Omega-3 and Omega-6 Intake Modifies Asthma Severity and Response to Indoor Air Pollution in Children

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At a Glance Commentary

Dietary intake of fatty acids, specifically omega-3 and omega-6, may modify pediatric asthma morbidity. We present associations between higher omega-6 intake and worse asthma severity and lung function in an urban cohort of children with asthma. Further, higher omega-3 intake was associated with diminished harmful effect of indoor PM exposure on respiratory symptoms, while higher omega-6 intake was associated with an amplified effect. Higher omega-6 intake also associated with an amplified effect of indoor PM on circulating neutrophil percentage, reflecting a modification of PM effects on systemic inflammation by fatty acid intake level. To our knowledge, this investigation represents the first evidence of a protective association between omega-3 and detrimental association between omega-6 and PM-induced asthma symptoms and systemic inflammation among school-age children with asthma. If confirmed in similar populations, alterations in omega-3 and omega-6 intake may provide opportunity for intervention to improve asthma health and reduce the harmful effects of indoor PM exposure.

"This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org"

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Abstract

Rationale: Higher indoor particulate matter (PM) concentrations are linked with increased asthma morbidity. Dietary intake of fatty acids, also linked with asthma outcomes, may influence this relationship.

Objectives: Determine (1) the relationship between omega-3 and omega-6 fatty acid intake and pediatric asthma morbidity, and (2) the association between fatty acid intake and strength of indoor, PM-related asthma symptoms, albuterol use, and systemic inflammation.

Methods: Analyses included 135 children with asthma enrolled in the AsthmaDIET Study. At baseline, 3, and 6 months, data included: week-long average home indoor concentration of $PM_{2.5}$ and PM_{10}, dietary intake of omega-3 and omega-6 fatty acids, daily symptoms, and peripheral blood leukocytes. Asthma severity and lung function were assessed at baseline. Multivariable regression models, adjusted for known confounders, were used to determine associations between each fatty acid and outcomes of interest, with interaction terms (fatty acids x PM) in longitudinal analyses.

Measurements and Main Results: Higher omega-6 intake associated with increased odds of increased asthma severity ($p=0.02$), and lower FEV_1/FVC ratio ($p=0.01$). Higher omega-3 intake associated with reduced effect of indoor $PM_{2.5}$ on symptoms ($p<0.01$), while higher omega-6 intake associated with amplified effect of indoor $PM_{2.5}$ on symptoms and circulating neutrophil percentage ($p<0.01$).

Conclusions: Omega-3 and omega-6 intake are associated with pediatric asthma morbidity, and may modify the asthmatic response to indoor PM.

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Text

Introduction

Dietary intake among minority, inner city children and adolescents diverges sharply from national nutritional guidelines[1-3]. This population is also disproportionately impacted by asthma[4], an inflammatory disease driven by environmental exposures, with dietary exposures also representing a potential driver of asthma morbidity[5]. Dietary intake among the children largely conforms to a "Western" diet, characterized by higher intakes of unhealthy/processed foods and omega-6 fatty acids, and lower intake of healthy foods such as fruits, vegetables, and items including omega-3 fatty acids[6,7]. These fatty acids are a source of biologically active molecules found in the lung, known as lipid-derived inflammatory mediators, providing biologic rationale for respiratory effects[8]. Despite these connections, few investigations examine effects of omega-3 and omega-6 on asthma-related morbidity within pediatric populations[9].

Furthermore, children in the inner city often inhabit environments with indoor pollutants levels, specifically particulate matter (PM), that far exceed standards for acceptable ambient levels set by the Environmental Protection Agency or acceptable indoor levels set by the World Health Organization[10-14]. Children with asthma spend a striking amount of the day (roughly 70% on average) indoors[15], and indoor home PM levels are independently associated with increased asthma morbidity[10]. Dietary exposure to excess omega-6 fatty acids (generally pro-inflammatory), and reduced omega-3 fatty acids (anti-inflammatory), may plausibly prime the asthmatic response to these additional environmental exposures, placing inner city children with asthma at undue risk of poor asthma outcomes.

