Examining associations between dietary inflammatory index in pregnancy, pro-inflammatory cytokine and chemokine levels at birth, and offspring asthma and/or wheeze by age 4 years.

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Abstract

Background—Few studies have demonstrated associations between maternal dietary inflammatory index (DII) during pregnancy and offspring asthma and/or wheeze.

Objective—The study aimed to assess associations between maternal DII during pregnancy and 1) offspring cord sera pro-inflammatory cytokines (IL-1β, IL-4, IL-6, IL-10, TNF-α) and chemokines (IL-8, MCP-1) at birth and 2) offspring asthma and/or wheeze at age 4 years.

Design—The Healthy Start study is a prospective pre-birth longitudinal study that recruited pregnant women in Denver, Colorado and tracked their offspring.

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Participants and setting—This paper used data from 1228 mother-child dyads enrolled in the Healthy Start study. Pregnant women were recruited in Denver, Colorado between 2009 and 2014, and offspring tracked until age four years.

Main outcome measures—Cord sera cytokines and chemokines were analyzed with multiplex panel immunoassays. Offspring diagnosis of asthma and/or wheeze by age 4 years was extracted from electronic medical records.

Statistical analyses performed—Unadjusted and adjusted linear and logistic regression models were used to assess associations. Covariates included factors such as nulliparity, race/ethnicity, gestational smoking, and maternal history of asthma.

Results—Unadjusted analysis showed that increasing maternal DII scores were associated with increased odds of child asthma and/or wheeze by 4 years (OR = 1.17; 95% CI: 1.07, 1.27), but the association was attenuated and no longer statistically significant in the adjusted model (OR = 1.15; 95% CI: 0.99, 1.33). There were no significant associations between DII scores and cord sera cytokine or chemokine levels.

Conclusions—The study showed that the inflammatory profile of the maternal diet was not associated with cytokines and chemokine levels at birth. The results suggested that a more inflammatory maternal diet was associated with increased odds of offspring asthma and/or wheeze by age 4 years, which could be considered of clinical relevance but the finding was not statistically significant at the 0.05 level.

Background

Asthma is a complex disease driven by both allergic and inflammatory processes.[1] Asthma is estimated to affect 10.4% of children in the United States (US). Early life factors, including maternal diet during pregnancy, have been associated with asthma outcomes in offspring.[2] Yet, the specific components of the diet or the overall diet patterns which are particularly relevant to the etiology of offspring allergy outcomes remain unknown.

Because single nutrients may not adequately capture the inflammatory potential of the maternal diet, interest has moved towards looking at more comprehensive measures. The dietary inflammatory index (DII),[3] is a literature-based summary measure of total diet which assigns positive weights to inflammatory foods and nutrients, such as trans fats, and negative weights to anti-inflammatory nutrients, such as omega-3 fatty acids. One recent study showed an association between maternal energy adjusted dietary inflammatory index[4] scores during pregnancy and offspring asthma outcomes over 10 years. Another study found an association between maternal DII scores[5] and offspring wheeze trajectories, but not asthma, up to 7.5 years of age.

While the exact mechanism by which maternal diet may affect offspring asthma is unknown, Georas et al.[6] suggest that inflammation-related pathways might contribute to the altered risk. The inflammatory potential of the maternal diet, together with the complex network

of immuno-pathological mechanisms of pregnancy, may affect offspring asthma and/or wheeze outcomes.[7] In particular, cord-blood cytokines may play a key role in offspring allergy outcomes.[8,9] Single nutrients from maternal diet do appear to influence levels of inflammatory cytokines in cord blood,[10–18] yet no study has examined the association between maternal DII and cord blood cytokines. It seems plausible that maternal DII may affect cord blood cytokines, as a cross-sectional study indicated that measures of DII in children's' diet are associated with levels of asthma-related inflammatory cytokines in their sera.[19]

The role of maternal dietary intake in pregnancy, driving or attenuating these immunological processes and subsequent asthma and/or wheeze outcomes, needs further investigation, because maternal diet in pregnancy is a modifiable potential risk factor.

The primary aim of this study was to assess the association between maternal DII scores during pregnancy and offspring diagnosis of asthma and/or wheeze. It was hypothesized that increased maternal DII scores during pregnancy would be associated with increased risk of offspring asthma and/or wheeze. The secondary aims of this study were: 1) to examine associations between maternal DII scores and cord sera levels of cytokines and chemokines; and 2) to examine associations between cord sera levels of cytokines and chemokines and offspring diagnosis of asthma and/or wheeze. It was hypothesized that maternal DII scores would be associated with cord sera cytokines and chemokines, that the effect of maternal DII scores on inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines (IL-8, MCP-1) might be exacerbated by maternal obesity, and that the effect of maternal DII scores on T-regulatory (IL-10) and Th2 (IL-4) cytokines might be exacerbated by maternal obesity and maternal history of asthma. It was hypothesized that cord sera levels of cytokines and chemokines would be associated with offspring risk of development of asthma and/or wheeze.

