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Associations of Seafood and Elongated n-3 Fatty Acid Intake with Fetal Growth and Length of Gestation: Results from a US Pregnancy Cohort

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Previous studies, mainly among populations with high consumption of seafood, have suggested that increased marine n-3 polyunsaturated fatty acid (PUFA) intake during pregnancy promotes longer gestation and higher birth weight. Few studies have isolated the contribution of fetal growth to birth weight. Using data from 2,109 pregnant women in Massachusetts enrolled in Project Viva from 1999 to 2002, the authors examined associations of marine n-3 PUFA and seafood intake with birth weight and birth-weight-for-gestational-age *z* value (fetal growth) using linear regression; length of gestation using median regression; and low birth weight, preterm delivery, and being small for gestational age using logistic regression. After adjustment for maternal and child factors, birth weight was 94 (95% confidence interval: 23, 166) g lower and fetal growth *z* value 0.19 (95% confidence interval: 0.08, 0.31) units lower in the highest compared with the lowest quartile of first-trimester n-3 PUFA intake. Results for the second and third trimesters were similar, and findings for seafood paralleled those for n-3 PUFA. Elongated n-3 PUFA intake and seafood intake were not associated with length of gestation or risk of preterm birth. Results from this US cohort support the conclusion that seafood intake during pregnancy is associated with reduced fetal growth.

birth weight; fatty acids, omega-3; fetal growth retardation; gestational age; prenatal nutrition; seafood

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Abbreviations: CI: confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acids; SFFQ, semiquantitative food frequency questionnaire.

Seafood is a primary dietary source of polyunsaturated fatty acids (PUFA) of the n-3 family. In particular, the elongated marine PUFA docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3) from seafood may confer health benefits throughout life. Several studies have demonstrated associations of diets rich in n-3 PUFA with reduced risk of adverse health conditions such as fatal and nonfatal cardiovascular disease (1, 2), cancers, and macular degeneration (3). Higher intake of DHA in infancy may improve early cognitive function and vision (4, 5).

In addition, recent studies have found that, during pregnancy, increased intake of seafood and the elongated n-3 PUFA contained therein may promote longer gestation and prevent preterm birth (6). While increased birth weight has also been associated with higher seafood consumption or n-3 PUFA intake in some investigations (7), other studies have found that higher exposure was associated with lower birth weight (8). However, most of these studies were performed among populations with very high seafood intake, and results may not be transferable to other regions. There are few data from US populations. In addition, both fetal growth and length of gestation contribute to attained birth weight. Many previous analyses have not removed the contribution of length of gestation to birth weight, making it difficult to determine whether n-3 PUFA exposure in fact influences fetal growth.

The purpose of the current study was to determine the extent to which higher dietary intake of seafood or the fatty

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acids DHA and EPA was associated with birth weight, birth weight adjusted for length of gestation (fetal growth), and length of gestation in a cohort of pregnant women in Massachusetts. We hypothesized that increased marine n-3 PUFA intake during pregnancy would be associated with increased fetal growth and longer gestation.

MATERIALS AND METHODS

Population and study design

Study subjects were enrolled from 1999 to 2002 in Project Viva, a prospective, observational cohort study of gestational diet, pregnancy outcomes, and offspring health. Recruitment and retention procedures have been described previously (9, 10). For a copy of the study questionnaires, contact the first author. Of 2,128 subjects who delivered a live infant, 2,109 (99 percent) completed at least one dietary questionnaire, and their data were included in the current analysis. We obtained information on first-trimester diet from 1,797, second-trimester diet from 1,663, and third-trimester diet from 2,070 of these women.

After obtaining informed consent, we collected demographic and health history information by interview and self-administered questionnaire (10). Institutional review boards of participating institutions approved the study. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki (11).

Dietary assessment

Participants completed semiquantitative food frequency questionnaires (SFFQs) at study enrollment, at 26–28 weeks of gestation, and in the first few days following delivery. The first and second SFFQs asked about the average frequency of consumption of over 140 specified foods and included additional questions about beverages, vitamins, and supplements. The first-trimester SFFQ asked about average consumption "during this pregnancy" (i.e., since the last menstrual period), and the second SFFQ asked about consumption "during the past 3 months." The limited post-delivery SFFQ had nine questions focused on major dietary contributors to fatty acid intake in the month prior to delivery.

