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Association of Blood Total Mercury with Dyslipidemia in a sample of U.S. Adolescents: Results from the National Health and Nutrition Examination Survey Database, 2011–2018

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Abstract

Background: Abnormal lipid profiles in adolescents predict metabolic and cardiovascular diseases in adulthood. While seafood consumption is the primary source of mercury exposure, it also provides beneficial nutrients such as omega-3 fatty acids (O3FA). Prior studies indicate that blood total mercury (TBHg) has endocrine disrupting effects and may be associated with abnormal lipid profiles in adolescents. However, the impact of beneficial nutrients on this relationship has not been examined. Our study investigated the relationship of TBHg with dyslipidemia and lipid profiles and potential confounding and modification of these relationships by sex, body mass index (BMI), selenium and O3FA from seafood consumption.

Methods: We examined 1,390 National Health and Nutrition Examination Survey participants 12-19 years of age from the 2011-2018 cycles. Using logistic and linear regression adjusted for survey design variables and stratified by sex *a priori*, we estimated the associations of TBHg and methylmercury with dyslipidemia, and with total cholesterol (TC), high (HDL-C) and low-density lipoprotein cholesterol (LDL-C) and triglycerides.

Results: The geometric mean of TBHg in this adolescent population was 0.44 μg/L. After controlling for socio-demographic covariates, BMI, serum selenium, age at menarche (females only) and average daily intake of O3FA; TBHg was significantly associated with higher TC levels (β=3.34, 95% CI: 0.19, 6.50; p<0.05) in females but not males. Methyl Hg was also associated with increased TC, as well as decreased HDL-C in females but not males. We did not find significant associations of Hg exposure with dyslipidemia, LDL-C or triglycerides levels in either male or female adolescents. However, we observed evidence of effect modification by BMI and serum selenium for associations of TBHg with TC levels in male and female adolescents, respectively.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

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Conclusion: Our findings of elevated TC levels in females but not males necessitates further research to better understand the underlying mechanisms driving these sex-specific associations.

Keywords

Metals; NHANES; Mercury; Dyslipidemia; Adolescents; Body mass index; Lipids

1. Introduction

Abnormal lipid profiles and dyslipidemia are related to a variety of cardiovascular risk factors including obesity, socio-economic factors, and environmental exposures (Kit et al., 2015; Lozano et al., 2016; Jackson et al., 2018; Fan et al., 2017). Fish contain a wide variety of constituents with positive and negative health effects, including effects on lipids (Abdelhamid et al., 2020). While intake of long chain omega-3-fatty acids is linked to reduced triglyceride levels, evidence remains weak for beneficial effects of omega-3-fatty acids on total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels (Abdelhamid et al., 2020). Selenium is an essential micronutrient and antioxidant linked to chelation of heavy metals such as mercury and alterations in lipid levels (Rayman, 2012). Most studies of the US population using the National Health and Nutrition Examination Survey (NHANES) databases found positive associations of selenium with TC, LDL-C, and triglycerides (Christensen et al., 2015; Bleys et al., 2008; Laclaustra et al., 2010).

Heavy metals such as lead, cadmium, and mercury (Hg) are endocrine disrupting chemicals that are linked to hormone dysregulation (Pollack et al., 2011; Kresovich et al., 2015), as well as cardiovascular and metabolic diseases across the life course (Thurston et al., 2007; Guallar et al., 2002; Poursafa et al., 2014). Adolescents in the U.S. are primarily exposed to Hg in the form of methylmercury through consumption of fish, shellfish, or marine mammals (United States Agency for Toxic Substances and Disease Registry, 1999; Karagas et al., 2012), with the highest mercury intake in the U.S. demonstrated in Asian populations with high seafood intake (Liu et al., 2018; Buchanan et al., 2015). Approximately 95% of methylmercury ingested after a fish meal is absorbed into the blood stream (Clarkson and Magos, 2006) and can be measured as total blood mercury (Buchanan et al., 2015). Health benefits vs risks of seafood vary by type of seafood. Beneficial nutrients such as selenium and omega-3 fatty acids (Nordgren et al., 2017) contrast with the negative effects of contaminants such as Hg (Sanders et al., 2019; Cho, 2021; Guallar et al., 2002).

Past studies of the US adolescent population using NHANES demonstrated overall linear associations of blood total mercury (TBHg) and methylmercury with TC, with the highest quartile of methylmercury associated with TC in one study in girls but not boys (Zhang et al., 2018). Another study showed positive associations between TBHg and TC among both male and female adolescents (Fan et al., 2017), while data from the Korean NHANES, showed positive associations for TBHg with TC and LDL-C in male but not in female adolescents (Cho et al., 2020; Jin et al., 2021). Studies in the adult population have also shown linear associations between TBHg and TC (Buhari et al., 2020), and positive associations of TBHg with TC, HDL-C, and LDL-C (Cho, 2017; Sohn et al., 2020).

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However, the majority of past studies using NHANES examined the relationship of Hg with individual lipid profiles but not with dyslipidemia. In the few available studies examining the relationship of Hg with individual lipids in adolescents, evidence for sex related differences is not consistent. Likewise, the impact of beneficial nutrients in seafood on the association of Hg with lipids has not been explored in many investigations.

Mechanisms driving the association of Hg exposure with dyslipidemia and abnormal lipid profiles are not fully understood with multiple pathways possibly involved. Hg exposure is linked to hormonal dysregulation and the activation of estrogen receptors (Krieg, 2007; Zhang et al., 2008), oxidative stress and inflammation (Gump et al., 2012), lipid peroxidation (Salonen et al., 1995; Lin et al., 1996; Kobal et al., 2004) and the development of obesity related metabolic disorders. Hg exposure was inversely associated with BMI and obesity in adults and children (Rothenberg et al., 2015; Buchanan et al., 2015; Bulka et al., 2019). Obesity influences lipid metabolism in the liver (Feingold, 2020) and is hypothesized to impact Hg metabolism, elimination and accumulation in the blood through changes in liver enzymes (Koeck et al., 2011). However, the role of obesity, which is increasing in U.S. adolescents and children (Cook and Kavey, 2011), on the relationship of Hg exposure with dyslipidemia and lipid profiles has not been well studied. The present study extends the analysis done by Zhang et al. (2018), which utilized only the 2011-2012 NHANES cycle. We utilized a sample of adolescents participating in the NHANES 2011-2018 cycles to substantially increase the sample size and examine associations in subgroups of this population. The objectives of our study were to 1) examine the relationship of Hg exposure with lipid profiles and dyslipidemia, 2) assess the impact of beneficial nutrients and age at menarche on this relationship, and 3) explore the biologic pathways by which BMI, selenium and omega-3-fatty acid intake might act as confounders and effect modifiers.

2. Materials and methods

2.1. Study Population

NHANES is a nationally representative cross-sectional survey conducted by the U.S. National Center for Health Statistics, Centers for Disease Control and Prevention, Atlanta, GA, USA (Centers for Disease Control and Prevention, 2021). Our study included only participants between 12-19 years of age from the NHANES 2011-2018 cycles. Excluded were 33,941 participants outside this age range, 2 participants who reported current use of anti-lipid medication, 3 participants with elevated LDL-C > 190 mg/dL which commonly presents in individuals with familial hypercholesterolemia, 1,863 persons with missing TBHg measurements, and 1,957 with missing data on lipids or covariates (Figure 1). The final study population included 1,390 participants 12-19 years of age.

2.2. Blood Total Mercury

TBHg was measured from whole blood specimens using inductively coupled plasma-dynamic reaction cell-mass spectrometry (ICP-DRC-MS). Measurements were obtained during the physical examination for participants aged 1 year and older for the 2011-2012 and 2017-2018 cycles. For the 2013-2016 cycles, TBHg was measured in all participants aged 1-11 years old, and a one-half sample of participants aged 12 years and older. The lower

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detection limits for TBHg were 0.16 μg/L and 0.28 μg/L for the 2011-2012 and 2013-2018 cycles, respectively. Samples in our analysis with TBHg analytic results below the lower detection limit were imputed by NHANES with a fill value of the lower detection limit divided by the square root of 2. Overall, the detection rate for TBHg used in our analysis was greater than 74%. We also conducted a sensitivity analysis using methyl Hg measured from whole blood specimens. Measurements for methyl Hg were performed similar to blood total mercury measurements as described above. The lower detection limits for methyl Hg were 0.12 μg/L and 0.26 μg/L for the 2011-2016 and 2017-2018 cycles, respectively. The detection rate for methyl Hg used in our analysis was greater than 80%.

2.3. Lipid Profiles & Dyslipidemia

Outcome measures for our analysis include lipid levels (TC, HDL-C, LDL-C, and triglycerides) and dyslipidemia defined as meeting one or more of the following criteria: LDL-C levels ≥ 130 mg/dL, TC levels ≥ 200 mg/dL, triglyceride levels ≥ 130 mg/dL and HDL-C levels < 40 (United States Department of Health & Human Services, National Heart Lung and Blood Institute, expert panel, 2011). TC, HDL-C, and triglycerides were measured on the Roche modular P chemistry analyzer for the 2011-2012 cycle. For the 2013-2018 cycles, TC, HDL-C, and triglycerides were measured on the Roche modular P and Roche Cobas 6000 chemistry analyzers. LDL-C was assessed using the Friedewald calculation as [total cholesterol – HDL-cholesterol – triglycerides/5] and is valid only for triglyceride measurements ≤ 400 mg/dL (Friedewald et al., 1972). HDL-C and TC were measured in participants 6 years and older while LDL-C and triglycerides were measured in participants aged 12 years and older who fasted for 8 hours or more but less than 24 hours. The lower limits of detection for TC, HDL-C and triglycerides were 4 mg/dL, 3 mg/dL and 9 mg/dL respectively for the 2013-2018 cycles. Lower limits of detection were not provided by NHANES for lipid profiles in the 2011-2012 cycle. Overall, no values were below the lower limits of detection for lipid profiles included in our analysis.

