ABSTRACT

Title of Thesis: MATERNAL MERCURY EXPOSURE, SEASON OF CONCEPTION AND ADVERSE BIRTH OUTCOMES IN AN URBAN IMMIGRANT COMMUNITY IN NEW YORK CITY

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Adverse birth outcomes such as preterm birth (PTB: < 37 weeks gestation) and low birthweight (LBW: <2500g) result in severe infant morbidity and mortality. In the United States, there are racial and ethnic differences in the prevalence of preterm birth and low birth weight. The focus of this study is to examine the association between frequency of maternal fish consumption during pregnancy, prenatal mercury exposure, and season of conception with preterm birth and low birth weight in a population of African-American, Caribbean and West Indian women in an urban immigrant community in New York City. The proportion of preterm births and low birth rates in this cohort of women was higher than reported in other studies of African-American and Caribbean births in New York City. There was no association between maternal urinary mercury or infant cord blood concentrations and either LBW or preterm birth. Infants conceived in winter (December, January, February) were at increased odds of low birthweight.

MATERNAL MERCURY EXPOSURE, SEASON OF CONCEPTION AND ADVERSE BIRTH OUTCOMES IN AN URBAN IMMIGRANT COMMUNITY IN NEW YORK CITY

by

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Dedication

This thesis is dedicated to my parents who
instilled a love of scholarship and life-long learning
and to my husband and children for their unconditional love
and support that made attaining this degree possible.

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Chapter 1: Introduction

Adverse birth outcomes such as preterm birth (< 37 weeks gestation), low birthweight (LBW: <2500g) and intrauterine growth restriction (IUGR) can result in severe infant morbidity and mortality.[1] In 2007, LBW infants had a mortality rate 25 times higher than non-LBW infants. Of the over four million births reported that year, 8.2% of infants born weighed less than 2500g, but these infants accounted for 68.7 % of all infant deaths.[2] While there are examples in which LBW infants have enhanced survival compared to non-LBW infants,[3] in the acute neonatal and post- natal period LBW is associated with respiratory distress syndrome, necrotizing enterocolitis, and death.[1] Long term conditions associated with preterm birth and LBW include blindness, deafness, hydrocephaly, mental retardation and cerebral palsy, end-stage renal disease, diabetes, hypertension, coronary heart disease, cerebrovascular disease, increased risk of asthma, and hospitalization for respiratory disease as adults. [1, 4-11]

Risk factors for preterm birth include previous preterm birth, black race, periodontal disease, and low maternal body-mass index.[12] Infant birthweight is impacted by fetal, maternal and placental factors and their interactions. LBW outcomes are most frequently the result of intra-uterine malnutrition caused by inadequate maternal-placental-fetal interchange and poor placental circulation.[13] Genetic, demographic, and socioeconomic factors, pre-existing medical conditions, complications during pregnancy, inadequacies in prenatal care, as well as consumption of tobacco, caffeine, illicit drugs and alcohol are associated with the risk of LBW.[13-17] In addition exposures to pollutants such as organochlorines, formaldehyde, nitrogen dioxide (NO_2), particulate matter ($PM_{2.5}$, PM_{10}),

and lead during pregnancy have been shown to be associated with depressed fetal growth or preterm birth.[13, 18-23]

In the United States, there are racial and ethnic differences in the prevalence of LBW and infant mortality.[2, 24-28] In 2007, non-Hispanic blacks had the highest rate of all-cause infant mortality (13.31 per 1000 live births) compared with all other racial ethnic groups examined. Non-Hispanic blacks also had the highest percentage of LBW infants (14.0%) compared to other racial ethnic groups. Infants of non-Hispanic black mothers had mortality rates associated with LBW nearly three times the rate for non-Hispanic white mothers.[2] Disorders related to short gestation and LBW were the leading causes of infant deaths for non-Hispanic black women as compared to non-Hispanic white and Hispanic women for whom congenital malformations, deformations and chromosomal abnormalities were the leading cause.[2]

For immigrant women, maternal place of birth (inside or outside the present country of residence) influences outcomes of low birth weight and preterm birth.[29] In some cases, recently migrated women have lower rates of adverse birth outcomes [25, 30, 31] but this advantage decreases with increasing years of residence and acculturation.[32] Cultural and dietary practices can vary among different ethnic groups. A plausible explanation for this observation may be changes in lifestyles, including dietary habits. For example, Caribbean populations have been shown to have a high level of fish and seafood intake compared to other populations in the United States.[33] Fish consumption has been positively and negatively associated with birthweight.[34] Increasing frequency of fish and shellfish consumption is also associated with an increased exposure to mercury.[35, 36] Indeed, the majority of mercury exposure is due to consumption of fish

and shellfish.[37] Mercury is a known neurotoxicant and neurodevelopmental disorders resulting from prenatal exposure to mercury have been documented, [37-41] however the impact of mercury and frequency of fish consumption on LBW is not defined. [36, 42] It is possible that the negative aspects of mercury exposure are outweighed by the benefits of fish and shellfish consumption rich in ω-3 fatty acids. Others have found that season of birth and season of conception have been associated with adverse birth outcomes.[43, 44]

The focus of this study is to examine the association between frequency of fish consumption, prenatal mercury exposure, and season of conception and preterm birth and LBW in a population of African-American, Caribbean and West Indian women in an urban immigrant community in New York City. Studies of racial ethnic groups in New York City have reported increased odds of low birth weight and preterm birth in some racial ethnic groups including immigrant communities.[24] This study is the first to examine specific exposures and risk of LBW and preterm in this New York City community.

Chapter 2: Background

2.1 Fish Consumption and Pregnancy

2.1.1 Omega-3 fatty acids and Adverse Birth Outcome

Omega – 3 fatty acids (also known as *n-3* or ω-3 fatty acids) are essential long chain fatty acids which are not synthesized by the human body and must be acquired through food. Omega – 3 fatty acids have the first double bond (sharing of two pairs of electrons) between the third and fourth carbons from the terminal end of the molecule. Seafood is a source of ω-3 fatty acids, including docosahexaenoic acid (DHA), an important structural component of the brain and the eye.[45] Prostaglandins, leukotrienes and other eicosanoids formed from ω-3 and ω-6 (fatty acids with the initial carbon – carbon double bond at the 6th carbon from the terminus) fatty acids are important in normal and pathologic gestation and parturition. Eicosanoids formed from ω-6 fatty acids are more potent than those formed from ω-3 fatty acids and have greater roles in inducing uterine contractions and cervical ripening. The imbalance of ω-3 to ω-6 fatty acids in the modern diet is suggested to have a role in preterm birth .[46] During the third trimester of pregnancy uptake of DHA is most rapid; additional consumption of foods high in DHA during the third trimester of pregnancy may be beneficial to the health of the developing fetus,[45] though the association between fish consumption and fetal growth and pregnancy outcomes is inconsistent. Some studies have shown an association of seafood intake with beneficial fetal outcomes at least among some sub-groups,[35, 47, 48] while others have shown no association or negative associations with outcome measurements.[49, 50] Supplementing pregnancies with ω-3 fatty acids either throughout the pregnancy or only in the third trimester has also had mixed results. In a systemic

review and meta-analysis Salvig et al. 2011 reported reduced rate of preterm birth and increased birth weight with marine ω-3 fatty acid supplementation during pregnancy, while Brantsaeter et al. 2012 found a negative association between ω-3 supplementation in pregnancy and infant head circumference. [47, 51] Inconsistencies in results may be explained by differences in the types of ingested seafood (e.g. fatty fish vs. lean muscle fish as in Halldorrson et al. 2007,[50] source and duration of supplementation with ω-3 fatty acids, or concomitant exposure to heavy metals and toxicants such as mercury and polychlorinated biphenyl compounds (PCBs) that results from fish consumption.[52, 53]

2.2 Mercury Exposure and Adverse Birth Outcome

Mercury (Hg) exists in the environment in three forms: elemental, inorganic, and organic mercury. Elemental mercury is the form found most often in the atmosphere. Inorganic and organic mercury are the forms found in water, soil, sediments, or plants and animals. Inorganic mercury exists either as Hg^{2+} as in mercuric (II) chloride ($HgCl_2$), mercuric (II) sulfide (HgS), or mercurous (I) chloride (such as Hg_2CL_2, also known as the natural metal calomel, a yellow fever treatment in 18th century). Organic mercury exists as forms of mercuric (II) acetate, methylmercuric chloride (CH_3HgCl), dimethyl mercury (C_2H_6Hg) or phenylmercuric acetate ($C_8H_8HgO_2$) .[37, 54] Organic and inorganic forms are odorless and exist in +2 valence state (mercurous chloride exists as Hg_2^{2+}). Metallic mercury is a heavy, mobile liquid metal; solid mercury is ductile and malleable.

Mercury is ubiquitous in the earth's crust. Elemental and inorganic mercury are released during natural processes such as volcanic activity and anthropogenic industrial processes (e.g. coal-burning power generation, gold ore refinement.[55] Emitted mercury settles in the environment through physical sedimentation, serving as a source of direct exposure to

humans or animals. Simulated models estimate that the largest deposition of mercury occurs in the northeast.[54] When mercury particles reach aquatic sediments, bacteria present in the sediments transform the inorganic mercury into methylated organic mercury compounds which are incorporated into aquatic plants that grow in the contaminated sediments. Aquatic animals may then ingest the sediment directly or the contaminated plants. Methylmercury binds to muscle tissues in the fish and bioaccumulates through the aquatic life-cycle and predator-prey relationship. Concentrations in fish tissue can be as high as 1,800 to 80,000 times that of the surrounding water [55] and predatory fish may contain the highest concentrations of methylmercury, serving as a main source of methylmercury exposure to humans.[37, 54] High concentrations of mercury may be found in shark, large tuna, sword fish, marlin and king mackerel. These fish contain mercury that may be 10-20 times higher than lower concentration fish such as herring, cod, Pollack, or shellfish such as shrimp or scallops.[38]

Due to the malleability of metallic mercury, it is also a component of dental amalgam used in dental restoration. Elemental mercury is then slowly released from the amalgams and inhaled as mercury vapor, swallowed as a liquid form, or converted to a mercuric salt that is swallowed or absorbed by the oral mucosa.[37, 56] Occupational exposures can occur from industries that use liquid mercury such as the manufacture of thermometers and electrical and mechanical devices or formally, seed fumigation. When liquid mercury vaporizes, harmful liquid mercury vapors may be inhaled and absorbed through the lung.[37] Elemental mercury is used in some traditional Asian medicines, skin lightening creams and in some religious ritualistic objects such as those sold in *botanicas*

important in certain Latino and Afro-Caribbean traditions, including Santería, Palo, Voodoo, and Espiritismo.[37, 38, 57, 58]

