U-shaped relationship between iodine status and thyroid autoimmunity risk in adults

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Abstract

Background: Iodine status has long been regarded as an environmental determinant for thyroid dysfunction, but its relationship with thyroid autoimmunity (TAI) is still controversial. Our study aimed to elucidate the relationship between iodine status and TAI through both a population-based study and a dose-response meta-analysis of eligible epidemiological studies.

Methods: A population-based, cross-sectional study was firstly carried out, which enrolled a total of 2808 Chinese adults. Odds ratio (OR) with 95% confidence interval (95% CI) was calculated through logistic regression analysis. A dose-response meta-analysis of eligible epidemiological studies was also carried out.

Results: The cross-sectional study showed an U-shaped relationship between iodine intake and TAI in adults. Compared with those with more than adequate iodine status, individuals with iodine deficiency, adequate iodine status and iodine excess all had higher risk of TAI, and the adjusted ORs were 1.50 (95% CI 1.03–2.17, $P = 0.032$), 1.50 (95% CI 1.09–2.07, $P = 0.013$) and 1.68 (95% CI 1.11–2.53, $P = 0.014$), respectively. The dose-response meta-analysis included 22 epidemiological studies with a total of 69,987 participants and further validated the U-shaped relationship between iodine intake and TAI in adults, which proved the significantly increased risk of TAI among individuals with either iodine deficiency or iodine excess. Stratified analysis of studies with low risk of confounding bias also identified similar findings.

Conclusion: The study suggests an U-shaped relationship between iodine intake and TAI in adults, and both iodine deficiency and iodine excess are risk factors of TAI in adults. The underlying mechanisms need to be elucidated in future studies.

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Introduction

Autoimmune thyroid diseases (AITDs) are autoimmune diseases occurring in the endocrine system and mainly include Hashimoto's thyroiditis (HT) and Graves' disease (GD) (1). Individuals with thyroid antibodies positivity are usually considered to suffer from thyroid autoimmunity (TAI) and its prevalence is over 10% in most populations (2, 3, 4). HT is the major type of TAI and the main cause of hypothyroidism, which is also the most common autoimmune disease. TAI can result

in thyroid dysfunction, and it also increases the risks of other common diseases, such as cardiovascular diseases, thyroid cancer and other autoimmune diseases (5, 6, 7, 8, 9, 10). Additionally, TAI is also associated with higher rates of complications during and after pregnancy, such as miscarriage and premature delivery (3, 11). Through numerous studies on TAI in the past two decades, it has been well accepted that TAI results from the interplay of multiple factors including susceptibility genetic variants

and environmental factors (12). Additionally, some factors have been identified as risk factors for TAI (13, 14), but its etiology is still largely not elucidated. Though most patients are asymptomatic, TAI can still cause much adverse impact on health. Therefore, it is essential to identify those important risk factors for TAI, especially for those modifiable risk factors. Some dietary factors have been identified as risk factors for TAI and are implicated in the development of TAI, such as selenium deficiency and vitamin D deficiency (15, 16).

Iodine is essential for the synthesis of thyroid hormone and iodine status has long been regarded as a key determinant of thyroid dysfunction (17). Optimization of iodine intake in the population is critical to reduce the prevalence of thyroid diseases (17). Previous studies have established that iodine deficiency is an important risk factor for both hypothyroidism and thyroid goiter (18). Despite numerous epidemiological studies on the impact of iodine intake on thyroid dysfunction, there are limited studies assessing the impact of iodine intake on TAI. Several epidemiological studies found that excessive iodine intake could increase the risk of TAI. A randomized controlled trial by Kahaly *et al.* also supported that iodine could induce TAI in patients with endemic goiter (19). However, other studies reported no obvious relationship between iodine status and TAI. Therefore, the link between iodine status and TAI is complex, and convincing evidence for the association of iodine status with TAI is still lacking (17). Therefore, to adequately elucidate the relationship between iodine status and TAI risk, we conducted both a cross-sectional study and a dose–response meta-analysis.

Methods

Participants

We first performed a population-based cross-sectional study. We reported the cross-sectional study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (20). In the cross-sectional study, 2824 individuals were randomly recruited from residents of Jinshan District of Shanghai in 2016, and 16 were excluded from this analysis for thyroidectomy. Finally, 2808 adults were enrolled, and all were from the Chinese Han population. All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Jinshan Hospital of Fudan University.

Clinical examination and laboratory testing

Data on age, gender, smoking, disease history and use of medications were collected. In the cross-sectional study, smoking individuals were defined as those current smokers. Fasting blood was used for laboratory testing. Thyroid antibodies including thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb) were tested using immunochemiluminometric assay (ICMA) method. The reference values for TPOAb and TGAb were 0–34 IU/L and 0–50 IU/L, respectively.