2.4. Covariates

Using a directed acyclic graph and prior literature, we identified and included information on a wide range of potential confounders (Appendix Figure 1) (Greenland et al., 1999; Textor et al., 2016). Our analysis included the following demographic characteristics: age in years, sex (male vs female), poverty to income ratio (categorized as < 1 for participants with family income below the official definition of poverty level vs ≥ 1 for participants with family income above the official definition of poverty level), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, non-Hispanic Asian or other race), and country of birth (native-born, vs foreign-born and < 5 years in the US, vs foreign born and > 5 years in the US). Furthermore, we included BMI for children/adolescents which was calculated based on percentiles and Z-scores of the child's sex and age for BMI and defined as underweight/normal weight (<85^{th} percentile) vs overweight (85^{th} to <95^{th} percentile) vs obese (≥ 95^{th} percentile) (United States Centers for Disease Control and Prevention, 2014).

We included information on fish and shellfish meals assessed for participants 1 year and older following the 24-hour dietary recall interview. We examined the average daily intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from all fish and shellfish

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included in the NHANES dietary database (categorized as no quantified average daily intake, vs < median average daily intake, vs > median average daily intake). Average daily intake of DHA & EPA (mg/d) from fish and shellfish was calculated as (*DHA & EPA* (g/100g fish) * 1000 mg/g) * *number of seafood meals in the last 30 days* * *meal size* (g fish)]/30 days. Our calculation used 1) estimates of DHA & EPA (g/100g fish) from the study by Mahaffey et al. (2008), 2) number of fish and shellfish meals as reported in the NHANES dietary database and 3) a median fish meal size of 89 g for males and 67g for females (United States Environmental Protection Agency, 2021). Finally, we included information on blood selenium measurement (ug/L), and age in years for attainment of menarche to control for puberty in female participants (categorized as < 12 years or ≥ 12 years). All female participants in our analysis had reached puberty.

2.5. Analytical Strategy

TBHg (μg/L) and triglyceride (mg/dL) measurements, were transformed to the natural log scale based on examined distributions. All statistical analyses were performed using SAS (9.4; SAS Institute Inc., Cary, NC) and plots were created using STATA (version 17, StataCorp, College Station, TX; Jann, 2014). For the descriptive analyses, we assessed means and 95% CI for continuous variables and frequencies and percentages for categorical variables. To examine significant differences in bivariate analyses, we used T-tests and X^2 tests for continuous and categorical variables, respectively. We adjusted for sampling clusters and strata in both descriptive and multivariable analysis. In the multivariable analysis assessing associations of TBHg with TC and HDL-C, our analytical sample (N=2,948) included individuals who were excluded from the NHANES fasting subsample and were missing triglyceride and LDL-cholesterol measurements. For this sub-analysis we constructed new 8-year weights calculated as one-fourth of WTMEC2YR for the 2011-2012 and 2017-2018 cycles and one-fourth of WTSH2YR for the 2013-2014 and 2015-2016 cycles (Centers for Disease Control and Prevention 2018). The remainder of our analysis (N=1,390) excluded individuals missing triglyceride and LDL-cholesterol measurements and did not utilize sampling weights due to the partial overlap in the fasting blood lipid subsample and mercury subsample. Instead, demographic variables were included as covariates in multivariable models (Schreinemachers et al., 2015; Korn and Graubard, 1991). We examined TBHg (μg/L) as a log transformed continuous measure and in quartiles.

Using multivariable linear and logistic regression, we examined associations of TBHg with average change in lipid levels and with the prevalence odds of dyslipidemia, respectively. Our analysis was stratified by sex *a priori* to assess sex related differences in the associations of TBHg with lipid levels and dyslipidemia. We constructed sequentially nested models with level 1 models controlling for age, survey cycles, poverty income ratio, country of birth and race; level 2 models controlled for covariates in level 1 plus BMI, serum selenium concentration and age at menarche (females only) while level 3 models controlled for covariates in level 2 plus average daily intake of DHA & EPA from fish and shellfish in the past 30 days. We also tested effect modification by BMI, serum selenium and average daily intake of DHA & EPA from fish and shellfish by including a product term to models and controlling for covariates specified in level 3 models. Subsequently, we performed stratified analysis to evaluate effect modification when the p-value for the product term was

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≤ 0.1 (Mickey and Greenland, 1989). We also conducted a sensitivity analysis assessing associations of methyl Hg with dyslipidemia and lipid profiles using level 3 models which controlled for socio-demographic covariates, BMI, serum selenium, age at menarche and intake of DHA & EPA from fish and shellfish. Our analytical sample was N=2,944 for the analysis assessing associations with TC and HDL-C and N=1,387 for the analysis assessing associations with dyslipidemia, triglycerides and LDL-C.

3. Results

Our analysis included 1,390 adolescents among whom 709 (51.0%) were male, 681 (49.0%) were female; 861 (61.9%) were underweight or normal weight, 223 (16.0%) were overweight and 306 (22.0%) were obese. The prevalence of dyslipidemia in this population was 24.3%, with male participants demonstrating higher prevalence of dyslipidemia compared to females (25.7% vs 22.9%, p=0.22). Overall, males demonstrated significantly lower levels of HDL-C compared to females (50.7 mg/dL vs 55.0 mg/dL; p=<0.0001) while females showed significantly higher levels of TC (158.9 mg/dL vs 152.4 mg/dL; p=0.001) compared to males. Male participants had higher TBHg concentrations and ingested more DHA & EPA from fish and shellfish while female participants had higher BMI (Table 1). The correlation coefficients of BMI percentiles and Z-scores for age and sex with lipids in our sample of adolescents aged 12-19 years were: males - TC (r=0.13; p= <.0001), HDL-C (r= −0.35; p= <.0001), triglyceride (r=0.33; p= <.0001), LDLC-C (r=0.17; p= <.0001); females - TC (r=0.009; p=0.74), HDL-C (r= −0.37; p= <.0001), triglycerides (r=0.18; p= <.0001), LDL-C (r=0.07; p=0.06) (not shown in tables). Table 2 presents mean (95% CI) of TBHg and lipid profiles for selected characteristics. The geometric mean (GM) of TBHg in this population was 0.44 μg/L. Mean TC, HDL-C, and LDL-C levels were 155.6 mg/dL, 52.8 mg/dL and 87.9 mg/dL respectively while GM for triglyceride was 64.0 mg/dL. Among racial/ethnic groups, we observed the highest TBHg GM in Asian participants and the lowest GM in white non-Hispanic participants (1.05 μg/L vs 0.34 μg/L; p=<0.0001). TBHg concentrations differed by country of birth/years lived in the US with the highest levels observed in foreign born participants residing less than 5 years in the U.S. (Table 2). TBHg concentrations increased with daily intake of DHA & EPA from fish and shellfish (Table 2) and was moderately correlated with average daily intake of DHA & EPA from fish and shellfish (r=0.43; p= <.0001; not shown in tables). Mean TC, LDL-C and triglycerides were significantly higher in participants with serum selenium levels above the median value (Table 2).

The results of multivariable linear regression analyses demonstrated sex-related differences in the association of TBHg with TC. In linear regression models controlling for socio-demographic covariates, BMI, serum selenium and age at menarche, TBHg was significantly associated with increased TC (β=4.15, 95% CI: 1.27, 7.03; p<0.05) levels in female participants. Controlling for average daily intake of DHA & EPA from fish and shellfish resulted in attenuated and significant estimates (β=3.34, 95% CI: 0.19, 6.50; p<0.05; (Table 3)). TBHg was not significantly associated with TC in males nor with HDL-C, LDL-C, and triglyceride levels in both males and females. In quartile exposure models stratified by sex and controlling for socio-demographic covariates, BMI, serum selenium, age at menarche and DHA & EPA from fish and shellfish, we observed significantly higher TC

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levels (β=7.54 mg/dL, 95% CI: 0.76, 14.32; p <0.05) in female participants with TBHg concentrations >0.70 μg/L (quartile 4) compared to those with TBHg concentrations of <0.20 μg/L (quartile 1) (Table 3).

Table 4 presents the results of multivariable logistic regression analyses for the association between TBHg concentration and dyslipidemia stratified by sex. We observed decreased prevalence odds of dyslipidemia in male participants and increased prevalence odds of dyslipidemia in females; however, our findings were not statistically significant (Table 4). In our analyses of effect modification, p-values were <0.1 for product terms for TBHg and BMI with TC levels in males and for TBHg and serum selenium with TC levels in females. This was further evaluated in stratified models, which indicated that in obese males (β=−3.56; 95% CI: −8.88, 1.75), TBHg was associated with decreased TC levels. In contrast, in underweight/normal weight males, TBHg was associated with increased TC levels (β=2.89; 95% CI: −0.21, 5.98) and in overweight, but not obese, males, TBHg was not associated with TC levels (β=0.40; 95% CI:−5.70, 6.51; Figure 2). TBHg was associated with increased TC levels in females with serum selenium levels above the median value (β=5.67; 95% CI: 0.39, 10.9) but not in those with serum selenium levels below the median value (β=0.29; 95% CI: −2.85, 3.42; Figure 2). Product terms for average daily intake of DHA & EPA from fish and shellfish were greater than 0.1, which did not support effect modification.

In sensitivity analysis models, controlling for socio-demographic covariates, BMI, serum selenium, age at menarche and DHA & EPA from fish and shellfish, methyl Hg was significantly associated with increased TC (β=3.71, 95% CI: 0.99, 6.42; p<0.05) levels in female participants (Appendix Table 1). We also observed significantly higher TC levels in females having methyl Hg concentrations of 0.23 μg/L - 0.51 μg/L (quartile 3) and concentrations >0.51 μg/L (quartile 4) compared to those with methyl Hg concentrations of <0.16 μg/L (quartile 1). Females having methyl Hg concentrations of 0.16 μg/L - 0.22 μg/L (quartile 2) in addition demonstrated significantly lower HDL-C levels compared to those in quartile 1 (Appendix Table 1).