Any metallic or inorganic mercury absorbed by the body is oxidized in the red blood cells, lungs and liver to a divalent inorganic cation.[37] This divalent inorganic cation may then either be reduced to the metallic or monovalent form which may be eliminated through respiration. Organic forms of methylmercury or phenyl mercury may also be converted to the divalent cationic form (Hg^{2+}) which can then be chemically reduced and eliminated through the inorganic pathway.[37] In the body, 90% of methylmercury is associated with red blood cell hemoglobin.[59] Mercury is excreted in the urine as inorganic Hg^{2+} and may be used as a proxy for exposure to mercury vapor and inorganic Hg sources. Inorganic mercury is also excreted in the feces as glutathione conjugates. Genetic polymorphisms that result in reduced availability of glutathione can result in prolonged retention of mercury in the body.[60] Demethylation of methylmercury may result in increased urinary mercury; high urinary mercury has been reported in individuals with high methylmercury intake.[61] The half-life of mercury in the urine is variable, ranging from 20 days to 90 days.[62] Adverse health effects in study populations have been reported at mean urinary concentrations of 20μg/L.[58] Background levels for urinary mercury range are considered to be 4 μg/L with 20 μg/L as the upper bound.[37]

In whole blood, the majority of mercury is methylmercury unless an acute exposure to inorganic mercury has recently occurred.[38, 63] Methylmercury has a half-life of 50 days in the blood.[59] Inorganic mercury is reported to have a half-life of 2-4 days in the blood though a slower elimination may occur that results in a half-life of 2-3 weeks.[38]

Adverse health effects from acute, intermediate or chronic metallic, inorganic or organic mercury exposure are numerous and potentially fatal. Exposure to metallic or inorganic mercury vapors or ingestion of metallic, inorganic or organic mercury results in toxicity to multiple organs, including the respiratory, hepatobiliary, urinary, gastrointestinal and nervous systems.[37, 64]

Neurologic effects may be severe as the central nervous system is extremely sensitive to toxicity from metallic and inorganic mercury exposure. Symptoms of mercury toxicity include tremors, emotional lability, insomnia, memory loss, neuromuscular changes, headaches, polyneuropathy, and cognitive dysfunction.[37] Neurologic toxicity may also occur after exposure to organic mercury vapors.

While occupational and accidental exposure to mercury is severe and may be fatal, the main exposure route as noted before is consumption of methylmercury concentrated in seafood. Seafood consumption is estimated as the source for 95% of methylmercury concentrations in the U.S. population.[38] In contrast to metallic and inorganic mercury that are very poorly absorbed through the gastrointestinal tract, 95% of methylmercury in ingested seafood is absorbed and distributed throughout the body within 30 hours.[55] Of the total amount distributed, 5% remains in the blood; double that amount is distributed to the brain. Methylmercury is limitedly reduced to inorganic mercury in the intestines (about 1% of body burden per day) while enterohepatic recycling allows for continued exposure. The majority (90%) of methylmercury is excreted in the feces, with the remainder excreted in the urine (10%).[55] Methylmercury interferes with neuronal division and migration, binds with microtubules impeding neuron development, and

binds to and creates changes in the structure of cellular DNA and RNA. Inorganic mercury salts do not pass through the blood-brain barrier easily.[55]

Developmental neurotoxicity of fetuses with resulting cognitive defecits in children has been documented in multiple studies and accident reports.[65, 66] Methylmercury is readily absorbed through the blood, crosses the placental membranes and then is distributed to the fetal brain which is exquisitely sensitive to the effects of methylhemoglobin.[37, 54] Using endpoints derived from studies of children exposed prenatally in the Faroe Islands, the Seychelles, and New Zealand, the EPA has calculated a reference dose of 0.1 μg/kg/day. Exposure to this daily dose would result in a maternal blood concentration of 5.8 μg/L methylmercury.[67] The ratio of methylmercury found in infant cord blood to maternal blood has been found to be 1.7,[38] therefore, to provide for a maximum of 5.8 μg/L methylmercury in infant cord blood requires that maternal blood methylmercury levels do not exceed 3.5 μg/L methylmercury resulting in a reduced reference dose of 0.058 μg/kg/day. Blood and hair mercury levels have been shown to increase with increasing fish consumption.[35, 65]

Studies of the association between mercury and adverse pregnancy outcomes have been inconsistent.[35] The association of mercury with fetal growth may not cease at parturition. Kim et al. (2011) found that at the highest quartile of mercury concentrations in late pregnancy (28-42 gestational weeks) maternal blood ($\geq$ 4.1 μg/L) and infant cord blood ($\geq$7.0 μg/L) at birth were inversely associated with infants' attained weight during the first 24 months of an infant's life.[42]

2.3 Season of Conception and Adverse Birth Outcome

The use of season of conception or birth serves as a proxy for exposures that vary temporally throughout the year. Temperature, air pollution [68] due to activities such as home heating in cooler months, increased industrial activity and nutritional habits and intake surrounding harvest periods or times of low food availability are examples of exposure that may influence a seasonal effect.[43, 68-70] Seasonal association with preterm birth and low birth weight has been reported in many studies, though seasonal effects vary according to latitude, the country's development status and the predominant infectious diseases for the area.[43] Vitamin D has been shown to have an association with increased risk of small for gestational (SGA) and LBW infants.[71] Serum 25-hydroxyvitamin D (25[OH]D) levels vary seasonally. Vitamin D is either consumed through diet or from the conversion of 7-dehydrocholoesterol into previtamin D in the skin, a process that requires ultraviolet B spectrum exposure. Endogenous cutaneous synthesis of cholecalciferol is reduced in individuals with increased skin pigmentation and low skin reflectance and is also affected by other modifiers such as sunscreen use, age and factors which decrease UVB absorption.[72] In one study of neonates, African-American infants had mean cord blood 25[OH]D levels almost half the mean levels of Caucasian infants (10.5 +/- 6.0 ng/ml and 19.5 +/- 9.6 ng/ ml); in both groups infants had lower cord blood 25[OH]D if born in November to March when compared to April to October.[73] In addition, for all seasons 65.5% of African American infants and 24% of Caucasian infants were deficient in vitamin D (25[OH]D <11 ng/ml).[73]

Chapter 3: Methods

3. 1 Study Description

A perspective study of pregnant women was conducted at the University Hospital of Brooklyn's Prenatal Clinic to investigate the association between maternal exposure to several pollutants and risk of adverse birth outcomes. The full study details are described elsewhere.[74] Briefly, women were recruited from October 2007 to December 2009. To be included in the study, women were required to be between the ages of 18-45. If women consented to participation, they completed a pretested, culturally appropriate questionnaire designed in cooperation with local community groups that included Caribbean physicians. The questionnaire assessed demographic and lifestyle factors that may contribute to mercury exposure such as medical history, use of mercury-containing products in the home, use of skin-lightening creams, occupational exposures, number of dental amalgams, and use of folk medicine products such as incense or candles, religious items, altars, ritualistic powders or packets, lotions, teas or drinks, charms or medals. Fish and shellfish consumption was estimated by showing participants a pictorial chart of various fish and shellfish species and asking the women about frequency of consumption during the current pregnancy. All women were provided with educational materials that described environmental sources of mercury and methods of for avoiding mercury exposure.

During the 6th to 9th month of pregnancy participants provided a "spot" urine sample. At delivery a neonatal cord blood specimen was collected for total mercury determination. Chart review at birth provided demographic data including mother's age, country of birth and date of immigration, race and ethnic origin, marital status and education level. The

initial study protocol was approved by SUNY Downstate's Institutional Review Board (IRB) and by the New York State Department of Health's IRB. A signed informed consent was received by each participant prior to participation.

Urine mercury specimens were collected and analyzed at SUNY Downstate and the Trace Elements Section of the Laboratory of Inorganic and Nuclear Chemistry, Wadsworth Center, NYS Department of Health (DOH) using methods described previously.[74] In brief, samples collected at SUNY were separated onsite into 2 mL and 10 mL aliquots. To adjust for diurnal variations in urine dilution, the 2 milliliter aliquot of urine was measured at SUNY for urine creatinine using the Alkaline Picrate Method and a Beckman Olympus Analyzer, Model AU-2700 (Beckman Coulter, Inc, Brea, CA). The 10mL aliquot was preserved with sulfamic acid to maintain inorganic mercury during shipment to the NYS DOH for analysis. At the NYS DOH, total urine Hg was determined using inductively coupled plasma – mass spectrometry (ICP-MS) (Perkin Elmer DRC II) in standard mode (m/z=202).[74] Values below the limit of detection for urinary mercury were set to 0.045 µg/L, one half of the limit of detection of 0.09 µg/L Hg.

At delivery physicians or midwives collected neonatal cord blood for analysis. Samples were stored at 4-6^{oC} until shipment to the NYS DOH for determination of total mercury by ICP-MS in standard mode as described elsewhere. Some samples developed fibrin clots. Sonification for one hour in an ultrasonic-bath was sufficient to dissipate the micro-clots. The method detection limit for cord blood mercury was 0.24 µg/L.[74]

3.2 Statistical Analysis

The original study database included 191 mother-infant pairs that with infant date of birth. For the purpose of this study, data analysis was restricted to singleton births (n=187). Observations that did not include week of gestation at birth, infant birthweight, were missing both cord blood mercury and urine mercury or urine creatinine (n=28) were excluded, resulting in a final database of 159 observations.

Dichotomous categorical variables were coded with the outcome of interest as 1 and the reference category as 0 (e.g. born outside the US = 1, born in the US = 0; preterm birth = 1, full term birth = 0; LBW (<2500g) = 1, NLBW (>2500g) = 0, etc.). Geometric mean and median cord blood and uncorrected and creatinine-corrected urine mercury were determined for each of the study variables. Results of analysis are compared to the values found in the larger study population,[74] population-weighted NYCHANES values[57] and NHANES urinary mercury data for 2007-2008 and 2009-2010. In women who were born outside the United States, the association between cord blood and urinary mercury and years of residence and percent of life spent residing in the United States was examined. The percent of life residing in the United States was calculated as the number of days from maternal immigration to the United States until the date of delivery divided by the number of days from the mother's date of birth to the date of delivery multiplied by 100 %. The Kruskal-Goodman Gamma and Kruskal-Wallis non-parametric tests were used to measure the association between maternal age-group, infant cord blood mercury, percent of life spent in the United States and years in the US and frequency of fish intake in women born outside the United States. The Wilcoxon-rank sum test was used to

examine the association between place of birth and never or almost never eating fish with eating fish greater than one time per month.

Univariate and multivariate linear regression was used to measure the association between demographic and life-style variables and cord blood and urinary mercury. Variables that were significantly associated in univariate analysis and that retained significance in the full model were included in the multivariate models.

Unconditional logistic regression was used to investigate the association between odds of LBW or preterm birth and study variables. Univariate logistic regression was performed using all study variables. Variables that were significantly associated with the odds of LBW or preterm birth were included in a multivariate logistic regression model. Additional analysis of the association of LBW or preterm birth and cord blood and urinary mercury included maternal age and racial/ ethnic group. LBW models also included term of birth.

The association between birthweight, infant length and infant head circumference and each of the study variables was performed using univariate and multivariate linear regression. Multivariate models included variables that were significantly associated in univariate analysis. If a variable lost significance in the full model, the variable was removed. If removal of the variable resulted in a final model that explained less variance (smaller adjusted-r^2) than the full model the variable was retained. Analysis of the association of birthweight, infant head circumference, and infant length with cord and urinary mercury was performed using linear regression. Models included age group,

education attainment, racial/ ethnic group, and living with partner/ spouse. Birthweight models included term of birth.

