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Methyl mercury, but not inorganic mercury, associated with higher blood pressure during pregnancy

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ABSTRACT

Prior studies addressing associations between mercury and blood pressure have produced inconsistent findings; some of this may result from measuring total instead of speciated mercury. This cross-sectional study of 263 pregnant women assessed total mercury, speciated mercury, selenium, and n-3 polyunsaturated fatty acids in umbilical cord blood and blood pressure during labor and delivery. Models with a) total mercury or b) methyl and inorganic mercury were evaluated. Regression models adjusted for maternal age, race/ethnicity, prepregnancy body mass index, neighborhood income, parity, smoking, n-3 fatty acids and selenium. Geometric mean total, methyl, and inorganic mercury concentrations were 1.40 μg/L (95% confidence interval: 1.29, 1.52); 0.95 μg/L (0.84, 1.07); and 0.13 μg/L (0.10, 0.17), respectively. Elevated systolic BP, diastolic BP, and pulse pressure were found, respectively, in 11.4%, 6.8%, and 19.8% of mothers. In adjusted multivariable models, a one-tertile increase of methyl mercury was associated with 2.83 mmHg (0.17, 5.50) higher systolic blood pressure and 2.99 mmHg (0.91, 5.08) higher pulse pressure. In the same models, an increase of one tertile of inorganic mercury was associated with −1.18 mmHg (−3.72, 1.35) lower systolic blood pressure and −2.51 mmHg (−4.49, −0.53) lower pulse pressure. No associations were observed with diastolic pressure. There was a non-significant trend of higher total mercury with higher systolic blood pressure. We observed a significant association of higher methyl mercury with higher systolic and pulse pressure, yet higher inorganic mercury was significantly associated with lower pulse pressure. These results should be confirmed with larger, longitudinal studies.

1. Introduction

Cardiovascular health is a major public health concern. More than 1 in 3 United States adults have some form of cardiovascular disease; cardiovascular disease and stroke are the leading cause of mortality in the United States (Lloyd-Jones et al., 2010). Cardiovascular disease risk factors such as exercise, weight, and blood pressure are also of high prevalence; therefore, the burden of cardiovascular disease is expected to continue over the next several decades (Lloyd-Jones et al., 2010). Of particular concern is hypertension among pregnant women, as hypertension during this period has been associated with future cardiovascular disease risk (Wilson et al., 2003).

Methyl mercury is a recognized neurological toxin; however, cardiovascular toxicity may also be an important outcome of mercury exposure (Virtanen et al., 2007). The main route of methyl mercury exposure is from consumption of fish and seafood. Literature on the relationship of mercury exposure with cardiovascular related outcomes showed inconsistent results. A large cohort study (n=1857) from Finland identified significant associations between total mercury in hair and acute cardiac death (Virtanen et al., 2012a). Myocardial

Abbreviations: LOD, Limit of detection; BMI, Body mass index; CDC, United States Centers for Disease Control and Prevention; CI, Confidence interval; DBP, Diastolic blood pressure; DHA, Docosahexaenoic acid; EtHg, Ethyl mercury; EPA, Eicosapentaenoic acid; Hg, Mercury; ICP-DRC-MS, Inductively coupled plasma dynamic reaction cell mass spectrometry; ICP-MS, Inductively coupled plasma mass spectrometry; IHg, Inorganic mercury; MeHg, Methyl mercury; ND, Not detected; PP, Pulse pressure; SBP, Systolic blood pressure; THg, Total mercury; THREE, Tracking Health Related to Environmental Exposures; US EPA, United States Environmental Protection Agency

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infarction was also associated with total toenail mercury in a multinational case-control study (Guallar et al., 2002). However, several nested case-control studies showed no association of total mercury in toenails (Mozaffarian et al., 2011; Yoshizawa et al., 2002), or blood with coronary heart disease, myocardial infarction, or cardiovascular disease.

A similar, mixed pattern appears with more subtle changes in cardiovascular health. Some studies have identified a link between total mercury in blood (Valera et al., 2009), hair (Yorifuji et al., 2010), or toenails (Choi et al., 2009) and worsening of cardiovascular risk factors such as blood pressure and heart rate variability; other studies using total whole blood (Nielsen et al., 2012) and urinary mercury (Park et al., 2013) have shown protective results. Of note is that none of the studies above focused on pregnant women. Although pregnancy is a lifestage of heightened susceptibility for cardiovascular risk, very few studies have focused on the potential effect of mercury exposures on cardiovascular health during pregnancy (Vigeh et al., 2006).

The differences in observed impact from mercury exposure noted above may be explained in part by differences in study methodology. In addition to mercury, fish and seafood are also sources of selenium and n-3 polyunsaturated fatty acids (n-3 PUFAs); both of these may provide benefits and act as negative confounders (Choi et al., 2008). It is known that different chemical forms of mercury have different toxicokinetics (Clarkson and Magos, 2006). However, studies to date mostly have relied on measurements of total mercury as a proxy for specific forms of mercury, which may result in errors of attribution. Additionally, the extent to which selenium and n-3 PUFAs have been included in the literature is variable; this makes it difficult to compare the studies to each other as well as to understand the true relationship of methyl mercury and cardiovascular risk (Karagas et al., 2012).

