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Sex-specific effects of blood cadmium on thyroid hormones and thyroid function status: Korean nationwide cross-sectional study

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ABSTRACT

Previous studies on blood cadmium (BCd) and changes in thyroid hormone levels are controversial. We investigated whether thyroid hormone levels and thyroid function status were associated with BCd according to sex in the Korean population. Our study included 1972 participants based on the 2013 Korea National Health and Nutrition Examination Survey (KNHANES) data. Participants whose thyroid-stimulating hormone (TSH) and free thyroxine (fT4) levels were altered physiologically or medically were excluded. Changes in TSH, fT4, and anti-thyroid peroxidase antibody (TPOAb) in men and women were analyzed by different characteristics: age, body mass index (BMI), smoking status, drinking status, BCd, and urine iodine-to-creatinine ratio (UI/Cre). Thyroid function status was classified as hypothyroidism, euthyroidism, and hyperthyroidism as defined by TSH and fT4 levels. Among the total participants, there was a negative correlation between BCd and fT4 ($r = -0.067$, $p = 0.003$). In men ($n = 1057$), fT4 levels decreased with increasing BCd quartile (p-for-trend = 0.002). After adjustment for age, BMI, smoking status, UI/Cre, and TPOAb, the association between BCd and hypothyroidism was significant in men (odds ratio = 1.813, $p = 0.032$) but not in women. These results suggest that cadmium accumulation is closely associated with thyroid dysfunction, and there is a difference in metabolic capacity according to sex.

1. Introduction

Cadmium is a well-known heavy metal recognized as an endocrine-disrupting chemical (EDC) [1]. Environmental exposure to EDCs leads to problems with human health and wildlife homeostasis [2,3]. Cadmium is contained in batteries, pigments, coatings, and crops and can travel through soil, water, and air. For the general population, the major sources of cadmium exposure are cigarette smoking in smokers and diet, such as lettuce, spinach, potatoes, peanuts, soybeans, and sunflower seeds, in non-smokers [4,5].

A few studies have revealed that cadmium exposure is associated with endocrine disruption, such as metabolic syndrome [6], diabetes [7], obesity [8], atherosclerosis [9,10], and reproductive toxicity [11–13]. However, the relationship between cadmium exposure and thyroid function remains controversial. Elevated levels of blood cadmium (BCd) or urine cadmium (UCd) may result in elevated, decreased, or unchanged triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), or thyroid autoantibodies, depending on sex [14].

To the best of our knowledge, studies of BCd and thyroid hormones based on nationwide data have been conducted in the United States (US) [15–18] and China [19]. However, previous nationwide studies had limitations, including that they did not measure free thyroxine (fT4) which better reflects the biological effects of thyroid hormone [20] or did not assess the relationship between thyroid function status and BCd, such as BCd and hypothyroidism. In addition, Asian eating habits are associated with an increase in BCd [21]. Although both the trend of eating cadmium-containing food and BCd levels are gradually declining in the Korean population [22], the level of BCd is still higher than that in the US, Canada, and Germany [23]. Further studies on the relationship between BCd and thyroid dysfunction in Asia are needed. For this reason, we aimed to determine which thyroid hormones,

Abbreviations: BCd, blood cadmium; BMI, body mass index; EDC, endocrine-disrupting chemical; fT3, free T3; fT4, free thyroxine; KNHANES, Korea National Health and Nutrition Examination Survey; OR, odds ratio; SD, standard deviation; T3, triiodothyronine; T4, thyroxine; Tg, thyroglobulin; TGAb, thyroglobulin antibody; TPOAb, anti-thyroid peroxidase antibody; TSH, thyroid-stimulating hormone; UCd, urine cadmium; UI/Cre, urine iodine-to-creatinine ratio; US, United States

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including fT4, and thyroid function status are associated with BCd according to sex using the Korean nationwide data.

2. Subjects and methods

2.1. Study participants

This cross-sectional study was based on the data of the Korea National Health and Nutrition Examination Survey (KNHANES) in 2013. KNHANES is a cross-sectional, population-based, nationwide survey that is regularly conducted by the Korea Centers for Disease Control and Prevention [24]. Of the 8018 participants, we initially selected individuals who underwent a BCd test (n = 2355). The blood tests for heavy metals were performed on a randomly selected one-third of the participants aged ≥10 years, by region, sex, and age [24]. The exclusion criteria were as follows: 1) participants whose thyroid hormone levels may be physiologically changed (elderly people over 65 years of age [n = 176] or pregnant women [n = 7]); 2) participants whose thyroid hormone levels were changed by surgery, radioiodine therapy, or medication (past medical history of thyroid cancer [n = 7], or hyperthyroidism, hypothyroidism, benign thyroid nodule, and Hashimoto's thyroiditis [n = 12]); and 3) participants who did not have data of urine iodine and creatinine levels (n = 181). A total of 1972 participants were enrolled in the final analysis. All participants gave written informed consent. The survey protocol was approved by the institutional review board of the Korean Centers for Disease Control and Prevention (2013-07CON-03-4C). All research was performed in accordance with relevant guidelines and regulations.

2.2. Exposure assessment

Cadmium was measured from venous whole blood samples taken during a visit under the standard KNHANES protocol. BCd levels (μg/L) were measured by graphite furnace atomic absorption spectrometry using the AAnalyst 600 (PerkinElmer, Finland). BCd was analyzed as both continuous and quartile variables. The diagnostic reliability and applicability of BCd as a measurement of cadmium exposure is described elsewhere [25].

