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Exposure To Heavy Metals In Relation To Thyroid Dysfunctions In U.s. Adults

Xiwen Liao
ceceliao94@gmail.com

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Cece (Xiwen) Liao

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Committee Chair:

Yawei Zhang

Committee Member:

Melinda Irwin

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Abstract

Background: Thyroid hormones are fundamental in regulating normal body functions like metabolism, development, and reproduction. There are a limited number of studies examining the association between thyroid dysfunctions and heavy metals, particularly population-based studies. The current study aimed to examine this relationship in the U.S. population.

Method: The current study used data of the National Health and Nutrition Examination Survey from 2007 to 2012. Study population included adults older than 20 years old without any medication that might impact thyroid hormones. Based on the clinical standard of thyroid dysfunctions, eligible participants were classified into two groups by their thyroid hormones: abnormal (either subclinical or overt thyroid disease) and normal. Both blood and urinary heavy metals were categorized into quintiles. Multivariate logistic regressions were performed to explore the effect of heavy metals in thyroid dysfunctions.

Results: Among 4207 study participants, 302 (7.2%) of them had abnormal thyroid function, including 274 (90.7%) subclinical diseases (164 hypothyroidism and 110 hyperthyroidism) and 28 (9.3%) overt diseases (22 hypothyroidism and 6 hyperthyroidism). Moreover, the current study found that urinary cadmium (OR: 2.05, 95% CI: 1.03, 4.06), antimony (OR: 2.24, 95% CI: 1.27, 3.94), and tungsten (OR: 2.38, 95% CI: 1.02, 5.54) were significantly associated with increased odds of thyroid dysfunctions.

Conclusion: Environmental exposure to heavy metals may pose particular risk to thyroid problems. The limited number of overt diseases prevented us from analyzing the effect of heavy metal exposure in relation to different thyroid disease status. Future studies should be warranted to fully understand the association between heavy metal and specific thyroid dysfunction.

Introduction

Thyroid hormones, including thyroid stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4), are important biomarkers of thyroid functions. Excess or deficiency of hormones may result in thyroid disorders like hypothyroidism and hyperthyroidism, the leading common endocrine disorders in the U.S. (Vanderpump, 2011). However, thyroid diseases often remain undiagnosed. According to The Colorado Thyroid Disease Prevalence Study, among 27 million people with thyroid dysfunction in the U.S., approximately haft of them (13 millions) were undiagnosed (Canaris et al., 2000). Moreover, Hollowell et al. (2002) estimated the prevalence of thyroid dysfunctions based on the National Health and Nutrition Examination Survey (NHANES) data. Their study showed that among individuals aged over 12 from 1988 to 1994, the prevalence of hypothyroidism was 4.6%, including 4.3% subclinical (asymptomatic) and 0.3% overt hypothyroidism. Similarly, the prevalence of hyperthyroidism was 1.2%, including 0.7% subclinical and 0.5% overt hyperthyroidism.

Common risk factors of hyper/hypothyroidism include sex, age, family history, radiation, and autoimmune disease like type 1 diabetes (Canaris et al., 2000). In addition, some studies have suggested associations between thyroid hormone alteration and exposure to heavy metals. Urinary mercury was consistently reported to be inversely associated with T3 and T4, and cadmium was positively associated with T3 and T4 (Chen, 2013; Yorita, 2013). In comparison, the association between blood and urine lead levels to thyroid hormones remains controversial. The study of Chen et al. (2013), used data from NHANES 2007 to 2008, reported that there was no association between thyroid hormones and blood lead levels. However, Yorita (2013), using the same NHANES population, suggested that lead in both blood and urine was associated with

decreased total thyroxine (TT4) at individual level. Additionally, the effect of metals may differ by sex. Luo and Hendryx (2014), using NHANES population from 2007 to 2010, observed a negative association of lead with TT4, and a positive association of cadmium with total triiodothyronine (TT3) among males. Among females, they reported a positive association between lead and free thyroxine (FT4) and no association between cadmium and any hormones.

The existing literature has provided suggestive evidence of a relationship between exposure to heavy metals and thyroid diseases. Using self-reported thyroid diseases status (any thyroid dysfunction), the study of Mendy et al. (2012) found a positive relationship between thyroid problems and exposure to urinary cadmium, cobalt, lead, and tungsten, though not statistically significant. However, there is a limited number of studies examining this direct association. As mentioned, many individuals with thyroid diseases are undiagnosed. The self-reported disease status may not accurately measure subclinical hyper/hypothyroidism. Using the combined NHANES data from 2007 to 2012, the current study used thyroid hormones to clinically define thyroid diseases, in order to examine the relationship between heavy metals and thyroid dysfunctions.

