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Maternal active asthma in pregnancy influences associations between polyunsaturated fatty acid intake and child asthma

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Abstract

Background: Studies examining effects of prenatal polyunsaturated fatty acid (PUFA) intake on childhood asthma show mixed results. Inconsistencies may result from not accounting for important modifying factors such as maternal asthma or child sex. Objective: To examine whether associations between prenatal PUFA intake and childhood asthma are modified by prenatal active maternal asthma or child sex in 412 mother-child dyads.

Methods: Energy-adjusted prenatal dietary and supplement intakes of omega-3 (n-3) and omega-6 (n-6) PUFAs were estimated using the Block98 Food Frequency Questionnaire, administered during pregnancy. Mothers reported asthma in children followed prospectively to 4.0±1.7 years. Generalized additive models with smooth terms for PUFA (n-3, n-6, n-6/n-3 ratio) effects were used to investigate associations between PUFAs and child asthma, without prespecifying the form of these relationships, including effect modification by active maternal asthma or child sex.

Results: Among mothers (40% black, 31% Hispanic), 22% had active asthma in pregnancy; 17.5% of children developed asthma. Lower maternal n-3-PUFA intake was significantly associated with risk of childhood asthma (p-value(p)=0.03), in particular among children of

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mothers with active asthma and low n-3- PUFA intake(p=0.01). This inverse association was more apparent in girls (p=0.01) compared to boys (p=0.30), regardless of maternal asthma status. For n-6-PUFA and the n6/n3 ratio, there was a lower risk of childhood asthma in the mid-range of intake and increased risk at higher intake (n-6-PUFA p=0.10, n6/n3 ratio p=0.13).

Conclusion: Consideration of factors that modify effects of prenatal PUFA intake on childhood asthma has implications for designing intervention strategies tailored to impact those at greatest risk.

Keywords

Polyunsaturated fatty acid; prenatal; maternal active asthma; childhood asthma; sex-specific effects; Developmental Origins of Health and Disease

INTRODUCTION

Asthma is a leading cause of morbidity across the lifecourse[1, 2] and disproportionately affects children living in economically disadvantaged and underserved communities[3]. It is important to identify modifiable factors in critical windows of development to inform prevention strategies that can be targeted toward those most likely to benefit. Asthma has origins *in utero*[4], and maternal intake of a range of micronutrients during fetal development is thought to play a role in early asthma programming[5–8].

Maternal long-chain polyunsaturated fatty acid (PUFA) intake in pregnancy has been reported to have associations with child asthma, with plausible mechanisms including impacts on oxidative stress and immune disruption contributing to asthma programming (e.g., imbalance of Th1/Th2 responses). PUFAs are thought to influence asthma development and symptoms via effects on systemic inflammation, cytokine release, oxidation, and microbial composition[9]. The most widely studied PUFAs are omega-6 (e.g. *n-6*; linoleic acid) and omega-3 (e.g. *n-3*; alpha-linoleic acid). Omega-6 PUFAs, primarily derived from vegetable oils, are metabolized into arachidonic acid which is further metabolized into pro-inflammatory mediators (e.g., eicosanoids, thromboxanes, leukotrienes, prostaglandins). Omega-3 PUFAs, primarily derived from fish, seafood, nuts, seeds, and marine and plant oils, are the major dietary sources of eicosapentaenoic acid and docosahexaenoic acid which have anti-inflammatory properties[10, 11]. Over time, dietary patterns have changed, with an increase in intake of pro-inflammatory *n-6* PUFAs relative to *n-3* PUFAs[12] from an equal balance (1:1) to as high as 30:1 in some Western cultures[13]. Changing patterns in PUFA intake have paralleled increases in asthma prevalence[12, 14, 15].

Benefits of higher prenatal *n-3* PUFAs on childhood asthma risk have been demonstrated in some observational[11, 16, 17] and interventional studies[18–20], however, findings are mixed, with others reporting borderline or null results[21–23]. Similarly, while some studies link increased prenatal *n-6* PUFA intake to childhood asthma risk, results are inconsistent[7, 11, 22, 23].

These disparate findings may in part be explained by lack of consideration of factors that modify the association between prenatal PUFA intake and offspring asthma[24]. It

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is established that children born to mothers with active asthma in pregnancy are at particular risk of developing asthma[25–28], and that improved prenatal asthma management is protective[29]. However, no study has specifically considered active asthma in pregnancy as a modifier of the relationship between maternal PUFA intake and children's asthma risk. In addition, sex-specific differences in fatty acid metabolism[30] and in susceptibility to exposures *in utero* that impact asthma development[7, 31–33], are documented.

The aim of these analyses was to examine whether associations between prenatal PUFA intake (*n-3* PUFA, *n-6* PUFA and *n-6*/*n-3* ratio) and child asthma are modified by maternal prenatal active asthma or child sex. We hypothesized that lower prenatal *n-3* PUFA intake and higher *n-6* intake would be associated with childhood asthma and that these associations would be greatest in children born to mothers with prenatal active asthma. While we hypothesized sex-specific effects, we had no *a priori* hypothesis regarding whether boys or girls would be more impacted.