Category criteria for iodine status

Urinary iodine concentration (UIC) is a well-known indicator of iodine intake and is currently the most useful biochemical marker of iodine status. In our study, we also used UIC to evaluate iodine nutrition. UIC was quantified using the ammonium persulfate method. According to UIC values, participants were divided into four groups: iodine deficiency (UIC <100 µg/L), adequate iodine status (UIC 100–199.9 µg/L), more than adequate iodine status (UIC 200–299.9 µg/L) and iodine excess status (UIC ≥300 µg/L) (21).

Diagnostic criterion for TAI

The outcome of interest was the prevalence of TAI in individuals with specific iodine status. TAI was referred to the presence of positive TPOAb or TGAb or a combination of these two antibodies. TPOAb positivity was defined as TPOAb >34 IU/L, and TGAb positivity was defined as TGAb >50 IU/L.

Statistical analysis

We calculated sample size before the cross-sectional study. When the expected odds ratio (OR) was defined as 1.50 and the proportion with TAI in the population was 15%, a sufficient power over 80% need at least 658 individuals in each group. There were four groups in our study and a total of 2632 individuals should be thus recruited. Continuous variables are presented as mean with standard deviation (s.d.) or median with interquartile range (IQR) based on their types of data distribution. Mann–Whitney *U* test or *t* test were used to compare the between-group difference. Categorical variables are presented as frequencies with percentages, and chi-square test was used to compare the difference between two groups. To uncover possible sources of bias, the difference in clinical

characteristics across those four ordered UIC groups was also analyzed. The trend in proportions across ordered UIC groups was assessed using Cochran–Armitage test. The trend for continuous variables across ordered UIC groups was assessed using ‘nptrend’ in STATA. OR with 95% confidence interval (95% CI) was calculated through logistic regression analysis. Both age and gender had long been regarded as important impact factors of UIC and could cause risk of bias, which were thus adjusted in the logistic regression analysis. Smoking, diabetes, BMI and hypertension were also regarded as possible confounding factors in the logistic regression analysis. Age and BMI were analyzed as continuous variables, while the other factors were analyzed as categorical variables. Subgroup analyses were performed by the types of thyroid antibodies and gender. STATA (version 12.0, StataCorp, USA) was used, and two-sided *P* values less than 0.05 were considered to be statistically significant.

Dose-response meta-analysis

To get a more comprehensive evaluation of the impact of iodine status on TAI risk, a dose-response meta-analysis was conducted in accordance with the guidance on conducting systematic reviews and meta-analyses of observational studies of etiology (COSMOS-E) (22). The research question was whether a dose-response relationship existed in the association between iodine status and TAI risk. Pubmed, EMBASE and Wanfang database were searched to identify relevant cross-sectional or cohort studies (up to 30 November 2018). No language limitation was applied. The following search strategy was used: (iodization OR iodized OR iodised OR iodine OR iodination) and (Thyroid peroxidase antibodies OR Thyroid peroxidase antibody OR Thyroglobulin antibodies OR Thyroglobulin antibody OR thyroiditis OR thyroid autoimmunity OR thyroid autoantibody OR thyroid autoantibodies). Potential studies were screened by reading title or abstract and then underwent a following full-text evaluation. The references of eligible studies were also reviewed to identify other possible studies. Studies were considered eligible if they satisfied the following inclusion criteria: (1) Using cohort or cross-sectional design; (2) Participants were adults, children or adolescents; (3) Exposure was iodine status; (4) Control was those individuals with certain category of iodine status such as iodine deficiency, adequate iodine status or more than adequate iodine status; (5) The outcome of interest was TAI, TPOAb positivity or TGAAb positivity; (6) Relative risk (RR) or OR with 95% CIs for at least three quantitative

categories of iodine status were reported. Reviews or studies without sufficient data were all excluded.

The following data were extracted by two investigator independently, such as the first author, year of publication, study design, number of cases, number of participants, confounding variables in the multivariable analysis, UIC testing method, definitions of TAI and risk estimates with 95% CIs in each category of iodine status. Standardized data extraction sheets were used and the discrepancy between the two investigators was solved by discussion with another investigator. Quality assessment was performed according to the Newcastle–Ottawa Quality Assessment Scale (NOS), and studies with scores no more than five points were deemed to have suboptimal quality. Moreover, the risk of bias of those included studies was further assessed by the general principles of COSMOS-E (22). Risk of confounding bias, selection bias and information bias was assessed qualitatively in three categories including ‘low risk’, ‘moderate risk’ and ‘high risk’ (22).

