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Maternal dietary inflammatory index score during pregnancy is not associated with the development of respiratory outcomes in early childhood

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Abstract

Maternal dietary inflammatory index score during pregnancy is not associated with the development of respiratory outcomes in early childhood

By Jenna Abdelhadi

Background: The inflammatory potential of maternal diet during pregnancy may influence the development of childhood wheeze and asthma.
Objective: To examine the relationship between the inflammatory potential of maternal diet during pregnancy and likelihood of developing wheeze and asthma in early childhood.
Methods: The Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) study is a prospective cohort of 1503 mother-child dyads in Shelby County, Tennessee. Second trimester maternal dietary and supplement intakes, assessed using the 2005 Block food frequency questionnaire, were used to calculate dietary inflammatory potential using the energy-adjusted dietary inflammatory index (E-DII®). E-DII is an *a priori* dietary pattern that classifies diets on a continuum from maximally anti-inflammatory to pro-inflammatory. Current wheeze (age 3y N=167; age 4-6y N=183) and ever asthma (age 4y N=136) were assessed by parental report. Recurrent wheeze was calculated from affirmative responses to current wheeze at age 3y and 4-6y (N=82). Multivariable logistic regression was used to assess the relationships between quartiles of maternal E-DII and child wheeze and asthma outcomes.
Results: The prevalence of age 3y current wheeze, age 4-6y current wheeze, recurrent wheeze, and ever asthma was 20.0%, 20.9%, 8.8%, and 14.9%, respectively. The E-DII scores ranged from -6.3 to 4.9 with mean -1.6. There was no association between E-DII and wheeze and asthma outcomes in adjusted analyses. The aOR for E-DII quartile 4 (pro-inflammatory) vs. quartile 1 (anti-inflammatory) was: 1.1 (95% CI: 0.70, 2.06) for age 3y current wheeze; 0.93 (95% CI: 0.57, 1.53) for age 4-6y current wheeze; 1.38 (95% CI: 0.69, 2.8) for recurrent wheeze; and 1.39 (95% CI: 0.80, 2.43) for ever asthma.
Conclusions: The inflammatory potential of second trimester maternal dietary and supplement intake, as assessed by the E-DII, was not associated with wheeze and asthma development in early childhood.

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Introduction

Childhood asthma is one of the most common chronic conditions worldwide and has expensive societal costs including healthcare expenses, loss of productivity from school absences, and increased risk for premature death.[1-3] The burden of this disease has been increasing over time, particularly in high-income countries, yet the etiology is not fully understood. It is believed to include a combination of genetic and environmental triggers, and the rising prevalence suggests an increasing influence of environmental factors such as diet.[4-9] More specifically, maternal diet is hypothesized to be linked to the development of childhood asthma through the developmental origins of disease hypothesis, which posits that *in utero* exposures influence developmental pathways during critical periods of prenatal and postnatal life.[10] Proposed mechanisms by which maternal diet affects childhood asthma risk include: 1) epigenetic mechanisms that alter gene expression, resulting in impaired fetal airway development[10,11] and 2) modulation of the fetal immune system.[8,12] The quality or quantity of *in utero* nutrient exposures may interact with genetic predispositions, resulting in the development of multiple immune system pathways.[8,13,14]

Although associations between maternal diet and childhood asthma have been explored, previous studies have primarily focused on individual nutrients and food groups.[15-22] For example, prior cohort studies have reported associations between increased maternal intake of vitamin E, vitamin D, and omega-3 polyunsaturated fatty acids and a decreased risk of wheeze or asthma in children.[15-19,23] Studies looking at specific foods found an association between increased maternal intake of fish and apples and a decreased risk of childhood wheeze and asthma, while meat consumption was

associated with an increased risk.[20-22,24] However, diets are complex and are comprised of multiple food groups that contain combinations of nutrients that interact with each other, and may provide differing effects based on the individual's underlying nutritional status.