METHODS

Sample

Participants were from the PRogramming of Intergenerational Stress Mechanisms (PRISM) pregnancy cohort, designed to examine associations between stress and other environmental exposures on child development. This study recruited n=938 women receiving prenatal care from the Beth Israel Deaconess Medical Center and East Boston Neighborhood Health Center in Boston, MA (from March 2011-December 2013) and Mount Sinai Hospital in New York City, NY (from April 2013-March 2019). Eligibility criteria included English- or Spanish-speaking, ≥18 years of age, and single gestation pregnancy. Exclusions included maternal intake of ≥7 alcoholic drinks/week prior to pregnancy recognition or any after pregnancy recognition, and congenital abnormalities that could impact participation. Ascertainment of dietary data was added after study initiation. Analyses include n=412 mother-child dyads recruited at mean standard deviation (SD): 22.2±9.1 weeks gestation with data on prenatal PUFA intake, active maternal asthma in pregnancy and child asthma. Procedures were approved by the relevant institutions' human studies committees; mothers provided written consent in their primary language.

Prenatal PUFA Intake

In the second trimester, women reported dietary and supplement intake over the prior three months via the semiquantitative Block98 Food Frequency Questionnaire (FFQ) administered in English and Spanish[34, 35]. The food list, based on the National Health and Nutrition Examination Survey III dietary recall, was modified to include a more extensive list of fish and seafood. For each food/beverage item, women were asked how often (rarely/never, daily, weekly, monthly) and how much (small, medium or large serving with portion size pictures provided) was consumed. Women also reported type and frequency of vitamins and other dietary supplements taken during pregnancy. Notably, US adults' intake of omega-3 are higher from dietary supplements than from foods[36]. FFQ intake was validated in this sample using 24-hour recalls[37].

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FFQ data were processed as previously described[37] and intake of *n-6*- and *n-3*-PUFA was calculated using methods described by Willett et al[38]. The usual dietary intake of PUFAs was estimated by using USDA food-composition tables. We calculated total *n-6* PUFA by combining total daily intake of linoleic acid and arachidonic acid, and total marine-derived *n-3* PUFAs by combining eicosopentanoic acid (EPA), docosapentanoic acid (DPA), and docosahexaenoic acid (DHA). We adjusted *n-3* and *n-6* PUFA levels for total energy intake using the residual method[38]. To use the residual method, we used expected dietary PUFA intake for the mean energy intake of the sample as a constant. We then added the mean dietary PUFA intake of the sample to the residual. The residual was derived from the regression of PUFA intake on total energy intake using the self-reported total energy intake[38] derived from the FFQ. We then added supplemental PUFA intakes to energy-adjusted dietary PUFA intakes to provide total energy-adjusted intakes for *n-3* and *n-6* PUFAs. The *n-6*/*n-3* ratio was calculated by dividing energy-adjusted *n-6* PUFAs by energy-adjusted *n-3* PUFAs.

Child asthma

Mothers were asked about their child's respiratory health at follow-up visits through telephone and face-to-face interviews at approximately 4-month intervals for the first 30 months, then annually. Child's asthma status was determined based on an affirmative response to: "Has your child ever had asthma [since birth]?", "Has a doctor or other healthcare provider ever said that your baby had asthma", "Does your baby currently take medicine for his/her asthma?" or "Has your baby been hospitalized overnight for asthma [since birth]?".

Maternal Active Asthma in Pregnancy

Maternal asthma history was classified based on an affirmative response to "Have you ever had asthma?" and/or "Have you ever gone to an emergency room/urgent care clinic for treatment of an asthma attack?" or "Have you ever been hospitalized overnight for asthma?". Maternal active asthma during pregnancy was defined as mothers with a history of asthma who answered yes to "Do you still have asthma?" during any prenatal visit, or those reporting at least one of the following within the past year: emergency visit or hospitalization for asthma, asthma symptoms (wheezing, shortness of breath, cough, chest tightness, nighttime awakenings due to asthma) and/or use of asthma medications (albuterol, inhaled corticosteroids, inhaled long-acting beta agonist-corticosteroid combination medications, oral steroids or leukotriene inhibitors).

Other Covariates

Mothers reported date of birth, race/ethnicity (white/Hispanic, black/black-Hispanic, Hispanic/non-black and other), education (low[high school or less] vs high[some college or above]) and pre-pregnancy height and weight; child sex was obtained from the medical record at birth. Pre-pregnancy body mass index (BMI) was calculated as weight(kg) divided by height(m) squared. Prenatal maternal smoking was affirmative if a mother reported smoking at any time during pregnancy in any prenatal visits and/or postnatal recalls. Prenatal secondhand smoke exposure was affirmative if a mother reported that she lived

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with any current smokers or had exposure to secondhand smoke for more than 1 hour per week at home, work or in restaurants during pregnancy.