Materials and Methods

Study design

The Healthy Start study is an observational, pre-pregnancy birth cohort study which recruited 1410 pregnant women from the obstetrics clinics at the University of Colorado Hospital (2009–2014). Women were included who had singleton pregnancies, no previous stillbirth, age of 16 or older at the time of consent, gestational age less than 24 weeks at the time of the baseline research visit, no fetal death, and no birth at less than 25 weeks of gestation. Women were excluded for asthma treated with steroid medication, cancer, pre-existing diabetes or psychiatric illness. Three pregnancy visits were conducted: early pregnancy (median 17 weeks of gestation), mid-pregnancy (median 27 weeks of gestation), and delivery (median 1 day after delivery). Written consent was obtained. The Healthy Start study protocol was approved by the Colorado Multiple Institutional Review Board. The Healthy Start study was registered as an observational study at clinicaltrials.gov as NCT02273297.

Assessment and measures

Maternal dietary inflammatory index (DII)—Maternal diet was measured throughout pregnancy using the Automated Self-Administered 24-hour dietary recall (ASA-24).[20] The ASA-24 has been validated against interviewer-administered recalls[21,22] by the National Cancer Institute and found to be comparable in terms of energy intake, nutrient content, and portion sizes. Supplement data were not available for the DII calculation. Participants were asked to complete 1 dietary recall per month. Approximately 76% of the participants completed 2 dietary recalls over the pregnancy, with a median of 2 recalls. Two recalls can be representative of the entire pregnancy, given that dietary intake is relatively stable across pregnancy[23] and two or more recalls are sufficient to estimate usual dietary intake, per the National Cancer Institute Dietary Assessment Primer.[24] Data from the ASA24 were collected and processed by the Diet, Physical Activity and Body Composition Core of the Nutrition Obesity Research Center at the University of North Carolina at Chapel Hill. Individual nutrients were derived from the recalls using the US Department of Agriculture Food and Nutrient Database for Dietary Studies, versions 1.0 and 4.1.[25] The NCI's measurement error model was used to derive usual dietary intake throughout pregnancy from the recalls.[26–28] The NCI method uses a two-part non-linear mixed effects model to estimate nutrient intake from a combination of single and multiple dietary recalls. The predicted intake scores were used for DII calculations. The original DII scores were based on 45 food components. The DII score used in this manuscript was based on 28 components extracted from the 24 hour dietary recalls, as previously described by Moore et al.[25] and shown in Table 1. The components used in the DII scores included energy, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, omega-3 polyunsaturated fatty acids, omega-6 fatty acids, trans-fat, carbohydrates, fiber, protein, cholesterol, iron, vitamin A, vitamin C, vitamin D, vitamin E, niacin, thiamin, riboflavin, vitamin B6, vitamin B12, folic acid, magnesium, zinc, selenium, alcohol and caffeine, as previously described by Moore et al.[25] One DII score was computed for each recall, and for mothers with more than one recall, the DII scores were averaged.

Child asthma and/or wheeze diagnosis—Children's medical record data was abstracted for 1261 Healthy Start participants who consented to child medical record review up to 4 years of age and whose records were available in the Epic medical records system. The medical records for the search terms "asthma" and "wheeze" were reviewed by clinicians and coded as no or yes diagnosis. The outcome of interest for the present paper was diagnosis of asthma and/or wheeze by age 4 years.

Cord sera cytokines and chemokines—Available frozen umbilical cord sera extracted at birth from 581 offspring of mothers enrolled in the Healthy Start study was analyzed for a range of cytokines and chemokines. Plasma cytokine/chemokine concentrations were determined by multiplex panel immunoassay according to manufacturer's instructions (EMD Millipore Corporation, Billerica, MA 01821). Cytokines including IL-1β, IL-4, IL-6, IL-10, and TNF-α; and chemokines IL-8 and MCP-1, were measured in pg/mL. For each analysis, samples were run in duplicate, and the coefficient of variation was computed as a quality control measure to show the variation between the duplicate runs. The coefficient of variation was computed as (Standard Deviation / Mean) * 100. The higher the coefficient

of variation, the greater the level of dispersion around the mean. The lower the value of the coefficient of variation, the more precise the estimate. If both replicates were out of range, the value was designated as being below (or above) the limit of detection. Values that were below the lower limit of detection were marked as "out-of-range low" and values that were above the upper limit of detection were marked as "out-of-range high". The cytokines and chemokines studied were previously selected to be analyzed for an NIH grant (R00ES025817), and included those that were related to either air pollution exposure or pregnancy/birth outcomes.

Cord sera cytokines and chemokines with <20% of values outside the detection range were treated as continuous variables.[1] When the cytokines or chemokines were treated as continuous variables, values below the limit of detection were assigned values equal to half the lowest value observed on the standard curve,[29,30] and values above the limit of detection were assigned values equal to 1.5 times the highest value on the standard curve. Cord sera cytokines and chemokines with 20% of values outside the detection range were treated as categorical variables, and dichotomized as detectable or not detectable.

