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Research Article

Associations between Thyroid Function and Blood and Urine Cadmium -

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ABSTRACT

Data from National Health and Nutrition Examination Survey for those aged >= 12 years for 2007-2012 were used to evaluate associations between the levels of urine and blood cadmium and thyroid hormones: Thyroid Stimulating Hormone (TSH), Free and Total Triiodothyronine (FT3, TT3), Free and Total Thyroxine (FT4, TT4), and Thyroglobulin (TGN). Separate regression models for iodine deficient males, iodine replete males, iodine deficient females, and iodine replete females were fitted. Total sample sizes used to analyze blood cadmium data were 1293, 3367, 1455, and 2586 for iodine deficient male, iodine replete males, iodine deficient females, and iodine replete females respectively. Total sample sizes used to analyze urine cadmium data were 444, 1122, 482, and 892 for iodine deficient male, iodine replete males, iodine deficient females, and iodine replete females respectively. For iodine deficient males, for one decile increase in the levels of blood cadmium, the adjusted levels of TT3 and TT4 increased by 0.007 ng/dL and 0.007 µg/mL respectively. For iodine replete males, for a 10% increase in the levels of blood cadmium, levels of TGN increased by 0.643%. For iodine deficient females, for one decile increase in the levels of blood cadmium, the levels of FT3 increased by 0.008 pg/mL and the levels of TT3 decreased by 0.012 ng/dL. For iodine replete females, for one decile increase in the levels of blood cadmium, the levels of FT3 increased by 0.006 pg/mL and the levels of TT3 decreased by 0.007 ng/dL. Blood cadmium levels did not affect the levels of TSH. The levels of urine cadmium were not found to affect the levels of any thyroid hormone.

Keywords: Thyroid hormones; Cadmium; FT4; TT3; TT4; TSH

INTRODUCTION

The impact of exposure to cadmium on the thyroid function has been investigated in animal as well as human studies for a while. Some of the studies that have investigated the association between exposure to cadmium and thyroid hormones among animals are by Mohamed, et al. [1], Buha, et al. [2], Hammouda, et al. [3] , Mori, et al. [4], and Gupta and Kar [5]. When compared with controls, elevated levels of thyroid stimulating hormones (TSH) were observed among cadmium treated rats [1]. Buha, et al. [2] reported triiodothyronine (T3) levels to be most prominently affected among rats with prolonged exposure to cadmium. Prenatal exposure to low doses of cadmium resulted in decreased levels of serum thyroxine (T4) levels in metallothione in I and II null neonatal mice [4]. In a study of male Wistar albino rats exposed to 200 ppm cadmium in water for 35 days, levels of TSH increased and the levels of T4 decreased [3]. In a study of 200 g body weight Wistar rats exposed to a dose of 2.5 mg/kg body weight cadmium chloride, plasma concentrations of T4 and T3 were observed to decrease without an increase in TSH levels [6]. Administration of cadmium chloride to chickens at the rate of 2.5 mg/kg body weight/day daily for 15 days resulted in decreased T3 without alterations in the levels of thyroxine or T4 [5]. Thus, exposure to cadmium seem to result in decreased levels of T3 and/or T4 but response to low levels of T3/T4 does not necessarily result in increased levels of TSH.

In a study of exposure to low concentrations of cadmium among outdoor workers in Italy (N = 210 males, 146 females), Rosati, et al. [7] reported negative correlations between urinary cadmium levels and free triiodothyronine (FT3) and free thyroxine (FT4) and a positive correlation between urinary cadmium and TSH levels. Luo and Hendryx, [8] reported effect of cadmium exposure on thyroid function to differ by gender. Yorita Christensen, [9] also reported positive association between urine cadmium and T3 and T4 in a study that used NHANES 2007-2008 data. Chen et al. (2013) used data from National Health and Nutrition Examination Survey (NHANES) for 2007-2008 and reported positive associations between urinary cadmium and total thyroxine (TT4), total triiodothyronine (TT3), FT3, and thyroglobulin (TGN). In their study, Chen, et al. [10] fitted separate regression models for adolescents and adults with log-transformed levels of thyroid hormones as dependent variables and age, gender, race/ethnicity, creatinine adjusted urine iodine, body mass index, and serum cotinine levels as independent variables. Overall, it seems exposure to cadmium among humans results in decreased levels of FT3 and/or FT4 but increased levels of TT3 and/or TT4 with possibly increased levels of TSH and TGN. These observations seem to be opposite to what has been reported in animal studies.