2.3. Outcome assessment

TSH (uIU/mL), fT4 (ng/dL), and anti-thyroid peroxidase autoantibody (TPOAb, IU/mL) were measured from venous blood samples using the electrochemiluminescence immunoassay method with a Cobas8000 E-602 (Roche, Germany). The reference ranges were as follow: TSH, 0.3–4.0 uIU/mL; fT4, 0.7–2.1 ng/dL; and anti-TPOAb, < 60 IU/mL. Thyroid function status was classified according to TSH and fT4 levels: 1) hypothyroidism, subjects with subclinical hypothyroidism (4 < TSH ≤10 uIU/mL and fT4 within the reference range) plus overt hypothyroidism (4 < TSH ≤10 uIU/mL and fT4 < 0.7 ng/dL or TSH ≥ 10 uIU/mL); 2) euthyroidism (TSH and fT4 within the reference range); 3) hyperthyroidism, subjects with subclinical hyperthyroidism (TSH < 0.3 uIU/mL and fT4 within the reference range) plus overt hyperthyroidism (TSH < 0.3 uIU/mL and fT4 > 2.1 ng/dL).

2.4. Covariates

Potential covariates considered were age, body mass index (BMI), smoking status, alcohol drinking status, and urine iodine-to-creatinine ratio (UI/Cre). Subgroups based on age were as follows: 10–19, 20–39, and 40–65 years. BMI was calculated as body weight in kilograms divided by the height in meters squared (kg/m^2) and classified as follows: underweight (BMI < 18.5 kg/m^2); normal (18.5 ≤ BMI < 25 kg/m^2); and obese (BMI ≥ 25 kg/m^2). Smoking status was classified as never- and ever-smoker. Alcohol drinking status was classified as never- and ever-drinker. Urine iodine (μg/L) was measured using a Clarus 600/600 T (Perkin Elmer, USA). The UI/Cre (μg/g) was calculated to reflect iodine intake [26,27].

2.5. Statistical analyses

All statistical analyses were performed using SPSS Statistics (version 21.0, IBM Inc., Chicago, IL, USA). The baseline characteristics were presented as mean ± standard deviation (SD) and (minimum, maximum) values for continuous variables and as frequencies with percentages for categorical variables. The statistical significance of differences in continuous variables between two groups and among multiple groups were determined through an independent sample *t*-test and a one-way Analysis of Variance, respectively. The statistical significance of differences in categorical variables was determined using Pearson's Chi-square test. Multiple logistic regression analysis was performed to assess the influence of BCd on thyroid status after adjustment for covariates. We considered p-value of < 0.05 as a statistically significant value, but cautioned against misinterpretations [28].

3. Results

3.1. Baseline characteristics

The baseline characteristics of 1972 participants according to sex are presented in Table 1. There were 1057 (53.6%) men and 915 (46.4%) women. The mean age of men and women was 37.27 and 38.85 years, respectively (range, 10–65 years). The mean BCd for men and women was 0.81 μg/L (range, 0.02–11.05 μg/L) and 0.96 μg/L (range, 0.05–3.95 μg/L), respectively. In women, the mean TSH and TPOAb levels were higher and fT4 was lower than in men. The proportion of hypothyroidism and hyperthyroidism was higher in women than in men.

3.2. Association between BCd and TSH, fT4, and TPOAb levels

The correlation between BCd and TSH, fT4, and TPOAb levels among total participants was assessed (Table 2). Within Pearson's

Table 1
Baseline characteristics.

	Mean ± SD [min, max] or n(%)	
	Men (n = 1057)	Women (n = 915)
Age	37.27 ± 15.94 [10, 65]	38.85 ± 15.97 [10, 65]
BMI (kg/m2) [1]	23.87 ± 3.61 [14.9, 40.8]	22.73 ± 3.52 [14.7, 49.0]
Smoking status [2]		
Ever Smoker	621 (61.9)	85 (9.5)
Never Smoker	382 (38.1)	799 (90.4)
Alcohol drinking status [3]		
Ever drinker	871 (89.9)	692 (80.7)
Never drinker	98 (10.1)	166 (19.3)
UI/Cre (ug/g)	475.64 ± 1137.43 [4.69, 15,772.39]	693.06 ± 1728.81 [11.34, 32,407.60]
BCd (μg/L)	0.81 ± 0.68 [0.02, 11.05]	0.96 ± 0.65 [0.05, 3.95]
TSH (uIU/mL)	2.55 ± 2.47 [0.00, 64.7]	2.92 ± 2.19 [0.00, 23.4]
fT4 (ng/dL)	1.28 ± 0.18 [0.5, 2.5]	1.19 ± 0.26 [0.6, 5.9]
TPOAb (IU/mL)	12.65 ± 46.84 [5.00, 1008.00]	32.19 ± 150.27 [5.00, 2484.00]
Thyroid function status		
Hypothyroidism	133 (12.6)	172 (18.8)
Euthyroidism	914 (86.5)	727 (79.5)
Hyperthyroidism	10 (0.9)	16 (1.7)

There were [1] 3, [2] 85, and [3] 145 subjects who had missing data.
BMI, body mass index; UI/Cre, urine iodine-to-creatinine ratio; BCd, Blood cadmium; TSH, thyroid-stimulating hormone; fT4, free thyroxine; TPOAb, anti-thyroid peroxidase antibody.

Table 2
Correlation between BCd and thyroid hormone levels.

