Omega-3 Fatty Acid Supplementation During Pregnancy and Respiratory Symptoms in Children

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BACKGROUND: Prenatal consumption of omega-3 fatty acids can act as an adjuvant in the development of the immune system and affect the inflammatory response of neonates.

METHODS: We conducted a double-blind, randomized, placebo-controlled trial in Cuernavaca, Mexico. We randomly assigned 1,094 pregnant women (18-35 years of age) to receive 400 mg/d of algal docosahexaenoic acid (DHA) or placebo from 18 to 22 weeks of gestation through delivery. Birth outcomes and respiratory symptoms information until 18 months were available for 869 mother-child pairs. Questionnaires were administered, and maternal blood samples were obtained at baseline. Maternal atopy was based on specific IgE levels. During follow-up, information on infants' respiratory symptoms was collected through questionnaires administered at 1, 3, 6, 9, 12, and 18 months of age. Negative binomial regression models were used to evaluate the effect of supplementation on respiratory symptoms in infants.

RESULTS: Among infants of atopic mothers, a statistically significant protective effect of DHA treatment was observed on phlegm with nasal discharge or nasal congestion (0.78; 95% CI, 0.60-1.02) and fever with phlegm and nasal discharge or nasal congestion (0.53; 95% CI, 0.29-0.99), adjusting for potential confounders.

CONCLUSIONS: Our results support the hypothesis that DHA supplementation during pregnancy may decrease the incidence of respiratory symptoms in children with a history of maternal atopy.

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ABBREVIATIONS: DHA = docosahexaenoic acid; IMSS = General Hospital of the Mexican Social Security Institute/Instituto Mexicano del Seguro Social; INSP = National Institute of Public Health/Instituto Nacional de Salud Pública; IR = incidence rate; IRR = incidence rate ratio; Th = T helper

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Allergy and asthma affect > 350 million people worldwide and are responsible for increased respiratory symptoms in children and adults.¹ In 2009, asthma was the 15th leading cause among the 20 leading causes of illness in Mexico, and it was ranked 13th in the state of Morelos (Mexico), with incidence rates of 348.8 per 100,000 inhabitants for the general population, 382.7 per 100,000 for infants < 1 year of age, and 742.5 per 100,000 for children 1 to 4 years of age.²

Immune system deficiencies and the presence of diseases such as respiratory infections trigger the presence of respiratory signs and symptoms.³ It is currently well known that the regulation of tolerance and immune system activation is crucial to health, and failure in the regulation of these responses can lead to recurrent infections, inflammatory diseases, and allergic reactions. Furthermore, many allergic and inflammatory processes in adulthood are believed to originate during fetal and neonatal periods, since these periods are key to immune adaptation.⁴ Different studies have also shown that immune abnormalities precede the

development of allergic diseases.⁵ Since the maternal diet can affect neonatal immune development and subsequently alter the allergic response in infants, the consumption or supplementation with omega-3 polyunsaturated fatty acids may play an important role, especially for the most susceptible individuals.⁶⁻⁸ However, the results of previous studies using omega-3 supplementation are inconsistent.

Because of the negative impact of respiratory disease on the quality of life and the high cost of long-term treatment of signs and symptoms, further research is needed to prevent such diseases.⁹ This study assesses whether supplementation with omega-3 fatty acids during pregnancy reduces the incidence of respiratory symptoms in children up to 18 months of age using data from a double-blind randomized placebo-controlled clinical trial in Cuernavaca, Mexico. We hypothesize that omega-3 fatty acid intake during pregnancy plays an important role in preventing the development of respiratory symptoms and allergic diseases in infants whose mothers have a history of atopy.

