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Formula with long chain polyunsaturated fatty acids reduces incidence of allergy in early childhood

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Abstract

Background—Allergy has sharply increased in affluent Western countries in the last 30 years. N-3 long chain polyunsaturated fatty acids (n-3 LCPUFAs) may protect the immune system against development of allergy.

Methods—We prospectively categorized illnesses by body system in a subset of 91 children from the Kansas City cohort of the DIAMOND (DHA Intake and Measurement of Neural Development) study who had yearly medical records through 4 years of age. As infants, they were fed either a control formula without LCPUFA (n=19) or one of three formulas with LCPUFA from docosahexaenoic acid (DHA) and arachidonic acid (ARA) (n=72).

Results—Allergic illnesses in the first year were lower in the combined LCPUFA group compared to the control. LCPUFAs significantly delayed time to first allergic illness ($p=0.04$) and skin allergic illness ($p=0.03$); and resulted in a trend to reduced wheeze/asthma ($p=0.1$). If the mother had no allergies, LCPUFAs reduced the risk of any allergic diseases (HR = 0.24, 95% CI = 0.1, 0.56, $p=0.001$) and skin allergic diseases (HR = 0.35, 95% CI = 0.13, 0.93, $p=0.04$). In contrast, if the mother had allergies, LCPUFAs reduced wheezing/asthma (HR = 0.26, 95% CI = 0.07, 0.9, $p=0.02$).

Conclusions—LCPUFA supplementation during infancy reduced the risk of skin and respiratory allergic diseases in childhood with effects influenced by maternal allergies.

Keywords

allergy; arachidonic acid; childhood; docosahexaenoic acid; infant formula; long chain polyunsaturated fatty acids; respiratory; skin

Introduction

Allergy has increased sharply in affluent Western countries in the last 30 years (1) at the same time that dietary intake of linoleic acid (LA, 18:2n-6) and the ratio of dietary n-6/n-3

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fatty acids have increased (2). Jenmalm and Duchon (3) suggest that an increase in the ratio of dietary n-6 to n-3 fatty acids is one factor responsible for the increase in allergy. It has been suggested that increasing n-3 long chain polyunsaturated fatty acid (n-3 LCPUFA) exposure during immune system development could favorably influence the immune system to be more resistant to allergy (3-7) and address an imbalance created by increased dietary n-6 fatty acid intake (3).

Evidence in favor of this theory is growing. Asthmatic children supplemented with fish oil rich in docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3) have amelioration of asthma symptoms when compared with an unsupplemented control group (8). Infants fed formulas supplemented with DHA and arachidonic acid (ARA, 20:4n-6) compared to unsupplemented formulas have immune cell distribution and cytokine profiles similar to those of human milk fed infants (9) and a higher proportion of antigen-mature lymphocytes (10).

However, results are mixed for the relationships between dietary n-3 LCPUFA intake or status in infancy and later allergy (11-16) and only one study has evaluated childhood allergy in children randomly assigned to formulas with or without LCPUFA during infancy (15). The authors of that retrospective study found that children fed DHA and ARA for the first year of life had fewer medically documented allergic illnesses and upper respiratory infections in the first 3 years of life, but their work has yet to be replicated. In this report, we prospectively compare medically documented illnesses to 4 years of age in a cohort of children randomized to control formula or DHA and ARA-supplemented formulas for the first 12 months of life.

Methods

Subjects and Illnesses

A subset of 91 children from the Kansas City cohort of the DIAMOND (DHA Intake and Measurement of Neural Development) study (registered as NCT00753818) consented to have their children followed to 6 years of age for developmental outcomes. To be eligible for the two-site primary study, infants needed to be healthy, exclusively formula-fed, singleton-birth, born between 37 and 42 weeks gestation with a birth weight between 2490 and 4200 grams, and 9 days old at time of randomization (17). Exclusion criteria were any maternal or infant condition likely to interfere with normal growth and development, history of intolerance to cow's milk and/or poor formula intake. Infants were also not eligible if their mother had a chronic infection, renal or hepatic disease, diabetes, alcoholism or a history of illicit drug use. Infants in the Kansas City cohort were born between September 2003 and September 2005. They constitute the sample included in this study.

In the DIAMOND (primary) study, infants were randomly assigned to either a control formula without DHA and ARA or one of three additional formulas that contained 0.64% of total fatty acids as ARA and either 0.32, 0.64 or 0.96% of total fatty acids as DHA. Both the two-site, primary study and the Kansas City follow-up to 6 years were approved by the Human Subjects Committee at the University of Kansas Medical Center (HSC #9198 and #10205).