Covariate data—Data regarding maternal race/ethnicity, parity, gestational smoking, maternal history of asthma, and age of introduction of solid foods were obtained through self-reported questionnaires. Maternal history of asthma was assessed using the following question, *"Has a health professional such as a doctor, physician assistant, or nurse practitioner ever told you that you have asthma?"* Pre-pregnancy weight was obtained from either medical records or self-reported early in pregnancy. Maternal height was measured at the first research visit via stadiometer. Pre-pregnancy BMI was calculated using pre-pregnancy weight (kg) divided by height (m) squared. Pre-pregnancy BMI was categorized as follows: lean (BMI <25 kg/m^2), overweight (BMI 25–29.99 kg/m^2), and obese (BMI 30 kg/m^2).[31] Observed gestational weight gain was calculated as the difference between the last available weight recorded during pregnancy and the pre-pregnancy weight.[32] Gestational weight gain was categorized as less than recommended, within the recommended range, or more than recommended (excessive weight gain) based on pre-pregnancy BMI categories, as described by the 2009 Institute of Medicine guidelines.[33] Information on total caloric intake during pregnancy (kcal/day) was obtained using repeated 24-hour recalls, as described above. Breastfeeding duration was computed as breastmilk months, a product of breastfeeding duration and intensity, using feeding information reported by mothers at the 18 months postnatal interview.[34]

Statistical Analysis

Descriptive statistics were computed for maternal and infant characteristics, including means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Descriptive statistics of demographic variables were compared between participants with and without cytokine/chemokine data. Continuous variables were compared between participants with and without cytokine/chemokine data using t-tests and Wilcoxon rank sum tests for normally distributed and non-normally distributed variables, respectively. Categorical variables were compared using Pearson chi-square tests. For each of the cytokines and chemokines, descriptive statistics were reported including the number

and percentage of values that were outside the detection range, the median, and interquartile range (IQR) of values.

Unadjusted and adjusted logistic regression models were fit to examine the association between continuous maternal DII scores and child diagnosis of asthma and/or wheeze by age 4 years old. The adjusted model included the following covariates that were selected using a directed acyclic graph[35] and that have also been associated with child asthma/wheeze outcomes in some, but not all studies: nulliparity,[36] gestational smoking,[37] maternal race/ethnicity,[38] pre-pregnancy BMI category,[39] maternal history of asthma,[40] total caloric intake during pregnancy (kcal/day), breastmilk months,[41] and age of introduction to solid foods.[42]

To examine the association between continuous maternal DII scores and cytokines and chemokines with <20% of values outside of the detection range, separate linear regression models were fit. Prior to fitting models for each of the cytokines and chemokines, the values of the cytokines and chemokines were natural log transformed to account for the positively skewed distributions for each of the cytokines and chemokines. Residual plots were examined to ensure the natural log transformation was a suitable choice to satisfy the assumption of normality. To examine the association between continuous maternal DII scores and cytokines with 20% values outside of the detection range, separate logistic regression models were fit to estimate the odds that the value of the cytokine was detectable.

For both cytokines and chemokines with <20% or 20% of values outside the detection range, unadjusted models included continuous maternal DII scores as the only predictor. Adjusted models were also fit for each cytokine/chemokine, with the covariates and hypothesized interactions tested determined *a priori* using directed acyclic graphs.[35] The adjusted models for the inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines (IL-8, MPC-1) included nulliparity, gestational smoking, maternal race/ethnicity, pre-pregnancy BMI category, and total caloric intake (kcal/day) as covariates. To test the hypothesis that the effect of maternal DII scores on inflammatory cytokines and chemokines may be exacerbated by maternal obesity, the multiplicative interaction term between DII and pre-pregnancy BMI category was evaluated. The adjusted models for the T-regulatory cytokine (IL-10) and Th2 cytokine (IL-4) included the same covariates as were included for the inflammatory cytokines, in addition to maternal history of asthma. To test the hypothesis that the effect of maternal DII scores on T-regulatory and Th2 cytokines may be exacerbated by maternal obesity and maternal history of asthma, the multiplicative interaction terms between maternal DII scores with pre-pregnancy BMI category and the multiplicative interaction term between maternal DII scores with maternal history of asthma were included. Non-significant interaction terms were removed, as suggested in Muller and Fetterman.[43]

The associations between levels of each cord sera cytokine and chemokine and offspring diagnosis of asthma and/or wheeze by age 4 years were examined using separate unadjusted and adjusted logistic regression models. Adjusted models included the following covariates selected using a directed acyclic graph:[35] nulliparity, gestational smoking, maternal race/ethnicity, pre-pregnancy BMI category, IOM gestational weight gain category, maternal history of asthma, breastfeeding duration, and age of introduction of solid foods.

Significance for all statistical hypothesis testing was assessed at an alpha level of 0.05. For all models, regression diagnostics were preformed including examination of residual plots and variance inflation factors.