Analysis

We examined the distribution of sample characteristics overall, by maternal active asthma status, and by child sex. Comparisons across groups were examined using the Wilcoxon rank sum and Chi-square tests for continuous and categorical variables, respectively. Given that extreme values can be more influential in GAMs than traditional regression models, extreme PUFA values (<1st percentile and >99th percentile) were winsorized *a priori* to reduce the impact of potentially spurious outliers while retaining the full sample size[39]. We determined the Spearman's correlation coefficient for *n-6* and *n-3* PUFA intake. We assessed the exposure-response relationships between PUFA intake (*n-3*, *n-6* and *n-6*/*n-3* ratio, considered separately) and child asthma using generalized additive models (GAMs) with a logit link (i.e. additive logistic regression). We used smooth penalized spline terms for PUFA intake to assess for the (potential nonlinear form of these) associations[40]. For multivariable-adjusted models, we considered covariates linked to both PUFA intake and asthma in previous research but not on the causal pathway. We formulated a Directed Acyclic Graph (eFigure 1, generated using DAGitty v3.0[41], available at:http://www.dagitty.net/) to determine the minimal sufficient adjustment set; this included maternal age, race/ethnicity, education, and pre-pregnancy BMI. Prenatal tobacco smoke exposures were considered in sensitivity analyses. In addition, models for *n-6* PUFAs are adjusted for *n-3* PUFA intake and models for *n-3* PUFAs are adjusted for *n-6* PUFA intake in primary analyses. Since intakes of *n-6* and *n-3* PUFAs were correlated (Spearman correlation coefficient=0.77, p<0.001) which may lead to unstable estimates in GAMs due to co-linearity or concurvity, we conducted sensitivity analyses considering each micronutrient (*n-6* and *n-3* PUFAs) separately without adjusting for the other. To examine effect modification on the association between prenatal PUFA intake and child asthma, we then stratified models by maternal active asthma status (active asthma vs no asthma history or prior asthma history that was not clinically active during the index pregnancy) or child sex. Effect modification by maternal active asthma status or child sex was also examined using factor-smooth interaction GAMs. In secondary analyses, we stratified by the combination of maternal asthma and child sex. Analyses were conducted using SAS (version 9.4; SAS Institute, Inc., Cary, NC) and R (version 3.5.1, 'mgcv' package; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Table I delineates sample characteristics. Women were primarily ethnic minorities (40.1% black, 31.3% Hispanic), 32.8% reported a high school education or less, and 22.1% had active asthma during pregnancy. Mothers with active asthma were more likely younger (median=28.1 vs 30.7 years, p=0.006) and black (56.0% vs 35.5%, p<0.001), and had a higher BMI (median=27.0 vs 23.9 mg/kg^2, p<0.001), compared to those without active asthma.

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Children were followed through age 4.0±1.7 years; there was no difference in duration of follow-up by maternal asthma status (p=0.21) and no difference in maximum follow-up length (6.8 vs 6.9 years, respectively). Seventy-two (17.5%) children had asthma, with a median age at initial report of 3.5 (1.6–4.9) years. A higher proportion of boys had asthma (boys:20.5% vs girls:14.2%, p=0.10). Mothers with active asthma had lower *n-3* PUFA intake (median=1.9 vs 2.0 g/day, p=0.03) and higher *n-6*/*n-3* ratio (median=8.2 vs 7.8, p=0.04) compared to those without active asthma; there was no difference in *n-6* intake by maternal asthma status (p=0.21). Examination of the proportion of children developing asthma based on tertiles of *n-3* PUFA (from lowest to highest tertiles:21.1%, 13.8%, and 17.5%) and *n-6* PUFA intake (from lowest to highest tertile:16.1%, 12.3%, and 24.1%), suggested non-linear associations. Maternal PUFA intakes were similar by offspring sex (all p>0.10).

Main Effects

We report associations between prenatal PUFA intakes and child asthma in the overall sample. In Figures 1–4, significant associations between PUFA intake and child asthma are demonstrated at the PUFA levels where the estimated pointwise 95% CI (shaded area) does not include zero. In Figure 1, the *n-3* PUFA intake was most significantly associated with higher log odds of childhood asthma at the lowest level of *n-3* intake (p-value of spline curve=0.03). For prenatal *n-6* PUFA intake, there was a protective effect on child asthma in the mid-range of intake, while an increased risk of child asthma was shown at higher intake and suggested at lowest intakes; a similar U-shaped pattern was seen for associations between *n-6*/*n-3* ratio and child asthma. However, the spline curves for *n-6* PUFA and *n-6*/*n-3* ratio did not reach statistical significance (p=0.10 and 0.13, respectively).

Effect Modification by Maternal Active Asthma or Child Sex

Maternal active asthma in pregnancy: We evaluated risk of childhood asthma across the continuum of maternal PUFA intakes by maternal active asthma status (Figure 2). Low *n-3* PUFA intake was more strongly associated with asthma in children born to mothers with active asthma (p-value=0.01) compared to non-active asthma (p-value=0.27). Higher prenatal *n-6* intake was more strongly associated with asthma in children of mothers with active asthma during pregnancy (p-value=0.04 for active asthma vs. p=0.8 for non-active asthma). Similarly, women with higher *n-6*/*n-3* ratios were more likely to have children who developed asthma, although it did not reach statistical significance in the stratified model for children born to mothers with active asthma (p-value=0.08). Results from factor-smooth interaction GAMs reinforced the fact that maternal active asthma status during pregnancy modifies the association between prenatal PUFA indicators and child asthma (eFigure 2a) given that the 95% CI's of the difference between curves for those with and without maternal active asthma did not uniformly contain zero.