Medical records were obtained prospectively annually and illnesses were categorized by body system (see Supplemental Table 1). Skin allergic illnesses included atopic dermatitis, eczema, contact dermatitis, and urticaria. All allergies included these diagnoses and wheezing/asthma, allergic conjunctivitis, allergic cough, allergic rhinitis, allergic sinusitis, non-specified allergy, drug allergy, and food allergy. Not all food allergies were confirmed by oral food challenge. In most cases, skin testing only was used to diagnose. Maternal history of allergy and other potentially influential environmental factors were self-reported.

Statistical Methods

Baseline characteristics were compared between groups using appropriate descriptive statistics, both by DHA dosing group and by pooling all DHA and ARA supplemented subjects into a single supplemented cohort, henceforth called the LCPUFA group (Table 1). Due to non-normal distribution of the variables and sample size, nonparametric tests were used to assess imbalance in baseline characteristics between the LCPUFA group and control. Fisher's exact tests and Wilcoxon tests were used for categorical and continuous characteristics, respectively.

The association of time to first illness with LCPUFA supplementation was investigated using log-rank and Wilcoxon tests and Kaplan-Meier survival curves. Potential covariates evaluated included maternal and household smoking, furred pets, daycare in the home, siblings in the home, and any maternal allergy. Only maternal allergy was influential and further exploration of the role of maternal allergies and time-varying effects were performed using Cox proportional hazards regression models. Sensitivity analyses were performed to evaluate the impact of missing maternal allergy data on the findings. Specifically, in the survival analysis including maternal allergies, maternal allergy status was coded as 'present,' 'absent' or 'missing' and the analysis replicated (Supplemental Table 2 and Figures 1-4). Since the results were robust, analysis using case-wise deletion for the missing maternal allergy status is reported. All results are considered hypothesis-generating, rather than confirmatory. Due to the exploratory nature of this study, no error rate adjustments were made for multiple testing. SAS® version 9.4 was used for all analyses.

Results

In the first year of life, the LCPUFA group compared to the control had less allergy (Chi-square, $p=0.033$), less skin allergy ($p=0.038$) (see Supplemental Table), and the mean illness-free time was significantly longer for all allergies and skin allergy (Table 2). Additionally, the hazard ratio (HR) for earlier diagnosis was significantly lower in the LCPUFA group compared to control for any allergic illnesses and skin allergic illnesses (Table 2). (See Figure 1 for survival curve for all allergic illnesses). There was also a nonsignificant trend for lower HR for longer illness-free time for wheezing/asthma in the LCPUFA group (Table 2). The incidence of at least one episode of allergic illness and the odds ratio (OR) of having at least one episode of allergic illness during the first four years of life did not significantly differ between groups (Table 2).

For all allergic illnesses, the effect of LCPUFA was found to interact with the presence of maternal allergy (Wald $\chi^2(1) = 4.5$, $p = 0.03$). The incidence of any allergic illness and skin

allergic illnesses during the first four years of life and the HR for earlier diagnosis were significantly lower in the subgroup of participants in the LCPUFA group whose mothers had no history of allergy. It did not differ in those whose mothers reported allergy (Table 3). Contrarily, the incidence of wheezing/asthma and the HR for earlier diagnosis were significantly lower in the subgroup of participants of the LCPUFA group whose mothers reported a positive history of allergy and did not differ in those whose mothers had no history of allergy (Table 3).

Survival curves for skin allergic illnesses and wheezing/asthma during the 4-year follow-up for each maternal allergy subgroup (yes or no) in the LCPUFA and control groups are shown in Figures 2 and 3. If the mother reported no allergy, the LCPUFA group had a 64% reduction in skin allergic illness ($p=0.04$, $HR = 0.35$) in the first 4 years of life compared to the control group, whereas LCPUFA and control groups did not differ if the mother reported history of allergy ($p=0.99$, $HR = 0.99$) (Figure 2). Differently, if the mother reported allergy, the LCPUFA group had a 74% reduction ($p=0.02$, $HR = 0.26$) in wheezing/asthma in the first 4 years of life compared the control group; whereas LCPUFA and control groups did not differ if the mother reported no history of allergy ($p=0.71$, $HR = 0.78$) (Figure 3).

Discussion

Our results are in accordance with existing data on a protective effect of LCPUFAs against allergic manifestations. Early introduction of fish to infants has been associated with reduced prevalence of eczema (18-20), allergic rhinitis (21, 22), and recurrent wheezing (23, 24). Likewise, two observational studies demonstrated that infants fed LCPUFA supplemented formula in the first year of life had reduced incidence of bronchitis/bronchiolitis (25, 26) and lower risk of multiple episodes of eczema (26). A retrospective chart review study of children fed formulas supplemented with DHA and ARA in the first year of life similar to the lowest amount of DHA and ARA fed in our study (0.32% DHA and 0.64% ARA) showed lower incidence and delayed onset of allergic manifestations during the first 3 years of life (15).

