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Prenatal Fish Oil Supplementation and Early Childhood Development in the Upstate KIDS Study

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Abstract

Fish oil contains omega-3 fatty acids, which play a vital role in fetal growth and development. In utero exposure to omega-3 fatty acids is exclusively dependent on maternal nutrition. Previous studies have suggested that prenatal fish oil supplementation has positive impacts on child neurodevelopment later in life. This study examines the associations between fish oil supplementation both before pregnancy and throughout pregnancy and subsequent child development. Mother-child pairs from the Upstate KIDS Study, a birth cohort consisting of children born between 2008 and 2010, were included. Self-reported prenatal fish oil supplementation data was available for 5,845 children (3807 singletons and 2038 twins). At multiple time points, from 4 months to 3 years of age, child development was reported by the parents on the Ages and Stages Questionnaire (ASQ). Five developmental domains were assessed: fine motor, gross motor, communication, personal-social and problem solving. Generalized linear mixed models were used to estimate odds ratios (OR) while adjusting for covariates. Primary analyses showed that the risk of failing the ASQ problem solving domain was significantly lower among children of women who took fish oil before pregnancy (OR 0.40, 95% CI: 0.18 – 0.89) and during pregnancy (OR 0.43, 95% CI: 0.22 – 0.83). Gender interaction was not statistically significant although stratified results indicated stronger associations among girls. Similarly, associations were primarily among singletons. Prenatal fish oil supplementation may be beneficial in regards to neurodevelopment. Specifically, it is associated with a lower risk of failing the problem solving domain up to 3 years of age.

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Statement of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards approved by the New York State Department of Health and the University of Albany Institutional Review Board (NYSDOH IRB #07-097; UAlbany #08-179) serving as the IRB designated by the National Institutes of Health for this study under a reliance agreement.

Keywords

Fish oil; prenatal; child development; omega-3 fatty acids; problem solving

Introduction

It is widely accepted that the intrauterine environment not only plays a pivotal role in fetal development but has the potential to cause lasting health effects in offspring.(1, 2) Maternal nutrition has a substantial influence on offspring neurodevelopment during early life due to increased fetal metabolic requirements and neurologic vulnerabilities.(3) Specifically, prenatal omega-3 fatty acid deficiencies have been linked to adverse impacts on brain development with potential effects evident throughout many life stages.(4, 5)

Long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA) are essential lipids involved in neurologic functions including: maintaining membrane fluidity(6), myelination(7), gene expression, signal transduction, and neural growth.(4) Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), the two most biologically active n-3 PUFAs(8), are nutrients vital for optimal growth and development during the fetal and early postnatal stages of life.(9) Perinatal brain maturation reaches its peak growth rate during the third trimester of gestation(6), requiring rapid DHA accretion into retinal and neural tissues.(10, 11) In response to increased fetal demands, maternal adipose deposits release stored fatty acids into the bloodstream at an enhanced rate during the final trimester, suggesting adequate n-3 PUFA intake is important in the time preceding conception as well as during pregnancy.(12) DHA and EPA enter fetal circulation through simple diffusion across the placenta driven by a concentration gradient.(13) In the adult liver, DHA is metabolically converted from alpha-linolenic acid (ALA); however, de novo synthesis is inefficient in humans(14) and elevated perinatal requirements cannot be met solely via endogenous formation.(15) Preformed n-3 PUFA, directly obtained through diet, accumulates more readily than those derived from precursor acids due to enhanced bioavailability.(15) Therefore, fetal intake is largely dependent on maternal nutrition(16), with the richest sources of DHA and EPA naturally present in seafood and fish.(8) Due to maternal dietary limitations and environmental health concerns, fish oil supplementation may be consumed as a substantial source of n-3 PUFA during pregnancy(17).

