British Journal of Nutrition (2009), **102**, 331–333
doi:10.1017/S0007114508199469

Invited Commentary

Early life programming of immune and lung function: can we now exclude a role of arachidonic acid exposure?

(First published online 23 January 2009)

It is generally agreed that incidence and prevalence of childhood atopy and its manifestations as allergy and asthma increased significantly over the period between 1960 and 2000[1]. Many consider changes in diet to have played a causal role in this[2,3]. Sensitisation to allergens occurs early in life[4,5] and there is evidence that many infants are born already sensitised to common allergens[6,7]. Thus, if diet does play a role, then exposures *in utero* and in early infancy (for example, through breast milk) are likely to be important. Hypotheses linking early nutrient exposure with later disease centre around inadequate or inappropriate nutrition creating an environment that favours sensitisation to allergens through effects that influence T lymphocyte differentiation to the pro-allergic Th2-type phenotype[3]. These effects could be exerted at the level of dendritic cells and events surrounding antigen presentation or at the level of regulatory T cells[3]. Among the different 'diet hypotheses', one that has received much attention relates to early exposure to high amounts of *n*-6 fatty acids. This was first proposed by Black & Sharp[8] and by Hodge *et al.* [9] who argued that the period over which incidence and prevalence of childhood atopy (and so, most likely, allergic sensitisation) increased coincides with the period over which linoleic acid intake increased. The essence of this hypothesis is described in Fig. 1. While there is supporting data that atopic disease is most prevalent when linoleic acid intake is highest[10–16] and that the increase in linoleic acid intake preceded the increase in atopic disease prevalence[17], the hypothesis requires that a high early exposure to arachidonic acid be associated with disease. In fact, studies attempting to relate fatty acid exposures from maternal blood, umbilical cord blood, breast milk and children's blood to childhood atopic sensitisation or to disease manifestations rarely show a role for arachidonic acid[18]. An article in the current issue of the *British Journal of Nutrition* investigates this further[19]. In this study, data on early exposure to arachidonic acid is related to lung function, presence of atopy and circulating inflammatory markers in 280 7-year-old Dutch children. Early arachidonic acid exposure is determined as maternal and umbilical cord plasma and umbilical cord tissue arachidonic acid content. Atopy was assessed according to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire; confirmation by clinical assessment would have strengthened the study. Lung function was assessed as peak expiratory flow at rest and before and after maximal physical exercise. Inflammatory markers reported were leucocyte numbers and plasma concentrations of fibrinogen, C-reactive protein, leptin and von Willebrand factor. No true 'immune' parameters were measured, such as total or allergen-specific IgE concentrations, T cell reactivity to likely allergens, or T cell phenotypes according to cytokine profiling. Again this is a weakness of the study. Nevertheless, the study is a valuable contribution to the literature in this field since it is the first attempt to relate early arachidonic acid exposure, which is measured robustly, to lung function in childhood. The authors found very few associations between maternal or fetal arachidonic acid levels and the outcomes reported. Those associations that were significant were not mechanistically consistent with one another, explained only a very low proportion (usually $<3\%$) of the variation in outcome, and became less significant or non-significant after adjusting for covariables. Thus the findings from this study discount a role for early arachidonic acid exposure on lung function and atopy at 7 years of age. This is an important finding.

Is this the end of the 'Black and Sharp hypothesis'? I think not. Firstly the findings of Dirix *et al.* [19] require confirmation by others using suitable datasets. Secondly, these new findings, although important, do not rule out an effect of early arachidonic acid exposure on atopic sensitisation, since that was not assessed directly or sufficiently robustly, or on T cell maturation or phenotype, since these were not assessed at all. Thirdly, although the hypothesis is based upon a direct link between *n*-6 fatty acids and risk of atopy, an additional consideration is that supply of *n*-3 fatty acids is important, the thinking being that *n*-3 fatty acids act to oppose the action of *n*-6 fatty acids[3]. This aspect was not investigated by Dirix *et al.* [19]. However, there are more data supporting a link between low *n*-3 PUFA exposure and increased risk of atopic sensitisation and of atopic manifestations than there are data supporting a role for high *n*-6 PUFA exposure[18,20]. Furthermore, the potential for a protective effect of very-long-chain *n*-3 PUFA has been examined in intervention studies in pregnant and lactating women and in children. These studies demonstrate that increased intake of these fatty acids by pregnant women alters cytokine patterns in maternal and cord blood[21,22], alters cord blood cytokine production[23], and decreases atopic sensitisation and severity of atopic dermatitis at 1 year of age[23]. Furthermore, increased intake of very-long-chain *n*-3 PUFA by women during breast-feeding was associated with higher production of interferon-γ upon stimulation of whole blood from children aged 2·5 years[24]. These studies suggest short- and long-term immunological

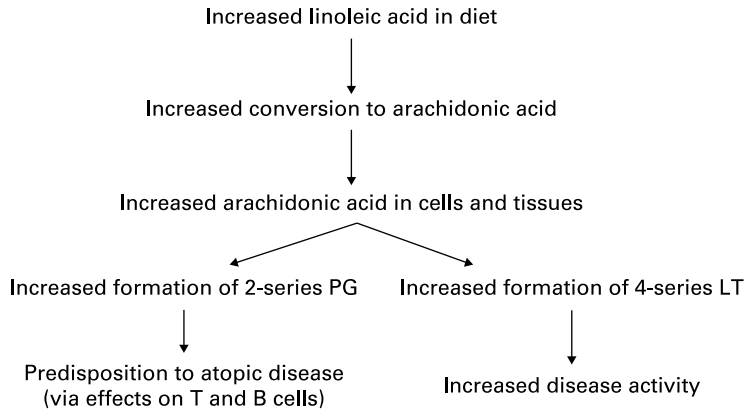

Fig. 1. Proposed causal link between high linoleic acid intake and increased risk of atopic sensitisation and disease manifestation. LT, leukotriene.

effects of maternal *n*-3 PUFA intake that might translate into reduced atopic disease sensitisation and severity in infants born to or suckled by those women. A study in infants given very-long-chain *n*-3 PUFA from the age of 6 months showed some protective effects on disease at 18 months and 3 years of age[25,26] but not at 5 years of age[27,28]. Taken together these data would suggest that a focus of attention onto low *n*-3 PUFA status and away from arachidonic acid exposure might be appropriate. The new data of Dirix *et al.* [19] support this conclusion, at least in part.

There is no conflict of interest.

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