	BCd		BCd 1Q [0-0.4193] (n = 493)	BCd 2Q [0.4193-0.7570] (n = 494)	BCd 3Q [0.7570-1.1860] (n = 495)	BCd 4Q [1.1860-11.05] (n = 490)	P for trend
	r	P-value					
TSH (uIU/mL)	0.008	0.718	2.71 ± 1.66	2.66 ± 1.79	2.78 ± 3.28	2.72 ± 2.31	0.888
fT4 (ng/dL)	−0.067	0.003	1.26 ± 0.17	1.24 ± 0.20	1.22 ± 0.20 *	1.21 ± 0.31 **	0.002
TPOAb (IU/mL)	0.033	0.145	14.39 ± 67.41	24.83 ± 128.00	18.36 ± 51.56	29.34 ± 153.03	0.135

r, pearson's correlation coefficient; *p < 0.05 compared to 1Q; ** p < 0.01 compared to 1Q.
BCd, blood cadmium; TSH, thyroid-stimulating hormone; fT4, free thyroxine; TPOAb, anti-thyroid peroxidase antibody.

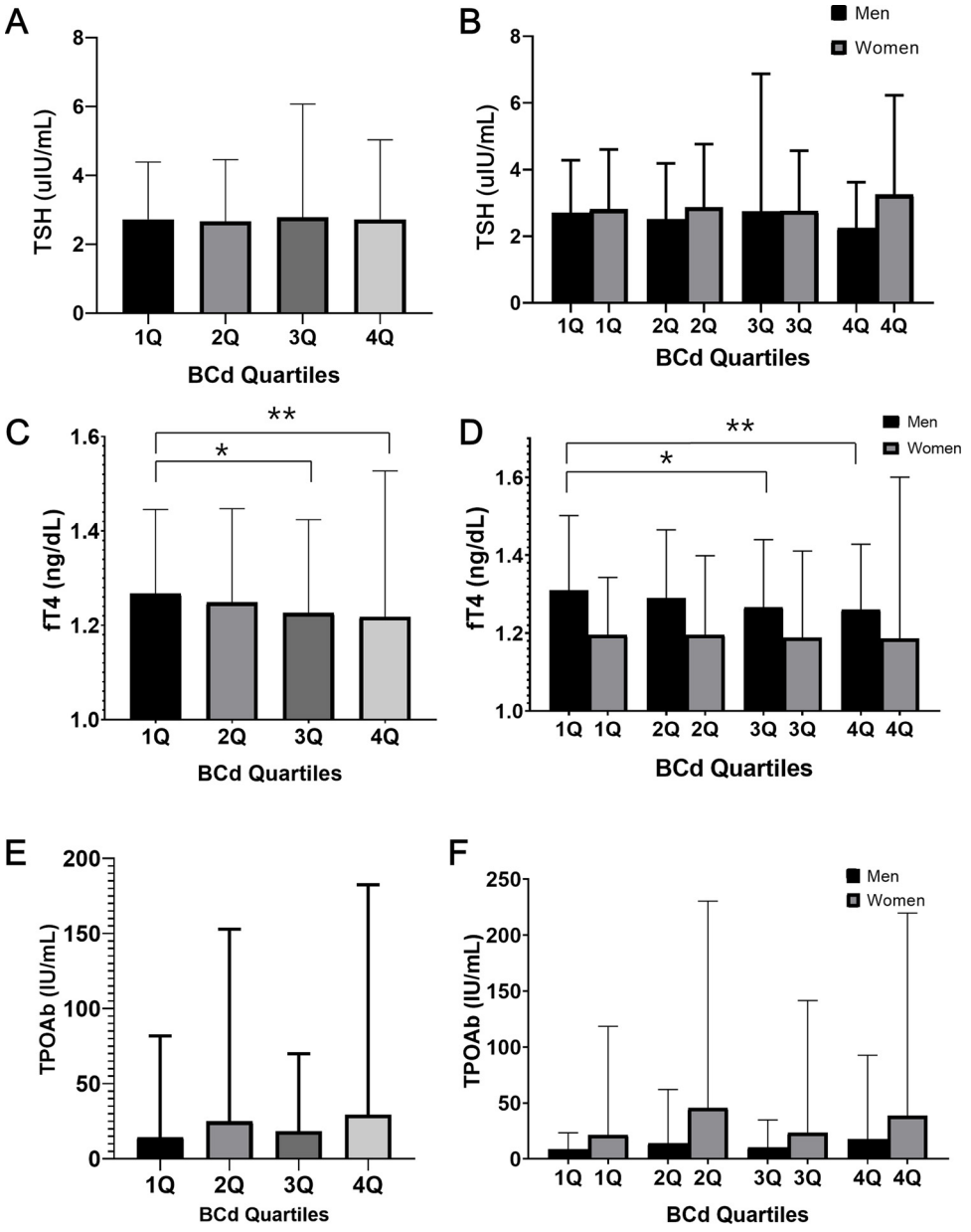

Fig. 1. Estimated thyroid hormone levels according to blood cadmium quartiles.
TSH levels according to (A) overall and (B) sex-specific BCd quartiles; fT4 levels according to (C) overall and (D) sex-specific BCd quartiles; TPOAb levels according to (E) overall and (F) sex-specific BCd quartiles.
The graphs depict mean and standard deviation. * denotes statistical significance at p < 0.05, ** denotes statistical significance at p < 0.001.
BCd, blood cadmium; TSH, thyroid-stimulating hormone; fT4, free thyroxine; TPOAb, anti-thyroid peroxidase antibody.

