up. In Zhangwu and Huanghua, after USI in 1996, the level of iodine intake changed from mildly deficient to more than adequate and from high to excessive, respectively. In a study by Yang et al.,<sup>17</sup> the prevalence of subclinical hyperthyroidism was significantly higher in Panshan (3.7%) and Zhangwu (3.9%) compared with Huanghua (1.1%) ( $p < 0.001$ ). The incidence of hyperthyroidism was also significantly increased in Panshan when the periods before (1991–1995) and after (1996–1999) USI were compared. In a follow-up study, the same population with chronic iodine intake for 5 years did not exhibit a significantly increased risk of autoimmune hyperthyroidism.<sup>18</sup> Another 5-year follow-up study by Teng et al.,<sup>19</sup> the cumulative incidence of subclinical hypothyroidism was significantly higher in Zhangwu and Huanghua compared with Panshan ( $p < 0.001$ ), but no significant differences were found in the incidence of hyperthyroidism or Grave's disease between the three regions.<sup>19</sup> In Chengsan and Rongxing, iodine intake after USI changed from mildly deficient to adequate and from no historical iodine deficiency to more than adequate, respectively.<sup>20</sup> The prevalence of subclinical hypothyroidism was significantly higher in

Table 1. Iodine intake and thyroid diseases in Europe

Reference	Country (region)	Survey year	Study type	Age (years)	Iodine source	MUI ( $\mu\text{g/l}$ )	Results (rate [%]/risk [95% CI])
Laurberg et al. (1998) <sup>10</sup>	Denmark (Jutland) Iceland	-	Cross-sectional	68 (66-70)	Iceland (dairy products)	Jutland (38) Iceland (150)	Female/Male 1) Jutland (hyperfunction): PR=12.2/3.2% 2) Iceland (hypofunction): PR=1.9/2.2%
Bülöw Pedersen et al. (2002) <sup>2)</sup>	Denmark (Aalborg, Copenhagen)	1998-2000	DanThyr (cohort, 2-year f/u)	0-80+	Salt IF	Aalborg (45) Copenhagen (61)	1) Hyperthyroidism: SRR=1.49 [1.22-1.81] 2) Hypothyroidism: SRR=0.73 [0.55-0.97]
Carle et al. (2006) <sup>11)</sup>	Denmark (Aalborg, Copenhagen)	1997-2000	DanThyr (cohort)	0-80+	Salt IF	Aalborg (45) Copenhagen (61)	1) Hypothyroidism: SIR=1.33 [1.15-1.55]; p<0.05 2) Spontaneous hypothyroidism: SIR=1.53 [1.29-1.80]; p<0.05 3) Non-spontaneous hypothyroidism: SIR=0.64 [0.43-0.96]; p<0.05
Bülöw Pedersen et al. (2006) <sup>3)</sup>	Denmark (Aalborg, Copenhagen)	1997-2004	DanThyr (cohort, 6-year f/u)	0-60+	Salt IF	Aalborg (45) Copenhagen (61)	Hyperthyroidism (age, years) 1) 20-39: RR=2.61 [2.14-3.19] 2) 40-59: RR=1.29 [1.10-1.52] 3) >60: RR=1.13 [1.0-1.28]
Bülöw Pedersen et al. (2007) <sup>14)</sup>	Denmark (Aalborg, Copenhagen)	1997-2005	DanThyr (cohort, 7-year f/u)	0-60+	Salt IF	Baseline/Late IF Aalborg (45/86) Copenhagen (61/99)	Hypothyroidism (late mandatory vs. baseline IF) 1) Overall: RR=1.23 [1.07-1.42] 2) Aalborg: RR=1.11 [1.11-1.66] 3) Copenhagen: RR=1.10 [0.90-1.34] 4) 20-39 years: RR=1.90 [1.28-2.84]
Vejbjerg et al. (2009) <sup>15)</sup>	Denmark (Aalborg, Copenhagen)	1997-1998, 2000	Cross-sectional (before vs. after IF)	18-65	Salt IF	Aalborg (53) Copenhagen (68)	Mild hypothyroidism (age, years female; p=0.01) 1) 18-22: OR=1.7 [1.0-2.8] 2) 25-30: OR=2.0 [1.2-3.2] 3) 40-45: OR=1.4 [0.8-2.3] 4) 60-65: OR=0.7 [0.5-1.1]
García-García et al. (2012) <sup>16)</sup>	Spain (Almería)	2007-2010	Cross-sectional	1-16	Dairy products	199.5	Thyroid autoimmunity/Autoimmune thyroiditis 1) Deficient: PR=2.6% [1.3-5.1]/1.3% [0.0-4.5] 2) Adequate: PR=2.9% [1.3-6.3]/1.3% [0.1-3.1] 3) Above requirements: PR=4.6% [2.9-7.8]/1.6% [0.1-3.7] 4) Excessive: PR=5.0% [2.6-9.6]/1.4% [0.0-4.1]