Method

The National Center for Health Statistics Research Ethics Review Board approved the study protocol of 2007-2010 (protocol 2005-06), and 2011-2012 (protocol 2011-17) NHANES, and all participants provided written informed consent (CDC, 2012). This cross-sectional study used NHANES data from 2007 – 2012. A total of 30,442 participants were included initially. The continuous NHANES data were designed to be nationally representative for the civilian, non-

institutionalized population of the United States, with a complex, multistage, probability-sampling design (CDC, 2012). Thyroid hormones were assessed in all eligible participants aged 12 years and older from 2007 to 2008, while only assessed in one third randomly selected subsample of participants aged 6 years and older from 2009 to 2012. In addition, urinary heavy metals were measured in a one third subsample of participants aged 6 years and older from 2007 to 2012. For the purpose of this study, the study was restricted to the NHANES population with available measurements of both thyroid hormones and heavy metals from 2007 to 2012. Moreover, the medical condition information was only available for those who aged 20 years and older. Thus, the current analyses included data from participants aged ≥20 years old (N=5,279). Individuals were further excluded if they met any of the exclusion criteria: were pregnant at the time of examination (N=59); had any cancer except non-melanoma skin cancer (N=409); self-report of taking medications that might have an impact on thyroid hormones, including desiccated thyroid, thyroid hormones, Levothyroxine, Liothyronine, and Thyroglobulin (N=278). There were 4533 individuals available for thyroid disease categorization (Figure 1).

Primary thyroid hormones of interest included TSH, FT4, and FT3. Eligible participants were first classified into three groups: subclinical disease (hyper/hypothyroidism), overt disease (hyper/hypothyroidism), and normal status. According to the American Association of Clinical Endocrinologists (Garber et al., 2012), the normal TSH range is 0.45 to 4.12 mIU/L for those who are not pregnant. Accordingly, subclinical hypothyroidism is defined as individuals with elevated TSH ($4.12 < TSH < 20$ mIU/L) as well as normal FT4 ($0.6 \leq FT4 \leq 1.6$ ng/dL) and FT3 ($2.5 \leq FT3 \leq 3.9$ ng/dL; CDC NHANES Laboratory Procedure Manual, 2012). Subclinical hyperthyroidism was defined as individuals with low TSH ($TSH < 0.45$ mIU/L) and normal FT4

and FT3 (CDC, 2012). Overt hypothyroidism were those with high TSH (TSH > 4.12 mIU/L) and low FT4 (FT4 < 0.6 ng/dL) and FT3 (FT3 < 2.5 ng/dL); overt hyperthyroidism were those with low TSH (TSH < 0.45 mIU/L) and high FT4 and FT3 (FT4>1.6 ng/dL or FT3 > 3.9 ng/dL). Normal group was defined as those with all TSH, FT3 and FT4 within normal limits. Participants with either subclinical or overt thyroid diseases were subsequently defined as abnormal status. In addition, 326 individuals were excluded from the analyses because they did not meet any of the disease definitions and might have other thyroid diseases that were of interest to the study. After exclusions, 4207 individuals were available for data analyses (Figure 1).

Both urinary and blood metals were included in the analyses only if they were available for all three years. This excluded urinary tin, manganese, strontium and blood manganese and selenium, which were available for years 2011 to 2012 only. Two urinary metals were further excluded from the analyses because more than 90% of the sample was below the limit of detection (LOD) (urinary platinum: 92.0% below LOD; urinary beryllium 99.9% below LOD). Cadmium, lead, and total mercury were measured in both blood and urine.

We used multivariate logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs). Each heavy metal was first examined in the regression model individually and all urinary/blood metals were examined together, while adjusting for other covariates. Both blood and urinary metals were categorized into quintiles. For metals that were detectable in less than 95% of the sample (urinary cadmium, antimony, tungsten, uranium, manganese, tin, blood mercury and cadmium), percentage below LOD was used as the reference group, and percentage above LOD was divided into quartiles. Metals that were detectable in more than 95% of the

sample were divided into quintiles directly, with the first quintile as the reference group. Multicollinearity was assessed among urinary metals and among blood metals respectively. Covariates included in the analyses were age (continuous), body mass index (BMI; underweight: less than 18.5 kg/m^2; normal: 18.5 to 24.9 kg/m^2; overweight: 25-29.9 kg/m^2, and obese: more than 30 kg/m^2), race (non-Hispanic white, non-Hispanic black, and other), sex (female and male), total lipid (continuous), and urinary creatinine (continuous). Total lipid was calculated as suggested by CDC, total lipid = 2.27 * total cholesterol + triglycerides + 62.3 (CDC, 2012). Creatinine was used as a covariate to count for variations in participants' age, gender, and race/ethnicity group. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