On all three instruments, items regarding fish queried intake of "canned tuna fish (3–4 oz.)" (1 ounce (oz.) = 28.3 g); "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.)." Response options on the first and second questionnaires ranged from "never/less than 1 per month" to "1 or more servings per day." On the third questionnaire, response options ranged from "never/less than 1 per week" to "2 or more servings per day." We combined responses to the four fish questions for each trimester and generated a count of monthly total fish servings by averaging within each category; for example, we coded "1–3 servings per month" as two servings per month.

The SFFQ was modified for use in pregnancy from a well-validated instrument used in the Nurses' Health Study and other large cohorts (12, 13). Additionally, we previously calibrated the first-trimester questionnaire against maternal blood fatty acid levels (14, 15). For every gram of dietary intake per day, erythrocyte concentrations of long-chain n-3 PUFA were higher by 1.7 percent in 72 Black women ($p = 0.09$) and by 4.8 percent in 132 White women ($p = 0.0001$).

To calculate nutrient intakes, we multiplied a weight assigned to frequency of use (proportional to daily use = 1) by the nutrient composition for the portion size specified for each food or vitamin supplement. We then summed contributions to intake across all foods and supplements to obtain total intake of a variety of nutrients for each subject (16). To estimate nutrients, we used the Harvard nutrient composition database, which is based primarily on US Department of Agriculture publications and is continually supplemented by other published sources and personal communications from laboratories and manufacturers (17–19). We excluded from analysis nine first- and eight second-trimester records with an implausible total energy intake (<600 or >6,000 kcal/day) or incomplete SFFQ.

Six subjects reported taking cod liver or fish oil supplements at the time of study enrollment. Exclusion of these subjects did not change estimates; therefore, their data remained in all analyses.

Ascertainment of birth data

We obtained infant birth weight in grams from the hospital medical record. We calculated length of gestation in days by subtracting the date of the last menstrual period from the date of delivery. Results of ultrasound examinations performed at 16–20 weeks of gestation were available for 79 percent of subjects at the time of this analysis. For 200 subjects (9 percent), gestational age according to the ultrasound differed from that according to the last menstrual period by more than 10 days, in which case we used the ultrasound result to determine length of gestation. We used the hospital and outpatient records to determine whether births were spontaneous or induced. We classified births as nonspontaneous if labor was induced or if a planned cesarean section was performed, whether or not rupture of membranes was spontaneous.

We determined birth weight for gestational age by using as a reference a combined 1999–2000 US natality data set (20). This method adjusts for gestational age and provides a normal z value measuring distance of the birth weight from the median for a given gestational age.

Statistical analysis

We first performed bivariate analyses to determine maternal and infant characteristics associated with birth weight, fetal growth, and length of gestation. Candidate variables included characteristics previously associated with fetal growth or length of gestation in the medical literature. All continuous covariates were modeled as categories to account for possible nonlinear associations with the outcomes. We included any variables for which values were missing in a "missing" category. Restricting analyses to study participants for whom data were not missing did not substantially change the results. We then performed multiple linear regression to determine independent subject characteristics that were predictors of birth weight and fetal growth. For length of gestation, the distribution was non-Gaussian. Therefore, to analyze length of gestation as an outcome, we used quantile (median) regression (21) to predict changes in the median length of gestation associated with each exposure of interest.

Next, we examined the associations of birth weight, fetal growth, and length of gestation with intake of elongated n-3 PUFA during pregnancy. We divided subjects into quartiles according to their intake of combined DHA + EPA. At the third trimester, because of the limited number of questions and fewer response categories, 3 percent of subjects were assigned to the first quartile and 47 percent were assigned to the second quartile. Therefore, we combined the first- and second-quartile groups for the third-trimester analyses.

To assess the independent effect of elongated n-3 PUFA intake on birth weight and fetal growth, we performed multivariable analyses by using linear regression and, for length of gestation, median regression. In this paper, all *p* values are two sided. We performed separate analyses for each trimester; because some subjects did not complete all three SFFQs, numbers varied among trimester-specific models. We included as covariates all subject characteristics listed in table 1 as well as site of study enrollment. We additionally assessed the relation between DHA + EPA consumption and the three outcomes after adjusting nutrient intake for total energy at the first and second trimesters; we used the multivariable nutrient residual method (22), which provides an estimate of nutrient effect independent of total energy intake. We repeated all analyses by using length of gestation as an outcome, excluding those subjects for whom a nonspontaneous birth occurred. For the 1,563 participants who completed both first- and second-trimester dietary questionnaires, we investigated whether intake at one trimester had a stronger association with the outcome than the other by including intake at both trimesters in the same model.

