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Associations of Prenatal Maternal Blood Mercury Concentrations with Early and Mid-Childhood Blood Pressure: A Prospective Study

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Abstract

Background—Childhood blood pressure (BP) is an important determinant of adult cardiovascular disease. Prenatal exposure to methylmercury through maternal fish consumption has been reported to increase the BP of children years later.

Methods—Mother-child pairs were enrolled from Project Viva, a prospective cohort study in Massachusetts. From second trimester maternal blood samples, we measured erythrocyte mercury concentration. Systolic BP in children, measured up to 5 times per visit in early and mid-childhood (median ages 3.2 and 7.7 years), was the primary outcome. We used mixed-effect regression models to account for variation in the number of BP measurements and to average effects over both time points.

Results—Among 1,103 mother-child pairs, mean (SD) second trimester total erythrocyte mercury concentration was 4.0 (3.9) ng/g among mothers whose children were assessed in early childhood and 4.0 (4.0) ng/g for children assessed in mid-childhood. Mean (SD) offspring systolic BP was 92.1 (10.4) mm Hg in early childhood and 94.3 (8.4) mm Hg in mid-childhood. After adjusting for mother and infant characteristics, mean second trimester blood mercury concentration was not associated with child systolic BP (regression coefficient, 0.1 mm Hg; 95% CI, −1.3 to 1.5 for quartile 4 vs. quartile 1) at either time period. Further adjusting for second trimester maternal fish consumption, as well as docosahexaenoic acid and eicosapentaenoic acid consumption, did not substantially change the estimates.

Conclusions—The results of this study demonstrate an absence of association between childhood blood pressure and low-level mercury exposure typical of the general US population.

Keywords

mercury; prenatal exposure; blood pressure

INTRODUCTION

Fish is the primary dietary source of omega-3 (n-3) polyunsaturated fatty acids, which may promote cardiovascular health by lowering resting heart rate and blood pressure (BP), improving endothelial function, increasing cardiac filling and myocardial efficiency, and decreasing vascular inflammation (Mozaffarian and Wu 2011). In fact, fish consumption, especially of species higher in omega-3 fatty acids, is associated with a markedly reduced risk of cardiovascular disease and sudden cardiac death (Chowdhury et al. 2012; Mozaffarian and Rimm 2006; Mozaffarian and Wu 2011). However, fish may also be contaminated with methylmercury, a toxic heavy metal that bioaccumulates in the food chain and concentrates in larger, predatory fish. Prenatal exposure to methylmercury from seafood consumption may impair the cardiovascular health in children (Mone et al. 2004).

Mercury readily crosses the placenta and enters fetal circulation, where it has adverse neurocognitive effects (National Research Council 2000). However, the tissue-specific effects of mercury on the fetal heart and vasculature are unknown (Castoldi et al. 2003; Clarkson 2002). A longitudinal cohort study in the Faroe Islands reported that higher prenatal methylmercury exposure was associated with greater mean systolic and diastolic BP at age 7 years (higher by 14.6 mm Hg and 13.9 mm Hg, respectively, for 10 vs. 1 µg/L of cord blood mercury concentrations). In addition, mercury had a greater effect on children with low birth weights (Sørensen et al. 1999). A study in the Republic of Seychelles found that higher prenatal methylmercury exposure was associated with higher diastolic BP (0.36 mm Hg per 1 part per million increase in prenatal methylmercury exposure) but not systolic BP, and only among boys at age 15 years (Thurston et al. 2007). No effect was seen in girls or at age 12 (Thurston et al. 2007). Information on fish consumption was not available in these studies.

The biologic plausibility of an association between methylmercury exposure and BP is supported by the fact that mercury promotes oxidative stress, mitochondrial dysfunction, and lipid peroxidation (Salonen et al. 1995; Shenker et al. 1999; Yin et al. 2007). Mercury also decreases vascular endothelial repair, reduces the availability of nitric oxide, induces endothelial dysfunction, and promotes vascular smooth muscle proliferation, all of which may theoretically increase the risk of cardiovascular dysfunction (Aguado et al. 2013; Furieri et al. 2011; Lemos et al. 2012; Wiggers et al. 2008).

Thus, the balance between the potential harms for the cardiovascular system from methylmercury in fish and the potential benefit from nutrients is unclear. We sought to determine whether prenatal maternal blood concentrations of methylmercury among US women were associated with the offspring's BP in childhood years later.