Among 4207 study participants, 302 (7.2%) had abnormal thyroid function. Specifically, 274 (90.7%) of those with abnormal function had subclinical thyroid diseases (164 hypothyroidism and 110 hyperthyroidism), and 28 (9.3%) had overt thyroid diseases (22 hypothyroidism and 6 hyperthyroidism). The remaining 3905 individuals were free of any thyroid disease. Moreover, among 174 participants reported having thyroid disease history, 68 of them were still diseased (but were not taking any medications that affected thyroid hormones). The average age of the disease-free participants was 47.6 years old (Table 1). In comparison, the average age of the abnormal group (both subclinical and overt) ($p=0.002$) and subclinical group ($p=0.005$) was significantly older than the normal group (50.8 years old and 50.6 years old, respectively). The majority of the study participants were Non-Hispanic Whites and obese, which were comparable among the study groups. All metals were detected in at least 70% of study participants. Urinary

cesium was detected in all study participants. Total blood mercury was detected among 91.8% participants free of any disease, which was significantly different from that of abnormal and subclinical participants. About 92.8% abnormal individuals (p=0.007) and 87.2% subclinical individuals (p=0.007) were detected with blood mercury.

No multicollinearity was found in either urinary or blood metals (Table 4 a & 4b). Odds ratios of individual urinary metals associated with thyroid disease are shown in Table 2, controlling for total lipids, sex, BMI, age, race, and urinary creatinine. As compared to the normal reference quintile group, the higher quintiles of urinary antimony and tungsten were significantly associated with increased odds of thyroid diseases. The odds of any thyroid disease (either overt or subclinical diseases) of those at the third quintile of antimony exposure was 2.24 times the odds of the reference quintile (95% CI: 1.27, 3.94). Similarly, the odds of thyroid disease of those at the forth quintile of antimony was 2.83 times higher than those at the reference group (95% CI: 1.57, 5.11). Urinary cadmium was barely significant in relation to thyroid disease when examined individually. After controlling for other metals in urine, the odds of disease for the first quintile of urinary cadmium was significantly higher than the odds of reference group (OR: 2.05, 95% CI: 1.03, 4.06), and urinary tungsten was significantly associated with subclinical thyroid diseases (OR: 2.38, 95% CI: 1.02, 5.54) (Table 2). No significant association was observed between blood metals and thyroid diseases (Table 3).

Discussion

Our study found that urinary cadmium, antimony, and tungsten were significantly associated with a higher odds of thyroid dysfunctions. Being consistent with our results, Mendy et al.

(2012), using NHANES data from 2007 to 2008, reported positive relationships between cadmium (OR=1.40, 95% CI: 0.78-2.50) and tungsten (OR=1.58, 95%CI: 0.93, 2.70) and self-reported thyroid disease, though not significant.

Cadmium is an established environmental toxicant that may disrupt thyroid hormone secretion (Vacchi-Suzzi et al., 2016). It interrupts with normal thyroid function through changes in peripheral hormone receptors, which eventually disturb the normal conversion of T4 into active T3 (Buha et al., 2018). Previous studies have consistently reported positive associations between urinary cadmium and individual thyroid hormones including total and free T3 and T4 (Chen et al., 2013; Yorita et al., 2013;). In addition, Yorita et al. (2013) found a negative relationship between cadmium and TSH, which was a suggestive pattern of hyperthyroidism. In our study, only low levels of urinary cadmium (first quintile) was associated thyroid abnormality, and the observed association became weakened/insignificant among participants with only subclinical disease status, which indicated an association between overt thyroid disease and cadmium exposure. Additionally, the discrepancy in results of urinary and blood cadmium was noticed. Only urinary cadmium was significantly associated with the outcomes. One possible reason may be that the urinary test is mainly used to reflect long-term heavy metal exposure, while the blood test reflects both long-term and recent exposures (Vacchi-Suzzi et al., 2016). Since the majority of the study participants were assumed to be naturally exposed to heavy metals in the environment, a urine test might be a more valid specimen for long-term exposure to heavy metals.

In addition to cadmium, the study of Yorita et al. (2013) has reported an association of urinary tungsten and increased TSH, but not FT3 or FT4. This finding suggested that tungsten was correlated with subclinical hypothyroidism, which was consistent with our result that high level of tungsten exposure was significantly associated with subclinical thyroid diseases. Underlying mechanism directly linking tungsten and thyroid diseases still remained unclear. But based on the animal study of Chatterjee et al. (1973), at a high concentration, tungsten reduced the ascorbic acid status in the adrenal gland of rats. In addition, studies have found that ascorbic acid (vitamin c) played a role in lowering stress hormones like cortisol produced by adrenal gland (Peters et al., 2001). Decreased vitamin C level associated high concentration of tungsten would lead to potential impairment of normal cortisol secretion, which further lead to elevated TSH level and subclinical hypothyroidism (Walter et al. 2012).