Elevated levels of blood cadmium have been reported to be associated with impaired kidney function [11,12], high prevalence of elevated C-reactive protein and fibrinogen [13], hepatitis B virus and Helicobacter pylori seropositivity [14] iron deficiency among children aged 3–19 years, [15] increased odds of prevalent stroke and prevalent heart failure [16], higher odds of age-related macular degeneration [17], and higher odds of balance dysfunction [18]. Elevated levels of urine cadmium have been reported to be associated with prediabetes [19], higher risk of osteoporosis among females aged ≥50 years [20], hepatic necroinflammation, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, liver-related mortality and liver cancer mortality [21], myocardial infarction among 45–79 years old [22], increased odds of breast cancer [23], bone loss in US women aged 42–60 years [24], higher odds of periodontal disease among US adults [25], and higher odds of learning disability among children aged 6–15 years [26].

Iodine is an essential element for normal functioning of thyroid. Inadequate supply of iodine can disrupt thyroid homeostasis possibly resulting in hypothyroidism and other thyroid disorders. Consequently, in order to evaluate the associations of extraneous chemicals and elements like cadmium with thyroid hormones, it is necessary that existing status of thyroid homeostasis be taken into account. This can be done if the models to evaluate these associations can be stratified by iodine sufficiency status. This can be done by classifying iodine sufficiency status as iodine deficient and iodine replete based on the standard definitions. For the purpose of the proposed study, iodine deficiency was defined as recommended by WHO [27] and models to evaluate associations of blood and urine cadmium with thyroid hormones were stratified by iodine sufficiency status as iodine deficient and iodine replete. In addition, prevalence of iodine deficiency is known to be higher among females. For example, for the NHANES 2007-2012, while 27.8% males were iodine deficient, 36.0% females were found to be iodine deficient. Because of the differentials in the prevalence of iodine deficiency between males and females, the associations of interest are also likely to be different among males and females and as such, it is prudent to fit

gender stratified models. With this, in mind, separate models should be fitted for iodine deficient males, iodine replete males, iodine deficient females, and iodine replete females. Chen, et al. [10] used 2007-2008 data from NHANES to evaluate the association of blood as well as urine cadmium with thyroid function but used gender as well as creatinine corrected urine iodine as independent variables in the regression models rather than fitting stratified models as described before. The use of urine iodine as a continuous variable implies that there is a linear association between log-transformed values of thyroid hormones and urine iodine in a dose-response manner. Chen, et al. [10] did not provide any data on regression coefficients between urine iodine and various thyroid hormones to evaluate this assumption but we computed correlations between log-transformed values of FT3, FT4, TT3, and TT4 for the data for NHANES 2007-2012 to test the adequacy of this assumption. The regression coefficients that creatinine adjusted urine iodine had with log-FT3, log-FT4, log-TT3, and log-TT4 were -3.57512E-8 ($p = 0.09$), 4.463243E-8 ($p = 0.09$), -5.2563E-8 ($p = 0.10$), and 6.022478E-8 ($p = 0.04$) respectively. As such, except for TT4, the linear association between creatinine corrected urine iodine and logs of FT3, FT4, and TT3 in a dose-response manner cannot be proved. Consequently, this study was undertaken to re-evaluate associations between urine and blood cadmium and thyroid hormones by fitting gender and iodine sufficiency stratified models for NHANES 2007-2012 data.

MATERIALS AND METHODS

Data source and data description

Data from NHANES for those aged >=12 years were downloaded and match merged from the data files on demographics, body measures, urine iodine, blood metals, standard chemistry, urine metals, fasting questionnaire, thyroid function, medical questionnaire, and serum cotinine. Sampling weights are created in NHANES to account for the probabilities of selection and response as well as total US population for selected combinations of gender, race/ethnicity and age. For the purpose of this study, variables selected for use were: gender (male, female), race/ethnicity (non-Hispanic white or NHW, non-Hispanic black or NHB, all Hispanics or HISP, other unclassified race/ethnicities or OTH), poverty income ratio, body mass index, fasting time in hours prior to the collection of blood and urine samples, serum albumin, blood cadmium, urine cadmium, smoking status (nonsmoker defined as those with serum cotinine < 10 ng/mL, smoker defined as those with serum cotinine >= 10 ng/mL), and iodine sufficiency status (iodine deficient defined as those with urine iodine < 100 ng/mL, iodine replete defined as those with urine iodine >= 100 ng/mL). In addition, for females only variables selected for use were: menopausal status (yes, no), premenarche status (yes, no), estrogen/progesterone use (yes, no), and number of live births as a measure of parity.

Data on thyroid function were available for TSH, FT3, FT4, TT3, TT4, TGN, thyroglobulin antibodies (TgAb) and thyroid peroxidase antibodies (TPOAb). Data on thyroid were available for the full NHANES sample for 2007-2008 but for 1/3 samples only for 2009-2010 and 2011-2012. While data for blood cadmium were available for full NHANES samples for all three cycles, because of the non-availability of thyroid data for full samples for 2009-2012, data on blood cadmium were analyzed for full sample for 2007-2008 and for 1/3 samples for 2009-2012. For urine cadmium, data were available for 1/3 samples only for all three NHANES cycles, as such, data for the purpose of data analyses was smaller for urine cadmium than for blood cadmium.