CI: confidence interval, f/u: follow-up, IF: iodine fortification, IR: incidence rate, MUI: median urinary iodine, PR: prevalence rate, RR: relative risk, SIR: standardized incidence rate, SRR: standardized rate ratio

**Table 2.** Iodine intake and thyroid diseases in Asia

Reference	Country (region)	Survey year	Study type	Age (years)	Iodine source	MUI ( $\mu\text{g}/\text{l}$ )	Results (rate [%]/risk [95% CI])
Konno et al. (1994) <sup>(23)</sup>	Japan	1992	Cross-sectional	$\geq 18$	Seaweed (kelp)	$\geq 75$	Hypothyroidism: Thyroid AB-in subjects with high UI (12.1%) vs. normal UI (2.3%) ( $p < 0.001$ )
Yang et al. (2002) <sup>(17)</sup>	China	1991–1995 1996–1999	Cross-sectional & longitudinal survey	$\geq 14$	USI	Panshan (103) Zhangwu (375) Huanghua (615)	Subclinical hyperthyroidism 1) PR=3.7% (P vs. H); $p < 0.001$ 2) PR=3.9% (Z vs. H); $p < 0.001$ 3) PR=1.1% (H)
Teng et al. (2006) <sup>(19)</sup>	China	1999–2004	Cross-sectional (5-year f/u)	$\geq 14$	USI	Panshan (84) Zhangwu (243) Huanghua (651)	Subclinical hypothyroidism 1) CI=0.2(P)/2.6(Z)/2.9(H)%; $p < 0.001$ 2) P vs. Z; $p < 0.001$ 3) P vs. H; $p < 0.001$
Yang et al. (2007) <sup>(8)</sup>	China	1999–2004	Cross-sectional (5-year f/u)	$\geq 14$	USI	Panshan (88) Zhangwu (214) Huanghua (634)	Hyperthyroidism 1) CI=1.4(P)/0.9(Z)/0.8(H)%; $p > 0.05$
Aminorroaya et al. (2009) <sup>(24)</sup>	Iran (Istahan)	2006	Cross-sectional (15 years after USI)	$> 20$	USI	Male (20.0 $\mu\text{g}/\text{dL}$ ) Female (20.6 $\mu\text{g}/\text{dL}$ )	Male (ret.) vs. Female 1) Subclinical hypothyroidism: OR=2.52 [1.70–3.73]; $p < 0.001$ 2) Overt hypothyroidism: OR=2.31 [1.32–4.04]; $p < 0.001$
Chung et al. (2009) <sup>(25)</sup>	Korea	2007–2008	Case-control	$\leq 34$ week	Breast milk	75	Subclinical hypothyroidism: EDI ( $< 30$ vs. 100 $\mu\text{g}/\text{kg}/\text{day}$ ) 1) Week 3 ( $p=0.033$ , 0 vs. 67%): 51.2 $\pm$ 45.5 vs. 149.0 $\pm$ 103.8 $\mu\text{g}/\text{kg}/\text{day}$ 2) Week 6 ( $p=0.032$ , 20 vs. 100%): 32.8 $\pm$ 35.5 vs. 92.1 $\pm$ 51.2 $\mu\text{g}/\text{kg}/\text{day}$
Teng et al. (2011) <sup>(20)</sup>	China	2007	Cross-sectional	$> 14$	USI	Chengshan/Rongxing (school children: 145/261; general population: 164/272)	Chengshan/Rongxing (%) 1) Hypothyroidism: PR=2.15/5.35%; $p < 0.000$ 2) Subclinical hypothyroidism: PR=1.99/5.03%; $p < 0.001$ 3) Hyperthyroidism: PR=3.52/1.89%; $p=0.002$ 4) Subclinical hyperthyroidism: PR=1.73/0.63%; $p=0.002$
Zou et al. (2012) <sup>(21)</sup>	China	2009 (Sep–Dec)	Cross-sectional	5–69	USI	146.7	Age (15–69 years, male/female (%)) 1) Hypothyroidism: PR=0.44/0.98%; $p < 0.05$ 2) Subclinical hypothyroidism: PR=7.3/11.03%; $p < 0.05$ Age (15–39 vs. 40–69 years) 1) Subclinical hyperthyroidism: PR=0.05/0.41%; $p < 0.05$ Excess/Sufficient/ID (%)
Du et al. (2014) <sup>(22)</sup>	China	–	Cross-sectional	$\geq 18$	Iodized table salt	Excess ( $> 400$ ) Sufficient (100–300) ID ( $< 100$ )	1) Overt hypothyroidism: PR=2.56/1.18/1.05%; $p=0.045$ 2) Subclinical hyperthyroidism: PR=0.58/0.20/1.95%; $p=0.003$

