Relations between various measures of iodine intake and thyroid volume, thyroid nodularity, and serum thyroglobulin[1–3]

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ABSTRACT

Background: Iodine intake can be measured in various ways, and each method may have advantages and disadvantages.

Objective: We sought to investigate the potential associations of various measures of iodine intake with thyroid volume, prevalence of thyroid nodules, and serum thyroglobulin. We also sought to identify, if possible, groups at risk of thyroid disease because of their food choices.

Design: This cohort study included 4649 randomly selected subjects with mild-to-moderate iodine deficiency; the subjects lived in 2 cities in Denmark. Iodine intake was estimated by using a food-frequency questionnaire and by measuring iodine excretion in spot urine samples. Thyroid volume and nodularity were measured with ultrasonography.

Results: In multiple linear regression models, significant inverse relations were found between thyroid volume and estimated 24-h iodine excretion, iodine intake from diet plus supplements, iodine intake from diet/kg body wt, and milk intake ($P = 0.001$ for all), but not urinary iodine excretion measured as a concentration ($P = 0.40$). All measures of iodine intake were significantly related to serum thyroglobulin concentration ($P \leq 0.002$), but only some measures of iodine intake were significantly related to the prevalence of thyroid nodules.

Conclusions: Even in a geographic area where mild iodine deficiency is common, a significant relation between iodine intake and thyroid volume was found. All measures of iodine intake, except iodine excretion measured as a urinary concentration, predicted thyroid volume. Serum thyroglobulin concentration appears to be a good marker of iodine status. Subgroups with low intakes of milk and milk products had an increased risk of thyroid disease. *Am J Clin Nutr* 2002;76:1069–76.

KEY WORDS Iodine intake, iodine excretion, thyroid volume, serum thyroglobulin, thyroid nodules, Denmark

INTRODUCTION

Iodine intake is important for thyroid function (1, 2). Marginal iodine intake can cause goiter, characterized by an enlarged thyroid gland. In addition to affecting thyroid size, iodine intake can influence the concentrations of thyroid hormones and thyroglobulin in the blood. Chronic iodine deficiency, including marginal iodine deficiency, increases serum thyroglobulin concentration (3, 4). Gutekunst et al (5) found a higher prevalence of thyroid nodules in an iodine-deficient area compared with an iodine-sufficient area.

In population studies, iodine intake is usually assessed by measuring iodine excretion in spot urine samples and is expressed relative to creatinine excretion or as a concentration (6). These methods have been shown to give reliable results for groups, but because of the large day-to-day variation, they cannot provide usable measures of iodine intake for individuals (7). Iodine intake can also be determined by using various dietary assessment methods such as the dietary record, food-frequency questionnaire (FFQ), and diet history interview. However, to determine an individual's habitual intake of nutrients such as iodine that occur in significant amounts in relatively few foods that are typically eaten infrequently, 20 to > 50 d of dietary records are needed (8). An FFQ or a diet history interview can overcome this problem by asking for the usual intake of relevant foods. The FFQ is often preferred because it is more cost-effective than the diet history interview.

Previous studies have not examined the usefulness of various iodine intake measures for assessing risk of thyroid disease, and serum thyroglobulin concentration has not been evaluated as a biomarker of iodine intake in populations with mild and moderate iodine deficiency. The present study was part of the Danish Investigation of Iodine Intake and Thyroid Diseases. In this study, iodine intake (determined by using an FFQ and by measuring iodine excretion in spot urine) and the size, structure, and function of the thyroid were examined in a population in which mild and moderate iodine deficiency are common.

The purpose of the current study was to relate commonly used measures of iodine intake to thyroid volume, the prevalence of thyroid nodules, and serum thyroglobulin concentrations, and, if possible, to identify risk groups for thyroid diseases in relation to food choices.

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SUBJECTS AND METHODS

The Danish Investigation of Iodine Intake and Thyroid Diseases took place at 2 centers in Denmark located in the cities of Aalborg and Copenhagen. A random sample was drawn from the civil registration system of all inhabitants of the regions around the 2 cities. The groups included were women aged 18–22, 25–30, 40–45, and 60–65 y and men aged 60–65 y. Altogether, 9274 subjects were invited to participate and 4649 (50.1%) enrolled in the study. Younger subjects were intentionally overrepresented because the study was designed for follow-up. Also, thyroid diseases are most common among women, and therefore more women than men were chosen. Men in the age group 60–65 y were selected to allow for comparison between the sexes and because the prevalence of thyroid abnormalities appears to increase with age. Children were not included because unpublished observations have shown no cases of goiter in schoolchildren. Of the 4649 subjects studied, 62 (1.3 %) were pregnant and 85 (1.8 %) were lactating. The examinations took place from 10 March 1997 to 1 June 1998. All examinations were conducted independently in the 2 cities. However, before the study began, all methods for gathering information and performing procedures were standardized. The respective regional ethical committees approved the study. All subjects provided written, informed consent. The cohort has been described in detail previously (9).