Materials and Methods

Experimental Design

A randomized, double-blind controlled trial was conducted. A total of 1,094 pregnant women were randomly assigned to receive 400 mg of docosahexaenoic acid (DHA) or placebo daily from midpregnancy (18-22 weeks of gestation) to delivery (National Institute of Public Health/Instituto Nacional de Salud Pública [INSP] Mexico: CI-011 in clinicaltrials.gov: NCT00646360). DHA was chosen as the supplement, as the aim of the original trial was to determine potentially beneficial effects of omega-3 fatty acid supplementation during pregnancy on infant neurodevelopment; DHA is the most abundant omega-3 fatty acid in the mammalian CNS.¹⁰ Of the 1,094 women randomized, 1,040 started treatment, and 973 completed the study. Five had stillbirths, and there were 968 live-born infants (963 single and five pairs of twins); for the present analysis, 869 mother-child pairs were included to have complete information from pregnancy until 18 months of follow-up (Fig 1). This study was conducted in collaboration with the Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia; INSP, Mexico; and the General Hospital of the Mexican Social Security Institute/Instituto Mexicano del Seguro Social (IMSS) in Cuernavaca, Mexico. The protocol was approved by the institutional review board at Emory University (CI:418) and by ethics and biosafety committees at the INSP. All procedures were explained to the participants, who signed an informed consent. The study data were reviewed periodically by an external data and safety monitoring committee.

Study Setting and Population

Participants were recruited at the General Hospital of the IMSS in Cuernavaca, Mexico, and three small health clinics within the IMSS system in Morelos, Mexico, during routine prenatal care visits between February 2005 and February 2007. In general, IMSS enrollees are from middle to low socioeconomic status.¹⁰ Using data from a major study,¹⁰ we estimated that a final sample of 338 infants per group would have at least 90% power to detect an effect size ≥ 0.25 SD for the major outcomes at the end of the study, assuming a significance level of $\alpha = 0.05$ for

a two-tailed test. We, therefore, planned to recruit at least 994 pregnancies, assuming a 15% loss to follow-up during pregnancy and a further 20% loss in infancy, to have 393 births and 338 mother-child pairs per group complete the study at 18 months of age. This sample size would allow us to detect differences in the symptoms of one for each 1,000 (1 SD) with at least 80% power. However, for the present report, we included 869 mother-child pairs (429 from DHA group and 440 from placebo group). This sample size would allow us to detect differences in all symptoms (except in coughing and coughing with phlegm) of one for each 1,000 (1 SD) and a power of 90% (Fig 1). Only 869 mother-child pairs (Fig 1) were included in the present report by having all the information from birth until 18 months of follow up, including laboratory results.

Eligibility Criteria

The women included in the clinical trial were between 18 and 35 years of age and were recruited between 18 and 22 weeks of gestation. All participants expressed their willingness to breastfeed exclusively or predominantly during at least the first 3 months of life of the newborn and stated their intention to live in their area of residence for at least 2 years after delivery. Exclusion criteria were women with high-risk pregnancies (pregnancy complications, including premature placental abruption, preeclampsia, pregnancy-induced hypertension, severe bleeding episode in pregnancy) or lipid absorption disorders, or who regularly consumed fish oil or DHA supplements or chronically used certain medications (eg, drugs for epilepsy).

Randomization and Blinding

We used block randomization to randomly create balanced replication of four treatments (two colors for DHA and two for control subjects) using a block size of eight. The list was generated for a sample size of 1,104. The assignment codes were placed in sealed envelopes at the beginning of the study. All study participants and members of the study team remained blinded to the treatment scheme throughout the intervention period of the study. Data were unblinded for the analytical study team after the last baby in the study was born and had reached 6 months of age, at which time the participants were no

Figure 1 – Consort diagram showing how subjects were progressed through the study and how the final study samples were obtained. DHA = docosa-hexaenoic acid; tx = treatment.

longer taking supplements. Since the study is ongoing for follow-up of children, the participants and fieldworkers remain blinded to the treatment allocation.

Intervention

Women received instructions to take two capsules per day of DHA or placebo from week 18 or 22 until delivery. The DHA capsules contained 200 mg of DHA derived from an algal source. The placebo capsules contained a mixture of corn and soy oil and were similar in appearance and taste to DHA capsules. Compliance was calculated as the total number of capsules actually consumed, expressed as a percentage of the total number expected to be consumed. Details have been described previously by Ramakrishnan et al.¹⁰

Measurement of Main Variables

Children were followed every 3 months from birth to 12 months and once more at 18 months of age using a clinical questionnaire, “Child Health History”; this questionnaire provided detailed information about the presence or absence of signs and respiratory symptoms and the number and duration of episodes. Although this respiratory symptoms questionnaire has not been validated in the Mexican population, we include some questions from the International Study of Asthma and Allergies in Childhood validated questionnaire used in the Mexican population.¹¹

