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Mercury and thyroid autoantibodies in U.S. women, NHANES 2007–2008

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ABSTRACT

Associations between positive thyroid autoantibodies and total blood mercury in women were evaluated using the National Health and Nutrition Examination Survey (NHANES), 2007–2008. Women are at increased risk for autoimmune disorders, mercury exposure has been associated with cellular autoimmunity and mercury accumulates in the thyroid gland. We used multiple logistic regression to evaluate the associations between total bloodmercury and thyroglobulin autoantibody antibody positivity and thyroid peroxidase autoantibody positivity in non-pregnant, non-lactating women aged 20 and older not currently using birth control pills or other hormone therapies, adjusted for demographic factors, menopausal status, nutrient intake and urine iodine ($n = 2047$). Relative to women with the lowest mercury levels (≤ 0.40 μg/L), women with mercury > 1.81 μg/L (upper quintile) showed 2.24 (95% CI = 1.22, 4.12) greater odds for thyroglobulin autoantibody positivity ($p_{trend} = 0.032$); this relationship was not evident for thyroid peroxidase autoantibody positivity. Results suggest an association between mercury and thyroglobulin autoantibody positivity.

1. Introduction

The heavy metal mercury accumulates in the human thyroid gland, as shown in studies of occupationally exposed workers (Falnoga et al., 2000; Nylander and Weiner, 1991) and industrially exposed residents (Falnoga et al., 2000). Higher levels of hair mercury, an indicator of organic mercury exposure (ATSDR, 1999), have been associated with detectable antinucleolar autoantibodies, biomarkers of cellular autoimmunity, in a non-occupationally-exposed, fish-eating riverine population (Silva et al., 2004). In addition, removal of inorganic mercury-containing dental amalgams resulted in significantly decreased levels of the thyroid autoantibodies thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb) (Sterzl et al., 2006) suggesting a positive association between mercury and these antibodies.

Thyroglobulin antibody is an antibody against the thyroid protein thyroglobulin, and thyroid peroxidase antibody is directed against thyroid peroxidase, a thyroid enzyme. Elevated levels of thyroid autoantibodies have been observed in patients with autoimmune disorders: TgAb in patients with systemic lupus erythematosus (Lu et al., 2006; Parente et al., 2009; Porkodi et al., 2004) and both TgAb and TPOAb in patients with autoimmune thyroiditis (Baskin, 2006), rheumatoid arthritis (Atzeni et al., 2008; Porkodi et al., 2004), pernicious anemia (Chan et al., 2009), fibromyalgia (Bazzichi et al., 2007; Pamuk and Cakir, 2007) and diabetes (Prazny et al., 2005). Women are at increased risk for autoimmune disease (Dunaif, 2010) and mortality (Walsh and Rau, 2000). The association between total blood mercury and thyroid autoantibodies, however, has not been evaluated in a U.S. population representative sample of adult women. Therefore, the primary objective of the current study is to examine this relationship in US women.

Studies have also shown that thyroid autoantibodies TgAb and TPOAb are prognostic indicators for long-term risk of hypothyroidism (Li et al., 2008; Vanderpump et al., 1995; Walsh et al., 2010), a disorder of thyroid hormone deficiency more prevalent in women and most commonly caused by autoimmune thyroiditis (NIH, 2011). Most recently, Hutfless et al. (2011) found increased odds for autoimmune thyroid disease associated with TgAb or TPOAb positivity during the 2–7 years preceding diagnosis. The measurement of thyroid stimulating hormone, or thyrotropin, is the most valuable test to diagnose hypothyroidism and subclinical hypothyroidism, or mildly elevated thyrotropin (Baskin, 2006). Walsh et al. (2010) showed that, among women with baseline thyrotropin levels above 4.0 μIU/ml coincident with TgAb or TPO positivity, the prevalence of hypothyroidism after 13 years was 85.7%. The relationship between mercury exposure and this indicator of autoimmune hypothyroidism risk, however, has not been evaluated in a large, population-representative sample. Therefore, a secondary aim of the current study is to evaluate the association between total blood mercury and elevated thyrotropin coincident with thyroid antibody positivity. A third aim was to evaluate the association between total blood mercury and thyrotropin in US women.