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The AsthmaDIET Study, an urban pediatric asthma cohort with detailed dietary and indoor environmental exposure measurement, provides an opportunity to simultaneously investigate the contributions of indoor PM and diet to pediatric asthma morbidity. We hypothesized that dietary intake of fatty acids would associate with measures of pediatric asthma health; specifically that higher omega-6 fatty acid intake would associate with increased asthma morbidity and that higher omega-3 fatty acid intake would associate with reduced asthma morbidity. We further hypothesized that omega-6 and omega-3 fatty acid intake would associate with amplified or diminished strength, respectively, of the asthmatic response to indoor PM. Some of the results of these studies have been previously reported in the form of an abstract[16,17].

Methods

Study Design

The AsthmaDIET Study was an environmental cohort study of 149 children with asthma in Baltimore City, Maryland. The study was approved by the Johns Hopkins Institutional Review Board; parental consent obtained.

Participants were: (1) aged 5-12 years, (2) diagnosed by a physician with asthma with symptoms and/or reliever medication use in the past 6 months, (3) free of food allergies, and (4) not taking antioxidant supplements at enrollment.

At baseline, demographics, medication use, body mass index (BMI), asthma severity, and lung function were assessed. Each participant underwent the following one-week

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assessments at baseline, 3 and 6 months: indoor PM concentrations, dietary intake, daytime and nocturnal asthma symptoms and albuterol use via daily diary, phlebotomy.

Exposure Assessments

Impactors designed to collect particles $\leq$2.5 µm ($PM_{2.5}$) and $\leq$10 µm (PM_{10}) were placed in the home, recording average week-long PM concentrations.

Dietary intake was assessed at the end of each monitoring week via a Baltimore-specific quantitative food frequency questionnaire (QFFQ) with 7-day recall[6], from which omega-3 and omega-6 intake were derived.

Further exposure assessment details are found in the online supplement.

Respiratory and Inflammatory Outcomes

Baseline asthma severity was defined via National Asthma Education and Prevention Program guidelines[18] using symptoms, medication use, activity interference, and spirometry (obtained via KoKo spirometer in accordance with American Thoracic Society guidelines[19]), as detailed in the online supplement. Predicted values for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were calculated by formulae of Hankinson et al.[20] Daily diary responses recorded symptoms and albuterol use at baseline, 3, and 6 months. Daytime asthma symptoms (trouble breathing, bother, activity limitation) were presented as none (0) or any symptom reported (1). Nocturnal awakenings and albuterol use were dichotomized to none versus any (use).

Whole blood leukocyte counts, as well as percentage neutrophils and percentage eosinophils, were measured at the end of each home monitoring week in serum samples.

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Statistical Analyses

Variable distribution was examined and log transformation completed when appropriate to meet model assumptions. Within subject, intraclass correlation (ICC) for exposure variables (PM, omega-6, and omega-3) was calculated via linear mixed model with random intercept to evaluate between- and within-individual variability. All analyses were performed using the individual fatty acid levels and a ratio (omega-6/omega-3) as predictors; because use of the ratio resulted in null effect, results are not presented.

Baseline associations between usual, or within-person average (average across visits by individual), fatty acid intake and asthma severity were tested via Kruskall-Wallis. Ordered logistic regression was used to model the association between fatty acid intake and odds ratio of worse asthma severity, adjusted for the opposing fatty acid, age, gender, body mass index (BMI), caloric intake, and caregiver education. Relationships between usual (within-person average) fatty acid intake and lung function were modelled via linear regression, adjusted for aforementioned covariates in addition to inhaled corticosteroid (ICS) use.

In repeated measure analyses, the modifying effects of fatty acid intake by visit on the association between weekly indoor PM exposure and daily outcomes (e.g., daytime symptoms, nocturnal awakenings, albuterol use) or weekly outcomes (e.g. peripheral blood leukocytes) were tested via two-way (omega-3 and PM or omega-6 and PM) interaction terms using generalized estimating equations (binomial family/logit link/exchangeable correlation/robust standard error for binary outcomes or Gaussian family/identity link/exchangeable correlation/robust standard error for continuous outcomes), adjusted for the aforementioned covariates and season. A sensitivity analysis adding air nicotine (online supplement) levels to

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account for secondhand smoke exposure, and an additional exploration for modification of omega and PM associations by atopy (online supplement) were performed to discern unique exposures or phenotypes that may influence observed relationships. Final models were chosen based on Wald tests of the interested regression terms, as well as satisfaction of appropriate modeling assumptions.

Analyses were completed using STATA version 15 (College Station, TX). Statistical significance was defined as $p < 0.05$.

