

EDITORIAL

Clinical & Experimental Allergy Dietary polyunsaturated fatty acids in the prevention of allergic inflammatory conditions: progress and perspectives

This editorial discusses the findings of the paper by Linnamaa et al. [13] pp. 1247–1255.

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Disease prevention is the ultimate goal in curbing the allergy epidemic. However, early intervention strategies are dependent on a comprehensive understanding of the modern environmental pressures that are driving the epidemic of immune disease. Complex modern dietary changes are among the leading candidates in the rise in many modern diseases, and are centrally implicated in epigenetic models that are evolving to explain how environmental changes modify future disease susceptibility through changes in early gene expression [1–3]. This has led to intense speculation that dietary modification during pregnancy and lactation may be a powerful avenue for reversing the rising disease risk.

Diet is arguably one of the most significant exposures in both the prenatal and postnatal periods. During pregnancy, maternal diet and dietary exposures influence virtually all aspects of fetal development including the developing immune system. In the postnatal period, enteric exposures, including colonizing bacteria and dietary components, are key players in the establishment of oral tolerance with implications for the development of allergic disease. Modern diets differ in many aspects from more traditional diets, with more processed and synthetic foods and less fresh fish, fruits and vegetables. As a result, there have been changes in the levels and patterns of various dietary components, including polyunsaturated fatty acids (PUFA). PUFA are classified into two principal families; the ω -6 (n-6) and n-3 families. The precursor

fatty acids, linoleic acid (LA) and α -linolenic acid (ALA) cannot be synthesized in humans and are accordingly regarded as essential fatty acids (EFA). A progressive decrease in the intake of n-3 PUFA in favour of n-6 PUFA, leading to a lower n-3/n-6 ratio, has been implicated in the allergy epidemic. The potential protective role of n-3 PUFA in allergic disease emerged through the known anti-inflammatory properties of these fatty acids and early observation studies reporting that consumption of oily fish in childhood (higher n-3/n-6 ratio) was associated with less wheeze and asthma [4].

The declining ratio of n-3/n-6 PUFA in modern diets could feasibly impact on early immune programming and the subsequent development of allergic disease, particularly as the metabolic products of n-6 PUFA are significantly more inflammatory than those of n-3 PUFA (reviewed in [5]). This could result in declining substrates for many n-3 PUFA anti-inflammatory metabolites including the recently discovered resolvins that actively assist in resolving inflammation [5]. Logically, this has led to interest in the role of n-3 PUFA supplementation in the prevention of allergic diseases. The first major allergy prevention study to address this used postnatal intervention (fish oil supplementation) beginning around 6 months of age. Although there was a transient reduction in wheeze at 18 months of age in the fish oil group, there was no long-term protective effect on any diagnosed allergic disease or allergic sensitization, as assessed at 5 years of age [6]. As Th2 allergic responses are already emerging by 6 months in allergic children (although many still asymptomatic) [7], we speculated that earlier intervention could be more successful. However, preliminary results from our ongoing 'Infant Fish Oil Study (IFOS)', also suggest no benefit when fish oil supplementation is started earlier, in the first week of life. Specifically, despite high-dose supplementation (280 mg docosahexaenoic per day) from birth to 6 months

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of age, there was no reduction in infant allergic outcomes at 12 months compared with a placebo group (N. D'Vaz, personal communication; unpublished data).

At the same time, there has been growing evidence that PUFA status in pregnancy, may have more significant effects on immune development and this is arguably when many aspects of developmental programming are more critical. Our initial study demonstrated neonatal immunomodulatory effects of maternal fish oil [8], and also provided preliminary evidence of a reduced risk of sensitization and other allergic outcomes [8]. Although the study was not powered to examine these clinical outcomes, children in the fish oil group were also three times less likely to have a positive skin prick test to egg at 1 year of age with a relative risk reduction of 54.6%. This fuelled further interest in maternal diet in pregnancy and a series of observational studies provided promising observations that maternal consumption of oily fish in pregnancy has protective effects on infant allergic outcomes ([9]; and others) although not unambiguously [10]. Now, the results of further PUFA intervention studies are beginning to emerge. A 16-year follow-up of a cohort of children included in a pregnancy fish oil supplementation study (originally performed to assess pregnancy outcomes such as gestational length) showed a reduction in subsequent asthma [11]. Another more recent study [12] has now demonstrated a significant reduction both in food allergy and IgE-associated eczema in infants whose mothers were supplemented with fish oil during pregnancy and lactation (compared with a placebo group). In this issue, Linnamaa *et al.* [13], report the results from a randomized controlled trial investigating the preventive effects of supplementing the maternal and infant diet with black currant seed oil (BCSO) on the development of eczema and allergic sensitization until 2 years of age. BCSO, which is rich in both n-6 and n-3 fatty acids and has a favourable n-3/n-6 ratio, or a placebo (olive oil), was administered to mothers during pregnancy and lactation, and then to the infants until 2 years of age. With 322 mothers enrolled, this study had the potential to be one of the largest supplementation studies. Unfortunately, but as is often the case in long-term follow-up studies, there was a high drop-out rate with 210 infants examined at 12 months and 177 followed up at 24 months. This hampered the intention-to-treat analysis and may have unavoidably introduced some biases to the results. The per-protocol analysis revealed a statistically significant reduction in the prevalence of eczema at 12 months of age in the treatment group compared with the placebo group. At this age, the severity of eczema, as assessed by Scoring Atopic Dermatitis, was also reduced in the treatment compared with the placebo group. The effects did not persist, and at 2 years of age there was no difference between the two groups in neither the prevalence nor the severity of eczema. Allergic sensitization was also assessed with no differences be-