The body of evidence supporting the beneficial fetal impacts of maternal fish oil supplementation is mounting.(18) Observational studies have found that cord blood n-3 PUFA concentrations are associated with improved language, cognitive, visual motor(19) and memory skills(20) among children aged 11 months through 12 years suggesting that prenatal n-3 PUFA intake is of importance with effects potentially spanning many years (21). Animal models suggest that maternal n-3 PUFA supplementation may be neuroprotective in regards to neonatal hypoxic-ischemic brain injury(22), hyperoxic injury(23), and prenatal stress-induced learning and memory deficits.(24) Several randomized controlled trials of fish oil during pregnancy have described beneficial associations among maternal supplementation and child outcomes such as: hand and eye coordination(17), problem solving skills(25), and neurologic development.(26, 27)

Additionally, research indicates that the effects of DHA on the developing brain may be impacted by gender and genotype (21). However, a consensus regarding n-3 PUFA supplementation and aforementioned benefits has not been reached. The literature as a whole is lacking consistent epidemiological evidence with numerous studies failing to observe child impacts stemming from in utero n-3 PUFA exposure. (28–30) The mixed results may be attributed, in part, to high attrition rates, lack of statistical power, diverse study designs, and varying time points for outcome assessment. Controversial studies have warranted further prospective research to investigate the potential long-term effects of prenatal fish oil intake and child development (29)). To our knowledge, no studies have examined the impact of prenatal n-3 PUFA supplementation on the neurodevelopment of twins. It has been demonstrated that while singleton newborns have higher mean erythrocyte DHA concentrations than their mothers at the time of birth, twins have lower levels suggesting fetal insufficiencies.(31) Additionally, multiples are known to be at increased risk of neurodevelopmental delays due to the elevated likelihood of adverse health outcomes such as low birth weight.(32)

This study aims to examine the association between maternal fish oil supplementation and subsequent child developmental capabilities up to 3 years of age. In addition, we investigate any divergences in these impacts among singletons and twins.

Methods

Study setting and participants

The Upstate KIDS Study is a population-based birth cohort in New York State (excluding the five New York City boroughs) originally designed to examine the impact of infertility treatment on child growth and development.(33) Participants were recruited from New York State livebirth registry and included mothers who gave birth between July 2008 and May 2010. All infants with birth certificates indicating conception by way of infertility treatment were recruited to participate in the study. Regardless of the means of conception, all multiple births were recruited. Singletons who were not conceived through infertility treatments were frequency matched on geographic residence and recruited at a ratio of 3:1 to those infants who were exposed to infertility treatment. In total, 5034 mothers were recruited, including mothers of singletons, twins and higher order births. All mothers provided written informed consent. The Institutional Review Boards (IRB) at the New York State Department of Health and the University at Albany approved the study and under a reliance agreement served as the IRBs designated by the National Institutes of Health.

Mother-child pairs were excluded from this analysis if the maternal questionnaire, which captured self-reported exposure information, was not completed. Additionally, due to limited numbers, triplets and quadruplets were excluded (n = 128 children and n = 42 mothers). When conducting primary analyses, one child was randomly selected from each twin pair and included with the eligible singletons (n = 4843). When examining plurality, both twin siblings were included in analyses (n= 2038) independent from the singleton children (n = 3807).

Exposure: Fish Oil Supplementation

At four months postpartum, mothers completed a self-administered questionnaire which inquired about their prior pregnancy with the participating child. Mothers were asked (yes/no) if they took fish oil (n-3 PUFA) more than once per week in the 12 months preceding pregnancy. A separate question queried if fish oil supplementation was taken more than one time per week during pregnancy.

Child Development: Ages and Stages Questionnaire and Parental Report

Recommended for use from infancy through early childhood, the Ages and Stages Questionnaire© (ASQ) is a validated parent-completed screening tool designed for early assessment of developmental delays.(34, 35) In the Upstate KIDS Study, children were evaluated at 4–6, 8, 12, 18, 24, 30, and 36 months of age utilizing the ASQ. The parents engaged in different activities with their children and then responded to questions on the ASQ rating their child's skills. Five developmental domains were assessed: fine motor, gross motor, communication, personal-social functioning, and problem solving.

The ASQ-2nd edition was used to screen the children at 4–6, 8, and 12 months of age. Released in 2009, the ASQ-3rd edition was used for screening from 18 through 36 months of age. The elements of each questionnaire were scored as follows: "yes" = 10 points, "sometimes" = 5 points, "not yet" = 0 points.(34, 36) The items from each domain were then summed with total scores ranging from 0 to 300 (60 points for each domain). Fails for each domain are defined as scores two standard deviations below the average score for the child's age which was derived from a US normative sample.(34, 36)

Covariates

Vital records in combination with self-reported information (where missing) provided demographic data on maternal age, race/ethnicity, educational achievement, marital status, and health insurance status. Health information including parental body mass index (BMI), parity, and maternal smoking history was obtained from the baseline questionnaire. Infant characteristics such as plurality and gender were collected from birth records and an infant questionnaire at 4 months.