Results

Study Population

Participants with complete, corresponding diet and PM data for one or more of the monitoring periods (n=135, Figure E1) were included. Mean age was 9.5 years (SD 2.2 years), and roughly half of the cohort was female (47%) and/or overweight/obese (50%). Participants were predominantly African-American (96%) with public insurance (91%), and the majority of caregivers (71%) reported at least a high school education. One third of participants had mild asthma (34%), one third moderate asthma (33%), and one third severe asthma (33%). The majority reported albuterol use (66%) within the last 2 weeks, and 47% reported ICS use. Mean FEV_1 percent predicted was 93.5%, but with noted variability between participants (SD 16.8%). Similarly, mean FEV_1/FVC ratio was 0.83, but also with substantial noted variability (SD 0.10). Mean average daily caloric intake was 3448 kcal. No data from analysis was excluded based on

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caloric estimates given that caloric intake values above relevant estimated energy requirements[21] did not correspond to outliers of omega-3 and omega-6 intake in this population sample (Figure E2, online supplement).

Within-person median (IQR) omega-6 and omega-3 levels were 4.64 g (3.37 to 6.35 g) and 0.32 g (0.21 to 0.45 g), respectively, with corresponding ICCs of 0.16 (95% CI: 0.07 – 0.31) and 0.20 (95% CI: 0.11 – 0.35). Within-person median (IQR) PM concentrations revealed $PM_{2.5}$ and PM_{10} levels of 26.8 μg/m^3 (19.0-40.4 μg/m^3) and 39.0 μg/m^3 (26.6-54.7 μg/m^3), respectively, with corresponding ICCs of 0.54 (95% CI: 0.44 – 0.64) and 0.53 (95% CI: 0.43-0.63).

Association between Average Fatty Acid Intake and Baseline Asthma Severity and Lung Function

Univariate associations between fatty acid intake and categories of asthma severity revealed a positive trend towards higher omega-6 intake and worse asthma severity (p=0.06, Figure 1A). After adjustment for confounders, each additional gram of omega-6 intake was associated with increased likelihood of higher asthma severity category (OR 1.29, p=0.02; Figure 1C). There was no statistically significant association between omega-3 intake and asthma severity in univariate or adjusted models (Figures 1B and 1D).

Regarding lung function, adjusted models similarly revealed an association between each additional gram of omega-6 intake and lower FEV_1/FVC (β -0.012, p=0.01) driven by reductions in FEV_1 (β -1.41, p=0.12) whereas omega-3 intake did not demonstrate statistically significant associations with lung function parameters in any models (data not shown).

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Fatty Acid Intake Modified Relationships between Repeated PM Measures, Symptoms, and Albuterol Use

Daytime symptoms were reported on 508 of 2068 days (19.8%), with individual symptom reports of trouble breathing on 18.8% of days, bother due to asthma on 16.5% of days, and limitation in activity due to asthma on 13.3% of days. Any albuterol use was reported on 468 of 2135 days (18.0%), and nocturnal symptoms were noted on 176 of 2412 days (6.8%). Total number of days varied by outcome measure due to missing daily diary responses from some of the participants.

Fully adjusted models including both omega-6 and omega-3 did not reveal a primary effect of $PM_{2.5}$ or PM_{10} exposure on daytime symptoms ($PM_{2.5}$: OR 1.00, p=0.90; PM_{10}: OR 0.99, p=0.75), albuterol use ($PM_{2.5}$: OR 0.97, p=0.51; PM_{10}: OR 0.96, p=0.44), or nocturnal symptoms ($PM_{2.5}$: OR 0.96, p=0.19; PM_{10}: OR 0.97, p=0.26). Likewise, omega-3 and omega-6 intake did not demonstrate primary associations with symptoms or albuterol use in adjusted models (data not shown). However, significant two-way interactions between each fatty acid and both indoor $PM_{2.5}$ and PM_{10} were noted for all outcomes.

Specifically, the association between $PM_{2.5}$ and daytime symptoms was augmented at higher levels of omega-6 intake (OR_{int}=1.02 per 1 g increase in omega-6, p_{intx}<0.01) and mitigated at higher levels of omega-3 intake (OR_{int}=0.96 per 0.1 g increase in omega-3, p_{intx}<0.01) (Figure 2). Intake of omega-3 and omega-6 similarly modified the association between PM_{10} and daytime symptoms, with augmentation at higher omega-6 (OR_{intx} 1.02 per 1 g increase omega-6, p_{intx}=0.03), and mitigation at higher omega-3 (OR_{intx} 0.97 per 0.1 g increase omega-3, p_{intx}=0.01) (Figure E3). The harmful effects of omega-6 on the relationship between

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$PM_{2.5}$ or PM_{10} and symptoms were most pronounced at lower levels of omega-3; conversely the beneficial effects of omega-3 were most pronounced at higher levels of omega-6. Adjustment for air nicotine did not alter results, nor were relationships influenced by atopic status of the participants (data not shown).