Rather than focusing on individual nutrients or food groups, dietary pattern analysis provides insight into the interactive and cumulative effects of nutrition on health outcomes. One such dietary pattern is the dietary inflammatory index (DII®), which classifies diets on a continuum from maximally anti-inflammatory (low scores) to maximally pro-inflammatory (high scores)[25]. The construct validity of the DII has been demonstrated with various inflammatory biomarkers in blood, including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) in nonpregnant adults.[26-28] With respect to asthma, higher DII scores were associated with increased odds of asthma, inflammation, and lung function in a cross-sectional study of adults.[28] Further, in an analysis of data from the National Health and Nutrition Examination Survey (NHANES), higher DII was associated with increased odds of current wheeze in adults and children, and decreased lung function in adults.[29]

The associations between the inflammatory potential of maternal diet during pregnancy and respiratory outcomes in offspring remain largely unexplored. Only one study to date has investigated the influence of the maternal Dietary Inflammatory Index (DII) during pregnancy, which demonstrated that higher DII score was associated with a higher risk of asthma in offspring.[30] However, this study examined data from a predominantly white population in Ireland, and results have yet to be reproduced in the literature. Because maternal inflammation during pregnancy may be an important component of childhood asthma pathogenesis, it is thus of interest to further examine the

potential relationship between maternal DII and childhood wheeze and asthma, especially in underrepresented populations. Our aim is to address this research gap by investigating the associations between maternal dietary inflammatory potential (measured by DII) during the second trimester of pregnancy and subsequent childhood wheeze and asthma development in childhood (ages 3 and 4-6 years) in a well-characterized cohort of predominantly African American mother-child dyads in the United States.

Methods

Study Population

Data were obtained from the Conditions Affect Neurocognitive Development in Early Childhood (CANDLE) study, a longitudinal prenatal cohort of 1503 mother-child dyads in Memphis, Tennessee. The cohort consists of women who at enrollment (2006 to 2011) were aged 16 to 40 years old, were between 16 and 27 weeks of gestation with a singleton pregnancy, and were able to speak and understand English[31,32]. The following criteria excluded participants: an existing chronic disease requiring medication other than asthma (e.g., hypertension, insulin dependent or Type II diabetes mellitus, sick cell disease or trait, renal disease, hepatitis, lupus erythematous, scleroderma, pulmonary disease, heart disease, human immunodeficiency virus); pregnancy complications including maternal red cell alloimmunization (Rh factor incompatibility permitted); prolapsed or ruptured membranes; oligohydramnios; complete placenta previa; and not intending to deliver at one of four participating hospitals.

Mother-child dyads were followed over time with study visits taking place in the clinic, home, and by phone. Study visits pertinent to this analysis are the enrollment visit

in the 2nd trimester, delivery visit, home visit 4 weeks after delivery, and age 3y and 4-6y clinic visits. All visits were conducted by research nurses or trained research assistants.[33]

Dietary Assessment

Maternal dietary intake was assessed with the 2005 Block Food Frequency Questionnaire (FFQ), administered by trained interviewers at enrollment (the second trimester). The 2005 Block FFQ adapted for this study elicited usual intake of 111 food, beverage, and supplement groups during the previous three months. The full FFQ has been shown to be a valid and reliable method to describe usual nutrient intake for groups and to rank individuals according to nutrients intake.[34,35] The Block FFQ assessed the frequency of intake and quantity of foods and supplements consumed with the aid of standardized pictures. Interviewers were trained and recertified bi-annually by registered dietitians based on a taped interview. The FFQ was processed using the *NutritionQuest* software (Berkeley, CA, USA) to yield daily macro and micronutrient, food and supplement intakes. Flavonoid intakes were calculated as previously described.[36,37]

Energy-adjusted Dietary Inflammatory Index (E-DII®)