CI: cumulative incidence, CIR: cumulative incidence rate, EDI: estimated daily iodine intake, f/u: follow-up, ID: iodine deficiency, IR: incidence rate, MUI: median urinary iodine, OR: odds ratio, PR: prevalence rate, UI: urinary iodide, USI: universal salt iodization

**Table 3.** Other dietary factors and thyroid diseases

Reference	Country (region)	Study type	Survey year	Dietary factor	Age (years)	Result (OR, [95% CI])
Ward et al. (2010) <sup>26)</sup>	US (Iowa)	Cohort	1955–1988	Nitrate (diet & water supplies)	55–69	Dietary nitrate ( $\leq 17.4$ vs. 41.1 mg nitrate-N/day) 1) Hypothyroidism: OR=1.24 [1.10–1.40]; p=0.001
Carlé et al. (2012) <sup>28)</sup>	Denmark	DanThyr (population based casecontrol)	1997–2001	Alcohol	Female (18–65) Male (60–65)	Overt hypothyroidism (1–10 units/week vs.) 1) 0 unit/week: OR=1.68 [1.02–2.77]; p<0.05 2) 11–20 units/week: OR=0.46 [0.25–0.83]; p<0.01 3) $\geq 21$ units/week: OR=0.52 [0.25–1.09]
Eifraimidis et al. (2012) <sup>30)</sup>	Netherlands	Amsterdam AITD (nested casecontrol)	–	Alcohol	18–65	Overt hypothyroidism ( $> 10$ units of alcohol/week vs.) 1) Baseline: OR=0.54 [0.14–2.06] 2) 1 year before event: OR=0.23 [0.05–1.04]; p=0.041 3) At event: OR=0.23 [0.05–1.06]; p=0.044
Carlé et al. (2013) <sup>29)</sup>	Denmark	DanThyr (population based casecontrol)	1997–2000	Alcohol	$\geq 18$	Grave's hyperthyroidism (maximum 1–2 units/week vs.) 1) 0 unit/week: OR=1.59 [1.02–2.48]; p<0.05 2) 3–10 units/week: OR=0.58 [0.40–0.85]; p<0.01 3) 11–20 units/week: OR=0.57 [0.36–0.91]; p<0.05 4) $\geq 21$ units/week: OR=0.29 [0.15–0.56]; p<0.001
Tonstad et al. (2013) <sup>27)</sup>	US, Canada	AHS-2 (longitudinal study)	2002–2008	Plant-based diet	$\geq 30$	Omnivore vs. lacto-ovo 1) Hypothyroidism: OR=1.09 [1.01–1.18]

AHS-2: the Adventist Health Study-2, AITD: autoimmune thyroid disease, CI: confidence interval, DanThyr: the Danish Investigation of Iodine Intake and Thyroid Diseases, f/u: follow-up, OR: odds ratio

Rongxing ( $p < 0.001$ ), whereas the prevalence of subclinical hyperthyroidism was significantly higher in Chengsan ( $p < 0.002$ ). Shanghai, the biggest coastal city in China, was considered as a non-iodine deficient disorders (IDD) region before the introduction of USI.<sup>21)</sup> Among females aged between 40 and 69, the prevalence of hypothyroidism ( $p < 0.05$ ) and subclinical hypothyroidism ( $p < 0.05$ ) was significantly higher than among males, and subclinical hyperthyroidism was significantly more frequent in individuals aged 40–69 compared with those aged 15–39 ( $p < 0.05$ ). Three other coastal areas in China with different iodine intake levels (i.e., deficient, sufficient, or excessive) were examined.<sup>22)</sup> Of these regions, significant regional differences in subjects with overt hypothyroidism were found, with 2.56% variation in excessive iodine intake, 1.18% variation in sufficient intake, and 1.05% variation in deficient intake ( $p = 0.045$ ). Additionally, regional differences were significant for the prevalence of subclinical hyperthyroidism ( $p = 0.003$ ), but not overt hyperthyroidism. In Japan, five coastal areas with high consumption of iodine from seaweed (i.e., kelp) were examined.<sup>23)</sup> In these regions, hypothyroidism was more prevalent in males with negative thyroid autoantibody (AB) who had higher urinary iodine (UI) excretion compared with those with normal UI excretion ( $p < 0.001$ ). In Iran, the overall prevalence of subclinical hypothyroidism was also significantly higher in females (12.8%) than in males (4.8%) 15 years after USI, which occurred in 1989 (OR=2.52 [1.70–2.73];  $p < 0.001$ ), but a correlation between iodine intake and hypothyroidism was not found.<sup>24)</sup> In Korea, the frequency of subclinical hypothyroidism in preterm infants born at 34 weeks of gestation or less was higher with high iodine intake from breast milk than with low iodine intake from breast milk both 3 weeks ( $p = 0.033$ ) and 6 weeks ( $p = 0.032$ ) after birth.<sup>25)</sup>