After deleting those from the database all those who were pregnant at the time of participating in NHANES, all those who reported having thyroid problems at the time of participating in NHANES, all those for whom TgAb > = 20 IU/mL and/or TPOAb > = 35 IU/mL, all those who were using one or more thyroid treatment drugs at the time participating in NHANES, all those who had a missing value for any variable selected for use in the data analysis, a total of 1293 iodine deficient males, 3367 iodine replete males, 1455 iodine deficient females, and 2586 iodine replete females were available for the analysis of blood cadmium data. A total of 444 iodine deficient males, 1122 iodine replete males, 482 iodine deficient females, and 892 iodine replete females were available for the analysis of urine cadmium data. Sample size details are given in table 1. For the purpose of data analyses, four databases, namely, for iodine deficient males, iodine replete males, iodine deficient females, and iodine replete females were generated.

Percent observations above the limit of detection for blood cadmium were 75.2% and 71.2% for iodine deficient and iodine replete males respectively and 82.1% and 78.5% for iodine deficient and iodine replete females respectively. Percent observations above the limit of detection for urine cadmium were 91.4% and 91.2% for iodine deficient and iodine replete males respectively and 93% for both iodine deficient and iodine replete females.

Statistical analysis

In order to normalize positively skewed data, log10 transformed variables were generated for all six thyroid variables TSH, FT3, FT4, TT3, TT4, and TGN, blood cadmium, urine cadmium, body mass index, serum albumin, and urine creatinine. Data analysis plan included fitting a regression model for each of the six thyroid variables for each of the four databases referred to above for a total of 24 regression models to evaluate the association of blood cadmium with thyroid variables and another 24 models to evaluate the association of urine cadmium with six thyroid variables. Each of these models had log10 transformed values of one of the six thyroid variables as dependent variable and for the models for males, the independent variables were: age (A12 or ages 12-19 years, A20 or ages 20-64 years, A65 or >= 65 years), race/ethnicity, and smoking status as categorical variables, and log10(body mass index), log10(serum albumin), log10(blood cadmium) or log10(urine cadmium), use of drugs other than thyroid treatment drugs with potential to affect thyroid function (yes, no), NHANES survey year as an ordinal variable to adjust for any changes over time, log10(urine creatinine) for the models for urine cadmium only as continuous variables for the models for both males and females, and number of live births, menopausal status, premenarche status, and estrogen/progesterone use as continuous variables for the models for females only.

In preliminary analysis, it was realized that additional insight into the associations of interest can be obtained if instead of using blood or urine cadmium as log10 transformed continuous variables, deciles of these variables as ordinal variables could be used as independent variables. Consequently, another 48 models were fitted with deciles of blood or urine cadmium as independent variables. Models fitted with log10 transformed values of blood or urine cadmium are henceforth referred to as Models A and models with deciles of blood or urine cadmium are referred to as Models B. It would have been ideal to use 1st through 10th deciles as the indicator variable. However, since over 25% of the observations for blood cadmium were below the limit of detection, a decision was made to use 3rd through 10th deciles as the ordinal variable.

Table 1: Sample sizes used in regression models by age, iodine sufficiency status, gender, race/ethnicity, and smoking status. Data from National Health and Nutrition Examination Survey 2007-2012.

	Iodine Deficient Males		Iodine Replete Males		Iodine Deficient Females		Iodine Replete Females	
	N	%	N	%	N	%	N	%
Blood Cadmium								
Total	1293	100.0	3367	100.0	1455	100.0	2586	100.0
Age: 12-19 years	225	17.4	668	19.8	248	17.0	494	19.1
Age: 20-64 years	884	68.4	2025	60.1	1007	69.2	1601	61.9
Age: >= 65 years	184	14.2	674	20.0	200	13.7	491	19.0
Non-Hispanic White	512	39.6	1476	43.8	584	40.1	1011	39.1
Non-Hispanic Black	324	25.1	677	20.1	369	25.4	563	21.8
Hispanics	339	26.2	976	29.0	380	26.1	840	32.5
Other	118	9.1	238	7.1	122	8.4	172	6.7
Nonsmokers	878	67.9	2459	73.0	1154	79.3	2127	82.3
Smokers	415	32.1	908	27.0	301	20.7	459	17.7
Urine Cadmium								
Total	444	100.0	1122	100.0	482	100.0	892	100.0
Age: 12-19 years	88	19.8	227	20.2	82	17.0	180	20.2
Age: 20-64 years	307	69.1	662	59.0	339	70.3	551	61.8
Age: >= 65 years	49	11.0	233	20.8	61	12.7	161	18.0
Non-Hispanic White	162	36.5	487	43.4	182	37.8	351	39.3
Non-Hispanic Black	121	27.3	223	19.9	126	26.1	198	22.2
Hispanics	125	28.2	330	29.4	136	28.2	282	31.6
Other	36	8.1	82	7.3	38	7.9	61	6.8
Nonsmokers	298	67.1	814	72.5	378	78.4	726	81.4
Smokers	146	32.9	308	27.5	104	21.6	166	18.6