The association between the season of conception and the odds of LBW or preterm birth was also examined using logistic regressions well as calculation of odds ratios for adverse birth events that occurred over three sequential months compared to the remainder of the year. Season of conception was determined by estimating which month pregnancy began. The beginning of pregnancy was determined by multiplying the reported number of weeks of gestation by seven and subtracting from the Stata numerical date of birth. Regression models were adjusted for preterm birth (in the LBW model), maternal age group and race/ ethnicity.

In all regression analyses, urinary mercury concentrations were controlled by using creatinine-corrected urine mercury concentrations as well as separate analyses that included urinary creatinine as a separate independent variable as suggested by Barr et al. for multiple regression analysis of population groups.[75] The inclusion of urinary creatinine in a model with uncorrected urinary mercury allows for appropriate adjustment for diurnal dilution effects while allowing independence of the statistical significance of the other model variables from the creatinine concentration.[75] Variable transformations were performed as needed in order to improve variable distributions to comply with test assumptions and improve model fit. Transformations that resulted in variables with a normal distribution or the lowest chi-square value for significant deviation from normal were used. Using this criteria, cord blood and creatinine corrected and uncorrected mercury were natural log transformed, infant head circumference was raised to the third power, and infant length and continuous birthweight were squared for analysis. In linear

regression models that included urinary creatinine, the square root of urinary creatinine was used. Appropriate post-regression analysis was performed to test for violations of model assumption, including examination of residuals for linear regression and comparisons of full logistic regression models with reduced models. Two outliers, one extremely preterm and small infant (27 weeks gestation, 33 cm length, 1105 grams) and one extremely long infant (37 weeks, 3050g and 63cm length) were excluded from the length regressions in order to comply with test assumptions. Deviations from model fit are reported as necessary.

3.3. NHANES DATA for 2007-2008 & 2009-2010

For comparison purpose, publicly available datasets of uncorrected and creatinine corrected urinary mercury in participants of 2007-2008 and 2009-2010 NHANES were obtained online. Geometric means and the 95th percentile of urinary mercury and creatinine corrected urine mercury in all women and in women between the ages of 16 and 49 were calculated using appropriate sample weights and study stratification variables necessary due to NHANES study design.

Chapter 4: Results

Study population characteristics are reported in Table 1. The majority of the study population was African-American or Caribbean/West Indian (85%), did not report special product use (92%), did not visit a botanic during pregnancy (94%), and did not use alcohol (95%) or tobacco (96%). Nineteen percent of infants were born preterm (<37 weeks) and 14 % were LBW (<2500g). Thirty-eight percent of women were under the age of 25 and 14% were over 35. Almost half (46%) had attended technical school or some college or more. Over half lived with a spouse or partner (51%) and did not have any dental amalgams (53%). Sixty-six percent of women consumed fish or shellfish at least once a week.

Median, geometric means and 95% confidence intervals for cord blood and uncorrected and corrected urinary mercury are reported in Table 2. Table 3 reports urinary and creatinine corrected urinary mercury concentrations in the study population as well as published 2004 NYC Health and Nutrition Examination Survey and the 2006-2009 NHANES results. Some observations were missing data for cord blood mercury (93 observations) or urinary mercury (11 observations). 98.5% of cord blood samples and 82.7% of urinary mercury samples were greater than the method detection limit (MDL). The number of observations included in each analysis is reported in Table 2. Histograms of cord blood mercury and uncorrected urinary mercury are shown in Figures 1 & 2 respectively, along with the EPA minimum risk level of 5.8 µg/L for blood mercury and a background level of 4.0 µg/L for urinary mercury.[37] 13.4% of infants had cord blood mercury levels >5.8 µg/L and 3.3% of women had urinary mercury levels greater than 4.0 µg/L.

Caribbean/ West Indian women had the highest cord blood (gm = 2.57 μg/L) and creatinine corrected (gm = 0.395 μg/L) urinary mercury. Trends of increasing mercury levels with increasing age, higher educational attainment, maternal birth outside of the U.S., and visiting a *botanica* were evident in both cord blood and urinary mercury. For cord blood mercury, higher geometric means were also seen with increasing frequency of maternal fish intake, mother living with a spouse or partner, infant birthweight greater than or equal to 2500 g, and term birth ($\geq$ 37 weeks gestation). Lower levels of cord blood mercury occurred with increasing numbers of dental amalgams and special product use. All women with infant cord blood measures did not use alcohol or tobacco.
Both corrected and uncorrected maternal urinary mercury increased with increasing maternal age, higher educational attainment, number of dental amalgams, maternal birth outside the United States, and special product use during pregnancy. Uncorrected maternal urinary mercury was also higher in women who used tobacco and alcohol. Uncorrected maternal urinary mercury was lower in women who visited a *botanica* during pregnancy and whose infants were born at term and who weighed over 2500g and decreased with increasing frequency of fish and shellfish consumption. Creatinine corrected urinary mercury was higher in women who used alcohol and who delivered infants weighing over 2500g. Creatinine corrected urinary mercury was lower in women who lived with a spouse/partner, used tobacco, or delivered at 37 weeks or greater.

In univariate linear regression, Caribbean/ West Indian women compared to African-American women had significantly different infant cord blood mercury values (Table 4). Other study variables associated with higher infant cord blood mercury were all

categories of fish consumption compared to almost never or never consuming fish during pregnancy having 4 to 6 dental amalgams compared to no amalgams, and maternal birth outside the U.S. (Table 4). In multivariate analysis, consuming fish more than 4 to 7 times per month as compared to almost never or never eating fish, having 4 to 6 or 7 or more dental amalgams compared to no dental amalgams, and maternal birth outside the U.S. resulted in significantly different levels of cord blood mercury (Table 4 and Figure 4).

Age, education level as well as having a higher number of dental amalgams were associated with uncorrected urinary mercury levels based on univariate linear regression (Table 5). In multivariate linear regression, differences between age group were not significant; educational attainment and number of dental amalgams remained in the model (Table 5). All models included urinary creatinine. Logistical regressions for creatinine corrected urinary mercury levels were identical to the uncorrected maternal urinary mercury in assessment of significant differences (data not shown).

Women who consumed fish or shellfish more frequently had infants with higher levels of cord blood mercury (Figure 3). This trend was strongest in women who were born outside of the United States (Table 6). None of the other categories had significantly different means as determined by linear regression analysis (data not shown). Two women (6.5%) born in US and 7 women (20%) born outside the United States had infant cord blood levels greater than 5.8 μg/L. In contrast to infant cord blood mercury levels, maternal urinary mercury did not differ by maternal place of birth (Table 3).

In women who were born outside the United States, infant cord blood mercury decreased with increasing percent of life spent in the United States (Figure 6). For each 10% increase in percent of life spent in the United States, infant cord blood decreases by 19% (see Figure 5, p = 0.001, 95% CI [-29.4, -8.1]%, Adj R-squared = 0.2932). In contrast, urinary mercury did not differ with percent of life spent in the United States. To explore this observation further, associations between fish consumption and age and fish consumption and years spent in the United States were examined. There is a positive relationship between fish consumption and maternal age group in all women born outside the U.S. (Kruskal-Goodman gamma, γ=0.2733 [0.0224, .5242]). There also was no relationship between categories of years in the United States (0-9 years, 10-19 years, $\geq$20 years) and fish consumption category (Kruskal-Goodman gamma, γ=-0.1479 [-0.4537, 0.1579]) for all women born outside the U.S. The Kruskal-Wallis non-parametric equality of populations rank test was used to determine differences in numbers of years in the United States, percent of life in the United States and infant cord blood mercury by fish consumption frequency. There was no significant difference in years in the U.S. (p= 0. 2835), percent of life spent in the United States (p=0.0866) or infant cord blood mercury (p= 0.0866) and all groups of fish consumption frequency in women born outside the United States.

Table 6 reports the results of univariate and multivariate logistic regressions of selected exposure variables associated with the outcomes of preterm birth and low birth weight. No association between these exposure variables and increased odds of preterm birth was observed. In multivariate analysis, women age 35 and over had an 1.23 times greater odds of preterm birth when controlled for maternal place of birth, but the likelihood of

the model as a whole was not significantly different than an intercept only model (Table 7). LBW was associated with preterm birth and alcohol use in both univariate and multivariate regressions (Table 7).

There was no association between LBW or preterm birth and either infant cord mercury or maternal creatinine corrected or uncorrected urinary mercury (Table 8). Additionally preterm birth models were not significantly better fit compared with the intercept-only model (Likelihood ratio test, $p>0.05$, data not shown). There was also no association between birthweight measured as a continuous variable, infant length, or infant head circumference and infant cord blood or maternal urinary mercury (Table 8). Models were also examined with data stratified by presence or absence of dental amalgams, no significant associations occurred (data not shown).

In univariate regressions preterm birth, and birthweight were associated with statistically differences in infant head circumference (Table 9). The race/ethnic group model accounted for only minimal variation and was not significantly different than an intercept only model. In the full model, preterm birth and birthweight retained significance with head circumference. Preterm birth and birthweight were significantly associated with infant length (Table 9).

The distribution of births by month pregnancy began are shown in Figure 7. There was a significant effect of season that pregnancy began on the risk of delivering LBW infants. Crude odds ratios for three month aggregates of odds of LBW compared with all other months are reported in Figure 8 along with 95% confidence intervals. The largest odds ratio is found in the three month aggregate of December, January, and February. When

controlled for preterm birth, maternal age group and racial/ethnic group, pregnancies that began in winter months (December, January and February) had 7.52 [1.65, 32.49] times the odds of resulting in a LBW infant than pregnancies that began in all other months (Table 10). The association of season of conception and preterm birth was similar, but not significant. The seasonal difference in birthweights is more evident in the preterm births (Figure 9).