4. Discussion

Our multivariable analysis of an adolescent sample in the NHANES 2011-2018 datasets found significant positive associations of TBHg and methyl Hg with TC in female but not male adolescents. We did not find any significant associations of TBHg with dyslipidemia, LDL-cholesterol, HDL-cholesterol, and triglycerides in either male or female participants. Controlling for the average daily intake of DHA & EPA from fish and shellfish also attenuated estimates of the association between TBHg exposure and lipids. While our sensitivity analysis using methyl Hg was generally consistent with the primary analysis, the second quartile of methyl Hg, which is derived almost entirely by fish consumption, was also associated with decreased HDL-C levels in female adolescents. Our findings support literature demonstrating associations of TBHg and methyl Hg with TC in US adolescents. Zhang et al. (2018) found positive associations of TC with TBHg and methyl mercury in US adolescents as well as significant associations with the highest quartile versus lowest quartile of methyl mercury with TC in female but not male adolescents. Fan et al. (2017) reported

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positive associations between TBHg and TC in US male and female adolescents while a study of Korean adolescents found positive associations between TBHg and high LDL-C and between hypercholesterolemia and the highest quartile of TBHg exposure in male but not female adolescents (Cho et al., 2020). Studies in the adult population demonstrated mixed findings on associations of TBHg with HDL-C (Cho, 2017; Sohn et al., 2020). The findings from our sensitivity models of decreased HDL-C levels in female adolescents warrants further investigation in future studies.

Elevated levels of TC with Hg exposure observed in our study are biologically plausible. While the relationship of Hg exposure with lipid profiles and dyslipidemia is not fully understood, relevant mechanisms have been implicated in experimental, animal, and human studies. Hg exposure may increase TC and the risk of dyslipidemia through sex specific genetic susceptibility to altered mercury metabolism, plasma lipid peroxidation, autoimmune dysfunction, endoplasmic reticulum stress, or other effects related to oxidative stress (Austin et al., 2014; Chauhan et al., 2019; Bjørklund et al., 2020; Kobal et al., 2004; Andreoli et al., 2017; McSorley et al., 2020). Hg exposure increases plasma levels of proinflammatory cytokines such as interleukin 1 beta and tumor necrosis factor alpha (Nyland et al., 2012) and decreases activity of paraoxonase 1 (Genchi et al., 2017) – an anti-oxidative enzyme which has been demonstrated to inhibit HDL and LDL oxidation and decrease the risk of cardiometabolic disease (Ayotte et al., 2011; Drescher et al.; 2014). Animal studies have demonstrated evidence of alteration in genetic activity and damage to genes responsible for lipid metabolism and energy regulation following mercury chloride ($HgCl_2$) exposure, with the expression of adipocyte gene mRNA for peroxisome proliferator-activated receptor alpha (PPARα) and peroxisome proliferator-activated receptor gamma (PPARγ) declining after $HgCl_2$ exposure (Shi et al., 2018; Kawakami et al., 2012). Glutamate dehydrogenase enzyme (GDH), glucose transporter 2 (GLUT2) protein and glucokinase (GCK) gene, which control lipid and glucose metabolism, and oxidative balance in the pancreatic islets cells of mice, have also been altered by methyl mercury exposure (Maqbool et al., 2016).

While the mechanisms outlined above support the association between Hg exposure and lipids, current evidence on pathways involved in sex related differences are unclear and may be linked to toxicokinetics of mercury, sex hormone related differences, and differing vulnerability to mercury toxicity (Nielsen, 1992; Nielsen and Hultman, 2002; Tan et al., 2009). Epidemiologic studies on these mechanisms and other interconnected pathways are limited. Methylmercury is potentially estrogenic and has been linked to breast cancer in women through calcium mobilization, impairment of endoplasmic reticulum and activation of estrogen receptors (Sukocheva et al., 2005). Paraoxonase 1 levels and estrogens which peak in levels during puberty and childbearing years (Walsh et al., 1999; Baker et al., 2003) provide cardioprotective effects and are higher in females (Ahmad et al., 2010; Winnier et al., 2007). Therefore, our findings demonstrating significantly higher TC and lower HDL-C levels in females may be linked to the disruption of these mechanisms by Hg exposure.

We also found evidence of sex specific effect modification by BMI and serum selenium in male and female adolescents, respectively. While these relationships are not fully understood, higher BMI is associated with abnormal lipid profiles in adolescents (Cook and Kavey, 2011), and inverse associations of Hg exposure with BMI and abdominal obesity

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in adults and with BMI Z-scores in children have been reported (Rothenberg et al., 2015; Buchanan et al., 2015; Bulka et al., 2019). Obesity influences lipid metabolism in the liver (Feingold, 2020) and may impact Hg elimination and accumulation in the blood through changes in hepatic enzymes such as glutathione (Koeck et al., 2011; Clarkson and Magos, 2006). Thus, obesity related change in hepatic secretion of Hg (Rothenberg et al., 2015) may result in metabolic disorders including impaired lipid metabolism. Estrogens are also involved in the regulation of hepatic lipid homeostasis (Savva and Korach-André, 2020), fatty acid metabolism and adipocyte differentiation (Rubinow, 2017). The estrogenic effect of Hg exposure may impact these mechanisms and can help explain our findings of effect modification by BMI in male adolescents.

In addition to our findings, other studies using the NHANES population found positive associations between selenium and TC (Christensen et al., 2015; Bleys et al., 2008; Laclaustra et al., 2010). The mechanisms involved in the sex specific relationship between serum selenium and lipids is also unclear. Hypothesized mechanisms may be related to lipoprotein metabolism and sex differences in estrogen activity, Hg elimination through the glutathione pathway and selenium metabolism (Spiller, 2018). Mercury binds the selenium sites in proteins which disrupts intracellular homeostasis and inhibits selenoprotein function (Spiller, 2018). In one animal study, impairment in selenoprotein synthesis was linked to alterations in genes responsible for metabolism, transport and synthesis of cholesterol (Sengupta et al., 2008). Some studies have also demonstrated sex differences in selenium activity and have linked estrogens with alterations to selenium distribution and metabolism (Choe, 2003; Lee, 2005; Seale, 2018; Hybsier, 2017).

Our study used a robust sample of US adolescents to explore biologically plausible pathways of sex, selenium and BMI on the relationship of TBHg with dyslipidemia and lipid profiles. We also controlled for a wide range of confounding variables, particularly key factors affecting both mercury metabolism and dyslipidemia. However, our study has limitations which should be considered in interpreting findings. First, we could not readily examine the role of sex hormones in the relationship of TBHg with dyslipidemia in our sample of adolescents due to the hormonal changes of puberty. However, we control for reproductive health and initiation of puberty among female participants using age at menarche as a proxy. Our analysis also employed a single pollutant model which does not account for possible co-exposure effects of other metals or pollutants in seafood such as polychlorinated biphenyls (PCBs). We also utilized 30-day dietary recall from NHANES to assess the frequency of consumption of fish and shellfish which may be subject to recall limitation and may not accurately reflect habitual consumption. In addition, due to the cross-sectional design of our study, we cannot establish temporality based on the observed associations.

4.1. Conclusion

We found significantly higher TC levels with increasing TBHg and methyl Hg concentrations in females but not male adolescents. Methyl Hg was also associated with decreased HDL-C levels in female adolescents. We also found evidence of effect modification by BMI and serum selenium in male and female adolescents, respectively. Since abnormal lipid profiles and dyslipidemia in adolescents may predict metabolic

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and cardiovascular disease in adulthood, additional studies are warranted to evaluate our findings. Future studies incorporating inflammatory markers and genetic biomarkers may improve our understanding of potential causal mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement section

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References

Abdelhamid AS, Brown TJ, Brainard JS, Biswas P, Thorpe GC, Moore HJ, Deane KH, Summerbell CD, Worthington HV, Song F, Hooper L, 2020. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. The Cochrane database of systematic reviews 3 (3), CD003177. doi:10.1002/14651858.CD003177.pub5. [PubMed: 32114706]

Ahmad S, Scott JE, 2010. Estradiol enhances cell-associated paraoxonase 1 (PON1) activity in vitro without altering PON1 expression. Biochemical and biophysical research communications 397 (3), 441–446. doi:10.1016/j.bbrc.2010.05.120. [PubMed: 20510879]

Andreoli V, Sprovieri F, 2017. Genetic Aspects of Susceptibility to Mercury Toxicity: An Overview. International journal of environmental research and public health 14 (1), 93. doi:10.3390/ijerph14010093. [PubMed: 28106810]

Austin DW, Spolding B, Gondalia S, Shandley K, Palombo EA, Knowles S, Walder K, 2014. Genetic variation associated with hypersensitivity to mercury. Toxicology international 21 (3), 236–241. doi:10.4103/0971-6580.155327. [PubMed: 25948960]

Ayotte P, Carrier A, Ouellet N, Boiteau V, Abdous B, Sidi EA, Château-Degat ML, Dewailly É, 2011. Relation between methylmercury exposure and plasma paraoxonase activity in Inuit adults from Nunavik. Environmental health perspectives 119 (8), 1077–1083. doi:10.1289/ehp.1003296. [PubMed: 21543280]

Baker L, Meldrum KK, Wang M, Sankula R, Vanam R, Raiesdana A, Tsai B, Hile K, Brown JW, Meldrum DR, 2003. The role of estrogen in cardiovascular disease. The Journal of surgical research 115 (2), 325–344. doi:10.1016/s0022-4804(03)00215-4. [PubMed: 14697301]

Bjørklund G, Peana M, Dadar M, Chirumbolo S, Aaseth J, Martins N, 2020. Mercury-induced autoimmunity: Drifting from micro to macro concerns on autoimmune disorders. Clinical immunology (Orlando, Fla.) 213, 108352. doi:10.1016/j.clim.2020.108352. [PubMed: 32032765]

Bleys J, Navas-Acien A, Stranges S, Menke A, Miller ER 3rd, Guallar E, 2008. Serum selenium and serum lipids in US adults. The American journal of clinical nutrition 88 (2), 416–423. doi:10.1093/ajcn/88.2.416 . [PubMed: 18689378]

Buchanan S, Anglen J, Turyk M, 2015. Methyl mercury exposure in populations at risk: Analysis of NHANES 2011-2012. Environmental research 140, 56–64. doi:10.1016/j.envres.2015.03.005. [PubMed: 25825131]

Buhari O, Dayyab FM, Igbinoba O, Atanda A, Medhane F, Faillace RT, 2020. The association between heavy metal and serum cholesterol levels in the US population: National Health and Nutrition Examination Survey 2009-2012. Human & experimental toxicology 39 (3), 355–364. doi:10.1177/0960327119889654. [PubMed: 31797685]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Bulka CM, Persky VW, Daviglus ML, Durazo-Arvizu RA, Argos M, 2019. Multiple metal exposures and metabolic syndrome: A cross-sectional analysis of the National Health and Nutrition Examination Survey 2011-2014. Environmental research 168, 397–405. doi:10.1016/j.envres.2018.10.022. [PubMed: 30388496]

Centers for Disease Control and Prevention (2014). Growth chart training: Recommended BMI-for-age Cutoffs. Retrieved from https://www.cdc.gov/nccdphp/dnpao/growthcharts/training/bmiage/page4.html last accessed January 1, 2022.

