Plasma Fatty Acid Patterns

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Fatty acids might play a role in asthma and allergy development as they can modulate immune responses. Results from this population-based cohort study among 4260 mother-child pairs showed that a maternal pattern of high n-6 PUFA concentrations in pregnancy was associated with a higher forced expiratory volume in 1 s/forced vital capacity and forced expiratory flow after exhaling 75% of forced vital capacity in the children at the age of 10 years. No associations of maternal fatty acid patterns with a child's asthma or allergy outcomes were observed.

Keywords: fatty acids ; child ; inhalant allergic sensitization and allergy ; pulmonary function ; prospective cohort study

1. Introduction

Maternal diet during pregnancy has been related to respiratory and allergy outcomes in childhood [1]. Among many dietary factors, fatty acids may play an important role as they can modulate immune responses and might thereby influence the development of asthma and related diseases. It has been hypothesized that omega-6 (n-6) PUFAs (polyunsaturated fatty acids) stimulate the production of pro-inflammatory metabolites, including prostaglandins, thromboxanes, and leukotrienes, leading to allergic inflammation, whereas omega-3 (n-3) PUFAs can inhibit inflammation [2][3]. However, more recent studies suggest that the inflammatory effects of n-6 and n-3 PUFAs might differ between individual fatty acids and not be the same in all tissues [4]. Less emphasis has been put on saturated fatty acids (SFA) and monounsaturated fatty acids (MUFA), which might also have immunomodulating properties [5]. Previous intervention and observational studies have mainly focused on maternal PUFAs in relation to a child's respiratory and allergy outcomes and provided inconsistent results [6][7][8][9][10]. A randomized controlled trial has shown that maternal supplementation with n-3 PUFAs during the third trimester of pregnancy reduces the risk of persistent wheeze or asthma in the children in the first 5 years of life with 7 percentage points, as compared to children of mothers in the control group, but has no effect on allergic sensitization [6]. We previously observed that higher total maternal n-6 PUFA concentrations during pregnancy were associated with a lower risk of asthma but not with airway inflammation [7]. Other observational studies have not found an association of maternal PUFA concentrations during pregnancy with asthma, lung function, or allergic sensitization in children [8][9][10]. However, these studies have been mainly performed among children in early childhood, while symptoms may arise at later ages. Furthermore, fatty acids interrelate with each other, and these synergistic or additive effects may be missed by previous studies that have examined fatty acids individually or in groups [11]. We aimed to overcome this by using fatty acid patterns, as this approach takes interrelations into account [12].

Therefore, our aim was to examine among 4260 children and their mothers participating in a population-based cohort study the associations of maternal plasma fatty acids patterns during pregnancy with a child's lung function, asthma, inhalant allergic sensitization, and physician-diagnosed inhalant allergy at school-age.

2. Discussion

In this population-based prospective cohort study, we observed that a fatty acid pattern characterized by high concentrations of maternal n-6 PUFAs in pregnancy was associated with a higher FEV_1/FVC and FEF_{75} in the children aged 10 years. Patterns characterized by high concentrations of most of the MUFAs or high concentrations of n-3 PUFAs were not consistently associated with a child's lung function. We did not observe any associations of maternal fatty acid patterns with asthma or allergy outcomes in the children at school-age.

2.1. Comparison with Previous Studies

Only a single previous study examined the associations of maternal PUFA concentrations during pregnancy with a child's lung function as measured by spirometry, showing no association of maternal PUFA concentrations during pregnancy with FEV_1 in 6-year-old children, but other lung function outcomes were not taken into consideration [8]. We previously observed in younger children that higher maternal γ-linolenic acid (18:3n-6) and dihomo-γ-linolenic acid (20:3n-6)

concentrations, both n-6 PUFAs, in pregnancy were associated with a lower airway resistance in the children at the age of 6 years, as measured by interrupter technique (Rint) [7]. We now additionally showed that a higher 'high n-6 PUFA' pattern during pregnancy, which includes both γ-linolenic acid and dihomo-γ-linolenic acid with high positive loadings, was associated with a better lung function at the age of 10 years, as reflected by FEV_1/FVC and FEF_{75}, which are more robust markers of airway obstruction.