Additionally, nutritional data was captured on self-reported questionnaires. At 4 months postpartum, mothers indicated (yes/no) if they had regularly consumed (> 1 time per week) numerous vitamins and dietary supplements (e.g., multivitamins, iron) throughout pregnancy. The baseline questionnaire also collected information on how many days per week the mothers took prenatal vitamins. In our analyses, regular prenatal vitamin consumption was defined as having taken the vitamins seven days per week due to the high frequency of adherence, 75% of mothers reported taking the vitamins every day.

The 12 month questionnaire inquired about how many servings of fish were consumed per week during pregnancy. For the analyses, fish consumption was treated as a dichotomous covariate (0 servings of fish eaten per week or > 0 servings of fish eaten per week) due to few mothers eating multiple servings per week.

Statistical Methods

The sociodemographic, nutritional, and infant characteristics of mother-child pairs relative to fish oil supplementation status were compared using the chi-squared test and independent sample *t* tests. The frequencies and percentages of ASQ domain failures by supplementation group were obtained and presented for each of the seven specific stages of screening. The outcomes were treated as binary variables (pass/fail) due to the original design of the tool which intends the ASQ to be used as an initial screening test accompanied by follow-up assessment in situations where a child fails any domain or there is parental concern (36).

To evaluate the associations between fish oil supplementation (before and during pregnancy) and any fail on the ASQ domains, generalized linear mixed models with a logit link function were used to estimate 95% confidence intervals (CI) and odds ratios (OR). Domain specific fails were estimated in the same manner. In all of the models, the mother-child pairs who did not consume supplementation were the reference group. The study's design of oversampling based on infertility treatment and multiples was accounted for by the use of sampling weights, which were derived from New York state birth certificate data, in the analyses. To account for repeated ASQ measures of development, an infant-level random intercept was included in all models.(33) Additionally, to further investigate temporal relationships, an interaction term between the time of the ASQ and fish oil supplementation status was tested in all models. When including both siblings in a set of twins a second random intercept was added to the models. The five domains were viewed as independent hypotheses since in clinical practice they are informative of distinct and tailored interventions and no corrections for multiple comparisons were made; therefore, $p < 0.05$ was considered significant.

Sensitivity analyses included several independent models. Due to the potential differences in neurodevelopment, stratified analyses were conducted by gender and plurality. Interaction terms were tested for between fish oil supplementation during pregnancy and gender as well as supplementation and plurality. To examine the impact of exposure duration, we separated the mothers who consumed fish oil supplementation exclusively before pregnancy from the mothers who supplemented solely during pregnancy. We also assessed the relationship among the mothers who indicated supplementing throughout both time points and ASQ fails.

Baseline data on maternal usage (yes/no) of rare supplements during pregnancy (echinacea, ginkgo biloba, kava kava, and St. John's wort) were combined due to rarity when we evaluated their association with the ASQ outcomes. Maternal pre-pregnancy BMI was included in separate models both as the World Health Organization's (WHO) classifications(37) and as a continuous variable.

Confounders were selected *a priori* based on previously described associations with the exposure and child developmental deficits (e.g., educational achievement(38), income(39), and maternal smoking during pregnancy(40)). Models were adjusted for maternal educational level, race/ethnicity, age, insurance, marital status, plurality, BMI, smoking during pregnancy, and the child's gender. Nutritional factors such as prenatal vitamin usage and fish consumption were adjusted for in a third model. Multiple imputations were used to generate ten independent datasets when there were missing covariate values for ten or more

mother-child pairs. Each of the ten imputed datasets were analyzed and the resultant data were then pooled to achieve complete analyses. In situations where less than ten pairs were missing specific covariate information, the data was imputed using the mean observed response from the existing dataset (e.g., insurance and smoking).(41)

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

In total, the analyses encompassed 4843 mother-child pairs with baseline characteristics displayed in Table 1. Mothers who took fish oil supplementation were more likely to be older, Non-Hispanic White, married, possess an advanced degree, have lower pre-pregnancy BMIs, use fertility treatment, and have private insurance. The same mothers were less likely to smoke during pregnancy when compared to those who did not consume fish oil supplements. With regards to nutrition, taking fish oil supplementation was associated with also taking prenatal vitamins and consuming fish during pregnancy. No differences were observed for child gender.