Centers for Disease Control and Prevention (2018). National Health and Nutrition Examination Survey: Analytic Guidelines, 2011-2014 and 2015-2016. Retrieved from https://wwwn.cdc.gov/nchs/data/nhanes/analyticguidelines/11-16-analytic-guidelines.pdf last accessed January 1, 2022

Centers for Disease Control and Prevention, 2021. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Questionnaire. 2011-2018 datasets. Retrieved from https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. last accessed January 10, 2022.

Chauhan S, Dunlap K, Duffy LK, 2019. Effects of Methylmercury and Theaflavin Digallate on Adipokines in Mature 3T3-L1 Adipocytes. International journal of molecular sciences 20 (11), 2755. doi:10.3390/ijms20112755. [PubMed: 31195622]

Cho HW, Kim SH, Park MJ, 2020. An association of blood mercury levels and hypercholesterolemia among Korean adolescents. The Science of the total environment 709, 135965. doi:10.1016/j.scitotenv.2019.135965. [PubMed: 31927427]

Cho YM, 2017. Fish consumption, mercury exposure, and the risk of cholesterol profiles: findings from the Korea National Health and Nutrition Examination Survey 2010-2011. Environmental health and toxicology 32, e2017014. doi:10.5620/eht.e2017014. [PubMed: 28859472]

Cho KY, 2021. Association of Blood Mercury Levels with the Risks of Overweight and High Waist-to-Height Ratio in Children and Adolescents: Data from the Korean National Health and Nutrition Examination Survey. Children (Basel, Switzerland), 8 (12), 1087. doi:10.3390/children8121087. [PubMed: 34943283]

Choe SY, Kim SJ, Kim HG, Lee JH, Choi Y, Lee H, Kim Y, 2003. Evaluation of estrogenicity of major heavy metals. The Science of the total environment 312 (1-3), 15–21. doi:10.1016/S0048-9697(03)00190-6. [PubMed: 12873394]

Christensen K, Werner M, Malecki K, 2015. Serum selenium and lipid levels: Associations observed in the National Health and Nutrition Examination Survey (NHANES) 2011-2012. Environmental research 140, 76–84. doi:10.1016/j.envres.2015.03.020 . [PubMed: 25836721]

Clarkson TW, Magos L, 2006. The toxicology of mercury and its chemical compounds. Critical reviews in toxicology 36 (8), 609–662. doi:10.1080/10408440600845619. [PubMed: 16973445]

Cook S, Kavey RE, 2011. Dyslipidemia and pediatric obesity. Pediatric clinics of North America 58 (6). doi:10.1016/j.pcl.2011.09.003, 1363–ix. [PubMed: 22093856]

Drescher O, Dewailly E, Diorio C, Ouellet N, Sidi EA, Abdous B, Valera B, Ayotte P, 2014. Methylmercury exposure, PON1 gene variants and serum paraoxonase activity in Eastern James Bay Cree adults. Journal of exposure science & environmental epidemiology 24 (6), 608–614. doi:10.1038/jes.2013.96. [PubMed: 24448003]

Fan Y, Zhang C, Bu J, 2017. Relationship between Selected Serum Metallic Elements and Obesity in Children and Adolescent in the U.S. Nutrients 9 (2), 104. doi:10.3390/nu9020104. [PubMed: 28165362]

Feingold KR, 2020. Obesity and Dyslipidemia. Endotext. MDText.com, Inc K. R. Feingold.

Friedewald WT, Levy RI, Fredrickson DS, 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clinical Chemistry 18, 499–502 [PubMed: 4337382]

Genchi G, Sinicropi MS, Carocci A, Lauria G, Catalano A, 2017. Mercury Exposure and Heart Diseases. International journal of environmental research and public health 14 (1), 74. doi:10.3390/ijerph14010074. [PubMed: 28085104]

Greenland S, Pearl J, Robins JM, 1999. Causal diagrams for epidemiologic research. Epidemiology (Cambridge, Mass.) 10 (1), 37–48. [PubMed: 9888278]

Guallar E, Sanz-Gallardo MI, van't Veer P, Bode P, Aro A, Gómez-Aracena J, Kark JD, Riemersma RA, Martín-Moreno JM, Kok FJ, 2002. Mercury, fish oils, and the risk of myocardial infarction.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

The New England journal of medicine, 347 (22), 1747–1754. doi:10.1056/NEJMoa020157. [PubMed: 12456850]

Gump BB, MacKenzie JA, Dumas AK, Palmer CD, Parsons PJ, Segu ZM, Mechref YS, Bendinskas KG, 2012. Fish consumption, low-level mercury, lipids, and inflammatory markers in children. Environmental research 112, 204–211. doi:10.1016/j.envres.2011.10.002. [PubMed: 22030286]

Hybsier S, Schulz T, Wu Z, Demuth I, Minich WB, Renko K, Rijntjes E, Köhrle J, Strasburger CJ, Steinhagen-Thiessen E, Schomburg L, 2017. Sex-specific and inter-individual differences in biomarkers of selenium status identified by a calibrated ELISA for selenoprotein. P. Redox biology 11, 403–414. doi:10.1016/j.redox.2016.12.025. [PubMed: 28064116]

Jackson SL, Yang EC, Zhang Z, 2018. Income Disparities and Cardiovascular Risk Factors Among Adolescents. Pediatrics 142 (5), e20181089. doi:10.1542/peds.2018-1089. [PubMed: 30333131]

Jann B, 2014. Plotting regression coefficients and other estimates in Stata. University of Bern Social Sciences Working Papers No. 1. Available from.

Jin T, Park EY, Kim B, Oh JK, 2021. Association between Blood Mercury Concentration and Prevalence of Borderline Hypercholesterolemia among Adolescents: The Korea National Health and Nutrition Examination Survey (KNHANES) 2010-2013 and 2016. Toxics 9 (10), 242. doi:10.3390/toxics9100242. [PubMed: 34678938]

Karagas MR, Choi AL, Oken E, Horvat M, Schoeny R, Kamai E, Cowell W, Grandjean P, Korrick S, 2012. Evidence on the human health effects of low-level methylmercury exposure. Environmental health perspectives 120 (6), 799–806. doi:10.1289/ehp.1104494. [PubMed: 22275730]

Kawakami T, Hanao N, Nishiyama K, Kadota Y, Inoue M, Sato M, Suzuki S, 2012. Differential effects of cobalt and mercury on lipid metabolism in the white adipose tissue of high-fat diet-induced obesity mice. Toxicology and applied pharmacology 258 (1), 32–42. doi:10.1016/j.taap.2011.10.004. [PubMed: 22019852]

Kit BK, Kuklina E, Carroll MD, Ostchega Y, Freedman DS, Ogden CL, 2015. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999-2012. JAMA pediatrics 169 (3), 272–279. doi:10.1001/jamapedi-atrics.2014.3216. [PubMed: 25599372]

Kobal AB, Horvat M, Prezelj M, Briski AS, Krsnik M, Dizdarevic T, Mazej D, Falnoga I, Stibilj V, Arneric N, Kobal D, Osredkar J, 2004. The impact of long-term past exposure to elemental mercury on antioxidative capacity and lipid peroxidation in mercury miners. Journal of trace elements in medicine and biology : organ of the Society for Minerals and Trace Elements (GMS) 17 (4), 261–274. doi:10.1016/S0946-672X(04)80028-2. [PubMed: 15139389]

Koek GH, Liedorp PR, Bast A, 2011. The role of oxidative stress in non-alcoholic steatohepatitis. Clinica chimica acta; international journal of clinical chemistry 412 (15-16), 1297–1305. doi:10.1016/j.cca.2011.04.013. [PubMed: 21514287]

Korn EL, Graubard BI, 1991. Epidemiologic studies utilizing surveys: accounting for the sampling design. American journal of public health 81 (9), 1166–1173. doi:10.2105/ajph.81.9.1166. [PubMed: 1951829]

Kresovich JK, Argos M, Turyk ME, 2015. Associations of lead and cadmium with sex hormones in adult males. Environmental research 142, 25–33. doi:10.1016/j.envres.2015.05.026. [PubMed: 26093239]

Krieg EF Jr, 2007. The relationships between blood lead levels and serum follicle stimulating hormone and luteinizing hormone in the third National Health and Nutrition Examination Survey. Environmental research 104 (3), 374–382. doi:10.1016/j.envres.2006.09.009. [PubMed: 17084837]

Laclaustra M, Stranges S, Navas-Acien A, Ordovas JM, Guallar E, 2010. Serum selenium and serum lipids in US adults: National Health and Nutrition Examination Survey (NHANES) 2003-2004. Atherosclerosis 210 (2), 643–648. doi:10.1016/j.atherosclerosis.2010.01.005. [PubMed: 20102763]

Lee SO, Nadiminty N, Wu XX, Lou W, Dong Y, Ip C, Onate SA, Gao AC, 2005. Selenium disrupts estrogen signaling by altering estrogen receptor expression and ligand binding in human breast cancer cells. Cancer research 65 (8), 3487–3492. doi:10.1158/0008-5472.CAN-04-3267. [PubMed: 15833885]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Lin TH, Huang YL, Huang SF, 1996. Lipid peroxidation in liver of rats administrated with methyl mercuric chloride. Biological trace element research 54 (1), 33–41. doi:10.1007/BF02785318. [PubMed: 8862759]