Symptomatic episode was defined for each sign and symptom, coded as 1 for the presence of at least one symptom or sign lasting ≥ 3 days or 0 otherwise. The combination of the presence of various symptoms or signs at the same time was also considered. The variables included in the analysis were: (1) coughing; (2) wheezing; (3) difficulty breathing; (4) wheezing and difficulty breathing; (5) coughing with wheezing and/or difficulty breathing; (6) coughing with phlegm; (7) phlegm, nasal discharge, and/or stuffy nose; (8) fever with phlegm and nasal discharge

or nasal congestion; (9) coughing with fever; and (10) wheezing with fever. Respiratory symptoms refer to the definitions previously listed.

Maternal Atopy

During pregnancy, a sample of maternal blood was obtained to determine specific IgE levels in plasma and establish the atopic status, using a Luminex flow cytometry (ImmuneTech, Inc) for the analysis. For the present report, we handle the specific IgE levels as dichotomous variable, considering two categories: positive, $\text{IgE} \geq 0.70$ IU/mL (atopic mother) and negative, $\text{IgE} < 0.70$ IU/mL (nonatopic mother) cutoff point levels. Some authors have noted that the range of values of IgE level between 0.67 and 1.31 IU/mL have been shown to be predictors of atopy.¹²

Measurement of Other Variables

Sociodemographic characteristics, lifestyle, and environmental exposure of the mothers were obtained using a questionnaire administered in home during the second trimester of pregnancy, and information about the child was obtained during the postnatal period. The questionnaire included questions about parental education, household income, and household characteristics (such as structure, family environment, and environmental factors associated with allergens [pets in home, vehicular traffic exposure, active and passive smoking]). Also, we obtained information about food consumption and dietary intakes of fatty acids from the mother using a previously validated food-frequency questionnaire for the Mexican population that was adapted for use in pregnant women, who were asked to recall intakes of 110 food items.¹³

Statistical Analysis

Crude incidences of respiratory symptoms up to 18 months of age were calculated according to maternal atopy and treatment groups (DHA or placebo). For each symptom, the adjusted incidence rate ratio (IRR) was calculated using a negative binomial regression model for the

TABLE 1] Characteristics of the Study Population

Variables	Treatment Group		Total
	Placebo	DHA	
Characteristics of the mother	440 (50.6)	429 (49.4)	869 (100.0)
Mother's age, mean (SD), y	26.2 (4.7)	26.3 (4.9)	26.3 (4.8)
BMI of mother, mean (SD)	26.2 (4.3)	25.8 (4.0)	26.0 (4.2)
Maternal overweight, BMI > 25			
No	193 (43.9)	188 (43.8)	381 (43.8)
Yes	247 (56.1)	241 (56.2)	488 (56.2)
Mother's education			
Primary or less	179 (40.7)	182 (42.4)	361 (41.5)
Secondary or more	261 (59.3)	247 (57.6)	508 (58.5)
Socioeconomic status			
Low	145 (33.0)	127 (29.6)	272 (31.3)
Medium	136 (30.9)	163 (38.0)	299 (34.4)
High	159 (36.1)	139 (32.4)	298 (34.3)
Maternal atopy by specific IgE			
Nonatopic	296 (67.3)	290 (67.6)	586 (67.4)
Atopic	144 (32.7)	139 (32.4)	283 (32.6)
Dietary intake of DHA, median (25th, 75th percentile), mg/d	54 (38, 93)	56 (38, 101)	55 (37, 99)
Child characteristics			
Sex of child			
Female	203 (46.1)	202 (47.1)	405 (46.6)
Male	237 (53.9)	227 (52.9)	464 (53.4)
Weight at birth, mean (SD), kg	3.2 (0.5)	3.2 (0.4)	3.2 (0.5)
Low birth weight (< 2,500 g)			
No	416 (94.6)	410 (95.6)	826 (95.1)
Yes	24 (5.5)	19 (4.4)	43 (5.0)
Total IgE level in cord, IU/mL			
Not detectable (<0.1)	139 (41.5)	150 (45.3)	289 (43.4)
Detectable (≥ 0.1)	196 (58.5)	181 (54.7)	377 (56.6)
Birth order			
No previous delivery	169 (38.4)	155 (36.1)	324 (37.3)
At least one	271 (61.6)	274 (63.9)	545 (62.7)
Type of delivery			
Normal	206 (46.8)	213 (49.7)	419 (48.2)
Cesarean	234 (53.2)	216 (50.4)	450 (51.8)
Environmental exposure			
Pets at home			
No	164 (41.1)	154 (40.2)	318 (40.7)
Yes	235 (58.9)	229 (60.0)	464 (59.3)
Cockroaches in the last 12 mo			
No	125 (31.3)	139 (36.3)	264 (33.8)
Yes	274 (68.7)	244 (63.7)	518 (66.2)

