

# **Clinical Evidence for the Role of Dietary Fatty Acids in Mucosal Immune Development: Mechanism of Action and Impact on Respiratory Health and Allergy**

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Interest is growing in the role of early life events and exposure in the etiology and prevention of disease. Diet and nutrition in pregnancy have a fundamental influence on fetal development, and focus is increasing on the role of key dietary nutrients in subsequent health or disease. This presentation explores the effects of dietary long-chain polyunsaturated fatty acids (LCPUFAs) on early immune development and their potential role in the development or the prevention of immune and inflammatory diseases, in particular allergy and asthma.

The extensive immunomodulatory properties of LCPUFAs are well recognized<sup>1</sup>; the effects are mediated through a number of potential mechanisms. Less is known about these effects in immature and developing systems. In addition to influences on production of eicosanoids, omega-3 (n-3) PUFAs can regulate T-cell function directly through effects on cell membrane fluidity and consequent cell signaling and gene transcription.<sup>2</sup>

Changing patterns of dietary LCPUFA intake are clearly relevant in pregnancy for the developing fetus. The intake of dietary anti-inflammatory n-3 PUFAs has progressively declined in Western diets, with a corresponding increase in proinflammatory n-6 PUFAs. This has resulted in considerably higher dietary intake ratios of n-6:n-3 LCPUFAs (20-30:1).<sup>3</sup>

Epidemiological and experimental data provide a plausible link between these dietary changes and the rise in allergic immune diseases.<sup>4</sup> Although difficult to prove, these associations are supported by the well-described difference in the immune effects of n-3 and n-6 LCPUFA in vivo and in vitro.

Early population studies suggested that the risk of asthma may be higher in children with higher n-6:n-3 diets, either in association with low consumption of fish<sup>5</sup> or high consumption of n-6 rich vegetable oils.<sup>6</sup> Several subsequent studies also have shown protective effects of fish oil. A well-known Australian study showed that children who regularly consumed oily fish were significantly less likely to develop asthma (odds ratio: 0.26).<sup>7</sup> Two more recent birth cohort studies also have reported that lower dietary n-6:n-3 intake (ie, higher fish intake) reduced the risk of developing asthma.<sup>8,9</sup> However, this has not been confirmed by all studies, and at least one large study found that higher fish intake was associated with a significantly higher prevalence of asthma (odds ratio: 1.117).<sup>10</sup> In general, because of the limitations of these population-based studies, focus has grown on well-controlled intervention studies, as described below.

A Western Australian (Perth) group undertook the first human intervention study using high-dose fish oil in pregnancy to investigate the effects of n-3 LCPUFAs on early immune development.<sup>11</sup> The group gave fish oil (3.7 g n-3 PUFAs/day) or placebo supplements to allergic women (n=98) for the final 20 weeks of pregnancy. Fish-oil supplementation (n=40) achieved significantly higher proportions of n-3 PUFAs in neonatal erythrocyte membranes (mean  $\pm$ SD, 17.75%  $\pm$ 1.85% as a percentage of total fatty acids) compared with the control group (n= 43, 13.69%  $\pm$ 1.22%,  $P < 0.001$ ). All neonatal cytokine (IL-5, IL-13, IL-10, and interferon gamma [IFN- $\gamma$ ]) responses (to all allergens) tended to be lower in the fish-oil group (statistically significant only for IL-10 in response to cat).

Although the authors examined the effects of maternal fish-oil supplementation on clinical outcomes in our intervention study,<sup>11</sup> the findings cannot be viewed definitively because the study was designed to assess immune function rather than clinical effects, which would have

required a larger population size. Dunstan et al<sup>11</sup> did note that infants in the fish-oil group were consistently less likely to develop clinical features, including food allergy, recurrent wheeze, persistent cough, diagnosed asthma, angioedema, or anaphylaxis, compared to the control group. Although there was no difference in the frequency of atopic dermatitis at 1 year of age, infants in the fish-oil group had significantly less severe disease (odds ratio: 0.09; 95% CI, 0.01–0.94;  $P=0.045$ ). Sensitization to egg was also less common in the fish-oil group. Although it is not possible to make conclusions from this, this study has provided justification for larger, long-term studies. Several larger studies in progress in Europe and Australia are specifically designed to assess this, and the results are awaited with great interest.

In addition to the associations mentioned above, the same group also investigated the effects of dietary n-3 PUFA supplementation during pregnancy on a) numbers and function of progenitors,<sup>12</sup> and b) the relationship between neonatal T-cell protein kinase (PKC) expression and subsequent allergic disease.<sup>13</sup> In short, percentages of cord blood (CB) CD34<sup>+</sup> cell numbers were higher after n-3 PUFA supplementation than after placebo, and significantly more IL-5-responsive CB eosinophil/basophil colony forming units were seen in the fish-oil group, compared with the control group. Furthermore, the authors identified neonatal T-cell PKC isozyme expression (namely PKCzeta) as a potential predictor of allergic disease.

In conclusion, it is probable that if LCPUFAs have clinically relevant effects, these are more likely to appear at a younger age before immune responses and clinical phenotype are established. We and others have shown that immunological abnormalities precede the development of allergic disease and are frequently evident at birth or in the first months of life.<sup>14</sup>  
<sup>16</sup> This also may explain why intervention studies in later childhood to reduce symptoms in established asthma have shown only weakly beneficial effects<sup>17</sup> or no effect.<sup>18</sup> As indicated

previously, a number of other ongoing studies will assess the effects of earlier supplementation, from birth or in pregnancy, with higher doses of n-3 PUFAs.

## References

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## Q & A

Q: The research looked at prenatal exposure and intervention. Dr Kuitunen showed what is going on in breast milk with urbanization or change in rural areas. During that time there would be a lot more of not just docosahexaenoic acid (DHA), but also eicosapentaenoic acid (EPA) and some other omega-3 oils. Such exposure to EPA soon after birth through breast milk might have some effect on mucosal development. Has anyone looked at either cultural differences in breast milk levels of fatty acids or supplementing lactating women with EPA and DHA?

Dr Noakes: Koletzko and colleagues reviewed 14 studies from 9 European countries and 10 studies from 7 African countries on fatty acids in mature human milk [Koletzko B et al: *J Pediatr* 1992;120(4 Pt 2):S62-S70]. They found the average composition data for milk fatty acids surprisingly consistent, despite marked differences in dietary composition in the areas studied. To respond to the last part of your comment, many groups have looked at this, including those of Robert Gibson, Susan Prescott, and Berthold Koletzko.

Q: How critical is EPA as a fatty acid for allergic disease prevention, and will DHA also lower prostaglandin E<sub>2</sub> levels?

Dr Noakes: Traditionally, investigators have looked at EPA, but now with the discovery of resolvins and the fact that DHA can produce D-series resolvins, I think people will now turn their attention to looking at both EPA and DHA.