Table 3
Thyroid hormone levels according to different groups.

	n (%)	TSH (uIU/mL)		fT4 (ng/dL)		TPOAb (IU/mL)	
		Mean ± SD	P-for-trend	Mean ± SD	P-for-trend	Mean ± SD	P-for-trend
Men (n = 1057)							
BCd quartile			0.078		0.002		0.089
1Q [0.02-0.4776]	264 (25.0)	2.70 ± 1.58		1.31 ± 0.19		8.65 ± 14.68	
2Q [0.4776-0.6890]	265 (25.0)	2.50 ± 1.69		1.28 ± 0.18		13.89 ± 48.14	
3Q [0.6890-1.0675]	264 (25.0)	2.74 ± 4.13		1.26 ± 0.17 *		10.24 ± 24.64	
4Q [1.0675-11.05]	264 (25.0)	2.24 ± 1.38		1.26 ± 0.17 **		17.80 ± 74.91	
Age			0.148		< 0.001		0.001
10-19	191 (18.1)	2.80 ± 1.69		1.32 ± 0.20		7.01 ± 5.50	
20-39	381 (36.0)	2.38 ± 1.29		1.32 ± 0.16		12.89 ± 44.26 *	
40-65	485 (45.9)	2.57 ± 3.29		1.23 ± 0.17 ***###		14.68 ± 56.75 *	
BMI (kg/m2) [1]			0.905		0.091		< 0.001
Underweight	17 (1.9)	2.23 ± 1.24		1.31 ± 0.21		5.76 ± 1.23	
Normal	528 (60.2)	2.51 ± 3.11		1.28 ± 0.17		11.71 ± 30.64 ***	
Obese	332 (37.9)	2.49 ± 1.59		1.25 ± 0.17		17.44 ± 73.77 *	
Smoking status [2]			0.001		0.002		0.021
Ever	621 (61.9)	2.35 ± 1.57		1.27 ± 0.17		14.71 ± 57.36	
Never	382 (38.1)	2.69 ± 1.57		1.30 ± 0.18		8.90 ± 19.23	
Alcohol drinking status [3]			0.341		0.091		0.254
Ever	871 (89.9)	2.43 ± 1.56		1.28 ± 0.17		13.28 ± 50.05	
Never	98 (10.1)	2.59 ± 1.45		1.31 ± 0.22		7.51 ± 7.23	
U I/Cre tertile			< 0.001		< 0.001		0.906
1T [4.69-110.33]	352 (33.3)	2.08 ± 1.09		1.31 ± 0.18		12.78 ± 44.76	
2T [110.33-265.78]	352 (33.3)	2.81 ± 3.75 ***		1.27 ± 0.18 *		13.36 ± 60.75	
3T [265.48-15,772.39]	353 (33.4)	2.74 ± 1.65 **		1.26 ± 0.17 **		11.81 ± 30.06	
Women (n = 915)							
BCd quartile			0.198		0.944		0.241
1Q [0.05-0.4810]	230 (25.1)	2.82 ± 1.82		1.19 ± 0.14		21.32 ± 97.18	
2Q [0.4810-0.8340]	228 (24.9)	2.87 ± 1.89		1.19 ± 0.20		45.51 ± 184.85	
3Q [0.8340-1.2990]	229 (25.0)	2.76 ± 1.81		1.18 ± 0.22		23.42 ± 118.17	
4Q [1.2990-3.95]	228 (24.9)	3.25 ± 2.98		1.18 ± 0.41		38.66 ± 181.05	
Age			0.044		0.195		0.112
10-19	144 (15.7)	2.95 ± 1.98		1.21 ± 0.18		20.64 ± 105.20	
20-39	316 (34.5)	2.70 ± 1.60		1.20 ± 0.20		22.40 ± 109.63	
40-65	455 (49.7)	3.07 ± 2.56 #		1.17 ± 0.32		42.65 ± 182.80	
BMI (kg/m2) [4]			0.847		0.147		0.745
Underweight (< 18.5)	49 (6.3)	2.97 ± 1.68		1.31 ± 0.68		18.59 ± 75.06	
Normal (≥18.5, < 25)	539 (69.3)	2.91 ± 2.38		1.18 ± 0.22		27.20 ± 174.05	
Obese (≥25)	190 (24.4)	3.02 ± 2.09		1.15 ± 0.23		35.83 ± 143.32	
Smoking status [5]			0.450		0.195		0.564
Ever	85 (9.6)	2.77 ± 2.11		1.26 ± 0.53		27.26 ± 79.76	
Never	799 (90.4)	2.96 ± 2.21		1.18 ± 0.22		33.22 ± 158.54	
Alcohol drinking status [6]			0.894		0.719		0.003
Ever	692 (80.7)	2.94 ± 2.27		1.19 ± 0.28		37.54 ± 171.22	
Never	166 (19.3)	2.92 ± 1.99		1.19 ± 0.23		16.22 ± 39.48	
U I/Cre tertile			< 0.001		0.460		0.734
1T [11.34-147.67]	305 (33.3)	2.60 ± 1.53		1.20 ± 0.19		32.65 ± 160.30	
2T [147.67-414.45]	305 (33.3)	2.95 ± 2.46		1.18 ± 0.33		36.74 ± 139.36	
3T [414.45-32,407.60]	305 (33.3)	3.22 ± 2.40 **		1.18 ± 0.26		27.20 ± 150.76	