(Continued)

TABLE 1] (continued)

Variables	Treatment Group		Total
	Placebo	DHA	
Presence of humidity			
No	251 (62.9)	258 (67.4)	509 (65.1)
Yes	148 (37.1)	125 (32.6)	273 (34.9)
Anyone smoke at home			
No	241 (60.4)	220 (57.4)	461 (59.0)
Yes	158 (39.6)	163 (42.6)	321 (41.1)

Data are presented as No. (%) unless otherwise noted. DHA = docosahexaenoic acid.

overdispersion of symptoms. Follow-up considered the exposure function in the model as natural logarithm for the episode of symptoms per person-day risk.¹⁴ Models were adjusted for child's sex, low birth weight, and mother's education level. In addition, the interaction was evaluated between treatment group and maternal atopy on the incidence of respiratory symptoms. Other variables were evaluated but not included in the final model because they were not significant ($P > .10$) and did not change

the coefficients by $> 10\%$. These included socioeconomic status, dietary intake of child at 12 and 18 months, maternal overweight, total infant IgE levels in umbilical cord, birth order, delivery type, breastfeeding during the first 6 months, presence of pets at home, humidity, and active and passive tobacco exposure. A residual diagnostic was performed to test the fit of the models.¹⁴ All analyses were performed using STATA version 11.0 (StataCorp LP).

Results

Table 1 shows the sociodemographic characteristics of the study population. Mean age of women was 26.3 years ($SD = 4.8$), more than one-half were overweight (56.2%), and only 58.5% completed secondary school. The intakes of dietary omega-3 fatty acid prior to entry into the trial in women were very low (median intake, 55 mg/d; interquartile range, 37-99 mg/d). In addition, 32.6% of the mothers were classified as atopic based on specific IgE levels, 50% of offspring were boys, and mean birth weight was 3.2 ($SD = 0.5$) kg. According to the determinations of total IgE levels, 56.6% of children had detectable IgE in the cord blood (≥ 0.1 IU/mL). More than one-half of the homes where children lived had pets (59.3%), and 41.1% of households reported having at least one person who smoked inside the home. Other baseline characteristics are presented in Table 1. There were no statistically significant differences in any of the main baseline characteristics measured between the children whose mothers received placebo and those receiving DHA.

In the crude analyses, the incidence rate (IR) for respiratory symptoms among children from atopic mothers was similar between treatment groups, except for "phlegm with congestion and/or nasal discharge," "fever with phlegm and congestion and/or nasal discharge," and "wheezing with fever." Children whose mothers received DHA supplementation had a lower risk of these symptoms compared with children whose mothers received placebo (25.7% [IRR = 0.74; 95% CI, 0.63-0.87], 48.3% [IRR = 0.52; 95% CI, 0.38-0.70], and 56.8%

[IRR = 0.43; 95% CI, 0.21-0.83], respectively). For children of nonatopic mothers, the incidence rate of "coughing with wheezing and/or breathing difficulty," "phlegm with congestion and/or nasal discharge," and "fever with phlegm and congestion and/or nasal discharge" were higher for children whose mothers received DHA (IRR = 1.26; 95% CI, 1.00-1.59; IRR = 1.13; 95% CI, 1.02-1.26; and IRR = 1.26; 95% CI, 1.04-1.53, respectively), (Table 2).