The frequencies of domain failures by supplementation group are presented in Supplemental Table 1. On average, 2–3% of children failed each domain. A higher percentage of children in the no fish oil group tended to fail than the fish oil group.

In the unadjusted analyses (Model 1), supplementation at both time points was significantly associated with a lower risk of failing multiple ASQ domains (Table 2). After adjustment for sociodemographic and maternal lifestyle factors (Model 2), the risk of failing the problem solving domain remained significantly lower among those who supplemented with fish oil before pregnancy (OR 0.40, 95% CI: 0.18 – 0.89) and during pregnancy (OR 0.43, 95% CI: 0.22 – 0.83). In model 2, fish oil supplementation before pregnancy was additionally related to a decreased risk of failing the communication and personal-social domains although the associations were borderline significant ($p<0.10$). A lower risk of failing the problem solving domain persisted in a third model which was further adjusted for prenatal vitamin usage and fish consumption (supplementation before pregnancy OR 0.40, 95% CI: 0.18 – 0.90 and during pregnancy OR 0.43, 95% CI: 0.22 – 0.84).

We were unable to detect a significant statistical interaction for supplementation during pregnancy and gender. Neither did an interaction between supplementation and plurality reach statistical significance. However, in gender stratified analyses, the risk of failing both the problem solving (OR 0.17, 95% CI: 0.03 – 0.95) and the personal-social (OR 0.33, 95% CI: 0.12 – 0.95) domains were significantly lower among girls whose mothers used fish oil supplementation but not in boys (OR 0.64; 95% CI: 0.30–1.36), when adjusted for sociodemographic factors. Also, a significant protective association with the problem solving domain was observed for singletons (OR 0.39, 95% CI: 0.19– 0.82) but not twins (OR 0.77, 95% CI: 0.33– 1.78).

When testing an interaction term between the time of the ASQ and supplementation status, some evidence suggested an interaction with the problem solving domain when the children were older (30 and 36 months); however, sporadic interactions were also observed at the 30-

month time point with the fine motor domain and overall fails (data not shown). No interactions were observed at other time points.

When trying to separate the effects of supplementation before pregnancy from during pregnancy, we still observed a protective association between supplementation and the risk of failing the problem solving domain (problem solving ORs: 0.68 before only and 0.80 during only). However, because many of the mothers were likely to supplement during both timeframes, precision was reduced and the findings did not reach statistical significance in models among mothers who only supplemented prior to pregnancy (4%) or only during pregnancy (8%) after excluding those who supplemented both before and during (7%).

The number of mothers who took rare supplements (e.g., St. John's Wort, Echinacea) during pregnancy was very low (n=31); therefore, we were unable to detect any association with ASQ scores. Due to many missing values, we ran analyses, adjusted for both sociodemographic and nutritional factors, for only those mother-child pairs with prenatal fish consumption data (n=2412) to compare with the analyses of the entire dataset which included imputed values. No notable differences in results were detected (i.e., problem solving OR adjusted for fish consumption: 0.57; 95% CI: 0.27–1.20). The use of WHO BMI categories in place of the continuous BMI value did not have an impact on results (data not shown).

Discussion

The results suggest that maternal prenatal fish oil supplementation may be beneficial to child neurodevelopment, specifically with regards to problem solving. Secondary analyses were suggestive of a positive relationship between fish oil supplementation and personal-social and problem solving skills among female children only. Similar effects on problem solving were apparent in singleton, but not twin, children.