Liu Y, Buchanan S, Anderson HA, Xiao Z, Persky V, Turyk ME, 2018. Association of methylmercury intake from seafood consumption and blood mercury level among the Asian and Non-Asian populations in the United States. Environmental research 160, 212–222. doi:10.1016/j.envres.2017.09.031. [PubMed: 29020643]

Lozano P, Henrikson NB, Morrison CC, Dunn J, Nguyen M, Blasi PR, Whitlock EP, 2016. Lipid Screening in Childhood and Adolescence for Detection of Multifactorial Dyslipidemia: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 316 (6), 634–644. doi:10.1001/jama.2016.6423. [PubMed: 27532918]

Mahaffey KR, Clickner RP, Jeffries RA, 2008. Methylmercury and omega-3 fatty acids: co-occurrence of dietary sources with emphasis on fish and shellfish. Environmental research 107 (1), 20–29. doi:10.1016/j.envres.2007.09.011. [PubMed: 17996230]

Maqbool F, Bahadar H, Niaz K, Baeeri M, Rahimifard M, Navaei-Nigjeh M, Ghasemi-Niri SF, Abdollahi M, 2016. Effects of methyl mercury on the activity and gene expression of mouse Langerhans islets and glucose metabolism. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association 93, 119–128. doi:10.1016/j.fct.2016.05.005. [PubMed: 27178136]

McSorley EM, van Wijngaarden E, Yeates AJ, Spence T, Mulhern MS, Harrington D, Thurston SW, Love T, Jusko TA, Allsopp PJ, Conway MC, Davidson PW, Myers GJ, Watson GE, Shamlaye CF, Strain JJ, 2020. Methylmercury and long chain polyunsaturated fatty acids are associated with immune dysregulation in young adults from the Seychelles child development study. Environmental research 183, 109072. doi:10.1016/j.envres.2019.109072. [PubMed: 32007747]

Mickey RM, Greenland S (1989). The impact of confounder selection criteria on effect estimation [published correction appears in American Journal of Epidemiology, 129(1), 125–137. doi:10.1093/oxfordjournals.aje.a115101.

Nielsen JB, Hultman P, 2002. Mercury-induced autoimmunity in mice. Environmental health perspectives 110 (Suppl 5), 877–881. doi:10.1289/ehp.02110s5877, Suppl 5. [PubMed: 12426151]

Nielsen JB, 1992. Toxicokinetics of mercuric chloride and methyl mercuric chloride in mice. Journal of toxicology and environmental health 37 (1), 85–122. doi:10.1080/15287399209531659. [PubMed: 1522616]

Nordgren TM, Lyden E, Anderson-Berry A, Hanson C, 2017. Omega-3 Fatty Acid Intake of Pregnant Women and Women of Childbearing Age in the United States: Potential for Deficiency? Nutrients 9 (3), 197. doi:10.3390/nu9030197. [PubMed: 28245632]

Nyland JF, Fairweather D, Shirley DL, Davis SE, Rose NR, Silbergeld EK, 2012. Low-dose inorganic mercury increases severity and frequency of chronic coxsackievirus-induced autoimmune myocarditis in mice. Toxicological sciences : an official journal of the Society of Toxicology 125 (1), 134–143. doi:10.1093/toxsci/kfr264. [PubMed: 21984480]

Pollack AZ, Schisterman EF, Goldman LR, Mumford SL, Albert PS, Jones RL, Wactawski-Wende J, 2011. Cadmium, lead, and mercury in relation to reproductive hormones and anovulation in premenopausal women. Environmental health perspectives 119 (8), 1156–1161. doi:10.1289/ehp.1003284. [PubMed: 21543284]

Poursafa P, Ataee E, Motlagh ME, Ardalan G, Tajadini MH, Yazdi M, & Kelishadi R (2014). Association of serum lead and mercury level with cardiometabolic risk factors and liver enzymes in a nationally representative sample of adolescents: the CASPIAN-III study. Environmental science and pollution research international, 21 (23), 13496–13502. doi:10.1007/s11356-014-3238-4. [PubMed: 25017868]

Rayman MP, 2012. Selenium and human health. Lancet (London, England) 379 (9822), 1256–1268. doi:10.1016/S0140-6736(11)61452-9. [PubMed: 22381456]

Rothenberg SE & Korrick SA & Fayad R (2015). The influence of obesity on blood mercury levels for U.S. non-pregnant adults and children: NHANES 2007–2010. Environmental Research; 138 173–180. doi:10.1016/j.envres.2015.01.018. [PubMed: 25721244]

Rubinow KB, 2017. Estrogens and Body Weight Regulation in Men. Advances in experimental medicine and biology 1043, 285–313. doi:10.1007/978-3-319-70178-3_14 . [PubMed: 29224100]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Salonen JT, Seppänen K, Nyyssönen K, Korpela H, Kauhanen J, Kantola M, Tuomilehto J, Esterbauer H, Tatzber F, Salonen R, 1995. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. Circulation 91 (3), 645–655. doi:10.1161/01.cir.91.3.645. [PubMed: 7828289]

Sanders AP, Mazzella MJ, Malin AJ, Hair GM, Busgang SA, Saland JM, Curtin P, 2019. Combined exposure to lead, cadmium, mercury, and arsenic and kidney health in adolescents aged 12-19 in NHANES 2009-2014. Environment international 131, 104993. doi:10.1016/j.envint.2019.104993. [PubMed: 31326826]

Savva C, Korach-André M, 2020. Estrogen Receptor beta (ERβ) Regula tion of Lipid Homeostasis-Does Sex Matter? Metabolites 10 (3), 116. doi:10.3390/metabo10030116. [PubMed: 32244965]

Schreinemachers DM, Ghio AJ, Sobus JR, Williams MA, 2015. Perchlorate Exposure is Associated with Oxidative Stress and Indicators of Serum Iron Homeostasis Among NHANES 2005-2008 Subjects. Biomarker insights 10, 9–19. doi:10.4137/BMI.S20089. [PubMed: 25673971]

Seale LA, Ogawa-Wong AN, Berry MJ, 2018. SEXUAL DIMORPHISM IN SELENIUM METABOLISM AND SELENOPROTEINS. Free radical biology & medicine 127, 198–205. doi:10.1016/j.freeradbiomed.2018.03.036. [PubMed: 29572096]

Sengupta A, Carlson BA, Hoffmann VJ, Gladyshev VN, Hatfield DL, 2008. Loss of housekeeping selenoprotein expression in mouse liver modulates lipoprotein metabolism. Biochemical and biophysical research communications 365 (3), 446–452. doi:10.1016/j.bbrc.2007.10.189. [PubMed: 17996733]

Shi Q, Sun N, Kou H, Wang H, Zhao H, 2018. Chronic effects of mercury on Bufo gargarizans larvae: thyroid disruption, liver damage, oxidative stress, and lipid metabolism disorder. Ecotoxicol. Environ. Saf 164, 500–509. doi:10.1016/j.ecoenv.2018.08.058. [PubMed: 30145490]

Sohn SH, Heo HC, Jo S, Park C, Sakong J, 2020. The association between mercury concentrations and lipid profiles in the Korean National Environmental Health Survey (KoNEHS) cycle 3. Annals of occupational and environmental medicine 32, e19. doi:10.35371/aoem.2020.32.e19. [PubMed: 32676197]

Spiller HA, 2018. Rethinking mercury: the role of selenium in the pathophysiology of mercury toxicity. Clinical toxicology (Philadelphia, Pa.) 56 (5), 313–326. doi:10.1080/15563650.2017.1400555. [PubMed: 29124976]

Sukocheva OA, Yang Y, Gierthy JF, Seegal RF, 2005. Methyl mercury influences growth-related signaling in MCF-7 breast cancer cells. Environmental toxicology 20 (1), 32–44. doi:10.1002/tox.20075. [PubMed: 15712295]

Tan SW, Meiller JC, Mahaffey KR, 2009. The endocrine effects of mercury in humans and wildlife. Critical reviews in toxicology 39 (3), 228–269. doi:10.1080/10408440802233259. [PubMed: 19280433]

Textor J, van der Zander B, Gilthorpe MS, Liskiewicz M, Ellison GT, 2016. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. International journal of epidemiology 45 (6), 1887–1894. doi:10.1093/ije/dyw341. [PubMed: 28089956]

Thurston SW, Bovet P, Myers GJ, Davidson PW, Georger LA, Shamlaye C, Clarkson TW, 2007. Does prenatal methylmercury exposure from fish consumption affect blood pressure in childhood? Neurotoxicology 28 (5), 924–930. doi:10.1016/j.neuro.2007.06.002. [PubMed: 17659343]

United States Agency for Toxic Substances and Disease Registry (ATSDR), 1999. Toxicological profile for Mercury. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA.