Additionally, we assessed the association of frequency of seafood intake with birth outcomes. Because a previous study had demonstrated an increased risk of preterm birth for subjects reporting no fish intake (6), we identified as a "zero category" women who reported, at the first- or second-trimester surveys, consuming less than one serving per month of all fish combined. We divided the remaining women into tertiles. We evaluated associations of seafood intake according to these four groups with the continuous outcomes of birth weight, length of gestation, and fetal growth by using linear and median regression, as described above. In addition, we assessed frequency of fish consumption with the bivariate outcomes low birth weight (<2,500 g), preterm birth (<259 days of gestation), and small for gestational age (<10th percentile compared with a standard US reference group) (20) by using logistic regression. Because the frequency response categories differed on the third-trimester questionnaire, with the lowest category available being "never/<1 serving per week" (as opposed to "never/<1 serving per month" on the other SFFQs), we did not include third-trimester seafood intake in our analyses.

We performed all bivariate analyses by using SAS version 8.2 software (SAS Institute, Inc., Cary, North Carolina) and regressions by using STATA version 7 software (Stata Corporation, College Station, Texas).

RESULTS

Subject characteristics and birth outcomes

Selected features of the 2,109 subjects included in this analysis are presented in table 1. Participant race/ethnicity reflected the diversity of the source population, including 16 percent Black, 7 percent Hispanic-American, and 6 percent Asian-American subjects. Maternal age ranged from 14 years to 44 years. For approximately half (56 percent) of the subjects, prepregnancy body mass index was between 19.8 kg/m^2 and 26.0 kg/m^2 (23) (table 1). Only 10 percent of subjects reported smoking during pregnancy, although information on smoking was unavailable for 7 percent.

Mean birth weight for the study cohort was 3,466 (95 percent confidence interval (CI): 3,441, 3,491) g, and mean birth weight adjusted for gestational age was 0.17 (95 percent CI: 0.13, 0.21) *z*-value units. Median length of gestation was 278 days (25th percentile, 272; 75th percentile, 284). Overall, the birth weight of 5 percent of the infants was less than 2,500 g, and 6 percent of the infants were below the 10th percentile of birth weight for gestational age. Approximately 7 percent of infants were born preterm (<37 completed weeks of gestation). Onset of 754 deliveries (36 percent) was not spontaneous.

Table 1 also displays associations of subject characteristics with birth weight, fetal growth, and length of gestation, simultaneously adjusted for all other covariates as well as enrollment site. Mothers who were Black or Asian, who had not had a previous pregnancy, or who smoked during the current pregnancy tended to deliver infants whose mean birth weights and fetal growth *z* values were lower (table 1). Mothers who were taller, had a higher prepregnancy body mass index, or gained more weight gave birth to larger infants.

Few subject characteristics were associated with length of gestation (table 1). Median length of gestation was shorter by approximately 2 days (95 percent CI: –3.4, –0.5) for Black mothers compared with White mothers. Second and later pregnancies were 1.4 days shorter (95 percent CI: –2.5, –0.3) than first pregnancies. For women who were taller, gained more weight, and had a higher educational level, gestation was slightly longer.

Seventy percent of subjects acknowledged consuming any alcohol after their last menstrual period but prior to learning they were pregnant, although only 8 percent continued to consume any alcohol after they learned they were pregnant. Few (2 percent) subjects reported any recreational drug use during pregnancy. After multivariable adjustment, neither alcohol nor drug use was related to birth outcomes. Measures

TABLE 1. Characteristics* associated with birth weight, fetal growth (birth-weight-for-gestational-age *z* value), or length of gestation among 2,109 pregnant women from Massachusetts enrolled in Project Viva, 1999–2002