The current study also found a significant association between high exposure to antimony in relation to thyroid dysfunctions. Although studies evaluating the impact of antimony on thyroid functions are limited, there is suggestive evidence supporting this observed relationship. Major sources of exposure to antimony include contaminated water, food, and occupational contact (Cooper et al., 2009). There was a concern regarding non-occupational exposure to antimony from the polyethylene terephthalate (PET) bottles or containers, as several studies from Europe and Canada indicating antimony leaching from PET bottled waters under summer time high temperature inside of car or garage (Westerhoff et al., 2008). Accordingly, Sax (2010) reported antimony that migrated from PET plastic bottled water to be a potential endocrine disruptor. Further, an animal study by Poon et al. (1998) showed that histopathological changes were presented in liver and thyroid of rats being exposed to the highest dose of antimony

contaminated drinking water. They found increased epithelial height and nuclear vehiculation in the thyroid as well as cytoplasmic vacuolation and inclusion in the pituitary gland, which might have negative impacts on TSH production (Poon et al., 1998). However, using NHANES data from 2007 to 2008, Yorita et al. (2013) reported no such association between antimony and any of the individual thyroid hormone, suggesting no association between thyroid disease and antimony. Differences between the current study and the study of Yorita (2013) could be due to the use of combined data from 2007 to 2012 by the current study and different methods of analysis.

One limitation of our study was that we used selected thyroid hormones to classify both overt and subclinical thyroid diseases. It should be noted that our main interests were primary subclinical or overt thyroid diseases, and there are other diseases that may cause changes in thyroid hormones. Thus, results should be interpreted with caution. Due to the limited number of overt thyroid diseases, we were not able to analyze the effect of heavy metal exposure and specific thyroid disease status. Furthermore, the cross-sectional nature of the NHANES data prevents us from making casual inferences of the observed associations. Based on the inconsistence of the observed association in urinary antimony, more population-based observational studies regarding exposure to heavy metal, particularly those understudied ones, in relation to thyroid diseases should be warranted.

Conclusion

Our study showed that environmental exposure to cadmium, antimony, and tungsten may pose particular risk to thyroid diseases. More studies should be warranted to fully understand the association between environmental heavy metal and subclinical or overt hyper/hypothyroidism.

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Table 1. Selected characteristics of study participants by disease status.

Characteristic	Normal (N= 3905) *		Abnormal (N=302) *			Subclinical (N=274) *		
	N	%	N	%	*p-value*	N	%	*p-value*
Age (mean, Sd)	47.6	17.0	50.8	18.0	***0.002***	50.6	18.1	***0.005***
Total lipids (mean, Sd)	637.2	164.1	637.2	148.8	*0.977*	637.5	146.8	*0.985*
Sex					*0.380*			*0.603*
Male	2016	51.6	148	49.0		137	50.0	
Female	1889	48.4	154	51.0		137	50.0	
Race/ethnicity					*0.396*			*0.334*
Non-Hispanic White	1633	41.8	138	45.7		127	46.4	
Non-Hispanic Black	822	21.1	57	18.9		52	19.0	
Other	1450	37.1	107	35.4		95	34.7	
BMI					*0.490*			*0.441*
Underweight	64	1.7	6	2.0		6	2.2	
Normal	1084	28.1	91	30.4		87	31.9	
Overweight	1325	34.4	90	30.1		84	30.8	
Obese	1380	35.8	112	37.5		96	35.2	
	Median	< LOD**	Median	< LOD		Median	< LOD	
Urinary metals								
Arsenic (ug/L)	8.6	1.5	7.6	1.4	*0.826*	7.7	1.5	*0.980*
Cadmium (ug/L)	0.2	6.4	0.2	8.1	*0.251*	0.2	8.6	*0.163*
Lead (ug/L)	0.5	3.0	0.5	2.4	*0.548*	0.5	2.2	*0.488*
Mercury (ug/L)	0.4	3.4	0.4	3.0	*0.848*	0.4	3.1	*0.899*
Barium (ug/L)	1.3	0.8	1.1	1.0	*0.669*	1.1	1.1	*0.552*
Cobalt (ug/L)	0.3	0.5	0.3	0.3	*0.667*	0.3	0.4	*0.741*
Cesium (ug/L)	4.5	0.0	4.2	0.0	*NA*	4.3	0.0	*NA*
Molybdenum (ug/L)	42.9	0.1	42.0	0.0	*0.694*	43.1	0.0	*0.708*
Antimony (ug/L)	0.1	31.8	0.1	27.6	*0.134*	0.1	28.3	*0.225*
Thallium (ug/L)	0.2	0.6	0.1	0.7	*0.777*	0.1	0.7	*0.676*
Tungsten (ug/L)	0.1	13.6	0.1	10.8	*0.166*	0.1	11.5	*0.331*
Uranium (ug/L)	0.0	14.6	0.0	11.5	*0.139*	0.0	11.5	*0.168*
Blood metals								
Cadmium (ug/L)	0.4	17.1	0.3	21.5	*0.142*	0.4	20.3	*0.314*
Lead (ug/dL)	1.3	0.3	1.3	0.6	*0.451*	1.4	0.6	*0.401*
Total Mercury (ug/L)	0.9	8.2	0.8	7.2	***0.007***	0.8	12.8	***0.007***

* numbers may not add to total due to missing value

**LOD=limit of detection

Table 2. Adjusted ORs* of individual urinary metals in relation to thyroid diseases.