Table 1. Study Population Characteristics (N = 159)

		N (Percent)
Race / Ethnicity		
	African- American	73 (46)
	Caribbean/ West Indian	62 (39)
	From African Continent (4), Latino (13) & Other (5)	22 (14)
Age group		
	Less than 25 yrs	61 (38)
	25 to 29 yrs	37 (23)
	30 to 34 yrs	39 (25)
	35 and over	22 (14)
Educational attainment		
	Some HS or less	36 (23)
	HS certificate	50 (31)
	Technical school, some college or more	73 (46)
Live with spouse/ partner		
	No	77 (48)
	Yes	81 (51)
Frequency of fish intake during this pregnancy		
	Almost never or never	54 (34)
	1-3 times per month	58 (36.5)
	4 - 7 times per month	23 (14.5)
	Several times per week	24 (15)
Number of dental amalgams		
	None	85 (53)
	1 to 3	40 (25)
	4 to 6	25 (16)
	7 or more	8 (5)
Born outside the United States		
	No	84 (53)
	Yes	75 (47)
Special product use		
	No	147 (92)
	Yes	9 (6)
Visit botanica during pregnancy		
	No	150 (94)
	Yes	8 (5)
Alcohol use		
	No	151 (95)
	Yes	6 (4)
Tobacco use		
	No	152 (96)
	Yes	5 (3)
Birthweight		
	Less than 2500g	23 (14)
	2500g and over	136 (86)
Term		
	Preterm (less than 37 weeks)	30 (19)
	Term (37 to 42 weeks)	129 (81)

Table 2. Cord Blood and Maternal Urinary Mercury

	Cord Blood Mercury (μg/L)				Maternal Urinary Mercury (μg/L)				Creatinine Corr. Urinary Mercury (μg/g)			
	N	Median	GM	95% CI	N	Median	GM	95% CI	N	Median	GM	95% CI
Race / Ethnicity												
African- American	29	1.49	1.57	[1.08, 2.28]	67	.500	.434	[.308, .611]	63	.347	.300	[.217, .414]
Caribbean/ West Indian	26	2.23	2.57	[1.95, 3.38]	59	.595	.513	[.368, .715]	59	.484	.395	[.298, .524]
From African Continent, Latino & Other	11	1.44	1.89	[.893, 4.01]	22	.250	.218	[.119, .400]	22	.280	.249	[.150, .413]
Age group												
< 25 yrs	28	1.555	1.70	[1.19, 2.44]	58	.360	.333	[.234, .474]	56	.280	.248	[.179, .344]
25 to 29 yrs	14	1.84	1.88	[1.17, 3.04]	35	.600	.490	[.326, .736]	35	.356	.349	[.252, .485]
30 to 34 yrs	16	2.23	2.51	[1.67, 3.77]	36	.562	.495	[.305, .804]	34	.566	.396	[.257, .609]
35 and over	9	2.3	2.27	[.906, 5.69]	21	.700	.435	[.207, .917]	21	.706	.416	[.225, .769]
Educational attainment												
Some HS or less	17	1.49	1.43	[.887, 2.30]	36	.360	.252	[.157, .406]	35	.265	.199	[.127, .314]
HS certificate	22	1.91	1.99	[1.32, 3.01]	48	.574	.427	[.285, .638]	47	.356	.336	[.231, .489]
Technical school, some college or more	28	2.205	2.41	[1.74, 3.35]	66	.567	.537	[.392, .738]	64	.529	.410	[.321, .524]
Lives with a spouse/ partner												
No	26	1.9	1.76	[1.10, 2.80]	71	.529	.443	[.310, .631]	69	.438	.345	[.258, .460]
Yes	41	1.99	2.14	[1.71, 2.68]	78	.500	.405	[.306, .535]	76	.366	.316	[.242, .412]
Frequency of fish intake												
Almost never or never	21	1.37	1.27	[.889, 1.80]	51	.500	.417	[.281, .618]	51	.281	.193	[.385, .273]
1-3 times per month	25	1.9	2.15	[1.43, 3.23]	55	.539	.465	[.326, .665]	52	.401	.369	[.270, .504]
4 - 7 times per month	10	2.74	3.08	[1.91, 4.97]	21	.500	.357	[.181, .703]	21	.502	.308	[.173, .549]
Several times per week	11	2.4	2.61	[1.45, 4.71]	23	.450	.366	[.200, .671]	22	.508	.368	[.213, .637]

Table 2 (continued). Cord Blood and Maternal Urinary Mercury

	Cord Blood Mercury (µg/L)				Maternal Urinary Mercury (µg/L)				Creatinine Corr. Urinary Mercury (µg/g)			
	N	Median	GM	95% CI	N	Median	GM	95% CI	N	Median	GM	95% CI
Number of dental amalgams												
None	36	2.245	2.45	[1.82, 3.30]	82	.413	.321	[.237, .436]	79	.303	.246	[.184, .327]
1 to 3	18	1.93	1.89	[1.22, 2.94]	37	.539	.500	[.304, .821]	37	.387	.368	[.257, .527]
4 to 6	7	1.11	1.15	[.512, 2.56]	25	1.20	.835	[.593, 1.18]	24	.710	.670	[.523, .857]
7 or more	5	1.44	1.31	[.372, 4.58]	6	.250	.255	[.061, 1.06]	6	.252	.296	[.070, 1.26]
Born outside the US												
No	32	1.4	1.41	[1.03, 1.94]	80	.500	.386	[.289, .516]	77	.331	.279	[.214, .365]
Yes	35	2.4	2.70	[2.03, 3.60]	70	.572	.453	[.320, .642]	69	.479	.381	[.285, .508]
Special product use												
No	59	1.9	2.11	[1.68, 2.65]	139	.500	.410	[.326, .516]	135	. .377	.313	[.255, .383]
Yes	6	2.115	1.74	[.631, 4.78]	9	.802	.558	[.164, 1.90]	9	.695	.520	[.190, 1.42]
Visit botanica												
No	63	1.9	1.98	[1.58, 2.49]	142	.500	.417	[.332, .523]	138	.380	.322	[.263, .393]
Yes	3	4.95	2.67	[.149, 47.77]	8	.572	.408	[.111, 1.50]	8	.453	.353	[.109, 1.14]
Alcohol use												
No	67	1.9	1.98	[1.59, 2.47]	142	.500	.401	[.319, .505]	139	.383	.316	[.258, .387]
Yes	0				6	.513	.634	[.196, 2.05]	5	.331	.419	[.138, 1.28]
Tobacco use												
No	67	1.9	1.98	[1.59, 2.47]	143	.500	.407	[.324, .510]	139	.383	.320	[.262, .391]
Yes	0	-	-	-	5	.600	.470	[.054, 4.06]	5	.331	.297	[.057, 1.54]
Infant birthweight												
Less than 2500g	10	1.7	1.90	[1.23, 2.92]	22	.550	.450	[.249, .812]	21	.387	.284	[.166, .488]
2500g and over	57	1.96	2.00	[1.55, 2.57]	128	.500	.411	[.322, .523]	125	.382	.330	[.267, .409]
Term of birth												
Preterm (<37 wks)	11	1.5	1.47	[1.10, 1.97]	29	.600	.539	[.338, .861]	28	.449	.351	[.226, .546]
Term (37 to 42_ wks)	56	1.985	2.10	[1.62, 2.72]	121	.500	.391	[.304, .504]	118	.352	.317	[.254, .395]

Table 3. Comparison of urinary and creatinine corrected urinary mercury in study, NYCHANES and NHANES populations.

	Urinary mercury (Õg/L)				Creatinine corrected urinary mercury (Õg/g)			
	N	**gm**	**gm 95% CI**	**95th Percentile [CI]**	**N**	**gm**	**gm 95% CI**	**95th Percentile [CI]**
Study Population	150	0.416	[.333, .519]	3.29 [1.92, 4.68]	146	.323	[.266, .393]	1.97 [1.48, 3.00]
NYC HANES (McKelvey et al. 2011) (57) (Population-weighted)								
All Women	1065	0.77	[0.71, 0.85]	4.76 [4.20, 5.76]	1065	0.86	[0.80, 0.93]	4.73 [4.21–5.40]
NHW (M&W)	532	0.67	[0.60, 0.75]	3.84 [3.50, 4.46]	532	0.72	[0.64, 0.80]	3.58 [3.12–4.40]
NHB (M&W)	395	0.89	[0.78, 1.00]	4.40 [3.62, 5.31]	395	0.63	[0.56, 0.70]	3.01 [2.58–3.67]
Caribbean Born Black (M&W)	97	1.39	[1.14, 1.70]	4.46 [3.61, 10.52]	97	1.13	[0.95, 1.34]	4.44 [3.01–6.98]
NHANES *≥16 & <50*								
All Women 2007-2008	560	0.471	[.408, .542]	2.82	560	0.494	[.447, .548]	2.24
All Women 2009-2010	670	0.413	[.360, .475]	2.62	670	0.459	[.398, .529]	2.11
NHW 2007-2008	212	0.442	[.353, .555]	2.82	212	0.496	[.423, .580]	2.24
NHW 2009-2010	278	0.376	[.314, .451]	2.46	278	0.457	[.376, .556]	2.09
NHB 2007-2008	128	0.556	[.416, .742]	4.12	128	0.481	[.381, .608]	2.77
NHB 2009-2010	117	0.543	[.441, .667]	3.30	117	0.410	[.327, .513]	1.92
All ages								
All Women 2007-2008(76)	1308	0.430	[.388, .478]	2.92 [2.27-4.17]	1308	0.520	[.469, .576]	2.83 [2.24, 3.50]
All Women 2009-2010	1461	0.397	[.356, .443]	2.61	1461	0.491	[.438, .550]	2.57

Table 4. Univariate and multivariate analysis of predictors of cord blood mercury.

Cord Blood Mercury	Univariate Analysis			Multivariate Analysis (adj r2 = 0.3409, N=64)		
	Percent change in geometric mean	P-value	Confidence interval for percent change in geometric mean	Percent change in geometric mean	P- value	Confidence interval for percent change in geometric mean
Race / Ethnicity						
African- American	-	Reference			Reference	
Caribbean/ West Indian	63.4	**0.047**	[0.7, 165.1]	-24.8	0.331	[-58.0, 34.7]
From African Continent, Latino & Other	20.4	0.561	[-36.2, 127.1]	-14.1	0.588	[-50.8, 50.0]
Age group						
Less than 25 yrs	-	Reference				
25 to 29 yrs	10.6	0.737	[-39.1, 101.1]			
30 to 34 yrs	47.3	0.181	[-16.9, 161.0]			
35 and over	33.3	0.415	[-33.8, 168.3]			
Educational attainment						
Some HS or less	-	Reference				
HS certificate	39.4	0.256	[-21.8, 148.4]			
Technical school, some college or more	68.9	0.062	[-2.6, 192.9]			
Live with a spouse/ partner						
No	-	Reference				
Yes	-18.1	0.384	[-48.0, 29.1]			
Frequency of fish intake during this pregnancy						
Almost never or never	-	Reference		-	Reference	
1-3 times per month	69.8	**0.043**	[1.8, 183.3]	36.7	0.178	[-136, 116.5]
4 - 7 times per month	143.2	**0.010**	[25.2, 372.4]	135.0	**0.005**	[31.2, 321.0]
Several times per week	106.4	**0.028**	[8.5, 292.8]	68.3	0.067	[-3.7, 194.1]
Number of dental amalgams						
None	-	Reference		-	Reference	
1 to 3	-22.8	0.318	[-53.7, 29.0]	-31.4	0.091	[-55.7, 6.4]
4 to 6	-53.2	**0.043**	[-77.6, -2.6]	-49.1	**0.034**	[-72.7, -5.2]
7 or more	-46.7	0.143	[-77.2, 24.3]	-62.7	**0.008**	[-81.9, -23.2]
Born outside the United States						
No	-	Reference		-	Reference	
Yes	91.4	**0.003**	[26.2, 190.3]	165.6	**0.000**	[56.7 350.2]
Special product use						
No	-	Reference				
Yes	-17.8	0.605	[-61.3, 74.6]			
Visit botanica during this pregnancy						
No	-	Reference				
Yes	34.8	0.582	[-54.1, 296.0]			
Alcohol use	All Cord blood observations were from women who did not use alcohol.					
Tobacco use	All Cord blood observations were from non-smoking women					

Table 5. Univariate and multivariate analysis of predictors of maternal urine mercury. All models included urinary creatinine as a covariate.

