

RESEARCH

Sex differences in risk factors for subclinical hypothyroidism

Jeonghoon Ha, Jeongmin Lee, Kwanhoon Jo, Dong-Jun Lim, Moo Il Kang, Bong Yun Cha and Min-Hee Kim

Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Correspondence should be addressed to M-H Kim: benedict@catholic.ac.kr

Abstract

Objective: To investigate the prevalence of subclinical hypothyroidism (SCH) in Korean adults and identify the risk factors for the occurrence of SCH by sex.

Design and methods: This study used data from the Sixth Korea National Health and Nutrition Examination Survey (KNHANES VI), a cross-sectional, nationally representative survey, which comprises a health interview survey, a health examination survey and a nutrition survey. To examine SCH, the reference range of thyroid-stimulating hormone (TSH) was defined using both the range provided by the test kit manufacturer (SCH-M) and a population-based range (SCH-P). We investigated the prevalence of SCH and its risk factors by sex using both reference ranges.

Results: The prevalence of SCH in Koreans according to SCH-M (0.35–5.5 μ IU/mL) was 5.6%, and 3.3% with SCH-P (0.62–6.68 μ IU/mL). For men, smoking significantly reduced the incidence of SCH, positive anti-thyroid peroxidase antibody (TPOAb) significantly increased the risk of SCH, and in an adjusted model, the risk of SCH in all quartiles increased as the urine iodine creatinine ratio (UICR) quartile increased. For women, positive TPOAb was confirmed as a risk factor for SCH, as was the highest UICR quartile. Furthermore, the odds ratio for SCH in urban vs rural residence was 1.78.

Conclusions: The prevalence rates of SCH were similar to those reported in the literature and previously known risk factors were confirmed using both TSH reference ranges. The notable findings from this study are that the increased risk of SCH with increased iodine intake was more marked in men than in women and that residential area may be a risk factor for SCH in women.

Key Words

- ▶ subclinical hypothyroidism
- ▶ prevalence
- ▶ urine iodine
- ▶ sex differences

Endocrine Connections
(2018) 7, 511–522

Introduction

Subclinical hypothyroidism (SCH) is defined as a mildly elevated serum thyroid-stimulating hormone (TSH) level with a serum free thyroxine (FT4) level within the normal range (1). While treatment of SCH is not mandatory in most cases, thyroid hormone replacement can be considered in pregnant patients who have TSH persistently >10 μ IU/mL, associated symptoms or are at high risk of overt hypothyroidism (2, 3). SCH is frequently detected in the population with a prevalence of 3–12% (4, 5). The prevalence is dependent on the TSH reference range used, and the TSH level is known to

be strongly influenced by sex, area of residence, iodine intake and the presence of autoantibodies (4, 6, 7). In iodine-rich areas, a prevalence of SCH of up to 18% has been reported (2, 7, 8). Thyroid diseases including SCH are known to be more prevalent in women than in men (9, 10). Approximately 5–15% of women are positive for thyroid autoantibodies, either anti-thyroid peroxidase antibody (TPOAb) or anti-thyroglobulin antibody (11, 12). The higher incidence of thyroid autoantibodies in women is reported to account for their higher incidence of thyroid disease (9, 13). However, other sex-specific risk

factors for SCH development have not been elucidated. In addition, the TSH reference range required to define the SCH varies depending on the target population, and the normal reference range varies between subgroups in the same population. For example, in a study of the Korean population, the prevalence of SCH varied from 0.16% to 17.63%, depending on the particular population being studied (2, 14, 15). In the present study, we investigated the prevalence of SCH in Korean adults based on data from the most recent nationally representative epidemiological survey, the Sixth Korea National Health and Nutrition Examination Survey (KNHANES VI) and examined the risk factors for the occurrence of SCH according to sex.

Methods

Study population

KNHANES VI was carried out by the Korea Centers for Disease Control and Prevention (CDC) and comprises a health interview survey, a health examination survey and a nutrition survey, using a stratified multistage probability sampling design. Informed written consent for participation was obtained from all study subjects. In addition, the study was approved by the Korea CDC Institutional Review Board. TSH reference range was calculated by two methods, and the subjects were divided into two groups according to the method used. First, we used the TSH reference range (0.35–5.5 μ IU/mL) provided by the manufacturers of the test kit (Roche Diagnostics) to define SCH (SCH-M). Of the 22,948 Korean participants, 4914 aged <19 years were excluded. Subjects who were pregnant ($n=10$), had delivered a child within the previous year ($n=62$), had a history of treatment for thyroid disease ($n=58$), for whom insufficient urine iodine data were available ($n=372$), for whom insufficient FT4 data were available or were not within the normal range ($n=12,159$) and for whom insufficient TSH data were available or were <0.35 μ IU/mL ($n=69$) were excluded from the analysis. Ultimately, 4888 participants were included in this study. Second, SCH was defined using a TSH reference range based on the enrolled population (0.62–6.68 μ IU/mL) (SCH-P). Of the initial 22,948 Korean participants, 4801 subjects were selected for this analysis by excluding those who did not meet the inclusion criteria (subjects aged <19 years ($n=4914$), pregnant ($n=10$), history of delivery within 1 year ($n=59$), history of treatment for thyroid disease ($n=57$), insufficient urine iodine data ($n=368$), insufficient FT4 data or not within the normal range ($n=12,643$) and insufficient TSH data or value <0.62 μ IU/mL ($n=167$).

Measurements

All measurements and questionnaires were collected by specially trained investigators. Detailed anthropometric measurements were carried out as in previous studies (16, 17, 18). Height and body weight were measured as part of the health examination. Body mass index (BMI) was calculated from the measured height and weight. BMI was categorized as underweight (<18.5 kg/m²), normal weight (≥ 18.5 kg/m², <23 kg/m²), overweight (≥ 23 kg/m², <25 kg/m²) or obese (≥ 25 kg/m²). Waist circumference was measured to the nearest 0.1 cm at the narrowest point between the lowest rib and the uppermost lateral border of the right iliac crest. Blood pressure was also measured by trained technicians using a Baumanometer mercury sphygmomanometer (WA Baum, Copiague, NY, USA), and all the subjects were seated for at least 5 min before the measurements were taken. Creatinine, TSH, FT4 and TPOAb were measured from sampled blood collected after overnight fasting. TSH was measured using an E-TSH kit (Roche Diagnostics), for which the reference range was 0.35–5.50 μ IU/mL. FT4 was measured using an E-Free T4 kit (Roche Diagnostics) for which the reference range was 0.89–1.76 ng/mL. TPOAb was measured using an E-Anti-TPO kit (Roche Diagnostics); the normal range for TPOAb in humans is <34.0 IU/mL. Serum creatinine was measured using a Hitachi Automatic Analyzer 7600-210 (Hitachi) and iodine intake status was evaluated using the urine iodine creatinine ratio (UICR) determined using inductively coupled plasma-mass spectroscopy (PerkinElmer). Socio-economic status was defined according to income categorized into quartiles. Chronic kidney disease (CKD) was divided into five stages based on the glomerular filtration rate by referring to the Kidney Disease Outcomes Quality Initiative classification (19).