All subjects completed questionnaires that requested information about smoking habits, alcohol consumption, previous thyroid disease, and thyroid disease in the family. Subjects were also asked to bring in all the dietary supplements they took, and the brand names, dosage, and frequency of use were recorded. If they forgot to bring the supplements (< 5% did so), they were interviewed about current supplement use.

Iodine intake

Iodine intake from foods and beverages was determined from an FFQ, and iodine intake from all types of supplements used by the subjects was noted carefully during the interview. The FFQ was given to the subjects when they arrived at the center and they were asked to complete it while they waited for a thyroid ultrasound examination and an interview. The FFQ, which has been validated and is described in more detail elsewhere (10), was semiquantitative. It included 53 iodine-rich food items such as fish, milk, eggs, cheese, drinking water (including coffee and tea), and other beverages. The variability in iodine content related to geography (eg, iodine in drinking water) and related to differences between products (eg, organic versus nonorganic milk) was taken into account in the calculations of iodine intake. Iodine intake was calculated for 4346 subjects. Iodized salt was illegal in Denmark at the time the study took place.

Iodine excretion

Spot urine samples were collected when the subjects visited the center; these samples were analyzed for iodine and creatinine. Urinary iodine excretion was expressed in 2 ways: as a concentration (available for 4616 subjects) and as the estimated 24-h iodine excretion (available for 4594 subjects). For the estimated 24-h iodine excretion, we calculated the iodine-to-creatinine ratio and multiplied the ratio by the expected daily creatinine excretion for the given individual. The expected 24-h creatinine excretion was determined on the basis of the method of Kesteloot and Joossens (11); some groups of subjects were combined because there was negligible variation. Thus, the figures that we used for 24-h creatinine excretion were 1.47 g for men, 1.23 g for women aged ≤ 49 y, and 1.07 for women aged 60–65 y (12).

Iodine in urine was measured in duplicate by using the cerium/arsenic method after alkaline ashing (13) as described previously (14). Urinary creatinine was determined with the kinetic modification of the Jaffe method (15).

Thyroid volume and nodules

An ultrasound examination of the thyroid was performed to determine thyroid volume and to detect and measure thyroid nodules. The examination was performed, as described previously (16), with a Sonoline Versa Pro (Siemens, Munich, Germany) with a 7.5-MHz, 70-mm linear transducer (effective length, 62 mm). Thyroid volume was calculated as the maximal length × width × depth × π/6 of each lobe (available for 4641 subjects). Thyroid enlargement was defined as a thyroid volume > 18 mL for women and > 25 mL for men, which corresponds to the mean + 3 SDs in iodine-sufficient populations (17). The number of distinct nodules > 5 mm in diameter and the diameter of each nodule were recorded; if there were > 3 nodules in a lobe, only the 3 largest were recorded. Before the present study, an interobserver study was performed in 25 subjects; good correlation and agreement were found between the 2 observers for thyroid volume ($r = 0.98$) and for prevalence of thyroid nodules ($\kappa = 0.72$) (16). A physical examination of the neck was performed (available for 4565 subjects) without knowledge of the results of the ultrasound examination, and goiter was classified according to World Health Organization criteria (1).

Blood samples were drawn and stored at −20 °C. Once the study was finished, samples were analyzed in a sequence that mixed samples from the 2 regions, from subjects of different ages and sexes, and from the different seasons of the year. Serum thyroglobulin concentration (available for 4583 subjects) and thyroid-stimulating hormone concentration (available for 4586 subjects) were analyzed with immunoluminometric assays (Lumitest; Brahms, Berlin). Thyroglobulin antibodies were measured by using a radioimmunoassay (DYNOtest; Brahms) with a functional assay sensitivity < 20 kU/L. Subjects with thyroglobulin antibodies > 20 kU/L (n = 627) were excluded from the serum thyroglobulin analyses because of the risk of analytic interference.

Statistical analyses

The relations between various measures of iodine intake and thyroid volume were investigated in 7 multiple linear regression models (general linear models) with log-transformed thyroid volume as the dependent variable. Each model included one measure of iodine intake and the variables found to be related to thyroid volume as independent variables. These variables included the city, subject group (age and sex), smoking (daily smoker or not daily smoker), drinking (≥ 8 drinks/wk or < 8 drinks/wk), and thyroid disease in the family.

