The Impact of Early Nutrition on Incidence of Allergic Manifestations and Common Respiratory Illnesses in Children

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Objective To investigate the incidence of allergic and respiratory diseases through age 3 years in children fed docosahexaenoic acid (DHA)- and arachidonic acid (ARA)-supplemented formula during infancy.

Study design Children who completed randomized, double-blind studies of DHA/ARA-supplemented (0.32%-0.36%/0.64%-0.72% of total fatty acids, respectively) versus nonsupplemented (control) formulas, fed during the first year of life, were eligible. Blinded study nurses reviewed medical charts for upper respiratory infection (URI), wheezing, asthma, bronchiolitis, bronchitis, allergic rhinitis, allergic conjunctivitis, otitis media, sinusitis, atopic dermatitis (AD), and urticaria.

Results From the 2 original cohorts, 89/179 children participated; 38/89 were fed DHA/ARA formula. The DHA/ARA group had significantly lower odds for developing URI (odds ratio [OR], 0.22; 95% confidence interval [CI], 0.08-0.58), wheezing/asthma (OR, 0.32; 95% CI, 0.11-0.97), wheezing/asthma/AD (OR, 0.25; 95% CI, 0.09-0.67), or any allergy (OR, 0.28; 95% CI, 0.10-0.72). The control group had significantly shorter time to first diagnosis of URI (P = .006), wheezing/asthma (P = .03), or any allergy (P = .006).

Conclusions DHA/ARA supplementation was associated with delayed onset and reduced incidence of URIs and common allergic diseases up to 3 years of age. *(J Pediatr 2010;156:902-6)*.

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The prevalence of allergic diseases is on the rise worldwide, affecting up to 30% of children with symptoms of atopic dermatitis (AD), asthma, and/or allergic rhinitis.[1-4] Strong correlations among the prevalences of these diseases have been demonstrated.[2,5] AD frequently precedes the onset of asthma and allergic rhinitis and is associated with more severe asthma.[5] Allergic rhinitis is manifested early in life in the majority of asthmatic children and can be considered a risk factor for asthma,[6] along with family history of allergy, parental asthma, and exposure to smoking early in life.[6] In the United States, approximately one-third of infants experience at least one wheezing episode in the first year of life.[7] Asthma, the most prevalent chronic illness in children, causes more than 1 million physician visits for children age 4 years and younger, and more than 2 million physician visits for 5- to 14-year-old children annually in the United States.[4] Each year, approximately 325 000 doctor visits in children under age 2 years are attributed to AD.[3,5]

Long-chain polyunsaturated fatty acids (LCPUFAs) are incorporated into membrane phospholipids of immune cells, where they serve as precursors for the synthesis of eicosanoids and docosanoids, which modulate immune cell function and inflammatory responses.[8,9] Allergic manifestations can be influenced by *n*-3 and *n*-6 LCPUFAs, including docosahexaenoic acid (DHA; 22:6*n*3) and arachidonic acid (ARA; 20:4*n*6), in the diet.[9,10] Analyses of breast milk composition have shown an association between higher levels of DHA and decreased incidence of allergic diseases in children age 18 months.[10] In addition, levels of *n*-3 LCPUFAs and the *n*-3:*n*-6 ratio in milk of allergic mothers were inversely associated with the incidence of AD in their children at age 1 and 4 years and asthma at age 4 years.[11]

Clinical and epidemiologic studies suggest that supplementation of preformed LCPUFAs in infants and children, via fish oil or DHA/ARA-enriched formula, may be protective toward allergic and respiratory diseases. Fish oil

AD	Atopic dermatitis
ARA	Arachidonic acid
CI	Confidence interval
DHA	Docosahexaenoic acid
FA	Fatty acid
HR	Hazard ratio
LCPUFA	Long-chain polyunsaturated fatty acid
OM	Otitis media
OR	Odds ratio
RAD	Reactive airway disease
URI	Upper respiratory infection

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supplementation started at around 6 months of age in infants with a family history of asthma was associated with significantly lower prevalence of parental reported wheezing at 18 months and cough associated with atopic sensitization at 3 years; however, at 5 years, the prevalence of allergic manifestations was similar for children with or without fish oil supplementation.[12] Dietary fish oil supplementation was associated with a significant decrease in the severity of asthma symptoms and airway hyperreactivity to acetylcholine in 4- to 17-year-old asthmatic children.[13] It also was associated with a decrease in serum inflammatory markers and antibiotic use and with increased pulmonary function in infants, children, and adults with cystic fibrosis.[14]

The primary objective of the current study was to assess the effects of DHA and ARA supplementation in infancy, consistent with worldwide human milk levels,[15] on the incidence of respiratory infections and allergic illnesses through 3 years of age.