Characteristic	%† of subjects	Difference in birth weight (g)		Difference in fetal growth (*z* value)		Difference in length of gestation (days)	
		Mean	95% CI‡	Mean	95% CI	Median	95% CI
Maternal height (m)							
<1.6	19	–241	–312, –170	–0.46	–0.58, –0.34	–0.4	–1.8, 1.0
1.6–<1.65	26	–166	–230, –104	–0.36	–0.46, –0.26	0.1	–1.2, 1.3
1.65–<1.7	26	–60	–123, 3	–0.15	–0.26, –0.05	1.5	0.3, 2.8
≥1.7 (referent)	29						
Gestational weight gain§							
Low	15	–149	–222, –87	–0.17	–0.29, –0.05	–0.5	–2.0, 0.9
Normal (referent)	35						
High	49	169	115, 222	0.24	0.15, 0.33	1.9	0.8, 3.0
Prepregnancy body mass index (kg/m^2)§							
Underweight (<19.8)	13	–18	–91, 56	–0.09	–0.21, 0.03	–1.0	–2.5, 0.5
Normal (19.8–26.0) (referent)	56						
Overweight (>26.0–29.0)	12	65	–11, 140	0.19	0.06, 0.31	–1.0	–2.5, 0.5
Obese (>29.0)	19	63	–3, 129	0.21	0.10, 0.32	–0.5	–1.8, 0.9
Infant sex female (vs. male)	48	–138	–184, –91	–0.33	–0.41, –0.26	0.2	–0.8, 1.1
Maternal age (years)							
14–<20	3	–164	–319, –9	–0.29	–0.54, –0.03	–1.7	–4.7, 1.4
20–<25	6	–64	–170, 43	–0.20	–0.37, –0.02	1.6	–0.5, 3.7
25–<30	21	–55	–118, 8	–0.13	–0.24, –0.03	0.8	–0.5, 2.0
30–<35 (referent)	42						
35–<40	23	17	–44, 78	0.02	–0.08, 0.12	–0.1	–1.3, 1.1
≥40	4	–59	–179, 61	–0.17	–0.37, 0.03	–0.4	–2.8, 2.0
Smoked during pregnancy (vs. no)	10	–72	–150, 6	–0.15	–0.28, –0.03	0.6	–1.0, 2.2
Gravidity >1 (vs. 1)	70	105	51, 160	0.22	0.13, 0.31	–1.4	–2.5, –0.3
Maternal race/ethnicity							
Asian	6	–244	–348, –139	–0.28	–0.45, –0.11	–3.4	–5.5, –1.3
Black	16	–178	–251, –104	–0.26	–0.38, –0.14	–1.9	–3.4, –0.5
Hispanic	7	–62	–159, 35	–0.05	–0.21, 0.11	–2.0	–3.9, –0.1
Other	4	–25	–151, 101	–0.00	–0.21, 0.20	–0.3	–2.8, 2.3
Non-Hispanic White (referent)	66						
Education							
High school or less	12	–45	–135, 45	–0.13	–0.28, 0.02	–0.5	–2.3, 1.2
Some college	23	–28	–95, 38	–0.11	–0.22, –0.0	0.3	–1.0, 1.7
College graduate (referent)	35						
Graduate degree	29	9	–50, 69	–0.04	–0.14, 0.06	1.6	0.4, 2.8

* Estimates of effect were simultaneously adjusted for all other characteristics in the table as well as for site of study enrollment.

† Percentages may not total 100 because of some missing values.

‡ CI, confidence interval.

§ Per 1990 Institute of Medicine guidelines (23).

of socioeconomic status such as income were also not associated with birth outcomes after we adjusted for other demographic characteristics.

Fish and n-3 PUFA consumption habits differed according to subject characteristics. Table 2 displays associations with first-trimester diet; results were similar for intake during the other two trimesters. Women who consumed more seafood, and consequently more elongated n-3 PUFA, tended to be older, more often non-White, more educated, and less likely to be experiencing their first pregnancy (table 2). Lower consumption of n-3 fatty acids or seafood was not associated with an increased likelihood of nonspontaneous birth (table 2).

TABLE 2. Characteristics of 1,797 pregnant women from Massachusetts enrolled in Project Viva who completed first-trimester dietary questionnaires, according to quartile of combined DHA* + EPA* fatty acid intake and frequency of seafood consumption reported during the first trimester of pregnancy, 1999–2002