The inflammatory potential of maternal diet measured during the second trimester was estimated using the E-DII, calculated from FFQ nutrient and supplement data.[25] We had data on 35 of the 45 DII parameters: alcohol, vitamin B12, vitamin B6, beta carotene, caffeine, carbohydrates, cholesterol, total energy, total fat, fiber, folic acid, iron, magnesium, MUFAs, niacin, n-3s, n-6s, protein, PUFAs, riboflavin, saturated fat, selenium, thiamin, trans fats, vitamin A, vitamin C, vitamin D, vitamin E, zinc, flavan-3-ol, flavones, flavonols, flavonones, anthocyanidins, and isoflavones. To account for the effect of total energy intake, nutrient intake values were energy adjusted using the density

method (i.e., amount per 1000 kcal of energy for DII components).[38] To avoid the arbitrariness resulting from using simple raw consumption amounts, DII scores were standardized to a representative range of dietary intake based on actual human consumption.[25] E-DII values were categorized as quartiles, where quartile 1 was least inflammatory and quartile 4 was most inflammatory. We present the E-DII+S (diet + supplements) findings as our primary results because the majority of the participants reported taking supplements when dietary intake was assessed during pregnancy. E-DII (diet only, without supplements) was considered as a secondary exposure of interest.

Outcomes

At the 3 and 4-6 year study visit, current wheeze was defined as the affirmative parental responses to questions derived from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[39] Children with an affirmative parental response to "Has your child ever had wheezing or whistling in the chest at any time in the past?" AND report of having at least one "attack" of wheeze in the previous 12 months were characterized as having current wheeze at the respective visit. Children were classified as having recurrent wheeze if they reported having current wheeze at both age 3y and age 4-6y. Ever asthma at age 4-6 y was defined as an affirmative parental response to the question, "Has your child ever been diagnosed with asthma?"

Covariates

CANDLE has detailed information on sociodemographic, maternal, birth, and child characteristics. For statistical analyses, maternal education attainment was categorized into 3 groups: ≤high school/GED, completed technical school or 2y of college, and completed college or higher training/degrees; maternal race was categorized

as Black, white, and other; maternal pre-pregnancy body mass index (BMI) was calculated as weight (kg) per height $(m)^2$ from maternal report of pre-pregnancy height and weight, and was treated as a continuous variable. Dichotomous measures included: maternal Medicaid receipt during pregnancy, maternal history of ever smoking, maternal history of asthma, and CANDLE child sex. Birthweight and maternal age were both treated as continuous variables. Covariate missing data ranged from 0.1% (n= 2) to 6.6% (n= 60).

Statistical Analysis

For the current analysis, we included mother-child dyads with data on maternal dietary intake during pregnancy and the age 3 and 4-6y outcomes of interest (Figure 1). Of the 1503 participants enrolled, dietary intake data were unable to be retrieved for 181 women; these data are considered missing at random, and these participants were excluded from the analysis. We excluded 157 mother-child pairs where women reported implausibly low (<1000 kcal/day) or high (>5000 kcal/day) total energy intake for pregnancy.[38] The analytical sample sizes for age 3y current wheeze, age 4-6y current child wheeze, age 4-6 recurrent wheeze, and age 4-6 ever asthma were N= 798, 914, 735, and 912, respectively. A child missing their age 3y study visit was still eligible to complete their age 4-6y study visit, explaining why the analytical samples are larger at 4-6y.

Data were analyzed using SAS® version 9.4 (SAS Institute, Cary, NC, USA). Two-sided P-values <0.05 were considered statistically significant. To examine potential for bias in our final sample, we compared baseline demographics between participants

excluded because of missing dietary or outcome information and those with complete data using Student's t-tests and χ^2 tests for sample means and proportions, respectively.

The exposure variables, E-DII+S and E-DII, were analyzed independently as continuous and categorical measures. Results are presented in quartiles of E-DII+S, using the lowest quartile (least inflammatory group) as the referent for interpretability. The outcome variables, age 3y current wheeze, age 4-6y current wheeze, age 4-6y recurrent wheeze, and age 4-6y ever asthma were dichotomous. Descriptive results are reported as mean ± standard error (SE) for continuous variables, or n (%) for categorical variables. Analysis of variance and chi-square tests were used to describe covariate data by quartile of E-DII+S.