In Table 3, it is evident that several other dietary factors were associated with thyroid diseases in recent cohort studies. In a study performed in the U.S., females with higher dietary nitrate intake were at a greater risk of hypothyroidism than those with lower dietary nitrate intake in Iowa (OR=1.24 [1.10–1.40];  $p = 0.001$ ).<sup>26)</sup> In individuals with a plant-based diet, and

particularly in lacto-ovo vegetarians, who eat dairy products and eggs, there is an increased risk of hypothyroidism compared with the risk among omnivore vegetarians, who consume animal products (OR=1.09 [1.01–1.18]).<sup>27)</sup> Large cohort studies were conducted to determine the association between alcohol intake and thyroid dysfunction. In Denmark, a significantly increased risk of hypothyroid cases was reported among non-drinkers compared with those who had alcohol consumption of between 1 and 10 units per week (OR=1.68 [1.02–2.77];  $p < 0.05$ ).<sup>28)</sup> Another study in Denmark showed a significantly reduced risk of developing Grave's hyperthyroidism in subjects with high alcohol intake (i.e.,  $\geq 21$  units per week; OR=0.29 [0.15–0.56];  $p < 0.001$ ).<sup>29)</sup> Additionally, in the Amsterdam Autoimmune Thyroid Disease (AITD) cohort study in the Netherlands, subjects who had consumed more than 10 units of alcohol per week after 5 years of follow-up showed a significantly reduced risk of developing overt hypothyroidism compared with baseline (OR=0.23 [0.05–1.06];  $p = 0.044$ ).<sup>30)</sup>

## Discussion

In previous studies, differences in iodine intake were major contributors to thyroid dysfunction, and both low and high iodine intake levels were correlated with thyroid abnormalities. After the initiation of salt iodization programs worldwide, significant efforts to prevent IDD have been realized, particularly in iodine-deficient regions. Excessive iodine intake due to dietary factors is more likely to be a health concern in iodine-sufficient regions compared with iodine-deficient regions due to the emergence of iodine-induced thyroid diseases. In general, hyperthyroidism is more common than hypothyroidism, whereas subclinical hypothyroidism is more common than subclinical hyperthyroidism. At present, due to large differences in the incidence of hypothyroidism, the association between the level of iodine intake and hypothyroidism is not clear.

In a study by Laurberg et al.,<sup>10)</sup> old age combined with high iodine intake was found to potentially accelerate the development of autoimmune thyroid disease. A similar study was conducted in a nursing home in

eastern Hungary, where elderly individuals aged over 60 years with high iodine intake showed a high prevalence of clinical and subclinical hypothyroidism compared with those in northern Hungary, where iodine intake was deficient.<sup>31)</sup> In Denmark, after the initiation of mandatory IF (i.e., household salt and salt for commercial bread production iodized to 13 ppm),<sup>13)</sup> changes in the pattern of thyroid dysfunction were observed. When the periods before and after IF were compared, the findings suggested that increased iodine intake in a population over time may reduce hyperthyroidism but increase autoimmune hypothyroidism, even in a region where iodine deficiency previously existed.<sup>32)</sup> Pedersen et al.<sup>12)</sup> also explained that a small difference in iodine intake, from mild to moderate deficiency, may contribute to remarkable differences in the incidence of hypothyroidism and hyperthyroidism in a population. The incidence of overt hyperthyroidism may also increase transiently after an increase in iodine intake.<sup>33)</sup> In particular, both hypothyroidism and hyperthyroidism were significantly increased after IF in the young and middle-aged populations.<sup>13,14)</sup>