When the multivariate models were adjusted for child's sex, low birth weight, and maternal education, we observed that the risk of presenting symptoms was always higher in children from the group of mothers who received placebo vs DHA supplementation (Table 3). For the placebo group, children of atopic mothers had an increased risk of respiratory symptoms, in particular for "coughing with wheezing and/or breathing difficulty" (IRR = 1.44; 95% CI, 0.94-2.23), "phlegm with congestion and/or nasal discharge" (IRR = 1.27; 95% CI, 0.96-1.67), and "wheezing with fever" (IRR = 1.91; 95% CI, 1.00-3.65). For the DHA group, children of atopic mothers had a decreased risk of "phlegm with nasal congestion or nasal discharge" (IRR = 0.78; 95% CI, 0.60-1.02) and "fever with phlegm with congestion and/or nasal discharge" (IRR = 0.53; 95% CI, 0.29-0.99) (Fig 2, Table 3). A significant interaction was observed between the mother's atopic status and the treatment group on the incidence of the following respiratory symptoms in child: "breathing difficulty" ($P = .094$), "coughing with wheezing and/or breathing difficulty" ($P = .091$), "phlegm with congestion and/or nasal

TABLE 2] IR and IRR of Respiratory Symptoms in Children Until 18 Mo

Respiratory Symptoms	Exposed (DHA)		Unexposed (Placebo)		IRR	
	Episodes/Person-D	IR ^a	Episodes/Person-D	IR ^a	IRR (95% CI)	P Value
Maternal atopy						
Coughing	374/67,257	5.6	382/68,596	5.6	0.999 (0.864-1.155)	.984
Wheezing	77/69,405	1.1	89/70,778	1.3	0.882 (0.642-1.211)	.422
Breathing difficulty	11/70,150	0.2	20/71,318	0.3	0.559 (0.242-1.224)	.121
Wheezing and/or breathing difficulty	88/69,340	1.3	109/70,617	1.5	0.822 (0.614-1.099)	.172
Coughing with wheezing and/or breathing difficulty	72/66,382	1.1	86/67,734	1.3	0.854 (0.616-1.182)	.325
Coughing with phlegm	233/65,223	3.6	251/66,324	3.8	0.944 (0.786-1.133)	.527
Phlegm with congestion and/or nasal discharge	273/64,565	4.2	371/65,219	5.7	0.743 (0.633-0.871)	<.001
Fever with phlegm with congestion and/or nasal discharge	65/64,095	1.0	127/64,710	2.0	0.517 (0.377-0.702)	<.001
Coughing with fever	78/66,787	1.2	98/68,087	1.4	0.811 (0.595-1.104)	.169
Wheezing with fever	14/68,935	0.2	33/70,269	0.5	0.432 (0.214-0.830)	.007
Maternal nonatopy						
Coughing	804/139,664	5.8	769/142,487	5.4	1.067 (0.965-1.179)	.201
Wheezing	175/144,799	1.2	173/147,056	1.2	1.027 (0.828-1.275)	.802
Breathing difficulty	36/145,867	0.2	28/148,104	0.2	1.305 (0.775-2.221)	.292
Wheezing and/or breathing difficulty	211/144,429	1.5	201/146,903	1.4	1.068 (0.876-1.302)	.507
Coughing with wheezing and/or breathing difficulty	169/137,856	1.2	137/141,133	1.0	1.263 (1.002-1.594)	.042
Coughing with phlegm	517/134,810	3.8	491/138,033	3.6	1.078 (0.951-1.222)	.233
Phlegm with congestion and/or nasal discharge	715/133,094	5.4	647/136,404	4.7	1.133 (1.017-1.262)	.022
Fever with phlegm with congestion and/or nasal discharge	236/132,104	1.8	192/135,467	1.4	1.260 (1.037-1.533)	.017
Coughing with fever	214/138,674	1.5	206/141,550	1.5	1.060 (0.872-1.290)	.548
Wheezing with fever	54/143,809	0.4	40/146,119	0.3	1.372 (0.895-2.12)	.130

IR = incidence rate; IRR = incidence rate ratio. See Table 1 legend for expansion of other abbreviation.