Results

Descriptive statistics

Table 2 reports descriptive statistics for maternal and offspring characteristics of the overall sample of Healthy Start participants who had both maternal DII scores and offspring electronic medical record data. Table 2 also compares descriptive statistics of maternal and offspring characteristics between the subset of participants with cytokine/chemokine data and the subset without cytokine/chemokine data. The mean±SD DII score for the overall sample was 0.40±1.6 points. Birthweight (g) was statistically, but not clinically, significantly higher in participants with cytokine data compared to participants without cytokine data (3270±437 vs. 3176±558, p=0.03). Maternal age, DII, total caloric intake, breastfeeding duration, gestational age, age of introduction of solids, nulliparity, gestational smoking, race/ethnicity, pre-pregnancy BMI, IOM gestational weight gain, maternal history of asthma, and child sex were not significantly different between those with and without cord sera cytokine and chemokine data.

Table 3 reports the frequency and percentage of values outside of the detection range for each cytokine/chemokine, and records whether the out-of-range values were low (below the lower limit of detection) or high (above the upper limit of detection). The median and IQR for levels of each cytokine/chemokine are also reported. Quality control data for the cytokines/chemokines analyzed are provided in Table 4.

Association between maternal DII scores and offspring diagnosis of asthma and/or wheeze

In the unadjusted analysis, there was a statistically significant association between maternal DII scores and child diagnosis of asthma and/or wheeze by 4 years of age (Table 5). Based on the results of the unadjusted model, the odds of child asthma and/or wheeze increased by approximately 17% per each one-unit increase in maternal DII score. When adjusting for covariates, the association between maternal DII scores and child diagnosis of asthma and/or wheeze was attenuated and no longer statistically significant (Table 5). Results from the adjusted model estimate that for each one-unit increase in maternal DII score, the odds of child asthma and/or wheeze increased by approximately 15%, while holding all other variables constant.

Associations between maternal DII scores and cord sera cytokine/chemokine levels

There were no significant associations between continuous maternal DII scores and cord sera levels of any of the cytokines or chemokines examined in the unadjusted models (Tables 6–7). The hypothesized interaction between maternal DII scores and pre-pregnancy BMI category for each of the cytokines/chemokines examined was non-significant (all p>0.05). In addition, the hypothesized interaction between maternal DII scores and maternal history of asthma for cord sera levels of IL-10 and IL-4 was also non-significant (all p>0.05). After

removing all non-significant interaction terms, results of the final adjusted models indicated that there were no statistically or clinically significant associations between maternal DII scores and cord sera levels of they cytokines/chemokines examined (Tables 6–7).

Associations between cord sera cytokine/chemokine levels and offspring diagnosis of asthma and/or wheeze

There were no statistically or clinically significant associations between any cord sera cytokines or chemokines measured and offspring diagnosis of asthma and/or wheeze by age 4 years in either the unadjusted or adjusted models (Table 8).

Discussion

The results of this study indicate that there is not a statistically significant association between maternal DII scores and child diagnosis of asthma and/or wheeze by age 4 years, after adjusting for potential confounders. There were no statistically or clinically significant associations between maternal DII scores and cord sera levels of IL-6, IL-8, TNF-α, MCP-1, IL-10, IL-1β or IL-4. There were no statistically or clinically significant associations between levels of the same cord sera cytokines and chemokines and offspring diagnosis of asthma and/or wheeze by age 4 years.

Two previous studies compared DII scores to asthma outcomes in the child. Chen et al.,[4] using an Irish cohort, reported that energy-adjusted DII scores were associated with higher risk of offspring asthma over the first 10 years of life. The authors corrected for a wide range of maternal lifestyle and sociodemographic factors. They did not adjust for race/ethnicity, as they studied a predominately Caucasian population. Hanson et al.[5] found no association in both unadjusted and adjusted models between DII and asthma in offspring up to 7.5 years. They did find an association between maternal DII scores and offspring wheeze trajectories.

This analysis used the DII, which is one of three previously established inflammatory indices. The E-DII differs from the conventional DII, as it accounts for physical activity levels and total caloric intake across age ranges (children vs. adults) and activity levels into account. The authors of the DII and E-DII have also developed a children's DII (C-DII). All three of the different versions of the DII are still being used in research studies.[3]

Based on the results of previous studies,[4,5] it was expected that maternal DII scores during pregnancy would be associated with offspring asthma and/or wheeze. In the unadjusted model, the association between DII scores during pregnancy and offspring asthma and/or wheeze was statistically significant and indicated that each one-unit increase in maternal DII scores was associated with approximately 17% increased odds of offspring asthma and/or wheeze by age 4 years. When adjusting for covariates, the effect size was attenuated such that each one-unit increase in maternal DII scores was associated with an approximate 15% increase in odds of offspring asthma and/or wheeze, holding all other variables constant. The effect size observed in the adjusted model was clinically meaningful, although statistical significance was lost as the confidence interval spanned the null value of 1 (95% CI = 0.99–1.33). The observed associations suggest that the higher the inflammatory potential of the maternal diet, the higher the risk of offspring asthma and/or wheeze.

Chen et al.[4] and Hanson et al.[5] relied on self-report by general practitioner or parents and parent report of wheeze and asthma using the International Study of Asthma and Allergies in Children (ISAAC) questions, respectively. In this study, asthma and wheeze outcome information was extracted from electronic medical records. Thus, the use of this objective measure of asthma/wheeze may have limited the possibility of information bias in this study.

