RESEARCH

Sex differences in risk factors for subclinical hypothyroidism

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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 µIU/mL) was 5.6%, and 3.3% with SCH-P (0.62–6.68 µIU/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

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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 µIU/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

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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 μIU/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 μIU/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 μIU/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 μIU/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/m^2), normal weight (≥18.5 kg/m^2, <23 kg/m^2), overweight (≥23 kg/m^2, <25 kg/m^2) or obese (≥25 kg/m^2). 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 μIU/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 μIU/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 μIU/mL). Although clinical practice guidelines suggest the use of population-based reference ranges for TSH (20), the upper limit of TSH (6.68 μIU/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.

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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 μIU/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; [a]classification of the area of residence is classified according to the administrative division of Korea; [b]iodine 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.

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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.

		Subclinical hypothyroidism (male)				Subclinical hypothyroidism (female)		
	Male total ($n=2545$)	No ($n=2434$)	Yes ($n=111$)	*P* value	Female total ($n=2343$)	No ($n=2163$)	Yes ($n=180$)	*P* value
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%0	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; [a]classification of the area of residence is classified according to the administrative division of Korea; [b]iodine 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.

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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 μIU/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 ± S.D., *n* (weighted %), statistics were carried out using Rao-Scott Chi-square test; [a]classification of the area of residence is classified according to the administrative division of Korea; [b]iodine 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.

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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.

		Subclinical hypothyroidism (male)				Subclinical hypothyroidism (female)		
	Male total ($n=2498$)	No ($n=2440$)	Yes ($n=58$)	***P* value**	**Female total** ($n=2303$)	No ($n=2204$)	Yes ($n=99$)	***P* value**
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; [a]classification of the area of residence is classified according to the administrative division of Korea; [b]iodine 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.

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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)				
19–29	Reference		Reference	
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)				
<18.5	Reference			
≥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]				
Rural	Reference			
Urban	0.72 (0.45–1.14)	0.163		
Family history of thyroid disease				
No	Reference			
Yes	0.99 (0.30–3.22)	0.982		
Smoking				
No	Reference			
Yes	0.57 (0.36–0.92)	**0.022**	0.58 (0.34–1.00)	**0.048**
UICR[b]				
Quartile 1	Reference		Reference	
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				
Absence	Reference		Reference	
Presence	5.03 (2.68–9.45)	**<0.001**	5.59 (2.82–11.09)	**<0.001**
CKD stage				
Stage 1, 2	Reference			
Stage 3, 4, 5	0.70 (0.26–1.94)	0.495		
Female				
Age (years)				
19–29	Reference		Reference	
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)				
<18.5	Reference			
≥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]				
Rural	Reference			
Urban	1.78 (1.15–2.75)	**0.010**		
Family history of thyroid disease				
No	Reference			
Yes	0.81 (0.38–1.75)	0.597		
Smoking				
No	Reference			
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; [a]classification of the area of residence is classified according to the administrative division of Korea; [b]iodine 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 Whickham 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				
Stage1, 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; [a]classification of the area of residence is classified according to the administrative division of Korea; [b]iodine 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.

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