The components of the composite daytime symptom variable (trouble breathing, bother, activity limitation) were examined separately, with fatty acid intake modifying the effects of $PM_{2.5}$ individually on trouble breathing, bother due to asthma, and activity limitation consistent with the composite score (Table 2). Results were similar for PM_{10} (Table E1). Intake of omega-6 additionally augmented the association between $PM_{2.5}$ and albuterol use (OR_{int}=1.03 per 1 g increase in omega-6, p_{intx}=0.02) and nocturnal symptoms (OR_{int}=1.02 per 1 g increase in omega-6, p_{intx}=0.04); no significant interaction was noted between omega-3 and $PM_{2.5}$ for these outcomes (Table 2). Intake of omega-6 additionally augmented the association between PM_{10} and nocturnal symptoms (OR_{int}=1.02 per 1 g increase in omega-6, p_{intx}=0.03); no significant interaction was noted between omega-6 and PM_{10} for albuterol use or for omega-3 and PM_{10} for albuterol use or nocturnal symptoms (Table E1).

Fatty Acid Intake Modified Relationships between Repeated PM Measures and Blood Neutrophils

Fully adjusted models including both omega-6 and omega-3 likewise did not reveal a primary association between $PM_{2.5}$ or PM_{10} exposure on total blood leukocyte counts (leukocyte counts log transformed to meet model assumptions, $PM_{2.5}$: β 0.0001, p=0.97; PM_{10}: β 0.002, p=0.65), percentage eosinophils ($PM_{2.5}$: β -0.08, p=0.07; PM_{10}: β -0.05, p=0.39), or

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percentage neutrophils ($PM_{2.5}$: β 0.21, p=0.34; PM_{10}: β 0.20, p=0.42). Likewise, omega-3 and omega-6 intake did not demonstrate primary associations with these outcomes (data not shown).

With regard to two-way interactions, the association between $PM_{2.5}$ and percentage neutrophils was augmented by increasing omega-6 intake (β_{int}=0.17 per 1 g increase in omega-6, p_{intx}<0.01) with no significant effects of omega-3 noted (Figure 2, Table E2, Figure E3). Results were similar by PM_{10} exposure (Table E2) Fatty acid intake did not demonstrate consistent, significant effects on the relationship between $PM_{2.5}$ or PM_{10} on total leukocyte counts or percentage eosinophils. Adjustment for air nicotine did not alter results, nor were relationships influenced by atopic status of the participants (data not shown).

Discussion

Poor dietary habits and high air pollution exposure are two risk factors that may contribute to disproportionate asthma burden in low income populations. We present data from a prospective cohort of children with asthma in Baltimore City, demonstrating associations between reported omega-3 and omega-6 fatty acid intake and asthma health. Specifically, higher omega-6 intake was linked to more severe asthma and reduced lung function. Furthermore, both omega-6 and omega-3 intake modified the association between indoor PM exposure, asthma symptoms, and albuterol use, with diminished strength of PM effects noted at higher levels of omega-3 and amplification of PM effects seen at higher levels of omega-6 intake. Higher omega-6 intake also associated with augmentation of PM effects on

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systemic inflammation (i.e., percent neutrophilia). To our knowledge, this investigation represents the first evidence of protective association between omega-3 and detrimental association between omega-6 and PM-induced asthma symptoms and systemic inflammation among school-age children with asthma.

Literature evaluating the association between omega-3 and omega-6 intake and pediatric asthma diagnosis has been mixed, and to our knowledge no epidemiologic evaluations have been published in cohorts limited to school-age children with asthma. Studies focused on asthma symptoms in mixed populations (pediatric asthma and non-asthma populations) demonstrate varied results[22-29], though favor a protective effect of omega-3 intake on respiratory symptoms and provide limited insight into omega-6 effects. Three small trials of fatty acid intake manipulation in children with asthma also provide mixed results[30-32], perhaps due to heterogeneity of design and population, though all demonstrated improvement in at least one outcome (lung function[30, 32] or systemic inflammation[31]) in response to omega-3 supplementation. Our data would suggest that both omega-3 intake augmentation and omega-6 intake reduction may present potent targets for future investigations aimed at reducing asthma morbidity within the present urban, pediatric population. Furthermore, the absolute levels of intake, rather than ratio of omega-6 to omega-3 intake, may be important in influencing asthma health.