SAS University Edition (www.sas.com) software was used to analyze all data. Specifically, SAS Proc SURVEYREG was used to fit regression models and to compute adjusted regression slopes thus taking into account sampling weights as well as variability attributable to stratification and clustering used in designing NHANES.

Laboratory methods

Laboratory methods used to measure thyroid variable are available at: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/THYROD_G.htm#

Description of Laboratory Methodology to measure blood cadmium at: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/PbCd_G.htm#

Description of Laboratory Methodology to measure urine cadmium at: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/UHM_G.htm#

Description of Laboratory Methodology to measure serum albumin at: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/BIOPRO_G.htm#

Description of Laboratory Methodology to measure urine iodine at: https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/UIO_G.htm#

Description of Laboratory Methodology and to measure urine creatinine at https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/ALB_CR_G.htm.

There was no change in laboratory methodology used to measure any of the thyroid variables over 2007-2012, but there was a change in the laboratory used to measure TT4 from University of Washington Medical Center, Department of Laboratory Medicine in 2009 to Collaborative Laboratory Services in 2010. Data for 2010 was corrected to account for this change in laboratories before being released in the public domain but a correction to post-2010 data as given below was recommended (https://wwwn.cdc.gov/Nchs/Nhanes/2011-2012/THYROD_G.htm#Analytic_Notes).

TT4 (modified) = 4.067036 + 5.492497*((uncorrected TT4/10.0)**3) - 5.673583*((uncorrected TT4/10.0)**3)*log(uncorrected TT4/10.0)

To make pre-2010 and post-2010 data compatible for the purpose of analysis, the above mentioned correction was applied to 2011-2012 TT4 data for the purpose of this study.

RESULTS

Univariate statistics

Unadjusted geometric means (UGM) and selected percentiles, namely, first quartile, median, third quartile, and 95th percentile with 95% confidence intervals by survey year for both blood cadmium and urine cadmium are given in Table 2. UGMs for blood cadmium for both 2007-2008 and 2009-2010 were higher than UGM for 2011-2012 (0.345 and 0.327 vs. 0.299 µg/L, Table 2, $p < 0.01$). While no statistical tests were conducted, medians, and third quartiles for 2007-2008 and 2009-2010 too were higher than those for 2011-2012. For urine

cadmium, first quartiles, and medians for 2007-2008 and 2009-2010 were higher than for 2011-2012. UGMs for 2007-2008, 2009-2010, and 2011-2012 were not found to be statistically different from each other. According to a document published by US Agency for Toxic Substances and Disease Registry (https://www.atsdr.cdc.gov/toxguides/toxguide-5.pdf), normal levels or geometric mean level of blood cadmium in humans (>= 1 year of age) is 0.315 µg/L and of urine cadmium (>= 6 years of age), it is 0.185 µg/L. Thus, the geometric mean levels ofblood cadmium for 2007-2008 and 2009-2010 and for 2005-2012 were above normal levels and for urine cadmium, they were above normal for all survey years. The Occupational Safety and Health Administration (OSHA) safety standard for cadmium in whole blood is 5 µg/L or lower and for urine cadmium, it is 3 µg/g of creatinine or lower (https://www.cdc.gov/biomonitoring/Cadmium_BiomonitoringSummary.html). Of the 8701 participants for which non-missing values of blood cadmium were available, only 17 (0.2%) participants had their blood cadmium levels > 5 µg/L.Of the 2837 participants for which non-missing values of urine cadmium and urine creatinine were available, only 63 (2.2%) participants had their creatinine corrected urine cadmium levels > 3 µg/g creatinine.

Blood cadmium

Iodine deficient males: Levels of any of the six thyroid variables were not affected by blood cadmium (Table 3) when blood cadmium was used as the log10 transformed variable in thee regression models (Model A). However, when blood cadmium was used as deciles in the regression models (Model B), levels of both TT3 (β = 0.0031, p = 0.03) and TT4 (β = 0.0032, *p* = 0.03) increased with increase in blood cadmium deciles (Table 4). For a unit increase in decile, levels of TT3 and TT4 increased by 0.007 ng/dL and 0.007 µg/mL respectively.