The hippocampus, frontal lobes, and basal ganglia of the brain, areas that are fundamental in higher-order cognition(42, 43), are all very receptive to DHA.(44) While the underlying mechanisms between n-3 PUFA and cognition remain unknown, several postulations exist. First, the accumulation of n-3 PUFA within the cell membranes may result in enhanced information processing speed which would thus lead to improved problem solving.(45) Supplementation of n-3 PUFA has also been associated with heightened attention which in turn is linked with improved cognition.(46, 47) Nonetheless, these findings are contested (56). A recent randomized controlled trial did not find any evidence supporting the long-term beneficial impacts of prenatal fish oil supplementation on child attention (48). Although the evidence is inconsistent (29), prenatal fish oil supplementation has been associated with modest improvements in gross motor function.(49) Previous research demonstrates that motor development may be indicative of later in life cognitive skills(50); therefore, it is possible that problem solving enhancements may be mediated by heightened gross motor abilities. While our study did not detect an effect on gross motor function, the ASQ may not be sensitive enough to capture these subtle variations. Another potential explanation is that DHA promotes neurite growth within the hippocampus and accumulates rapidly in the fetal brain at the same time as critical myelination and synaptogenesis.(4, 51)

n-3 PUFA deficiency has been related to the suppression of the biosynthesis of catecholamines, neurotransmitters that are essential for learning and memory function(52), in the offspring of rats.(53) The role of n-3 PUFA on cognitive function in the developing as well as the aged brain has been previously demonstrated.(54) Models in geriatric animals suggest that fish oil supplementation may play a neuroprotective role in aging by increasing neurogenesis in the hippocampus and reversing changes in retinoid receptors.(55) n-3 PUFA supplementation has been shown to improve synaptic plasticity, learning, and memory in matured rats.(56) Aged rats fed a diet supplemented with n-3 PUFA had decreased hippocampal levels of lipid peroxide and improved learning abilities.(57) In humans, increased fish consumption and n-3 PUFA intake has been associated with a decreased risk of developing Alzheimer's disease (58), although this association is not unanimously supported (59). Both infants and the elderly are vulnerable populations with regard to many exposures. It is likely that the observed positive cognitive impacts of n-3 PUFA supplementation in aged populations occur through the same pathways as during the early stages of life.(4) While many studies have focused on the impact of n-3 PUFA on the development of brain regions such as the frontal lobe in school-aged children, our study shows that the beneficial association is present early in life, specifically in children 3 years and younger.

The potential for fetal insufficiencies of n-3 PUFA during critical windows of development is of concern due to the transition of many to Westernized diets high in saturated fats and low in polyunsaturated fatty acids, specifically n-3 PUFA.(60, 61) The American food industry has become much more reliant on processed foods which are often void of n-3 due to the desire for increased shelf life.(62) With the transition of corn and grain based livestock feeds, animals have become n-3 deficient and thus, our meat sources lack n-3 PUFA as well. (62) In developing countries, access to food sources rich in n-3 PUFA is limited due to geographic as well as economic challenges.(63) Moreover, pregnant women have been advised to limit seafood consumption to reduce fetal exposure to chemical pollutants commonly present such as polychlorinated biphenyls (PCBs) and methylmercury(18, 64), both of which are known neurotoxicants that cross the placenta.(65) Therefore, fish oil supplementation, typically free from contaminants found in fish and seafood, may be a valuable alternative source of n-3 PUFA.(8, 14)

Associations between maternal supplementation and lower risks of failing the personal-social and problem solving domains of the ASQ were significant among female, but not male, children, suggesting potential gender modification. Independent of dietary intake, females typically have greater blood lipid concentrations of DHA than males.(66) In early life, females begin storing DHA in adipose deposits in order to support the growth and development of future offspring(54, 67); therefore, higher quantities of the nutrient are required. Additionally, females have a greater capacity to convert ALA into EPA and DHA than males.(14) Suggested mechanisms include differences among rates of β-oxidation, adipose tissue composition, and sex hormone function between the genders.(66) A study of the human placental transcriptome discovered that maternal n-3 PUFA supplementation during pregnancy is associated with more pronounced placental gene expression in females compared to males.(68) A randomized double-blind controlled trial described a correlation between postnatal DHA supplementation in preterm infants and Bayley Mental

Development Index (MDI) scores at 18 months' corrected age among females only.(69) Using National Health and Nutritional Examination Survey (NHANES) data, a study found the positive relationship between n-3 fatty acid intake and cognition to be twice as strong for school-aged females when compared to males.(67) Similarly, animal research has suggested that fish oil supplementation during pregnancy results in improved social behavior; however, this finding did not take gender into account.(70)

Compared to singletons, twins typically have a higher rate of neurodevelopmental deficits mainly due in part to factors such as low birth weight, smaller gestational age, higher maternal age and socioeconomic status.(71, 72) When stratifying by plurality in our study, the beneficial association on problem solving was significant for singletons but not twins. Similarly, a randomized clinical trial examining maternal fish oil supplementation and pregnancy outcomes failed to detect effects in twin pregnancies.(73) Due to the inclusion of the aforementioned covariates in our analyses, it is possible that the positive effect of fish oil supplementation was not apparent. Additionally, the sample size of twins was smaller than that of singletons.