	Normal (N=3905)	Abnormal (N=302) **			Subclinical (N=274) **		
	N	N	OR† (95% CI)	Adj. OR‡ (95% CI)	N	OR† (95% CI)	Adj. OR‡ (95% CI)
cadmium							
Q0	779	53	1.00	1.00	49	1.00	1.00
Q1	755	75	1.88 (0.99, 3.58)	**2.05 (1.03, 4.06)**	66	1.88 (0.96, 3.65)	2.07 (0.98, 4.22)
Q2	768	49	1.23 (0.63, 2.42)	1.32 (0.63, 2.73)	42	1.03 (0.50, 2.11)	1.13 (0.52, 2.47)
Q3	764	60	1.37 (0.69, 2.74)	1.45 (0.68, 3.10)	56	1.38 (0.68, 2.83)	1.47 (0.67, 2.23)
Q4	776	60	1.07 (0.50, 2.27)	1.02 (0.44, 2.34)	56	1.11 (0.51, 2.43)	1.05 (0.44, 2.51)
antimony							
Q0	1222	82	1.00	1.00	76	1.00	1.00
Q1	650	56	1.51 (0.91, 2.52)	1.52 (0.87, 2.63)	52	1.57 (0.92, 2.68)	1.60 (0.44, 2.51)
Q2	680	47	1.52 (0.88, 2.640	1.57 (0.86, 2.86)	39	1.35 (0.74, 2.45)	1.40 (0.73, 2.69)
Q3	637	58	**2.24 (1.27, 3.94)**	**2.19 (1.17, 4.08)**	52	**2.24 (1.24, 4.03)**	**2.24 (1.16, 4.30)**
Q4	653	54	**2.83 (1.57, 5.11)**	**3.09 (1.60, 5.94)**	50	**2.77 (1.50, 5.14)**	**3.11 (1.57, 6.20)**
tungsten							
Q0	522	32	1.00	1.00	31	1.00	1.00
Q1	839	70	1.76 (0.93, 3.33)	1.81 (0.92, 3.60)	60	1.55 (0.80, 3.03)	1.69 (0.83, 3.48)
Q2	844	61	1.63 (0.84, 3.17)	1.65 (0.78, 3.46)	56	1.58 (0.80, 3.16)	1.72 (0.79, 3.73)
Q3	813	67	1.83 (0.92, 3.65)	1.57 (0.72, 3.44)	60	1.76 (0.86, 3.61)	1.62 (0.71, 3.70)
Q4	815	67	**2.55 (1.26, 5.15)**	2.13 (0.95, 4.80)	62	**2.61 (1.26, 5.41)**	**2.38 (1.02, 5.54)**
uranium							
Q0	560	34	1.00	1.00	31	1.00	1.00
Q1	824	77	1.52 (0.83, 2.77)	1.25 (0.66, 2.39)	69	1.44 (0.76, 2.74)	1.26 (0.63, 2.51)
Q2	836	57	1.10 (0.58, 2.08)	0.88 (0.44, 1.77)	51	1.17 (0.60, 2.28)	0.99 (0.47, 2.08)
Q3	823	61	1.42 (0.75, 2.69)	1.10 (0.54, 2.25)	58	1.55 (0.79, 3.02)	1.28 (0.60, 2.71)
Q4	799	68	1.47 (0.77, 2.80)	1.07 (0.52, 2.22)	60	1.46 (0.73, 2.89)	1.11 (0.51, 2.40)
arsenic							
Q0	774	57	1.00	1.00	52	1.00	1.00
Q1	744	73	1.07 (0.63, 1.81)	1.01 (0.56, 1.82)	65	1.04 (0.60, 1.81)	1.02 (0.55, 1.90)
Q2	767	52	0.80 (0.45, 1.45)	0.75 (0.39, 1.44)	46	0.73 (0.39, 1.36)	0.68 (0.34, 1.38)
Q3	758	62	0.99 (0.57, 1.74)	0.96 (0.50, 1.82)	56	0.97 (0.54, 1.75)	0.96 (0.49, 1.89)
Q4	792	52	0.88 (0.49, 1.59)	0.83 (0.42, 1.64)	49	0.91 (0.49, 1.69)	0.90 (0.44, 1.83)
lead							
Q0	764	61	1.00	1.00	57	1.00	1.00
Q1	773	55	0.85 (0.49, 1.49)	0.73 (0.40, 1.36)	52	0.80 (0.45, 1.42)	0.67 (0.35, 1.27)
Q2	789	57	1.06 (0.61, 1.85)	0.94 (0.49, 1.78)	46	0.79 (0.44, 1.43)	0.66 (0.33, 1.32)
Q3	754	61	1.06 (0.58, 1.94)	1.00 (0.49, 2.02)	57	1.02 (0.55, 1.89)	0.90 (0.43, 1.87)
Q4	762	63	1.07 (0.56, 2.06)	0.89 (0.41, 1.90)	57	0.90 (0.45, 1.77)	0.69 (0.31, 1.53)
mercury							
Q0	791	67	1.00	1.00	61	1.00	1.00
Q1	739	56	0.87 (0.49, 1.55)	0.96 (0.52, 1.76)	54	0.89 (0.50, 1.61)	0.96 (0.51, 1.81)
Q2	760	65	0.94 (0.54, 1.66)	1.01 (0.55, 1.88)	55	0.79 (0.43, 1.46)	0.82 (0.43, 1.60)
Q3	773	55	0.97 (0.56, 1.70)	1.02 (0.54, 1.91)	50	0.95 (0.54, 1.70)	0.97 (0.50, 1.87)
Q4	783	56	0.95 (0.55, 1.66)	0.98 (0.52, 1.85)	51	0.89 (0.50, 1.58)	0.86 (0.44, 1.68)
barium							
Q0	762	52	1.00	1.00	46	1.00	1.00
Q1	771	74	1.61 (0.95, 2.72)	1.54 (0.88, 2.70)	66	1.41 (0.81, 2.43)	1.33 (0.74, 2.39)
Q2	760	65	1.63 (0.95, 2.78)	1.59 (0.89 2.87)	61	1.48 (0.85, 2.57)	1.39 (0.75, 2.57)
Q3	780	55	1.12 (0.62, 2.01)	1.13 (0.58, 2.17)	49	0.98 (0.53, 1.81)	0.96 (0.48, 1.90)
Q4	769	51	1.12 (0.59, 2.13)	1.07 (0.52, 2.19)	47	1.05 (0.54, 2.03)	0.97 (0.47, 2.04)