MATERIALS AND METHODS

The Institutional Review Board of Harvard Pilgrim Health Care approved all study protocols, and all procedures were conducted in accordance with established ethical standards (Declaration of Helsinki 2008). Mothers provided written informed consent at the time of recruitment and again for their children's participation at each visit after delivery, including early- and mid-childhood. Children provided verbal assent at the mid-childhood visit.

Participants

Participants were enrolled in Project Viva, a prospective pre-birth cohort study in Massachusetts. Between April 1999 and July 2002, we recruited pregnant women at their initial prenatal visit to Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts (Gillman et al. 2004). Recruitment and retention procedures for this longitudinal cohort have been described elsewhere (Oken E et al. 2014). Women were eligible to enroll if they presented to their initial prenatal visit at <22 weeks of gestation, had a singleton pregnancy, did not plan to move away from the study area prior to delivery, and could complete study forms in English. To be included in this analysis, women had to have second trimester blood samples collected.

Data Collection

Red blood cell mercury concentrations—At the second study visit, we collected maternal blood samples in Vacutainer tubes (Becton, Dickinson and Company) containing ethylenediaminetetraacetic acid. The tubes were centrifuged at 2,000 rpm for 10 minutes at 4 °C to separate plasma from erythrocytes, which were then washed with chilled saline. Erythrocyte aliquots were stored at -70 °C until analysis.

Total mercury concentration was measured using the Direct Mercury Analyzer 80 (Milestone Inc.). Results were reported as mercury concentration in the original red cell sample. The detection limit was 0.5 ng/mL of sample. Blood samples from the interlaboratory study program from INSPQ/ Laboratoire de Toxicologie, Quebec, were used as the quality control samples to monitor the accuracy and interday and intraday repeatability of the analysis. Concentrations of the quality control samples ranged from 3 ng/mL to 30.09 ng/mL. Percentage recoveries of these samples were between 87% and 104%. The interday repeatability ranged from 1.5% to 11.7%, and the intraday repeatability ranged from 0.2% to 11.4%. Percentage differences for duplicate analysis of quality control samples ranged from 0.04% to 12.4%.

Blood pressure in children at early and mid-childhood—At the early and mid-childhood study visits, trained research assistants measured each child's BP up to five times, at 1-minute intervals, using biannually calibrated Dinamap Pro 100 or Pro 200 (Critikon Inc.) automated BP monitors. The conditions of measurement were recorded, including the activity of the child (sleeping, quiet awake, active awake, or crying at the early childhood visit and quiet, still, talking, or moving at the mid-childhood visit); cuff size (child, small

adult, adult, large adult); arm used for the measurement; and position (sitting, semi-reclining or standing).

Covariates—We studied covariates that were of *a priori* interest as independent predictors of child cardiovascular health. Using questionnaires and interviews, we collected information at study enrollment on maternal age, race/ethnicity, education, prenatal smoking and alcohol consumption, marital status, pre-pregnancy height and weight (from which we calculated body mass index [BMI]), and history of hypertension.

Maternal second trimester fish intake, measured on an ordinal scale of servings per week, was assessed with a food-frequency questionnaire (FFQ). The FFQ is modeled on one that has been extensively used in several other cohort studies and was previously validated for erythrocyte fatty acid content during pregnancy (Donahue SM et al. 2009; Fawzi et al. 2004; Rimm EB et al. 1992; Willett WC et al. 1985). The FFQ assessed average frequency of consumption of over 140 foods and beverages, as well as vitamin and supplement use, over the past 3 months. We multiplied a weighted value assigned to the frequency of consumption on the FFQ by the nutrient composition of each item to obtain specific nutrient intake. We derived nutrient estimates from the Harvard nutrient composition database (Hu et al. 2002; Iso et al. 2001). We used the nutrient residuals method to energy adjust the estimates of micronutrient intake (Willett WC et al. 1998).

Infant birth weight and date was obtained from the hospital clinical record, and gestational age was calculated using the last menstrual period. If the estimate of gestational age from the second trimester ultrasound differed by more than 10 days, we used the ultrasound measurement instead. Z scores for gestational age-adjusted birth weight (a measure of fetal growth) were calculated from US national natality data (Oken et al. 2003). The duration of breast-feeding was determined from questionnaires administered 6 and 12 months postpartum.