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2. Methods

Data on total blood mercury, thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb) and thyrotropin were obtained from the 2007–2008 National Health and Nutrition Examination Survey (NHANES) files (CDC, 2010a). The analytic sample domain was restricted to survey participants aged 20 and older without missing values for total blood mercury, TgAb and TPOAb, thyrotropin, menopausal status, and urinary iodine, as iodine levels have been linked with autoimmune thyroid disorders (Powell et al., 1999). The sample was further limited to survey participants with a reliable recall of 24-hour dietary intake (CDC, 2011a) in order to adjust for the possible confounding influence of eicosapentaenoic acid (EPA), an n-3 polyunsaturated fatty acid that may beneficially affect thyroid (Makino et al., 2001) and autoimmune function (Ergas et al., 2002; Simopoulos, 2002), and is derived from fish oil, a potential source of mercury exposure (ATSDR, 1999). Further, in consideration of pregnancy (Baskin, 2006) and estrogen (Klecha et al., 2008) as potential influences with regard to thyroid function, pregnant or lactating women were excluded from the analytic sample domain, as were women who reported taking estrogen either for birth control or hormone therapy, consistent with previous NHANES research on thyroid-related measures (Surks and Hollowell, 2007): 227 participants were consequently excluded. The resultant sample consisted of 2047 women aged 20–80 years.

Dichotomous variables were created for race/ethnicity (non-Hispanic white relative to non-white) and menopausal status. A categorical variable was also created for NHANES-estimated EPA intake (none, above and below the sample median of 0.008 gm) based upon 24-hour dietary recall (CDC, 2011a). Continuous variables for total blood mercury (Hg) and urine iodine were log-transformed to address skewed distributions. Based upon sample frequency distributions for women, the following categorical variables were created for total blood mercury (Hg): quintile 1: $\leq$0.40 μg/L (referent), quintile 2: Hg$>$0.40 and Hg$\leq$0.68 μg/L, quintile 3: Hg$>$0.68 and Hg$\leq$1.06 μg/L, quintile 4: Hg$>$1.06 and Hg$\leq$1.81 μg/L, and quintile 5: Hg$>$1.81 μg/L.

Dichotomized variables were created for positive laboratory results for thyroglobulin antibody ($>$4.0 IU/mL) and for thyroid peroxidase antibody ($>$9 IU/mL) per CDC definitions for normal laboratory values derived from the NHANES sample (CDC, 2010b, 2010c), and for thyrotropin $>$4.0 μIU/mL per Walsh et al. (2010). A variable for hypothyroid risk was defined as thyrotropin $>$4.0 μIU/mL with either thyroglobulin antibody $>$4.0 IU/mL or thyroid peroxidase antibody $>$9 IU/mL, per longitudinal study findings of Walsh et al. (2010).

Statistical analysis was conducted using SAS (Cary, NC) version 9.2 and incorporated primary sampling units and strata. Trained NHANES interviewers conducted in person 24-hour dietary recall interviews for a subsample of participants. The current study sample was limited to this NHANES subsample, and NHANES dietary subsample weights were used in statistical analysis. Logistic regression procedures were conducted to evaluate the relationship between Hg quintiles and thyroid antibody and thyrotropin outcomes in accordance with complex survey design recommendations (CDC, 2011b). Multiple logistic regression analysis was used to statistically adjust for the potential influences of age in years, race/ethnicity, menopausal status, EPA, and urinary iodine. A dichotomous variable for serum cotinine above and below the sample median was also considered as a covariate based on associations between smoking and some autoimmune diseases (Arnson et al., 2010), but did not show an association here and was not included in the final model.

Odds ratios and 95% confidence intervals are reported as measures of effect. Additionally, we used a trend test to evaluate dose–response and report p-values for the trend of odds ratios. We evaluated both multivariable-adjusted and unadjusted models.

3. Results

There were 227 women excluded who reported either current pregnancy or lactation status, or who reported current use of birth control pills or hormone therapy. Compared to the 2047 women included in the study sample, this excluded subset was younger (mean age 31 years vs. 52 years), and although their mean total blood mercury levels were lower (1.16 μg/L vs. 1.31 μg/L), the latter difference was not statistically significant. A lower proportion of the excluded women showed elevated thyroid autoantibodies and thyrotropin relative to the included sample.

Women with thyroglobulin antibody positivity showed non-significantly higher mercury levels (1.44 μg/L; SD = 1.73) compared to women without thyroglobulin antibody positivity (1.29; SD = 1.50); however, this pattern was not observed for the other thyroid outcome measures (Table 1). For the outcome measures of thyroglobulin antibody positivity, thyroid peroxidase antibody positivity and elevated thyrotropin, cases were, on average, older compared to noncases, and greater proportions were non-Hispanic white and menopausal.

Multiple logistic regression results provided evidence to suggest a positive association between thyroglobulin antibody positivity and the highest Hg quintile relative to the lowest Hg quintile (OR = 2.24; 95% CI = 1.22, 4.12; p_{trend} = 0.032). This relationship was not evident for any other outcome measure (Table 2). Results were similar in unadjusted analysis, as well as in the model with a continuous total blood mercury measure.