Definition of SCH

SCH was defined as normal serum FT4 levels with serum TSH levels above the reference range. However, SCH-M (0.35–5.5 μ IU/mL) differed from that defined using the 2.5–97.5 percentiles of serum TSH levels in the studied population (SCH-P, 0.62–6.68 μ IU/mL). Although clinical practice guidelines suggest the use of population-based reference ranges for TSH (20), the upper limit of TSH (6.68 μ IU/mL) acquired from the population data was higher than the cut-off values for SCH usually used in clinical practice. However, the clinical value of TSH upper limit values requires verification. Thus, we analyzed the data using both SCH-M and SCH-P.

Statistical analysis

Statistical analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC, USA). *P* values <0.05 were considered significant. Data are expressed as numbers and percentages or as means±s.d. Differences between subjects with SCH and without SCH were evaluated using the Wilcoxon rank-sum test or the χ^2 test, as appropriate. Differences between the four quartiles of serum TSH level were determined using a generalized linear model (Duncan’s test of multiple comparisons). Multivariable adjusted logistic regression analysis was conducted to determine odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of SCH across variables. Because of the complex sampling design, a sampling weight method was

used to assign participants representative of the Korean population for the analysis of data. Detailed characteristics of the statistical analysis of KNHANES have been reported previously (16, 21).

Results

Baseline characteristics of the subjects

Using the manufacturer’s suggested TSH reference range (SCH-M)

The baseline characteristics of 4888 participants were analyzed, as were age, sex, BMI, region of residence, family history of thyroid disease, smoking status, UICR quartile,

Table 1 Baseline characteristics of subjects when kit manufacturer suggested TSH reference range (0.35–5.5 μ IU/mL) is used.

	Total subjects (n=4888)	Subclinical hypothyroidism		P value
		No (n=4597)	Yes (n=291)	
Age (years)				0.064
19–29	998 (20.4%)	944 (20.5%)	54 (18.6%)	
30–39	897 (18.4%)	855 (18.6%)	42 (14.4%)	
40–49	956 (19.6%)	903 (19.6%)	53 (18.2%)	
50–59	1016 (20.7%)	935 (20.4%)	81 (27.8%)	
60–69	927 (19.0%)	877 (19.1%)	50 (17.2%)	
70 and above	94 (1.9%)	83 (1.8%)	11 (3.8%)	
Sex				<0.001
Male	2545 (53.9%)	2434 (54.8%)	111 (39.7%)	
Female	2343 (46.1%)	2163 (45.2%)	180 (60.3%)	
BMI (kg/m ²)				0.436
<18.5	210 (4.0%)	197 (4.1%)	13 (4.5%)	
≥18.5, <23	1891 (38.1%)	1788 (38.4%)	103 (35.4%)	
≥23, <25	1168 (24.4%)	1096 (24.3%)	72 (24.7%)	
≥25	1619 (33.5%)	1516 (33.2%)	103 (35.4%)	
Region of residence ^a				0.307
Rural	1312 (25.6%)	1239 (25.8%)	73 (22.8%)	
Urban	3576 (74.4%)	3358 (74.2%)	218 (77.2%)	
Family history of thyroid disease				0.787
No	4644 (95.0%)	4366 (95.0%)	278 (95.4%)	
Yes	244 (5.0%)	231 (5.0%)	13 (4.6%)	
Smoking				<0.001
No	2679 (54.3%)	2477 (53.4%)	202 (70.4%)	
Yes	2209 (46.7%)	2120 (46.6%)	89 (29.6%)	
UICR ^b				<0.001
Quartile 1	1246 (25.1%)	1207 (25.8%)	39 (13.0%)	
Quartile 2	1216 (25.0%)	1159 (25.3%)	57 (21.1%)	
Quartile 3	1198 (24.8%)	1122 (24.7%)	76 (26.6%)	
Quartile 4	1228 (25.1%)	1109 (24.2%)	119 (39.3%)	
Anti-TPO Ab				<0.001
Absence	4556 (93.5%)	4325 (94.4%)	231 (78.0%)	
Presence	332 (6.5%)	272 (5.6%)	60 (22.0%)	
CKD stage				0.494
Stage 1, 2	4707 (96.0%)	4428 (96.0%)	279 (96.8%)	
Stage 3, 4, 5	181 (4.0%)	169 (4.0%)	12 (3.2%)	

*Data are presented as mean±s.d., n (weighted %), statistics were carried out using Rao-Scott Chi-square test; ^aclassification of the area of residence is classified according to the administrative division of Korea; ^biodine intake status was evaluated by urine iodine creatinine ratio, quartile 1: <Q1 (141.53203438), quartile 2: ≥Q1 and <Q2 (281.81447737), quartile 3: ≥Q2 and <Q3 (664.64655625), quartile 4: ≥Q3.



the presence of TPOAb and CKD staging (Table 1). The subjects were distributed evenly in age between 19 and 69 years, and only 94 subjects were aged over 70 years. There were 2343 (46.1%) women, most of whom were urban area residents (74.4%). Overall, 4644 (95.0%) subjects had no family history of thyroid disease and 2679 (54.3%) were non-smokers. UICR was uniformly distributed by quartile, and TPOAb was undetectable in 4556 (93.5%) subjects. Most participants (96%) were found to be in CKD stages 1 and 2. The results of analysis of baseline characteristics by sex are summarized in Table 2. There was a clear difference between men and women for smoking status: of the 2545

men, 1933 (76.0%) were smokers, while only 276 of 2343 (11.8%) women were smokers.

Using the population-based TSH reference range (SCH-P)

A total of 4801 subjects were analyzed for the same variables as shown in Table 1; 2303 (46.1%) were women and most (74.3%) were urban area residents. Details are shown in Table 2. UICR was uniformly distributed by quartile, and TPOAb was undetectable in 4472 (93.4%) participants. As shown in Table 2, there was a significant

Table 2 Association with subclinical hypothyroidism according to gender when kit manufacturer suggested TSH reference range is used.