At the early and mid-childhood study visits, trained research assistants measured child weight (early childhood: Seca model 881, Seca Corp; mid-childhood: Tanita model TBF-300A, Tanita Corporation of America, Inc.) and height (Shorr stadiometer, Shorr Productions) using standard techniques. We calculated BMI and age- and sex-specific BMI z-scores from Centers for Disease Control and Prevention reference data (National Center for Health Statistics).

Statistical Methods

We assessed bivariate associations of maternal and child characteristics with child systolic BP in early and mid-childhood using separate linear regression models with the outcome as the mean of the (up to) five BP measurements at each visit. The associations between predictors and covariates with child BP were similar at both outcome time points, and BP in early childhood was correlated with BP in mid-childhood ($r=0.28$). To improve power and prediction, we incorporated the two outcome time points in the same analysis using mixed-effect regression models, with an indicator for time as both a fixed- and random-effect covariate (Laird and Ware 1982).

Each BP measurement was treated as a repeated measure. In all models, we adjusted for BP measurement conditions (child state and position, arm used, and measurement sequence number) to minimize measurement error, as well as for child exact age and sex. Systolic BP was the main outcome because it predicts later outcomes better than does diastolic BP and is measured more accurately with the Dinamap (Chobanian et al. 2003; Whincup et al. 1992). In all multivariate models, we examined second trimester mercury concentration in quartiles.

We created four multivariate models. Model 1 was adjusted for visit (early or mid-childhood), measurement conditions, and child age and sex. In Model 2, we also adjusted for potential confounders, including maternal age, race/ethnicity, education, marital status, pre-pregnancy BMI, smoking status, and second trimester BP, as well as child BMI z-score and fetal growth z-score. In model 3, we adjusted Model 2 for maternal second trimester fish intake, and in Model 4, for docosahexaenoic acid+eicosapentaenoic acid (DHA+EPA), as measured in the food frequency questionnaire intake.

Not all participants had complete data, although most were missing only one or two measures. We therefore used multiple imputation to generate several plausible values for each missing characteristic (Horton and Kleinman 2007; Rubin). A “completed” data set comprised the observed data and one imputed value for each missing value. We replicated this analysis across completed data sets and then combined them in a structured manner that reflects the true amount of information in the observed data. This process recovers information in participants with missing data without presuming that the imputed values are known true values. We generated 50 complete data sets and combined multivariable modeling results (Proc MIANALYZE) in SAS version 9.3 (SAS Institute, Cary NC).

From these multiple imputation results, we report adjusted differences estimated from regression coefficients and 95% confidence intervals (CI). The data met the assumptions of all statistical tests. Alpha was set at 0.05, and all tests were two-tailed.

RESULTS

Characteristics of Mothers and Offspring

Of 2,128 women who delivered a live singleton infant, we excluded 45 whose infant had a gestational age at birth less than 34 weeks and another 489 who did not have a second trimester blood draw. Of 1594 women with information on prenatal mercury concentrations, we examined 1,031 children in early childhood and 865 in mid-childhood (1,103 mother-child pairs total; Table 1).

Compared with the 980 women who were not included in this analysis, the 1,103 mothers in the present study were more likely to be white (74% vs. 60%), to be college graduates (71% vs. 58%), to be slightly older (mean age, 32.4 vs. 31.2 years), and to have lower pre-pregnancy BMI (24.6 vs. 25.1 kg/m²). However, included and excluded participants did not differ in mean gestational age at birth (39.6 vs. 39.6 weeks), pregnancy weight gain (15.7 vs. 15.6 kg), or child sex (48.3% vs. 49.1% female).

Among mothers who attended the early childhood visit, 75.6% were white, 65.4% had a pre-pregnancy BMI below 25 kg/m², 5.0% reported a history of high BP, and 22.8% reported consuming more than 2 servings of fish/week during the second trimester. Maternal characteristics at the mid childhood visit were similar (Table 1). Among the 1,103 mothers, mean second trimester total erythrocyte mercury concentration was 4.0 ng/g for those who provided information at the early or mid-childhood visits (medians from lowest to highest quartile: 1.0, 2.2, 3.8, and 7.0 ng/g). As expected, self-reported second trimester fish intake and estimated DHA+EPA intake were strongly associated with maternal blood mercury levels. A serving/week increase in self-reported second trimester fish intake was associated with a 1.03 ng/g (95% CI 0.84, 1.21) increase in second trimester blood mercury level. A gram/day increase in second trimester DHA+EPA was associated with a 7.59 ng/g (95% CI 5.91, 9.27) increase in second trimester blood mercury level.