4. Discussion

We report a novel association in U.S. women between total blood mercury and thyroglobulin autoantibody positivity (TgAb).

4.1. Biological plausibility of mercury's autoimmune effects

The scientific literature supports the biological plausibility of mercury's autoimmune effects. Hypothesized mechanisms of action for mercury's potential to induce autoimmunity include mercury-induced protein alterations resulting in acquired cell-specific antigenicity (Powell et al., 1999), and mercury-induced stimulation of T lymphocytes leading to polyclonal B lymphocyte activation and formation of multiple autoantibodies (Pusey et al., 1990). Experimental studies have shown low level mercury exposures to induce autoimmune reactions in mice with and without genetic susceptibility (Abedi-Valugerdi, 2008; Pollard et al., 2001). Low concentrations of inorganic and organic mercury have been shown to disrupt cytokine signaling, a key factor in both infectious and autoimmune disease susceptibility (Gardner et al., 2009, 2010). Further, higher levels of hair mercury, an indicator of organic mercury exposure (ATSDR, 1999), have been associated with detectable antinucleolar autoantibodies, biomarkers of cellular autoimmunity, in non-occupationally-exposed human subjects (Silva et al., 2004).

4.2. Broader autoimmune and health implications

Our finding of an association between mercury and TgAb merits consideration of the possible health implications of elevated TgAb. Thyroglobulin antibody positivity, alone, is not a definitive diagnostic indicator of thyroid disease; however, thyroglobulin antibodies are elevated in more than 90% of patients with Hashimoto (autoimmune) thyroiditis (Nicoll et al., 2010). Thyroglobulin antibodies are elevated in patients with other autoimmune-related diseases, for example, in 50% of patients with pernicious anemia and 20% of patients with systemic lupus erythematosus (Nicoll et al., 2010). In addition to systemic lupus erythematosus (Lu et al., 2006; Parente et al., 2009; Porkodi et al., 2004) and pernicious anemia (Chan et al., 2009), elevated levels of TgAb have also been shown in patients with other autoimmune-related disorders such as rheumatoid arthritis (Porkodi et al., 2004), fibromyalgia (Bazzichi et al., 2007; Pamuk and Cakir, 2007), chronic urticaria (Aamir et al., 2008; Verneuil et al., 2004),and type 1 diabetes (Prazny et al., 2005). Therefore, associations observed between mercury and TgAb may more broadly indicate a relationship between mercury and human autoimmunity. Further, thyroglobulin antibody positivity, but not TPO positivity, was associated with increased odds for thyroid cancer (Kim et al., 2010).

Table 1
Unweighted sample descriptive statistics, women aged 20 years and older[a], NHANES 2007–2008.

	Thyroglobulin antibodies > 4 IU/mL (n = 183 cases/n = 1864 noncases)	Thyroid peroxidase antibodies > 9 IU/mL (n = 323 cases/n = 1724 noncases)	Thyrotropin > 4 μIU/mL (n = 177 cases/n = 1870 noncases)	Thyrotropin > 4 μIU/mL coincident with thyroid antibody positivity (n = 85 cases/n = 1962 noncases)
Total blood mercury (μg/L): mean (SD)	1.44 (1.73)/1.29 (1.50)	1.30 (1.44)/1.31 (1.54)	1.11 (1.30)/1.32 (1.54)[b]	1.21 (1.53)/1.31 (1.52)
Cases/noncases				
Age, years: mean (SD)	56 (17)/52 (17)[b]	55 (16)/52 (17)[b]	59 (17)/52 (17)[b]	56 (17)/52 (17)[b]
Cases/noncases				
Urine iodine (μg/L): Mean (SD)	197.09 (171.34)/723.63 (17,738.45)	268.00 (1154.07)/753.11 (18,438.09)	548.43 (2215)/688.69 (17,697.63)	441.94 (2230.21)/686.72 (17,284.06)
Cases/noncases				
% Cases/noncases comprised by nonHispanic white women	60%/45%[b]	54%/46%[b]	59%/41%[b]	61%/39%[b]
% Cases/noncases by estimated 24 hr EPA intake:				
None	30%	25%	27%	29%
Below median	37%	41%	37%	38%
Above median	33%	34%	36%	33%
% Cases/noncases comprised by menopausal women	67%/33%[b]	65%/35%[b]	71%/29%[b]	65%/35%

[a] Non-lactating, non-pregnant, not currently using birth control pills or hormone therapy.
[b] Significant difference between affected and unaffected at $\alpha = 0.05$.