The statistical analysis also took into account many other factors previously associated with development of asthma and/or wheeze or inflammatory processes. These covariates included nulliparity,[36] gestational smoking,[37] maternal race/ethnicity,[38] pre-pregnancy BMI category,[39] maternal history of asthma,[40] and total caloric intake during pregnancy (kcal/day). Chen et al.[4] adjusted for socioeconomic status, maternal education, maternal smoking during pregnancy, alcohol intake during pregnancy, total caloric intake, maternal age, pre-pregnancy BMI, parity, and child's sex. Hanson et al.[5] adjusted for maternal education, race/ethnicity, smoking in pregnancy, pre-pregnancy BMI, maternal and paternal asthma, and child's sex. Therefore, the adjusted models from the two other studies and the present study all included gestational smoking and pre-pregnancy BMI as covariates, but other covariates differed, which could also explain the different results.

No previous studies have explored the relationship between maternal DII during pregnancy and cord blood cytokines and chemokines. In the development of the DII, a score was assigned to each nutrient/food based on their inflammatory potential: e.g. '+1' if the pro-inflammatory cytokines IL-1β, IL-6, TNF-α or CRP increased, and '−1' if the anti-inflammatory cytokines increased. It was therefore expected that higher maternal DII scores would be positively associated with pro-inflammatory cytokines and chemokines (IL-1β, IL-6, TNF-α, MCP-1, IL-8).[19] and negatively associated with anti-inflammatory cytokines such as IL-10.[44] Yet there were no significant associations between maternal DII scores with any of the cord sera inflammatory markers. There were no significant associations between any of the cord sera cytokines and chemokines and offspring diagnosis of asthma and/or wheeze by age 4 years. A challenge of studying cytokine and chemokine levels is that there are no established reference levels indicating high or low levels for cytokines or chemokines. Thus, it is unclear what changes in cytokines are clinically significant, if any. The only cord blood cytokine previously showing an association with wheeze[45] or atopic diseases (including asthma)[45–47] was lower levels of IFN-y, but this cytokine was not included in the panel for this study.

Strengths

The strength of this study is the data presented from a well-characterized multi-ethnic, and socio-economic diverse cohort with a large sample size, including a range which enabled taking various relevant covariates into account. The authors were able to study the association between a measure of total dietary intake (DII) during pregnancy, physician diagnosed offspring asthma and/or wheeze, and a range of cytokines and chemokines in cord sera. This is the first study to report on the association between maternal DII and cord sera cytokines levels as a possible underlying mechanism for the development of offspring allergies.

Limitations

However, the results may be limited as only one Th2 and one T-regulatory cytokine were measured. Measuring cytokines in cord blood mononuclear cells, after sufficient stimulation with antigen, may be preferable to using frozen cord sera. Measurements of cytokines in frozen cord sera may fail as there is the risk that most measurements will fall below limits of detection. In the present study, the levels detected were mostly within the limits of detection, and followed standard curves, suggesting that the measurements from sera are reasonable. Because the measurements seemed reasonable, it is unlikely that measurement error biased the hypothesis testing results towards or against the null hypothesis. Other limitations included the potential bias associated with the self-report of dietary intake.[48,49] In addition, although the statistical models adjusted for the association between DII and asthma and or wheeze for nulliparity,[36] gestational smoking,[37] maternal race/ethnicity,[38] pre-pregnancy BMI category,[39] maternal history of asthma,[40] total caloric intake during pregnancy (kcal/day), breastmilk months, and age of introduction to solid foods, the authors did not adjust for other measured or non-measured confounders, such as other environmental exposures and maternal health behaviors. This may have biased the results, either towards or away from the null. Similarly, the models examining the association between DII and cytokines were not adjusted for environmental exposures and maternal health behaviors.

One other possible limitation is the choice of the index itself or the inclusion of only 28 components of an index based on 45 components. In addition, dietary supplements were not included when calculating the DII; results may differ when supplemental nutrients are considered. Maternal diet pre-conception and even paternal diet might affect asthma outcomes as well.[50] The DII has been shown to be associated with a range of health outcomes.[19,25,51–56] This paper's lack of a statistically significant result for the association between DII and offspring asthma/wheeze in the adjusted model may reflect low power and suggest the need to study the result in a cohort with a larger sample size, as the effect size was clinically meaningful (p=0.06). Another possibility would be to re-study the associations in a cohort where all 45 components of the DII could be measured, or the E-DII index could be used.

Conclusions

The results from this study did not indicate that a pro-inflammatory diet profile during pregnancy, as measured by the DII, was associated with cord blood cytokines and chemokines. Clinically meaningful results were found that suggested a more inflammatory maternal diet was associated with increased odds of offspring asthma and/or wheeze by age 4 years, but the finding was not statistically significant at the 0.05 level. Cord sera cytokines and chemokine levels were not associated with offspring asthma and/or wheeze by age 4 years. These findings suggest that further studies are required to establish the role of pro-inflammatory diet patterns during pregnancy on cord blood cytokines and chemokines and offspring asthma and wheeze.