Methods

Two cohorts of children who had previously completed randomized double-blind trials in published (cohort A)[16] and unpublished (cohort B) (E. Birch, unpublished data, 2003) studies, in which they received a routine cow's milk-based formula supplemented with DHA and ARA or a similar unsupplemented formula, were eligible for this study. Exclusively formula-fed, healthy term infants recruited from 2 Dallas area hospitals were enrolled in cohorts A and B. All infants were singleton births, born between 37 and 40 weeks of gestational age. They were randomly assigned to receive one of the following formulas from age ≤5 days through 12 months: control formula (Enfamil with iron; Mead Johnson Nutrition, Evansville, Indiana) or DHA/ARA formula (control + DHA and ARA as 0.32%-0.36% of total fatty acids [FA] [17 mg/100 kcal] and 0.64%-0.72% of total FA [34 mg/100 kcal]; Enfamil LIPIL; Mead Johnson Nutrition). The primary objective of the study for cohort A was to evaluate the effect of DHA/ARA supplementation on sweep visual evoked potential acuity, an objective measure of visual cortex maturity. The primary objective of the study for cohort B was to characterize the effects of LCPUFAs on metabolic parameters, including lipoprotein profile, antioxidant status, and hydroelectrolytic balance.

Current Study

Letters were sent to parents of children who had completed the study from cohorts A and B described above, requesting consent and release of their child's medical records. Medical records were requested for those children whose parents signed an informed consent. At least 2 attempts were made to obtain the medical records. Guided by standardized instructions, study nurses, blinded to the formula received, reviewed the children's medical charts for diagnoses of upper respiratory infection (URI), wheezing, asthma, reactive airway disease (RAD), bronchiolitis, bronchitis, pneumonia, allergic rhinitis, allergic conjunctivitis, otitis media (OM), sinusitis, food allergy, AD, contact dermatitis, urticaria, and drug allergy.

Ethics

This research protocol observed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. The trial is registered with clinicaltrials.gov (NCT00740974).

Statistical Analyses

Original diagnoses were classified into diagnosis categories according to established rules (**Table I**; available at www.jpeds.com). Specifically, bronchiolitis, asthma, and RAD were classified as wheezing if diagnosed in children under age 2 years. Children under age 2 years diagnosed with sinusitis, bronchitis, or allergic rhinitis were classified under a diagnosis of URI. Children of any age with concurrent diagnoses of OM and URI, allergic rhinitis, sinusitis, or bronchitis were classified as under a diagnosis of OM.

The proportion of children in each formula group having at least one event was compared using the χ^2 test. To adjust for covariates, multiple logistic regression was used to examine the association between formula supplementation and allergy-related or nonallergic respiratory illnesses. Covariates included family history of allergy (mother, father, and/or sibling), sex, and smoking in the home. Further analyses using an ordinal model examined the number of distinct episodes. For allergy-related diagnoses, an episode was considered new when the last visit for the same diagnosis occurred more than 7 days earlier, except for allergic rhinitis (30 days earlier). For nonallergic events, a 30-day rule was used. For the ordinal analysis, the number was truncated at 3, due to sparse frequency of more than 3 episodes; thus, a frequency of >3 was entered into the model as a frequency of 3. Calculated odds ratios (ORs) in the ordinal model represent an increased risk between each level (0, 1, 2, or 3 episodes). A Cox proportional hazards model, including the previously mentioned covariates, was used to examine the time to first diagnosis of an allergic manifestation or common respiratory illness. Finally, the number of doctor visits was examined using analysis of covariance and the covariates listed above. A log transformation of this outcome variable was necessary for analysis, due to the distribution of the data. For this reason, geometric means and 95% confidence intervals (CIs) are reported. A P value of <.05 was considered statistically significant for all analyses. All analyses were performed using SAS version 9 (SAS Institute, Cary, North Carolina).