Iodine replete males: There was a positive association between TGN levels and blood cadmium using Model A (β = 0.0672, *p* = 0.03, Table 3). For a 10% increase in blood cadmium, there was a 0.64% increases in TGN. Using Model B, no statistically significant associations were observed between blood cadmium deciles and any of the six thyroid variables (Table 4).

Iodine deficient females: Levels of TT3 decreased with increase in the levels of blood cadmium (β = -0.0403, p < 0.01, Table 3). For a 10% increase in blood cadmium, there was a 0.38% decrease in the levels of TT3. Similar result was observed for Model B (β = -0.0052, p < 0.01, Table 4). For a unit change in blood cadmium decile, there

Table 2: Unadjusted geometric means (UGM), first quartile (Q1), median, third quartile (Q3), and 95th percentiles with 95% confidence intervals for blood cadmium (BCD) and urine cadmium (UCD) in µg/L by survey year. Data from National Health and Nutrition Examination Survey 2007-2012.

	Survey Year	UGM	Q1	Median	Q3	95th percentile
BCD	2007-2008	0.345 (0.324 - 0.367)	0.14 (0.114 - 0.166)	0.288 (0.275 - 0.301)	0.554 (0.485 - 0.624)	1.676 (1.397 - 1.955)
	2009-2010	0.327 (0.312 - 0.343)	0.14 (0.109 - 0.171)	0.28 (0.261 - 0.3)	0.543 (0.512 - 0.575)	1.396 (1.225 - 1.567)
	2011-2012	0.299 (0.284 - 0.315)	0.131 (0.103 - 0.158)	0.259 (0.242 - 0.276)	0.487 (0.442 - 0.531)	1.69 (1.533 - 1.848)
	2005-2012	0.323 (0.313 - 0.333)	0.139 (0.138 - 0.14)	0.276 (0.267 - 0.284)	0.526 (0.498 - 0.555)	1.594 (1.475 - 1.712)
UCD	2007-2008	0.208 (0.194 - 0.223)	0.102 (0.092 - 0.113)	0.206 (0.183 - 0.229)	0.431 (0.393 - 0.469)	1.095 (0.914 - 1.276)
	2009-2010	0.21 (0.191 - 0.231)	0.102 (0.081 - 0.123)	0.211 (0.19 - 0.232)	0.407 (0.365 - 0.448)	1.158 (0.932 - 1.383)
	2011-2012	0.188 (0.171 - 0.208)	0.087 (0.069 - 0.105)	0.184 (0.145 - 0.224)	0.409 (0.356 - 0.463)	1.027 (0.777 - 1.276)
	2005-2012	0.208 (0.197 - 0.220)	0.098 (0.09 - 0.105)	0.205 (0.19 - 0.219)	0.423 (0.396 - 0.45)	1.088 (0.963 - 1.213)

Table 3: Regression coefficients with p-values for log10 of blood and urine cadmium for selected thyroid variables along with percent change in untransformed values of thyroid variables for a 10% change in the untransformed values of blood or urine cadmium. Data from National Health and Nutrition Examination Survey 2007-2012. Statistically significant changes are shown in bold letters.

Blood Cadmium								
	Iodine Deficient Males		**Iodine Replete Males**		**Iodine Deficient Females**		**Iodine Replete Females**	
Dependent variable in log10 of	β (p)	Change 10*	β (p)	Change 10*	β (p)	Change 10*	β (p)	Change 10*
Thyroid Stimulating Hormone	0.061 (0.16)	0.583	0.01685 (0.44)	0.161	0.08984 (0.08)	0.860	0.01008 (0.79)	0.096
Free Triiodothyronine	0.00346 (0.61)	0.033	-0.00312 (0.55)	-0.030	-0.01105 (0.12)	-0.105	-0.00599 (0.33)	-0.057
Free Thyroxine	-0.01211 (0.24)	-0.115	0.0066 (0.41)	0.063	0.01757 (0.09)	0.168	**0.02046 (0.01)**	**0.195**
Total Triiodothyronine	0.01669 (0.17)	0.159	0.00168 (0.8)	0.016	**-0.04025 (0)**	**-0.384**	-0.01795 (0.06)	-0.171
Total Thyroxine	0.01955 (0.07)	0.186	-0.00293 (0.74)	-0.028	0.00021 (0.99)	0.002	0.01383 (0.12)	0.132
Thyroglobulin	0.03131 (0.5)	0.299	**0.06721 (0.03)**	**0.643**	0.0771 (0.18)	0.738	**0.10624 (0.02)**	**1.018**
Urine Cadmium								
Thyroid Stimulating Hormone	-0.02346 (0.43)	-0.224	0.00734 (0.73)	0.070	0.0308 (0.24)	0.294	0.035 (0.24)	0.334
Free Triiodothyronine	-0.00697 (0.24)	-0.066	0.00255 (0.5)	0.024	-0.00469 (0.36)	-0.045	-0.00858 (0.06)	-0.082
Free Thyroxine	-0.00808 (0.42)	-0.077	-0.00299 (0.55)	-0.028	0.00305 (0.71)	0.029	-0.00178 (0.82)	-0.017
Total Triiodothyronine	0.00932 (0.32)	0.089	0.01079 (0.18)	0.103	-0.00134 (0.89)	-0.013	0.00436 (0.57)	0.042
Total Thyroxine	-0.00028 (0.98)	-0.003	-0.00428 (0.54)	-0.041	-0.00358 (0.76)	-0.034	-0.00817 (0.34)	-0.078
Thyroglobulin	0.03922 (0.41)	0.374	-0.04762 (0.11)	-0.455	0.04611 (0.39)	0.440	0.00548 (0.89)	0.052

