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Maternal prenatal fish consumption and cognition in mid childhood: Mercury, fatty acids, and selenium

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ABSTRACT

Background: Few studies of maternal prenatal fish intake have included biomarkers of exposure to mercury, long-chain n-3 fatty acids, and selenium, which are hypothesized to mediate associations with child neurodevelopment.
Objectives: Examine associations of maternal prenatal fish intake with child neurodevelopment accounting for biomarkers.
Methods: In 1999–2002 we enrolled pregnant women into the Project Viva cohort. At median 27.9 weeks gestation, we estimated maternal fish intake using food frequency questionnaires, and collected blood. We assayed erythrocytes for total mercury and selenium, and plasma for fatty acids including n-3 docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). In mid-childhood (median 7.7 years), we administered cognitive tests including the Kauffman Brief Intelligence Test (KBIT). We performed multivariable linear regression analyses adjusting for maternal and child characteristics including home environment and maternal intelligence.
Results: Among 1068 pairs (872 with blood), mean (SD) exposures were: maternal fish intake 1.7 (1.5) servings/week, mercury 4.0 (3.6) ng/g, DHA + EPA 98.4 (41.8) mcg/ml, selenium 205.6 (34.6) ng/ml. Child KBIT verbal scores (mean 112.2, SD 15.0) were not related to any exposures: maternal fish intake (0.15; 95% CI: −0.50, 0.79), mercury (0.08; −0.18, 0.35), DHA + EPA (0.01; −0.22, 0.24), and selenium (0.20; −0.09, 0.50). Associations with KBIT nonverbal scores and tests of memory and visual motor abilities were similarly null. Mutual adjustment for each of the exposure measures did not substantially change estimates.
Conclusions: In this population with an average fish consumption of about 1 1/2 weekly servings, we did not see any evidence for an association of maternal prenatal fish intake, or of mercury, DHA + EPA, or selenium status, with verbal or non-verbal intelligence, visual motor function, or visual memory at median 7.7 years of age.

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1. Introduction

Debate about the optimal amount and type of fish intake during pregnancy is ongoing and fervent. In 2001 the US Food and Drug Administration and Environmental Protection Agency released an advisory recommending that pregnant women and women of childbearing age limit their fish intake to <12 oz per week to minimize fetal exposure to methylmercury, an environmental contaminant that is concentrated in fish and is a known fetal neurotoxicant (Food and Drug Administration, 2001; Goyer et al., 2000; Nesheim and Yaktine, 2007). This initial guideline did not consider that fish is also a rich source of many beneficial nutrients including the elongated n-3 polyunsaturated

Abbreviations: BMI, body mass index; CI, confidence interval; DHA, docosahexaenoic acid 3; EPA, eicosapentaenoic acid; FFQ, food frequency questionnaire; HOME, Home Observation Measurement of the Environment; IQR, inter quartile range; KBIT, Kaufman Brief Intelligence Test; OR, odds ratio; ppm, parts per million (mcg/g); WRAML, Wide Range Assessment of Memory and Learning; WRAVMA, Wide Range Assessment of Visual Motor Abilities.

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fatty acids (PUFA) docosahexaenoic acid and eicosapentaenoic acid (DHA, EPA) that might benefit brain development (Nesheim and Yaktine, 2007), although updated guidance published in 2004 and 2014 discussed nutritional value of fish and recommended consumption of a minimum of 8 weekly ounces of fish lower in mercury (US Department of Health and Human Services, 2004; US Food and Drug Administration, 2014). There was concern that the 2001 advisory resulted in lower overall intake of fish, perhaps resulting in net public health harm (Oken et al., 2003; Shimshack and Ward, 2010). Also, guidelines for methylmercury exposure were based on populations with high methylmercury exposure or very frequent seafood consumption. Whether the less frequent habitual fish intake typical of most US populations might also result in toxicity was not available in published literature.

Over the past 15 years, several investigations of populations with moderate fish consumption have found no evidence of neurodevelopmental harm, and some suggestion of benefit, from greater maternal fish intake, even above 12 weekly ounces (Hibbeln et al., 2007; Lederman et al., 2008; Oken et al., 2008; Valent et al., 2013). Some of these studies also found statistical (but not clinical) evidence that prenatal mercury levels below the current benchmark dose were associated with poorer development (Lederman et al., 2008). For example, in our previous analysis of 341 mother-child pairs enrolled in the Project Viva cohort in Massachusetts, we found that higher maternal fish intake >2 servings/week was associated with better child cognitive test performance in early childhood (3–5 years) compared with <1 monthly fish meal, but higher mercury levels were associated with poorer test scores (Oken et al., 2008). However, we performed only two cognitive tests in these young children, did not see an association of maternal red cell fatty acid concentration with child cognition, and did not have any information on selenium, a nutrient that may protect against mercury's toxic effects (Ralston and Raymond, 2010).