Multivariable logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (95% CI) between maternal E-DII and each respiratory outcome. Potential confounders were identified *a priori* based on established associations from the literature and the hypothesized associations with maternal diet during pregnancy, with specific consideration given to the temporal relationship between prenatal exposures and development of child respiratory outcomes. Our minimally adjusted model (model 1) considered maternal educational attainment and Medicaid status at enrollment. For our fully adjusted model (model 2), we further included maternal age, pre-pregnancy BMI, maternal history of ever smoking, maternal self-reported asthma history, sex of CANDLE child, and child's birthweight. Logistic regressions modeling E-DII+S and E-DII as continuous variables were also performed.

Potential effect modification by each covariate was examined by including each individual factor and its cross-product term with the continuous E-DII variable in

separate fully adjusted models. There was evidence of effect modification by maternal history of smoking at age 3y current wheeze (p= 0.03), and so stratified analyses were performed for smoking and non-smoking mothers for that outcome only.

Results

Participant Characteristics

Participant characteristics are presented by quartile of maternal E-DII+S in Table 1. Approximately 20% of children in the study had wheeze at ages 3 and 4y, though the proportion with recurrent wheeze from 3 to 4-6y was 11%. At age 4-6, about 15% of women reported that their child had been diagnosed with asthma. The prevalence of each respiratory outcome did not differ significantly by quartile of E-DII+S. Maternal education, race, Medicaid status, age at enrollment, age at enrollment, pre-pregnancy BMI, and child birthweight significantly differed by quartiles of E-DII+S. Overall, higher educational attainment was associated with more anti-inflammatory diet. The proportion of African American women was higher with increasing quartile of E-DII+S, while proportion of white women was lower. Medicaid participation increased but maternal age decreased with increasing E-DII+S quartile. Mean self-reported pre-pregnancy BMI was normal in quartile 4, and overweight in quartiles 1 through 3. Maternal history of smoking was highest in quartiles 3 and 4 at 12% and 15%, respectively, though differences across quartiles were not significant. Child birthweight tended to be lower for women reporting more inflammatory diets. Child sex and maternal asthma history did not differ by quartiles of E-DII.

E-DII+S scores ranged from -6.4 to 4.9 with a mean of -1.6. In comparison, E-DII scores ranged from -4.5 to 5.5 with a mean of 0.6. Overall, removing supplements worsened participant E-DII scores (Spearman correlation = 0.94). Energy-adjusted micronutrients with decreasing mean ± standard deviation (SD) from quartiles 1 to 4 included dietary alpha-carotene, total beta carotene, total vitamin A, total vitamin C, total alpha-tocopherol, and total selenium. Energy-adjusted micronutrients with increasing mean ± SD included average daily grams of omega-3 and omega-6.

Characteristics of maternal diet during pregnancy are presented by quartiles of E-DII+S in Table 2. All energy-adjusted mean nutrient intakes differed significantly across quartiles, with the exception of average daily omega-6 ($p= 0.79$). Total energy and proportion of energy from fat increased with increasing quartile; while proportion of kcal from protein and carbohydrate differed by quartile, there was no observable linear trend. Supplement use was greater than 96% in all quartiles except quartile 4, where it was 80%.

Adjusted associations between quartiles of E-DII+S and E-DII with age 3y current child wheeze, age 4-6y current child wheeze, age 4-6y recurrent wheeze, and age 4-6y asthma are presented in Table 3. There was no association between E-DII+S or E-DII with any of the wheeze or asthma outcomes examined in the unadjusted (data not presented) or adjusted models. From the fully adjusted model, the aOR for E-DII+S quartile 4 (most pro-inflammatory) vs. quartile 1 (most anti-inflammatory) was: 1.1 (95% CI: 0.70, 2.06) for age 3y current wheeze; 0.93 (95% CI: 0.57, 1.53) for age 4-6y current wheeze; 1.38 (95% CI: 0.69, 2.8) for recurrent wheeze; and 1.39 (95% CI: 0.80, 2.43) for ever asthma.