The median UIC, mean UIC or the midpoint of the upper and lower boundaries was assigned as the corresponding iodine intake for each risk estimate. If the lowest or the highest category of iodine intake was a half-open interval, their interval length was assumed to be same with that of the adjacent category. The possible nonlinear dose-response relationship between iodine status and TAI risk was assessed through restricted cubic splines, and four knots at 5, 35, 65 and 95% of the full distribution were utilized (23). In the dose-response meta-analysis, generalized least-square regression model was used (23, 24). Both the spline model and the linear model were used in the dose-response meta-analysis, and the curve linearity was thus tested through the difference between the spline model and the linear model and the *P* value for the difference above was also calculated (23). The risk estimates were pooled using a random-effect model (25). Stratified analyses by risk of confounding bias were also performed. Sensitivity analysis was then performed by excluding studies with suboptimal quality or high risk of bias. All statistical analyses were performed with STATA version 12 (StataCorp LP), and *P* value less than 0.05 was considered to be statistically significant.

Results

Characteristics of participants

The characteristics of the 2808 participants are given in Supplementary Table 1 (see section on

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supplementary data given at the end of this article). The median UIC was 164.5 µg/L (IQR: 111.1–235.6). 359 (12.8%) were found to have TAI, 266 (9.5%) had TPOAb positivity and 308 (11.0%) had TGAb positivity. Supplementary Table 1 also shows the comparison of clinical characteristics between men and women participants. Table 1 shows the difference in the clinical characteristics across those four ordered UIC groups (Table 1). As shown in Table 1, participants with high UIC had younger age, lower BMI, lower prevalence of diabetes, lower prevalence of hypertension than those with lower UIC ($P < 0.05$, Table 1). No obvious difference in other clinical characteristics across those four ordered UIC groups was observed (Table 1). There was no obvious difference in both the level of TPOAb ($P = 0.15$) and the level of TGAb ($P = 0.19$) across those four UIC groups (Table 1). When using the adequate iodine group as reference, TPOAb level was not higher in the iodine deficiency group ($P = 0.53$), the more than adequate iodine group ($P = 0.13$) and the iodine excess group ($P = 0.32$). When using the more than adequate iodine group as reference, TPOAb level was also not higher in the iodine deficiency group ($P = 0.13$). When using the adequate iodine group as reference, TGAb level was not higher in the iodine deficiency group ($P = 0.27$), the more than adequate iodine group ($P = 0.61$) and the iodine excess group ($P = 0.17$).

UIC and TAI

The prevalence of TAI over those four ordered UIC groups is shown in Table 2, which suggested a clear U-shaped curve (Table 2). Compared with those with more than adequate iodine status (9.3%), there was a higher prevalence of TAI in participants with iodine deficiency (14.4%),

adequate iodine status (13.5%) and iodine excess (13.7%) (Table 2). Multivariate logistic regression analysis also confirmed the U-shaped relationship between iodine intake and TAI (Table 2). Compared with those with more than adequate iodine status, individuals with iodine deficiency, adequate iodine status and excessive iodine status all had higher risk of TAI, and the adjusted ORs were 1.50 (95% CI 1.03–2.17, $P = 0.032$), 1.50 (95% CI 1.09–2.07, $P = 0.013$) and 1.68 (95% CI 1.11–2.53, $P = 0.014$), respectively. Subgroup analysis in men also found an obvious U-shaped relationship between iodine intake and TAI (Table 2). The relationship between iodine intake and TAI in women was also likely to be U shaped, but the outcomes were not statistically significant (Table 2).

The relationship between iodine intake and TPOAb positivity was shown in Supplementary Table 2, and the relationship between iodine intake and TGAb positivity was shown in Supplementary Table 3. The relationship of iodine intake with TPOAb positivity and TGAb positivity was both U shaped in men but was not in women.

Dose-response meta-analysis

Flow chart of study selection for the meta-analysis was shown in the Supplementary Fig. 1. A total of 5191 abstracts were identified through literature search. After excluding studies that did not fulfill the inclusion criteria, 185 candidate studies were further evaluated by reading full texts. Another 164 studies were further excluded and 21 studies from literature were eligible into meta-analysis (26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46). Therefore, a total of 22 studies (21 studies from literature and our cross-sectional study) were finally included. Main characteristics of those studies is

Table 1 Comparison of clinical characteristics of adults with different urinary iodine concentration.