Child sex: In models stratified by sex, associations between prenatal *n-3* and *n-6* PUFA intake and child asthma appeared to be stronger in girls compared to boys (Figure 3). The inverse association between *n-3* PUFA intake and child asthma was more apparent in girls (curve p-value=0.01) compared to boys (p=0.30). For *n-6* PUFA intake, the U-shape association was more apparent in girls (p-value=0.03), where there was a protective effect on

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child asthma in the mid-range of intake and increased risk of child asthma at higher intake and suggested at lowest intakes, compared to boys (p=0.63). Similarly, among girls, higher levels of *n-6*/*n-3* ratio were associated with increased risk of child asthma; however, we did not find statistically significant associations for the smoothed associations of the *n-6*/*n-3* ratio with child asthma (p=0.16 for girls, p=0.43 for boys). Results from factor-smooth interaction GAMs suggested that child sex was an effect modifier of the relationship between prenatal *n-3* PUFA intake and child asthma, but not for relationships of prenatal *n-6* PUFA or the *n-6*/*n-3* ratio with child asthma (eFigure 2b).

Exploratory Analyses

We next evaluated associations between *n-3* PUFAs and risk of childhood asthma stratified by both maternal active asthma status and child sex (Figure 4). Among girls born to mothers without active asthma, lower *n-3* PUFA intake was significantly associated with higher risk of asthma (p-value=0.04). A similar relationship, both in pattern and magnitude of association, was observed among girls born to mothers with active asthma, although associations did not reach statistical significance (p-value=0.08). Associations between *n-3* PUFA and child asthma in boys born to mothers with and without active asthma were not significant (p-value=0.12 and 0.59, respectively). Smooth effect estimates of the relationships of prenatal *n-6* PUFA intake and *n-6*/*n-3* ratio with log odds of children's asthma, stratified by maternal asthma status and child sex, are provided in the online supplement (eFigure 3). No significant differences were evident (p-values>0.1 for all spline curves). Results of the sensitivity analysis for the *n-3* PUFA model not adjusted for *n-6* PUFA intake were unchanged, while the *n-6* PUFA model not adjusted for *n-3* PUFA intake was similar, with a slightly attenuated effect at the higher *n-6* level. Sensitivity analyses including prenatal maternal smoking and secondhand smoke exposure *in utero* did not substantively change our findings (data not shown).

DISCUSSION

These analyses support our primary hypothesis, that mothers with lower *n-3* and higher *n-6* PUFA intakes prenatally were more likely to have children diagnosed with asthma. As posited, the association was stronger in children born to mothers with prenatal active asthma. Finally, when we further examined sex-specific differences, low maternal prenatal *n-3* intake was most strongly associated with risk of asthma among girls. Identification of these modifying factors can guide interpretation of future observational studies, identify subgroups most likely to benefit in clinical trials, and direct research to elucidate underlying mechanisms of asthma programming *in utero*.

Ours is the first study to consider maternal prenatal active asthma as a modifier of associations between prenatal PUFA intake and asthma in early childhood. Maternal asthma history is more strongly associated with offspring asthma than paternal history, in particular for asthma diagnosed before age 5 years[33, 42]. Further, active asthma[28] and asthma severity and control during pregnancy contribute to asthma risk in the developing child[25, 26, 29]. In a case-control study, moderate-to-severe uncontrolled asthma during pregnancy was associated with a 27% higher risk of offspring asthma compared to mild

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controlled asthma[25]. A large prospective population-based registry study (n~7000) found an increased risk of early-onset persistent asthma in children born to mothers with asthma in pregnancy categorized as mild uncontrolled (Prevalence Ratio (PR)=1.19, 95% CI=1.05–1.35), moderate-to-severe controlled (PR=1.33, 95% CI=1.09–1.63), and moderate-to-severe uncontrolled (PR=1.37, 95% CI=1.17–1.61) relative to mild controlled asthma [26]. A randomized controlled trial demonstrated that improved prenatal maternal asthma control was associated with reduced risk of offspring asthma at age 4–6 years[29]. More active, uncontrolled asthma is associated with a shift in inflammatory mediators toward a Th2-dominated inflammatory milieu (reviewed in [6, 21]) which may work in concert with higher intake of pro-inflammatory *n-6* PUFAs and lower intake of more anti-inflammatory *n-3* PUFAs to impact asthma risk in the developing fetus. Future research is needed to directly investigate mechanistic pathways.

Two prior studies report differences in the association between prenatal PUFA intake and offspring asthma by maternal asthma history, but neither considered active prenatal asthma. In a Southern US birth cohort comprised primarily of lower income African Americans, higher prenatal plasma levels of *n-6* PUFAs were associated with increased asthma in 4 to 6 year olds born to women with a history of asthma[7]. In a pooled analysis of 18 birth cohorts (European and US), Stratakis *et al.*[43] reported that higher cord blood *n-3* PUFAs were protective against asthma in preschool-aged children with no parental history of asthma or hay fever[43]. Differences in sample composition and inclusion of asthma history, rather than active prenatal asthma, may contribute to the discrepancy with our findings. Notably, we observed that lower prenatal *n-3* PUFA intake was associated with increased risk of child asthma however only at the lowest levels of *n-3* PUFA intake. Similarly, the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) trial, which randomized pregnant mothers (26% with asthma history) to *n-3* PUFA supplementation or placebo, found that the risk of offspring wheeze or asthma by age 3–5 years was lower in the intervention group, with the strongest beneficial effect among mothers with baseline *n-3* PUFA levels in the lowest tertile[18].