	Male total (n=2545)	Subclinical hypothyroidism (male)		P value	Female total (n=2343)	Subclinical hypothyroidism (female)		P value
		No (n=2434)	Yes (n=111)			No (n=2163)	Yes (n=180)	
Age (years)				0.696				0.017
19–29	530 (20.8%)	504 (20.7%)	26 (23.4%)		468 (20.0%)	440 (20.3%)	28 (15.6%)	
30–39	491 (19.3%)	472 (19.4%)	19 (17.1%)		406 (17.3%)	383 (17.7%)	23 (12.8%)	
40–49	502 (19.7%)	481 (19.8%)	21 (18.9%)		454 (19.4%)	422 (19.5%)	32 (17.8%)	
50–59	502 (19.7%)	481 (19.8%)	21 (18.9%)		514 (21.9%)	454 (21.0%)	60 (33.3%)	
60–69	470 (18.5%)	451 (18.5%)	19 (17.2%)		457 (19.5%)	426 (19.7%)	31 (17.2%)	
70 and above	50 (2.0%)	45 (1.8%)	5 (4.5%)		44 (1.9%)	38 (1.8%)	6 (3.3%)	
BMI (kg/m ²)				0.168				0.393
<18.5	65 (2.6%)	64 (2.5%)	1 (0.9%)		145 (6.2%)	133 (6.0%)	12 (4.8%)	
≥18.5, <23	837 (32.9%)	808 (33.7%)	29 (26.2%)		1054 (50.0%)	980 (44.0%)	74 (38.9%)	
≥23, <25	659 (25.9%)	631 (26.2%)	28 (25.2%)		509 (21.7%)	465 (22.1%)	44 (27.6%)	
≥25	984 (38.7%)	931 (37.6%)	53 (47.7%)		635 (27.1%)	585 (27.9%)	50 (28.7%)	
Region of residence ^a				0.161				0.009
Rural	693 (27.2%)	658 (25.6%)	35 (32.4%)		619 (26.4%)	581 (26.1%)	38 (16.5%)	
Urban	1852 (72.8%)	1776 (74.4%)	76 (67.6%)		1724 (73.6%)	1582 (73.9%)	142 (83.5%)	
Family history of thyroid disease				0.981				0.596
No	2442 (96.0%)	2334 (95.7%)	108 (95.8%)		2202 (94.0%)	2032 (94.1%)	170 (95.2%)	
Yes	103 (4.0%)	100 (4.3%)	3 (4.2%)		141 (6.0%)	131 (5.9%)	10 (4.8%)	
Smoking				0.020				0.093
No	612 (20.1%)	577 (24.2%)	35 (35.8%)		2067 (88.2%)	1900 (88.7%)	167 (93.1%)	
Yes	1933 (79.9%)	1857 (75.8%)	76 (64.2%)		276 (11.8%)	263 (11.3%)	13 (6.9%)	
UICR ^b				0.001				0.003
Quartile 1	774 (30.4%)	760 (30.5%)	14 (13.2%)		472 (20.1%)	447 (20.0%)	25 (13.9%)	
Quartile 2	643 (25.2%)	617 (25.1%)	26 (23.5%)		573 (24.5%)	542 (25.5%)	31 (17.2%)	
Quartile 3	587 (23.1%)	556 (23.8%)	31 (30.1%)		611 (26.1%)	566 (25.9%)	45 (25.0%)	
Quartile 4	541 (21.3%)	501 (20.6%)	40 (33.2%)		687 (29.3%)	608 (28.6%)	79 (43.9%)	
Anti-TPO Ab				<0.001				<0.001
Absence	2442 (96.0%)	2348 (96.5%)	94 (84.7%)		2114 (90.2%)	1977 (91.8%)	137 (73.6%)	
Presence	103 (4.0%)	86 (3.5%)	17 (15.3%)		229 (9.8%)	186 (8.2%)	43 (26.4%)	
CKD stage				0.491				0.694
Stage 1, 2	2445 (96.0%)	2338 (96.1%)	107 (97.3%)		2262 (96.5%)	2090 (95.9%)	172 (96.5%)	
Stage 3, 4, 5	100 (4.0%)	96 (3.9%)	4 (2.7%)		81 (3.5%)	73 (4.1%)	8 (3.5%)	

*Data are presented as mean ± s.d., n (weighted %), statistics were carried out using Rao-Scott chi-square test; ^aclassification of the area of residence is classified according to the administrative division of Korea; ^biodine intake status was evaluated by urine iodine creatinine ratio, quartile 1: <Q1 (141.53203438), quartile 2: ≥Q1 and <Q2 (281.81447737), quartile 3: ≥Q2 and <Q3 (664.64655625), quartile 4: ≥Q3.

difference between men and women in the frequency of smokers. The baseline values of other variables are similar to those shown in Table 1 and are summarized in Table 3. Table 4 shows the baseline characteristics analyzed by sex.

Prevalence of SCH in the Korean population

When SCH-M was used, the prevalence of SCH in Korea was 5.6% (291 subjects) (Table 1) of whom 180 (60.3%) were women. TPOAb was detected in 60 (22.0%) subjects with SCH. There were 119 subjects in the highest quartile of UICR, accounting for 39.3% of all subjects with SCH. The prevalence of SCH differed significantly based on sex, the presence of TPOAb and UICR quartile ($P < 0.001$).

As shown in Table 2, the prevalence of SCH was 4.4% (111 of 2545) in men and 7.7% (180 of 2343) in women.

When SCH-P was used, SCH was confirmed in 157 participants with a prevalence of 3.3%. As with SCH-M, the occurrence of SCH significantly differed based on sex, presence of TPOAb and UICR quartile (Table 3).

In addition, there was a significant difference in the incidence of SCH according to smoking status regardless of the reference range used (Tables 1 and 3). However, when we analyzed male and female subjects separately using SCH-M, this difference was observed only in men (Table 2). As shown in Table 4, the prevalence of SCH using SCH-P was found to be 2.3% in men (58 of 2498 men) and 4.3% in women (99 of 2303 women).

Table 3 Baseline characteristics of subjects when population-based TSH reference range (0.62–6.68 $\mu\text{IU/mL}$) is used.