Characteristics	Deficiency	Adequate	More than adequate	Excessive	P
Number	568	1253	616	371	–
Urinary iodine concentration	68.0 (52.7–88.0)	148.8 (126.0–172.2)	241.5 (218.7–261.9)	652.1 (332.4–1971.6)	<0.001
Age (years)	46.5 (14.4)	44.5 (15.6)	41.3 (16.1)	39.8 (17.1)	<0.001
BMI (kg/m ²)	24.1 (3.7)	24.4 (3.8)	24.0 (3.8)	23.8 (3.8)	0.02
Smoking (n (%))	113 (19.9)	353 (28.2)	185 (30.0)	101 (27.2)	0.12
Type 2 diabetes (n (%))	86 (15.1)	174 (13.9)	70 (11.4)	39 (10.5)	0.01
Hypertension (n (%))	191 (33.6)	410 (32.7)	174 (28.2)	94 (25.3)	0.005
Iodized salt intake (n (%))	396 (69.7)	955 (76.2)	513 (83.3)	315 (84.9)	0.09
TSH (mIU/L)	2.7 (1.8–3.2)	2.7 (1.7–3.2)	2.7 (1.7–3.3)	2.9 (1.7–3.6)	0.05
TPOAb (U/mL)	9.0 (6.3–13.8)	8.8 (6.5–12.6)	8.6 (6.3–12.2)	8.6 (6.5–12.0)	0.15
TGAb (U/mL)	11.9 (10.0–15.4)	11.5 (10.0–15.2)	11.6 (10.0–14.7)	12.4 (10.0–15.4)	0.19

Normally distributed variables were expressed as mean $\pm$ s.d., non-normally distributed variables as median with IQR and categorical variables as number with percentages (%). Urinary iodine concentrations: low, <100 µg/L; adequate, 100–199.9 µg/L; more than adequate, 200–299.9 µg/L; excessive, ≥ 300 µg/L.

BMI, body mass index; TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TSH, thyroid-stimulating hormone.

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Table 2 Risk of thyroid autoimmunity in adults with different urinary iodine concentrations.

Urinary iodine	Number	TAI (%)	Crude OR		Adjusted OR*	
			OR (95% CI)	P	OR (95% CI)	P
Total						
Deficiency	568	82 (14.4)	1.65 (1.16–2.37)	0.006	1.50 (1.03–2.17)	0.032
Adequate	1253	169 (13.5)	1.53 (1.11–2.10)	0.009	1.50 (1.09–2.07)	0.013
More than adequate	616	57 (9.3)	1	–	1	–
Excessive	371	51 (13.7)	1.56 (1.05–2.34)	0.029	1.68 (1.11–2.53)	0.014
Men						
Deficiency	217	21 (9.7)	2.50 (1.22–5.10)	0.012	2.83 (1.34–5.99)	0.006
Adequate	633	52 (8.2)	2.09 (1.12–3.89)	0.021	1.98 (1.06–3.71)	0.033
More than adequate	316	13 (4.1)	1	–	1	–
Excessive	213	19 (8.9)	2.28 (1.10–4.73)	0.026	2.31 (1.11–4.83)	0.026
Women						
Deficiency	351	61 (17.4)	1.22 (0.80–1.87)	0.349	1.19 (0.77–1.82)	0.433
Adequate	620	117 (18.9)	1.35 (0.93–1.97)	0.117	1.34 (0.92–1.96)	0.129
More than adequate	300	44 (14.7)	1	–	1	–
Excessive	158	32 (20.3)	1.48 (0.89–2.44)	0.128	1.43 (0.86–2.38)	0.166

Urinary iodine concentrations: low, <100 µg/L; adequate, 100–199.9 µg/L; more than adequate, 200–299.9 µg/L; excessive, ≥300 µg/L.

*Confounding factors in the multiple logistic regression analysis included age, sex, BMI, smoking, diabetes and hypertension.

OR, odds ratio.

shown in Table 3. All 22 studies used cross-sectional design, and sample size ranged from 209 to 15,008, with a total of 69,987 participants (Table 3). Among these 22 articles, most were conducted in Asians ($n=17$), and the other five studies were from Europe (Table 3). Five studies focused on the association of iodine intake with TAI in children, and the other studies mainly assessed the relationship in adults (Table 3). Only three studies reported adjusted risk estimates and had low risk of confounding bias, but the other studies did not exclude the impact of confounding factors such as age and gender, which were considered at higher risk of confounding bias (Supplementary Table 4). All studies had low risk of information bias, and most studies had low risk of selection bias (Supplementary Table 4). According to the NOS criteria, most studies scored more than five points and thus had good quality, but three studies scored five or less and were considered to have suboptimal quality (Supplementary Table 4).

