



From the Pages of allergywatch®

Recent advances in asthma



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Do Fish Oil Supplements During Pregnancy Prevent Asthma?

Low intake of n-3 long-chain polyunsaturated fatty acids (LCPUFAs) during pregnancy may be associated with an increased risk of childhood wheezing and asthma. Most previous trials of this issue have been underpowered, with inconclusive results. This randomized controlled trial with long-term follow-up evaluated the effects of n-3 LCPUFA supplementation during pregnancy on the risk of wheeze and asthma in offspring. At 24 weeks' gestation, 736 pregnant women were assigned to supplementation with fish oil, containing 2.4 g of n-3 LCPUFA, or olive oil. Both parents and investigators were unaware of the children's group assignments for the first 3 years of follow-up, and the investigators for an additional two years. Rates of persistent wheeze or asthma were compared between groups. Of 695 children enrolled in the trial, 95.5% completed 3 years of follow-up. Persistent wheeze or asthma developed in 16.9% of children assigned to n-3 LCPUFA supplementation, compared to 23.7% with olive oil: hazard ratio (HR) 0.69. The effect was even larger in a prespecified subgroup of children whose mothers had low baseline levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA): HR 0.46. The n-3 LCPUFA supplementation group also had a lower rate of lower respiratory tract infections: 31.7% versus 39.1%, HR 0.75. Other secondary outcomes were similar between groups, including allergic sensitization, eczema, and asthma exacerbations. Taking supplemental fish oil during the third trimester of pregnancy may reduce the risk of

persistent wheeze or asthma in offspring. The intervention effect is stable from age 2 through 5 years, with the largest benefit among women in the lowest one-third of baseline n-3 LCPUFA levels.

Comments by Chitra Dinakar, MD: High-dose third trimester supplementation of the n-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), derived from fish oil, significantly reduced the absolute risk of persistent wheeze or asthma during the first 5 years of a child's life, particularly in children of mothers with low baseline blood levels of EPA and DHA. As pointed out by Ramsden et al in an accompanying editorial, it is important to note that the dose of EPA plus DHA provided in this trial (2.4 g per day) was approximately 15 to 20 times the average U.S. normal dietary intake, and further safety studies of this high dose need to be done before adopting this approach.

Bisgaard H, Stokholm J, Chawes BL, et al.
Fish Oil–Derived Fatty Acids in Pregnancy and Wheeze and
Asthma in Offspring.
N Engl J Med. 2016;375:2530–2539.
Ramsden CE.
Breathing Easier with Fish Oil—A New Approach to Preventing
Asthma?
N Engl J Med. 2016;375:2596–2598.

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Sex-Specific Risk Factors for Childhood Wheeze and Longitudinal Phenotypes of Wheeze

Boys and girls differ in wheezing and asthma prevalence, but relatively little is known about sex-specific risk factors for childhood wheeze, or about the longitudinal trajectory of wheezing. These issues were addressed using data from a large prebirth cohort study. The analysis included 1,623 children enrolled in Project Viva, which was designed to assess prenatal and perinatal factors affecting maternal and child health. Atopy risk was not a selection factor. Mothers made annual reports of childhood wheezing symptoms. Sex-specific risk factors for wheezing from birth to mid-childhood were analyzed, along with longitudinal wheeze phenotypes and associated sex-specific risk factors. Paternal asthma was a risk factor for wheezing in both sexes, but was stronger in boys: odds ratio 2.15, compared to 1.53 in girls. Several other factors were stronger in girls than boys, including black or Hispanic race/ethnicity, birth weight for gestational age z score, and duration of breastfeeding. On phenotype analysis, 74.1% of children had no or infrequent wheeze, 12.7% had early transient wheeze, and 13.1% had persistent wheeze. In both sexes, risk factors for persistent wheeze included maternal asthma, bronchiolitis in infancy, and atopic dermatitis. Paternal asthma was a significant risk factor in boys only, OR 4.27; while black or Hispanic race/ethnicity was specific to girls: OR 3.23 and 3.60, respectively.

Some sex-specific risk factors for childhood wheeze and a persistent wheezing phenotype are identified. Paternal asthma appears to be a significant risk factor for boys, while race/ethnicity may increase risk among girls. The authors discuss the implications for individual prognosis and treatment for childhood wheezing and asthma.

Comments from Stanley M. Fineman, MD: Knowledge of sex-specific risk factors for childhood asthma may have prognostic and clinical implications in the management of children with wheezing. This well designed study using data from a large prospective birth cohort followed children until 9 years of age and reported that paternal asthma was an important predictor of persistent wheeze in boys, whereas being black or Hispanic was a stronger risk factor in girls. Three wheezing phenotypes were identified with risk factors being associated with each frequently depending on the sex of the child. The fact that paternal asthma was a predictor for persistent wheeze in boys was novel.