The 7 measures of iodine intake were: iodine excretion expressed as a concentration, estimated 24-h iodine excretion, total iodine intake (from the diet plus supplements), iodine intake from the diet, iodine intake from the diet/kg body wt, milk intake, and iodine intake index. The iodine intake index was defined as either low or high. A low iodine intake index was < 75 g fish/wk and < one-half glass of milk/d and a high iodine intake index was > 200 g of fish/wk and ≥ 0.5 L milk/d. All kinds of milk and milk products were included in the milk intake. Likewise, the relations between the 7 iodine intake measures and palpable goiter, thyroid

TABLE 1
Thyroid volume and prevalence of nodules, serum thyroglobulin concentration, and urinary iodine excretion and concentration in subjects in the 2 cities

	Copenhagen	Aalborg
Thyroid volume (mL)	11.9 (9.0–16.2) [2426][1]	13.6 (10.1–18.8)[2] [2215]
Prevalence of nodules (%)		
Solitary nodules	18.3	13.9
Multiple nodules	16.9	15.3
Serum thyroglobulin (μg/L)	11.5 (6.2–20.2) [2062]	15.4 (7.8–29.8)[2] [1866]
Estimated 24-h iodine excretion (μg)	111 (74–180) [2419]	74 (48–126)[2] [2175]
Iodine concentration in spot urine samples (μg/L)	68 (38–112) [2422]	53 (30–90) [2194]

[1] Median with 25th to 75th percentiles in parentheses and *n* in brackets.
[2] Significantly different from the Copenhagen value, $P < 0.001$ (Mann-Whitney *U* test).

enlargement, and thyroid nodules were examined by using 7 logistic regression models with the same independent variables as described above.

The effects of different iodine intake measures on serum thyroglobulin concentration were examined by using 7 multiple linear regression models with log-transformed serum thyroglobulin as the dependent variable. Each model included variables found to be related to serum thyroglobulin, which were the city, subject group (age and sex), smoking (daily smoker or not daily smoker), thyroid enlargement, thyroid structure (regular, single nodule, or multinodular), hyperthyroidism (thyroid-stimulating hormone < 0.2 mU/L), and one measure of iodine intake as independent variables.

The linear models were used to estimate geometric means of thyroid volume and serum thyroglobulin, respectively, adjusted for confounders. Interactions between relevant variables were investigated. The only significant interaction was between milk intake as a categorical variable and city in the model with log thyroid volume as the dependent variable. However, when milk intake was entered as a continuous variable, the interaction disappeared. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) version 10.0 (SPSS Inc, Chicago).

RESULTS

The results for thyroid volume, prevalence of nodules, serum thyroglobulin concentrations, and iodine excretion in the 2 cities have been published (9, 18, 19) but are summarized in **Table 1**. The populations of the 2 cities were found to have mild-to-moderate iodine deficiency on the basis of the iodine concentrations in spot urine samples.

Thyroid enlargement

The results of 7 multiple linear regression models with log thyroid volume as the dependent variable are shown in **Table 2**. The models include various different measures of iodine intake but are otherwise similar. Iodine intake expressed as urinary iodine concentration in spot urine samples and as the iodine intake index was not significantly related to log thyroid volume whereas the other measures of iodine intake were significantly related to log thyroid volume when included in the model. Iodine intake from supplements was included separately in models 4 to 7 and it was negatively, but not significantly, associated with log thyroid volume.

In multiple logistic regression models with thyroid enlargement as the dependent variable (**Table 3**) and the same independent variables as were included in the multiple linear regression models, the same measures of iodine intake were significantly associated with the dependent variable (ie, thyroid enlargement) as in the multiple linear regression models. The only exception was that the association with iodine intake from the diet was not significant.

In logistic regression models with the same independent variables used in the multiple linear regression models, no relation was found between iodine intake and palpable goiter 1b or higher. Among the subjects not being treated for thyroid disease, 108 subjects were classified with palpable goiter 1b or higher and 4233 were classified without goiter or with goiter 1a.

Thyroid nodules

Logistic regression models were used to test the relations between iodine intake measures and the presence of all solitary nodules > 5 mm against no nodules and of solitary nodules > 10 mm against no nodules (**Table 4**). Likewise, logistic regression models were used to test all multiple nodules > 5 mm against no nodules and multiple nodules > 10 mm against no nodules. Some statistically significant relations with iodine intake measures were found.

Serum thyroglobulin concentration

The results of the multiple linear regression analyses with log serum thyroglobulin concentration as the dependent variable and various measures of iodine intake included as independent variables are shown in **Table 5**. All measures of iodine intake were significantly inversely related to log serum thyroglobulin when included in these models. Intake of iodine from supplements was included in models 4, 5, 6, and 7 and was significantly inversely related to log serum thyroglobulin in all of these models.