Odds ratios comparing quartiles 2-4 to quartile 1 of the E-DII+S were relatively close to the null in unadjusted estimates; adjusted models did not drastically alter these findings. Modeling E-DII without supplements lowered these odds ratios, though all findings remained null. There was no evidence of a dose-response relationship with quartiles of E-DII, with and without supplements.

There was evidence of effect measure modification by maternal smoking history in the analyses for age 3y current wheeze only (p= 0.03). No effect measure modification was evident for any other outcomes. To address this potential effect measure modification by smoking, we performed analyses for age 3y current wheeze stratified by maternal smoking history (Table 4). Odds ratios for non-smoking mothers were predominantly above 1 for E-DII+S and under 1 for E-DII, though none were statistically significant. However, modeling E-DII+S as a continuous variable in the stratified analyses resulted in odds ratios above 1 that were borderline significant for smoking mothers (OR 1.46, 95% CI 1.03, 2.06 and OR 1.50, 95% CI 1.03, 2.19 for minimally and fully adjusted models, respectively). This effect was not observed for non-smoking mothers.

Discussion

In this prospective analysis of the inflammatory potential of maternal diet during pregnancy estimated by the E-DII and childhood wheeze and asthma development, we found no evidence of an association. Research on the influence of maternal dietary quality on offspring respiratory outcomes, especially in regards to inflammatory potential, is highly limited. To the best of our knowledge, only one study thus far has

explored these associations using E-DII scores, which found that more proinflammatory diets are associated with a higher risk of offspring asthma.[30] This study was performed in a cohort of 862 mother-child pairs in Ireland, and children were followed for the first ten years of life. Contrary to our analyses, this study explored associations between maternal diet and childhood respiratory outcomes at 9 years of age, in addition to 3y and 5y.

Other prior research has focused predominantly on maternal adherence to the Mediterranean diet and has produced mixed results. Six prospective observational studies have examined the relationship between maternal dietary patterns during pregnancy and the development of childhood respiratory outcomes using other *a priori* or empirically defined dietary patterns.[30,40-45] Three studies used an *a priori* Mediterranean diet pattern[40-42], two derived diet patterns empirically[43,44], and one study used both empirical and two *a priori* diet patterns, Alternative Healthy Eating Index – Pregnancy and the Mediterranean diet.[45] The studies took place in Greece, Japan, Singapore, Spain, the UK, and the US. They considered wheeze, persistent and recurrent wheeze, and asthma in children ranging in ages 1y to 7y as respiratory outcomes.

Consistent with our findings, four of the six prospective observational studies reported no association between maternal dietary pattern during pregnancy and childhood wheeze or asthma development.[40,42,43,45] The two studies with significant findings reported a protective association between maternal better quality dietary patterns during pregnancy and the development of child wheeze and persistent wheeze.[41,44] These included a study in Menorca, Spain (n= 460 children) in which adherence to a Mediterranean diet during pregnancy was inversely associated with persistent wheeze in offspring at age 6.5 years of age (OR 0.22; 95% CI 0.08, 0.58).[41] The other study

investigated this relationship among 745 mother-child pairs in Spain and found no association (OR 0.97, 95% CI 0.77, 1.24); however, it is important to note that this study only assessed wheeze diagnoses in the first year of life.[40]

In a cohort study in Osaka, Japan, an empirically derived "Western" diet pattern was inversely associated with wheeze in offspring at age 16 to 24 months (OR quartile 4 vs quartile 1 0.59; 95% CI 0.35, 0.98).[44] In this cohort, wheeze was also assessed using questions adapted from ISAAC and the observed prevalence was 22%, similar to our findings. However, the study population was younger than CANDLE children and at an age when there are myriad determinants of wheeze. The Western pattern was characterized by high intake of vegetable oil, salt-containing seasonings, beef and pork, processed meats, eggs, chicken, and white vegetables, and low intake of fruit, soft drinks, and confectioneries and was positively correlated with high intakes of α-linolenic acid, vitamin E, and β-carotene. In analyses adjusting for α-linolenic acid and vitamin E intake, the association with the Western diet pattern was no longer significantly associated with child wheeze, suggesting these nutrients may be driving this association. Additionally, information on dietary supplements was not used in their calculation of dietary intake. However, differences in study design, sample populations, definitions of maternal diet, and age at outcome ascertainment could all have contributed to the heterogeneity of the results from preceding studies.