First-trimester intake	Continuous characteristics (mean (SD*))				Dichotomous characteristics (% of subjects)				
	Age (years)	Body mass index (kg/m^2)	Weight gain (kg/4 weeks)	Height (m)	College graduate	Non-Hispanic White race/ ethnicity	Gravidity >1	Smoked during pregnancy	Non-spontaneous birth
DHA + EPA									
Quartile 1	31.4 (5.1)	24.6 (5.2)	1.6 (0.6)	1.64 (0.07)	64	77	65	5	36
Quartile 2	31.9 (4.9)	24.7 (5.0)	1.5 (0.6)	1.65 (0.07)	66	76	67	3	36
Quartile 3	32.5 (4.7)	24.5 (5.4)	1.6 (0.6)	1.65 (0.07)	76	71	70	4	35
Quartile 4	32.1 (4.9)	24.6 (5.4)	1.6 (0.5)	1.65 (0.07)	75	62	72	4	32
p† for trend	<0.0001	0.96	0.36	0.22	<0.0001	<0.0001	0.02	0.47	0.18
Seafood									
No intake	31.0 (5.4)	24.3 (4.9)	1.6 (0.5)	1.64 (0.07)	60	74	65	6	35
Tertile 1	31.9 (4.9)	24.7 (5.2)	1.6 (0.6)	1.65 (0.07)	68	75	66	4	35
Tertile 2	32.5 (4.8)	24.5 (5.3)	1.6 (0.6)	1.65 (0.07)	72	70	69	3	36
Tertile 3	33.1 (4.7)	24.8 (5.5)	1.6 (0.5)	1.65 (0.07)	73	66	73	4	33
p† for trend	<0.0001	0.48	0.73	0.17	0.0003	0.003	0.01	0.31	0.67

* DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SD, standard deviation.

† Two-sided *p* value.

Elongated n-3 PUFA intake, fetal growth, and length of gestation

Combined DHA and EPA (DHA + EPA) intake ranged from 0 g to more than 2.5 g per day (table 3). On bivariate analysis, increasing consumption of elongated n-3 PUFA was associated with decreased birth weight and decreased fetal growth (table 3). The effect appeared similar for intake in each of the three trimesters. In the first trimester, for example, subjects in the highest quartile of DHA + EPA intake delivered infants whose birth weights were approximately 100 g lighter (3,421 g vs. 3,520 g), and whose z values were 0.18 points less (0.10 vs. 0.28), than those in the lowest quartile. On this unadjusted analysis, quartile of combined DHA + EPA intake was not associated with the dichotomous outcomes low birth weight or small for gestational age (data not shown). We found no differences in length of gestation according to intake of DHA + EPA in any trimester (table 3). Reduced intake of DHA + EPA was not associated with increased risk of preterm birth, nor did exclusion of nonspontaneous births alter the null association of fatty acid consumption with either length of gestation or preterm birth (data not shown).

After we adjusted for maternal and infant characteristics associated with fetal growth and birth weight, the association of increased DHA + EPA intake with decreased birth weight and fetal growth remained. Table 4 displays the effect of quartile of n-3 PUFA intake on birth weight and fetal growth, adjusted for all covariates included in table 1. Effect sizes on this multivariable analysis were similar, although slightly smaller, compared with the unadjusted effects reported in table 3. Energy adjustment changed effect estimates minimally; for example, in the first trimester, women in the lowest quartile of energy-adjusted DHA + EPA intake delivered infants whose birth weights were 86 (95 percent CI: 14, 159) g lower and fetal growth z values 0.22 (95 percent CI: 0.10, 0.34) units lower than for women in the highest quartile. Even after adjustment for subject characteristics, consumption of DHA + EPA remained unassociated with length of gestation (table 4) and preterm birth, with an odds ratio of 1.1 (95 percent CI: 0.7, 1.9) for the lowest compared with the highest quartile of intake in the first trimester.

Because maternal race/ethnicity was strongly associated with both fetal growth and seafood intake, we repeated analyses by using the subgroup of Whites only to ensure that residual confounding by race did not explain our findings. The association between greater intake of DHA + EPA and reduced fetal growth remained and was slightly stronger in magnitude for the White mothers only. For first-trimester intake, for example, fetal growth z value was 0.26 (95 percent CI: 0.12, 0.40) units higher in the first, 0.16 (95 percent CI: 0.02, 0.30) units higher in the second, and 0.07 (95 percent CI: –0.07, 0.21) units higher in the third quartile compared with the highest quartile of fatty acid intake (p for trend < 0.001). Birth weight was 121 (95 percent CI: 34, 203) g, 75 (95 percent CI: –8, 158) g, and 19 (95 percent CI: –64, 101) g higher in the first, second, and third quartiles, respectively, compared with the highest quartile of fatty acid intake (p for trend = 0.001).