^aIR rate per 1,000 inhabitants.

discharge" ($P = .016$), "fever with phlegm with congestion and/or nasal discharge" ($P = .014$), and "wheezing with fever" ($P = .012$). When comparing these symptoms exclusively between the children whose mothers were supplemented, the symptoms decreased for the group of children whose mothers were atopic, unlike the group of children whose mothers were atopic and received placebo (Fig 3).

Discussion

The results of the present analysis show that for the children whose mothers were atopic, the risk ratio for respiratory symptoms was slightly lower in the group of children

whose mothers received DHA supplementation compared with placebo. The protective effect of DHA supplementation was higher, especially for the combinations of symptoms ("phlegm with congestion and/or nasal discharge" and "fever with phlegm with congestion and/or nasal discharge"). This is consistent with observations that children with a family history of atopy tend to more frequently develop respiratory tract infections as well as with results from previous DHA supplementation studies.^{8,15}

Although the results of the previous studies on the effects of supplementation with omega-3 fatty acids on

TABLE 3] Association Between Respiratory Symptoms and Maternal Atopy in Children Until 18 Mo, by Treatment Group, Morelos, Mexico

Symptoms	Placebo		DHA		Interaction
	IRR (95% CI)	P Value	IRR (95% CI)	P Value	P Value ^a
Coughing					
Nonatopic	1	...	1	...	...
Atopic	1.042 (0.872-1.246)	.648	0.967 (0.811-1.152)	.704	.558
Wheezing					
Nonatopic	1	...	1	...	...
Atopic	1.079 (0.754-1.543)	.678	0.929 (0.63-1.371)	.712	.554
Breathing difficulty					
Nonatopic	1	...	1	...	...
Atopic	1.660 (0.672-4.102)	.272	0.629 (0.296-1.338)	.228	.094
Wheezing and/or breathing difficulty					
Nonatopic	1	...	1	...	...
Atopic	1.165 (0.806-1.685)	.416	0.887 (0.604-1.301)	.539	.284
Coughing with wheezing and/or breathing difficulty					
Nonatopic	1	...	1	...	...
Atopic	1.444 (0.937-2.225)	.096	0.853 (0.547-1.333)	.486	.091
Coughing with phlegm					
Nonatopic	1	...	1	...	...
Atopic	1.061 (0.842-1.336)	.615	0.923 (0.727-1.171)	.510	.412
Phlegm with congestion and/or nasal discharge					
Nonatopic	1	...	1	...	...
Atopic	1.269 (0.964-1.669)	.089	0.779 (0.596-1.018)	.068	.016
Fever with phlegm with congestion and/or nasal discharge					
Nonatopic	1	...	1	...	...
Atopic	1.442 (0.857-2.427)	.168	0.532 (0.287-0.986)	.045	.014
Coughing with fever					
Nonatopic	1	...	1	...	...
Atopic	0.996 (0.669-1.483)	.984	0.742 (0.499-1.105)	.142	.314
Wheezing with fever					
Nonatopic	1	...	1	...	...
Atopic	1.906 (0.997-3.646)	.051	0.543 (0.264-1.116)	.097	.012

All models were adjusted by child's sex, low birth weight, and maternal education. See Table 1 and 2 legends for expansion of abbreviations.

^aInteraction with maternal atopy and supplementation group.

the allergic diseases such as asthma are inconclusive, our results demonstrate a protective effect of DHA supplementation mainly among children of mothers with history of atopy, who were more susceptible to respiratory symptoms. Omega-3 fatty acids are shown to have anti-inflammatory activity by decreasing the production of proinflammatory cytokines (IL-1 and IL-6) and reducing inflammatory processes (decreases in prostaglandin E2, thromboxane A2, leukotriene B4, and increases in

thromboxane A3, prostaglandin PG13, and leukotriene B5).^{16,17} DHA and eicosapentaenoic acid have been shown to inhibit the conversion of arachidonic acid to leukotrienes and reduce the production of platelet activating factor, which causes pulmonary edema, accumulation of eosinophils in the lung tissue, and bronchial hyperactivity.^{16,17}

Although the effect of DHA supplementation on the incidence of some symptoms was not statistically significant,

