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Fish oil supplementation during pregnancy is protective against asthma/wheeze in offspring

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Trial Registration:

The trial was approved by the Institutional Review Boards of the participating institutions and at Brigham and Women's Hospital and is registered with [NCT00920621](https://clinicaltrials.gov/ct2/show/study/NCT00920621)). Written informed consent was obtained from all women at recruitment.

To the Editor

The diagnosis of asthma in childhood has doubled in recent decades and is now estimated to affect as many as one in five young children across the USA and Europe^{1,2}. Attempts at early intervention and prevention, such as encouraging breastfeeding, administering probiotics, and reducing exposure to allergens have not lowered the incidence². Prenatal supplementation with Vitamin D₃³ and fish oil derived fatty acids (i.e. n-3 long chain polyunsaturated fatty acids (LCPUFAs))⁴ such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have recently been shown to reduce asthma/recurrent wheeze

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in children⁵. An inverse association has also been reported between low maternal EPA, DHA, and total n-3 fatty acid levels during pregnancy with increased risk of non-atopic persistent wheeze in their offspring by the age of 6 years⁵. However, a complete understanding of how these nutritional interventions, and their potential interactions may affect asthma development remains limited. The aims of this current study were two-fold: (1) to assess the relationship between fish oil supplementation during pregnancy (derived using a food frequency questionnaire (FFQ)) with asthma/recurrent wheeze in offspring by age three; and (2) to evaluate a possible interaction effect between prenatal fish oil supplementation and prenatal vitamin D₃ levels on the development of asthma/recurrent wheeze. We used children from the Vitamin D Antenatal Asthma Reduction Trial (VDAART) which enrolled 881 pregnant women at 10–18 weeks gestation, randomized them to 400 IU vs. 4,400 IU of vitamin D₃, then followed these women and their offspring for the development of asthma/recurrent wheeze by age three, as described previously^{3,6}. Of these 881 pregnant women, a total of 804 (91.26%) mother-child pairs completed the FFQ at 10–18 weeks of gestation (1st trimester); of these 776 (88.08%) mother-child pairs also completed the FFQ at 32–38 weeks of gestation (3rd trimester).

Univariate and multivariable logistic regression models were used to evaluate the effect of fish oil on asthma/wheeze. Specifically, we utilized fish oil supplementation measures from the FFQ that were taken in the form of capsules (yes/no) during the 1st and 3rd trimester of pregnancy. This measure of maternal fish oil supplementation and an interaction term for fish oil supplementation and baseline 25OHD (deficient concentration <30 ng/mL versus sufficient 25OHD concentration ≥ 30 ng/mL)^{3,7}, were used as predictors in a model to assess their association with the incidence of physician-diagnosed asthma/recurrent wheeze at age three years in the offspring, as defined in the primary VDAART paper³ and in the online supplement (see article's Online Repository at www.jaci-inpractice.org). While we have previously shown that vitamin D supplementation in pregnancy reduced the risk of asthma and recurrent wheeze in 3-year old children⁶, we observed that the effect was dependent on the maternal level of 25OHD at entry into the trial³. Thus, this analysis only used 25OHD levels at baseline as the index of exposure to prenatal vitamin D. Fish oil dosage was defined by the strength (in mg) of each capsule mother takes per week. We considered fish oil intake in both the 1st and the 3rd trimester of pregnancy. Survival analysis utilizing a Weibull regression model⁸ was also used to assess the fish oil and asthma/recurrent wheeze relationship in the first three years of life. Ultra-performance liquid chromatography–tandem mass spectroscopy (UPLC-MS/MS) based metabolomic profiling conducted at the Broad Institute (Massachusetts Institute of Technology, Cambridge, MA, USA) was performed on plasma samples from a subset of women⁹ at the 1st trimester (n=107, including seven mothers (6.5%) who reported taking fish oil supplements) and the 3rd trimester (n=103, including five mothers (4.9%) who reported taking fish oil supplements). Two n-3 LCPUFAs metabolites: eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were evaluated using univariate regression models for an association with asthma/recurrent wheeze and with fish oil intake. Given the prior literature, we hypothesized that fish oil and Vitamin D reduce the risk of asthma/wheeze in offspring, and therefore utilized one-sided P values and confidence intervals to test these associations. Analyses were conducted using statistical software R version 3.2.3, and the CRAN survival package.