DISCUSSION

In this study, we assessed the relations between 7 different measures of iodine intake and measures of thyroid pathology as well as serum thyroglobulin concentration. It was found that all measures of iodine intake except urinary iodine excretion expressed as a concentration were significantly inversely related to log-transformed thyroid volume. Likewise, all measures of iodine intake were significantly inversely related to log serum thyroglobulin concentration, whereas the relation between iodine intake and the occurrence of thyroid nodules was less clear. Furthermore, we found that a low total iodine intake and a low milk intake were both risk factors for thyroid enlargement.

Thyroid size and urinary iodine excretion are currently the 2 most widely used measures of iodine status (20). When different geographical areas are compared, a relation between these 2 measures is found (21). However, this relation is rarely observed within a geographical area (4, 22). In the present study, the urinary iodine concentration was not significantly related to thyroid volume when

TABLE 2
Multiple linear regression models with log thyroid volume as the dependent variable and various measures of iodine intake as the independent variables[1]

	Geometric mean thyroid volume (95% CI)	*P*
Model 1: iodine concentration in spot urine samples (μg/L)		0.400
<20 (*n* = 504)	14.0 (13.5, 14.6)	
20–49.9 (*n* = 1233)	14.1 (13.7, 14.5)	
50–99.9 (*n* = 1502)	13.7 (13.4, 14.1)	
≥100 (*n* = 1135)	13.8 (13.4, 14.2)	
Model 2: estimated 24-h urinary iodine (μg/d)		0.001
<50 (*n* = 771)	14.4 (13.9, 14.9)	
50–99.9 (*n* = 1698)	14.0 (13.7, 14.4)	
100–149.9 (*n* = 808)	14.0 (13.5, 14.4)	
≥150 (*n* = 1145)	13.3 (13.0, 13.7)	
Model 3: iodine intake from diet plus supplements (μg/d, in quintiles)		0.001
≤80 (*n* = 831)	14.7 (14.2, 15.2)	
81–126 (*n* = 819)	13.9 (13.4, 14.3)	
127–187 (*n* = 825)	13.9 (13.4, 14.3)	
188–256 (*n* = 829)	13.4 (13.0, 13.8)	
>256 (*n* = 831)	13.7 (13.3, 14.2)	
Model 4: iodine intake from diet (μg/d, in quintiles)[2]		0.050
≤70 (*n* = 827)	14.5 (14.0, 15.0)	
71–98 (*n* = 823)	13.7 (13.3, 14.2)	
99–130 (*n* = 823)	13.8 (13.4, 14.3)	
131–175 (*n* = 820)	13.8 (13.3, 14.2)	
>175 (*n* = 842)	13.7 (13.3, 14.2)	
Model 5: iodine intake from diet/kg body wt (μg/kg)[2]		0.001
≤1.0 (*n* = 807)	14.9 (14.4, 15.3)	
1.1–1.4 (*n* = 823)	14.1 (13.7, 14.6)	
1.5–1.9 (*n* = 910)	13.7 (13.3, 14.1)	
2.0–2.5 (*n* = 727)	14.0 (13.5, 14.5)	
>2.5 (*n* = 802)	13.0 (12.6, 13.4)	
Model 6: iodine intake index[2,3]		0.141
Low (*n* = 203)	14.5 (13.8, 15.1)	
Middle (*n* = 3383)	13.8 (13.6, 14.1)	
High (*n* = 380)	13.9 (13.1, 14.7)	
Model 7: milk intake (glasses/d)[2,4]		0.001
0–0.2 (*n* = 612)	14.9 (14.4, 15.5)	
0.3–1.0 (*n* = 1085)	13.9 (13.5, 14.3)	
1.1–2.0 (*n* = 1198)	13.8 (13.5, 14.2)	
2.1–3.0 (*n* = 402)	14.1 (13.5, 14.8)	
>3.0 (*n* = 782)	13.4 (12.9, 13.9)	

[1] All models include the following variables: city, subject group (age and sex), smoking (daily smoker or not daily smoker), drinking (≥8 drinks/wk or <8 drinks/wk), and thyroid disease in the family; $P < 0.001$ for all these variables. Subjects being treated for thyroid disease ($n = 77$) were not included in the analysis.

[2] When iodine intake from supplements was included in the model, P = 0.071, 0.098, 0.058, and 0.066 for models 4, 5, 6, and 7, respectively.

[3] Low, <75 g fish/wk and <one-half glass milk/d; high, >200 g fish/wk and ≥0.5 L milk/d.