The correlation between first- and second-trimester DHA + EPA intake was strong (Spearman's r = 0.63) among the 1,563 participants who completed both SFFQs. When we fit our model including both first- and second-trimester DHA + EPA intake, in quartiles, higher intake at the first trimester

TABLE 3. Birth outcomes according to quartile of combined DHA* + EPA* intake in each trimester: unadjusted data from pregnant women from Massachusetts enrolled in Project Viva, 1999–2002

Quartile of combined DHA + EPA intake	Continuous outcomes			
	DHA + EPA intake in g/day (mean (range))	Birth weight in g (mean (SD*))	Fetal growth *z* value (mean (SD))	Days of gestation (median (25th percentile, 75th percentile))
First trimester (*n* = 1,797)				
Quartile 1	0.02 (0–0.05)	3,520 (609)	0.28 (1.0)	276 (272, 285)
Quartile 2	0.09 (0.06–0.12)	3,472 (564)	0.19 (1.0)	276 (271, 284)
Quartile 3	0.18 (0.12–0.24)	3,462 (582)	0.15 (1.0)	277 (272, 285)
Quartile 4	0.36 (0.24–2.53)	3,421 (560)	0.10 (0.9)	278 (272, 283)
p† for trend		0.01	0.003	1.0
Second trimester (*n* = 1,663)				
Quartile 1	0.02 (0–0.05)	3,523 (562)	0.25 (1.0)	277 (272, 285)
Quartile 2	0.09 (0.06–0.12)	3,541 (526)	0.28 (1.0)	277 (272, 285)
Quartile 3	0.18 (0.12–0.23)	3,447 (537)	0.10 (0.9)	277 (272, 285)
Quartile 4	0.38 (0.24–2.71)	3,461 (546)	0.13 (1.0)	277 (272, 284)
p† for trend		0.02	0.009	0.27
Third trimester (*n* = 2,070)				
Quartiles 1 + 2	0.05 (0–0.06)	3,507 (563)	0.23 (1.0)	279 (272, 284)
Quartile 3	0.09 (0.06–0.11)	3,473 (598)	0.20 (1.0)	276 (272, 284)
Quartile 4	0.27 (0.11–1.72)	3,394 (597)	0.06 (1.0)	275 (272, 283)
p† for trend		0.0003	0.002	0.01

* DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SD, standard deviation.

† Two-sided *p* value.

remained associated with reduced fetal growth, with a *z* value 0.18 (95 percent CI: 0.33, 0.04) units higher in the lowest quartile of intake (*p* for trend = 0.01 across quartiles). However, in this model, second-trimester DHA + EPA intake was unassociated with fetal growth (*p* for trend = 0.64).

Seafood consumption

Frequency of fish consumption during pregnancy showed a trend toward an inverse association with birth weight and fetal growth and was unassociated with length of gestation. On unadjusted analysis, an increase in first-trimester fish consumption from less than one serving per month to more than two servings per week was associated with a decrease in *z* value from 0.22 to 0.16 and a decrease in birth weight from 3,487 g to 3,452 g. The similarity of these results to the analysis of elongated n-3 PUFA intake came as no surprise: the four fish questions asked about in the SFFQ contributed approximately 87 percent of the data on DHA intake and over 90 percent of the information on EPA intake.

After multivariable adjustment, there was still a suggestion of an inverse association between frequency of fish intake and fetal growth, although this relation was statistically significant at the conventional standard of $p < 0.05$ for only the first trimester (table 5). However, we found no indication of a relation with length of gestation. Additionally, in contrast to findings from other studies (6), there was no association of seafood intake with the dichotomous outcomes low birth weight, small for gestational age, and preterm delivery (results not shown).

DISCUSSION

In this US cohort, increased consumption of the elongated n-3 PUFA DHA and EPA was associated with reduced birth weight, resulting from reduced fetal growth but not altered length of gestation. Adjustment for subject characteristics only moderately reduced the strength of the associations. The magnitude of association was modest—approximately a 90-g difference in birth weight between the lowest and highest quartiles of intake.

We did not detect any association of higher seafood or elongated n-3 PUFA intake with length of gestation. Exclusion of nonspontaneous births did not alter our results. In contrast, several previously published studies have demonstrated longer gestation among women who consume fish more frequently (6) or who were assigned randomly to receive supplemental elongated n-3 fatty acids during pregnancy (24, 25). Additionally, higher levels of n-3 PUFA in maternal and umbilical cord blood have been associated with longer gestation (26–28). However, not all studies have detected an association of higher fish intake or blood fatty acid levels with longer gestation (7, 29–31).