While relationships between *n-3* PUFA intake were more linear, associations between *n-6* intake and the *n-6*/*n-3* ratio and child asthma were U-shaped. Specifically, mid-range prenatal *n-6* PUFA intake was associated with reduced odds of asthma in children, but as *n-6* PUFA intake and *n-6*/*n-3* ratios increased, intake was associated with increased odds of asthma in children. Effects were again most evident among children born to mothers with active prenatal asthma. There are prior reports of non-linear relationships between PUFAs and diseases[44, 45], including a prospective cohort study in Sweden reporting non-linear (inverse J-shaped) associations between *n-6* PUFA levels measured at age 8 years and subsequent asthma[46]. While factors contributing to non-linear effects remain unclear, they may reflect underlying biologic factors or interactions with intake of other nutrients[47].

We observed sex-specific differences, with low maternal *n-3* PUFA intake most strongly associated with asthma risk in girls. Sex-specific differences in associations between PUFAs, maternal asthma, and childhood asthma development may be driven by underlying differences in lung development, sex hormones (e.g., estrogen), and fatty acids metabolism[48–51]. In the primarily African American population referenced above, Rosa *et*

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al. also observed sex-specific effects, but found the highest risk among boys born to mothers with ever asthma and a higher *n-6*/*n-3* ratio[7]. The differing sociodemographic makeup, as well as consideration of ever asthma rather than active prenatal asthma, may contribute to the variable findings. Notably, prior work shows sex-specific differences in fetal growth[52] and placental gene expression[53] in pregnancies complicated by asthma, with girls being more impacted. In placental tissue from pregnancies complicated by asthma, Osei-Kumeh and colleagues[53] found 65 differentially expressed genes involved in growth, inflammation and immune function, of which 6 genes were altered in male placentas and 59 genes in female placentas. These and other fundamental molecular mechanisms operating through the sexually dimorphic placenta should be explored in future studies.

We acknowledge both strengths and some weaknesses. We leveraged a racially/ethnically diverse urban sample and considered active asthma during pregnancy. Prenatal PUFA intake was measured via an FFQ, a validated and widely used tool ~~to~~ assess average dietary intake over time, including prenatally. Notably, the FFQ was validated in our study population through 24-hour dietary recalls[37] and incorporates PUFA intake from both dietary sources and supplement use, an important contributor to total PUFA intake[36]. Moreover, because PUFA intake and maternal asthma status were reported during pregnancy, prior to the outcome of interest, we expect any misclassification to be non-differential. In addition, we used GAMs, which provided flexibility to investigate non-linear, and perhaps more biologically relevant, relationships.

It is also worth noting some limitations. We were unable to consider timing in gestation of reported PUFA intake because the FFQ was completed in the second trimester of pregnancy. However, intake has been shown to be stable prior to and across pregnancy[54]. Childhood asthma is self-reported which introduces the possibility of differential misclassification; however, our data does not support this. If mothers with asthma were more likely to recognize symptoms, seek care, and report asthma diagnosis in their children at an earlier age, we would expect children of women with asthma to have an earlier age at asthma diagnosis. However, in this study, asthma was diagnosed at an older age in children of mothers with active asthma in pregnancy. Unfortunately, we were unable to evaluate more detailed characteristics of maternal and child asthma, including endotypes, degree of control, and asthma medication compliance due to sample size limitations, but this will be important to consider in future studies. Finally, we cannot rule out the potential contribution of unmeasured confounders.

This analysis highlights the importance of considering active maternal asthma as a modifier of the relationship between prenatal PUFA intake and childhood asthma risk. Consideration of factors that modify associations between prenatal PUFA intake on respiratory disease in children has implications for designing intervention strategies tailored to impact those at greatest risk.

Supplementary Material

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Abbreviations/acronyms

PUFA	Polyunsaturated Fatty Acid
SD	standard deviation
FFQ	Food Frequency Questionnaire
BMI	body mass index
kg	kilograms
m	meters
GAMs	generalized additive models
n-3	Omega-3
n-6	Omega-6
PR	Prevalence Ratio
CI	Confidence Interval
IQR	Interquartile range
SHS	Secondhand smoke

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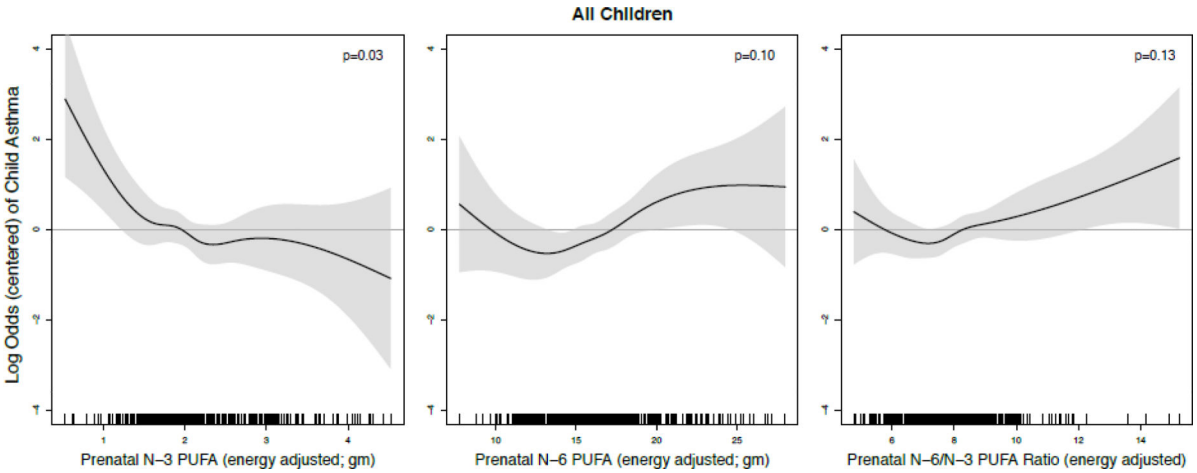

Figure 1. Log odds of childhood asthma across continuum of prenatal PUFA intake, overall sample.