Results

A total of 179 infants were enrolled in the original studies between 1997 and 2003 and received either the control or

Table II. Characteristics of the study population

Variable	Control	DHA/ARA	*P* value
Birth weight, g*	3641 ± 624	3618 ± 426	.72
Birth length, cm*	50.8 ± 3.40	50.3 ± 3.02	.46
Weight at 1 year, g*	9920 ± 1252	10 143 ± 906	.32
Length at 1 year, cm*	74.8 ± 5.46	75.3 ± 2.14	.91
Weight at 3 years, g*	14 900 ± 1981	15 148 ± 1357	.75
Height at 3 years, cm*	96.0 ± 5.18	95.5 ± 4.08	.80
Male†	23 (45%)	21 (55%)	.34
Caucasian†	43 (84%)	37 (97%)	.07
Hispanic†	4 (8%)	5 (13%)	.41
Number of family members with allergy†			
0	16 (31%)	12 (32%)	.57
1	14 (27%)	7 (18%)	
≥2	21 (41%)	19 (50%)	
Any allergy in the family†	35 (69%)	26 (68%)	.98
Smoking in the home†	5 (10%)	7 (18%)	.24

*Reported as mean ± standard deviation; *t*-test.
†Reported as n (%); χ^2 test.

Table III. Incidence of at least one event of allergic manifestation or common respiratory illness during the first 3 years of life

Diagnosis/combination of diagnoses	Control (n = 51)		DHA/ARA (n = 38)		
	n	%	n	%	*P* value
Wheezing/asthma	18	35	6	16	.04
AD	17	33	7	18	.12
Wheezing/asthma/AD	28	55	10	26	.007
Any allergy*	31	61	13	34	.013
URI	39	76	17	45	.002
OM	39	76	27	71	.56
Nonallergic respiratory illnesses†	43	84	30	79	.51

The χ^2 test was used to compare proportions between the control and DHA/ARA groups.
*Any one of the following manifestations: wheezing, asthma, AD, allergic rhinitis, allergic conjunctivitis, food allergy, and urticaria.
†Nonallergic respiratory illnesses include URI, OM, sinusitis, bronchitis, bronchiolitis, and pneumonia.

DHA/ARA formula. Of these infants, 147 had completed the original studies and were eligible to participate in the current study. Medical records were reviewed for 89 (61%) of the eligible infants, of which 51 received control formula and 38 received DHA/ARA formula (**Figure**; available at www.jpeds.com). Anthropometric and sex characteristics of participants in the current study were similar to those of participants in the original cohort studies, with the single exception of a higher proportion of Caucasian children in the current study.

Characteristics of the study population, including family history of allergy and smoking in the home, were similar in the 2 groups (**Table II**). In addition, the age (in weeks) when infants began to consume study formula and the number of weeks that study formula was consumed were similar in the 2 groups (0.55 vs 0.54, $P = .59$; 51.0 vs 52.9, $P = .83$, respectively).

The number of children with one or more episodes of allergic manifestations or common respiratory illnesses during the first 3 years of life is shown in **Table III**. The OR of having at least one event of allergic manifestation or common respiratory illness during the first 3 years of life after adjusting for sex, family history of allergy, and smoking is shown in **Table IV**.

After adjusting for covariates, the DHA/ARA group had significantly lower odds of having an increased number of episodes of URI (OR, 0.32; 95% CI, 0.14-0.75; $P = .008$), wheezing/asthma (OR, 0.31; 95% CI, 0.10-0.90; $P = .03$), wheezing/asthma/AD (OR, 0.29; 95% CI, 0.12-0.72; $P = .008$), or any allergy (OR, 0.30; 95% CI, 0.12-0.73; $P = .008$) during the first 3 years of life compared with the control group (**Table V**; available at www.jpeds.com). In addition, there was a tendency toward a lower number of episodes of combined nonallergic respiratory illnesses in the DHA/ARA group ($P = .06$). There was no difference in the number of episodes of AD analyzed in isolation or OM.