The goal of this research is to determine the association of total, methyl and inorganic mercury with blood pressure, while accounting for the potential for negative confounding by selenium and n-3 PUFAs. To evaluate this goal, we completed a cross-sectional study of pregnant women from Baltimore, Maryland.

2. Materials and methods

The Baltimore THREE Study (Tracking Health through Environmental Exposures) is a cross-sectional birth cohort. This study was conducted with approval of the Johns Hopkins School of Medicine Institutional Review Board as well as the Johns Hopkins Department of Gynecology and Obstetrics' Maternal and Fetal Research Committee.

Details on the study design and data management have been published previously (Wells et al., 2012). Briefly, inclusion criteria included having a singleton birth at the Johns Hopkins Hospital from November 2004-March 2005 and availability of sufficient umbilical cord blood to conduct laboratory analyses; 300 out of 612 births met these criteria. Given our exclusion of infants from multiple births, and the fact that low birthweight infants were more likely to have insufficient cord blood for laboratory analyses, this study population had somewhat fewer low birth weight infants compared to all births at the hospital. Otherwise, the study population was representative of all births at Johns Hopkins Hospital during this time. However, it was not a representative sample of the community as a whole (Herbstman et al., 2007). For the current analysis, births without data on total mercury (n=8), smoking status (n=1), median household income (n=4), umbilical cord serum fatty acids (n=12), selenium (n=11), and blood pressure (n=3) were also excluded from analyses. Therefore, a total of 263 mothers were included in analyses.

Umbilical cord blood was collected by trained clinical staff, using standardized techniques (Witter et al., 2001). Metals were analyzed at the Inorganic and Radiation Analytical Toxicology Branch at the United States Centers for Disease Control and Prevention (CDC) using inductively coupled plasma mass spectrometry (ICP-MS). The method for total mercury (THg) was assessed using whole blood SRM955c standards; accuracy of measurements with this method are within 5% of target values (Jones et al., 2017). The limit of detection (LOD) for THg in our samples was 0.33 μg/L (THg); the six samples < LOD were replaced with LOD/√2 for analyses.

Additionally, inorganic mercury (IHg), methyl mercury (MeHg) and ethyl mercury (EtHg) were measured using high performance liquid chromatography linked with inductively coupled plasma mass spectrometry, this method is described in detail previously (Sommer et al., 2014; Verdon et al., 2008). Only one infant had an EtHg level > the LOD, so EtHg values are not included in the this analysis. The other LODs for mercury compounds were 0.48 μg/L (MeHg) and 0.75 μg/L (IHg). The method accuracy was verified using whole blood reference materials from NIST (SRM 955c Level 3) and Centre de Toxicologie du Québec whole blood proficiency testing samples. The relative standard deviations were 8.3% (IHg) and 6.3% (MeHg); results analyzed by our method compared to certified target values with a slope of 1.05 and r^2=0.986, all falling within certified ranges (Sommer et al., 2014).

There were 44 MeHg and 201 IHg values below the limit of detection (LOD). Because MeHg and IHg had a high proportion (> 10%) of values < LOD, we first imputed values < LOD using values that were observed via spectrometry even while being below the LOD; 24 of MeHg and 125 of IHg observations met this criterion. The remainder of values, 20 (7.6%) MeHg and 76 (28.9%) IHg observations that were not quantifiable (i.e., not detected) were imputed using the lowest observed value divided by the square root of two. Imputed values have a greater coefficient of variation in comparison to values > LOD. To minimize the potential impact of this uncertainty, mercury measurements were classified as tertiles for analyses (high/medium/low). Sensitivity analyses using mercury as a continuous variable were also conducted to confirm that the use of tertiles did not substantially influence our results.

Continuous blood pressure measurements were collected as part of routine care during labor and delivery with a General Electric Corometrics model 120 series fetal monitor (GE Healthcare, Little Chalfont, UK). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the time of admission to labor and delivery was extracted from medical records, as described previously (Wells et al., 2012). Elevated blood pressure was defined as SBP ≥140 mmHg or DBP ≥90 mmHg; given the differences in recommended data collection used in this study, these were not considered tantamount to the presence of hypertension. Pulse pressure (PP) was calculated from both the average and maximum estimates as SBP minus DBP. PP ≥60 mmHg was considered elevated. Medical records were used to identify diagnoses of chronic hypertension, pregnancy-related hypertension, and use of hypertensive medications; having any of these was considered having hypertension during pregnancy.

Umbilical cord serum was used to assess serum selenium, cotinine, and fatty acids. The CDC's Inorganic and Radiation Analytical Toxicology Branch measured umbilical cord serum selenium concentrations using inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS); these measures were verified using serum reference materials. The LOD for selenium was 5 μg/L; all measurements were > LOD. Our previous work suggested that there is a nonlinear association between selenium and blood pressure; therefore, selenium was incorporated into models using a linear spline with a knot at the median value (70 μg/L) (Wells et al., 2012). CDC laboratories assessed umbilical cord serum cotinine using liquid chromatography in conjunction with atmospheric pressure ionization mass spectrometry; LOD was 0.015 ng/mL.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in umbilical cord serum were determined at the National Institute of Alcohol Abuse and Alcoholism using automated fast gas chromatography (Lin et al., 2012). Accuracy for both fatty acids are > 99% or higher in comparison to the conventional methods (Lepage and Roy assay), and both within-run and between-run coefficient of variance was < 5% (Lin et al., 2012). All fatty acid values were above the LOD, which was