In men, [1] 180 subjects with age < 19 were excluded, and [2] 54 and [3] 88 subjects had missing data.
In women, [4] 137 subjects with age < 19 were excluded, and [5] 31 and [6] 57 subjects had missing data.
* p < 0.05, ** p < 0.01, and *** p < 0.001 compared to first subgroup. # p < 0.05, ### p < 0.001 compared to second subgroup.
BCd, blood cadmium; TSH, thyroid-stimulating hormone; fT4, free thyroxine; TPOAb, anti-thyroid peroxidase antibody; BMI, body mass index; UI/Cre, urine iodine-to-creatinine ratio.

correlation analysis, BCd showed a significant negative correlation with fT4 (r = -0.067, p = 0.003). When BCd was divided into quartiles, the fT4 levels showed a decreasing trend from the lowest to the highest BCd quartile: 1.26 ± 0.17 ng/dL, 1.24 ± 0.20 ng/dL, 1.22 ± 0.20 ng/dL, and 1.21 ± 0.31 ng/dL, respectively (p-for-trend = 0.002). Especially in the third and fourth BCd quartiles, the fT4 levels decreased compared to the first BCd quartile (p = 0.014 and 0.003, respectively). Though BCd had no significant correlation with TSH and TPOAb, the TPOAb level was highest in the highest BCd quartile. Fig. 1, illustrates the TSH, fT4, and TPOAb values according to overall and sex-specific BCd quartiles.

3.3. Sex-specific TSH, fT4, and TPOAb levels in different groups

Table 3 shows sex-specific TSH, fT4, and TPOAb levels according to multiple groups: BCd quartiles, age group, BMI group, smoking status, alcohol drinking status, and UI/Cre tertiles. In men, fT4 levels changed significantly according to BCd quartiles (p-for-trend = 0.002). The fT4 levels of the lowest to highest BCd quartile were 1.31 ± 0.19 ng/dL, 1.28 ± 0.18 ng/dL, 1.26 ± 0.17 ng/dL, and 1.26 ± 0.17 ng/dL, respectively; the fT4 decreased in the third and fourth quartiles compared to the first quartile (p < 0.05 and < 0.01, respectively). In the highest BCd quartile, the TSH level was lowest and the TPOAb level was highest without statistical significance. Thyroid hormone levels changed according to the following considered covariates: TSH differed according to smoking status and UI/Cre tertiles (p < 0.01, all); fT4 levels differed

Table 4
Logistic regression models between BCd and hypothyroid status.

	Hypothyroid status					
	Overall (n = 1972)		Men (n = 1057)		Women (n = 915)	
BCd	OR [95% CI]	P-value	OR [95% CI]	P-value	OR [95% CI]	P-value
Crude	1.014 [0.843-1.221]	0.881	1.856 [1.237-2.784]	0.003	0.801 [0.625-1.026]	0.080
Model 1	0.980 [0.794-1.210]	0.851	1.946 [1.193-3.174]	0.008	0.759 [0.562-1.026]	0.073
Model 2	0.948 [0.764-1.175]	0.624	1.817 [1.060-3.115]	0.030	0.764 [0.558-1.044]	0.091
Model 3	0.947 [0.760-1.179]	0.625	1.813 [1.053-3.122]	0.032	0.745 [0.543-1.023]	0.069

Model 1 : adjusted for Age and BMI.
Model 2 : adjusted for model 1 plus smoking status.
Model 3 : adjusted for model 2 plus UI/Cre and TPOAb.
BCd, blood cadmium.

according to age group, smoking status, and UI/Cre tertiles ($p < 0.01$, all); and TPOAb levels differed according to age group, BMI group, and smoking status ($p < 0.05$, all).

In women, no differences in TSH, fT4, or TPOAb levels were found according to the BCd quartiles. In highest BCd quartile, the TSH level was highest without statistical significance. TSH levels differed according to age group and UI/Cre tertiles ($p < 0.05$, all), and TPOAb levels differed according to drinking status ($p = 0.003$). However, the level of fT4 did not differ according to any of the covariates.

The trend in obesity and hypothyroidism was similar to previous study [29]. There was inverse correlation between BMI and fT4 in men and women, although not statistically significant. For this reason, we considered BMI as one of possible confounder of hypothyroidism on next step.

3.4. Adjusted logistic regression models between BCd and hypothyroid status

Logistic regression analysis was performed to determine the effect of BCd on the prevalence of hypothyroid status (Table 4). Participants with hyperthyroidism were excluded during the analysis. Logistic regression models were adjusted as follows: model 1, age and BMI; model 2, model 1 plus smoking status which can confound BCd levels; and model 3, model 2 plus UI/Cre and TPOAb, reflecting iodine intake and autoimmunity which are common causes of hypothyroidism [30]. After adjustment, the odds ratios (ORs) of BCd to hypothyroid status increased significantly in men (OR range 1.053–3.122, $p = 0.032$), while decreased without significant correlation in women.

4. Discussion

Our results showed that there is a negative correlation between BCd and fT4. In men, fT4 levels significantly changed according to BCd quartiles, age group, smoking status, and UI/Cre tertiles. We analyzed the relationship between BCd and thyroid function status, classified by TSH and fT4 levels. The association between BCd and hypothyroidism in men was significant even after adjustment for age, BMI, smoking status, UI/Cre, and TPOAb.