Urine Mercury	Univariate Analysis			Multivariate Analysis		
	Percent change in geometric mean	P-value	Confidence interval for percent change in geometric mean	Percent change in geometric mean	P- value	Confidence interval for percent change in geometric mean
Race / Ethnicity						
African- American	-	Reference				
Caribbean/ West Indian From African Continent, Latino & Other	35.5	0.155	[-11.0, 106.1]			
	-11.6	0.681	[-51.1, 59.8]			
Age group						
Less than 25 yrs	-	Reference				
25 to 29 yrs	43.1	0.158	[-13.2, 135.7]			
30 to 34 yrs	66.4	**0.048**	[0.30, 175.8]			
35 and over	55.7	0.143	[-14.1, 182.2]			
Educational attainment						
Some HS or less	-	Reference		-	Reference	
HS certificate	64.1	0.057	[-1.6, 173.5]	55.6	0.081	[-5.3, 155.6]
Technical school, some college or more	95.9	**0.007**	[21.0, 217.1]	84.6	**0.013**	[13.8, 199.5]
Live with a spouse/ partner						
No	-	Reference				
Yes	7.8	0.701	[-26.6, 58.2]			
Frequency of fish intake during this pregnancy						
Almost never or never	-	Reference				
1-3 times per month	43.6	0.127	[-9.9, 128.9]			
4 - 7 times per month	21.7	0.527	[-34.1, 124.7]			
Several times per week	36.4	0.314	[-25.7, 150.2]			
Number of dental amalgams						
None	-	Reference		-	Reference	
1 to 3	39.2	0.147	[-11.1, 118.0]	21.9	0.395	[-22.9, 92.8]
4 to 6	175.4	**0.000**	[63.2, 364.5]	158.8	**0.000**	[54.3, 334.1]
7 or more	26.1	0.633	[-51.6, 228.2]	2.8	0.955	[-60.5, 167.5]
Born outside the United States						
No	-	Reference				
Yes	35.8	0.121	[-7.9, 100.1]			
Special product use						
No	-	Reference				
Yes	73.1	0.182	[-22.9, 288.6]			
Visited botanica during this pregnancy						
No	-	Reference				
Yes	16.8	0.719	[-50.2, 173.9]			
Alcohol use during this pregnancy						
No	-	Reference				
Yes	30.6	0.623	[-55.3, 281.6]			
Tobacco use during this pregnancy						
No	-	Reference				
Yes	-7.4	0.888	[-68.2, 170.1]			

Table 6. Infant cord blood mercury by maternal place of birth and frequency of fish intake.

Place of birth	Frequency of fish intake	N	Geometric mean infant cord blood mercury (µg/L)*	95% C.I.
United States	Almost never or never	12	**0.997** [a,]	[0.61, 1.64]
	>1 time per month	20	**1.74**	[1.15, 2.63]
Outside the United States	Almost never or never	9	**1.74** [a,b]	[1.03, 2.94]
	>1 time per month	26	**3.15** [b]	[2.25, 4.41]

*Superscripts with same letters are significantly different from each other ($p<0.05$, Wilcoxon rank sum test)

Table 7. Predictors of preterm birth and LBW

Preterm Birth	**Odds Ratio**	**P-value**	**95% CI for Odds Ratio**	**LR**
Univariate- None				
Multivariate				
Age group				5.037
Less than 25 yrs	1	Reference		p=0.284
25 to 29 yrs	1.22	0.732	[0.39, 3.80]	
30 to 34 yrs	1.80	0.291	[0.60, 5.35]	
35 and over	3.43	**0.045**	[1.02, 11.5]	
Born outside the US				
No	1	Reference		
Yes	0.54	0.166	[0.23, 1.29]	
LBW				
Univariate				
Preterm Birth				41.85
No	1	Reference		p=0.000
Yes	**26.8**	**0.000**	[8.99, 79.91]	
Alcohol use during this pregnancy				4.402
No	1	Reference		p=0.036
Yes	**6.55**	**0.027**	[1.24, 34.7]	
Multivariate				
Alcohol use during this pregnancy				45.447
No	1	Reference		p=0.000
Yes	**9.93**	**0.035**	[1.17, 84.21]	
Preterm birth				
No	1	Reference		
Yes	**28.80**	**0.000**	[9.13, 90.84]	

Table 8. Association of cord and urinary mercury with preterm birth, LBW, head circumference and length. Logistic regressions were adjusted for maternal age group, and racial ethnic group. Linear regressions were adjusted for age group, education attainment, racial/ ethnic group, and living with partner/ spouse. Birthweight models also included term of birth. Uncorrected urine mercury models also included urine creatinine. Logistic models were tested against models that included only racial/ ethnic and age groups and preterm term in LBW models.

Logistic Regressions	**Odds ratio increase per unit increase in variable**	**P-value**	**Confidence Interval**	**LR***	**p-value Model**
LBW					
Cord Mercury (n=66)	1.07	0.725	[0.72, 1.61]	0.12	0.732
Urine Mercury (n=144)	0.8	0.618	[0.42, 1.67]	0.87	0.648
Creatinine Corrected Urine Mercury (n=144)	0.51	0.306	[0.14, 1.87]	1.20	0.272
Preterm Birth					
Cord Mercury (n=66)	0.65	0.122	[0.38, 1.12]	4.29	0.038
Urine Mercury (n=144)	0.85	0.501	[0.53, 1.37]	2.08	0.353
Creatinine Corrected Urine Mercury (n=144)	0.78	0.499	[0.38, 1.59]	0.49	0.485
Linear Regressions	**Change in outcome variable with 10% increase in sample mercury**	**P-value**	**Confidence Interval**	**Adjusted r^2**	**p-value Model**
Birthweight (in grams)					
Cord Mercury (n=64)	4.63	0.456	[-7.75, 17.01]	0.3305	0.000
Urine Mercury (n=140)	-0.68	0.832	[-7.04, 5.68]	0.3274	0.000
Creatinine Corrected Urine Mercury (n=140)	-1.29	0.691	[-7.71, 5.12]	0.2985	0.000
Head Circumference (cubed, in cm^3)					
Cord Mercury (n=64)	64.1	0.340	[-69.5, 197.9]	0.1053	0.096
Urine Mercury (n=137)	3.25	0.931	[-71.4, 77.9]	0.2298	0.000
Creatinine corrected Urine Mercury (n=137)	3.81	0.919	[-70.1, 77.7]	0.2261	0.000
Length (squared, in cm^2)					
Cord Mercury (n=62)	-0.25	0.963	[-11.0, 10.5]	0.0501	0.245
Urine Mercury (n=133)	-1.83	0.448	[-6.50, 2.85]	0.2047	0.000
Creatinine corrected Urine Mercury (n=133)	-1.83	0.440	[-6.50, 2.85]	0.2110	0.000

*LR = Likelihood Ratio. Likelihood ratios with p values ≤ 0.05 signify models with significantly fit with reduced models not containing variable of interest.

Table 9. Factors associated with infant head circumference and length.

Head Circumference

Univariate

	Change in cubic head circumference (cm^3)	**P-value**	**95% confidence interval for change in cubic head circumference (cm^3)**	**Adj-r^2**	**P-value Model**
Race/ ethnicity(N=153)				0.0162	0.1085
African- American	-	Reference			
Caribbean/ West Indian	1949.33	**0.050**	[1.01, 3897.64]		
From African Continent, Latino & Other	1929.07	0.171	[-843.11, 4701.24]		
Preterm birth (N=155)				0.2097	0.000
No	-	Reference			
Yes	-6726.14	**0.000**	[-8780.18, -4672.11]		
Birthweight (per $gram^2$ change) (N=155)	0.001	**0.000**	[0.000, 0.001]	0.4265	0.000
Multivariate (N=153)				0.4577	0.000
Preterm birth No	-	Reference			
Yes	-2629.70	**0.009**	[-4606.55, -652.86]		
Birthweight (per $gram^2$ change)	0.0009	**0.000**	[0.0007, 0.001]		
Race/ ethnicity(N=153)					
African- American	-	Reference			
Caribbean/ West Indian	1157.15	0.119	[-299.7, 2614.03]		
From African Continent, Latino & Other	1142.28	0.277	[-925.9, 3210.43]		

Length

Univariate (n=146[a])	Change in length (in cm^2)	P-value	95% Confidence interval for change in length (in cm^2)		
Preterm Birth	-360.44	**0.000**	[-469.75, -251.14]	0.2225	0.000
Birthweight (per $gram^2$ change)	0.00007	**0.000**	[0.00006, 0.00008]	0.5426	0.000
Multivariate (n=146[a])				0.5590	0.000
Birthweight (per $gram^2$ change)	0.00006	**0.000**	[0.00005, 0.00007]		
Preterm Birth	-119.8	**0.013**	[--213.72, -25.92]		

[a]Two observations were removed as outliers in order to comply with test assumptions.

Table 10. Association of season of conception and adverse birth outcomes. Models were adjusted for preterm birth, maternal age group and race/ ethnicity. Dates are coded as Spring (March 1 – May 31), Summer (June 1 – August 31), Fall (September 1 – November 31) and Winter (December 1 – February 28/9). N=157 for all models, there were 23 LBW infants and 30 preterm infants in total. All birthweight models were significantly different than the constant only model. Likelihood ratio tests of seasonal models with models without season are reported in table. Preterm models were not significantly different than reduced models.

LBW	Odds Ratio	95% Conf. Interval	P-value	LR & P-value vs. reduced model
Season of conception				LR=7.67
Winter (Dec, Jan, Feb)	**1**	Reference		p=0.0533
Spring (Mar, Apr, May)	**0.14**	[0.02, 0.84]	**0.032**	
Summer (Jun, Jul, Aug)	**0.16**	[0.03, 0.89]	**0.036**	
Fall (Sep, Oct, Nov)	**0.09**	[0.01, 0.65]	**0.017**	
Dec, Jan, Feb vs. All other months	**7.52**	[1.65, 34.29]	**0.009**	**LR=7.27, p=0.007**

Preterm Birth	Odds Ratio	95% Conf. Interval	P-value	LR & P-value vs. reduced model
Season of conception				LR=1.24
Winter (Dec, Jan, Feb)	1	Reference		p= 0.7425
Spring (Mar, Apr, May)	0.81	[0.24, 2.75]	0.735	
Summer (Jun, Jul, Aug)	0.58	[0.17, 1.98]	0.382	
Fall (Sep, Oct, Nov)	1.01	[0.28, 3.64]	0.991	
Dec, Jan, Feb vs. All other months	1.29	[0.47, 3.53]	0.626	LR= 0.27, p= 0.604

*LR = Likelihood Ratio. Likelihood ratios with p values ≤ 0.05 signify models with significantly fit with reduced models not containing variable of interest.

Figure 1. Histogram of cord blood mercury (µg/L).

