Asthma is the most common chronic illness diagnosed in children. Despite the relatively steady trends in incidence observed in developed countries over the past 10 years [1], asthma remains one of the most frequent causes of hospital admissions in children, representing a major societal and public health concern [2]. The extensive body of epidemiological evidence examining the causes of asthma shows that this is a complex multifactorial disorder, with a combination of genetic, environmental and lifestyle-related factors involved in its causal pathway.

The possible modulating role of diet on the risk of childhood asthma has generated much scientific interest over the past two decades. Several components of diet contain multiple beneficial properties that could potentially contribute to the primary prevention of asthma. In particular, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are omega-3 (n-3 or ω-3) long-chain polyunsaturated fatty acids (LCPUFAs) located in the cell membranes, and which are present at high levels in fish and seafood, have been recognised for their anti-inflammatory properties, as well as for supporting development and maturation of the immune system [3]. Both EPA and DHA can serve as substrate for specialised pro-resolving mediators, an umbrella term for compounds with anti-inflammatory properties [4]. A higher availability of EPA and DHA in cell membranes leads to decreased availability of arachidonic acid and to increased competition for both the cyclooxygenase and lipoxygenase enzymes, resulting in decreased synthesis of arachidonic acid-derived eicosanoids [5]. This leads to a reduction in the synthesis of pro-inflammatory prostaglandins and leukotrienes, to a shift in the Th1/Th2 cytokine balance, and to reducing the production of immunoglobulin E, all of which are involved in the pathogenesis of asthma.

Due to the potential protective effect of these biological properties against asthma, the relationship of EPA and DHA intake with asthma risk has been widely studied in epidemiological studies [6], although a recent pooled analysis from 18 birth cohorts concluded that there was no consistent evidence of a protective effect of fish or seafood intake during pregnancy on asthma risk in children up to 8 years of age [7]. The lack of consistency of findings in observational studies was recently confirmed in another systematic review [8]. Evidence from randomised controlled trials (RCTs) using fish oil supplementation during pregnancy or lactation has shown that maternal intake of fish oil resulted in higher levels of omega-3 LCPUFAs in the offspring, reduction of pro-inflammatory cytokine production, and in a lower risk of allergenic food sensitisation the first year of life [8]. Furthermore, two RCTs from Denmark have shown that supplementation of pregnant women with omega-3 LCPUFAs can prevent asthma in the offspring. OLSEN et al. [9] investigated the long-term effect of supplementation with fish oil versus olive oil on adolescent asthma risk using health registry-based linkage. The study was a follow-up analysis of an RCT during pregnancy, originally conducted to test whether the intervention reduced premature birth. It showed that children of mothers who had received fish oil had a reduced risk of incident asthma up to age.
16 years, compared to those whose mothers were supplemented with olive oil (hazard ratio 0.37, 95% CI 0.15–0.92). This effect was observed regardless of the baseline fish intake of the mother at the time of randomisation. More recently, BISGAARD et al. [10] confirmed that fish oil supplementation, compared to olive oil supplementation, in pregnancy reduced the incidence of persistent wheeze/asthma in the offspring up to 5 years of age.

What about omega-3 intake in childhood? Most cohort studies investigating the association of omega-3 LCPUFAs and asthma have focused on maternal or infant exposure, and short-term incidence during early childhood, with very little epidemiological evidence from studies examining dietary omega-3 intake in mid-childhood and the risk of asthma in adolescence. Although less frequently diagnosed than in early childhood, asthma onset during puberty represents a major challenge to the quality of life of youngsters [11]. Its risk has been associated with a number of environmental, early-life and hormonal risk factors, including low birthweight, early airway obstruction and early pubertal maturation [12–14]. An analysis from the Swedish BAMSE birth cohort study found no evidence that early life (year 1) or mid-childhood intake of fish was associated with asthma at puberty (age 12 years), although intake of omega-3 LCPUFAs was not studied [15].

The longitudinal study by TALAEI et al. [16] in the current issue of the European Respiratory Journal helps to fill the scientific gap in our understanding of the relationship of EPA and DHA intake in childhood and subsequent asthma incidence in adolescence. Analysing data from 4543 children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC), the authors investigated the longitudinal association of EPA and DHA intake from fish, measured using a food frequency questionnaire at approximately 4.5 and 7 years of age, and incidence of asthma at age 11 or 14 years. Current doctor-diagnosed asthma was defined at three time-points, namely 7.5, 11 and 14 years of age. Asthma incidence at 11 and 14 years of age was defined amongst children who at age 7.5 years were not identified as having current doctor-diagnosed asthma. To strengthen causal inference, the authors explored whether the associations of EPA and DHA intake from fish with asthma incidence were modified by a common fatty acid desaturase (FADS) gene variant, a representative single nucleotide polymorphism (SNP) of FADS2, namely rs1535. FADS genes encode the enzymes catalysing the endogenous conversion of upstream fatty acids into EPA and DHA and into arachidonic acid (an omega-6 LCPUFA). The rationale for investigating this gene–nutrient interaction, *a priori*, was that carriers of the minor G allele of rs1535 are known to have lower plasma EPA and DHA concentrations [17, 18]. The authors therefore predicted that G allele carriers (over half of the children in this cohort) would derive greater benefit from a higher dietary intake of omega-3 fatty acids. This same polymorphism had previously been shown to modify the effect of prenatal fish oil supplementation on risk of offspring wheeze/asthma [10].

Interestingly, TALAEI et al. [16] found no evidence of association between intake of EPA and DHA from fish at 7 years of age and subsequent asthma incidence in the cohort overall. However, when stratifying the analyses by the child’s FADS genotype, a higher intake of these fatty acids was associated with a lower risk of incident asthma in G allele carriers, but not in those who were homozygous for the A allele. The effect size was large: a halving of the odds ratio comparing top versus bottom quartile of EPA plus DHA intake in those carrying the G allele. This association became stronger when the authors compared children who had consistently high, versus consistently low, intake at both 4 and 7 years of age. These statistically significant gene–nutrient interactions were then replicated in an independent Swedish birth cohort (BAMSE). Importantly, these associations were not confounded by maternal EPA and DHA intake during pregnancy.

Whilst the observational nature of these findings means that we cannot be certain that they represent a causal effect, TALAEI et al. [16] went to considerable lengths to adjust for potential confounders and to test the robustness of the findings through various sensitivity analyses. Importantly, they confirmed a biologically plausible gene–nutrient interaction and replicated this in an independent cohort, thus ruling out chance as an explanation for the main finding, and greatly strengthening causal inference. Most gene–environment interactions reported in the asthma literature have not been replicated, let alone in the same paper. At present, strategies for the primary prevention of asthma are lacking [19]. These latest findings suggest that improving diet in mid-childhood may not be too late to reduce asthma risk in adolescence, and that in the future, adoption of a personalised prevention approach, informed by genotype, may enable such intervention to achieve maximum benefit.

Conflict of interest: V. Garcia-Larsen has nothing to disclose.
References

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