*Percent change in the untransformed values of thyroid variables for a 10% increase in untransformed values of blood or urine cadmium.

was a decrease of 0.012 ng/dL in the level of TT3. However, for a unit increase in blood cadmium decile, there was a 0.008 ng/dL increase in the level of FT4 (p = 0.01, Table 4).

Iodine replete females: Levels of FT3 (β = 0.0205, p = 0.01) as well as TGN (β = 0.1062, p = 0.02) increased with increase in the levels of blood cadmium (Table 3). However, for a unit increase in blood cadmium decile, while FT3 levels increased (β = 0.0026, p = 0.04, Table 4), levels of TT3 decreased (β = 0.003, p = 0.02, Table 4).

Urine cadmium

Irrespective of gender and iodine sufficiency status, levels of none of the six thyroid variables were affected by the either the levels of urine cadmium (Table 3) or the change in urine cadmium deciles (Table 4).

DISCUSSION

The differences between the results generated by Chen, at al. [10] and this study should be expected because of differences in how data were analyzed and also possibly because of the differences in study period covered by Chen, et al. [10] and this investigation. Chen, et al. [10] used 2007-2008 NHANES data while this study used NHANES 2007-2012 data and the levels of both blood cadmium and urine cadmium were lower for 2011-2012 when compared with 2007-2008 (Table 2). While Chen, et al. [10] found positive associations between urine cadmium and TT3, TT4, and TGN for adults and with FT4 for adolescents, levels of urine cadmium were not found to affect the levels of any of the six thyroid hormones for this study irrespective of gender, iodine sufficiency status, and the type of regression models fitted, namely, Models A which used log10 transformed values of blood and urine cadmium as one of the independent variables (Table 3) or Models B which used indicators for blood and urine cadmium deciles as one of the independent variables (Table 4). Chen, et al. [10] observed a positive association between blood cadmium and FT3 for adolescents and with TGN for adults. For this study also, a positive association was observed between blood cadmium and TGN but for replete males (β=0.0672, p=0.03) and females (β=0.1062, p=0.02) only when Model A was fitted. In addition, the use of blood deciles instead of log10 transform of blood cadmium as an independent variable revealed additional association that could not be observed when log10 transforms of blood cadmium was sued as an independent variable. However, these association were gender and iodine sufficiency specific. For iodine deficient males only, a positive association between blood cadmium deciles and TT3 (β=0.0031, p=0.03) and TT4 (β=0.0032, p=0.03) was observed but this association was observed to be in the opposite direction for TT3 for both iodine deficient (β= -0.0052, p<0.01) and iodine replete females (β= -0.003, p=0.02). In addition, for both iodine deficient (β=0.0035, p=0.01) and iodine replete females (β=0.0026, p=0.04), positive association were observed between blood cadmium deciles and FT4. Thus, several conclusions can be drawn from the results of this study. First, associations between blood lead and thyroid hormones can be gender as well as iodine sufficiency specific. Mode of blood cadmium used as independent variable may reveal different associations in magnitude as well as direction.

None of the variabilities observed in the levels of T3 and/or T4 found in this study was accompanied by corresponding changes in TSH levels which is what was found by most, if not all animal studies reviewed here. However, while most of the animal studies reported decreasing levels of TT3 and/or TT4 as a result of exposure to cadmium, it was for only females that such a decreases in TT3 was observed. For iodine deficient males, instead of a decrease, an increase in TT3 and TT4 levels was observed. In the opinion of this author, in this reverse association between TT3/TT4 and blood cadmium, iodine sufficiency status and possibly gender has a role to play.It may be of interest to find out what kind of difference severe iodine deficiency versus moderate iodine deficiency will make in magnitude of change in TT3/TT4 levels. It does not seem investigating a dose-response association between urine iodine and thyroid hormones

Table 4: Regression coefficients with p-values for log10 of blood or urine cadmium for selected thyroid variables along with change in untransformed values of thyroid variables for one decile change in the untransformed values of blood or urine cadmium. Data from National Health and Nutrition Examination Survey 2007-2012. Statistically significant changes are shown in bold letters.