United States Department of Health & Human Services, National Heart, Lung, and Blood Institute, Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents, 2011. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics 128 (Supplement 5), S213–S256. doi:10.1542/peds.2009-2107C. [PubMed: 22084329]

United States Environmental Protection Agency, 2021. Exposure Factors Handbook Chapter 10. Exposure Factors Handbook: 2011 Edition. Retrieved from https://www.epa.gov/expobox/exposure-factors-handbook-chapter-10 last accessed January 13, 2022

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Walsh BW, Spiegelman D, Morrissey M, Sacks FM, 1999. Relationship between serum estradiol levels and the increases in high-density lipoprotein levels in postmenopausal women treated with oral estradiol. The Journal of clinical endocrinology and metabolism 84 (3), 985–989. doi:10.1210/jcem.84.3.5571. [PubMed: 10084583]

Winnier DA, Rainwater DL, Cole SA, Williams JT, Dyer TD, Blangero J, MacCluer JW, Mahaney MC, 2007. Sex-specific QTL effects on variation in paraoxonase 1 (PON1) activity in Mexican Americans. Genetic epidemiology 31 (1), 66–74. doi:10.1002/gepi.20191. [PubMed: 17136774]

Zhang X, Wang Y, Zhao Y, Chen X, 2008. Experimental study on the estrogen-like effect of mercuric chloride. Biometals : an international journal on the role of metal ions in biology, biochemistry, and medicine 21 (2), 143–150. doi:10.1007/s10534-007-9102-y. [PubMed: 17588195]

Zhang Y, Xu C, Fu Z, Shu Y, Zhang J, Lu C, & Mo X (2018). Associations between total mercury and methyl mercury exposure and cardiovascular risk factors in US adolescents. Environmental science and pollution research international, 25(7), 6265–6272. doi:10.1007/s11356-017-0905-2. [PubMed: 29247408]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

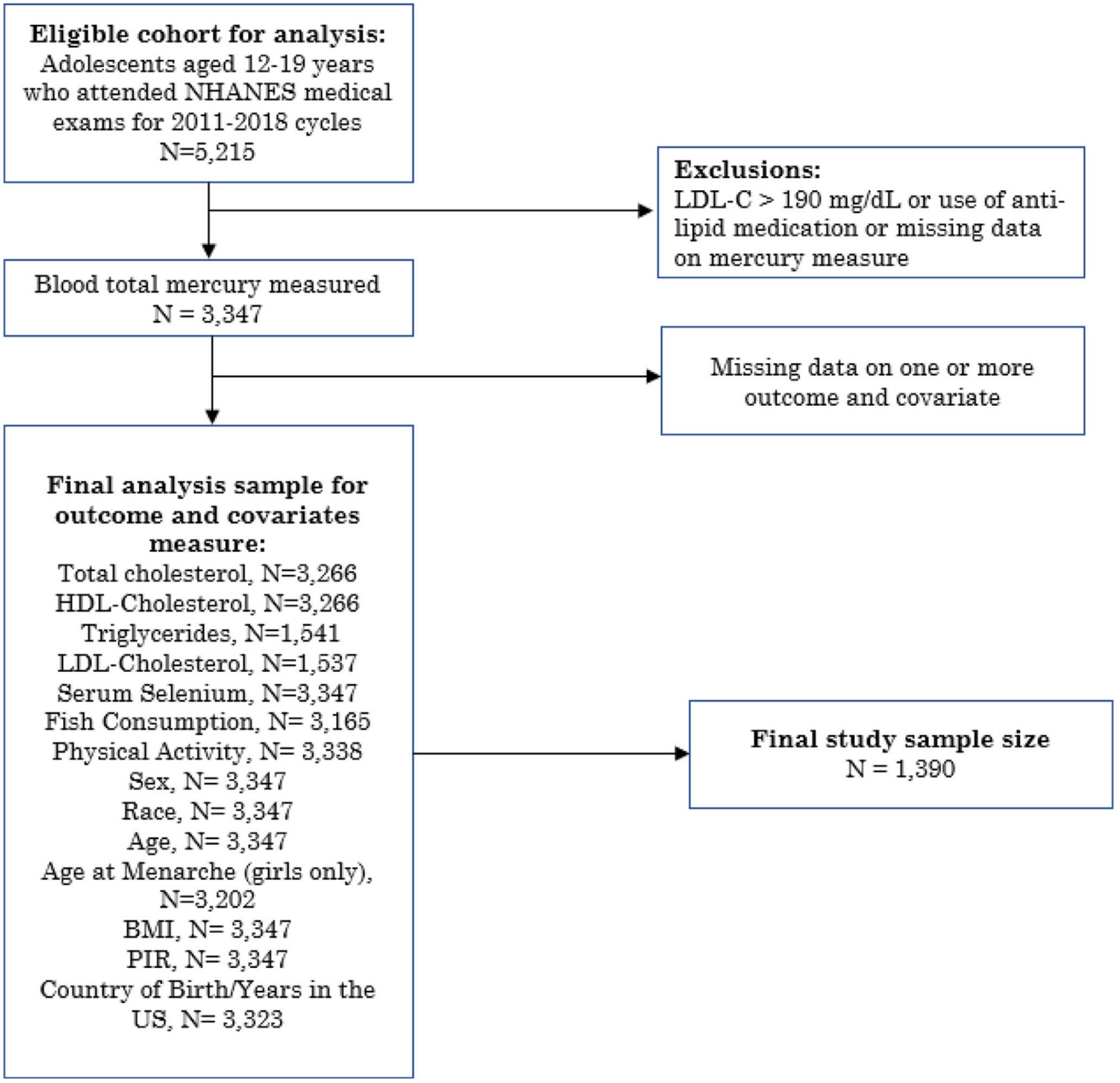

Figure 1.

Eligible participants and participants included in the analyses of the relationship between blood total mercury and dyslipidemia, NHANES: 2011-2018 HDL, High density lipoproteins; LDL, Low density lipoproteins; BMI, body mass index; PIR, poverty to family income ratio.

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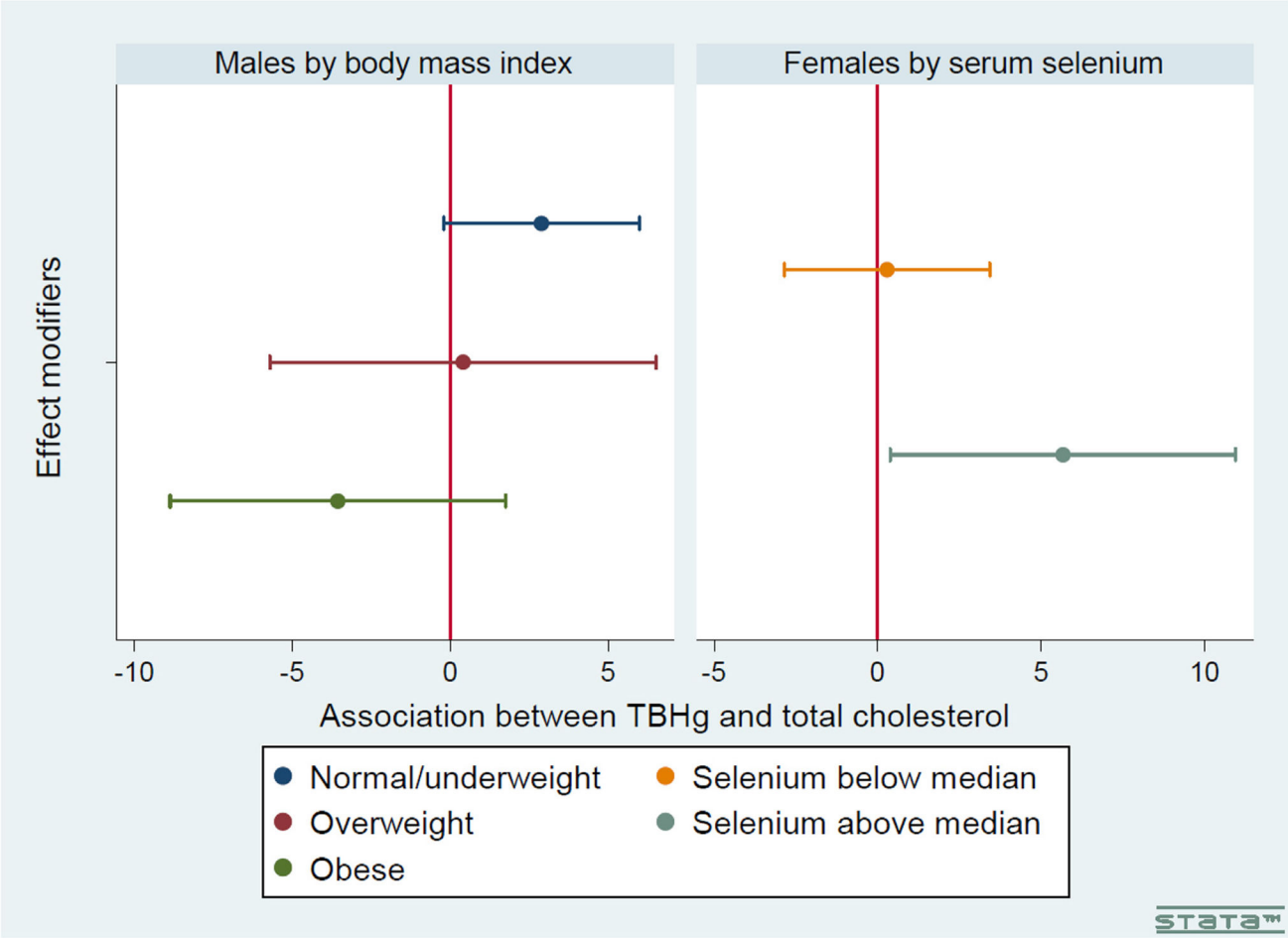

Figure 2.
Modification of the effect of blood total mercury (μg/L) on total cholesterol levels in male and female participants

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Table 1

Distribution of selected characteristics, blood total mercury (μg/L) and lipid profiles (mg/dL) in US adolescents, stratified by participant sex (n=1,390)