TABLE 4. Associations* of combined DHA† + EPA† fatty acid intake with birth weight, fetal growth, and length of gestation: data by trimester of intake from pregnant women from Massachusetts enrolled in Project Viva, 1999–2002

Quartile of combined DHA + EPA intake	Δ Birth weight		Δ Fetal growth		Δ Length of gestation	
	Grams	95% CI†	*z* value	95% CI	Days	95% CI
First trimester (*n* = 1,797)						
Quartile 1	94	23, 166	0.19	0.08, 0.31	0.3	–1.3, 1.9
Quartile 2	35	–36, 107	0.06	–0.05, 0.18	–0.3	–1.9, 1.3
Quartile 3	32	–39, 103	0.03	–0.08, 0.15	0.6	–1.0, 2.2
Quartile 4 (referent)						
p‡ for trend	0.01		0.001		0.88	
Second trimester (*n* = 1,663)						
Quartile 1	50	–19, 119	0.10	–0.02, 0.22	0.3	–1.4, 2.1
Quartile 2	49	–19, 117	0.09	–0.03, 0.21	–0.4	–2.1, 1.3
Quartile 3	–23	–92, 47	–0.06	–0.18, 0.06	0.3	–1.4, 2.0
Quartile 4 (referent)						
p‡ for trend	0.06		0.03		0.79	
Third trimester (*n* = 2,070)						
Quartiles 1 + 2	90	33, 147	0.14	0.04, 0.23	0.5	–0.7, 1.7
Quartile 3	11	–58, 81	0.03	–0.09, 0.14	–0.7	–2.2, 0.8
Quartile 4 (referent)						
p‡ for trend	0.001		0.003		0.36	

* Effect estimates were adjusted for enrollment site, infant sex, and maternal age, height, intrapartum weight gain, prepregnancy body mass index, race/ethnicity, smoking during pregnancy, education, and gravidity, all in categories as shown in table 1.

† DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; CI, confidence interval.

‡ Two-sided *p* value.

It is possible that length of gestation is shortened only when seafood intake is very infrequent. In one study, risk of preterm birth increased more than three times for women who reported that they had never consumed seafood meals of any type compared with those who reported consuming seafood meals often (6). Because we did not discriminate between intake less than once per month and less frequently in Project Viva, we cannot exclude the possibility that very infrequent consumption was associated with increased risk of early birth.

Our results were contrary to our hypothesis that intake would be directly associated with fetal growth. Several observational studies have demonstrated higher birth weight in association with increased seafood consumption (6, 7, 29, 32). However, this effect was explained by longer length of gestation rather than increased fetal growth. Similarly, in a randomized controlled trial, whereas birth weight was higher in a group of women provided supplemental fish oil compared with olive oil, this increase disappeared after adjustment for length of gestation (33).

The preponderance of published evidence suggests that although increased marine fatty acid consumption may perhaps cause higher infant birth weight through prolonged gestation, it does not promote fetal growth. In fact, our study, along with others, suggests that higher intake of fish and elongated n-3 PUFA may somewhat reduce fetal growth. In particular, analyses of fatty acid blood levels suggest that elongated n-3 PUFA may reduce, rather than promote, fetal growth. In a study of 182 women residing in the Faroe Islands, umbilical cord serum EPA was inversely associated with birth weight adjusted for gestational length (8). Similarly, in a study of 627 infants in the Netherlands, cord plasma DHA was negatively related to weight standard deviation scores (34). Administering fish oil supplements to pregnant rats has also resulted in reduced birth weight despite longer gestation (35, 36). These prenatal data are supported by results from postnatal feeding trials, in which preterm infants given formula supplemented with marine oils containing EPA and DHA demonstrated reduced postnatal growth (4, 37).

Another possible explanation for the inverse association of n-3 PUFA with fetal growth is that environmental pollutants in seafood may adversely affect fetal growth. Although concentrations of mercury and polychlorinated biphenyls were associated with PUFA levels in one study by Grandjean et al. (8), the contaminants did not appear to affect fetal growth. However, this conclusion remains somewhat controversial (38). To date, we have not ascertained levels of these toxins in the Project Viva population.