The permanence of the potential impacts of in utero exposures is one of the critical facets regarding "fetal programming".(74) A recent prospective cohort identified a temporary increase in child neurodevelopment followed by an accelerated decline in these skills among children born to obese mothers, suggesting a dynamic temporal association.(75) Our study identified significant interactions with problem solving at 30 and 36 months and in utero supplementation status; however, this relationship may be attributed to more appreciable problem solving skills at older ages. Furthermore, while intermittent interactions were also observed at 30 months with fine motor and overall fails, no other interactions were detected at additional time points. Due to the inconsistencies of the interactions, our study does not present strong evidence regarding the temporality of the neurologic associations.

Supporting the criticality of the in utero exposure time point, prenatal n-3 PUFA deficiencies have been strongly linked with decrements in cognitive function and neurodevelopment.(53, 54) An autopsy study found that term infants had appreciably higher DHA contents in the frontal cortex than those infants who were in the second trimester(76), demonstrating the elevated requirement of n-3 PUFA during the final trimester of gestation. Animal models show that the learning deficits associated with shortages of n-3 PUFA during this critical prenatal period are challenging to reverse(77) and reduce brain plasticity and performance in adulthood.(78) With a half-life in the human brain of approximately two and a half years, DHA content remains for a substantial amount of time.(79) While we cannot rule out postnatal n-3 PUFA exposures in our current study (e.g., infant formulas supplemented with DHA (80)), research suggests that the positive impacts of this prenatal exposure may be long-lasting, even after continuous supplementation has ceased.(70, 80)

This study faced some limitations. First, exposure data on maternal fish oil consumption was captured on the maternal baseline questionnaire as a dichotomous variable (once or more per week), limiting our ability to distinguish specific dose or the exact frequency of supplementation. However, information on prenatal vitamins suggests the majority took them every day. Second, the ASQ is a validated screening instrument but not a diagnostic

tool; therefore, results may not be appropriate for direct comparison with outcomes from diagnostic developmental assessment tools. Lastly, both fish oil supplementation and child performance on the ASQ were assessed using maternal report which could potentially introduce bias. However, our analyses were strengthened by the notable sample size of greater than 4,800 mother-child pairs. The longitudinal approach with multiple collected ASQ data points employed by the Upstate KIDS Study is a valuable design aspect. Previous research warranted future studies including children of multiple gestations.(81) Our analyses examined twins in addition to singletons and independently.

Despite limitations from the observational nature of our study design, we found that reported maternal fish oil supplementation, both before and during pregnancy, was protective against failing the problem solving domain of the ASQ with the association persisting until three years of age. Furthermore, our findings suggest that female children experienced the greatest benefit from maternal supplementation with lower risks of personal-social and problem solving deficits significantly correlated to prenatal fish oil exposure. Given that pregnant women are advised to increase n-3 PUFA intake to aid fetal brain development while concurrently restricting fish and seafood consumption, our findings demonstrate the potential value of fish oil supplementation as an alternate source of n-3 PUFA during pregnancy. Future research needs to focus on clearing up discrepancies in the literature, establishing optimal dosages, identifying the ideal timing and duration of supplementation, the persistence of subsequent health outcomes, gender interactions, and impacts on children of multiple births.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Maternal baseline characteristics by fish oil supplementation status