	Total subjects (n=4801)	Subclinical hypothyroidism		P value
		No (n=4644)	Yes (n=157)	
Age (years)				0.011
19–29	984 (20.4%)	957 (20.6%)	27 (17.2%)	
30–39	882 (18.4%)	863 (18.5%)	19 (12.2%)	
40–49	939 (19.6%)	904 (19.5%)	35 (22.3%)	
50–59	997 (20.8%)	950 (20.5%)	47 (29.9%)	
60–69	908 (18.9%)	883 (19.0%)	25 (15.9%)	
70 and above	91 (1.9%)	87 (1.9%)	4 (2.5%)	
Sex				<0.001
Male	2498 (53.9%)	2440 (54.5%)	58 (36.4%)	
Female	2303 (46.1%)	2204 (45.5%)	99 (63.6%)	
BMI (kg/m ²)				0.944
<18.5	207 (4.0%)	199 (4.0%)	8 (4.2%)	
≥18.5, <23	1859 (38.3%)	1795 (38.2%)	64 (38.9%)	
≥23, <25	1141 (24.2%)	1103 (24.2%)	38 (25.7%)	
≥25	1594 (33.5%)	1547 (33.6%)	47 (31.2%)	
Region of residence ^a				0.076
Rural	1293 (25.7%)	1258 (25.9%)	35 (19.1%)	
Urban	3508 (74.3%)	3386 (74.1%)	122 (80.9%)	
Family history of thyroid disease				0.119
No	4565 (95.1%)	4411 (95.0%)	154 (98.0%)	
Yes	236 (4.9%)	233 (5.0%)	3 (2.0%)	
Smoking				<0.001
No	2641 (54.5%)	2534 (54.0%)	107 (70.8%)	
Yes	2160 (45.5%)	2110 (46.0%)	50 (29.2%)	
UICR ^b				<0.001
Quartile 1	1226 (25.1%)	1204 (25.5%)	22 (11.8%)	
Quartile 2	1196 (25.0%)	1167 (25.2%)	29 (21.9%)	
Quartile 3	1179 (24.9%)	1140 (25.0%)	39 (24.0%)	
Quartile 4	1200 (25.0%)	1133 (24.3%)	67 (42.3%)	
Anti-TPO Ab				<0.001
Absence	4472 (93.4%)	4357 (94.1%)	115 (72.2%)	
Presence	329 (6.6%)	287 (5.9%)	42 (27.8%)	
CKD stage				0.099
Stage 1, 2	4627 (96.0%)	4474 (96.1%)	153 (98.3%)	
Stage 3, 4, 5	174 (4.0%)	170 (3.9%)	4 (1.7%)	

*Data are presented as mean \pm s.d., n (weighted %), statistics were carried out using Rao-Scott Chi-square test; ^aclassification of the area of residence is classified according to the administrative division of Korea; ^biodine intake status was evaluated by urine iodine creatinine ratio, quartile 1: <Q1 (141.53203438), quartile 2: \geq Q1 and <Q2 (281.81447737), quartile 3: \geq Q2 and <Q3 (664.64655625), quartile 4: \geq Q3.

Risk factors associated with SCH

Tables 5 and 6 show the ORs for the occurrence of SCH for each variable according to the TSH reference range used and sex. Table 5 shows the relationship between different variables and the occurrence of SCH based on SCH-M. In the adjusted model, smoking significantly reduced the incidence of SCH in men (OR 0.58, CI: 0.34–1.00, $P=0.048$). We also found that when TPOAb was positive, the occurrence of SCH was significantly

increased in both crude (OR 5.03, CI: 2.68–9.45, $P<0.001$) and adjusted (OR 5.59, CI: 2.82–11.09, $P<0.001$) models. For urine iodine, the risk of SCH increased as the UICR quartile increased in the adjusted model (Table 5). For women, positivity for TPOAb was confirmed as a risk factor for SCH, as was the highest iodine quartile (OR 2.41, CI: 1.44–4.05, $P<0.001$). In addition, the OR for SCH in urban vs rural residence was 1.78 (CI: 1.15–2.75, $P=0.010$). Similar results (summarized in Table 6) were obtained using SCH-P.

Table 4 Association with subclinical hypothyroidism according to gender when population-based TSH reference range is used.

	Male total (n=2498)	Subclinical hypothyroidism (male)		P value	Female total (n=2303)	Subclinical hypothyroidism (female)		P value
		No (n=2440)	Yes (n=58)			No (n=2204)	Yes (n=99)	
Age (years)				0.852				0.009
19–29	526 (21.1%)	513 (21.1%)	13 (22.4%)		458 (19.9%)	444 (20.1%)	14 (14.1%)	
30–39	481 (19.3%)	472 (19.4%)	9 (15.5%)		401 (17.4%)	391 (17.7%)	10 (10.2%)	
40–49	492 (19.7%)	479 (19.6%)	13 (22.4%)		447 (19.4%)	425 (19.3%)	22 (22.3%)	
50–59	490 (19.6%)	477 (19.5%)	13 (22.4%)		507 (22.0%)	473 (21.5%)	34 (34.2%)	
60–69	461 (18.5%)	452 (18.5%)	9 (15.5%)		447 (19.4%)	431 (19.6%)	16 (16.2%)	
70 and above	48 (1.8%)	47 (1.9%)	1 (1.8%)		43 (1.9%)	40 (1.8%)	3 (3.0%)	
BMI (kg/m ²)				0.999				0.867
<18.5	63 (2.5%)	62 (2.4%)	1 (2.5%)		144 (6.3%)	137 (6.0%)	7 (5.2%)	
≥18.5, <23	824 (33.0%)	804 (33.5%)	20 (33.9%)		1035 (44.9%)	991 (43.8%)	44 (41.7%)	
≥23, <25	644 (25.8%)	629 (26.0%)	15 (25.6%)		497 (21.6%)	474 (22.0%)	23 (25.9%)	
≥25	967 (38.7%)	945 (38.1%)	22 (38.0%)		627 (27.2%)	602 (28.2%)	25 (27.2%)	
Region of residence ^a				0.710				0.009
Rural	683 (27.3%)	666 (25.9%)	17 (28.4%)		610 (26.5%)	592 (26.0%)	18 (13.8%)	
Urban	1815 (72.7%)	1774 (74.1%)	41 (71.6%)		1693 (73.5%)	1612 (74.0%)	81 (86.2%)	
Family history of thyroid disease				N/A				0.297
No	2398 (96.0%)	2340 (95.7%)	58 (100.0%)		2167 (94.1%)	2071 (94.1%)	96 (96.8%)	
Yes	100 (4.0%)	100 (4.3%)	0 (0.0%)		136 (5.9%)	133 (5.9%)	3 (3.2%)	
Smoking				0.375				0.147
No	608 (24.3%)	592 (24.9%)	16 (30.9%)		2033 (88.3%)	1942 (88.8%)	91 (93.6%)	
Yes	1890 (75.7%)	1848 (75.1%)	42 (69.1%)		270 (11.7%)	262 (11.2%)	8 (6.4%)	
UICR ^b				0.003				0.033
Quartile 1	763 (30.5%)	756 (30.4%)	7 (11.2%)		463 (20.1%)	448 (19.8%)	15 (12.1%)	
Quartile 2	630 (25.2%)	617 (25.0%)	13 (21.0%)		566 (24.6%)	550 (25.4%)	16 (22.4%)	
Quartile 3	577 (23.1%)	562 (24.0%)	15 (28.7%)		602 (26.1%)	578 (26.1%)	24 (21.3%)	
Quartile 4	528 (21.2%)	505 (20.6%)	23 (39.1%)		672 (29.2%)	628 (28.7%)	44 (44.2%)	
Anti-TPO Ab				<0.001				<0.001
Absence	2396 (96.0%)	2349 (96.3%)	47 (82.6%)		2076 (90.1%)	2008 (91.5%)	68 (66.2%)	
Presence	102 (4.0%)	91 (3.7%)	11 (17.4%)		227 (9.9%)	196 (8.5%)	31 (33.8%)	
CKD stage				0.626				0.071
Stage 1, 2	2404 (96.2%)	2348 (96.3%)	56 (97.4%)		2223 (96.5%)	2126 (95.8%)	97 (98.8%)	
Stage 3, 4, 5	94 (3.8%)	92 (3.7%)	2 (2.6%)		80 (3.5%)	78 (4.2%)	2 (1.2%)	