tween the two groups. Over the years, it has been debated to which extent the phenotype of infant eczema is truly atopic, and in future intervention studies it would be interesting to evaluate the effects of PUFA more specifically on IgE-associated eczema. Nonetheless, the results of this study suggest that supplementing maternal and infant diet with EFA may reduce the prevalence of eczema, and emphasize the role of EFA in inflammatory allergic conditions, particularly in the first year of life.

Whether the beneficial effect of BCSO supplementation is due to effects on fetal immune programming through maternal supplementation, or is a result of the combination of both maternal and infant supplementation is uncertain. So far, limited data from intervention studies suggest that benefits may be greater during pregnancy [8, 11, 12] than the postnatal period. It is also logical that the effects and the mechanisms could vary with developmental age and may be different in pregnancy compared with the postnatal period. Thus, while a recent meta-analysis found no benefit of PUFA supplementation in the primary prevention of allergic disease [14], this analysis pooled the data from prenatal and postnatal intervention studies. We argue that while the ultimate conclusion may be unaltered at this stage, this approach to pooling data from prenatal and postnatal studies may conceal potential differences in the effect of PUFA according to developmental age. Future meta-analyses, when new studies are published, should ideally examine prenatal and postnatal studies separately. Currently, there are several large ongoing studies that will hopefully clarify the role of n-3 PUFA in allergy prevention more definitively. Perhaps the largest and potentially most definitive of these studies (with supplementation of more than 650 women in pregnancy) is the 'DHAAllergy' study conducted in Adelaide, Australia. The initial results (1 year outcomes) are anticipated this year.

Another important consideration is the potential variation in responsiveness and effectiveness of a dietary intervention between individuals. There is mounting evidence that functional genetic polymorphisms in specific pathways can modify effects of environmental exposures, such that any disease-modifying effects may vary with an individual's genotype. This is likely to confer individual differences in the effects of any intervention and has highlighted the still futuristic concept of 'individualized medicine' that could ultimately tailor treatment and prevention strategies according to individual genetics. In the context of fatty acids, functional polymorphisms have been identified in the metabolic pathways of fatty acid metabolism [15]. These genetic polymorphisms could potentially modify the relationship between the environmental exposure and the biological effects. Studies have demonstrated that levels of LA and ALA and their biologically active long-chain PUFA products, are influenced not only by the diet but also by genetic variants. Genetic variants of the fatty acid desaturase 1 fatty acid desaturase 2 (FADS1 FADS2) gene cluster are associated with

variations in the PUFA in cell membranes [15], although at this stage, the relationship with allergic disease needs further study. So far, none of the n-3 PUFA intervention studies targeting allergy prevention have examined for any heterogeneity in the biological effects according to genetic polymorphisms in these metabolic pathways.

In summary, there is clear evidence of the anti-inflammatory properties of n-3 PUFA. In addition to epidemiological data, this has provided a strong basis to explore a role in allergy prevention. So far, limited data from intervention studies suggest that benefits may be the greatest in the prenatal period before the immune predisposition for allergic disease has become established. As of yet, no specific recommendations can be given for the use of n-3 PUFA in allergy prevention, but larger currently ongoing studies are anticipated to provide clearer answers. These larger studies may have the further capacity to also examine how functional genetic polymorphisms impact upon the relative effects of the environmental exposures and the developing phenotype. This research needs to occur in tandem with new epigenetic research programmes, which are now heavily focused on how environmental exposures interact with gene expression in early life. PUFA are among many dietary changes that are implicated in the rise in many modern inflammatory diseases [16], emphasizing the need to also examine other complex dietary interactions. Collectively, these observations highlight that maternal diet has enormous potential to influence many aspects of development, and that the role of dietary modifications should remain a research priority in the prevention of allergic disease.

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