The major hormone secreted by the thyroid gland is T4. T4 in the blood is totally secreted by the thyroid. In contrast, only 20% of serum T3 is secreted by the thyroid and 80% is produced by deiodination of T4 in peripheral tissues. The measurement of fT4, the protein-unbound form, reflects the biological effect better than the measurement of T4 [20]. Therefore, fT4 is more suitable for evaluating thyroid dysfunction than T4 or T3. In this study it is a strength to evaluate thyroid function using fT4.

Cadmium causes oxidative stress in the endocrine organs, resulting in organ secretory abnormalities. Exposure to cadmium in pancreatic beta-cells results in oxidative stress and mitochondrial dysfunction [31] and reduces glucose-stimulated insulin secretion [32]. When male rats are exposed to cadmium and lead, reactive oxygen species increased in the testes, reducing testosterone production, sperm count, motility, and viability. The testicular toxicity of cadmium was higher than that of lead [33]. Similarly, the accumulation of cadmium in the thyroid gland can cause oxidative stress and mitochondrial dysfunction of the thyroid follicular cells [34], decreasing T4 synthesis and secretion, and a subsequent decrease in fT4.

Research on cadmium exposure and thyroid hormone changes have been performed in many animal and human studies. The results of rat experiments showed that T4 in males decreased following exposure to cadmium [14]. In addition, T4 was decreased by cadmium toxicity in pregnant rats [35]. The relationship between cadmium and TSH remains controversial [14]; several studies have shown that TSH increased following cadmium exposure [36,37]. One study also reported that cadmium exposure decreased T4 and T3 but not TSH, suggesting non-thyroidal illness [38]. Monkey experiments have shown that cadmium-containing diets for four to six months resulted in reduced T4 levels [39]. Taken together, cadmium exposure in animals is associated with the trend of hypothyroxinemia.

Research on human subjects revealed various results. Nationwide studies performed in the US were based on National Health and Nutrition Examination Survey data, and TSH, T3, free T3 (fT3), T4, fT4, and thyroglobulin (Tg) levels were measured. The results showed that UCd was positively correlated with T3, fT3, T4, and Tg [15,16]; moreover, BCd was negatively correlated with TSH [16,18]. In addition, the degree of dysregulation in the pituitary-thyroid axis was different according to sex [17]. A nationwide study performed in China was based on the Survey on Prevalence in East China for Metabolic Disease and Risk Factors data, and TSH, T3, T4, thyroglobulin antibody (TGAb), and TPOAb levels were measured [19]. According to its results, BCd had a positive correlation with TGAb and the prevalence of hypothyroid status in women, but not with TPOAb. In Italy, 277 outdoor workers were enrolled to study the relationship between cadmium exposure and TSH, fT3, and fT4 levels [40]; the UCd levels were negatively correlated with fT3 and fT4 and positively correlated with TSH. These results should be interpreted in view of the fact that multivariate EDCs that can alter thyroid hormones [41,42] cannot be completely limited in human studies. Perhaps human thyroid hormone levels vary biphasically due to the complex etiology of EDCs.

Like the previous human-based studies, our study also showed results that differed depending on sex. It is noteworthy that although the mean BCd levels of men were lower than that of women, the BCd levels in men were related to decreased fT4 and the prevalence of hypothyroidism. In addition, even after adjusting for UI/Cre and TPOAb reflecting the main cause of hypothyroidism [30], the effect of BCd on the prevalence of hypothyroidism in men significant, while it was not relevant in women. Presumably, as women have additional sex-specific risk factors of hypothyroidism, such as pregnancy and childbirth [30], the impact of BCd on hypothyroidism may be less clear than for men. The mechanism of the sex-specific outcome is still unclear. Further

research on the sex-specific metabolic capacity of cadmium and thyroid dysfunction is needed.

Regarding thyroid autoimmunity, our study showed that TPOAb was not associated with BCd. This is consistent with the results of Chinese study [19]. However, it is interesting that TPOAb tends to be higher in the highest BCd quartiles in total participants and men. As our study excluded those who were undergoing treatment for autoimmune thyroid disease, including Hashimoto's thyroiditis, there may be an association between BCd and TPOAb in the excluded participants. Additional studies on the relationship between TPOAb and BCd through other participant selection methods are warranted, especially in Asian populations.

Our study had some limitations. First, the causal relationship could not be clarified due to its cross-sectional design. Second, it was difficult to determine the amount and duration of each individual's cadmium exposure. Third, the possible confounding effects of other EDCs on thyroid function was not considered. Despite these limitations, it is meaningful that we evaluated the thyroid function status in consideration of fT4; our study is the first to identify the relationship between BCd and fT4 in a nationwide population. Furthermore, we reported sex-specific effect of BCd on hypothyroidism, which was valid after adjusting for important confounders.

In conclusion, BCd level is negatively associated with fT4 levels and increases the prevalence of hypothyroidism, especially in Korean men.

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Author contributions

S.M.C conceived and designed the study. S.M.C. analyzed the data and wrote the manuscript. J.S.M and K.C.W made the critical review for intellectual content. J.S.M, J.S.Y, K.C.W, and H.W.L reviewed the paper. All authors have approved the final version to be submitted.