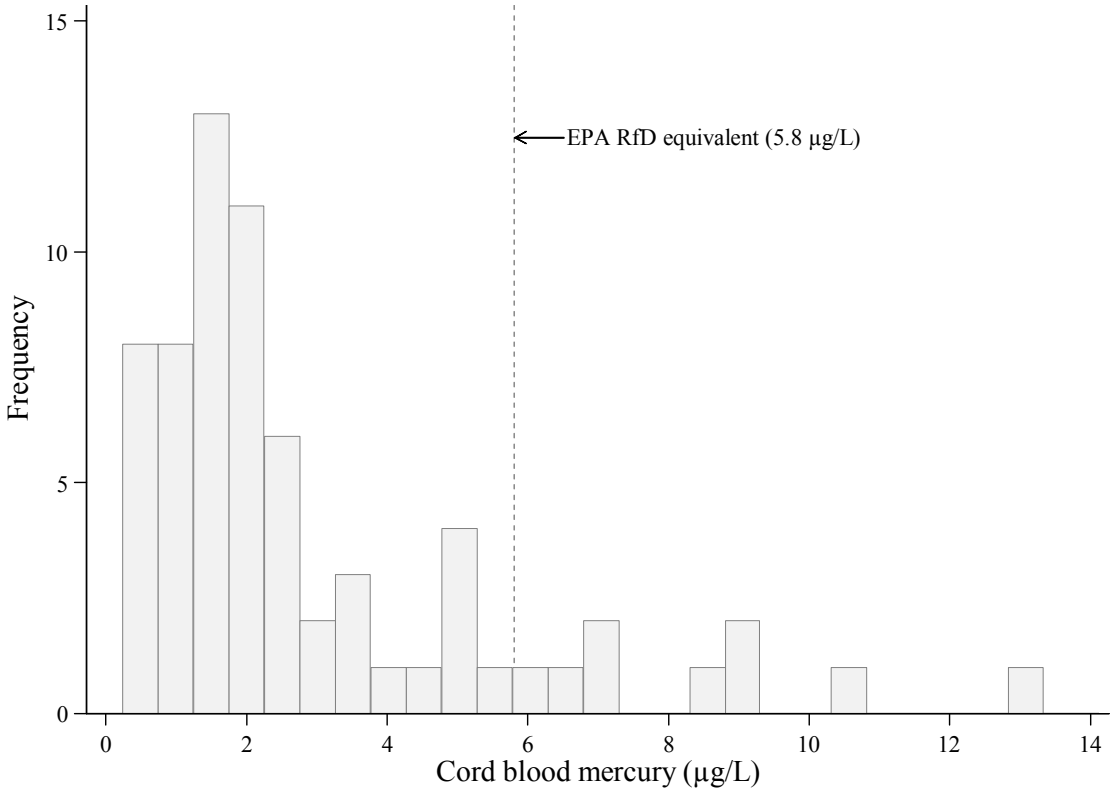


Figure 2. Histogram of maternal urinary mercury observations.

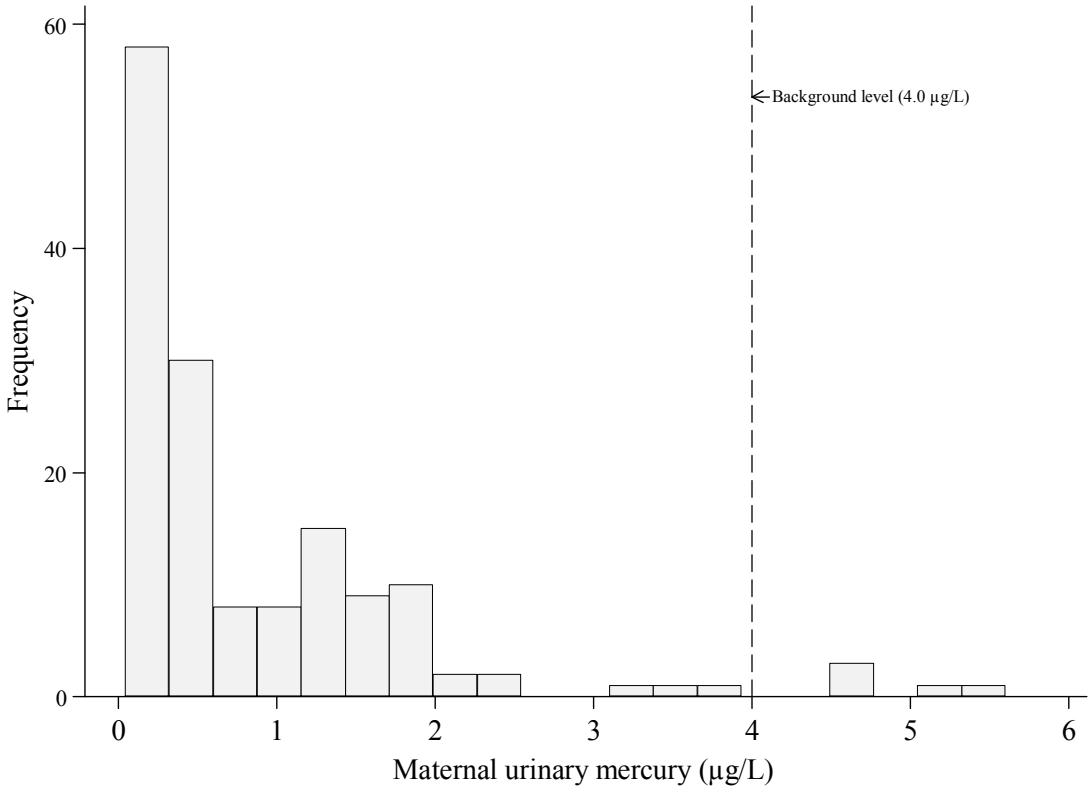


Figure 3. Box plot distribution of cord blood mercury (µg/L) by frequency of fish intake during pregnancy and place of birth. Gray dashed line indicates EPA RfD (5.8µg/L)

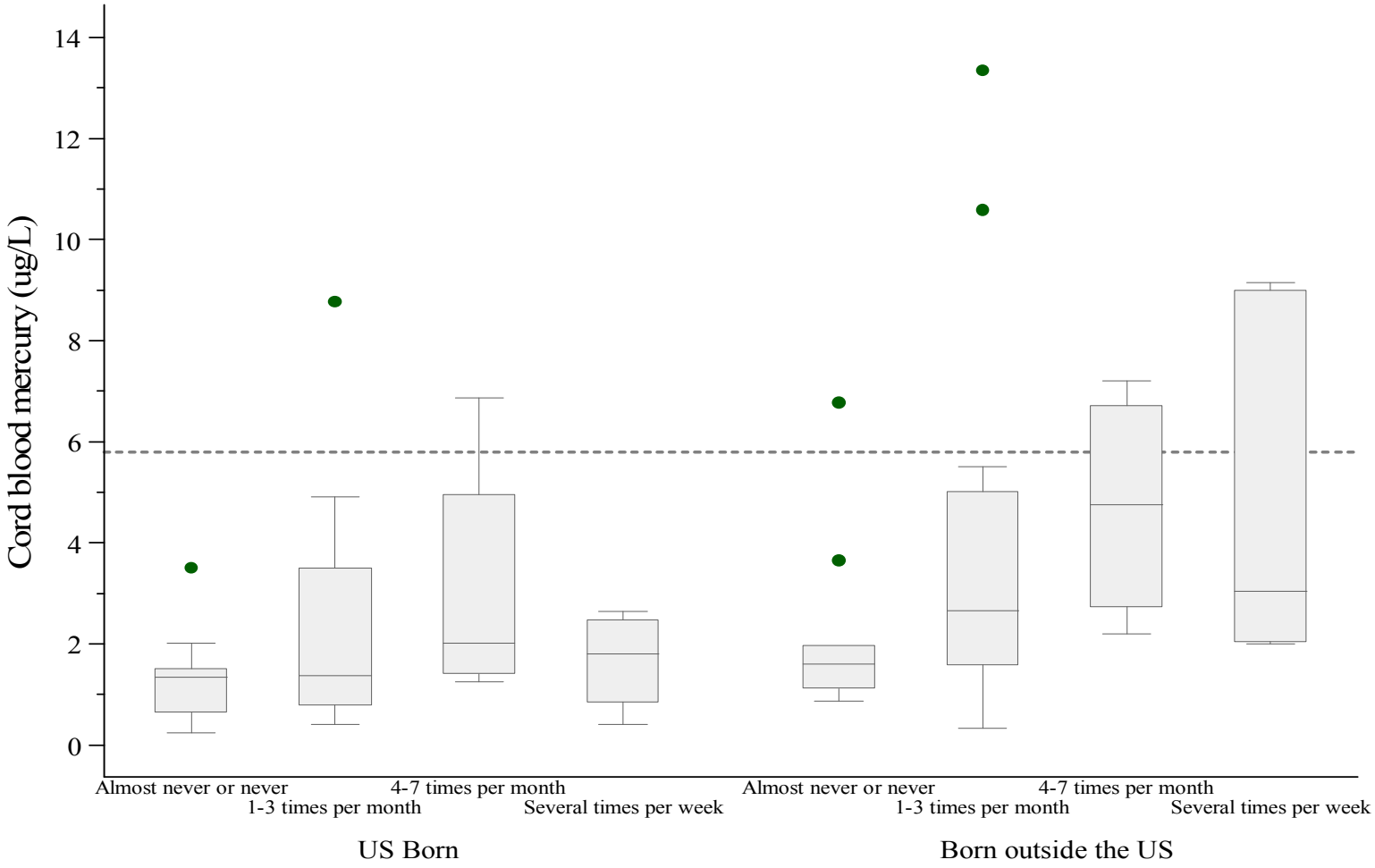


Figure 4. Box plot distribution of urinary mercury by number of dental amalgams.

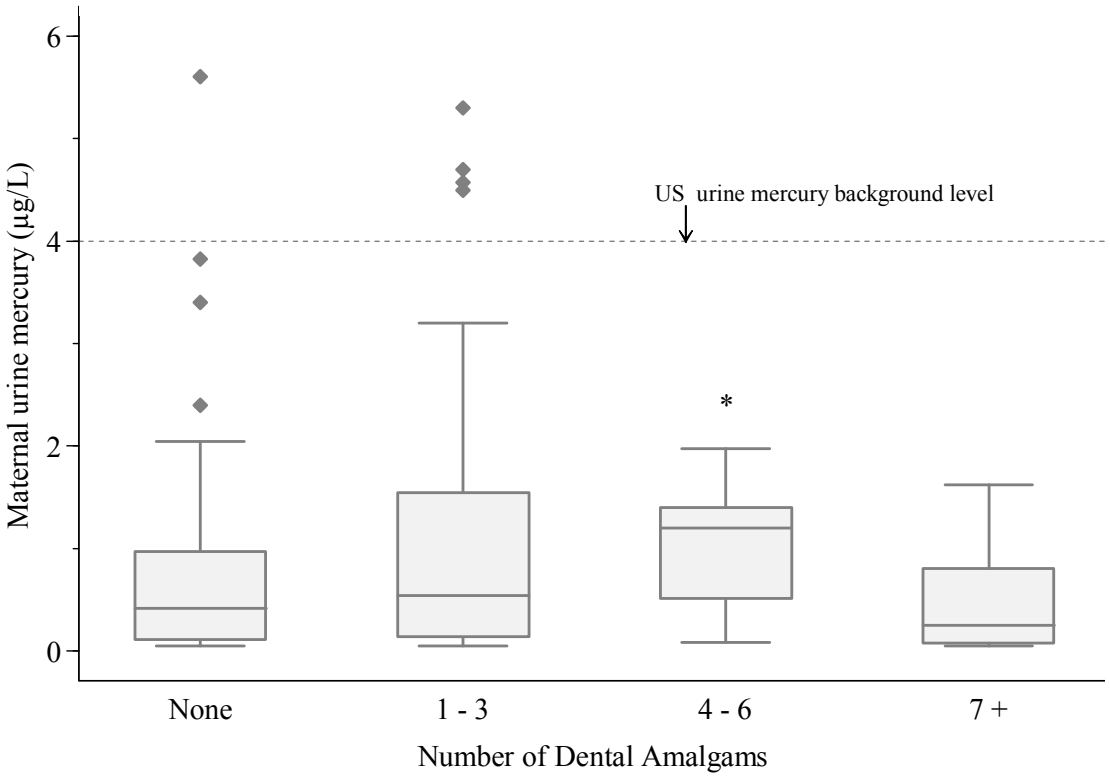


Figure 5. Natural log of cord blood mercury (Õg/L) by percent of maternal life spent in the United States if mother born outside the United States.