Tse SM, Rifas-Shiman SL, Coull BA, et al.
Sex-specific risk factors for childhood wheeze and longitudinal phenotypes of wheeze.
J Allergy Clin Immunol. 2016;138:1561–1568.

Severity of Asthma Associated with Animal Dander Specific IgE in Northern Sweden

Sensitization to indoor allergens plays a major role in asthma, although the association between these allergens and asthma symptoms remains unclear. This study assessed the relationship between sensitization to dog and cat allergen and asthma symptoms, in a northern area with low exposure to other indoor allergens. The study included participants from an ongoing population-based cohort study in northern Sweden—an area where the climate discourages indoor allergens such as cockroach, dust mite, and fungi. Specific IgE to cat and dog allergens were measured in serum samples from 963 participants at age 19 years. Associations of cat and dog sensitization with the presence, severity, and persistence of asthma were assessed. Titers of specific IgE for cat and dog allergens were strongly associated with asthma prevalence and severity. Out of 103 patients with asthma at 19 years, 50 had asthma before 12 years. In this group, the odds ratio for asthma associated with any animal dander-specific IgE was 9.2. The association was even stronger, odds ratio 13, for high-titer IgE antibodies of 17.5 IU/mL or higher. Specific IgE to Fel d 1 and Can f 5 were both associated with prevalent asthma. These data from northern Sweden suggest that high titers of animal dander-specific IgE antibodies are strongly associated with the presence and severity of asthma in young adults. For those diagnosed with asthma before age 12, specific IgE to pets is strongly

related to asthma. Having a cat or dog at home was not a significant predictor of sensitization or asthma, highlighting the presence of pet allergens throughout the community.

Comments from Stanley M. Fineman, MD: “Should we get rid of our pet because our child has asthma?” How many times have we heard parents ask this question? These researchers used a unique cohort of children living above the Arctic Circle, with no dust mite or cockroach exposure, to examine the association of cat or dog exposure and sensitization with persistence of asthma. The authors report that the presence of sIgE to cat or dog in these children was related to the both prevalence and severity of asthma. Interestingly there was a high percentage of children without pets who had elevated sIgE to cat &/or dog indicating that pet dander exposure outside the home is clinically relevant. So our answer to our patients may not be so easy, but having additional data is helpful.

Perzanowski MS, Ronmark E, James HR, et al.
Relevance of specific IgE antibody titer to the prevalence, severity, and persistence of asthma among 19-year-olds in northern Sweden.
J Allergy Clin Immunol. 2016;138:1582–1590.

Might Star Wars Technology Solve the Challenge of Asthma Heterogeneity?

Molecular and genetic markers, particularly in readily accessible specimens, may lead to new approaches to identifying patients for targeted therapies for severe asthma. This study used gene-expression profiles in peripheral blood to identify subgroups of patients with severe asthma. The analysis included 610 asthmatic and control subjects from the Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes (U-BIOPRED) study. Important differences in blood transcript profiles and molecular pathways were assessed, including differences in subjects with mild/moderate and severe asthma and the effects of oral corticosteroid treatment. Patient clusters were created on the basis of gene expression patterns, independent of clinical findings. The results showed differential

expression of 1,693 genes for subjects with severe asthma versus nonasthmatic subjects. The differences between nonasthmatic subjects and the nonsmoking severe asthma and mild/moderate asthma subgroups were significantly related to each other, although with a greater effect size in the severe asthma subgroup. On assessment of biologic pathways, most of the differences between subgroups reflected differences in circulating immune cells. Severe asthma was associated with increased chemotaxis, migration, and myeloid cell trafficking and decreased B-lymphocyte development and hematopoietic progenitor cells and lymphoid hypoplasia. Cluster analysis identified subgroups of patients with severe asthma who had differing responses to oral corticosteroids. The study

identifies differences in peripheral blood gene expression for patients with asthma, including severe asthma, versus nonasthmatic subjects. Transcript profiles also identify subgroups of patients with severe asthma, including differential responses to oral corticosteroids. The study shows “major differences in the activity of circulating cells that do not follow the currently applied clinical classification based on severity of asthma.”

Comments from Bradley E. Chipps, MD: This study used blood transcriptomic technology to characterize subgroups of

asthmatics, including a 1,700 gene severe asthma disease signature. This is a very important observation that opens the door to developing better diagnostic biomarkers and targeted therapies. Stay tuned!

Bigler J, Boedigheimer M, Schofield JPR, et al.
A severe asthma disease signature from gene expression profiling of peripheral blood from U-BIOPRED cohorts.
Am J Respir Crit Care Med. 2017;195:1311–1320.