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References

[1] I. Iavicoli, L. Fontana, A. Bergamaschi, The effects of metals as endocrine disruptors, J. Toxicol. Environ. Health B Crit. Rev. 12 (3) (2009) 206–223.
[2] D.H. Lee, Evidence of the possible harm of endocrine-disrupting chemicals in humans: ongoing debates and key issues, Endocrinol. Metab. (Seoul) 33 (1) (2018) 44–52.
[3] D.H. Lee, Can air pollution biologically hinder efforts to lose body weight? Diabetes Metab. J. 42 (4) (2018) 282–284.
[4] ATSDR, Public Health Statement : Cadmium, (2012) (Accessed 07.25 2018), https://www.atsdr.cdc.gov/ToxProfiles/tp5-c1-b.pdf.
[5] L. Jarup, Hazards of heavy metal contamination, Br. Med. Bull. 68 (2003) 167–182.
[6] B.K. Lee, Y. Kim, Blood cadmium, mercury, and lead and metabolic syndrome in South Korea: 2005-2010 Korean National Health and Nutrition Examination Survey, Am. J. Ind. Med. 56 (6) (2013) 682–692.
[7] L. Barregard, G. Bergstrom, B. Fagerberg, Cadmium exposure in relation to insulin production, insulin sensitivity and type 2 diabetes: a cross-sectional and prospective study in women, Environ. Res. 121 (2013) 104–109.
[8] A.A. Tinkov, T. Filippini, O.P. Ajsuvakova, J. Aaseth, Y.G. Gluhcheva, J.M. Ivanova, G. Bjorklund, M.G. Skalnaya, E.R. Gatiatulina, E.V. Popova, O.N. Nemereshina, M. Vinceti, A.V. Skalny, The role of cadmium in obesity and diabetes, Sci. Total Environ. 601-602 (2017) 741–755.
[9] A.A. Tinkov, T. Filippini, O.P. Ajsuvakova, M.G. Skalnaya, J. Aaseth, G. Bjorklund, E.R. Gatiatulina, E.V. Popova, O.N. Nemereshina, P.T. Huang, M. Vinceti, A.V. Skalny, Cadmium and atherosclerosis: a review of toxicological mechanisms and a meta-analysis of epidemiologic studies, Environ. Res. 162 (2018) 240–260.
[10] S. Fittipaldi, V.M. Bimonte, A. Soricelli, A. Aversa, A. Lenzi, E.A. Greco, S. Migliaccio, Cadmium exposure alters steroid receptors and proinflammatory cytokine levels in endothelial cells in vitro: a potential mechanism of endocrine disruptor atherogenic effect, J. Endocrinol. Invest. (2018).
[11] A. Lafuente, The hypothalamic-pituitary-gonadal axis is target of cadmium toxicity. An update of recent studies and potential therapeutic approaches, Food Chem. Toxicol. 59 (2013) 395–404.
[12] J.K. Kresovich, M. Argos, M.E. Turyk, Associations of lead and cadmium with sex hormones in adult males, Environ. Res. 142 (2015) 25–33.
[13] M. Nasiadek, M. Danilewicz, K. Sitarek, E. Swiatkowska, A. Darago, J. Stragierowicz, A. Kilanowicz, The effect of repeated cadmium oral exposure on the level of sex hormones, estrous cyclicity, and endometrium morphometry in female rats, Environ. Sci. Pollut. Res. Int. 25 (28) (2018) 28025–28038.
[14] A. Buha, V. Matovic, B. Antonijevic, Z. Bulat, M. Curcic, E.A. Renieri, A.M. Tsatsakis, A. Schweitzer, D. Wallace, Overview of cadmium thyroid disrupting effects and mechanisms, Int. J. Mol. Sci. 19 (5) (2018).
[15] A. Chen, S.S. Kim, E. Chung, K.N. Dietrich, Thyroid hormones in relation to lead, mercury, and cadmium exposure in the National Health and Nutrition Examination Survey, 2007-2008, Environ. Health Perspect. 121 (2) (2013) 181–186.
[16] K.L. Yorita Christensen, Metals in blood and urine, and thyroid function among adults in the United States 2007-2008, Int. J. Hyg. Environ. Health 216 (6) (2013) 624–632.
[17] J. Luo, M. Hendryx, Relationship between blood cadmium, lead, and serum thyroid measures in US adults - the National Health and Nutrition Examination Survey (NHANES) 2007-2010, Int. J. Environ. Health Res. 24 (2) (2014) 125–136.
[18] R.B. Jain, Y.S. Choi, Interacting effects of selected trace and toxic metals on thyroid function, Int. J. Environ. Health Res. 26 (1) (2016) 75–91.
[19] X. Nie, Y. Chen, Y. Chen, C. Chen, B. Han, Q. Li, C. Zhu, F. Xia, H. Zhai, N. Wang, Y. Lu, Lead and cadmium exposure, higher thyroid antibodies and thyroid dysfunction in Chinese women, Environ. Pollut. 230 (2017) 320–328.
[20] D.L. Kasper, A.S. Fauci, S.L. Hauser, D.L. Longo, J.L. Jameson, J. Loscalzo, Thyroid Gland Disorders, Harrison's Manual of Medicine, 19e, McGraw-Hill Education, New York, NY, 2016.
[21] S. Park, B.K. Lee, Strong positive association of traditional Asian-style diets with blood cadmium and lead levels in the Korean adult population, Int. J. Environ. Health Res. 23 (6) (2013) 531–543.
[22] C.S. Moon, H.R. Yang, H. Nakatsuka, M. Ikeda, Time trend of cadmium intake in Korea, Environ. Health Prev. Med. 21 (3) (2016) 118–128.
[23] J.W. Seo, B.G. Kim, Y.M. Kim, R.B. Kim, J.Y. Chung, K.M. Lee, Y.S. Hong, Trend of blood lead, mercury, and cadmium levels in Korean population: data analysis of the Korea National Health and Nutrition Examination Survey, Environ. Monit. Assess. 187 (3) (2015) 146.
[24] S. Kweon, Y. Kim, M.J. Jang, Y. Kim, K. Kim, S. Choi, C. Chun, Y.H. Khang, K. Oh, Data resource profile: the korea national health and nutrition examination survey (KNHANES), Int. J. Epidemiol. 43 (1) (2014) 69–77.
[25] J. Angerer, U. Ewers, M. Wilhelm, Human biomonitoring: state of the art, Int. J. Hyg. Environ. Health 210 (3-4) (2007) 201–228.
[26] P. Vejbjerg, N. Knudsen, H. Perrild, P. Laurberg, S. Andersen, L.B. Rasmussen, L. Ovesen, T. Jorgensen, Estimation of iodine intake from various urinary iodine measurements in population studies, Thyroid 19 (11) (2009) 1281–1286.
[27] N. Knudsen, E. Christiansen, M. Brandt-Christensen, B. Nygaard, H. Perrild, Age- and sex-adjusted iodine/creatinine ratio. A new standard in epidemiological surveys? Evaluation of three different estimates of iodine excretion based on casual urine samples and comparison to 24 h values, Eur. J. Clin. Nutr. 54 (4) (2000) 361–363.
[28] S. Greenland, S.J. Senn, K.J. Rothman, J.B. Carlin, C. Poole, S.N. Goodman, D.G. Altman, Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations, Eur. J. Epidemiol. 31 (4) (2016) 337–350.
[29] N. Knudsen, P. Laurberg, L.B. Rasmussen, I. Bulow, H. Perrild, L. Ovesen, T. Jorgensen, Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population, J. Clin. Endocrinol. Metab. 90 (7) (2005) 4019–4024.
[30] C.G. Roberts, P.W. Ladenson, Hypothyroidism, Lancet 363 (9411) (2004) 793–803.
[31] K.C. Chang, C.C. Hsu, S.H. Liu, C.C. Su, C.C. Yen, M.J. Lee, K.L. Chen, T.J. Ho, D.Z. Hung, C.C. Wu, T.H. Lu, Y.C. Su, Y.W. Chen, C.F. Huang, Cadmium induces apoptosis in pancreatic beta-cells through a mitochondria-dependent pathway: the role of oxidative stress-mediated c-Jun N-terminal kinase activation, PLoS One 8 (2) (2013) e54374.
[32] M. El Muayed, M.R. Raja, X. Zhang, K.W. MacRenaris, S. Bhatt, X. Chen, M. Urbanek, T.V. O'Halloran, W.L. Lowe Jr, Accumulation of cadmium in insulin-producing beta cells, Islets 4 (6) (2012) 405–416.
[33] C. Pandya, P. Pillai, L.P. Nampoothiri, N. Bhatt, S. Gupta, S. Gupta, Effect of lead and cadmium co-exposure on testicular steroid metabolism and antioxidant system of adult male rats, Andrologia 44 (Suppl 1) (2012) 813–822.
[34] S.A. Jancic, B.Z. Stosic, Cadmium effects on the thyroid gland, Vitam. Horm. 94 (2014) 391–425.
[35] M. Yoshizuka, N. Mori, K. Hamasaki, I. Tanaka, M. Yokoyama, K. Hara, Y. Doi, Y. Umezu, H. Araki, Y. Sakamoto, et al., Cadmium toxicity in the thyroid gland of pregnant rats, Exp. Mol. Pathol. 55 (1) (1991) 97–104.
[36] M.G. Wade, S. Parent, K.W. Finnson, W. Foster, E. Younglai, A. McMahon, D.G. Cyr, C. Hughes, Thyroid toxicity due to subchronic exposure to a complex mixture of 16 organochlorines, lead, and cadmium, Toxicol. Sci. 67 (2) (2002) 207–218.
[37] A. Lafuente, P. Cano, A. Esquifino, Are cadmium effects on plasma gonadotropins, prolactin, ACTH, GH and TSH levels, dose-dependent? Biometals 16 (2) (2003) 243–250.