Because our preliminary pooled results suggested an obvious difference in the association of iodine intake with TAI between children and adults, we performed the dose-response meta-analysis in adults and children separately. Dose-response meta-analysis of those 17 studies in adults revealed an obvious U-shaped association between iodine intake and TAI in adults with the lowest TAI risk at the UIC of 300 µg/L ($P_{\text{Nonlinearity}} < 0.0001$, Fig. 1), and both low iodine status and excessive iodine status could increase TAI risk in adults. The U-shaped curve between iodine intake and TAI in adults when the adequate iodine status (UIC 100–199.9 µg/L) was used as reference (Supplementary Fig. 2).

Dose-response meta-analysis of three studies with adjusted risk estimates and low risk of confounding bias also identified an U-shaped association between iodine intake and TAI in adults with the lowest TAI risk at the UIC of 250 µg/L ($P_{\text{Nonlinearity}} < 0.0001$, Fig. 2). Dose-response meta-analysis of 14 studies without adjusted risk estimates and high risk of confounding bias further identified an U-shaped association between iodine intake and TAI risk in adults ($P_{\text{Nonlinearity}} < 0.0001$, Supplementary Fig. 3). After excluding studies with moderate risk or high risk of selection bias, the U-shaped association between iodine intake and TAI risk in adults still existed ($P_{\text{Nonlinearity}} < 0.0001$, Supplementary Fig. 4). Moreover, dose-response meta-analysis of 14 studies with good quality according to NOS criteria also revealed an U-shaped association between iodine intake and TAI in adults ($P_{\text{Nonlinearity}} < 0.0001$, Supplementary Fig. 5).

Dose-response meta-analysis of 13 studies on TPOAb positivity in adults also suggested an U-shaped association between iodine intake and TPOAb positivity in adults ($P_{\text{Nonlinearity}} = 0.007$). Dose-response meta-analysis of 12 studies on TGAb positivity further proved an obvious U-shaped association between iodine intake and TGAb positivity in adults ($P_{\text{Nonlinearity}} < 0.0001$).

There were only five studies assessing the association between iodine intake and TAI in children. Dose-response meta-analysis of those five studies suggested a nonlinear association between iodine intake and TAI in children with the lowest TAI risk at the UIC of 50 µg/L ($P_{\text{Nonlinearity}} = 0.022$), but the U-shaped association was not observed (Supplementary Fig. 6). When the UIC

Table 3 Summary of published studies on the associations of iodine intake with thyroid autoimmunity.