[4] Fish intake and water intake were included in the analysis but not in the final model because these variables were not significantly related to log thyroid volume.

TABLE 3
Logistic regression models with thyroid enlargement (thyroid volume >18 mL for women and >25 mL for men) as the dependent variable and various measures of iodine intake as the independent variables[1]

	Odds ratio (95% CI)	*P*
Model 1: iodine concentration in spot urine samples (μg/L)		0.357
<20 (*n* = 504)	1.00	
20–49.9 (*n* = 1233)	1.01 (0.80, 1.26)	
50–99.9 (*n* = 1502)	0.90 (0.72, 1.13)	
≥100 (*n* = 1135)	0.81 (0.61, 1.08)	
Model 2: estimated 24-h urinary iodine (μg/d)		<0.001
<50 (*n* = 771)	1.00	
50–99.9 (*n* = 1698)	0.74 (0.57, 0.95)	
100–149.9 (*n* = 808)	0.72 (0.57, 0.89)	
≥150 (*n* = 1145)	0.54 (0.41, 0.70)	
Model 3: iodine intake from diet plus supplements (μg/d, in quintiles)		0.036
≤80 (*n* = 831)	1.00	
81–126 (*n* = 819)	0.94 (0.71, 1.24)	
127–187 (*n* = 825)	0.90 (0.68, 1.19)	
188–256 (*n* = 829)	0.94 (0.71, 1.24)	
>256 (*n* = 831)	0.68 (0.51, 0.89)	
Model 4: iodine intake from diet (μg/d, in quintiles)[2]		0.107
≤70 (*n* = 827)	1.00	
71–98 (*n* = 823)	0.94 (0.71, 1.25)	
99–130 (*n* = 823)	1.00 (0.75, 1.33)	
131–175 (*n* = 820)	0.83 (0.63, 1.10)	
>175 (*n* = 842)	0.73 (0.55, 0.97)	
Model 5: iodine intake from diet/kg body wt (μg/kg)[2]		<0.001
≤1.0 (*n* = 807)	1.00	
1.1–1.4 (*n* = 823)	0.62 (0.46, 0.84)	
1.5–1.9 (*n* = 910)	0.68 (0.50, 0.91)	
2.0–2.5 (*n* = 727)	0.58 (0.43, 0.77)	
>2.5 (*n* = 802)	0.46 (0.34, 0.62)	
Model 6: iodine intake index[2,3]		0.545
Low (*n* = 203)	1.22 (0.85, 1.74)	
Middle (*n* = 3383)	1.00	
High (*n* = 380)	0.68 (0.49, 0.94)	
Model 7: milk intake (glasses/d)[2]		0.049
0–0.2 (*n* = 612)	1.00	
0.3–1.0 (*n* = 1085)	0.93 (0.65, 1.33)	
1.1–2.0 (*n* = 1198)	0.83 (0.63, 1.09)	
2.1–3.0 (*n* = 402)	0.75 (0.57, 0.99)	
>3.0 (*n* = 782)	0.65 (0.48, 0.88)	

[1] All models include the following variables: city, subject group (age and sex), smoking (daily smoker or not daily smoker), drinking (≥8 drinks/wk or <8 drinks/wk), and thyroid disease in the family; $P < 0.01$ for all these variables. Subjects being treated for thyroid disease ($n = 77$) were not included in the analysis.

[2] Iodine intake from supplements was included in the model.

[3] Low, <75 g fish/wk and <one-half glass milk/d; high, >200 g fish/wk and ≥0.5 L milk/d.

TABLE 4
Relations between the occurrence of thyroid nodules and different measures of iodine intake[1]