The hazard ratio (HR) for the time to first diagnosis of allergic manifestations or common respiratory illnesses is shown in **Table VI**. The HR reflects the odds that a child who is in the DHA/ARA group will be diagnosed with an allergic manifestation or common respiratory illness before a child in the control group.

The total number of doctor visits for diagnosis or treatment of illness tended to be greater in the control group than in the DHA/ARA group (mean, 5.30; 95% CI, 3.32-8.17 vs 3.14; 1.81-5.09; $P = .06$). Similarly, there was a tendency toward more doctor visits in the control group for AD (mean, 0.34; 95% CI, 0.15-0.55 vs 0.12; 0.0-0.31; $P = .053$) and wheezing/asthma (mean, 0.51; 95% CI, 0.20-0.90 vs 0.17; 0.0-0.48; $P = .07$). The control group had significantly more doctor visits than the DHA/ARA group for URI (mean, 2.18; 95% CI, 1.33-3.36 vs 0.93; 0.40-1.67; $P = .009$), wheezing/asthma/AD (mean, 0.83; 95% CI, 0.43-1.35 vs 0.26; 0.0-0.62; $P = .012$), and any allergy (mean, 0.96; 95% CI, 0.51-1.55 vs 0.34; 0.03-0.76; $P = .015$). There was no difference between the 2 groups in the number of visits due to OM or in the number of visits due to combined nonallergic respiratory illnesses.

Discussion

Our data show that the infants fed formula supplemented with DHA (0.32%-0.36% of total FA) and ARA (0.64%-0.72% of total FA) starting within the first week of life and continuing for 1 year had a reduced incidence and delayed onset of URI, common allergic diseases, and wheezing or asthma compared with infants fed formula without DHA/ARA. The DHA/ARA group also had fewer doctor visits due to these illnesses throughout the first 3 years of life.

Longitudinal studies suggest that an important risk factor for severe asthma later in life is the occurrence of frequent wheezing before 3 years of age.[1,7] In this age group, it is difficult to differentiate wheezing of allergic bronchospasm from wheezing linked to lower respiratory infection. In addition, early lower respiratory tract infection with wheezing caused by respiratory syncytial virus or rhinovirus significantly increases the risk of subsequent childhood wheezing

Table IV. OR of having at least one event of allergic manifestation or common respiratory illness during the first 3 years of life

Diagnosis/combination of diagnoses	OR	95% CI	*P* value
Wheezing/asthma	0.32	0.11-0.97	.043
AD	0.41	0.14-1.16	.09
Wheezing/asthma/AD	0.25	0.09-0.67	.006
Any allergy*	0.28	0.10-0.72	.008
URI	0.22	0.08-0.58	.002
OM	0.68	0.26-1.83	.45
Nonallergic respiratory illnesses†	0.66	0.22-2.03	.47

Multiple logistic regression analysis; ORs are expressed for DHA/ARA compared with control, adjusted for sex, family history of allergy, and smoking in the home.
*Any one of the following manifestations: wheezing, asthma, AD, allergic rhinitis, allergic conjunctivitis, food allergy, and urticaria.
†Nonallergic respiratory illnesses include URI, OM, sinusitis, bronchitis, bronchiolitis, and pneumonia.

Table VI. HR for time to first diagnosis of allergic manifestations or common respiratory illnesses during the first 3 years of life

Diagnosis/combination of diagnoses	HR	95% CI	*P* value
Wheezing/asthma	0.35	0.14-0.89	.03
AD	0.49	0.20-1.20	.12
Wheezing/asthma/AD	0.33	0.16-0.69	.004
Any allergy*	0.39	0.20-0.76	.006
URI	0.44	0.24-0.78	.006
OM	0.78	0.47-1.28	.32
Nonallergic respiratory illnesses†	0.70	0.43-1.14	.16

Cox proportional hazards analysis; HRs are expressed for DHA/ARA compared with control, adjusted for sex, family history of allergy, and smoking in the home.
*Any one of the following manifestations: wheezing, asthma, AD, allergic rhinitis, allergic conjunctivitis, food allergy, and urticaria.
†Nonallergic respiratory illnesses include URI, OM, sinusitis, bronchitis, bronchiolitis, and pneumonia.

and decreases lung function in childhood.[7,17,18] Moreover, the nonatopic and atopic asthma phenotypes are not easily identified in young children.[19] Consequently, in the current study, any wheezing-related diagnosis before age 2 years was classified as wheezing, given the nonspecific nature of these conditions in this age group. Similarly, given that the mean onset age of allergic rhinitis is 2 years,[6] any allergic rhinitis diagnosis before age 2 was classified as URI.