Study (Ref.)	Country	Design	Participants (mean or median age; female, %)	Mean or median UIC ($\mu\text{g/L}$)	UIC determination method	Adjustment or matching factors	Outcomes
Wang 2004 (46)	China	Cross-sectional	3606 participants (aged 7–74 years; 53.4%)	NA	Ammonium persulfate method	None	TAI
Dogan 2011 (43)	Turkey	Cross-sectional	1000 participants (14.6 years; 50.0%)	NA	Ammonium persulfate method	None	TAI
Zhang 2011 (45)	China	Cross-sectional	1093 participants (52.3 years; 47.9%)	236.4 (IQR: NA)	Ammonium persulfate method	None	TMAb; TGAb
Zhang 2011 (44)	China	Cross-sectional	1683 participants (41.1 years; 48.9%)	254.9 (s.d.: 44.6)	Ammonium persulfate method	None	TPOAb; TGAb
Garcia-Garcia 2012 (42)	Spain	Cross-sectional	1387 participants (8.4 years; 48.8%)	199.5 (s.d.: 101.4)	Ammonium persulfate method	None	TAI
Zimmermann 2013 (41)	12 countries	Cross-sectional	2,512 participants (9.4 years; 49.8%)	151 (Range: 1–1883)	Ammonium persulfate method	None	TPOAb; TGAb
Habimana 2014 (40)	Belgium	Cross-sectional	209 participants (27.0 years; 100.0%)	138 (IQR: 57–321)	Ammonium persulfate method	None	TPOAb
Johner 2014 (39)	Germany	Cross-sectional	6101 participants (aged 6–17 years; 45.0%)	120.5 (IQR: NA)	Ammonium persulfate method	None	TPOAb
Shi 2015 (38)	China	Cross-sectional	7190 participants (aged 19–40 years; 100.0%)	152.6 (IQR: NA)	Ammonium persulfate method	Age, weeks of gestation, and BMI	TPOAb; TGAb
Qin 2016 (37)	China	Cross-sectional	1492 participants (45.2 years; 60.0%)	238.9 (s.d.: 162.0)	Ammonium persulfate method	None	TAI; TPOAb; TGAb
Guo 2016 (36)	China	Cross-sectional	1591 participants (aged over 18 years; NA)	130.7 (IQR: 77.4–198.9)	Ammonium persulfate method	None	TPOAb; TGAb
Wang 2016 (35)	China	Cross-sectional	1424 participants (aged no less than 18 years; 60.6%)	222.6 (IQR: NA)	Ammonium persulfate method	None	TAI
Chen 2017 (34)	China	Cross-sectional	1678 participants (61.7 years; 63.5%)	106.4 (IQR: 71.5–158.5)	Ammonium persulfate method	Age, sex, educational status, current smoker, current drinker, BMI, and TSH	TAI
Ye 2017 (33)	China	Cross-sectional	2794 participants (27.4 years; 100.0%)	155.0 (NA)	Ammonium persulfate method	None	TPOAb; TGAb
Xiao 2017 (31)	China	Cross-sectional	2282 participants (40.6 years; 47.7%)	230.1 (IQR: 148.4–352.8)	Ammonium persulfate method	None	TAI; TPOAb; TGAb
Liu 2017 (32)	China	Cross-sectional	2936 participants (42.9 years; NA)	146.1 (NA)	Ammonium persulfate method	None	TPOAb; TGAb
Hu 2018 (30)	China	Cross-sectional	2644 participants (aged no less than 18 years; 48.9%)	173.8 (IQR: 118.6–249.3)	Ammonium persulfate method	None	TPOAb; TGAb
Sha 2018 (29)	China	Cross-sectional	2827 participants (aged no less than 18 years; 49.8%)	258.7 (95% CI 76.6–1506.4)	Ammonium persulfate method	None	TPOAb; TGAb
Kang 2018 (28)	Korea	Cross-sectional	1288 participants (aged 6–19 years; 44.8%)	449 (range 15–21,905)	Mass spectrometry device	None	TPOAb
Kim 2018 (27)	Korea	Cross-sectional	6434 participants (38.0 years; 41.1%)	291.7 (IQR: 157.4–666.9)	Mass spectrometry device	None	TPOAb
Chen 2019 (26)	China	Cross-sectional	15,008 participants (45.5 years; 57.7%)	205.2 (IQR: 65.7–537.7)	Ammonium persulfate method	None	TAI
Present study	China	Cross-sectional	2,808 participants (43.6 years; 50.9%)	164.5 (IQR: 111.1–235.6)	Ammonium persulfate method	Age, sex, BMI, smoking, diabetes and hypertension	TAI; TPOAb; TGAb

NA, not available; RR, risk ratio.

Figure 1

U-shaped association between iodine intake and thyroid autoimmunity in adults in the dose-response meta-analysis of 17 studies in adults. The reference level of UIC is 300 µg/L. The black solid line represents the odds ratio and the long black dash line represents 95% confidence intervals of the fitted nonlinear trend. The short dash line represents the linear trend. The spline model was the optimal model, while the curve for the linear model was shown to display the difference in the patterns between the spline model and the linear model.

increased from 50 µg/L to 250 µg/L, the risk of TAI in children gradually increased. However, risk of TAI in children no longer increased when UIC was over 250 µg/L (Supplementary Fig. 6).

Discussion

Iodine intake has long been regarded as an environmental determinant for thyroid dysfunction, but its relationship with TAI is still controversial. Additionally, most previous studies did not adjust the influence of other confounding factors such as gender and age, and thus, were unable to evaluate the independent impact of iodine status on TAI risk. Our cross-sectional study adjusted the influence of confounding factors through multivariate logistic regression analysis, and thus was able to evaluate the independent role of iodine status on TAI risk. Additionally, we also performed a dose-response meta-analysis of 22 epidemiological studies, which was the first dose-response meta-analysis investigating the impact of iodine status on TAI risk. The cross-sectional study showed an U-shaped relationship between iodine intake and TAI in adults.

Figure 2

U-shaped association between iodine intake and thyroid autoimmunity in adults in the dose-response meta-analysis of three studies in adults with low risk of confounding bias. The reference level of UIC is 250 µg/L. The black solid line represents the odds ratio and the long black dash line represents 95% confidence intervals of the fitted nonlinear trend. The short dash line represents the linear trend. The spline model was the optimal model, while the curve for the linear model was shown to display the difference in the patterns between the spline model and the linear model.

The dose-response meta-analysis further validated the U-shaped relationship between iodine intake and TAI in adults, which proved the significantly increased risk of TAI among individuals with either iodine deficiency or excessive iodine status. Therefore, the study provides strong epidemiological evidence for the U-shaped relationship between iodine intake and TAI in adults, and both iodine deficiency and iodine excess are risk factors of TAI.