	Multiple nodules		Solitary nodules	
	All (n = 3819)[2]	>10 mm (n = 3648)[3]	All (n = 3746)[4]	>10 mm (n = 3412)[5]
Model 1: iodine concentration in spot urine samples	NS	NS	NS	NS
Model 2: estimated 24-h urinary iodine (μg/d)	NS	NS	P = 0.031	NS
<50			1.00	
50–99.9			1.26 (0.95, 1.66)[6]	
100–149.9			1.17 (0.84, 1.61)	
≥150			0.90 (0.66, 1.22)	
Model 3: iodine intake from diet plus supplements (μg/d)	P = 0.006	NS	P = 0.026	NS
≤80	1.00		1.00	
81–126	0.61 (0.45, 0.84)		0.97 (0.72, 1.29)	
127–187	0.66 (0.48, 0.90)		0.84 (0.62, 1.13)	
188–257	0.60 (0.44, 0.81)		0.67 (0.49, 0.91)	
>257	0.64 (0.47, 0.88)		0.70 (0.51, 0.95)	
Model 4: iodine intake from diet (μg/d)[7]	P = 0.030	NS	NS	NS
≤70	1.00			
71–98	0.74 (0.55, 1.00)			
99–130	0.74 (0.54, 1.00)			
131–175	0.66 (0.48, 0.90)			
>175	0.62 (0.45, 0.85)			
Model 5: iodine intake from diet/kg body wt (μg/kg)[7]	P = 0.002	P = 0.024	P = 0.080	P = 0.060
≤1.0	1.00	1.00	1.00	1.00
1.1–1.4	0.91 (0.68, 1.21)	0.93 (0.67, 1.28)	0.81 (0.60, 1.09)	1.11 (0.74, 1.68)
1.5–1.9	0.68 (0.50, 0.91)	0.70 (0.50, 0.98)	0.85 (0.63, 1.13)	0.94 (0.62, 1.43)
2.0–2.5	0.63 (0.45, 0.87)	0.66 (0.46, 0.96)	0.78 (0.57, 1.07)	1.04 (0.67, 1.62)
>2.5	0.58 (0.42, 0.80)	0.61 (0.43, 0.87)	0.63 (0.46, 0.87)	0.56 (0.34, 0.92)
Model 6: iodine intake index[7,8]	NS	NS	NS	NS
Model 7: milk intake (glasses/d)[7]	P = 0.012	P = 0.088	P = 0.011	NS
0–0.2	1.00	1.00	1.00	
0.3–1.0	0.73 (0.55, 0.97)	0.78 (0.57, 1.08)	0.82 (0.61, 1.10)	
1.1–2.0	0.75 (0.57, 0.99)	0.82 (0.60, 1.13)	0.83 (0.62, 1.11)	
2.1–3.0	0.57 (0.38, 0.86)	0.63 (0.40, 0.99)	1.01 (0.70, 1.46)	
>3	0.58 (0.42, 0.82)	0.61 (0.42, 0.89)	0.56 (0.39, 0.80)	

[1] All models include the following variables: city, subject group (age and sex), smoking (daily smoker or not daily smoker), drinking (≥8 drinks/wk or <8 drinks/wk), and thyroid disease in the family. Subjects being treated for thyroid disease (n = 77) were not included in the analysis.
[2] Subjects with solitary nodules were not included; of the 3819 subjects included in the analysis, 668 had multiple nodules.
[3] Subjects with solitary nodules and subjects with multiple nodules <10 mm were not included; of the 3648 subjects included in the analysis, 497 had multiple nodules >10 mm.
[4] Subjects with multiple nodules were not included; of the 3746 subjects included in the analysis, 595 had a solitary nodule.
[5] Subjects with multiple nodules and subjects with solitary nodules <10 mm were not included; of the 3412 subjects included in the analysis, 261 had a solitary nodule >10 mm.
[6] Odds ratio with 95% CI in parentheses.
[7] Iodine intake from supplements included in the model.
[8] Low, <75 g fish/wk and <one-half glass milk/d; high, >225 g fish/wk and ≥0.5 L milk/d.

included in a multiple linear regression model if we controlled for other factors affecting thyroid volume, such as smoking and thyroid disease in the family. In contrast to iodine excretion in spot urine samples, the FFQ provides a measure of the individual's habitual iodine intake. The FFQ is therefore expected to be a better method for predicting increased thyroid size than is iodine excretion in urine samples. On the other hand, iodine intake expressed as estimated 24-h iodine excretion was significantly related to thyroid volume when included in a similar model. An individual's iodine intake cannot be determined by measuring iodine excretion in one spot urine sample. Thus, a strong relation between iodine excretion and thyroid parameters cannot be expected, especially when iodine excretion is expressed as a concentration in which the actual dilution of the sample is not corrected for. The subjects' values for both measures of iodine excretion were classified into 4 groups according to amount. The chance that a given individual will be placed in the correct group on the basis of one spot urine sample is probably greater when iodine excretion is expressed as estimated 24-h iodine excretion than when it is expressed as a concentration. In a validation study performed with a subgroup of the study population (n = 108), the correlation between estimated 24-h iodine excretion and actual 24-h iodine excretion was P = 0.58 (P < 0.001), indicating that estimated 24-h iodine excretion is a reasonable measure of iodine excretion.