	Maternal fish oil supplementation before pregnancy		Maternal fish oil supplementation during pregnancy	
Maternal Characteristics	**Yes**	**No**	**Yes**	**No**
Number (%)	534 (11.0)	4309 (89.0)	737 (15.2)	4106 (84.8)
Maternal age in years, mean (SD) *b, c*	33.2 (5.5)	30.1 (6.0)	32.7 (5.4)	30 (6.1)
Maternal race/ethnicity *b, c*				
Non-Hispanic White	441 (82.6)	3459 (80.3)	625 (84.8)	3275 (79.8)
Non-Hispanic Black	11 (2.1)	216 (5.0)	18 (2.4)	209 (5.1)
Non-Hispanic Asian	16 (3.0)	110 (2.6)	32 (4.3)	94 (2.3)
Hispanic	26 (4.9)	265 (6.2)	23 (3.0)	268 (6.5)
Mixed race or ethnicity/ Other	40 (7.5)	259 (6.0)	39 (5.3)	260 (6.3)
Married *b, c*	505 (94.6)	3768 (87.4)	697 (94.6)	3576 (87.1)
Maternal Education *b, c*				
Less than high school	12 (2.3)	257 (6.0)	11 (1.5)	258 (6.4)
High school graduate or GED	25 (4.7)	595 (14.0)	38 (5.2)	582 (14.3)
Some college	60 (11.4)	843 (19.7)	75 (10.3)	828 (20.4)
College degree	206 (39.1)	1423 (33.0)	289 (39.5)	1340 (33.0)
Advanced degree	224 (42.5)	1153 (27.0)	319 (43.6)	1058 (26.0)
Pre-pregnancy BMI (kg/m^2), mean (SD) *b, c*	26.2 (6.2)	27.2 (6.9)	26.0 (6.2)	27.3 (6.9)
Private Insurance *b, c*	470 (88.0)	3145 (73.0)	657 (89.1)	2958 (72.0)
Smoked during pregnancy *b, c*	27 (5.1)	675 (15.7)	47 (6.4)	655 (16.0)
Maternal nutrition during pregnancy				
Prenatal Vitamin use *a b, c*	446 (84.5)	3128 (73.8)	612 (84.7)	2962 (73.3)
Fish Consumed *a, b, c*	192 (63.6)	1202 (57.0)	281 (64.9)	1113 (56.2)
Singleton birth *b c*	406 (61.4)	3401 (65.6)	554 (60.4)	3253 (66.0)
Male	340 (51.4)	2644 (51.0)	469 (51.2)	2515 (51.0)

GED, General Equivalency Diploma

a Data are missing for the following before multiple imputation: prenatal vitamin (n=78), fish consumption (n=2431)

b $p < 0.05$ for comparison between fish oil supplementation before pregnancy and no supplementation before pregnancy.

c $p < 0.05$ for comparison between fish oil supplementation during pregnancy and no supplementation during pregnancy.

Table 2

Odds ratio for risk of developmental delays by maternal fish oil supplementation status

	n	Model 1 (Unadjusted)	p-value	Model 2[a]	p-value
Fish Oil Supplementation before pregnancy					
Any fail	4668	0.69 (0.47 – 1.03)	0.068	0.76 (0.51 – 1.14)	0.176
Fine motor	4682	0.54 (0.29 – 0.99)	0.046	0.61 (0.32 – 1.15)	0.122
Gross motor	4686	0.90 (0.48 – 1.70)	0.742	0.93 (0.47 – 1.82)	0.823
Communication	4689	0.46 (0.24 – 0.87)	0.016	0.53 (0.27 – 1.04)	0.064
Personal-social	4684	0.54 (0.30 – 0.97)	0.040	0.57 (0.30 – 1.06)	0.073
Problem solving	4676	0.35 (0.16 – 0.74)	0.006	0.40 (0.18 – 0.89)	0.026
Fish Oil Supplementation during pregnancy					
Any fail	4668	0.71 (0.50 – 0.99)	0.049	0.82 (0.58 – 1.18)	0.273
Fine motor	4682	0.51 (0.29 – 0.88)	0.017	0.64 (0.36 – 1.15)	0.128
Gross motor	4686	0.89 (0.52 – 1.53)	0.679	1.01 (0.57 – 1.80)	0.966
Communication	4689	0.70 (0.43 – 1.15)	0.160	0.81 (0.49 – 1.36)	0.415
Personal-social	4684	0.62 (0.39 – 1.01)	0.053	0.74 (0.44 – 1.22)	0.226
Problem solving	4676	0.34 (0.18 – 0.63)	0.001	0.43 (0.22 – 0.83)	0.014

[a]Model 2 adjusts for maternal race/ethnicity, age, education, insurance, married, plurality, smoking during pregnancy, BMI and infant gender.