Primary Endpoint

Mean (SD) child systolic BP was 92.1 (10.4) mm Hg in early childhood and 94.3 (8.4) mm Hg in mid-childhood.

Maternal smoking during pregnancy, hypertension, and higher pre-pregnancy BMI were associated with higher child systolic BP in mid-childhood (Table 2). Gestational age at birth was inversely associated with child systolic BP at both early and mid-childhood. Child BMI z-scores were directly associated systolic BP measured at the same visit. Second trimester maternal fish consumption was not associated with child systolic BP (Table 2).

Second trimester blood mercury concentration was not associated with child systolic BP, either in unadjusted analysis (Table 3, Model 1) or after adjusting for parent and child characteristics (difference between quartile 4 and quartile 1, 0.08 mm Hg; 95% CI, -1.32 to 1.48). Further adjustments for fish consumption (0.32 mm Hg; 95% CI -1.23 to 1.88; Model 3), as well as DHA and EPA consumption (0.00 mm Hg; 95% CI -1.50 to 1.51, Model 4), yielded similarly null associations (Table 3). Neither maternal prenatal fish consumption (zero v. >2 servings per week: 0.79 mm Hg; 95% CI, -1.01 to 2.60) nor DHA+EPA intake (0.53 mm Hg; 95% CI, -2.58 to 3.65) was associated with child systolic BP (from Models 3 and 4).

DISCUSSION

Childhood BP is an important determinant of adult cardiovascular disease and hypertension risk (Lauer and Clarke 1989). The potential mechanisms by which early life factors, including environmental toxicant exposure, may influence BP regulation are largely unknown. The literature on the cardiotoxicity of prenatal mercury exposure is sparse and contradictory, so we sought to examine this association in a cohort of US mother-child pairs. We found that higher prenatal mercury exposure was not associated with any difference in systolic BP in early and mid-childhood among a population with generally low mercury exposure.

Sørensen et al. reported an association between prenatal methylmercury exposure and childhood BP among 7-year-old children from the Faroe Islands with substantially (~10x)

higher mercury exposures. In that analysis, the association between mercury exposure and blood pressure was modified by birth weight. For children with low birth weight (<3700 g), an increase in cord blood mercury concentration from 1 to 10 µg/L of cord blood was associated with a mean increase in systolic (20.9 mm Hg; 95% CI, 10.9 to 31.0) and diastolic (24.4 mm Hg; 95% CI, 14.0 to 34.7) BP. For children with a birth weight above 3700 g, the same incremental increase in mercury concentration in cord blood was associated with a 9.6-mm Hg (95% CI, 1.2 to 18.1) increase in systolic BP and a 6.7-mm Hg (95% CI, -2.0 to 15.5) increase in diastolic BP. By comparison, in the Seychelle Islands cohort, also a highly exposed population, Thurston et al. found an association between prenatal methylmercury exposure and diastolic BP only in adolescent boys (mean, 0.36 mmHg per ppm methylmercury; SE, 0.12). This association seems likely to have been a chance finding, given that there is no explanation as to why the effect would be only on diastolic BP and seen only in boys at age 15 but not at younger ages or among girls.

Much of the literature on prenatal methylmercury exposure has focused on methylmercury as a neurotoxicant and the harm to neurodevelopment. The cardiovascular risk of methylmercury exposure has also been more extensively explored in adults than in children. Methylmercury exposure has a known effect on the autonomic nervous system, and in particular on heart rate variability (Lim et al. 2010; Valera et al. 2008; Valera et al. 2011; Valera et al. 2012; Yaginuma-Sakurai et al. 2010). Mercury exposure has also been associated with an increased risk of myocardial infarction and accelerated progression of carotid atherosclerosis (Choi et al. 2009; Salonen et al. 2000). In a case-control study among men with a first diagnosis of myocardial infarction compared to representative controls in European countries and Israel, Guallar et al., found that the highest mercury exposure (measured from toenails) was associated with an increased risk of myocardial infarction, for which hypertension is a major risk factor. This group argued that high mercury concentrations may reduce the beneficial effects of fish consumption on cardiovascular health (Guallar et al. 2002).