The influence of maternal allergy on incidence of infant allergy has been documented. Higher cord blood IgE levels have been observed in infants of allergic mothers, compared to infants with paternal or no atopic heredity, and may predict subsequent development of infant's eczema (27). A decreased cumulative incidence of IgE-mediated disease up to 2 years of age was observed in children at high risk of allergy who had higher EPA and DHA levels in plasma phospholipids associated with maternal EPA/DHA supplementation during pregnancy and lactation (28).

In the current study, LCPUFA supplementation to the infant appeared to counteract the risk factor of maternal allergy by protecting against wheezing/asthma in children whose mothers reported maternal allergy but not in those whose mothers did not report maternal allergy. Unexpectedly, skin illnesses were most common in children of women who did not have allergy. This finding seems counter to the evidence that maternal allergy increases the risk of all allergies in offspring. On the other hand, our observation that LCPUFA protected against skin allergic illness only in children of mothers without allergy is consistent with at least two

other reports: n-3 supplementation promoted lower Th2:Th1 chemokine ratio in infants of mothers without but not with maternal allergy (4); and LCPUFA supplementation through fish intake during pregnancy decreased food sensitization in children of mothers without but not children with mothers with allergy (29). Most studies do not account for maternal allergy and at least one study of LCPUFA supplementation excluded infants not considered at increased risk of allergy due to maternal allergy (13). Interestingly, with regard to our results and those of others (4, 29), no effect of postnatal fish oil supplementation on any diagnosed allergy, eczema or food allergy was found in the first year of life. These results suggest that LCPUFA may have different mechanisms in relation to protection against allergy. In the current study, as well as others (9, 15), infant formula was supplemented with both DHA and ARA. It's becoming apparent that both DHA and ARA (a combination of n-3 and n-6 LCPUFA) may be protective for allergy (30).

A limitation of this study is that the control group is relatively small compared to the pooled LCPUFA group. However, the source of the study population was a randomized, double-blind placebo-controlled study, and the pooled LCPUFA and control groups did not differ in demographic, birth characteristics or other risk factors for allergy, which minimizes the likelihood of significant bias in the study. Moreover, the number of participants followed in this study proved to be sufficient to demonstrate significant differences between the control and LCPUFA groups, which are clinically relevant. A second limitation of this study is that only maternal allergy was considered in the family history. This is related to the nature of secondary data analysis. Additional details about paternal or sibling allergy were not collected. Strengths of the study include its prospective design and reliance on medically documented events.

The results of the current study add to the evidence that supplementation of infant formula with DHA and ARA in the first year of life delays allergy and has a protective effect against allergy in early childhood. Significant interactions between maternal allergy and LCPUFA for wheezing/asthma and skin allergic illness that were in opposite directions suggest varied mechanisms of LCPUFA protection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Kaplan-Meier Survival Curves for all allergic illnesses by type of formula. The x-axis is event-free time (in months) from birth to four years. The y-axis is the probability of remaining illness-free to time X . The two curves represent survival for LCPUFA compared to controls for all allergic illness. Children supplemented with LCPUFA as infants had less allergic illness in the first 12 months ($p=0.033$) and longer illness-free time ($p = 0.04$) compared to the control.

Figure 2.

Kaplan-Meier Survival Curves for skin allergic illnesses by type of formula and history of maternal allergy. The x -axis is event-free time (in months) from birth up to four years. The y -axis is the probability of remaining illness-free to time x . The four curves represent survival for LCPUFA with history of maternal allergy (solid, $n = 25$), LCPUFA with no history (dot-dash, $n = 28$), control with history (short dash, $n = 9$) and control with no history (long dash, $n = 8$). If mother reported no allergy, the LCPUFA group had less risk of skin allergy than the control group ($\chi^2 = 10.7$, $p = 0.001$) whereas LCPUFA and control groups did not differ if mother reported allergy ($\chi^2 = 0.01$, $p = 0.9$).

Figure 3.

Kaplan-Meier Survival Curves for wheezing/asthma by type of formula and history of maternal allergy. The x-axis is event-free time (in months) from birth up to four years. The y-axis is the probability of remaining illness-free to time x . The four curves represent survival for LCPUFA with history of maternal allergy (solid, $n = 25$), LCPUFA with no history (dot-dash, $n = 28$), control with history (short dash, $n = 9$) and control with no history (long dash, $n = 8$). If mother reported allergy, the LCPUFA group had less risk of wheezing/asthma than the control group ($\chi^2 = 5.3$, $p = 0.02$) whereas LCPUFA and control groups did not differ if mother reported no history of allergy ($\chi^2 = 0.14$, $p = 0.8$).