In the present study, our primary aim was to examine associations of maternal prenatal fish consumption with multiple cognitive outcomes including overall intelligence in mid-childhood (6–10 years). Our secondary aim was to examine associations of the toxicant (mercury) and nutrients (DHA + EPA) richly sourced from fish, with the same outcomes. Additionally, we examined whether concentrations of elongated fatty acids or selenium modified the associations of mercury with cognitive outcomes.

2. Methods

2.1. Participants

We studied participants in Project Viva, a prospective longitudinal cohort study designed to examine prenatal diet and other health factors in relation to pregnancy and child health outcomes. From 1999 to 2002, Project Viva staff enrolled pregnant women attending prenatal care visits at 8 obstetrical offices of Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts. Exclusion criteria included multiple gestation, inability to answer questions in English, gestational age ≥22 weeks at initial prenatal care appointment, and plans to move away from the area prior to delivery. We completed in-person visits with mothers during pregnancy in the late first (median 9.9 weeks of gestation) and second (median 27.9 weeks) trimesters. We saw mothers and children in the hospital during the delivery admission and during infancy (median age 6.3 months), early childhood (median 3.2 years) and mid-childhood (median 7.7 years). Full details of recruitment and follow-up at through mid-childhood have been reported (Oken et al., 2015) and all study aims and questionnaires are available on our website (https://www.hms.harvard.edu/viva/). Institutional review boards of participating institutions approved the study protocols and mothers gave written informed consent at enrollment and child follow-up.

Of the 2128 live births, we obtained cognitive outcome measures at in-person visits with 1110 children (65% of the 1708 who had not disenrolled and thus remained eligible for that visit). Of these, we also had information on maternal mid-pregnancy exposures from 1068 pairs, who comprised the main cohort for our analysis of prenatal fish intake with cognitive outcomes. We also collected mid-pregnancy blood from 872 mothers, who form the analytic sample for our analyses of prenatal biomarkers and child cognition. The mothers included in the analytic sample were very similar in many respects to the overall cohort (Table S1) including in fish intake (13% with ≥3 weekly fish servings), but were slightly older (mean 32.2 vs. 31.8 years), had higher annual household income at enrollment (64% vs. 58% > $70,000), and had higher IQ (KBIT 106.7 vs. 105.4 points).

2.2. Exposures

Maternal diet. At the mid-pregnancy and post-delivery visits, mothers completed semiquantitative food frequency questionnaires (FFQ), which we modified for pregnancy from a well-validated instrument used in several large cohort studies (Rimm et al., 1992; Willett et al., 1985). The mid-pregnancy questionnaire quantified average frequency of consumption of over 140 foods and beverages during the previous three months. The limited post-delivery questionnaire had 9 questions focused on major dietary contributors to fatty acid intake in the month prior to delivery. Both instruments assessed consumption of fish and shellfish (hereafter "seafood") with four questions: "canned tuna fish (3–4 oz)"; "shrimp, lobster, scallops, clams (1 serving)"; "dark meat fish, e.g. mackerel, salmon, sardines, bluefish, swordfish (3–5 oz)"; and "other fish, e.g. cod, haddock, halibut (3–5 oz)". Six frequency response options ranged from "never/<1 per month" to "1 or more servings per day." We combined responses to the four questions to estimate average total fish intake.

We also used the FFQs to estimate intake of DHA and EPA. We used the Harvard nutrient database, which is based on US Department of Agriculture publications as well as other published sources and personal communications, and has been used in Project Viva and other cohort studies of n-3 fatty acid intake (Hu et al., 2002; Oken et al., 2004; US Department of Agriculture Agricultural Research Service, 1999). We have previously validated these questionnaires against erythrocyte and plasma levels of elongated n-3 fatty acids (Fawzi et al., 2004; Oken et al., 2014).

Maternal blood. At the second trimester visit, we obtained blood specimens in vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA). We centrifuged tubes at 2000 rpm for 10 min at 4 °C to separate plasma from erythrocytes (red blood cells), which we then washed with chilled saline. We stored erythrocyte and plasma aliquots at −70 °C, but did not store any whole blood. We collected umbilical cord blood by venipuncture after delivery of the infant, and stored plasma at −70 °C. We did not retain cord erythrocytes.

We measured maternal and cord plasma fatty acids using liquid-gas chromatography, and report fatty acid concentrations in mcg/ml. Analytic methods have good within-run precision (coefficient of variance <5.4%) and been previously validated (Lin et al., 2012). For this analysis, we used the sum of DHA and EPA, the two long-chain n-3 polyunsaturated fatty acids that are found in highest concentrations in fish and are of greatest interest for neurodevelopment.

We measured total mercury in erythrocytes using the Direct Mercury Analyzer 80 (Milestone Inc., Monroe, CT). A separate aliquot of erythrocytes was provided for mercury analysis, and we used the entire sample to minimize errors resulting from possible inhomogeneity resulting from the red cell membranes, which we have observed in the past when using sub-aliquots. Results were reported as mercury content in the original red cell sample. The detection limit was 0.5 ng/g of sample, and percent recovery for QC standards was 90–110%. For the selenium assay, we analyzed erythrocyte samples after digestion at room temperature for 24 h with nitric acid, followed

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