Blood Cadmium								
	Iodine Deficient Males		Iodine Replete Males		Iodine Deficient Females		Iodine Replete Females	
Dependent variable in log10 of	β (p)	Change*	β (p)	Change*	β (p)	Change*	β (p)	Change*
Thyroid Stimulating Hormone	0.01006 (0.08)	0.023	0.0011 (0.72)	0.003	0.01041 (0.09)	0.024	0.00102 (0.78)	0.002
Free Triiodothyronine	0.00019 (0.81)	0	-0.00037 (0.62)	-0.001	-0.00142 (0.09)	-0.003	-0.00112 (0.16)	-0.003
Free Thyroxine	-0.00125 (0.39)	-0.003	0.00131 (0.27)	0.003	**0.00346 (0.01)**	**0.008**	**0.00259 (0.04)**	**0.006**
Total Triiodothyronine	**0.00305 (0.03)**	**0.007**	0.00015 (0.87)	0	**-0.00516 (0)**	**-0.012**	**-0.00298 (0.02)**	**-0.007**
Total Thyroxine	**0.00318 (0.03)**	**0.007**	0.0001 (0.94)	0	0.00001 (1)	0	0.00131 (0.31)	0.003
Thyroglobulin	0.00084 (0.9)	0.002	0.00764 (0.13)	0.018	0.00846 (0.3)	0.02	0.00936 (0.13)	0.022
Urine Cadmium								
Thyroid Stimulating Hormone	-0.00561 (0.36)	-0.013	0.00074 (0.84)	0.002	0.00454 (0.36)	0.011	0.0038 (0.5)	0.009
Free Triiodothyronine	-0.00133 (0.23)	-0.003	0.00094 (0.17)	0.002	-0.00103 (0.32)	-0.002	-0.00152 (0.11)	-0.004
Free Thyroxine	-0.00069 (0.7)	-0.002	0.00001 (1)	0	0.00007 (0.96)	0	-0.00048 (0.77)	-0.001
Total Triiodothyronine	0.00179 (0.34)	0.004	0.00256 (0.07)	0.006	-0.00016 (0.93)	0	0.00099 (0.49)	0.002
Total Thyroxine	0.00017 (0.94)	0	0.00015 (0.9)	0	-0.00121 (0.54)	-0.003	-0.0015 (0.37)	-0.003
Thyroglobulin	0.00052 (0.95)	0.001	-0.00864 (0.15)	-0.02	0.006 (0.48)	0.014	-0.00248 (0.76)	-0.006

*Change in the untransformed values of thyroid variables for a decile increase in untransformed values of blood or urine cadmium. Changes are in μIU/mL for thyroid stimulating hormone, in pg/mL for free triiodothyronine in ng/dL for free thyroxine, in ng/dL for total triiodothyronine, in μg/mL for total thyroxine, and in ng/mL for thyroglobulin.

could be very useful. Iodine deficiency may have to reach a certain levels before its effect on thyroid hormone levels can be observed or even possible.

Another issue which is even more important is the form of association between thyroid hormones and the chemicals of interest that should be assumed. Certainly a linear association in the log scales have been the most popular choice as was used in this and many other studies including Chen, et al. [10]. Even if the assumed linear association in log scales is the perfect choice, the issue of relative clinical meaningfulness and importance of the change in thyroid hormones associated with a change in the chemical of interest should be considered. For example, for this study, a 10% change in blood cadmium was associated with a 0.38% decrease in the levels of FT3 for iodine deficient females (Table 3). In the real world measurements, it means that a change from say, 3.0 µg/L to 3.3 µg/L in blood cadmium will be associated with a change of say 100 ng/dL to 100.384 ng/dL in the levels of TT3. Does a change of 0.384 ng/dL in ng/dL provide enough information to be clinically meaningful or help in clinical decision making? May be, maybe not. But there is an alternate way of generating similar information which may be more helpful in making clinical judgements. Instead of computing changes based on per unit measurements of, for example, blood cadmium, compute changes based on a change from one quartile to another, or from one decile to another as was done in the alternate models fitted for this study, or even for an interquartile range as was done by Chen, et al. [10]. Computed changes associated with quartiles, heptiles, or deciles are more meaningful because not only they are likely to be larger in magnitude but also absolute is scale rather relative, for example, in percents. Fitting spline functions between chemical of interest and thyroid hormone of interest can help deciding if quartiles, quintiles, or deciles are the most appropriate percentiles to select. Number of nodes used to fit spline function can help in this respect. Popular softwares like SAS provides routines that can be used to fit spline functions. Quartiles, quintiles, deciles etc. can then be used as indicator/ordinal or categorical variables in the statistical models.