[38] M.A. Pavia Junior, B. Paier, M.I. Noli, K. Hagmuller, A.A. Zaninovich, Evidence suggesting that cadmium induces a non-thyroidal illness syndrome in the rat, J. Endocrinol. 154 (1) (1997) 113–117.
[39] J. Mehta, D. Dhawan, M. Mehta, R. Kumar, J.S. Chopra, R.R. Sharma, Effect of dietary cadmium intake on serum thyroxine and triiodothyronine concentrations in rhesus monkeys, Toxicol. Lett. 34 (1) (1986) 85–88.
[40] M.V. Rosati, L. Montuori, T. Caciari, C. Sacco, M. Marrocco, G. Tomei, B. Scala, A. Sancini, V. Anzelmo, S. Bonomi, F. Tomei, Correlation between urinary cadmium and thyroid hormones in outdoor workers exposed to urban stressors, Toxicol. Ind. Health 32 (12) (2016) 1978–1986.
[41] S.M. Ferrari, P. Fallahi, A. Antonelli, S. Benvenga, Environmental issues in thyroid diseases, Front. Endocrinol. (Lausanne) 8 (2017) 50.
[42] M. Boas, K.M. Main, U. Feldt-Rasmussen, Environmental chemicals and thyroid function: an update, Curr. Opin. Endocrinol. Diabetes Obes. 16 (5) (2009) 385–391.