In Asia, a region where iodine deficiency was considerably severe before USI, more than 400 million people were once affected by IDD.<sup>34)</sup> In China, iodine intake increased countrywide with USI to control IDD, implemented since 1996. Regions such as Zhangwu, with a sudden change in iodine intake after previous iodine deficiency, showed the most rapid progression in the transition from subclinical to overt hypothyroidism.<sup>19)</sup> The cited study explained that the rate of progression to hypothyroidism in subjects who had high levels of anti-thyroid peroxidase antibody or thyroglobulin at baseline was directly correlated with iodine intake. In contrast, high or excessive iodine intake in regions where iodine deficiency (i.e., mild, but not severe) previously existed did not significantly increase the prevalence of overt hyperthyroidism.<sup>18,20)</sup> In Korea, a region where iodine intake is relatively sufficient, daily iodine intake of brown seaweed (*Undaria pinnatifida*) soup by mothers during the early postpartum period was greater than 2000  $\mu\text{g}/\text{day}$ .<sup>35)</sup> The recommended daily iodine intake for pregnant and lactating women is 250  $\mu\text{g}/\text{day}$ .<sup>1)</sup> Therefore, excessive iodine

intake by mothers that directly transferred to preterm infants through breast milk was associated with an increased risk of subclinical hypothyroidism compared with the risk among those with low iodine intake from breast milk.

Thyroid dysfunction is also influenced by other dietary factors. In previous epidemiological studies, nitrate intake was considered as a potential cancer risk factor due to contamination of drinking water.<sup>36–38)</sup> Regarding thyroid function, nitrate can competitively inhibit iodide uptake,<sup>39,40)</sup> which may cause a reduction in thyroid hormone production.<sup>41)</sup> In an assessment of the Iowa Women's Health Study, high nitrate intake through drinking water consumption and private well use seemed to increase the risk of ovarian cancer in postmenopausal women.<sup>38)</sup> Similarly, a study by Ward et al.<sup>26)</sup> found a significantly increased risk of both thyroid cancer and hypothyroidism in females with high dietary nitrate intake living in the same region, but no significant association was found for nitrate ingestion via drinking water. Alcohol, also known as a potential human carcinogen, showed a protective effect on thyroid dysfunction in large cohort studies in both Denmark and the Netherlands. However, due to the complexity of alcohol's effect on the immune system, thyroid autoimmunity that responds to alcohol intake is not clearly understood yet. Further studies need to address the possible mechanism of alcohol that modulates thyroid function.

Regarding plant-based diets, recent studies suggested that vegan proteins may provide a protective effect against certain cancers, obesity, and cardiovascular diseases, with increased activity of glucagon.<sup>42)</sup> According to recent studies, a substantially decreased risk of type 2 diabetes was associated with a vegetarian diet (i.e., vegan and lacto-ovo) compared with a non-vegetarian diet.<sup>43,44)</sup> However, Leung et al.<sup>45)</sup> stated that there is growing concern about plant-based diets causing insufficient mineral intake (i.e., iodine). In a study by Tonstad et al.,<sup>27)</sup> there was a tendency toward a lower risk of hypothyroidism associated with a vegan diet, but overall, a vegetarian diet was not associated with increased risk of hypothyroidism.

Related to thyroid diseases, the frequency of thyroid

cancer has also been significantly increasing over the last few decades due to genetic and environmental factors.<sup>46)</sup> However, the influence of nutrition or food on thyroid cancer has not been completely confirmed due to the complexity of the great number of variables. The primary cause of hypothyroidism, or autoimmune thyroiditis, can be aggravated by excess iodine intake,<sup>19)</sup> and it is considered to be a predisposing factor for thyroid cancer.<sup>47)</sup> In a recent meta-analysis, high intake of fish containing abundant iodine was associated with an increased thyroid cancer risk in non-iodine-deficient areas (RR=1.18 [1.03–1.35]).<sup>48)</sup> Therefore, certain specific dietary components with high iodine content may increase the risk of thyroid cancer as well.

In conclusion, adverse health effects were shown in a population with high or excessive iodine intake within a few years after IF. In particular, excessive iodine intake greater than 300  $\mu\text{g}/\text{day}$  is highly discouraged in populations in regions where iodine deficiency previously existed because these populations are more vulnerable to adverse health consequences, such as iodine-induced hyperthyroidism and autoimmune thyroid diseases.<sup>1)</sup> Tolerance of high iodine intake is quite variable between individuals, and health problems are not immediately apparent. Therefore, populations in both iodine-deficient and iodine-sufficient regions should adhere to the optimal level of iodine intake via diet, and iodine intake should also be monitored in individuals at risk of thyroid dysfunction. Further epidemiological studies examining diverse dietary factors and the occurrence of thyroid diseases in different geographical locations should be performed.

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