Several epidemiologic studies of adults have found that mercury exposure is associated with higher systolic BP (Choi et al. 2009; Valera et al. 2009). However, Mozaffarian et al. found that data from two large, prospective cohort studies (the Health Professionals Follow-up Study and the Nurses' Health Study) did not support an association between methylmercury exposure and an increased risk of hypertension or coronary artery disease in men or women, with a median follow-up time of 11.3 years. (Mozaffarian and Shi et al. 2011).

Strengths and Limitations of the Study

Strengths of the current study include measurements of a wide variety of maternal and child characteristics and the use of rigorous methods for measuring exposure and outcome. Blood mercury concentration is a more accurate measure of exposure than dietary assessment, given the difficulties in recalling fish species and quantifying species-specific mercury levels (Groth 2010). We used total mercury concentrations in maternal second-trimester erythrocytes as the measure of fetal methylmercury exposure. Maternal first- and second-trimester blood mercury concentrations closely correlate with blood mercury at delivery and in cord blood (Ramirez et al. 2000; Sakamoto et al. 2004; Vahter et al. 2000). In previous

work in Project Viva, we found that maternal erythrocyte mercury concentrations were strongly and directly correlated with mercury in maternal hair collected at delivery and inversely with child cognition in early childhood (Oken et al. 2008).

Additionally, we used rigorous, standardized measures of BP using repeated measures and clear documentation of conditions that might influence levels. We included two childhood time points, neither of which showed any associations with prenatal mercury concentrations. Therefore, it is unlikely we missed an early effect that attenuated in mid-childhood.

This study also has several limitations. High-level mercury exposure is not prevalent in Project Viva participants. Most of the studies assessing the relationship between methylmercury exposure and BP have been conducted in populations with moderate levels of fish consumption and mercury exposure (e.g., island populations with daily fish consumption and arctic Inuit populations) (Sørensen et al. 1999; Thurston et al. 2007; Valera et al. 2012). However, the fish and dietary DHA intake of mothers in Project Viva was similar to that reported for the general North American population (Knobeloch et al. 2005; Traynor et al. 2013). Although the lack of a wide range of exposure could have masked an association at higher levels, the low-level exposure is more representative of the general US population. We studied preschool and school age children, so it is possible that an effect becomes manifest only in adolescence or adulthood. A transient effect of prenatal mercury exposure on blood pressure in infancy or toddler years may be possible, and may be a marker of susceptibility to prenatal mercury, but the lifetime impact of such an effect is unknown. Additionally, we estimated DHA and EPA intake by FFQ, which could introduce measurement error and therefore we may not have fully accounted for the negative confounding from nutrients. However, we and others have previously reported moderate to strong associations between long-chain n-3 fatty acid intake estimated by FFQ and blood fatty acid concentrations, suggesting that FFQ is a reliable method for estimating nutrient intake during pregnancy (Donahue SM et al. 2009; Fawzi WW et al. 2004).

Conclusions

Insight into the environmental contributors to prenatal programming of childhood BP is critical to the broader understanding of the longitudinal development of adult hypertension. Fish is an important source of dietary protein throughout the world and contains numerous beneficial nutrients, including polyunsaturated fatty acids, vitamin D, selenium, and iodine. Dietary guidelines for pregnant women must weigh the nutritional benefits of fish and the contaminant risk. The results of this study do not support an association between childhood blood pressure and low-level mercury exposure typical of the general US population.

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Table 1

Characteristics of 1,103 Mother-Child Pairs in a Study Assessing the Association between Maternal Mercury Consumption and Children's Blood Pressure in Early and Mid-Childhood. Participants were enrolled in Project Viva.