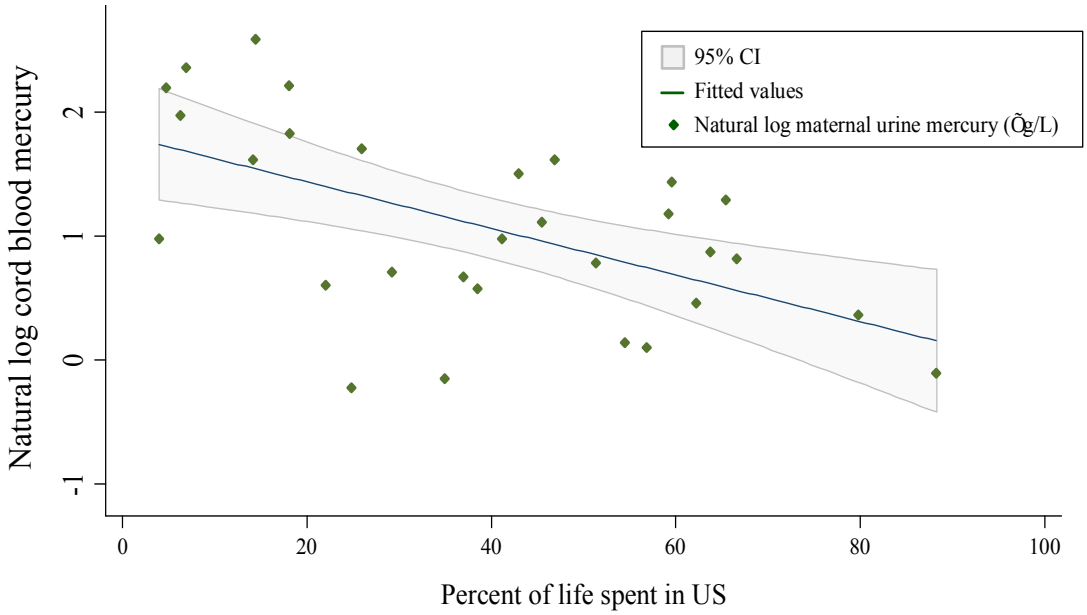


Figure 6. Natural log urine mercury by percent of life spent in US

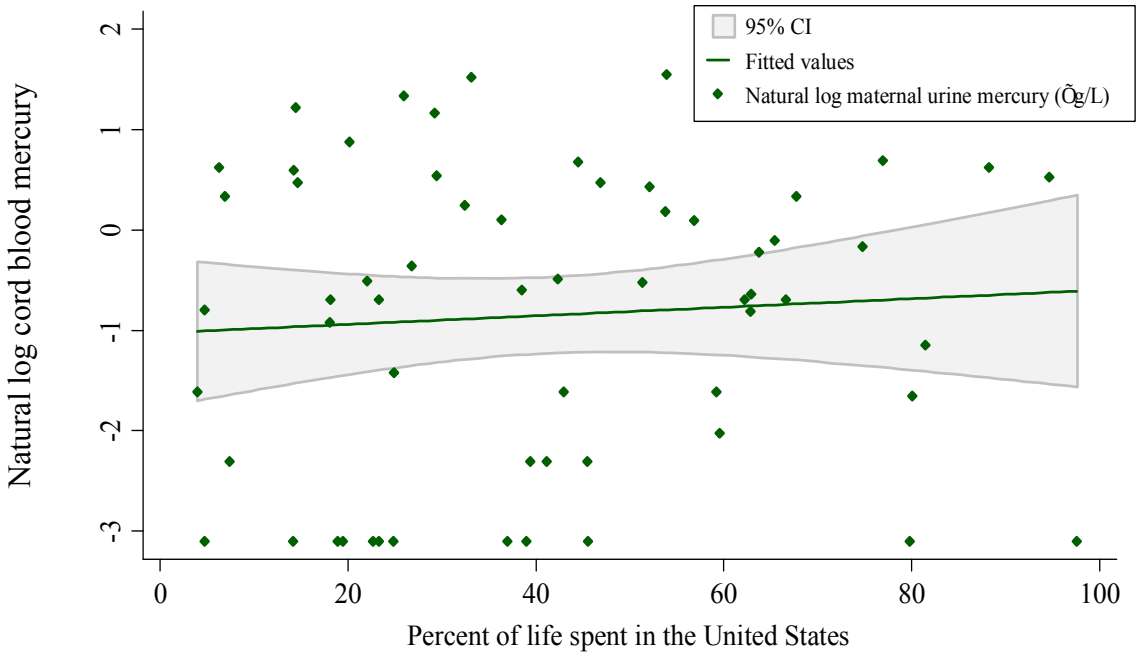


Figure 7. Percent of infants that were LBW by month of conception

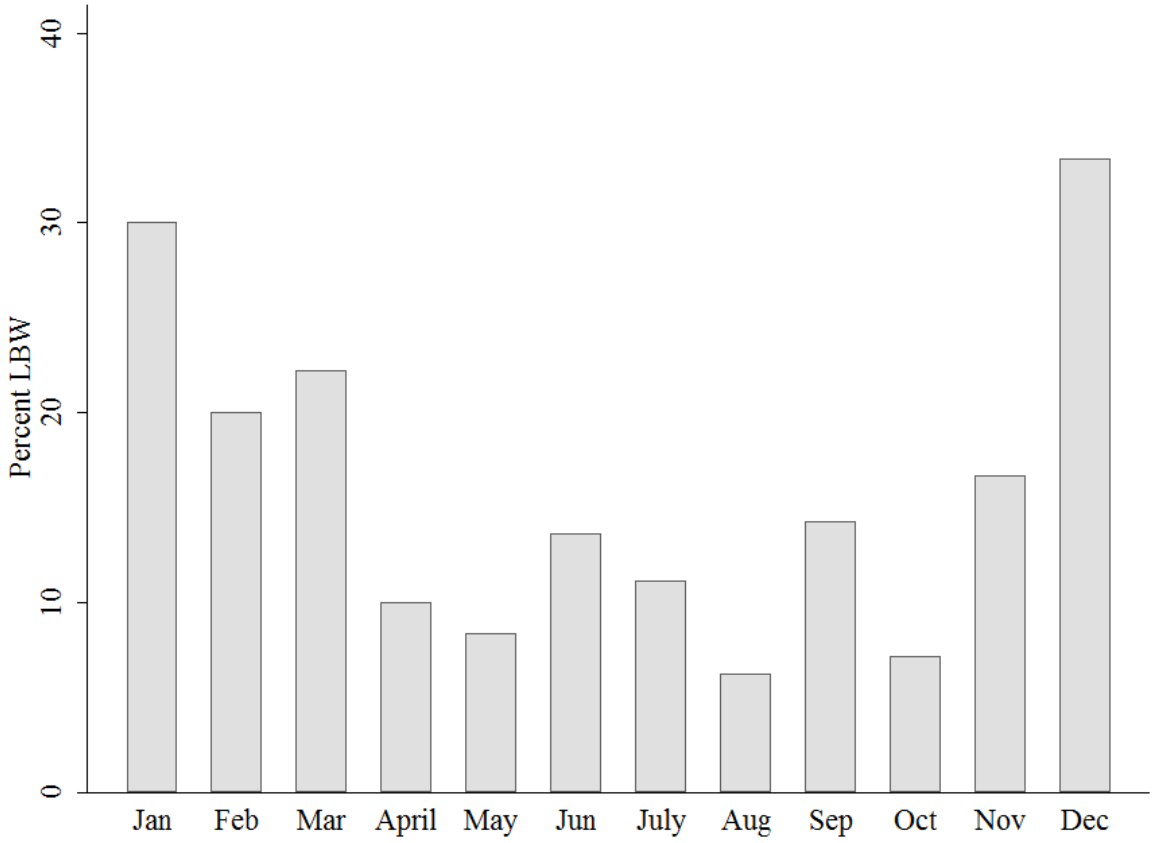


Figure 8. Odds ratios for LBW (three month groupings, vertical bars represent 95% confidence intervals).