Lines reflect pointwise effect estimates in log odds. Significant associations between PUFA intake and child asthma are demonstrated at levels where the 95% CI (shaded area) does not include zero.

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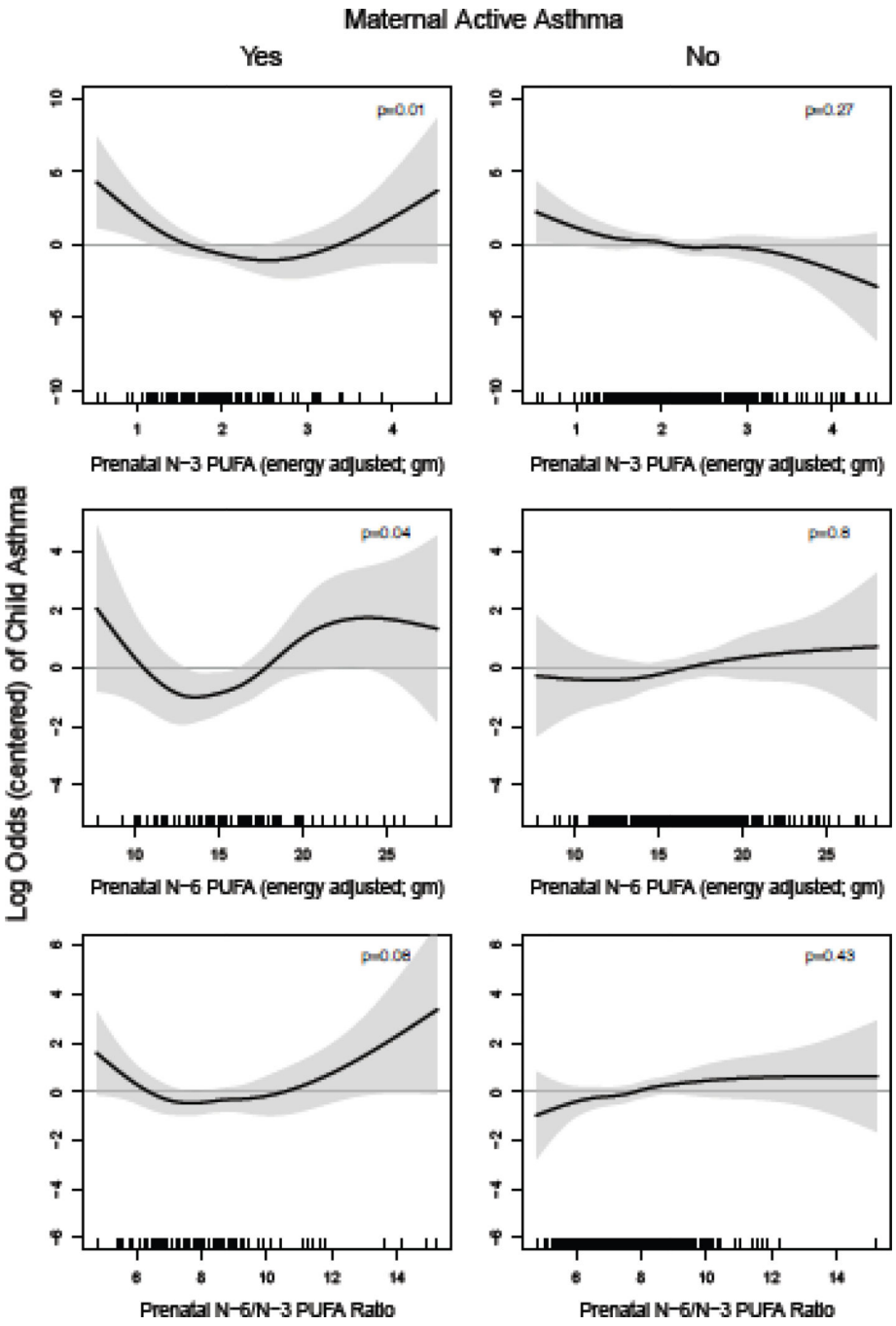

Figure 2. Log odds of childhood asthma across continuum of prenatal PUFA intake, stratified by maternal active asthma status.

Line reflects pointwise effect estimates in log odds. Significant associations between PUFA intake and child asthma are demonstrated at levels where the 95% CI (shaded area) does not include zero.