The consequence of iodine status on human health has gained rapidly growing concerns in the past decade, and iodine status has long been regarded as a key determinant of thyroid disorders in adults (17, 47). World Health Organization (WHO) suggests that an adequate UIC should be between 100 and 200 µg/L, and an UIC in the range of 200–299 µg/L and >300 µg/L indicate more than adequate intake and the presence of excessive iodine, respectively (21). According to the criteria of iodine status above, there are a large percentage of persons with either iodine deficiency or excessive iodine (28, 48, 49). It has been clear that iodine deficiency can result in impaired production of thyroid hormones and thus cause adverse effects on human health. Iodine deficiency can induce

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a number of iodine deficiency disorders (IDDs), such as hypothyroidism and goiter (50). Many countries have implemented universal salt iodization (USI) to eliminate IDDs, and iodine prophylaxis interventions have improved iodine status and reduced the prevalence of IDDs worldwide (51, 52).

Though iodine supplementation is essential in preventing IDDs, the adverse impact of iodine excess intake has to be taken into account. Currently, it remains a medical challenge to optimize iodine intake (53). Some studies also have shown an adverse impact of USI on the prevalence of other thyroid diseases such as hyperthyroidism (54). Therefore, a careful monitoring of iodine status is required to optimize USI and decrease the risk of thyroid disorders (55, 56). Additionally, though numerous studies have been performed to define the impact of iodine intake on various thyroid diseases such as thyroid cancer, TAI and hypothyroidism, no definite conclusion is available (17). Current studies suggest that the impact of iodine on different types of thyroid diseases is likely inconsistent, and the acceptable UIC range may thus vary in monitoring iodine supplementation across different types of thyroid diseases (17).

Similar to other thyroid diseases, optimization of iodine intake is also critical for the effective reduction of TAI prevalence. The classification method for iodine nutrition from WHO is mainly based on the relationship between UIC and IDDs such as hypothyroidism and thyroid goiter, in which the recommended UIC for the prevention of IDDs is within 100–199.9 µg/L (21). TAI is an autoimmune disease occurring in thyroid and has an obviously distinct pathogenic mechanism when compared with IDDs. Our study suggests an optimal iodine intake of UIC between 200 and 300 µg/L for the prevention of TAI, while those with UIC either less than 200 or more than 400 µg/L are at increased risk of TAI. Therefore, iodine supplementation or salt iodization are recommended for individuals with iodine deficiency to reduce TAI risk, but avoiding excessive intake is also essential to reduce TAI risk. Additionally, because either iodine excess status or iodine deficiency can increase TAI risk, the monitoring of iodine status is essential to improve the benefits of iodine supplementation and minimize its adverse influence by avoiding excessive intake.

The association between iodine intake and TAI is still controversial in children. An epidemiological study by Tsatsoulis *et al.* reported that children with TAI had obviously higher UIC than Non-TAI controls (57). A large cross-sectional study by Zimmermann *et al.* revealed that TAI risk was not increased by either iodine

deficiency or iodine excess in children (41). The current dose–response meta-analysis included only five studies assessing the association between iodine intake and TAI in children, and showed a nonlinear association between iodine intake and TAI in children with the lowest TAI risk at the UIC of 50 µg/L (Supplementary Fig. 6), which was different from the U-shaped relationship in adults. However, owing to the limited number of eligible studies in children, our study was still unable to establish a definite relationship between iodine intake and TAI risk in children. Considering the critical significance of iodine status in children, future studies are recommended to define the impact of iodine status on TAI risk in children.

As shown in the Supplementary table 4, confounding bias is a major threat to the validity of the pooled outcomes in our study. Both age and gender have long been regarded as important impact factors for both UIC and TAI, and they may cause the risk of confounding bias. However, most included studies did not adjust for age and gender, which increased the risk of confounding bias. Considering the limited number of studies with low risk of confounding risk, the findings in our study still need to be validated in more future studies with adequate adjustment for confounding factors. Besides, our cross-sectional study suggested that participants with high UIC had lower BMI, lower prevalence of diabetes and lower prevalence of hypertension than those with lower UIC (Table 1), suggesting that diabetes, BMI and hypertension were possible confounding factors. Therefore, to adequately assess the relationship between iodine and TAI risk, future studies need adjusting for all possible confounding factors through multivariate logistic regression analysis.

