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Invited Commentary

Invited commentary in response to PUFA status at birth and allergy-related phenotypes in childhood: a pooled analysis of the Maastricht Essential Fatty Acid Birth and Rhea birth cohorts

Regular inclusion of fish in the maternal diet during pregnancy appears to be a beneficial whole food nutritional strategy approach to reducing the growing worldwide burden of allergic disease. Observational cohort studies have found higher maternal fish intakes in pregnancy to be associated with reduced child allergic outcomes, including reduced eczema[1–4], reduced wheeze or asthma[2,5,6] and reduced allergen sensitisation[7]. There has been one randomised controlled trial (RCT) investigating maternal oily fish consumption (two portions of salmon per week) during pregnancy, and this trial found that regular fish consumption beneficially modified neonatal immune responses[8]; however, this small RCT (*n* 123) was not powered adequately for clinical allergic disease outcomes. Fish is an excellent dietary whole food source of potential anti-inflammatory and immunomodulatory nutrients including *n*-3 PUFA. In accordance, an increase in allergic diseases over recent decades has coincided with a decreased intake of *n*-3 PUFA in the diet of many communities and a corresponding increase in consumption of *n*-6 PUFA.

In this issue of the *British Journal of Nutrition*, Stratakis *et al.*[9] present findings from two European birth cohorts, the Maastricht Essential Fatty Acid Birth cohort in the Netherlands and the Rhea (Mother–Child) birth cohort in Crete, Greece. This new analysis combines pooled individual data from these two cohorts from Western and Southern Europe and adds to the evidence base regarding the influence of PUFA status at birth on childhood allergic disease outcomes. Their major findings include an association between a higher ratio of *n*-3:*n*-6 fatty acids in cord blood at birth with a lower risk of child wheeze and asthma at 6–7 years of age. In individual fatty acid analyses, this association was found with higher EPA and DHA concentrations in cord blood. There were however no associations with rhinitis and eczema symptoms at 6–7 years of age.

Several RCT have investigated maternal supplementation during pregnancy with *n*-3 PUFA rich fish oils for effects on offspring allergic disease outcomes. Collectively these RCT have found that *n*-3 PUFA supplementation during the second and/or third trimester of pregnancy may decrease the risk of allergen sensitisation and allergic disease in the offspring[10–13]. Beneficial immunomodulatory effects in cord blood have also been demonstrated[10,14,15], in particular maternal fish oil supplementation in pregnancy lowers neonatal oxidative stress[14] and neutrophil production of leukotriene B4, which correlated with reduced Toll-like receptor-4-mediated inflammatory responses[15]. The new findings in this issue of the *British Journal of Nutrition*, by Stratakis *et al.*[9] are in accordance with those from two RCT conducted in Denmark by Bisgaard *et al.* (*n* 695)[16] and Olsen *et al.* (*n* 533)[12]. Both of these Danish trials found that after maternal supplementation of about 900 mg DHA and 1300 mg EPA per d in pregnancy, child wheeze or asthma at 3–5 years of age[16] and asthma at 16 years of age[12] were significantly reduced. Interestingly a RCT conducted in Australia with similar sample size (*n* 706), but with a different maternal fish oil supplementation of 800 mg DHA and 100 mg EPA per d in pregnancy, found no difference in parent reported asthma at 6 years of age[17]. However this trial did identify beneficial effects earlier in childhood, especially reduced egg sensitisation and atopic eczema at 1 year of age[13]. This raises the question as to whether the differences in wheeze and asthma outcomes were related to differences between the Danish and Australian studies in EPA supplementation dose and/or other genetic, dietary, environmental and lifestyle factors.

Research in this field is not straightforward and inconsistencies in our evidence base to date are likely to reflect the inherent complexity of each individual's diet, difficulties with accurate quantification of dietary intakes, and interplay with many other factors. It is important to consider the dietary source of fatty acid intakes and associated other dietary factors. For example, other potential anti-inflammatory and immunomodulatory nutrients found in oily fish like Se and vitamin D, may be playing an important role. Our diets are not comprised of just one or two specific foods (or nutrients) and the combined interaction effects, although often difficult to disentangle, need to be a focus of future research. We still require more RCT investigating whole foods (e.g. fish) or dietary patterns (e.g. the Mediterranean Diet) based interventions, with adequate sample sizes and high retention rates. In particular within new studies, we also need the tracking of PUFA status at multiple-time points during pregnancy, at birth, during infancy and at least two-three times within the childhood years to enable an improved understanding of whether there is a critical period or a long-term fatty acid status association with allergic disease development. Finally, it is important to consider the sub-group findings from the recently published Bisgaard *et al.* RCT[16], where the preventive effect of maternal supplementation appeared to be driven primarily by children of mothers who

had low blood levels and low dietary intakes of EPA and DHA at randomisation, as well as the children of mothers with a fatty acid desaturase (*FADS*) genotype associated with low EPA and DHA blood levels. These findings highlight the importance of targeting pregnant women with the *FADS* genotype, as well as those with a low dietary intake of these fatty acids, as examples of potential future personalised approaches to allergy prevention. It will be essential for future studies to investigate the role of individual genetic polymorphisms and their influence on the interplay between nutritional status in early life and allergic disease outcomes.

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