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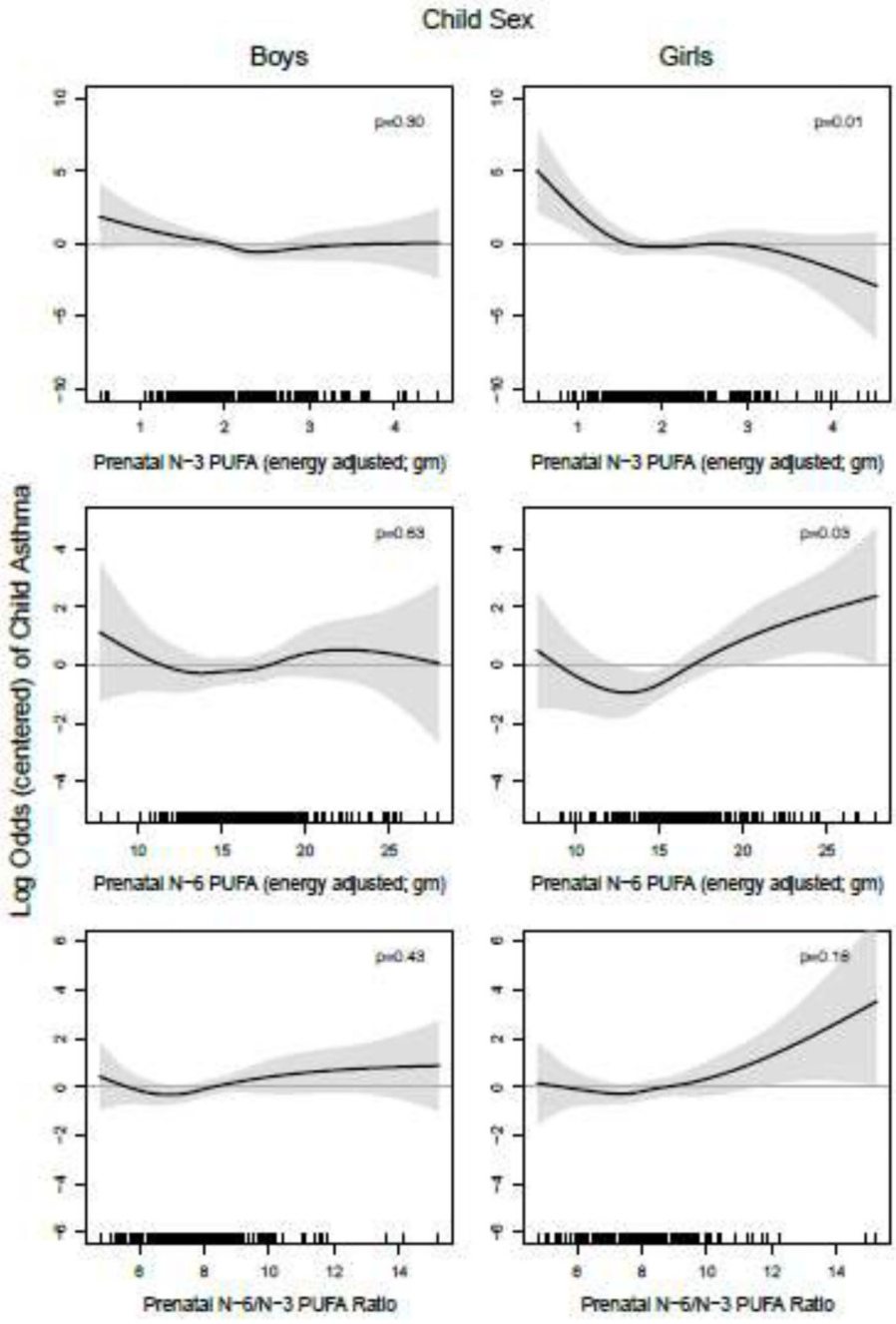

Figure 3. Log odds of childhood asthma across the continuum of prenatal PUFA intake, stratified by child sex.

Line reflects pointwise effect estimates in log odds. Significant associations between PUFA intake and child asthma are demonstrated at levels where the 95% CI (shaded area) does not include zero.

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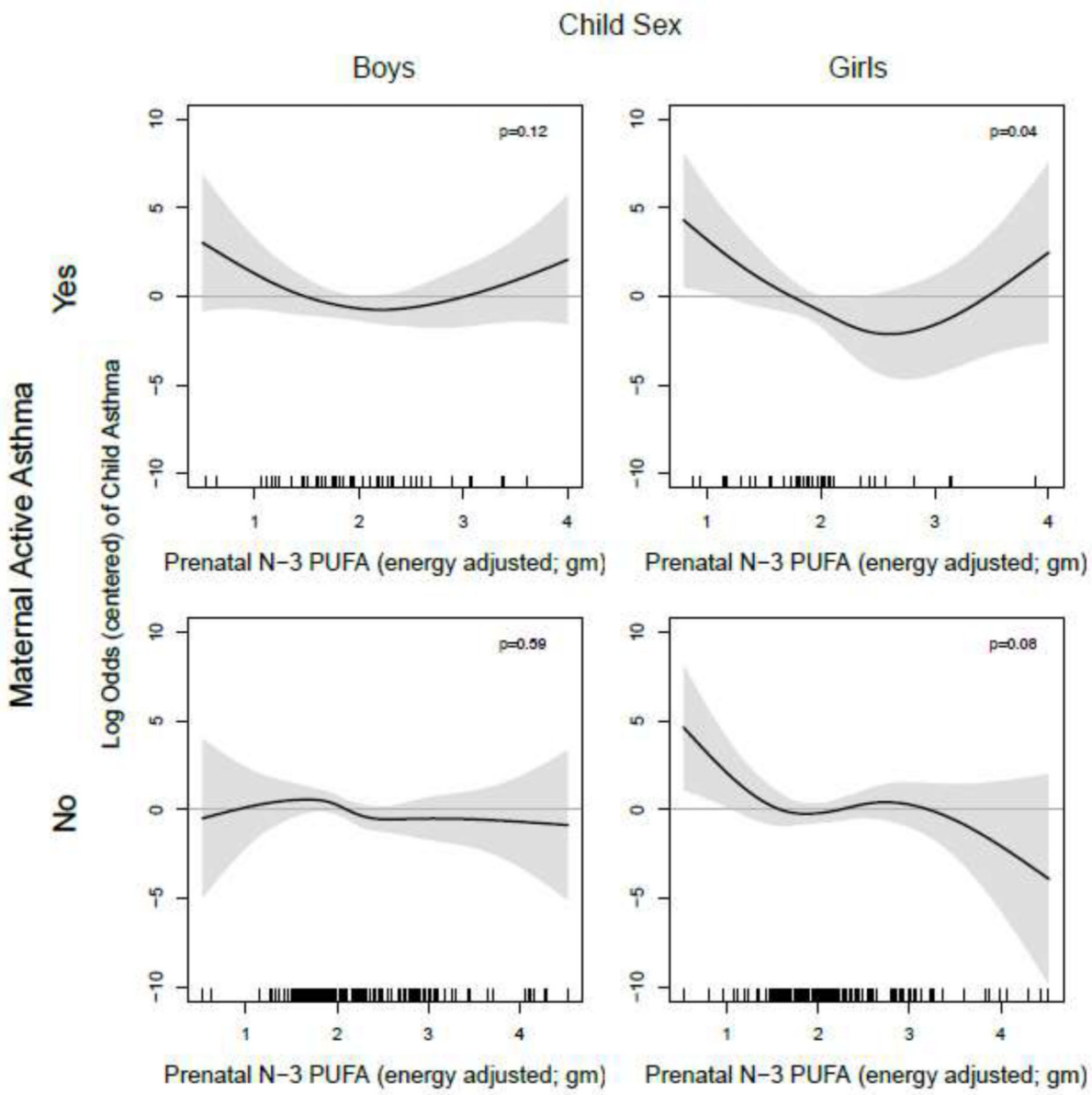