Baseline Characteristics

Table 1

	LCPUFA Supplemented ¹			Pooled LCPUFA (N = 72)	Control (N = 19)	P ²
	0.32% DHA (N = 25)	0.64% DHA (N = 19)	0.96% DHA (N = 28)			
Male gender, <i>n</i> (%)	10 (42%)	6 (33%)	11 (42%)	27 (38%)	7 (37%)	0.9
Race, <i>n</i> (%) African-American	12 (48%)	12 (63%)	18 (64%)	42 (58%)	17 (89%)	0.1
White	9 (36%)	7 (37%)	7 (25%)	23 (32%)	2 (11%)	
Other	4 (16%)	0 (0%)	3 (11%)	7 (10%)	0 (0%)	
Smoking in home, <i>n</i> (%)	9 (53%)	7 (44%)	8 (35%)	24 (33%)	9 (47%)	0.2
Maternal allergy, <i>n</i> (%)	8 (50%)	5 (33%)	12 (55%)	25 (35%)	9 (47%)	0.3
Pets in home, <i>n</i> (%)	8 (39%)	8 (50%)	6 (26%)	22 (31%)	7 (37%)	0.3
Daycare attendance, <i>n</i> (%)	15 (88%)	15 (94%)	19 (82%)	49 (68%)	14 (74%)	0.1
Birth weight (kg), median (range)	3.5 (2.7, 4.1)	3.3 (2.9, 4.1)	3.4 (2.8, 4.0)		3.2 (2.8, 4.1)	0.5
Birth length (cm), median (range)	50.5 (46.7, 54.4)	50 (47, 54.5)	50.4 (46.6, 54.5)		49.5 (46, 53.3)	0.2
Birth head circumference (cm), median (range)	35 (32.5, 36.2)	34 (32, 37)	34 (31.5, 36.5)		34.6 (32.3, 37)	0.6
Mother's formal education (yrs), median (range)	12 (10, 16)	12 (10, 16)	12 (8, 18.5)		12 (9, 21)	0.6

¹ Values for smoking in home, maternal allergies, pets in home and daycare attendance were missing for some children and percentages were calculated based on parents who returned the questionnaire.

² *P*-values from Fisher exact tests and Wilcoxon tests comparing categorical and continuous characteristics, respectively, between the Pooled LCPUFA and Control groups.

Table 2

Illness Rates and Illness Free Time by Group

Group	n (%) with illness within 4 years ^I	Mean (SE) Illness-free Time (in months) LCPUFA N=72	Control N=19	HR (95% CI)	p
<i>All Allergic Illnesses</i>					
LCPUFA	49 (68%)				
Control	14 (74%)	22.1 (2.1)	7.3 (1.5)	0.64 (0.4, 1.2)	0.04
<i>Skin Allergic Illness</i>					
LCPUFA	27 (38%)	32.8 (2.1)	9.9 (1.6)	0.55 (0.3, 1.1)	0.05
Control	10 (53%)				
<i>Wheeze/Asthma</i>					
LCPUFA	21 (29%)	37.9 (1.7)	34 (4.5)	0.6 (0.3, 1.4)	0.1
Control	8 (42%)				

^I Odds ratios and 95% CI for all allergic illness, skin allergic illness, wheeze/asthma are 0.76, 95% CI = 0.2, 2.4; 0.54, 95% CI = 0.4, 1.2; and 0.57, 95% CI = 0.2, 1.6, respectively, P>0.05 for all 3 comparisons.

Table 3
Information on Illness Rates and Timing by Maternal Allergy History^I

Group	<i>n</i> (%) with illness within 4 years		HR (95% CI)	<i>p</i>
	LCPUFA (<i>N</i> = 53)	Control (<i>N</i> = 17)		
<i>All Allergic Illnesses</i>				
Maternal Allergy (<i>N</i> = 34)	15 (60%)	5 (56%)	0.99 (0.4, 2.7)	0.9
No Maternal Allergy (<i>N</i> = 36)	23 (82%)	8 (100%)	0.24 (0.1, 0.6)	0.001
<i>Skin Allergic Illness</i>				
Maternal Allergy (<i>N</i> = 34)	9 (36%)	3 (33%)	0.99 (0.3, 3.7)	0.9
No Maternal Allergy (<i>N</i> = 36)	12 (43%)	6 (75%)	0.35 (0.1, 0.9)	0.04
<i>Wheeze/Asthma</i>				
Maternal Allergy (<i>N</i> = 34)	5 (20%)	5 (56%)	0.26 (0.07, 0.9)	0.02
No Maternal Allergy (<i>N</i> = 36)	9 (32%)	3 (38%)	0.78 (0.2, 2.9)	0.8

^IInformation was not available on history of maternal allergy for 21 subjects—2 in the control and 19 in the LCPUFA group.