The mechanism of TAI is still largely elusive. T cells and B cells are the main parts of adaptive immune system which are considered to exert critical roles in the development of TAI, but recent studies indicate that innate immunity is also an essential part in the etiology of TAI (1, 58, 59). Similar to other autoimmune diseases, TAI is preceded by an absence of immune balance among immune cells such as T cells, B cells and macrophages (58). Previous studies have established that both genetic and environmental risk factors are involved in the etiology of TAI, both of which may initiate the autoimmune attacks to thyroid antigens by breaking up the immune balance among immune cells (58). Though high iodine has been identified as an important risk factor of TAI, the underlying molecular mechanisms have not yet been sufficiently clarified. Some studies proposed several possible explanations below. Firstly, excessive iodine intake could increase thyroglobulin immunogenicity and

TAI risk by unmasking a cryptic epitope on thyroglobulin, which could initiate the autoimmune process during TAI development (60). Additionally, the direct cytotoxic injury of thyroid cells caused by iodine has been well defined, which is an important event underlying the increased risk of TAI among individuals with excessive iodine intake (61, 62, 63). Finally, the direct stimulatory effect of iodine on immune cells may also be involved in the development of TAI. For instance, iodine could promote IgG synthesis in human peripheral blood lymphocytes in vitro, which indicated that iodine may enhance antibody synthesis by immune cells (64). However, the molecular mechanisms for the stimulatory effect of iodine on immune cells are largely not explored, which need to be elaborated in future studies.

The findings from the current study reveal iodine deficiency as a risk factor for TAI. The finding was supported by one previous study by Mooij *et al.* which reported that iodine deficiency could induce thyroid autoimmune reactivity and increased intrathyroidal dendritic cells, CD4⁺ T cells and CD8⁺ T cells in Wistar rats (65). There are several possible explanations for the increased risk of TAI in individuals with iodine deficiency. Firstly, since patients with thyroid nodular goiter often have concurrent thyroid antibodies, iodine deficiency thus may indirectly increase the TAI prevalence by increasing the prevalence of thyroid nodular goiter and causing damages to thyroid tissues (17, 66, 67, 68, 69). In addition, several studies have found that iodine can contribute to redox balance and iodine deficiency increases the degree of oxidative stress which may further promote immune response and increase autoimmune attack (70, 71, 72). Finally, TSH level is intensively related to iodine status, and iodine deficiency can result in increased TSH level (17, 73). Some studies found that TSH have an important role in regulating both the function of the immune system and immune response (74, 75, 76, 77, 78, 79, 80, 81). Therefore, the increased TSH level among hypothyroidism individuals caused by iodine deficiency may induce aberrant immune response and further promote the development of TAI. However, the mechanisms underlying the increased risk of TAI among individuals with iodine deficiency are still largely unknown and need to be elucidated in more future studies.

There were several limitations in our study. Firstly, there was obvious difference in the assays or cutoffs of thyroid antibodies in those studies, which may result in the difference in the reported associations of iodine intake with thyroid antibodies. Secondly, we only assessed the status of TPOAb and TGAb by a cross-sectional study of nearly 3000 participants and did not evaluate the impact

of iodine intake on risk of thyroid-stimulating hormone receptor antibodies (TRAb) positivity. The prevalence of TRAb is relatively low, and a study with a larger number of participants is necessary to adequately evaluate the impact of iodine intake on risk of TRAb positivity. Thirdly, most included studies used cross-sectional study design and thus had limited ability to assess the causality relationship between iodine and TAI. The relationship between iodine intake and TAI found in this study still needs to be validated in more prospective cohort studies or clinical controlled trials. Fourthly, apart from iodine status, there are also several other factors affecting TAI risk, such as gender, age and smoking. However, the interactions of iodine with other risk factors in the development of TAI are so far poorly defined, and future studies are needed to uncover them. Fifthly, most included studies were performed in Asian populations, and the findings may be unable to be generalized to other populations, such as Caucasians and Africans. More studies from Caucasians and Africans are needed to validate the relationship between iodine intake and TAI risk. Finally, there is a high possibility for iodine–gene interactions in the development of TAI. However, the iodine–gene interaction in the development of TAI is so far largely elusive. For instance, studies on the relationship between iodine status and TAI risk among individuals with predisposing genetic factors are still lacking, and further studies are warranted.

In conclusion, the findings in our study provide convincing evidence for the U-shaped relationship between iodine intake and TAI risk in adults, and both iodine deficiency and excessive iodine status are risk factors of TAI among adults. The findings have important clinical implications for iodine interventions, and monitoring iodine status is essential for an optimal iodine status. However, uncertainty remains about the relationship between iodine intake and TAI in specific populations such as children and those with predisposing genetic factors or family history, and it requires evidence from more longitudinal studies. Moreover, the pathogenic mechanisms underlying the roles of iodine in TAI are still largely elusive, and more studies are warranted to better elucidate those mechanisms.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0212>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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