Acknowledgement

Abbreviations:

DII	Dietary inflammatory index
IL	Interleukin
MCP	Monocyte chemoattractant protein
TNF	Tumor necrosis factor
IFN	Interferon
PCR	Polymerase chain reaction
ELISA	Enzyme-linked immunosorbent assay
Th	T-helper cell
BMI	Body mass index
IOM	Institute of Medicine
Kg	Kilogram
M	meter
IQR	Interquartile range
pg	picogram
mL	milliliter
SE	Standard error
SD	Standard deviation
CI	Confidence interval

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Practice Implications

- There is very little understanding about how to manipulate the maternal diet in pregnancy to prevent offspring allergy, including asthma and/or wheeze outcomes.

- There is currently no guidance that we can provide to pregnant women to prevent asthma and/or wheeze in their offspring.

- The findings of this paper suggest that increases in the inflammatory profile of the maternal diet may be associated with increased odds of asthma and/or wheeze in offspring, but further studies are required to establish the role of proinflammatory diet patterns during pregnancy on offspring asthma and wheeze.

Research snapshot

Research question:

Does a pro-inflammatory diet in pregnancy relate to pro-inflammatory cytokine and chemokine levels at birth and offspring asthma and/or wheeze at age 4 years?

Key findings:

In this prospective pre-birth cohort that included 1228 mother-child dyads from the Healthy Start Study, Denver, Colorado, US, a pro-inflammatory diet during pregnancy was not significantly associated with cord blood cytokine or chemokine levels. The results suggested that a more inflammatory maternal diet was associated with increased odds of offspring asthma and/or wheeze by age 4 years, but the finding was not statistically significant at the 0.05 level (p=0.06). These findings could be considered clinically significant.

Food Parameter	Effect	Included in computation of DII[a] score for present study[b]
Alcohol	Negative (anti-inflammatory)	X
Vitamin B12	Positive (pro-inflammatory)	X
Vitamin B6	Negative (anti-inflammatory)	X
β-Carotene	Negative (anti-inflammatory)	
Caffeine	Negative (anti-inflammatory)	X
Carbohydrate	Positive (pro-inflammatory)	X
Cholesterol	Positive (pro-inflammatory)	X
Energy	Positive (pro-inflammatory)	X
Eugenol	Negative (anti-inflammatory)	
Total fat	Positive (pro-inflammatory)	X
Fiber	Negative (anti-inflammatory)	X
Folic acid	Negative (anti-	X

	inflammatory)	
Garlic	Negative (anti-inflammatory)	
Ginger	Negative (anti-inflammatory)	
Fe[c]	Positive (pro-inflammatory)	X
Mg[d]	Negative (anti-inflammatory)	X
MUFA[e]	Negative (anti-inflammatory)	X
Niacin	Negative (anti-inflammatory)	X
n-3 Fatty acids	Negative (anti-inflammatory)	X
n-6 Fatty acids	Negative (anti-inflammatory)	X
Onion	Negative (anti-inflammatory)	
Protein	Positive (pro-inflammatory)	X
PUFA[f]	Negative (anti-inflammatory)	X
Riboflavin	Negative (anti-inflammatory)	X

Saffron	Negative (anti-inflammatory)	
Saturated fat	Positive (pro-inflammatory)	X
Se[g]	Negative (anti-inflammatory)	X
Thiamin	Negative (anti-inflammatory)	X
Trans fat	Positive (pro-inflammatory)	X
Turmeric	Negative (anti-inflammatory)	
Vitamin A	Negative (anti-inflammatory)	X
Vitamin C	Negative (anti-inflammatory)	X
Vitamin D	Negative (anti-inflammatory)	X
Vitamin E	Negative (anti-inflammatory)	X
Zn[h]	Negative (anti-inflammatory)	X
Green/black tea	Negative (anti-inflammatory)	
Flavan-3-ol	Negative (anti-	

		inflammatory)
	Flavones	Negative (anti-inflammatory)
	Flavonols	Negative (anti-inflammatory)
	Flavonones	Negative (anti-inflammatory)
	Anthocyanidins	Negative (anti-inflammatory)
	Isoflavones	Negative (anti-inflammatory)
	Pepper	Negative (anti-inflammatory)
	Thyme/oregano	Negative (anti-inflammatory)
	Rosemary	Negative (anti-inflammatory)

Figure.

Food parameters included in the computation of the dietary inflammatory index (DII[a]) in the Healthy Start cohort

a) DII: dietary inflammatory index

b) An "X" indicates that the food component was included in the computation of DII scores for the present analysis

c) Fe: Iron

d) Mg: Magnesium

e) MUFA: Monounsaturated fatty acids

f) PUFA: Polyunsaturated fatty acids

g) Se: Selenium

h) Zn: Zinc

Table 1.