		Sex		
Characteristics	**Total; N=1,390**	**Male; N=709**	**Female; N=681**	**p-value**
Blood total mercury μg/L) ††	0.44 (0.41, 0.48)	0.46 (0.42, 0.51)	0.42 (0.39, 0.46)	0.05
Total cholesterol (mg/dL) †	155.56 (153.72, 157.41)	152.41 (150.11, 154.70)	158.85 (155.92, 161.78)	0.001
HDL cholesterol (mg/dL) †	52.81 (52.02, 53.61)	50.72 (49.78, 51.66)	54.99 (53.78, 56.20)	<0.0001
LDL cholesterol (mg/dL) †	87.89 (86.29, 89.48)	86.69 (84.72, 88.66)	89.13 (86.77, 91.49)	0.10
Triglycerides (mg/dL) ††	64.00 (61.94, 66.12)	63.66 (61.08, 66.35)	64.35 (61.38, 67.47)	0.72
Dyslipidemia	0.44 (0.41, 0.48)	0.46 (0.42, 0.51)	0.42 (0.39, 0.46)	0.05
Acceptable	1052 (75.68)	527 (74.33)	525 (77.09)	0.22
Abnormal	338 (24.32)	182 (25.67)	156 (22.91)	
Hypercholesterolemia (total cholesterol ≥ 200)	112 (8.06)	47 (6.63)	65 (9.54)	0.08
Hypo-HDL-cholesterolemia (HDL-C < 40)	156 (11.22)	101 (14.25)	55 (8.08)	0.01
Hyper-LDL-cholesterolemia (LDL-C ≥ 130)	85 (6.12)	42 (5.92)	43 (6.31)	0.78
Hypertriglyceridemia (triglyceride ≥ 130)	141 (10.14)	80 (11.28)	61 (8.96)	0.17
Survey cycle				
2011-2012	513 (36.91)	265 (37.38)	248 (36.42)	0.99
2013-2014	270 (19.42)	137 (19.32)	133 (19.53)	
2015-2016	217 (15.62)	110 (15.51)	107 (15.71)	
2017-2018	390 (28.06)	197 (27.79)	193 (28.34)	
Age (years) †	15.47 (15.31, 15.62)	15.44 (15.24, 15.63)	15.50 (15.31, 15.69)	0.56
Body mass index				
Underweight/Normal	861 (61.94)	459 (64.74)	402 (59.03)	0.09
Overweight	223 (16.04)	104 (14.67)	119 (17.47)	
Obese	306 (22.01)	146 (20.59)	160 (23.50)	
Poverty to family income ratio				
≥1	859 (61.80)	446 (62.91)	413 (60.65)	0.35
<1	531 (38.20)	263 (37.09)	268 (39.35)	
Race/Ethnicity				

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Characteristics	Total; N=1,390	Sex		p-value
		Male; N=709	Female; N=681	
Non-Hispanic White	390 (28.06)	200 (28.21)	190 (27.90)	ref
Non-Hispanic Black	367 (26.40)	194 (27.36)	173 (25.40)	0.69
Non-Hispanic Asian	164 (11.80)	83 (11.71)	81 (11.89)	0.87
Hispanic	393 (28.27)	192 (27.08)	201 (29.52)	0.45
Other Race	76 (5.47)	40 (5.64)	36 (5.29)	0.81
Country of birth/Years in the US				
Native Born	1229 (88.42)	633 (89.28)	596 (87.52)	ref
Foreign Born and less than 5 years	60 (4.32)	31 (4.37)	29 (4.26)	0.97
Foreign Born and greater than 5 years	101 (7.27)	45 (6.35)	56 (8.22)	0.13
Average daily intake of DHA & EPA from fish and shellfish				
None reported††	566 (40.72)	264 (37.24)	302 (44.35)	0.080
< median (37.4 mg/day for males and 29.0 mg/day for females)	412 (29.57)	205 (31.32)	207 (27.75)	
≥ median (37.4 mg/day for males and 29.0 mg/day for females)	412 (29.71)	240 (31.45)	172 (27.90)	
Serum selenium µg/L) †	189.60 (187.56, 191.64)	191.04 (188.54, 193.54)	188.10 (185.85, 190.35)	0.02

Data were presented as

† mean (95% CI), or

†† geometric mean (95% CI) or number (%).

HDL, High density lipoproteins; LDL, Low density lipoproteins; Ref, reference level.

Dyslipidemia: LDL-C ≥ 130 mg/dL or TC levels ≥ 200 mg/dL or TG levels ≥ 130 mg/dL or HDL-C levels ≤ 40.

††† None reported: Refused to answer, did not know, or did not consume any fish or shellfish within the past 30 days.

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Table 2

Mean (95% CI) of total blood mercury (μg/L) and lipid profiles (mg/dL) for selected characteristics, National Health and Nutrition Examination Survey Database, 2011–2018 (n=1,390)

Characteristic	Blood Total Mercury (μg/L)	Total Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	Triglycerides (mg/dL)
	GM† (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	GM† (95% CI)
Overall	0.44 (0.41, 0.48)	155.56 (153.72, 157.41)	52.81 (52.02, 53.61)	87.89 (86.29, 89.48)	64.00 (61.94, 66.12)
Survey cycle					
2011-2012	0.49 (0.41, 0.58)**	157.77 (155.25, 160.28)	52.28 (51.16, 53.39)	89.20 (87.31, 91.09)	70.72 (67.01, 74.64)**
2013-2014	0.48 (0.42, 0.56)	155.36 (150.82, 159.90)	53.16 (51.16, 55.17)	87.43 (84.07, 90.79)	63.86 (59.90, 68.09)
2015-2016	0.45 (0.41, 0.50)	152.85 (149.97, 155.72)	54.35 (51.80, 56.89)	85.30 (81.76, 88.84)	55.56 (50.92, 60.62)
2017-2018	0.37 (0.34, 0.40)	154.31 (149.87, 158.75)	52.42 (51.15, 53.69)	87.91 (83.88, 91.94)	60.79 (56.72, 65.16)
Body mass index					
Underweight/Normal	0.45 (0.42, 0.50)	154.26 (152.10, 156.42)	55.75 (54.71, 56.80)**	85.34 (83.56, 87.13)**	58.13 (55.85, 60.51)**
Overweight	0.43 (0.37, 0.48)	158.42 (154.63, 162.20)	50.98 (49.30, 52.67)	91.59 (88.33, 94.84)	68.12 (63.49, 73.10)
Obese	0.43 (0.38, 0.47)	157.15 (153.18, 161.12)	45.87 (44.83, 46.90)	92.34 (88.94, 95.74)	80.13 (74.26, 86.47)
Age category (years)					
12 - 15	0.41 (0.37, 0.44)**	152.82 (150.16, 155.48)**	53.38 (52.35, 54.42)**	85.01 (82.91, 87.10)	62.36 (59.62, 65.24)
16 - 19	0.48 (0.44, 0.53)	158.31 (156.01, 160.60)	52.24 (51.38, 53.10)	90.77 (88.69, 92.84)	65.67 (63.05, 68.41)
Age at menarche (years); females only					
Greater than 12	0.45 (0.41, 0.50)**	160.59 (157.20, 163.97)**	55.99 (54.52, 57.46)**	90.05 (87.35, 92.74)**	63.84 (60.26, 67.63)
Less than 12	0.38 (0.34, 0.42)	155.71 (151.71, 159.72)	53.19 (51.72, 54.66)	87.48 (83.62, 91.34)	65.28 (61.22, 69.62)
Poverty to family income ratio					
≥1	0.44 (0.40, 0.48)	155.65 (153.47, 157.83)	52.99 (52.04, 53.93)	88.11 (86.13, 90.08)	62.99 (60.42, 65.67)
<1	0.45 (0.41, 0.50)	155.42 (152.24, 158.59)	52.53 (51.48, 53.57)	87.53 (84.75, 90.31)	65.65 (62.28, 69.21)
Race/Ethnicity					
White Non-Hispanic (Reference)	0.34 (0.30, 0.38)	154.70 (152.04, 157.36)	51.82 (50.57, 53.08)	87.33 (85.16, 89.50)	68.51 (64.73, 72.51)
Black Non-Hispanic	0.46 (0.41, 0.52)**	156.70 (153.05, 160.35)	54.69 (53.38, 56.00)	89.76 (86.51, 93.01)	52.17 (49.22, 55.30)**
Asian Non-Hispanic	1.05 (0.91, 1.22)**	161.12 (154.50, 167.73)	54.43 (52.53, 56.32)**	91.40 (86.48, 96.31)	66.95 (61.03, 73.45)
Hispanic	0.38 (0.35, 0.42)	153.84 (150.60, 157.08)	51.77 (50.36, 53.17)**	85.53 (82.81, 88.25)	71.40 (67.63, 75.39)

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Characteristic	Blood Total Mercury (µg/L)	Total Cholesterol (mg/dL)	HDL Cholesterol (mg/dL)	LDL Cholesterol (mg/dL)	Triglycerides (mg/dL)
	GM† (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	GM† (95% CI)
Other Race	0.47 (0.38, 0.56) **	151.42 (142.84, 160.00)	50.74 (48.15, 53.32)	86.30 (78.85, 93.76)	62.29 (55.76, 69.58)
Country of birth					
Native Born (Reference)	0.42 (0.39, 0.46)	155.20 (153.19, 157.21)	52.71 (51.93, 53.48)	87.73 (86.02, 89.44)	63.60 (61.58, 65.69)
Foreign Born and less than 5 years	0.79 (0.61, 1.03) **	165.38 (153.39, 177.38)	54.43 (49.49, 59.38)	94.43 (86.05, 102.82)	69.22 (58.07, 82.50)
Foreign Born and greater than 5 years	0.57 (0.46, 0.70) **	154.16 (148.60, 159.72)	53.11 (50.04, 56.18)	85.89 (80.89, 90.90)	65.85 (58.21, 74.49)
Average daily intake of DHA & EPA from fish and shellfish					
None reported	0.30 (0.28, 0.32) **	153.40 (150.40, 156.41)	52.43 (51.45, 53.42)	85.93 (83.15, 88.70)	65.54 (62.53, 68.70)
< median (37.4 mg/day for males and 29.0 mg/day for females)	0.46 (0.42, 0.51)	156.43 (153.7, 159.16)	52.72 (51.39, 54.04)	88.95 (86.57, 91.32)	63.15 (59.53, 66.98)
≥ median (37.4 mg/day for males and 29.0 mg/day for females)	0.72 (0.64, 0.80)	157.65 (153.63, 161.67)	53.42 (52.05, 54.80)	89.52 (86.30, 92.73)	62.77 (60.35, 65.28)
Serum selenium µg/L)					
< median (186.64 µg/L)	0.44 (0.39, 0.48)	152.67 (150.09, 155.25) **	53.29 (52.32, 54.26)	85.26 (83.11, 87.41) **	60.57 (57.97, 63.29) **
≥ median (186.64 µg/L)	0.45 (0.41, 0.49)	158.41 (156.04, 160.78)	52.34 (51.13, 53.56)	90.48 (88.45, 92.50)	67.56 (64.48, 70.78)

Data were presented as mean (95% CI), or

† geometric mean (95% CI)

HDL, High density lipoproteins; LDL, Low density lipoproteins.