Figure 4. Log odds of childhood asthma across continuum of prenatal *n-3* PUFA intake, stratified by maternal active asthma and child sex.

Line reflects pointwise effect estimates in log odds. Significant associations between PUFA intake and child asthma are demonstrated at levels where the 95% CI (shaded area) does not include zero.

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Table I.

Participant Characteristics: PRISM Study

	All Children (N=412)		Maternal Active Asthma Yes (n=91)		No (n=321)		Child sex Boys (n=215)		Girls (n=197)	
Maternal age at delivery										
years (median, IQR)	30.0	(25.4–34.2)	28.1	(23.8–32.8)	30.7	(26.2–34.4)	29.8	(25.2–33.3)	30.4	(25.4–35.2)
Maternal pre-pregnancy BMI										
kg/m^2 (median, IQR)	24.8	(22.1–29.8)	27.0	(23.8–32.9)	23.9	(21.8–28.7)	25.0	(22.5–30.1)	24.4	(21.7–29.3)
Maternal education (n, %)										
≤12 years	135	32.8	35	38.5	100	31.2	63	29.3	72	36.6
Maternal race/ethnicity (n, %)										
White	92	22.3	10	11.0	82	25.6	43	20.0	49	24.9
Black	165	40.1	51	56.0	114	35.5	87	40.5	78	39.6
Hispanic	129	31.3	26	28.6	103	32.1	71	33.0	58	29.4
Other	26	6.3	4	4.4	22	6.9	14	6.5	12	6.1
Active asthma in pregnancy (n, %)										
Yes	91	22.1	--	--	--	--	50	23.3	41	20.8
Prenatal maternal smoking (n, %) [a]										
Yes	49	11.9	16	17.6	33	10.3	25	11.6	24	12.2
Prenatal SHS exposure (n, %) [b]										
Yes	92	22.3	28	30.8	64	19.9	52	24.2	40	20.3
Child asthma (n, %)										
Yes	72	17.5	28	30.8	44	13.7	44	20.5	28	14.2
Child sex (n, %)										
Boys	215	52.2	50	55.0	165	51.4	--	--	--	--
Child age at first report of asthma										
years (median, IQR)	3.5	(1.6–4.9)	3.7	(2.0–5.0)	3.1	(1.6–4.7)	3.4	(1.5–5.0)	3.5	(1.8–4.5)
Maternal total PUFA intake [c]										
Total *n-3* PUFA grams/day (median, IQR)	2.0	(1.7–2.5)	1.9	(1.6–2.4)	2.0	(1.7–2.5)	2.0	(1.7–2.6)	2.0	(1.7–2.4)
Total *n-6* PUFA grams/day (median, IQR)	16.2	(14.1–18.3)	15.7	(13.5–18.6)	16.3	(14.4–18.2)	16.3	(14.1–18.5)	16.2	(14.2–18.2)
Total *n-6*/*n-3* ratio ratio (median, IQR)	7.9	(6.8–8.8)	8.2	(6.9–9.2)	7.8	(6.8–8.7)	7.9	(6.8–8.6)	8.0	(6.9–9.0)

[a] Mother reported smoking at any time during pregnancy in prenatal visit/postnatal recall.

[b] Mother reported living with current smokers during pregnancy or secondhand smoke (SHS) exposure for >1 hour/week at home, work or restaurants.

[c] Sum of energy-adjusted dietary PUFA intake (adjusted for total energy intake) and PUFA supplements.