Symptomatic, Severe

* $P < 0.05$
† $0.05 < P < 0.10$

Figure 2 – Association between severe respiratory symptoms and maternal atopy for children until 18 mo, by treatment group, Morelos, Mexico. Models were adjusted by child's sex, low birth weight, and maternal education. The reported IRR corresponds to the history of maternal atopy by specific IgE levels (exposed group) and the reference category corresponds to no history of maternal atopy. IRR = incidence rate ratios for symptoms (a measure of relative risk). See Figure 1 legend for expansion of other abbreviation.

results clearly showed a decreased risk, especially for the presence of combinations of symptoms, particularly for children whose mothers were supplemented and who had a history of atopy, in contrast to mothers without this characteristic. This is very important in public health, since the atopy of the mother is a risk factor that can be inherited by the child; however, the DHA supplementation during pregnancy could decrease the risk and promote the reduction of the incidence of respiratory symptoms in early life.¹⁸⁻²⁰ The effects of omega-3 fatty acids on the immune system may also vary according to age and polarization, the state of the T helper (Th) 1/Th2 system, the dose of omega-3 fatty acids, and T cells.^{8,15,16} In a study, our group reported that the maternal supplementation with omega-3 during pregnancy may modulate global methylation levels and the Th1/Th2 balance in infants. Therefore, the epigenetic mechanisms could provide attractive targets for prenatal modulation and prevention of inflammatory disorders and potentially other related diseases in childhood and adulthood.²¹

Our results also complement previous results with follow-up of infants up to 3 months²² and confirm the protective role of DHA supplementation during pregnancy. They also identify the role of maternal atopy as a modifying factor in the protective role of DHA in children's

respiratory symptoms. In the present study, the beneficial effect of maternal supplementation with omega-3 fatty acid was restricted to infants born to atopic mothers. We have no explanation for the lack of effect in infants born to nonatopic mothers. One possibility is that infants born to nonatopic mothers had, in general, fewer respiratory symptoms in early life, and, thus, a much larger study may be required to determine whether this group could benefit from maternal supplementation.

The issue of dietary supplementation with omega-3 fatty acids or with fish consumption is controversial. In a systematic review, Kremmyda et al²³ reviewed epidemiologic studies of maternal fish consumptions and concluded that (1) there was evidence of a protective effect of maternal fish consumption on infant atopic outcomes, (2) maternal fish consumption during lactation may increase the risk of infant atopic outcomes, and (3) the evidence for any beneficial effects from infant/child intake was inconsistent. A recent publication from the Generation R study²⁴ shows just how complicated this area is. The impact of maternal fish consumption during pregnancy differs with the type of fish consumption. This study included 2,976 mothers, and fish intake was prospectively monitored. Overall, there was no association between maternal fish consumption during pregnancy

Figure 3 – Interaction between mother's atopic status and treatment group on the incidence of respiratory symptoms. Models were adjusted by child's sex, low birth weight, and maternal education. See Figure 1 legend for expansion of abbreviation.

and the risk of wheeze in the infant offspring. However, maternal shellfish intake was associated with a small increase in wheeze risk, and consumption of fatty fish increased the risk of childhood eczema. Thus, more research is required to settle these controversies.

Our study has several strengths. The double-blinded randomized nature of the study design strengthens the results and increases internal and external validity. The baseline characteristics of the infants were similar for both supplementation groups, and neither the mothers nor the field personnel knew to which group the mothers were assigned.

However, it is important to note the limitation that our questionnaire of respiratory symptoms is not validated in Mexican populations, and respiratory symptoms were reported by the mother; therefore, we were unable to

distinguish between, for example, allergy and viral infection diseases. Mothers could have misreported the respiratory symptoms of their infants; nevertheless, this would have led to a random misclassification and an underestimation of the associations. In addition we believe that given our study population, the results can be extrapolated to the population of infants seen at the IMSS, a health system that covers 60% of the general Mexican population.²⁵

Conclusions

In summary, our results support the hypothesis that DHA supplementation during pregnancy may decrease the incidence of respiratory symptoms in children with a history of maternal atopy. These results are important to public health and suggest that intervention should be targeted toward the most susceptible population.

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