The similarity of our results regardless of trimester suggests that the biologic effect of n-3 PUFA intake on reducing fetal growth occurs throughout pregnancy. Alterna-

TABLE 5. Associations* of frequency of total seafood intake with birth weight, fetal growth, and length of gestation: data from pregnant women from Massachusetts enrolled in Project Viva, 1999–2002

Frequency of total seafood intake†	Δ Birth weight		Δ Fetal growth		Δ Length of gestation	
	Grams	95% CI‡	*z* value	95% CI	Days	95% CI
First trimester (*n* = 1,797)						
No intake (*n* = 233)	70	–18, 158	0.13	–0.01, 0.28	–0.8	–2.7, 1.1
Tertile 1 (*n* = 597)	48	–21, 117	0.08	–0.03, 0.20	0.2	–1.3, 1.7
Tertile 2 (*n* = 568)	7	–62, 77	–0.01	–0.12, 0.10	–0.4	–2.0, 1.1
Tertile 3 (*n* = 399)						
p§ for trend	0.05		0.02		0.99	
Second trimester (*n* = 1,663)						
No intake (*n* = 215)	21	–64, 105	0.09	–0.06, 0.24	0.5	–1.3, 2.3
Tertile 1 (*n* = 564)	39	–27, 105	0.06	–0.05, 0.18	0.1	–1.3, 1.4
Tertile 2 (*n* = 493)	–29	–96, 38	–0.05	–0.17, 0.07	–0.8	–2.2, 0.6
Tertile 3 (*n* = 391)						
p§ for trend	0.19		0.08		0.55	

* Effect estimates were adjusted for enrollment site, infant sex, and maternal age, height, intrapartum weight gain, prepregnancy body mass index, race/ethnicity, smoking during pregnancy, education, and gravidity, all in categories as shown in table 1.

† The lowest group reported consuming none/<1 serving of seafood per month; the remaining subjects were divided into tertiles, with the highest intake group used as the referent.

‡ CI, confidence interval.

§ Two-sided *p* value.

tively, because individual dietary fatty acid composition changed only moderately throughout pregnancy in the Project Viva cohort, there may be a critical period for exposure that is difficult to ascertain in this observational study. In fact, in our analysis including diet at both trimesters, DHA + EPA intake in the first trimester was significantly associated with fetal growth, whereas second-trimester intake was not. Thus, the association of fetal growth with second-trimester diet may be more a reflection of tracking of diet across pregnancy than a direct effect of diet later in pregnancy.

Our study has many strengths. We collected prospective data from a relatively large number of pregnant women, including other biologic, demographic, and nutritional predictors of fetal growth and length of gestation, in addition to detailed information regarding intake of foods, supplements, and nutrients during pregnancy. We assessed diet at multiple points during pregnancy. We included a measure of fetal growth independent of length of gestation, allowing us to distinguish these different contributors to birth weight.

Nevertheless, results should be interpreted in consideration of some limitations. As with all observational studies, it is possible that we did not completely adjust for known factors associated with the outcomes; additionally, unmeasured systematic differences between women who choose more or less dietary seafood could explain our findings. In this analysis, we did not include possible effects of other nutrients such as alpha-linolenic acid, a precursor of elongated n-3 PUFA. However, only a very small amount of dietary alpha-linolenic acid is converted to DHA (39).

Diet was assessed by self-report and thus may have been subject to bias. Additionally, the results of the validation study suggest that the SFFQ may not be as valid a measure of n-3 fatty acid intake among Black women compared with White women. Given the relatively small number of Black participants, we were not able to perform a stratified analysis among Blacks only. Future studies might investigate whether associations of fatty acid intake with fetal growth are present for Blacks.

Since our participants were relatively older and well educated and all resided in eastern Massachusetts, findings may not be generalizable to other populations of pregnant women. However, the amount of n-3 PUFA intake reported by our subjects approximates the range of intake by pregnant women in the few other studies describing fatty acid consumption. In 1987–1988, the US Department of Agriculture estimated a daily consumption of 0.1 g/day of DHA + EPA by women of childbearing age (1), which would fall within our second quartile. In small recent studies, mean DHA + EPA intake was 0.23 g/day among pregnant women in Canada (39) and 0.22g/day among pregnant women in Holland (40), both within the third quartile of our group.

In the current study, we found a modest decrease in fetal growth associated with increased maternal marine n-3 PUFA consumption during pregnancy, corresponding to a birth-weight difference of approximately 90 g between the lowest and highest quartiles of intake. To what extent the slightly reduced fetal growth is likely to be harmful is unknown but probably small during the neonatal period. With the ongoing longitudinal follow-up of the children in this cohort, we will be able to study the longer-term consequences of maternal n-3 PUFA ingestion for the child, including influences upon growth, cognitive development, allergic disorders, and cardiovascular risk.

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