Maternal and offspring characteristics of the Healthy Start pre-birth observational cohort stratified by participants with and without cytokine data

	Overall sample	Subset with cytokine data	Subset without cytokine data	
Sample size (N)	1228	553	675	
Continuous variables	**mean ± SD**[a]	**mean ± SD**[a]	**mean ± SD**[a]	**p-value**[b]
Maternal characteristics				
Dietary inflammatory index	0.40 ± 1.6	0.41 ± 1.5	0.39 ± 1.6	0.85
Age at delivery (years)	27.8 ± 6.2	27.5 ± 6.2	28.1 ± 6.2	0.12
Total caloric intake (kcal/day)	2065 ± 387	2059 ± 387	2069 ± 386	0.65
Breastfeeding duration (breastmilk months)[34]	8.34 ± 6.8	8.01 ± 6.6	8.62 ± 6.9	0.17
Offspring characteristics				
Birthweight (grams)	3219 ± 509	3270 ± 437	3176 ± 558	0.03
Gestational age at birth (weeks)	39.3 ± 1.7	39.5 ± 1.3	39.1 ± 2.0	0.20
Age solid foods introduced (months)	6.16 ± 2.0	6.07 ± 1.9	6.24 ± 2.0	0.06
Categorical variables	**n (%)**	**n (%)**	**n (%)**	**p-value**[b]
Maternal characteristics				
Nulliparous	592 (48)	281 (51)	311 (46)	0.10
Smoking in pregnancy	103 (8)	50 (9)	53 (8)	0.45
Race/ethnicity				0.99
Non-Hispanic white	658 (54)	295 (53)	363 (54)	
Non-Hispanic black	188 (15)	85 (15)	103 (15)	
Hispanic	305 (25)	137 (25)	168 (25)	
Other[c]	77 (6)	36 (7)	41 (6)	
Pre-pregnancy body mass index[31]				0.37
Lean (<25 kg/m^2)	671 (55)	290 (52)	381 (56)	
Overweight (25–29.99 kg/m^2)	309 (25)	147 (27)	162 (24)	

	Overall sample	Subset with cytokine data	Subset without cytokine data	
Obese (≥30 kg/m²)	248 (20)	116 (21)	132 (20)	
IOM[d] gestational weight gain[33]				0.34
Less than recommended	294 (24)	122 (22)	172 (26)	
Within recommended range	353 (29)	161 (29)	192 (29)	
More than recommended	578 (47)	270 (49)	308 (46)	
Maternal history of asthma	202 (16)	95 (17)	107 (16)	0.54
Offspring characteristics				
Sex - female	588 (48)	262 (47)	326 (48)	0.75

[a] SD: Standard deviation

[b] p-value for hypothesis test comparing demographic variables between those with or without any cytokine data. Statistical tests included t-tests for normally distributed continuous variables, Wilcoxon rank sum tests for non-normally distributed continuous variables, and chi-square tests for categorical variables.

[c] Other race/ethnicity includes non-Hispanic Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multi-racial

[d] IOM: Institute of Medicine

Table 2.

Levels of cytokines and chemokines in cord sera of Healthy Start participants (N=581)

Cytokine/chemokine	Values outside detection range		Median (pg/mL)^b	IQR^a (pg/mL)^b
	n (%)	Direction^c		
Inflammatory cytokines				
IL^d-1β	313 (54.0)	Low	0.06	0.06–0.41
IL^d-6	2 (0.3)	High	9.80	4.66–24.47
TNF^e-α	0 (0.0)	-	32.63	25.19–41.49
Inflammatory chemokines				
IL^d-8	1 (0.2)	High	15.62	8.12–33.00
MCP^f-1	4 (0.7)	High	664.59	484.2–909.1
T-regulatory cytokine				
IL^d-10	0 (0.0)	-	12.95	8.61–23.36
Th2^g cytokine				
IL^d-4	194 (33.0)	Low	1.89	0.06–7.11

$^{a)}$IQR: Interquartile range

$^{b)}$Median and IQR were computed for each cytokine/chemokine with values belowdetection range set equal to 0.5*lowest standard and values above detection range set equal to 1.5*highest standard.

$^{c)}$Describes the direction of values that were outside the detection range as "high" (above upper limits of detection) or "low" (below lower limits of detection)

$^{d)}$IL: Interleukin

$^{e)}$TNF: Tumor necrosis factor

$^{f)}$MCP: Monocyte chemoattractant protein

$^{g)}$Th: T-helper cell

Table 3.

Summary of the coefficient of variation for each of the cytokines and chemokines studied

Cytokine/chemokine	mean ± SD	median	IQR^a
Inflammatory cytokines			
IL^b-1β	6.1 ± 6.3	6.0	0.0 – 7.4
IL^b-6	5.7 ± 5.0	4.7	2.0 – 7.9
TNF^c-α	6.1 ± 4.9	5.0	2.4 – 8.5
Inflammatory chemokines			
IL^b-8	5.5 ± 4.3	4.6	2.4 – 7.9
MCP^d-1	6.6 ± 5.4	5.4	2.6 – 9.8
T-regulatory cytokine			
IL^b-10	5.9 ± 4.8	4.9	2.6 – 8.3
Th2^e cytokine			
IL^b-4	4.1 ± 3.7	4.9	0.0 – 6.2

[a] IQR: Interquartile range

[b] IL: Interleukin

[c] TNF: Tumor necrosis factor

[d] MCP: Monocyte chemoattractant protein

[e] Th: T-helper cell

Table 4.