*Data are presented as mean ± s.d., n (weighted %), statistics were carried out using Rao-Scott Chi-square test; ^aclassification of the area of residence is classified according to the administrative division of Korea; ^biodine intake status was evaluated by urine iodine creatinine ratio, quartile 1: <Q1 (141.53203438), quartile 2: ≥Q1 and <Q2 (281.81447737), quartile 3: ≥Q2 and <Q3 (664.64655625), quartile 4: ≥Q3. N/A, not available.

Table 5 Logistic regression analysis of subjects with subclinical hypothyroidism (kit manufacturer suggested TSH reference range is used).

	Crude model		Adjusted model	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Male				
Age (years)	Reference		Reference	
19–29				
30–39	0.63 (0.32–1.25)	0.290	0.58 (0.29–1.19)	0.136
40–49	0.70 (0.38–1.31)	0.507	0.66 (0.33–1.32)	0.236
50–59	0.75 (0.40–1.43)	0.706	0.62 (0.30–1.28)	0.196
60–69	0.75 (0.38–1.50)	0.720	0.60 (0.27–1.31)	0.199
70 and above	1.25 (0.43–3.62)	0.338	0.97 (0.32–2.93)	0.955
BMI (kg/m ²)	Reference		Reference	
<18.5				
≥18.5, <23	1.48 (0.20–11.23)	0.793		
≥23, <25	1.76 (0.12–13.68)	0.770		
≥25	2.55 (0.34–19.08)	0.112		
Region of residence ^a	Reference		Reference	
Rural				
Urban	0.72 (0.45–1.14)	0.163		
Family history of thyroid disease	Reference		Reference	
No				
Yes	0.99 (0.30–3.22)	0.982		
Smoking	Reference		Reference	
No				
Yes	0.57 (0.36–0.92)	0.022	0.58 (0.34–1.00)	0.048
UICR ^b	Reference		Reference	
Quartile 1				
Quartile 2	2.17 (1.06–4.43)	0.926	2.52 (1.27–5.02)	0.009
Quartile 3	2.93 (1.51–5.68)	0.110	3.57 (1.86–6.84)	0.001
Quartile 4	3.75 (1.92–7.34)	0.002	4.41 (2.28–8.52)	<0.001
Anti-TPO Ab	Reference		Reference	
Absence				
Presence	5.03 (2.68–9.45)	<0.001	5.59 (2.82–11.09)	<0.001
CKD stage	Reference		Reference	
Stage 1, 2				
Stage 3, 4, 5	0.70 (0.26–1.94)	0.495		
Female				
Age (years)	Reference		Reference	
19–29				
30–39	0.91 (0.49–1.69)	0.105	0.74 (0.40–1.36)	0.328
40–49	1.15 (0.64–2.07)	0.518	0.87 (0.48–1.58)	0.646
50–59	2.05 (1.19–3.53)	0.013	1.33 (0.76–2.35)	0.320
60–69	1.12 (0.62–2.04)	0.441	0.74 (0.39–1.42)	0.367
70–	2.14 (0.81–5.64)	0.194	1.61 (0.60–4.27)	0.341
BMI (kg/m ²)	Reference		Reference	
<18.5				
≥18.5, <23	1.09 (0.53–2.26)	0.491		
≥23, <25	1.54 (0.72–3.29)	0.144		
≥25	1.27 (0.60–2.70)	0.757		
Region of residence ^a	Reference		Reference	
Rural				
Urban	1.78 (1.15–2.75)	0.010		
Family history of thyroid disease	Reference		Reference	
No				
Yes	0.81 (0.38–1.75)	0.597		
Smoking	Reference		Reference	
No				
Yes	0.58 (0.30–1.11)	0.098	0.64 (0.33–1.23)	0.177

(Continued)

Table 5 Continued.

	Crude model		Adjusted model	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
UICR ^b				
Quartile 1	Reference		Reference	
Quartile 2	1.18 (0.63–2.23)	0.350	1.17 (0.62–2.21)	0.636
Quartile 3	1.45 (0.83–2.54)	0.873	1.46 (0.82–2.60)	0.203
Quartile 4	2.34 (1.40–3.90)	<0.001	2.41 (1.44–4.05)	<0.001
Anti-TPO Ab				
Absence	Reference		Reference	
Presence	4.00 (2.59–6.16)	<0.001	4.06 (2.63–6.28)	<0.001
CKD stage				
Stage 1, 2	Reference			
Stage 3, 4, 5	0.85 (0.37–1.94)	0.695		

*Data are presented OR (95% CI), statistics were carried out using logistic regression; ^aclassification of the area of residence is classified according to the administrative division of Korea; ^biodine intake status was evaluated by urine iodine creatinine ratio, quartile 1: <Q1 (141.53203438), quartile 2: ≥Q1 and <Q2 (281.81447737), quartile 3: ≥Q2 and <Q3 (664.64655625), quartile 4: ≥Q3.

Discussion

This study separately evaluated factors related to high prevalence of SCH in men and women to identify sex-specific risk factors for SCH. In both sexes, regardless of whether SCH-P or SCH-M was applied, TPOAb positivity and high-iodine intake were related to the development of SCH. However, it was observed that the effect of iodine excess was more marked in men than in women. Urban residence was associated with SCH only in women.