4.3. Differential effects of mercury species on thyroid autoimmunity

The discrepant finding that mercury was positively associated with thyroglobulin antibody positivity, but not thyroid peroxidase antibody positivity cannot be explained by the current study. Experimental research, however, demonstrated that thyroid peroxidase enzyme, the enzyme targeted by thyroid peroxidase enzyme antibody, was susceptible to inhibition by mercuric chloride (inorganic mercury), but not by methyl-mercury (organic mercury) (Nishida et al., 1990), whereas both mercuric chloride and methyl-mercury inhibited the iodination of thyroglobulin (Kawada et al., 1980), the protein targeted by thyroglobulin autoantibodies. Iodide uptake by thyroid follicular cells is the initial step in thyroid hormone synthesis, and blockage of iodide accumulation, or "trapping" induced by xenobiotics, may result in disrupted thyroid function, similar to iodine deficiency (Klaassen, 2008). Therefore, it is possible that different forms of mercury exert differential effects on thyroid autoimmunity in humans, and that exposure to methyl-mercury is more likely to be associated with increased thyroglobulin antibodies (Kawada et al., 1980; Nishida et al., 1990), perhaps by disrupting iodide uptake. The blood mercury measure used in our study likely reflects methyl-mercury exposure from fish consumption, the dominant source of methyl-mercury exposure in the general population (ATSDR, 1999). Further research is merited to elucidate the biological mechanisms underlying the potential biological interactions between mercury species and iodine with regard to thyroid autoantibodies in women. Larger epidemiological studies with sufficient power to stratify by iodine deficiency status may shed additional insights.

4.4. Study limitations and strengths

This cross-sectional analysis of a short-term biomarker of mercury exposure, total blood mercury levels, and concurrent measures of TgAb, TPOAb and thyrotropin precludes us from ascertaining whether these measures showed intra-individual variability over time; however, single baseline measures of elevated thyrotropin coincident with positive thyroid autoantibodies were predictive of hypothyroid risk in longitudinal evaluation (Walsh et al., 2010). A limitation of the current study, however, is the relatively small number of cases with this hypothyroid risk factor, and consequently, power to detect statistically significant mercury effect estimates for the outcome of elevated thyrotropin coincident with thyroid antibody positivity.

In line with the mechanistic literature on mercury (Abedi-Valugerdi, 2008; Pollard et al., 2001; Pusey et al., 1990), the mercury-thyroglobulin antibody association may reflect initiation of a general autoimmune effect, as opposed to a sustained thyroid-specific impact. Of note, the thyroid peroxidase antibody test has greater sensitivity for diagnosing autoimmune thyroid disease compared to the thyroglobulin antibody test (Nicoll et al., 2010). The extent to which women in the current study with positive findings for thyroglobulin antibodies would also show positive findings for other autoantibodies, such as serum antinucleolar antibodies, which have also been associated with hair mercury levels in a riverine fish-eating population (Silva et al., 2004), is unknown. Another study limitation is that, unlike hair mercury, total blood mercury represents shorter term exposure; therefore, without measures of exposure duration, interpretations are precluded regarding the effects of sustained exposures over time. Further, differentiating sources of mercury exposure or organic/inorganic forms would be helpful. Future studies could also consider long-term dietary intake and/or serum nutrient measures for EPA to better interpret the influence of this covariate. Our use of available 24-hour estimated dietary recall information due to unavailability of actual serum levels of eicosapentaenoic acid may have contributed to information bias. Additional nutrients such as selenium also merit consideration (Rayman, 2008).

Table 2
Overall sample: Unadjusted and adjusted logistic regression[a] results for the relationship between total blood mercury (Hg) and thyroid outcome measures; women aged 20 years and older[b], NHANES 2007–2008.