** $p < 0.05$

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Table 3

Beta estimates and 95% CI for association of blood total mercury (μg/L) with lipid profiles (mg/dL) in US adolescents, stratified by sex, National Health and Nutrition Examination Survey Database, 2011–2018

Lipid profiles	Blood Total Mercury (μg/L)†					
	Continuous β (95% CI)	Quartile 1 β (95% CI)	Quartile 2 β (95% CI)	Quartile 3 β (95% CI)	Quartile 4 β (95% CI)	p for trend (Quartile)
Female;						
Total Cholesterol (mg/dL) **						
Level 1	4.66 (1.73, 7.58) **	Ref	2.05 (−3.63, 7.72)	2.14 (−3.15, 7.43)	10.2 (3.71, 16.7) **	0.02
Level 2	4.15 (1.27, 7.03) **	Ref	1.44 (−4.33, 7.21)	1.61 (−3.77, 6.99)	9.09 (2.79, 15.4) **	0.03
Level 3	3.34 (0.19, 6.50) **	Ref	1.09 (−4.79, 6.97)	0.69 (−4.74, 6.13)	7.54 (0.76, 14.3) **	0.11
HDL Cholesterol (mg/dL) **						
Level 1	0.61 (−0.87, 2.09)	Ref	1.14 (−1.80, 4.08)	−0.02 (−2.42, 2.38)	1.46 (−1.47, 4.40)	0.57
Level 2	0.36 (−0.97, 1.69)	Ref	0.89 (−1.78, 3.56)	−0.18 (−2.29, 1.92)	1.19 (−1.62, 3.99)	0.55
Level 3	0.32 (−1.07, 1.70)	Ref	0.87 (−1.82, 3.56)	−0.23 (−2.46, 2.00)	1.11 (−1.66, 3.89)	0.54
LDL Cholesterol (mg/dL) **						
Level 1	1.60 (−1.45, 4.65)	Ref	−3.30 (−9.14, 2.55)	3.17 (−2.90, 9.25)	−0.01 (−6.17, 6.16)	0.19
Level 2	1.36 (−1.61, 4.33)	Ref	−3.40 (−9.12, 2.33)	2.30 (−3.84, 8.43)	−0.60 (−6.64, 5.44)	0.24
Level 3	0.50 (−2.65, 3.64)	Ref	−3.84 (−9.68, 2.00)	1.13 (−5.13, 7.40)	−2.48 (−9.12, 4.15)	0.25
Triglycerides (mg/dL)†						
Level 1	0.01 (−0.03, 0.06)	Ref	0.05 (−0.06, 0.16)	−0.0002 (−0.09, 0.09)	0.05 (−0.07, 0.16)	0.73
Level 2	0.001 (−0.04, 0.04)	Ref	0.02 (−0.07, 0.12)	−0.04 (−0.14, 0.06)	0.01 (−0.10, 0.11)	0.73
Level 3	0.01 (−0.04, 0.05)	Ref	0.03 (−0.07, 0.12)	−0.03 (−0.13, 0.07)	0.01 (−0.10, 0.13)	0.76
Male;						
Total Cholesterol (mg/dL) **						
Level 1	1.20 (−1.16, 3.56)	Ref	2.26 (−2.47, 6.99)	5.20 (−0.22, 10.62)	1.12 (−4.45, 6.69)	0.18
Level 2	1.18 (−1.14, 3.49)	Ref	2.27 (−2.61, 7.14)	5.11 (−0.46, 10.67)	0.68 (−4.80, 6.15)	0.21
Level 3	1.27 (−1.43, 3.98)	Ref	2.24 (−2.65, 7.12)	5.03 (−0.94, 11.01)	0.53 (−5.50, 6.55)	0.21
HDL Cholesterol (mg/dL) **						
Level 1	0.59 (−0.60, 1.78)	Ref	−0.60 (−3.12, 1.91)	1.33 (−1.53, 4.18)	0.39 (−2.15, 2.94)	0.36
Level 2	0.60 (−0.51, 1.71)	Ref	−0.72 (−3.04, 1.61)	1.35 (−1.19, 3.90)	0.79 (−1.60, 3.17)	0.14

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Lipid profiles	Blood Total Mercury (μg/L)†					
	Continuous β (95% CI)	Quartile 1 β (95% CI)	Quartile 2 β (95% CI)	Quartile 3 β (95% CI)	Quartile 4 β (95% CI)	p for trend (Quartile)
Female;						
Level 3	0.18 (−0.96, 1.33)	Ref	−0.89 (−3.19, 1.41)	0.91 (−1.56, 3.39)	−0.13 (−2.52, 2.25)	0.39
LDL Cholesterol (mg/dL) **						
Level 1	1.73 (−0.68, 4.15)	Ref	3.03 (−2.79, 8.85)	4.02 (−0.72, 8.76)	3.93 (−1.97, 9.83)	0.40
Level 2	1.58 (−0.90, 4.06)	Ref	2.72 (−2.82, 8.25)	3.51 (−1.06, 8.08)	3.39 (−2.42, 9.21)	0.48
Level 3	1.64 (−1.24, 4.52)	Ref	2.74 (−2.61, 8.10)	3.55 (−1.15, 8.25)	3.46 (−2.73, 9.65)	0.48
Triglycerides (mg/dL) †**						
Level 1	0.01 (−0.04, 0.06)	Ref	0.11 (−0.04, 0.24)	0.11 (−0.01, 0.22)	0.06 (−0.06, 0.18)	0.32
Level 2	−0.01 (−0.06, 0.04)	Ref	0.05 (−0.07, 0.17)	0.05 (−0.05, 0.15)	−0.01 (−0.12, 0.09)	0.52
Level 3	−0.004 (−0.06, 0.05)	Ref	0.05 (−0.07, 0.17)	0.06 (−0.05, 0.16)	0.0004 (−0.11, 0.12)	0.54

Analytical sample for total cholesterol and HDL-cholesterol was 2,948 (males=1,537, females=1,411).

Analytical sample for LDL cholesterol and triglyceride was 1,390 (males=709, females=681).

HDL, High density lipoproteins; LDL, Low density lipoproteins. Ref, reference level.

† Blood total mercury and triglycerides were log transformed.

** Estimates for associations of TBHg with TC, HDL-C and LDLC can be interpreted as β* log(1.X). E.g. β* log(1.10) for a 10 μg/L increase in TBHg concentration while estimates for the association of TBHg with triglyceride can be interpreted as 1.10^β for a 10 μg/L increase in TBHg concentration. Level 1 model controlled for age, poverty income ratio, country of birth and race.

Level 2 model controlled for covariates in level 1 plus survey cycles, body mass index, serum selenium concentration and age at menarche (females only).

Level 3 model controlled for covariates in level 2 plus average daily intake of DHA & EPA from fish and shellfish.

TBHg quartile levels in females – quartile 1: < 0.21 μg/L; quartile 2: 0.21 μg/L - 0.38 μg/L; quartile 3: 0.39 μg/L - 0.70 μg/L; quartile 4: > 0.70 μg/L. TBHg quartile levels in males – quartile 1: < 0.21 μg/L; quartile 2: 0.21 μg/L - 0.38 μg/L; quartile 3: 0.39 μg/L - 0.72 μg/L; quartile 4: > 0.72 μg/L.

** $p < 0.05$.

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Table 4:

Odds ratios and 95% CI for association of blood total mercury (μg/L) with dyslipidemia in US adolescents stratified by sex, National Health and Nutrition Examination Survey Database, 2011–2018 (n=1,390)

	Blood Total Mercury (μg/L)†					
	Continuous OR (95% CI) n=1,390	**Quartile 1 OR (95% CI) n=404**	**Quartile 2 OR (95% CI) n=293**	**Quartile 3 OR (95% CI) n=345**	**Quartile 4 OR (95% CI) n=348**	**p for trend (Quartile)**
Male						
Level 1	0.98 (0.76, 1.25)	Ref.	1.05 (0.64, 1.71)	0.95 (0.57, 1.59)	1.00 (0.56, 1.79)	0.99
Level 2	0.94 (0.71, 1.24)	Ref.	0.98 (0.59, 1.62)	0.82 (0.49, 1.40)	0.89 (0.48, 1.64)	0.89
Level 3	0.90 (0.66, 1.22)	Ref.	0.94 (0.56, 1.57)	0.78 (0.45, 1.34)	0.81 (0.42, 1.54)	0.81
Female						
Level 1	1.25 (0.92, 1.71)	Ref.	0.81 (0.46, 1.44)	1.17 (0.70, 1.98)	1.35 (0.66, 2.75)	0.46
Level 2	1.25 (0.91, 1.72)	Ref.	0.83 (0.47, 1.48)	1.16 (0.70, 1.94)	1.35 (0.65, 2.78)	0.54
Level 3	1.15 (0.85, 1.57)	Ref.	0.80 (0.44, 1.43)	1.05 (0.62, 1.76)	1.13 (0.55, 2.35)	0.74

Dyslipidemia: LDL-C ≥ 130 mg/dL or TC levels ≥ 200 mg/dL or TG levels ≥ 130 mg/dL or HDL-C levels < 40.

†Blood total mercury was log transformed. Ref, reference level.

Level 1 model controlled for age, poverty income ratio, country of birth and race.

Level 2 model controlled for covariates in level 1 plus survey cycles, body mass index, serum selenium concentration and age at menarche (females only).

Level 3 model controlled for covariates in level 2 plus average daily intake of DHA & EPA from fish and shellfish.

TBHg quartile levels in females – quartile 1: < 0.21 μg/L; quartile 2: 0.21 μg/L - 0.38 μg/L; quartile 3: 0.39 μg/L - 0.70 μg/L; quartile 4: > 0.70 μg/L.

TBHg quartile levels in males – quartile 1: < 0.21 μg/L; quartile 2: 0.21 μg/L - 0.38 μg/L; quartile 3: 0.39 μg/L - 0.72 μg/L; quartile 4: > 0.72 μg/L.