cobalt							
Q0	772	62	1.00	1.00	55	1.00	1.00
Q1	773	54	0.80 (0.47, 1.36)	0.64 (0.35, 1.18)	47	0.75 (0.42, 1.33)	0.62 (0.32, 1.20)
Q2	765	67	1.21 (0.70, 2.08)	1.05 (0.55, 2.01)	62	1.25 (0.71, 2.21)	1.12 (0.56, 2.23)
Q3	785	48	0.85 (0.45, 1.60)	0.73 (0.34, 1.54)	46	0.90 (0.47, 1.75)	0.78 (0.35, 1.72)
Q4	747	66	1.16 (0.61, 2.22)	1.05 (0.49, 2.26)	59	1.21 (0.61, 2.38)	1.11 (0.49, 2.48)
cesium							
Q0	756	70	1.00	1.00	61	1.00	1.00
Q1	772	55	0.69 (0.40, 1.19)	0.57 (0.30, 1.10)	51	0.73 (0.41, 1.30)	0.71 (0.35, 1.43)
Q2	750	73	0.82 (0.47, 1.43)	0.66 (0.31, 1.39)	67	0.88 (0.49, 1.58)	0.83 (0.37, 1.86)
Q3	779	50	0.79 (0.43, 1.45)	0.60 (0.26, 1.39)	44	0.87 (0.46, 1.64)	0.74 (0.30, 1.80)
Q4	785	49	0.55 (0.27, 1.11)	0.43 (0.17, 1.08)	46	0.59 (0.28, 1.23)	0.49 (0.18, 1.32)
molybdenum							
Q0	769	59	1.00	1.00	55	1.00	1.00
Q1	777	53	0.87 (0.50, 1.53)	0.89 (0.48, 1.64)	46	0.88 (0.49, 1.59)	0.93 (0.48, 1.78)
Q2	762	67	1.60 (0.93, 2.76)	1.52 (0.79, 2.92)	60	1.61 (0.91, 2.85)	1.55 (0.77, 3.11)
Q3	779	53	1.06 (0.55, 2.02)	0.98 (0.45, 2.12)	47	0.97 (0.49, 1.94)	0.90 (0.39, 2.06)
Q4	755	65	2.18 (0.60, 4.33)	2.04 (0.92, 4.50)	61	2.28 (0.67, 4.65)	2.03 (0.88, 4.68)
thallium							
Q0	757	62	1.00	1.00	57	1.00	1.00
Q1	759	70	0.63 (0.36, 1.11)	0.67 (0.35, 1.28)	60	0.51 (0.28, 1.24)	0.51 (0.25, 1.04)
Q2	773	67	1.03 (0.61, 1.75)	1.11 (0.56, 2.20)	60	0.99 (0.58, 1.72)	1.03 (0.50, 2.11)
Q3	782	53	0.72 (0.39, 1.32)	0.79 (0.36, 1.75)	49	0.70 (0.37, 1.31)	0.75 (0.33, 1.72)
Q4	771	45	0.73 (0.38, 1.40)	0.88 (0.37, 2.07)	43	0.75 (0.38, 1.46)	0.89 (0.36, 2.20)