Using SCH-M, the overall prevalence of SCH in Korea was 6.0% (4.4% in men, 7.7% in women). Using SCH-P, the overall prevalence of SCH was 3.3% (2.3% in men, 4.3% in women). The prevalence of SCH in Korea was reported previously to be 0.1–5.4% based on data from health care examinations (15, 22, 23, 24, 25). However, these studies had limitations: their data were not representative of the whole population because the TSH cut-off levels used were different, and the results included only those subjects who underwent health care examinations. However, it is noteworthy that a similar prevalence was confirmed in our study using both a population-based TSH cut-off (SCH-P) and that suggested by the manufacturer of a commonly used kit (SCH-M).

Although the prevalence of SCH varies with geographical region, race, age, sex and TSH measurement method, most studies report that age, presence of autoantibody, female sex and iodine intake are risk factors for SCH (2). Most epidemiological studies have shown a higher prevalence of SCH in women than in men, but the underlying cause of this female predominance is unclear (2). The higher prevalence of autoantibodies is one possible cause. Pedersen *et al.* analyzed 4649 Danish subjects and

reported that autoantibodies were more frequent in women (26). The prevalence of SCH was also associated with the presence of TPOAb. In the USA, National Health and Nutrition Examination Survey (NHANES) III reported a trend to higher prevalence of SCH in subjects who were positive for TPOAb (4). The Wickham survey reported similar results to those of NHANES III and showed that the ORs of developing overt hypothyroidism were four times higher in subjects with positive autoantibodies (27). Iodine intake is another risk factor for SCH. Excessive iodine intake is known to cause thyroid dysfunction through direct toxic effects or immunological alterations (28). The prevalence of SCH has been shown to differ depending on whether it is reported from iodine-sufficient areas or from areas with an iodine deficit. According to the Laurberg study conducted in Northern Europe in 1998, the prevalence of SCH in Iceland, which is an iodine-sufficient area, was 18%, while that in the iodine-deficient area of Jutland, Denmark was 3.8% (7). A study in China by Teng *et al.* reported that the prevalence of SCH differed between three regions according to their iodine intake, and a significant association between SCH and iodine intake was confirmed (29).

In our study, previously known risk factors for SCH were identified in both sexes regardless of the reference range used. The presence of TPOAb and the highest quartile of UICR increased ORs significantly in both men and women. Interestingly, we found that the change in risk of SCH according to the magnitude of iodine excess differed between sexes. Based on our results, men are more vulnerable to excessive iodine intake in terms of development of SCH; a modest increase in iodine intake leads to a rapid increase in SCH risk. This finding was

Table 6 Logistic regression analysis of subjects with subclinical hypothyroidism (population-based TSH reference range is used).

	Crude model		Adjusted model	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Male				
Age (years)				
19–29	Reference		Reference	
30–39	0.64 (0.25–1.66)	0.656	0.56 (0.20–1.53)	0.254
40–49	0.87 (0.37–2.08)	0.665	0.76 (0.29–2.00)	0.581
50–59	1.10 (0.48–2.56)	0.239	0.81 (0.31–2.15)	0.674
60–69	0.78 (0.28–2.20)	0.940	0.54 (0.16–1.89)	0.336
70 and above	0.39 (0.05–3.09)	0.434	0.27 (0.03–2.07)	0.205
BMI (kg/m ²)				
<18.5	Reference			
≥18.5, <23	0.99 (0.13–7.59)	0.986		
≥23, <25	0.97 (0.12–7.71)	0.959		
≥25	0.98 (0.13–7.55)	0.986		
Region of residence ^a				
Rural	Reference			
Urban	0.88 (0.46–1.71)	0.710		
Family history of thyroid disease				
No				
Yes	N/A	N/A		
Smoking				
No	Reference			
Yes	0.74 (0.38–1.45)	0.377	0.73 (0.34–1.58)	0.423
UICR ^b				
Quartile 1	Reference		Reference	
Quartile 2	2.27 (0.84–6.16)	0.749	2.57 (0.92–7.13)	0.071
Quartile 3	3.24 (1.21–8.63)	0.312	3.75 (1.34–10.51)	0.012
Quartile 4	5.14 (2.06–12.83)	0.002	5.80 (2.22–15.15)	<0.001
Anti-TPO Ab				
Absence	Reference		Reference	
Presence	5.47 (2.42–12.33)	<0.001	5.65 (2.33–13.71)	<0.001
CKD stage				
Stage 1, 2	Reference			
Stage 3, 4, 5	0.70 (0.17–2.96)	0.629		
Female				
Age (years)				
19–29	Reference		Reference	
30–39	0.86 (0.374–2.01)	0.162	0.67 (0.28–1.63)	0.379
40–49	1.60 (0.75–3.44)	0.487	1.17 (0.53–2.59)	0.694
50–59	2.74 (1.28–5.88)	0.002	1.68 (0.76–3.74)	0.202
60–69	1.19 (0.49–2.85)	0.668	0.73 (0.28–1.89)	0.519
70–	1.31 (0.33–5.20)	0.963	0.97 (0.25–3.69)	0.960
BMI (kg/m ²)				
<18.5	Reference			
≥18.5, <23	1.10 (0.43–2.84)	0.871		
≥23, <25	1.36 (0.50–3.71)	0.419		
≥25	1.11 (0.41–2.99)	0.920		
Region of residence ^a				
Rural	Reference			
Urban	2.18 (1.19–3.99)	0.011		
Family history of thyroid disease				
No	Reference			
Yes	0.52 (0.15–1.82)	0.306		
Smoking				
No	Reference			
Yes	0.54 (0.23–1.26)	0.155	0.60 (0.25–1.40)	0.237

(Continued)

Table 6 Continued.

	Crude model		Adjusted model	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
UICR ^b				
Quartile 1	Reference		Reference	
Quartile 2	1.45 (0.63–3.37)	0.921	1.40 (0.59–3.29)	0.445
Quartile 3	1.34 (0.64–2.80)	0.621	1.31 (0.61–2.81)	0.493
Quartile 4	2.52 (1.30–4.88)	<0.001	2.67 (1.35–5.26)	0.005
Anti-TPO Ab				
Absence	Reference		Reference	
Presence	5.49 (3.26–9.22)	<0.001	5.33 (3.19–8.90)	<0.001
CKD stage				
Stage 1, 2	Reference			
Stage 3, 4, 5	0.28 (0.06–1.24)	0.093		

*Data are presented OR (95% CI), statistics were carried out using logistic regression; ^aclassification of the area of residence is classified according to the administrative division of Korea; ^biodine intake status was evaluated by urine iodine creatinine ratio, quartile 1: <Q1 (141.53203438), quartile 2: ≥Q1 and <Q2 (281.81447737), quartile 3: ≥Q2 and <Q3 (664.64655625), quartile 4: ≥Q3.