Outcome measure	No. cases	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Thyroglobulin antibodies > 4 IU/mL: (n = 183 cases and 1864 noncases)			
Continuous, log-transformed Hg:	183	1.74 (1.22, 2.48)	1.83 (1.21, 2.78)
Hg Quintiles:			
Q1: ≤0.40 μg/L (referent)	35	1.00	1.00
Q2: 0.40 < Hg ≤ 0.68 μg/L	45	1.60 (0.96, 2.68)	1.69 (0.98, 2.94)
Q3: 0.68 < Hg ≤ 1.06 μg/L	29	1.03 (0.56, 1.90)	1.09 (0.58, 2.05)
Q4: 1.06 < Hg ≤ 1.81 μg/L	31	1.23 (0.73, 2.08)	1.29 (0.75, 2.20)
Q5:1.81 < Hg ≤ 15.10 μg/L	43	2.14 (1.28, 3.56)	2.24 (1.22, 4.12)
P-value for trend:		0.018	0.032
Thyroid peroxidase antibodies > 9 IU/mL: (n = 323 cases and 1724 noncases)			
Continuous, log-transformed Hg:	323	1.19 (0.91, 1.56)	1.21 (0.92, 1.60)
Hg Quintiles:			
Q1: ≤0.40 μg/L (referent)	70	1.00	1.00
Q2: 0.40 < Hg ≤ 0.68 μg/L	62	0.86 (0.43, 1.68)	0.86 (0.42, 1.73)
Q3: 0.68 < Hg ≤ 1.06 μg/L	65	0.95 (0.53, 1.71)	0.98 (0.53, 1.83)
Q4: 1.06 < Hg ≤ 1.81 μg/L	60	0.96 (0.65, 1.41)	0.95 (0.64, 1.40)
Q5:1.81 < Hg ≤ 15.10 μg/L	66	1.06 (0.70, 1.60)	1.07 (0.70, 1.63)
P-value for trend:		0.623	0.611
Thyrotropin > 4 μIU/mL: (n = 177 cases and 1870 noncases)			
Continuous, log-transformed Hg:	177	0.91 (0.65, 1.28)	0.89 (0.62, 1.29)
Hg Quintiles:			
Q1: ≤0.40 μg/L (referent)	39	1.00	1.00
Q2: 0.40 < Hg ≤ 0.68 μg/L	48	1.11 (0.62, 2.00)	1.11 (0.59, 2.09)
Q3: 0.68 < Hg ≤ 1.06 μg/L	31	1.13 (0.76, 1.70)	1.18 (0.76, 1.82)
Q4: 1.06 < Hg ≤ 1.81 μg/L	32	0.89 (0.53, 1.51)	0.84 (0.50, 1.43)
Q5:1.81 < Hg ≤ 15.10 μg/L	27	0.99 (0.54, 1.83)	0.97 (0.50, 1.89)
P-value for trend:		0.664	0.551
Thyrotropin > 4 μIU/mL coincident with thyroid antibody positivity[c]: (n = 85 cases and 1962 noncases)			
Continuous, log-transformed Hg:	85	1.21 (0.73, 2.01)	1.24 (0.77, 1.99)
Hg Quintiles:			
Q1: ≤0.40 μg/L (referent)	21	1.00	1.00
Q2: 0.40 < Hg ≤ 0.68 μg/L	18	0.82 (0.33, 2.04)	0.83 (0.31, 2.28)
Q3: 0.68 < Hg ≤ 1.06 μg/L	15	1.38 (0.71, 2.68)	1.45 (0.73, 2.89)
Q4: 1.06 < Hg ≤ 1.81 μg/L	17	0.67 (0.32, 1.42)	0.67 (0.29, 1.56)
Q5:1.81 < Hg ≤ 15.10 μg/L	14	1.32 (0.62, 2.80)	1.35 (0.58, 3.09)
P-value for trend:		0.588	0.586

[a] Statistically adjusted for age (years), race, menopausal status, estimated 24-hour dietary intake of eicosapentaenoic acid, and urine iodine; both unadjusted and adjusted models use complex survey design weights.
[b] Non-lactating, non-pregnant, not currently using birth control pills or hormone therapy.
[c] Either thyroglobulin antibodies > 4 IU/mL or thyroid peroxidase antibodies > 9 IU/mL.

A strength of this study is the use of a US probability sample to produce findings that are generalizable to the US population of non-pregnant, non-lactating women not currently using birth control pills or hormone therapy. Total blood mercury is a biomarker of recent exposure (ATSDR, 1999; EFSA, 2004) temporally relevant to current thyroid antibody and thyrotropin measures, as samples of each of these analytes were collected at the same time at the Medical Examination Center.

5. Conclusions

To the best of our knowledge, this is the first epidemiologic study to investigate the relationship between mercury and thyroid autoantibodies. We report an association between blood mercury and thyroglobulin antibody positivity in US women. Statistical adjustment for covariates did not substantially alter these relationships. Although we do not know the association between mercury and overt autoimmune disease among the women in this study, earlier research identified thyroglobulin antibody positivity as characteristic of other autoimmune diseases. Given widespread exposure to low-levels of mercury in the general population, longitudinal research is merited to evaluate associations between biomarkers of mercury exposure and conditions associated with elevated thyroglobulin autoantibodies, such as systemic lupus erythematosus, fibromyalgia, pernicious anemia, diabetes, rheumatoid arthritis, autoimmune thyroiditis, and thyroid cancer.

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