*adjusted for total lipid, sex, bmi, age, race, and urinary creatinine

** numbers may not add to total due to missing value

† univariate analysis

‡ multivariate analysis

Table 3. Adjusted ORs* of blood metals in relation to thyroid diseases.

Normal (N= 3905)		Abnormal (N=302) **			Subclinical (N=274) **		
	N	N	OR† (95% CI)	Adj. OR‡ (95% CI)	N	OR† (95% CI)	Adj. OR‡ (95% CI)
cadmium							
Q0	775	63	1.00	1.00	56	1.00	1.00
Q1	817	49	0.68 (0.40, 1.18)	0.70 (0.40, 1.21)	45	0.71 (0.40, 1.27)	0.74 (0.41, 1.31)
Q2	756	60	1.01 (0.60, 1.69)	1.04 (0.62, 1.75)	52	1.03 (0.60, 1.78)	1.09 (0.63, 1.89)
Q3	779	72	1.00 (0.50, 1.69)	1.02 (0.60, 1.73)	65	1.06 (0.62, 1.83)	1.11 (0.64, 1.94)
Q4	774	57	0.80 (0.47, 1.39)	0.82 (0.46, 1.47)	55	0.83 (0.47, 1.48)	0.88 (0.48, 1.60)
lead							
Q0	767	55	1.00	1.00	51	1.00	1.00
Q1	814	54	0.82 (0.46, 1.45)	0.82 (0.46, 1.47)	45	0.73 (0.40, 1.32)	0.73 (0.40, 1.34)
Q2	760	67	1.15 (0.67, 2.00)	1.15 (0.66, 2.03)	61	1.00 (0.57, 1.78)	1.00 (0.56, 1.80)
Q3	799	59	0.91 (0.51, 1.63)	0.93 (0.52, 1.69)	56	0.85 (0.47, 1.54)	0.86 (0.47, 1.59)
Q4	761	66	0.87 (0.47, 1.61)	0.86 (0.45, 1.65)	60	0.72 (0.38, 1.38)	0.70 (0.36, 1.39)
mercury							
Q0	761	70	1.00	1.00	66	1.00	1.00
Q1	757	64	0.91 (0.55, 1.50)	0.91 (0.55, 1.50)	54	0.82 (0.49, 1.38)	0.82 (0.48, 1.38)
Q2	794	47	0.65 (0.37, 1.12)	0.64 (0.37, 1.12)	43	0.58 (0.33, 1.04)	0.58 (0.33, 1.04)
Q3	791	58	0.99 (0.60, 1.62)	1.00 (0.60, 1.65)	52	0.94 (0.56, 1.56)	0.95 (0.57, 1.60)
Q4	798	62	0.90 (0.54, 1.49)	0.90 (0.54, 1.50)	58	0.80 (0.47, 1.36)	0.81 (0.48, 1.38)