Absence of any associations between urine cadmium and any of the thyroid functions in this study was contrary to what was reported by Rosatai, et al. [7] among outdoor workers with low exposure to cadmium. However, when urine cadmium levels in this study and the study by Rosalti, et al. [7] were compared, the exposure levels to cadmium in their study were still higher as compared to this study and this may be why there were no associations between urine cadmium and thyroid variables in this study. In the study by Rosati, et al. [7], minimum, maximum, median, mean, and geometric mean levels of urine cadmium were: 0.2, 19, 0.5, 1.58 (SD = 1.9), and 0.97 ng/g creatinine respectively. For this study, minimum, maximum, median, mean, and geometric mean levels were: 0.08, 21.54, 0.213, 0.483 (SD = 1.011), and 0.212 ng/g creatinine respectively.

Final thoughts

Some of the low to very low percent changes associated with thyroid hormones as shown in Tables 3 and 4, even though statistically significant, may tempt someone to conclude that cadmium does not really affect thyroid function and/or the effect may not be clinically significant. However, such a temptation is unfounded, inappropriate, and incorrect because a low percent change may, in fact, may be associated with a relatively large, clinically significant change in magnitude depending up on the scale used to measure the associated thyroid hormone. What is clinical significance should be based on the magnitude of change and not percentage change. This is true even more here because cadmium values and thyroid variable values are measure in different scales. For example, a 10% change in blood cadmium (range: 0.011 to 8.81 ng/mL) may be as small as 0.001 ng/mL but may be followed by a 0.4% decrease in TT3 (range 42 o 563) which may be as little as 0.0162 and as high as 0.2248 ng/dL. Thus, a determination whether or not it is useful to study the effect of exposure to cadmium on thyroid function cannot be made based on percentage changes only because a small percentage change may mean a relatively large change in absolute magnitude which may be clinically meaningful in practical treatment situations.

It should be carefully noted that analysis plan for the data for this study did not include evaluation of the effect of iodine sufficiency on the levels of thyroid hormones. In fact, an assumption was made that thyroid function is affected by the iodine sufficiency and as such, separate models were fitted for both males and females who were iodine deficient and those who were iodine replete. It will be inappropriate and incorrect to look at the results generated by these four sets of models independently and try to come up with a conclusion about the effect of iodine sufficiency on thyroid function. In order to assess the impact of iodine sufficiency on thyroid function, iodine sufficiency status must be included in the regression models as a continuous or categorical independent variable. While fitting regression models with iodine sufficiency as an independent variable in the models was not the stated aim of this study, I did evaluate how iodine sufficiency status (iodine deficient vs. iodine replete) may affect the observed levels of each of the six thyroid variables in a univariate space. The results are provided as supplemental Table S1. As can be seen, in the univariate space, serum thyroglobulin were higher among iodine deficient as compared to those who were iodine replete (11.0 vs. 9.5 ng/mL, $p < 0.01$). Thyroid stimulating hormone levels were lower among those who were iodine deficient as compared to those who were iodine replete (1.45 vs 1.51 µIU/mL). The observed levels of FT3, FT4, TT3, and TT4, however, did not vary with iodine sufficiency status in the univariate space.The results may not be the same if association between thyroid function variables and iodine sufficiency is assessed in the multivariate space.

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Table S1: Observed unadjusted geometric means with 95% confidence intervals by iodine sufficiency status for thyroid hormones. Data from National Health and nutrition Examination Survey 2007-2012.

Thyroid Variable	Iodine Sufficiency Status		
	Iodine Deficient	Iodine Replete	*p*
Thyroid Stimulating Hormone in mIU/mL	1.451 (1.397 - 1.507)	1.518 (1.484 - 1.552)	0.02
Free Triiodothyronine in pg/mL	3.227 (3.203 - 3.252)	3.233 (3.206 - 3.26)	0.67
Free Thyroxine in ng/dL	0.795 (0.785 - 0.804)	0.787 (0.776 - 0.798)	0.13
Total Triiodothyronine in ng/dL	115.748 (114.281 - 117.234)	114.84 (113.371 - 116.328)	0.14
Total Thyroxine in µg/dL	7.547 (7.464 - 7.631)	7.507 (7.432 - 7.582)	0.39
Thyroglobulin in ng/mL	10.995 (10.284 - 11.756)	9.541 (9.143 - 9.956)	<0.01