N/A, not available.

consistent regardless of the TSH cut-off used. Using SCH-M, the ORs for SCH increased 2.5 times in the second quartile, 3.6 times in the third quartile and 4.4 times in the highest quartile relative to the lowest quartile (adjusted model shown in Table 5). When SCH-P was used, the ORs for SCH increased 2.6 times in the second quartile, 3.8 times in the third quartile and 5.8 times in the highest quartile (adjusted model shown in Table 6). In contrast, no sharp increase in ORs was observed in women as their UICR quartile increased. Even for those women in the highest quartile for UICR, the ORs did not exceed 3 (2.4 with SCH-M and 2.7 with SCH-P (Tables 5 and 6, respectively).

Although the reason for this difference is not clear, there are several possible explanations. First, although the thyroid is the main reservoir for iodine intake, breast and cervical tissues are known to be involved in extrathyroidal iodine storage (30); thus, women are more capable of providing storage for excess iodine. Therefore, it may be that accumulation of excess iodine in the extrathyroidal tissues, which would attenuate iodine accumulation in the thyroid, may mitigate the adverse effects of excessive iodine intake on the development of SCH. Second, estrogen has been demonstrated to have effects on thyroidal iodine uptake and TPO activity in animal models (31). Previous studies suggested that oestradiol might regulate iodide uptake via its action on the sodium/iodide symporter (NIS) and TPO, proteins that play important roles in thyroid hormone biosynthesis (32, 33, 34). Oestradiol directly stimulates iodine uptake while regulating iodine uptake via reducing NIS or TPO gene expression (33). It is thought that oestradiol may regulate the effect of iodine on thyroid function. Because of the role of estrogen, the

degree of response to iodine intake may differ in men and women. In other words, estrogen may modulate the effect of excessive iodine on thyroid tissue in women, which may reduce the risk of SCH. However, considering that thyroid dysfunction frequently occurs in women, additional research is needed to evaluate other factors such as the concentrations of oestradiol and other co-factors.

Another distinctive finding of our study is the increased risk associated with the area of residence. In women, the risk of SCH was significantly higher in urban area residents than in rural area residents regardless of the TSH cut-off level used. The risk of SCH in urban residents was 1.78 times higher using SCH-M and 2.18 times higher using SCH-P (Tables 5 and 6, respectively). Although the underlying mechanism of this difference is unclear, it is possible that urban women have more opportunities to consume high-iodine meals or supplementation. However, a detailed survey to elucidate the lifestyle or food-intake patterns in terms of iodine exposure would be required to establish this.

Our study has several limitations. First, it is a cross-sectional study and hence does not prove causality. Second, the presence of thyroid disease, dementia or other medical illness was self-reported. The use of medication and the detailed history of treatment were also assessed based on the information participants provided.

In conclusion, we examined the prevalence of SCH and the associated risk factors in the Korean population using the most recently released nationally representative data. The TSH reference ranges were calculated using two methods (the values proposed by the test kit manufacturer and population-based values) and the risk factors associated with SCH were analyzed. The prevalence rates

of SCH were similar to those reported in the literature and previously known risk factors were confirmed using both TSH reference ranges. The notable findings of this study are that the increase in the risk of SCH with increasing iodine intake is more marked in men than in women and that residential area could be a risk factor for SCH in women. Further studies are needed to identify the mechanisms involved in these effects.

Declaration of interest

The authors report that they have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

The consultation for statistical analysis was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (Grant number: H114C1062).

References

- 1 Fatourehchi V. Subclinical hypothyroidism: an update for primary care physicians. In *Mayo Clinic Proceedings*, pp 65–71. Amsterdam, the Netherlands: Elsevier, 2009.
- 2 Kim YA & Park YJ. Prevalence and risk factors of subclinical thyroid disease. *Endocrinology and Metabolism* 2014 **29** 20–29. (<https://doi.org/10.3803/EnM.2014.29.1.20>)
- 3 Rosário PW, Carvalho M & Calsolari MR. Natural history of subclinical hypothyroidism with TSH ≤ 10 IU/L: a prospective study. *Clinical Endocrinology* 2016 **84** 878–881. (<https://doi.org/10.1111/cen.12939>)
- 4 Hollowell J. T (4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 489–499. (<https://doi.org/10.1210/jcem.87.2.8182>)
- 5 Kim WG, Kim WB, Woo G, Kim H, Cho Y, Kim TY, Kim SW, Shin M-H, Park JW & Park H-L. Thyroid stimulating hormone reference range and prevalence of thyroid dysfunction in the Korean population: Korea National Health and Nutrition Examination Survey 2013 to 2015. *Endocrinology and Metabolism* 2017 **32** 106–114. (<https://doi.org/10.3803/EnM.2017.32.1.106>)
- 6 Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, Rago T, Grasso L, Valeriano R & Balestrieri A. The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 561–566.
- 7 Laurberg P, Pedersen KM, Hreidarsson A, Sigfusson N, Iversen E & Knudsen PR. Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. *Journal of Clinical Endocrinology and Metabolism* 1994 **78** 765–769. (<https://doi.org/10.1210/jcem.83.3.4624>)
- 8 Konno N, Makita H, Yuri K, Iizuka N & Kawasaki K. Association between dietary iodine intake and prevalence of subclinical hypothyroidism in the coastal regions of Japan. *Journal of Clinical Endocrinology and Metabolism* 1998 **78** 393–397. (<https://doi.org/10.1210/jcem.78.2.8106628>)
- 9 Bjoro T, Holmen J, Kruger O, Midthjell K, Hunstad K, Schreiner T, Sandnes L & Brochmann H. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trøndelag (HUNT). *European Journal of Endocrinology* 2000 **143** 639–647. (<https://doi.org/10.1530/eje.0.1430639>)
- 10 Tunbridge W, Evered D, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T & Smith P. The spectrum of thyroid disease in a community: the Wickham survey. *Clinical Endocrinology* 1977 **7** 481–493. (<https://doi.org/10.1111/j.1365-2265.1977.tb01340.x>)
- 11 Cignini P, Cafà EV, Giorlandino C, Capriglione S, Spata A & Dugo N. Thyroid physiology and common diseases in pregnancy: review of literature. *Journal of Prenatal Medicine* 2012 **6** 64.
- 12 Kroopnick JM & Kim CS. Overview of hypothyroidism in pregnancy. In *Seminars in Reproductive Medicine*. Stuttgart, Germany: Thieme Medical Publishers, 2016.
- 13 Strieder TG, Prummel MF, Tijssen JG, Ender E & Wiersinga WM. Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy female relatives of patients with autoimmune thyroid disease. *Clinical Endocrinology* 2003 **59** 396–401. (<https://doi.org/10.1046/j.1365-2265.2003.01862.x>)
- 14 Choi H, Park Y, Kim H, Choi S, Lim S, Park D, Jang H, Cho N & Cho B. Prevalence of subclinical hypothyroidism in two population based-cohort: Ansong and KLoSHA cohort in Korea. *Journal of Korean Thyroid Association* 2010 **3** 32–40.
- 15 Chung JH, Kim BJ, Choi YH, Shin MH, Kim SH, Min YK, Lee MS, Lee MG & Kim KW. Prevalence of thyrotoxicosis and hypothyroidism in the subjects for health check-up. *Journal of Korean Society of Endocrinology* 1999 **14** 301–313.
- 16 Kim J. Association between serum vitamin D, parathyroid hormone and metabolic syndrome in middle-aged and older Korean adults. *European Journal of Clinical Nutrition* 2015 **69** 425–430. (<https://doi.org/10.1038/ejcn.2014.192>)
- 17 Lee S, Han K, Yang H, Kim H, Cho J, Kwon H, Park Y, Cha B & Yoon K. A novel criterion for identifying metabolically obese but normal weight individuals using the product of triglycerides and glucose. *Nutrition and Diabetes* 2015 **5** e149. (<https://doi.org/10.1038/nutd.2014.46>)
- 18 Song YS, Oh TJ, Kim KM, Moon JH, Choi SH, Jang HC, Park KS & Lim S. Application of the 2013 American College of Cardiology/American Heart Association Cholesterol Guideline to the Korean National Health and Nutrition Examination Surveys from 1998 to 2012. *Diabetes and Metabolism Journal* 2017 **41** 38–50. (<https://doi.org/10.4093/dmj.2017.41.1.38>)
- 19 Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Tamura MK & Feldman HI. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *American Journal of Kidney Diseases* 2014 **63** 713–735. (<https://doi.org/10.1053/j.ajkd.2014.01.416>)
- 20 Baloch Z. Guidelines Committee & National Academy of Clinical Biochemistry. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003 **13** 3–126. (<https://doi.org/10.1089/105072503321086962>)
- 21 Tran BT, Jeong BY & Oh J-K. The prevalence trend of metabolic syndrome and its components and risk factors in Korean adults: results from the Korean National Health and Nutrition Examination Survey 2008–2013. *BMC Public Health* 2017 **17** 71. (<https://doi.org/10.1186/s12889-016-3936-6>)
- 22 Choi JK, Kim JS, Hwang CH, Kim DH, Hwang SW, Cho B & Jul BY. Subclinical hypothyroidism and coronary risk factors in women above 55 years. *Journal of the Korean Academy of Family Medicine* 2002 **23** 96–103.
- 23 Jung CH, Sung KC, Shin HS, Rhee EJ, Lee WY, Kim BS, Kang JH, Kim H, Kim SW & Lee MH. Thyroid dysfunction and their relation to cardiovascular risk factors such as lipid profile, hsCRP, and waist hip ratio in Korea. *Korean Journal of Internal Medicine* 2003 **18** 146. (<https://doi.org/10.3904/kjim.2003.18.3.146>)
- 24 Lee WY, Oh KW, Rhee EJ, Jung CH, Kim SW, Yun EJ, Tae HJ, Baek KH, Kang MI & Choi MG. Relationship between subclinical