In addition to demonstrating an association between fatty acid intake, asthma severity and lung function, our results show that fatty acid intake may determine individual susceptibility to air pollution exposure. Associations between higher indoor PM concentrations and increased asthma symptoms, exacerbations, and reduced lung function in urban children

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are well-established[33], and short-term PM exposure is linked to increased peripheral blood neutrophilia in healthy volunteers[34]. Because PM exposure is an established and potent contributor to pediatric asthma morbidity and systemic inflammation, the importance of omega-3 and omega-6 intake to the asthmatic response to PM further strengthens the relevance of our findings.

Though not yet fully understood, the health effects on PM exposure are suggested to be mediated through biologic mechanisms including airway and systemic oxidative stress and inflammation[35,36]. Omega-6 and omega-3 fatty acids are sources of lipid-derived inflammatory and pro-resolving mediators, metabolites that arbitrate pulmonary and systemic inflammation [8] and are plausible as biologic mediators of the PM response. The omega-3 fatty acids alpha-linoleic acid, eicosapentaenoic acid, and docosahexaenoic acid are precursors of resolvins, protectins, and maresins. These three classes of molecules regulate neutrophil infiltration, coordinate clearance of apoptosed neutrophils by macrophages, and adjust cytokine production in response to inflammatory triggers to promote resolution of inflammation[37]. In contrast, omega-6 fatty acids play a more complex role as precursors for both pro- and anti-inflammatory mediators. Arachadonic acid (AA) is a precursor for pro-resolving mediators called lipoxins (i.e. LXA_4)[38-41] and prostaglandin E2 (PGE_2)[42], which inhibit pro-inflammatory cytokines/leukotrienes and inflammatory cell recruitment, and increase smooth muscle relaxation in the lungs. However, the potential anti-inflammatory omega-6 effects are counterbalanced and perhaps overwhelmed by pro-inflammatory effects. AA also serves as the precursor for phosphodiesterase 2 (PDE_2), which likely contributes to bronchoconstriction and may increase pro-inflammatory cytokine production[43], and cysteinyl leukotrienes, which

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contribute to bronchoconstriction, increased vascular permeability and mucus secretion, airway remodeling, and the release of additional pro-inflammatory cytokines[44,45]. The relative concentrations of these biologically active molecules may plausibly influence individual response to PM.

Emerging data support a role for mitigation of air pollution health risks via nutrition in a range of chronic diseases[46,47]. Murine studies demonstrate protection against $PM_{2.5}$-induced pulmonary and systemic inflammation and oxidative stress in mice with augmented tissue levels of omega-3[48]. Consistent with these effects, limited omega-3 supplementation trials in human populations suggest protection against the inflammatory effects of PM. For example, in a randomized double-blind controlled trial of 50 elderly adults in Mexico City, Romieu et. al demonstrated that omega-3 supplementation was associated with increasing plasma anti-oxidant activity, hypothesized to act as a defense against PM[49]. One prior study demonstrated mitigation of nasal lavage IL-8 levels in response to ambient air pollution among children with asthma who reported dietary intake consistent with a Mediterranean Diet (characteristically high in omega-3)[50].

Several limitations to the current investigation are noted. Omega-3 and omega-6 intake were obtained through FFQ assessment, with the possibility of exposure misclassification or residual confounding due to over- or under-report of dietary intake by the children in the study. However, caregivers were enlisted for completion of surveys and to assist with meal recall, thus improving accuracy. Total caloric intake values (Table 1) do not demonstrate the underreporting noted in other pediatric studies[51,52]. Intake assessment targeted foods demonstrated to be consumed in the local community based on previous research[6], providing