The incidence of wheezing illness in the DHA/ARA group was significantly lower than expected based on population studies. In a prospective cohort of 1246 children, roughly 45% and 35% demonstrated wheezing in the second and third years of life, respectively.[7] These results, as well as others,[17] are consistent with the incidence of wheezing/asthma of 35% during the first 3 years of life in the control group of the current study and more than double that in the DHA/ARA group in the current study. The incidence of URI in the control group of the current study (76%) was comparable with that reported in a study that used criteria similar to those adopted in the current study;[20] that is, only events that generated a doctor visit were analyzed, and URI was not recorded if a diagnosis of OM was reported concomitantly.

Allergy-associated outcomes may be influenced by supplementation with LCPUFAs during pregnancy. Prenatal supplementation with fish oil increased postpartum breast milk DHA concentration, which was significantly correlated with levels of IgA in the breast milk.[21] IgA may prevent antigen entry at the intestinal mucosa, thus reducing the risk of allergy.[22] Accordingly, by 1 year of age, infants in the former study were significantly less likely to develop severe AD.[23] Fish oil supplementation of pregnant women was also associated with decreased cord blood mRNA of allergy-related molecules interleukin (IL)-4, IL-13, and CC chemokine receptor type 4.[24] A lower prevalence of food allergy and IgE-mediated AD was apparent in the first year of life in infants whose mothers received fish oil supplementation during pregnancy through 3-4 months of lactation.[25] Similarly, fish consumption during pregnancy was shown to protect against AD in children 1 and 2 years of age,[26,27] and wheezing associated with allergic sensitization at 6 years of age.[26] In a recent study, 9- to 12-year-old healthy children consuming milk supplemented with fish oil had significantly reduced episodes and duration of illnesses, mainly URI and diarrhea, during the 6-month supplementation period.[28] In an open-label study, healthy infants who received formula supplemented with DHA (0.32% of total FA) and ARA (0.64% of total FA) had a lower incidence of bronchiolitis/bronchitis during the first year of life compared with infants who received formula with lower or no DHA and ARA supplementation.[29]

Immune responses to respiratory syncytial virus infection lead to IgE-mediated hypersensitivity reactions with the release of leukotrienes (inflammation-related mediators derived from LCPUFAs[8]) and can result in bronchiolitis.[30] In the current study, the DHA/ARA group had a lower incidence of wheezing/asthma during the first 3 years of life, a longer time before the first diagnosis, and fewer episodes of wheezing/asthma compared with the control group. The DHA/ARA group also showed a trend toward lower risk of developing AD. In addition, the DHA/ARA group had a lower incidence of URI, a longer time before the first diagnosis, and fewer episodes of URI. The benefit of formula supplemented with DHA/ARA might be related to viral infections but not bacterial infections, as suggested by the similar incidence, number of episodes, and time to first diagnosis of OM in the 2 groups.

An important limitation of the current study is that although randomized, controlled trials were the source of the study population, the current outcomes herein were not part of the original protocol and thus were obtained by chart review. As with any such review, participants lost to follow-up, missing charts, and missing visits are to be expected; however, given the apparent balance between the control and intervention groups, it seems unlikely that any significant bias was introduced by this process. Moreover, this study was adequately powered to demonstrate clinically relevant differences between the control and DHA/ARA groups. These results provide support for the hypothesis that supplementation of formula with DHA/ARA may modify immune development, thereby reducing rates of atopic

and respiratory illnesses. Nonetheless, although this study adds to the pool of emerging data indicating that DHA/ARA supplementation might indeed modulate immune development, a prospective, double-blind, randomized, controlled trial is needed to confirm these findings. ■

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Table I. Diagnosis categories, allergic diagnoses, and nonallergic respiratory diagnoses