Of the 804 mothers with FFQ data from the 1st trimester, 50 mothers (6.2%) took fish oil supplements and 175 mothers (21.8%) had sufficient levels of 25OHD (Table E1). The univariate regression models found that both fish oil supplementation (OR=0.41; 95% CI: $-\infty$, 0.81; one-sided P=0.016) and sufficient 25OHD levels (OR=0.61; 95% CI: $-\infty$, 0.87; one-sided P=0.010) in the 1st trimester were significantly associated with a reduced risk of asthma/recurrent wheeze among offspring (Table 1). The Weibull analysis gave similar results: the risk of asthma/recurrent wheeze was significantly lower among children of mothers who took prenatal fish oil (14% versus 28%, N=804, Figure 1, HR=0.45; 95% CI $-\infty$, 0.84; one-sided P=0.018). There was no statistically significant interaction of fish oil supplementation with 25OHD levels (OR=0.94; 95% CI: 0.12, 5.25; P=0.473) (Table 1).

Analysis of fish oil into dosage categories suggested that the protective effect of fish oil was driven by the highest doses; with the greatest decrease in risk seen in those women who took more than 500 mg/week (N=28) relative to those women who took none (OR=0.19; 95% CI: $-\infty$, 0.66; one-sided P=0.014) (Table 1). A test for trend also supported the fish oil intake asthma/recurrent wheeze relationship, with an increased protective effect seen with increased dosage of fish oil (one-sided P=0.010). Fish oil supplementation remained protective against asthma/wheeze after adjusting for potential confounders (maternal education and race) (Table E2, OR= 0.49; 95% CI: $-\infty$, 0.99; one-sided P=0.047), however due to low numbers in certain strata when accounting for these variables, these analyses were unstable (Table E1). Ninety-two percent of the 50 women who took fish oil supplements were college graduates compared to 60% of the non-users, and 70% were white compared to 39% respectively (Table E1). Replication in a larger population is necessary to fully assess the effect of these variables on the outcome.

Twenty-four of the 50 mothers continued to take fish oil supplements in the 3rd trimester. We observed the greatest reduction in risk of asthma/recurrent wheeze among the offspring of these 24 mothers who took fish oil during both the 1st and 3rd trimesters compared to none at all (OR=0.38; 95% CI: $-\infty$, 1.06; one-sided P=0.06, Table 1). The increased reduction in risk with duration of supplementation was supported by a test for trend (one-sided P=0.039).

Additionally, although we were underpowered to investigate PUFAs in the mothers, higher levels of DHA in the mothers during their 1st trimester were significantly associated with a reduced risk of asthma/recurrent wheeze among their offspring (OR=0.43; 95% CI: $-\infty$, 0.96; one-sided P=0.042, Table 1). Similarly, higher levels of EPA also demonstrated a decreased risk, although this association did not meet statistical significance (OR=0.80; 95% CI: $-\infty$, 1.52; one-sided P=0.288, Table 1). In the 3rd trimester, there was evidence of a decreased risk of asthma/wheeze in offspring with increasing maternal PUFA levels: EPA (OR=0.43; 95% CI: $-\infty$, 0.92; one-sided P=0.034, Table 1) and DHA (OR=0.49; 95% CI: $-\infty$, 1.07; one-sided P=0.067, Table 1). Blood metabolite levels for both EPA (Estimate: 0.91; 95% CI: $-\infty$, 1.30; one-sided P= 9.9×10^{-5}) and DHA (Estimate: 0.68; 95% CI: $-\infty$, 1.03; one-sided P= 9.7×10^{-4}) reached statistical significance in the 3rd trimester (Table E3); EPA's effect was also significant in the 1st trimester (Estimate: 0.55; 95% CI: $-\infty$, 0.91; one-sided P= 5.7×10^{-3} , Table E3). Therefore, these findings are consistent with the FFQ analyses; one of the most frequently employed methods for nutritional epidemiological investigations¹⁰. The main strength of this study is the assessment of the relationship

between PUFA intake and asthma/wheeze utilizing the FFQ. Our results suggest that there is a protective effect of maternal fish oil intake on the development of asthma/recurrent wheeze in offspring during the first three years of their life, which is in agreement with the study by Bisgaard *et al.*⁶. The results based on maternal PUFA levels also support this conclusion. Moreover, there is evidence of a dose-response protective effect against asthma/recurrent wheeze. We did not identify a significant interaction between fish oil supplementation and baseline 25OHD, which is again consistent with Bisgaard *et al.*'s findings.⁶ In conclusion, both fish oil and vitamin D₃ are recommended during pregnancy; however, a more comprehensive assessment of vitamin D₃ and fish oil supplementation during pregnancy may provide further insight into the biological mechanisms at play.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Implications:

Early life asthma represents a significant public health burden. Prenatal supplementation with fish oil derived fatty acids (i.e. n-3 long chain polyunsaturated fatty acids (LCPUFAs)) and Vitamin D₃ could modulate the risk of asthma/recurrent wheeze in offspring.

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Figure 1.

Kaplan-Meier survival estimates demonstrating offspring's asthma or recurrent wheeze free proportion by fish oil intake status. The red curve corresponds to offspring from mothers who took fish oil (Fish oil positive) and blue curve to those from mothers who did not take fish oil (Fish oil negative). In this time to event analysis, the event corresponds to either the occurrence of asthma or recurrent wheeze. The hazard ratio (HR) for time to first event of either asthma or recurrent wheeze by age 3 years obtained using Weibull regression model was 0.45 (One-sided 95% CI $-\infty$, 0.84; one-sided $P=0.018$).

Table 1.

Association of fish oil and baseline 25OHD (univariate models); fish oil and baseline 25OHD interaction (multivariate interaction model) in mothers at 1st (N=804; 50 with fish oil intake, 175 with sufficient 25OHD) and 3rd trimester (N=776; 40 with fish oil intake, 421 with sufficient 25OHD); with asthma/wheeze in children by age 3 years (logistic regression models). Univariate dose-response model highlights the effect of fish oil on asthma/wheeze when stratified by dosage. For the 3rd trimester, duration of supplementation was supported by a test for trend and analyzing the categories comparing the mothers with fish oil intake in both 1st and 3rd trimester (N=24) to those that took it at either one time point (N=42) or not at all (N=710).

Models for outcome asthma/wheeze	N	OR	One-sided (95% CI)	One-sided P-value	Test for trend
1st trimester	804				
Univariate models					
Fish oil	47	0.41	−∞, 0.81	0.016	
Maternal 25OHD	163	0.61	−∞, 0.87	0.010	
DHA	107	0.43	−∞, 0.96	0.042	
EPA	107	0.80	−∞, 1.52	0.288	
Univariate dose response					
Fish oil dose (Test for trend)	747	0.64	−∞, 0.88		0.010
No fish oil	701	1.00			
Fish oil dose < 250mg	11	0.88	−∞, 2.69	0.424	
Fish oil dose ≥250mg and <500mg	9	0.67	−∞, 2.52	0.308	
Fish oil dose ≥500mg	26	0.19	−∞, 0.66	0.014	
Multivariate interaction model					
Fish oil	47	0.45	−∞, 1.03	0.056	
Maternal 25OHD	163	0.64	−∞, 0.91	0.020	
Fish oil × 25OHD *	19	0.94	0.12, 5.25	0.946	
3rd trimester	776				
Univariate models					
Duration of fish oil supplementation (Test for trend)	722	0.65	−∞, 0.97		0.039
No fish oil intake	661	1.00			
Either time point	39	0.72	−∞, 1.36	0.196	
Intake in both 1 st and 3 rd trimester	22	0.38	−∞, 1.06	0.060	
Maternal 25OHD	395	0.68	−∞, 0.89	0.010	
DHA	103	0.49	−∞, 1.07	0.067	
EPA	103	0.44	−∞, 0.92	0.034	

N: Subjects with available data for the predictor and the outcome asthma/recurrent wheeze in models

Abbreviations: 25OHD: 25-hydroxyvitamin D, EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid Missing data: Asthma/wheeze status was missing for 57 mothers in the 1st trimester and 54 mothers analyzed in the 3rd trimester. Baseline 25OHD was missing for four mothers in the 1st trimester and nine mothers in the 3rd trimester.

* Two-sided P-Values and CIs for the interaction term

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