*adjusted for total lipid, sex, bmi, age, and race

** numbers may not add to total due to missing value

† univariate analysis

‡ multivariate analysis

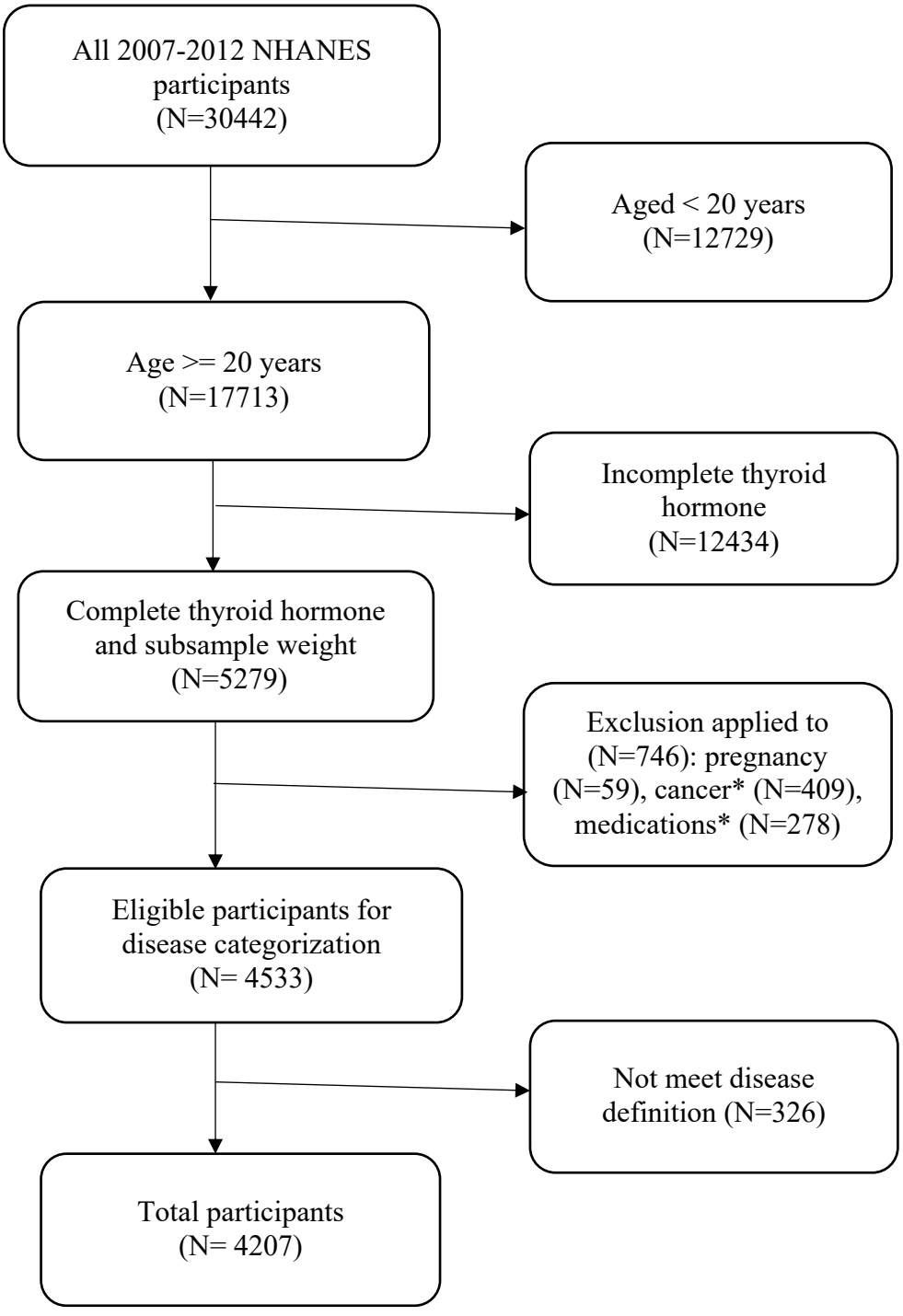
Table 4a. Correlation coefficients between urinary metals

Metals (log transformed)	arsenic	barium	cadmium	cobalt	cesium	molybdenum	lead	antimony	thallium	tungsten	uranium	mercury
arsenic	1.000	0.032	0.135	0.045	0.148	0.096	0.054	0.082	0.173	0.035	0.041	0.104
barium	-	1.000	0.095	0.117	0.185	0.122	0.075	0.134	0.140	0.035	0.057	0.042
cadmium	-	-	1.000	0.131	0.307	0.176	0.168	0.159	0.266	0.039	0.117	0.144
cobalt	-	-	-	1.000	0.167	0.171	0.056	0.062	0.160	0.039	0.022	0.036
cesium	-	-	-	-	1.000	0.323	0.179	0.135	0.553	0.087	0.111	0.202
molybdenum	-	-	-	-	-	1.000	0.119	0.151	0.306	0.129	0.127	0.121
lead	-	-	-	-	-	-	1.000	0.146	0.157	0.024	0.118	0.041
antimony	-	-	-	-	-	-	-	1.000	0.150	0.059	0.104	0.041
thallium	-	-	-	-	-	-	-	-	1.000	0.076	0.088	0.219
tungsten	-	-	-	-	-	-	-	-	-	1.000	0.042	0.255
uranium	-	-	-	-	-	-	-	-	-	-	1.000	0.029
mercury	-	-	-	-	-	-	-	-	-	-	-	1.000

Table 4b. Correlation coefficients between blood metals

Metals (log transformed)	cadmium	lead	mercury
cadmium	1.000	0.149	0.027
lead	-	1.000	0.059
mercury	-	-	1.000

Figure 1. Flow chart of study participant selection



*any cancer except non-melanoma skin cancer
*medications that may impact thyroid hormones: desiccated thyroid, thyroid hormones, Levothyroxine, Liothyronine, Thyroglobulin