Diagnosis in medical chart	Diagnosis categories for statistical analysis: < 2 years	≥ 2 years	New episode time
Allergic diagnoses			
Wheezing	Wheezing	Wheezing or asthma*	7 days
Asthma	Wheezing	Asthma	7 days
RAD	Wheezing	Asthma	7 days
Bronchiolitis	Wheezing	Bronchiolitis	7 days
Wheezing + asthma	Wheezing	Asthma	7 days
Wheezing + RAD	Wheezing	Asthma	7 days
Wheezing + bronchiolitis	Wheezing	Wheezing or asthma*	
AD	AD	AD	7 days
Contact dermatitis	Contact dermatitis	Contact dermatitis	7 days
Allergic rhinitis	URI	Allergic rhinitis	30 days
Allergic conjunctivitis	Allergic conjunctivitis	Allergic conjunctivitis	7 days
Food allergy	Food allergy	Food allergy	7 days
Urticaria	Urticaria	Urticaria	7 days
Drug allergy	Drug allergy	Drug allergy	7 days
Nonallergic respiratory diagnoses			
OM	OM	OM	30 days
URI	URI	URI	30 days
Sinusitis	URI	Sinusitis	30 days
Bronchitis	URI	Bronchitis	30 days
Bronchitis + URI	URI	URI	30 days
OM + URI or sinusitis or bronchitis or allergic rhinitis	OM	OM	30 days
Pneumonia	Pneumonia	Pneumonia	30 days

*If asthma or RAD occurred any time after 2 years of age, then wheezing was classified as asthma.

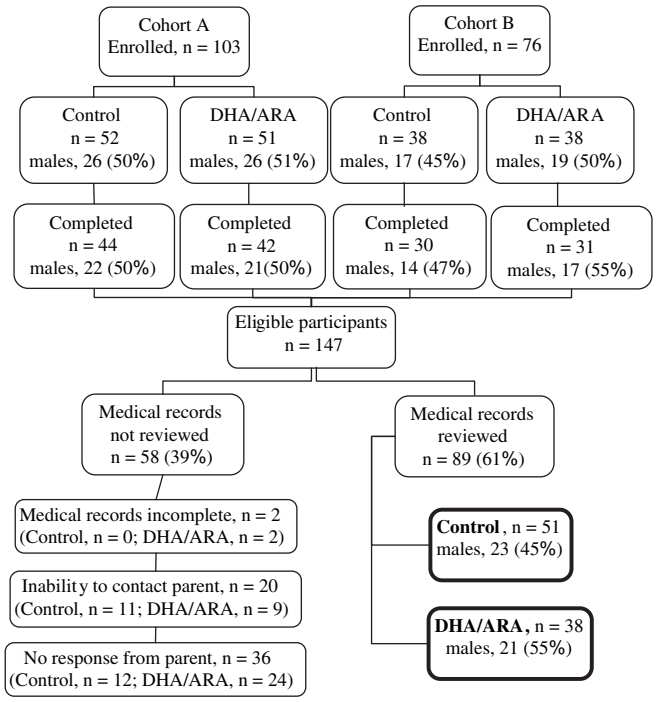

Figure. Flow of study participants.

Table V. OR of having an increased number of episodes of allergic manifestations or common respiratory illnesses during the first 3 years of life

Diagnosis/combination of diagnoses	OR	95% CI	*P* value
Wheezing/asthma	0.31	0.10-0.90	.03
AD	0.42	0.15-1.17	.10
Wheezing/asthma/AD	0.29	0.12-0.72	.008
Any allergy*	0.30	0.12-0.73	.008
URI	0.32	0.14-0.75	.008
OM	0.75	0.35-1.63	.47
Nonallergic respiratory illnesses†	0.44	0.19-1.15	.06

Ordinal analysis; ORs are expressed for DHA/ARA compared with control, adjusted for sex, family history of allergy, and smoking in the home.
*Any one of the following manifestations: wheezing, asthma, AD, allergic rhinitis, allergic conjunctivitis, food allergy, and urticaria.
†Nonallergic respiratory illnesses include URI, OM, sinusitis, bronchitis, bronchiolitis, and pneumonia.