Like most previous cohort studies on maternal fatty acid concentrations and an individual participant meta-analysis on the maternal intake of fish, being the main source of n-3 PUFAs, we did not find associations of maternal n-3 or n-6 PUFA's during pregnancy with asthma, inhalant allergic sensitization, or physician-diagnosed inhalant allergy [8][9][10][13]. However, we previously observed in our cohort that a higher maternal total n-6 PUFA concentration was associated with a lower risk of asthma, whereas we did not find an association of a 'high n-6 PUFA' pattern with asthma in the current study [7]. Differences might be due to assessment of PUFAs in groups versus patterns, or the age at which asthma was assessed, as at a younger age it is difficult to distinguish asthma from a viral-induced wheeze. A recent literature-based meta-analysis of randomized controlled trials mainly included studies with a follow-up until infancy and did not find a beneficial effect of n-3 PUFA supplementation in pregnancy on wheezing or asthma in the children [14]. Randomized controlled trials with a longer follow-up until school-age or young adulthood suggested that prenatal n-3 PUFA supplementation reduced the risk of asthma, although no consistent effect on lung function or allergy development was observed [6][15][16][17]. The beneficial effect of high-dose n-3 PUFA supplementation on asthma was the strongest in children of mothers with the lowest n-3 PUFA concentrations. Fish intake in The Netherlands and in the Generation R cohort is relatively low compared to other European countries [13][18]. It might be that the range of n-3 PUFA concentrations was too narrow in our cohort to detect a beneficial effect of higher maternal n-3 PUFA concentrations on a child's asthma. Another explanation for the inconsistent results might be that the intervention trials were mainly performed in late pregnancy, whereas we assessed maternal n-3 PUFA concentrations in mid-pregnancy.

To our best knowledge, no previous studies examined the associations of maternal SFA and MUFA concentrations with a child's respiratory or allergy outcomes at school-age. Although one study in Japanese mothers did not find an association of SFA or MUFA intake estimated from a questionnaire in pregnancy with wheezing at preschool age [19]. More studies on the effect of patterns of maternal PUFA, SFA, and MUFA concentrations at different time-points in pregnancy with a child's respiratory and allergy outcomes at older ages are needed.

2.2. Interpretation of the Results

The observation of an association between high n-6 PUFA and better lung function at 10 years might be related to the immunological effects of a 'high n-6 PUFA' pattern. Arachidonic acid (20:4n-6), an important component in this pattern, can be converted into metabolites, including prostaglandin E2 (PGE_2) [2]. Although PGE_2 might enhance allergic inflammation, it seems to have an opposing and anti-inflammatory effect in the airway system [3]. Airway epithelium and smooth muscle are the main producers of PGE_2, and PGE_2 reduces bronchoconstriction, relaxes airway smooth muscle, and inhibits the recruitment of inflammatory cells and mast cell mediators [20][21]. These effects might contribute to a higher FEV_1/FVC ratio and FEF_{75}. The fatty acid metabolism and, consequently, the production of metabolites, including PGE_2, might depend on genetic factors and differ between mothers or children with and without a history of atopic diseases [22]. However, although some *p*-values for interaction were significant, we did not observe differences in results among groups after stratification. We therefore considered that interaction between maternal ethnic background, maternal asthma or atopy, child's sex, and child's asthma or allergy and fatty acid patterns on the associations with lung function was minimally present. N-3 PUFAs might inhibit fetal T-helper 2 (Th2) responses through effects on the expression of genes and the production of pro-inflammatory eicosanoids, thereby lowering the risk of asthma and allergy [23]. During pregnancy, docosahexaenoic acid (22:6n-3) concentrations, one of the main n-3 PUFAs, increase until 18 weeks of gestation through mobilization from maternal stores, but concentrations decline to a deficiency in the third trimester [24]. This might explain the different observations between the randomized controlled trials in the third trimester and our study in mid-pregnancy.

The 'MUFA and SFA' pattern was characterized by high positive loadings of most of the MUFAs and of the SFAs—myristic acid (14:0) and palmitic acid (16:0)—but high negative loadings of the SFAs—margaric acid (17:0) and stearic acid (18:0). Different SFAs and MUFAs, such as palmitic acid and oleic acid, might have opposite inflammatory effects, which might explain a lack of association of this pattern with respiratory or allergy outcomes [25]. Furthermore, although PUFAs are transferred over the placenta, the fetus might synthesize MUFAs and SFAs de novo from glucose [26]. Maternal MUFA and SFA concentrations might, therefore, not fully reflect the fetal status of these fatty acids.

Despite the small effect estimates and absence of an association with clinical disease, our findings might be of importance from a developmental and population perspective. Fatty acid concentrations might partly depend on genetic and metabolic influences, although maternal diet might also play a role as 7.5% of the variation in the fatty acid patterns in our population was explained by differences in food intake [12]. Our results, therefore, suggest that future intervention studies should explore, in addition to the intake of maternal n-3 PUFAs, the intake of n-6 PUFAs and the interrelation between the different PUFA's, as well as the role of genetic and metabolic influences in relation to respiratory and allergy outcomes in the children later in life.

3. Conclusions

A maternal fatty acid pattern characterized by high levels of n-6 PUFAs in mid-pregnancy was associated with a better lung function, especially a higher FEV_1/FVC ratio and FEF_{75}, in school-aged children. We did not find consistent associations of fatty acid patterns with asthma or allergy outcomes. Future studies on the causality and clinical implications of the relation of a pattern of high n-6 PUFA concentrations in pregnancy with a better lung function in school-aged children are needed.

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