Variable	Mother-child pairs who attended early childhood visit (n=1,031)	Mother-child pairs who attended mid-childhood visit (n=865)
Mothers during pregnancy		
2 nd trimester erythrocyte mercury, mean (SD), ng/g	4.0 (3.9)	4.0 (4.0)
2 nd trimester DHA + EPA intake, mean (SD), gm/day	0.2 (0.2)	0.2 (0.2)
2 nd trimester fish intake, mean (SD), servings/week	1.6 (1.4)	1.6 (1.5)
3 rd trimester systolic BP, mean (SD), mm Hg	111.3 (8.3)	110.9 (8.4)
Age, n (%)		
<25 years	65 (6.3)	67 (7.7)
25 to 30 years	201 (19.5)	172 (19.9)
30 to 35 years	440 (42.7)	346 (40.0)
35 years	325 (31.5)	280 (32.4)
Race/ethnicity, n (%)		
Black	116 (11.3)	124 (14.4)
Hispanic	51 (5.0)	42 (4.9)
White	779 (75.6)	625 (72.3)
Other	84 (8.2)	73 (8.5)
College graduate, n (%)		
No	285 (27.7)	253 (29.3)
Yes	746 (72.3)	612 (70.7)
Married or cohabitating, n (%)		
No	63 (6.1)	62 (7.2)
Yes	968 (93.9)	803 (92.8)
Smoking status at enrollment, n (%)		
Never	712 (69.1)	617 (71.3)
Former	213 (20.6)	168 (19.5)
Smoked during pregnancy, n (%)		
	106 (10.3)	80 (9.3)
Pre-pregnancy BMI, n (%)		
<25 kg/m ²	674 (65.4)	572 (66.1)
25–<30 kg/m ²	225 (21.8)	185 (21.4)
30 kg/m ²	132 (12.8)	108 (12.5)
History of high blood pressure, n (%)		
No	980 (95.0)	822 (95.0)
Yes	51 (5.0)	43 (5.0)
2nd trimester fish consumption, n (%)		
0 servings/week	127 (12.4)	104 (12.0)
>0 to 2 servings/week	669 (64.9)	558 (64.5)
>2 servings/week	235 (22.8)	203 (23.5)

Variable	Mother-child pairs who attended early childhood visit (n=1,031)	Mother-child pairs who attended mid-childhood visit (n=865)
Children		
Gestation length, mean (SD), weeks	39.6 (1.4)	39.7 (1.4)
Fetal growth, mean (SD), z-score	0.22 (0.95)	0.22 (1.06)
Breast feeding duration, mean (SD), months	6.5 (4.7)	6.5 (4.7)
First born, n (%)		
No	545 (52.9)	449 (51.9)
Yes	486 (47.1)	416 (48.1)
Female, n (%)		
No	528 (51.2)	439 (50.8)
Yes	503 (48.8)	426 (49.2)
Child characteristics at outcome visit		
Age, mean (SD), months	39.2 (4.1)	94.8 (9.8)
Systolic BP, mean (SD), mm Hg	92.1 (10.4)	94.3 (8.4)
Height, mean (SD), cm	97.4 (4.6)	128.4 (7.5)
Weight, mean (SD), kg	15.7 (2.2)	28.4 (7.2)
BMI, mean (SD), kg/m ²	16.5 (1.5)	17.1 (2.9)
BMI, mean (SD), z-score	0.43 (1.05)	0.35 (1.07)

DHA + EPA, docosahexaenoic acid+eicosapentaenoic acid; SD, standard deviation; BMI, body mass index; BP., blood pressure

Table 2

Unadjusted Effect Estimates of Maternal and Child Characteristics with Child Systolic Blood Pressure in Early and Mid-Childhood among 1,103 Mother-Child Pairs.

Variable	Estimate (95% CI)	
	Early Childhood (n=1,031)	Mid-Childhood (n=865)
MOTHERS		
2nd trimester erythrocyte mercury, ng/g		
First quartile	0.0 (ref)	0.0 (ref)
Second quartile	1.1 (−0.9 to 3.0)	−1.3 (−3.1 to 0.5)
Third quartile	1.5 (−0.4 to 3.5)	0.5 (−1.2 to 2.2)
Fourth quartile	1.3 (−0.5 to 3.2)	−1.1 (−2.9 to 0.6)
2nd trimester DHA + EPA intake, gm/day	1.8 (−2.4 to 6.0)	0.6 (−3.0 to 4.2)
2nd trimester fish intake, servings/week	0.00 (−0.5 to 0.5)	0.2 (−0.3 to 0.6)
3rd trimester systolic BP, mmHg	0.1 (0.00 to 0.2)	0.2 (0.1 to 0.2)
Age, n		
<25 years	−2.5 (−5.3 to 0.3)	−0.4 (−2.6 to 1.9)
25 to 30 years	0.6 (−1.3 to 2.4)	1.4 (−0.2 to 3.0)
30 to 35 years	0.1 (−1.4 to 1.6)	0.3 (−1.1 to 1.6)
35 years	0.0 (ref)	0.0 (ref)
Race/ethnicity, n		
Black	0.7 (−1.4 to 2.8)	1.0 (−0.6 to 2.6)
Hispanic	0.7 (−2.3 to 3.6)	−1.9 (−4.5 to 0.7)
White	0.0 (ref)	0.0 (ref)
Other	0.2 (−2.1 to 2.6)	0.5 (−1.6 to 2.5)
College graduate, n		
No	0.0 (ref)	0.0 (ref)
Yes	0.2 (−1.2 to 1.7)	−0.6 (−1.8 to 0.7)
Married or cohabitating, n		
No	0.0 (ref)	0.0 (ref)
Yes	−0.7 (−3.5 to 2.0)	−1.2 (−3.4 to 1.0)
Smoking status, n		
Never	0.0 (ref)	0.0 (ref)
Former	1.1 (−0.4 to 2.7)	1.9 (0.5 to 3.3)
Smoked during pregnancy	0.1 (−2.1 to 2.2)	2.1 (0.1 to 4.0)
Pre-pregnancy BMI, kg/m²		
<25	0.0 (ref)	0.0 (ref)
25 to 30	−0.4 (−2.0 to 1.2)	1.6 (0.3 to 3.0)
30	1.1 (−0.9 to 3.1)	2.7 (1.0 to 4.4)
High blood pressure, n		
No	0.0 (ref)	0.0 (ref)
Yes	2.7 (−0.3 to 5.7)	5.6 (3.0 to 8.2)
2nd trimester fish consumption, servings/week		