The results suggest that thyroid volume decreases when going from the lowest quintile of iodine intake to the second-lowest quintile, with a leveling off at higher intakes; this indicates that the lowest quintile of iodine intake is clearly insufficient. The same applies when iodine intake is expressed as a low intake of fish and milk (iodine intake index), although this relation is weak, or when expressed as milk intake

TABLE 5
Multiple regression models with log serum thyroglobulin concentration as the dependent variable and various measures of iodine intake as the independent variables[1]

	Geometric mean serum thyroglobulin (95% CI)	*P*
Model 1: iodine concentration in spot urine samples (μg/L)		<0.001
<20 (*n* = 420)	29.0 (24.9, 33.6)	
20–49.9 (*n* = 1058)	25.5 (22.3, 29.0)	
50–99.9 (*n* = 1294)	24.5 (21.5, 27.9)	
≥100 (*n* = 956)	19.4 (17.0, 22.1)	
Model 2: estimated 24-h urinary iodine (μg/d)		<0.001
<50 (*n* = 663)	33.0 (28.7, 38.0)	
50–99.9 (*n* = 1384)	24.6 (21.6, 28.0)	
100–149.9 (*n* = 696)	22.1 (19.3, 25.3)	
≥150 (*n* = 959)	18.9 (16.5, 21.6)	
Model 3: iodine intake from diet plus supplements (μg/d, in quintiles)		<0.001
≤80 (*n* = 704)	29.2 (25.4, 33.6)	
81–126 (*n* = 699)	24.9 (21.7, 28.7)	
127–187 (*n* = 702)	22.5 (19.6, 26.0)	
188–256 (*n* = 710)	20.2 (17.5, 23.3)	
>256 (*n* = 701)	20.0 (17.4, 23.0)	
Model 4: iodine intake from diet (μg/d, in quintiles)[2]		0.002
≤70 (*n* = 700)	26.6 (23.1, 30.7)	
71–98 (*n* = 701)	23.1 (20.1, 26.5)	
99–130 (*n* = 695)	22.1 (19.3, 25.5)	
131–175 (*n* = 694)	23.0 (19.9, 26.4)	
>175 (*n* = 726)	22.0 (19.1, 25.3)	
Model 5: iodine intake from diet/kg body wt (μg/kg)[2]		<0.001
≤1.0 (*n* = 674)	27.7 (24.0, 31.9)	
1.1–1.4 (*n* = 704)	23.0 (20.0, 26.5)	
1.5–1.9 (*n* = 767)	23.0 (20.0, 26.4)	
2.0–2.5 (*n* = 629)	21.5 (18.7, 24.8)	
>2.5 (*n* = 737)	21.6 (18.8, 24.8)	
Model 6: iodine intake index[2,3]		0.001
Low (*n* = 173)	28.1 (17.3, 25.2)	
Middle (*n* = 2878)	23.1 (20.3, 26.2)	
High (*n* = 322)	20.9 (23.9, 33.0)	
Model 7: milk intake (glasses/d)[2,4]		<0.001
0–0.2 (*n* = 536)	25.6 (22.1, 29.7)	
0.3–1.0 (*n* = 913)	24.5 (21.3, 28.1)	
1.1–2.0 (*n* = 1010)	23.1 (20.2, 26.4)	
2.1–3.0 (*n* = 333)	23.4 (19.9, 27.4)	
>3 (*n* = 676)	20.2 (17.6, 23.3)	

[1] Subjects being treated for thyroid disease (*n* = 77) and subjects with thyroglobulin antibodies >20 kU/L (*n* = 627) were not included in the analysis. All models include the following variables: city, subject group (age and sex), smoking (daily smoker or not daily smoker), thyroid enlargement (thyroid volume >18 mL for women and >25 mL for men), thyroid structure (regular, single nodule, multinodular), and hyperthyroidism (TSH > 0.2 mU/L or TSH < 0.2 mU/L); $P < 0.001$ for all these predictors. TSH, thyroid-stimulating hormone.

[2] Iodine intake from supplements was included in the model, $P < 0.001$ in all models.

[3] Low, <75 g fish/wk and <one-half glass milk/d; high, >225 g fish/wk and ≥0.5 L milk/d.

[4] Fish intake and water intake were included in the analysis but not in the final model because none of these variables were significantly related to log serum thyroglobulin.

only. The relation between milk intake and thyroid volume reflects the importance of milk as an iodine source in the study population.

The variables city of residence, age-and-sex category, smoking, alcohol intake, and thyroid diseases in the family were all factors which, apart from iodine intake, were important for thyroid volume in this population with mild-to-moderate iodine deficiency. If city of residence was not included in the model, the relations between measures of iodine intake and thyroid volume were stronger (data not shown).