- thyroid dysfunction and femoral neck bone mineral density in women. *Archives of Medical Research* 2006 **37** 511–516. (<https://doi.org/10.1016/j.arcmed.2005.09.009>)
- 25 Oh MK, Cheon KS, Jung SM, Ryu DS, Park MS, Cheong SS, Kim JS & Park BG. Prevalence of thyroid diseases among adult for health check-up in a Youngdong area of Kwangwon province. *Journal of the Korean Academy of Family Medicine* 2001 **22** 1363–1374.
- 26 Pedersen IB, Knudsen N, Jørgensen T, Perrild H, Ovesen L & Laurberg P. Thyroid peroxidase and thyroglobulin autoantibodies in a large survey of populations with mild and moderate iodine deficiency. *Clinical Endocrinology* 2003 **58** 36–42. (<https://doi.org/10.1046/j.1365-2265.2003.01633.x>)
- 27 Vanderpump M, Tunbridge W, French J, Appleton D, Bates D, Clark F, Evans JG, Hasan D, Rodgers H & Tunbridge F. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clinical Endocrinology* 1995 **43** 55–68. (<https://doi.org/10.1111/j.1365-2265.1995.tb01894.x>)
- 28 Mahmoud I, Colin I, Many M-C & Deneff J-F. Direct toxic effect of Iodide in excess on Iodine-deficient thyroid glands: epithelial necrosis and inflammation associated with lipofuscin accumulation. *Experimental and Molecular Pathology* 1986 **44** 259–271. ([https://doi.org/10.1016/0014-4800\(86\)90040-7](https://doi.org/10.1016/0014-4800(86)90040-7))
- 29 Teng W, Shan Z, Teng X, Guan H, Li Y, Teng D, Jin Y, Yu X, Fan C & Chong W. Effect of iodine intake on thyroid diseases in China. *New England Journal of Medicine* 2006 **354** 2783–2793. (<https://doi.org/10.1056/NEJMoa054022>)
- 30 Ahad F & Ganie SA. Iodine, iodine metabolism and iodine deficiency disorders revisited. *Indian Journal of Endocrinology and Metabolism* 2010 **14** 13.
- 31 Lima LP, Barros IA, Lisbôa PC, Araújo RL, Silva AC, Rosenthal D, Ferreira AC & Carvalho DP. Estrogen effects on thyroid iodide uptake and thyroperoxidase activity in normal and ovariectomized rats. *Steroids* 2006 **71** 653–659. (<https://doi.org/10.1016/j.steroids.2006.03.007>)
- 32 Boccabella AV & Alger EA. Influence of estradiol on thyroid: serum radioiodide concentration ratios of gonadectomized and hypophysectomized rats. *Endocrinology* 1964 **74** 680–688. (<https://doi.org/10.1210/endo-74-5-680>)
- 33 Canaris GJ, Manowitz NR, Mayor G & Ridgway EC. The Colorado thyroid disease prevalence study. *Archives of Internal Medicine* 2000 **160** 526–534. (<https://doi.org/10.1001/archinte.160.4.526>)
- 34 Furlanetto TW, Nguyen LQ & Jameson JL. Estradiol increases proliferation and down-regulates the sodium/iodide symporter gene in FRTL-5 cells. *Endocrinology* 1999 **140** 5705–5711. (<https://doi.org/10.1210/endo.140.12.7197>)

Received in final form 1 March 2018

Accepted 7 March 2018

Accepted Preprint published online 7 March 2018