Associations between maternal dietary inflammatory index scores and offspring diagnosis of asthma/wheeze by age 4 years in mother-child dyads of the Healthy Start pre-birth cohort

Model	N	Odds ratio	95% CI[a]	p-value
Unadjusted	1228	1.17	1.07, 1.27	<0.001
Adjusted[b]	959	1.15	0.99, 1.33	0.06

[a]CI: Confidence interval

[b]Adjusted for the following covariates: nulliparous, gestational smoking, maternal race/ethnicity, pre-pregnancy body mass index category[31], maternal history of asthma, total caloric intake during pregnancy (kcal/day), breastfeeding duration[34], and age solid foods introduced.

Table 5.

Associations between maternal dietary inflammatory index score and natural log levels of cord sera cytokines and chemokines in mother-child dyads of the Healthy Start pre-birth cohort

Outcome	Unadjusted (N=573)			Adjusted[a] (N=571)		
	β[b]	SE[c]	p-value	β[b]	SE[c]	p-value
IL[d]-6	−0.03	0.04	0.40	−0.03	0.05	0.60
IL[d]-8	0.003	0.03	0.92	0.01	0.04	0.82
TNF[e]-α	0.01	0.01	0.57	0.001	0.02	0.93
MCP[f]-1	0.01	0.01	0.63	0.03	0.02	0.14
IL[d]-10	−0.01	0.02	0.80	−0.01	0.03	0.88

[a] Adjusted for the following covariates: nulliparous, gestational smoking, maternal race/ethnicity, pre-pregnancy body mass index category[31], and total caloric intake during pregnancy (kcal/day). The model for IL-10 additionally adjusts for maternal history of asthma.

[b] The beta estimate represents the change in log-pg/mL of each outcome per each one-unit increase in maternal dietary inflammatory index score.

[c] SE: Standard error

[d] IL: Interleukin

[e] TNF: Tumor necrosis factor

[f] MCP: Monocyte chemoattractant protein

Table 6.

Associations between maternal dietary inflammatory index score and the odds of the cord sera cytokine value being detectable in the Healthy Start pre-birth cohort

Outcome	Unadjusted (N=573)			Adjusted[a] (N=571)		
	Odds ratio[b]	95% CI[c]	p-value	Odds ratio[b]	95% CI[c]	p-value
IL[d]-1β	0.94	0.84, 1.04	0.23	1.02	0.89, 1.18	0.75
IL[d]-4	1.02	0.91, 1.14	0.76	1.01	0.87, 1.17	0.93

[a] Adjusted for the following covariates: nulliparous, gestational smoking, maternal race/ethnicity, pre-pregnancy body mass index category[31], and total caloric intake during pregnancy (kcal/day). The model for IL-4 additionally adjusts for maternal history of asthma.

[b] The odds ratio represents the change in the odds that the outcome is detectable per a one-unit increase in maternal dietary inflammatory index score.

[c] CI: Confidence interval

[d] IL: Interleukin

Table 7.

Associations between cord sera cytokines/chemokines and offspring diagnosis of asthma and/or wheeze by age 4 years in the Healthy Start pre-birth cohort

Predictor	Unadjusted (N=560)			Adjusted[a] (N=441)		
	Odds ratio[b]	95% CI[c]	p-value	Odds ratio[b]	95% CI[c]	p-value
IL[d]-6	1.000	1.000, 1.001	0.47	1.000	1.000, 1.001	0.30
IL[d]-8	1.001	1.000, 1.002	0.15	1.001	0.999, 1.002	0.40
TNF[e]-α	1.006	0.995, 1.017	0.31	1.01	0.99, 1.02	0.31
MCP[f]-1	1.000	0.999, 1.000	0.48	1.000	1.000, 1.000	0.90
IL[d]-10	1.00	0.995, 1.004	0.69	1.00	0.99, 1.01	0.99
IL[d]-1β	1.03	0.79, 1.52	0.89	1.18	0.73, 1.90	0.51
IL[d]-4	0.85	0.57, 1.28	0.44	0.81	0.49, 1.33	0.40

[a)]Adjusted for the following covariates: nulliparous, gestational smoking, maternal race/ethnicity, pre-pregnancy body mass index category[31], Institute of Medicine gestational weight gain category[33], maternal history of asthma, breastfeeding duration[34], and age solid foods introduced.

[b)]The odds ratio (OR) represents the change in the odds of offspring asthma/wheeze diagnosis per a 1-pg/mL increase for the following biomarkers: IL-6, IL-8, TNF-α, MCP-1, and IL-10. For the cytokines IL-1β and IL-4, the OR represents the difference in the odds of offspring asthma/wheeze between those with cytokine values below the detection limit (reference level) vs those with detectable levels of the cytokine.

[c)]CI: Confidence interval

[d)]IL: Interleukin

[e)]TNF: Tumor necrosis factor

[f)]MCP: Monocyte chemoattractant protein