Elevated serum thyroglobulin concentration was found to be an indicator of chronic iodine deficiency (3). The increased serum thyroglobulin concentration found in iodine deficiency could be a result of abnormal metabolism of thyroglobulin in the thyroid (23) or simply could reflect a correlation with the amount of thyroid tissue; thus, thyroglobulin concentration would be higher in iodine deficiency with increased thyroid volume. Serum thyroglobulin concentration was found to be elevated in goiter patients (24), and in comparative studies of areas that differed in terms of iodine status, lower serum thyroglobulin concentrations were reported in iodine-sufficient areas than in iodine-deficient areas (5, 25). In agreement with this, serum thyroglobulin concentration was significantly related to thyroid enlargement and to city of residence when included in multivariate linear models in our study population (18). Furthermore, a significant decrease in serum thyroglobulin concentration with increasing iodine concentration in urine was reported in Austria (4) and a drop in serum thyroglobulin concentration after iodine supplementation was found in pregnant women (26). Other variables, such as presence of thyroid nodules and concentrations of thyroid stimulating hormone, appear to influence serum thyroglobulin concentrations as well, whereas no relation between thyroid volume and serum thyroglobulin concentrations was found in an iodine-sufficient area (27).

In the present study, we found that serum thyroglobulin concentration was strongly inversely related to iodine intake when included in multiple linear regression models. Not only iodine excretion, but also iodine intake, intake of iodine-rich foods (iodine intake index), and milk intake were significantly inversely related to serum thyroglobulin concentration. This suggests that serum thyroglobulin concentration is a sensitive marker for iodine intake or iodine status, not only in iodine deficiency but also with a broader range of iodine intakes.

Nodular goiter is mainly the consequence of thyroid enlargement resulting from iodine deficiency (28, 29). Although Gutekunst et al (5) and Szabolcs et al (25) reported higher prevalences of thyroid nodules in areas with lower iodine intakes than in areas with higher iodine intakes, this relation has not been a universal finding in epidemiologic studies of iodine status (30, 31). Likewise, a higher prevalence of multinodular toxic goiter was found in an area with a typical iodine intake of ≈60 μg/d compared with an area with a typical iodine intake of ≈300 μg/d (32, 33). In the present study, the lowest intakes of iodine and low milk intake were both associated with the occurrence of thyroid nodules when compared with high intakes, although in general the associations with iodine intake measures were not clear. One explanation could be the broad age range of the subjects in this study. However, when only the oldest age group was included in the analyses, the results remained the same. In contrast with the findings of Laurberg et al (2, 33), we observed no clear difference between individuals with multiple nodules and individuals with solitary nodules in the effect of iodine intake.

Body size and body composition might affect the iodine requirement (34). Therefore, iodine intake relative to body weight might be a good indicator of iodine status. This was confirmed in the present study because this measure was predictive of thyroid volume and serum thyroglobulin concentration, and it was the measure that showed the most consistent relation to prevalence of thyroid nodules.

The risk of enlarged thyroid volume and increased serum thyroglobulin concentrations was higher in Aalborg (western part of Denmark) than in Copenhagen (eastern part of Denmark), as described by Knudsen et al (9, 18). This difference in risk can be explained mainly by the different iodine content of drinking water (35, 36) and, to a minor degree, of milk (35). However, total water intake (which included coffee, tea, etc.) was not found to be related to thyroid volume when included in the multiple linear regression model, whereas milk intake was. The iodine content of milk is somewhat higher than is the iodine content of water, which makes milk an important iodine source in Denmark. This association is shown by the higher thyroid volume, higher serum thyroglobulin concentration, and higher occurrence of thyroid nodules in subgroups with low milk intake. Fish has a natural, although varying, content of iodine, but fish intake was not related to thyroid volume in this population. In Denmark, the intake of fish in general is quite low (median intake: 10–15 g/10 MJ) (37), which could probably explain this finding. Furthermore, we cannot exclude the possibility that subjects were misclassified into the fish-intake groups. The association between actual iodine intake from dietary supplements and log thyroid volume was only of borderline significance when entered in the models. The reason could be that the amount of iodine consumed in dietary supplements is not a long-term predictor of iodine intake.

The results of the current study were found in a population with only mild-to-moderate iodine deficiency. One could speculate that this population had more serious iodine deficiency in the past and that the results of the current study were related to that more serious deficiency. However, studies of adult Danish populations in the 1960s and 1970s (38–40) showed urinary iodine excretion values that were similar to those in this study.

In conclusion, even in this population with mild-to-moderate iodine deficiency, a significant relation between iodine intake and thyroid volume was found. All measures of iodine intake, except urinary iodine excretion expressed as a concentration, were predictors of thyroid volume. This study confirms previous findings that serum thyroglobulin concentration is a good marker of iodine status and that serum thyroglobulin could be used as an objective measure of iodine status in a population. Within the population studied, subgroups with low intakes of milk and milk products have an increased risk of thyroid disease.

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