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content validity to the assessment. And while reported fatty acid intake levels have not been compared to red blood cell membrane fatty acid levels, a biologic measure unavailable in this cohort, reported fatty acid intake has been correlated with cell membrane levels in other studies using FFQ methodology, providing validity to the approach[53,54]. The diet of the children in the presented Baltimore City cohort was highly skewed towards low omega-3 intake (median 0.31 g), typical of an American-style diet. While low omega-3 intake is consistent with prior reports of dietary intake in Baltimore City and other urban minority populations[6,7], increasing confidence in dietary results, the generally low levels of omega-3 intake in the cohort limit accuracy of extrapolation regarding potential effect of high-dose omega-3 supplementation or dietary intake, as provided in previous trials, within this population. The investigations herein bear repeating in a population with a higher representation of a "healthy" and balanced diet. Furthermore, adequate daily intakes in this age group are defined as 0.9-1.6 g/day of omega-3 (alpha-linoleic acid) and 10-16 g/day omega-6 (linoleic acid), based on average intake levels in healthy populations[21]. Intake of both omega-3 and omega-6 fell below adequate intake levels within this cohort. Despite overall low levels of omega-6 intake, a trend towards harm with increasing intake was noted, and may have implications on the appropriateness of adequate intake recommendations in populations with asthma. Applicability of conclusions to pediatric cohorts with notably different distributions of intake warrants further investigation.

Despite noted limitations, the study design and original results demonstrate important strengths. Prospective design with multiple visits per participant adds potency to conclusions and provides the power necessary to examine the complex relationships between diet, environmental exposures, and asthma-related morbidity. While ambient exposures are widely

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characterized and often based on modelling or predicted exposures, studies examining the effect of indoor exposures on asthma health are less prevalent. This owes to the cost and time commitment necessary to directly sample individual home environments. However, given high concentrations of PM in the indoor environment in this population[55,56], the amount of time children with asthma spend in the home environment[15], and therefore the relative contribution of indoor pollutants to daily exposures, the indoor environment is highly relevant and provides distinct but complementary evidence to studies of outdoor PM exposures, representing a further strength of the current analysis. The population of children with asthma represented here, minority, largely of low socioeconomic status, and living in an urban environment, are disproportionately affected by asthma and asthma morbidity[4], and are exposed to poor diet[6, 7] and excessive indoor air pollution[11,12]. Identification of two modifiable risk factors (dietary intake and indoor air quality) for asthma-related morbidity in this population is a major strength. Finally, though the data are observational, the presentation of consistent relationships between omega-3 and omega-6 in regards to symptoms as well as systemic inflammation outcomes lends consistency of effect, an additional criteria necessary for the establishment of causality.

In summary, we present results from an inner-city pediatric cohort with asthma demonstrating an association between higher omega-6 levels and increased asthma severity, and modification by reported omega-3 (protective) and omega-6 (harmful) fatty acid intake of the association between indoor PM exposure and asthma symptoms and systemic inflammation. These results highlight that this highly vulnerable and at-risk population has potentially two modifiable exposures (unfavorable fatty acid intake profiles and high indoor PM

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exposures) combining to effectively worsen asthma morbidity. As evidence continues to gather regarding an effect of dietary intake on pediatric asthma health, it will be critical to scrutinize the contribution and role of diet in the context of environmental exposures linked to respiratory morbidity. It is possible that the collective improvement of both dietary and indoor air exposures may have the greatest impact on improving asthma health.

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Figure Legends

Figure 1: Fatty Acid Intake and Associations with Asthma Severity. Univariate associations between reported omega-3 (Panel A, OR per 0.1 g increase) and omega-6 (Panel B, OR per 1 g increase) intake and asthma severity shown in Tukey plots. P-values via Kruskall-Wallis equality of populations rank test. Predicted probability of severe persistent asthma (based on the ordered logistic regression using four categories of asthma severity) by intake of omega-3 (Panel C) and omega-6 (Panel D); point estimates and 95% confidence intervals represented with each fatty acid adjusted for the other.

Figure 2: Marginal Effects of Indoor $PM_{2.5}$ on Daytime Symptoms and Peripheral Neutrophil % is Modified by Fatty Acid Intake. Predicted probability of daytime symptoms (Panel A, n=2467 person-days) and peripheral neutrophil percentage (Panel B, n=264 serum samples) per 10 $\mu g/m^3$ increase in $PM_{2.5}$ at levels from -1 to +1 IQR of reported intake in the AsthmaDIET Study. Omega-6 and omega-3 included simultaneously in generalized estimating equation model above, adjusted for age, gender, BMI, caloric intake (quadratic term for symptoms outcome only), caregiver education, ICS use, and season. To display relationships, each model is held constant at the median level of the opposing fatty acid. *=statistical significance

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