Variable	Estimate (95% CI)	
	Early Childhood (n=1,031)	Mid-Childhood (n=865)
0	-1.1 (-3.5 to 1.2)	0.8 (-1.3 to 2.8)
>0 to 2	-0.9 (-2.5 to 0.7)	0.3 (-1.1 to 1.7)
>2	0.0 (ref)	0.0 (ref)
CHILDREN		
Gestation length, weeks	-0.5 (-1.0 to -0.1)	-0.4 (-0.8 to 0.0)
Fetal growth, z-score	-0.2 (-0.8 to 0.5)	-0.1 (-0.7 to 0.4)
Breast feeding duration, months	0.0 (-0.2 to 0.1)	0.0 (-0.2 to 0.1)
First born, n		
No	0.0 (ref)	0.0 (ref)
Yes	1.3 (0.0 to 2.6)	0.5 (-0.7 to 1.6)
Female		
No	0.0 (ref)	0.0 (ref)
Yes	-0.5 (-1.8 to 0.7)	-0.2 (-1.3 to 1.0)
Characteristics at outcome visit		
Age, months	0.2 (0.0 to 0.3)	0.2 (0.1 to 0.2)
Height, cm	0.4 (0.3 to 0.6)	0.3 (0.3 to 0.4)
Weight, kg	1.1 (0.8 to 1.4)	0.5 (0.4 to 0.5)
BMI, kg/m ²	1.2 (0.8 to 1.6)	1.0 (0.8 to 1.2)
BMI, z-score	1.7 (1.1 to 2.4)	2.7 (2.1 to 3.2)

DHA + EPA, docosahexaenoic acid+eicosapentaenoic acid

Table 3

Association of Second Trimester Maternal Blood Mercury Concentrations with Child Systolic Blood Pressure among 1,103 Mother-Child Pairs

Regression coefficients for associations between maternal blood mercury concentrations and child systolic blood pressure (95% confidence interval)				
Blood mercury	Model 1	Model 2	Model 3	Model 4
First quartile	0.0 (ref)	0.0 (ref)	0.0 (ref)	0.0 (ref)
Second quartile	−0.1 (−1.6 to 1.3)	0.0 (−1.4 to 1.3)	0.0 (−1.4 to 1.4)	−0.1 (−1.5 to 1.3)
Third quartile	0.9 (−0.5 to 2.4)	0.8 (−0.5 to 2.2)	0.9 (−0.5 to 2.3)	0.8 (−0.6 to 2.2)
Fourth quartile	−0.1 (−1.5 to 1.4)	0.1 (−1.3 to 1.5)	0.2 (−1.3 to 1.8)	0.0 (−1.5 to 1.5)

Model 1. Adjusted for visit (early or mid childhood) and measurement conditions

Model 2. Model 1 + maternal age, race/ethnicity, education, marital status, pre-pregnancy BMI, smoking during pregnancy, third trimester SBP and child age, sex, fetal growth z-score, and BMI z-score.

Model 3. Model 2 + maternal second trimester fish intake

Model 4. Model 2 + maternal second trimester DHA + EPA intake