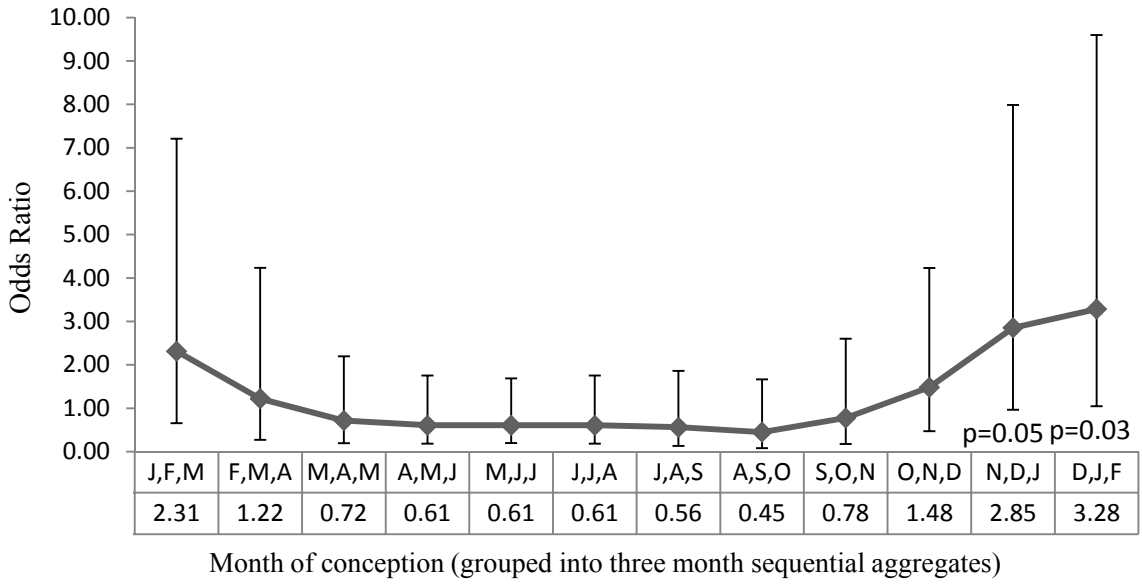
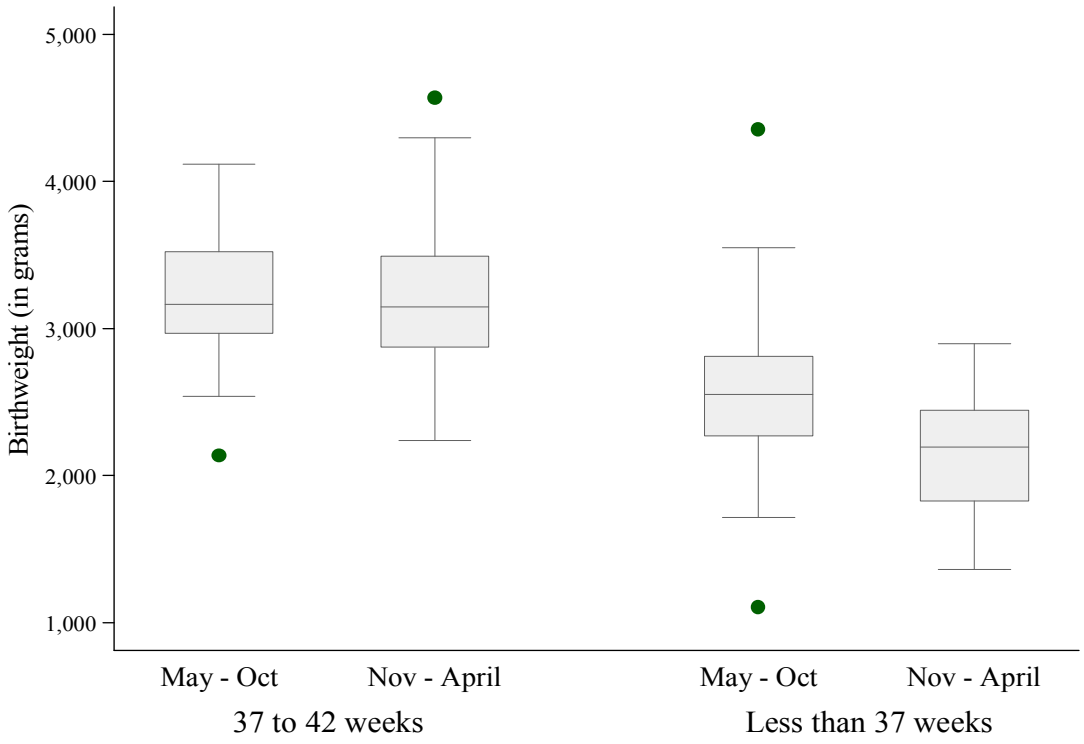


Figure 9. Box plots of infant birthweight by time of year and week of gestation at birth.



Chapter 5: Discussion

Preterm birth and LBW disproportionately affect minority populations and have adverse acute and long term impact. The proportion of preterm births and low birth rates in this cohort of women was higher than that reported in other studies of African-American and Caribbean births in New York City.[26] It is evident that interventions are needed to reduce the proportion of preterm birth and LBW in this community. Identification of specific exposures associated with preterm birth and LBW is also necessary to target interventions that would result in the greatest impact on pregnancy outcomes. Previous studies have reported cultural practices that may increase Caribbean–immigrant exposure to mercury.[57] This study examines the association between ethnicity or maternal nativity (US vs. non-US born) and mercury exposure or the odds of delivering a LBW infant and the odds of adverse pregnancy outcomes by season of conception.

5.1 Mercury

Uncorrected urinary mercury geometric means in this population are lower than the population- weighted values reported by McKelvey et al.(2011) for all women and NHW, NHB and Caribbean born black men and women.[57] The study population uncorrected and corrected urinary mercury values are also lower than those found in the 2007-2008 and 2009-2010 NHANES for NHB women age 16-49 and are similar to NHW women age 16-49 for the same time periods (Table 3). A nationwide trend in decreasing urinary mercury levels has been previously reported using the NHANES data.[77] Since mercury emissions have remained static over the past decade,[78] it is possible that the reductions in urinary mercury are due to increased education and decreasing activities that may lead to mercury exposure.

There was an association between place of maternal birth and infant cord blood mercury measurements. In contrast, there was no association between place of maternal birth and either preterm birth or LBW. Caribbean/ West Indian women delivered infants with significantly higher levels of cord blood mercury, but statistical significance was lost after controlling for frequency of fish intake, number of dental amalgams, and maternal place of birth. The decrease in cord blood mercury evident with increasing number of dental amalgams may represent higher educational or socioeconomic status in women who are able to receive dental care and who may also refrain from eating fish that historically have high levels of mercury contamination. The trend of increasing cord blood mercury with increased frequency of fish consumption is consistent with previous studies and findings for the entire cohort.[74] An interesting finding was the indirect relationship of cord blood mercury and either years in the United States or percent of life spent in the United States for women born outside the United States. Mercury has a half-life of 50 days in blood, within five half- lives or 250 days, 97 percent of a woman's methylmercury burden should be removed from her blood. This may suggest that women who are recent immigrants are continuing practices that expose them to higher levels of mercury, but that these practices change with the number of years living in the United States. Women born outside the United States who have recently immigrated may consume fish higher in methylmercury than women who have lived in the United States for longer periods of time and for more of their lives. It is interesting to note that the cord blood mercury levels for infants from women in the highest fish consumption group were statistically significantly higher in infants of women born outside the US than infants of women born in the US. It is possible that women who were born in the US were more

aware of the dangers of mercury and chose the types of fish they consumed accordingly. Women who almost never or never eat fish and were born outside the US had significantly higher infant cord blood mercury measurements, suggesting an independent source of mercury exposure in those women. The absence of infant cord blood mercury levels greater than 5 µg/L in preterm infants could suggest that fish consumption has a beneficial effect on gestation length as seen in other studies [79, 80] or could have resulted from sampling error as a result of a small sample of preterm infants.

In contrast to infant cord blood mercury, inorganic mercury measured in maternal urine did not vary with years or percent of life spent in the United States. Educational interventions should continue and include additional provisions for recently immigrated women to raise awareness of the sources and dangers of methylmercury. The association of urinary mercury and number of dental amalgams is consistent with known exposures of mercury.

There was no association between infant cord blood or urinary mercury measurements with LBW or continuous anthropometric outcomes and no association of maternal urinary mercury with preterm birth. It is possible that the small sample size resulted in insufficient power to detect a difference. The cord blood mercury levels in this study are much lower than others that have reported LBW associated with mercury such as found by Foldpang et al. (1990)[81] who reported a mean infant cord blood mercury level of 21.0 µg/L compared to the highest level in this study which is 13.4 µg/L. The population studied by Foldspang was exposed to mercury through consumption of whale and seal organs and meat resulting in high levels. Associations of preterm birth with increasing maternal age (35 years of age and over) and LBW with preterm birth and

alcohol use during pregnancy found in this study are consistent with present understandings of risk factors for preterm birth and LBW.

5.2 Season

Another interesting finding in this survey is the association of low birth weight in infants conceived in December, January and February. Ford (2011) found a similar association of small for gestational age infants and conception in winter.[82] By itself, season is not a direct exposure, but instead serves as a proxy for geophysical, environmental exposures such as air pollution and psychosocial events such as annual religious holidays.[83, 84] Further examination of environmental exposures during the winter months is needed. Vitamin D is produced in smaller quantities in the Northern Hemisphere in winter due to decreased UV light intensity and skin coverage from increased layers of clothing. Additionally, cutaneous vitamin D synthesis is inefficient in individuals with heavily pigmented skin and is likely to be lower in this population of African American and Caribbean black women. Vitamin D levels in this cohort of women would inform the observation of a seasonal effect. Exposure to air pollutants may also increase in the winter.[85] Levels of indoor and outdoor non-volatile polycyclic aromatic hydrocarbons (PAHs) have been shown to increase in the heating season in New York City[86] and levels of ambient volatile organic compounds benzo[a]pyrene, toluene, ethylbenzene, and xylene were higher in winter in a Camden, New Jersey study.[87] The increased incidence of infectious diseases in the winter also cannot be ruled out as a factor in the increased odds of low birth weight seen in the winter months. Increases in odds of LBW due to seasonal effects need to be further explored.

5.3 Limitations

Convenience sampling of the population may have resulted in selection bias if women who chose to complete the questionnaire and provide urine samples, access to their delivery and medical information were different than women who chose not to participate in the survey. Additionally, while mercury levels in urine and blood were measured, levels of ω-3 fatty acids were not, therefore it is not known if women who consumed the highest levels of fish and seafood actually had higher level of ω-3 fatty acids than women who consumed less fish or seafood. Fish consumption is considered beneficial in pregnancy due to the association of fish consumption with increased levels of ω-3 fatty acids. The lack of ω-3 fatty acid measurements may have resulted in misclassification of the exposure to ω-3 fatty acids, masking the true association between ω-3 fatty acid levels and adverse birth outcomes. Seafood consumption was self-reported, subject to recall or other normative biases. Seafood consumption is also a potential source of PCBs. PCB measurements were not examined in this study.

Classification of the season of conception could be subject to misclassification bias due to the use of week of gestation at birth to back-calculate to the date of conception. Estimation of gestational age using either a woman's recall of the first day of her last menstrual period or ultra-sound dating may be inaccurate and could result in misclassification.[88, 89] Additionally, the inclusion of women whose pregnancy began within a few days of the end of a season may have biased the association since the majority of the beginning of the first trimester would have occurred during the adjacent

season. This non-differential misclassification would bias the resulting association toward the null hypothesis. In light of this consideration, the association found in this study may actually be greater than reported.

Other parameters that may have influenced birthweights such as parity, maternal height, weight and body mass index[90, 91] were unavailable and were not included in regression models. Infant gender was available only for 62 infants and was not considered in the analysis. Neighborhood-level effects such as the level of neighborhood organization, ethnic density and other psychosocial factors have been associated with preterm birth and/ or LBW but were not examined in this study.[92-95]

Cord blood mercury measurements were only available for 66 infants which may have provided insufficient power to adequately detect an association between cord blood mercury and adverse outcomes. In addition, the small numbers of outcomes compared to the number of parameters included in a logistic regression may result in unstable models and inaccurate strength and direction of association.[96] To avoid unstable models, logistic regressions were adjusted for fewer variables than the linear regressions.

Chapter 6: Conclusions

This study is consistent with other studies that do not show an association between prenatal mercury exposure mercury and preterm and term LBW. The relatively higher levels of infant cord blood mercury from mothers born outside the United States as well as the evidence of higher levels in women who have immigrated more recently suggests that interventions in newly immigrated women would be warranted to help decrease prenatal exposure to methylmercury. Policy solutions for the reduction of emissions and educational campaigns to promote consumption of low methylmercury containing fish should continue to be encouraged and implemented. Further examination of the factors that may influence the seasonal association with LBW is needed.

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