In our current study, mean E-DII was 0.6 with a range of -4.5 to 5.6, suggesting the average maternal diet was slightly pro-inflammatory. The inclusion of supplements in the calculation of E-DII+S shifted the mean down to -1.6 with a range of -6.3 to 4.9; this was expected, given that many nutrients contained in supplements have lower (more anti-

inflammatory) effects on E-DII scores. In contrast, in a study of pregnant women from Durham County, NC, E-DII scores calculated from 27 food parameters ranged from -5.0 to 5.0 with a median score of -1.4, suggesting their baseline diets were more anti-inflammatory.[46] However, this study has not reported on the associations between E-DII and childhood respiratory outcomes, and baseline characteristics of the sample differed from that in our analyses. Overall, a greater proportion of mothers were white and were college graduates, whereas the mothers in our sample were predominantly African American and were less likely to have completed college.

In a recent analysis using the 2007-2012 US National Health and Nutrition Examination Survey (NHANES), higher E-DII was associated with current wheeze among adults and children with atopic wheeze.[29] Higher E-DII also was associated with decreased FEV1 in adults without asthma or wheeze, but was not associated with lung function in children or current asthma in adults or children. In adults with asthma, higher DII scores were associated with increased concentrations of IL-6 and reduced lung function as measured by forced expiratory volume in one second (FEV_1). The DII was positively associated with CRP in previous studies among obese pregnant women (this was true of both energy adjusted and total scores), but was not associated with cytokine concentrations (IL-12, IL-17, IL-4, IL-6, and TNF-α).[46-48]

Our study is not without limitations. First, child respiratory outcomes in our data were collected by maternal report rather than a medical professional and may be prone to bias. Additionally, maternal participants with missing diet data were significantly different from participants with dietary intake data at enrollment. Participants missing diet or outcome data were 2 years younger on average (24.9 vs. 26.7 years), less likely to

have completed college (22.8 vs. 36.8%) or report breastfeeding 4 weeks postpartum (47.3 vs. 54.1%), had slightly lower BMIs (26.8 vs 27.9 kg/m^2) , and were more likely to be Black (70.5 vs. 63.0%), on Medicaid (70.1 vs. 53.4%), or report ever smoking (13.5 vs. 11.0% %). These individuals were excluded from the analysis, and thus there is some possibility that our results may be biased.

Further, the results from our study may not be applicable to a broader population. This analysis was conducted among a limited cohort of women residing in Shelby County, TN, who tended to consume relatively unhealthy diets; nevertheless, the vast majority of participants reported using dietary supplements. Additionally, information on environmental causes of wheeze and asthma, such as air pollution and household triggers (i.e., dust and mold), were not available and were not able to be adjusted for in our analyses. While they are presumably not associated with maternal diet, their potentially large contribution may skew the results. Further, it is unclear whether assessing outcomes at ages 3 and 4-6 years of age is too early to detect an association; assessing at an older age may allow for greater accuracy of diagnosis and provide a clearer picture. Finally, we detected an association between E-DII+S and age 3y current wheeze among smokers only; however, this analysis included a small number of smokers (n= 81), and thus further analyses with larger sample sizes of smoking mothers are needed.

Strengths of our study include the use of both prospectively collected wheeze and asthma data. While wheeze has determinants other than asthma, it is an important outcome in its own right – approximately 48% of US children have suffered one episode of wheeze by age 6.[49] Although it is difficult to predict subsequent asthma risk, 40% of young children will experience continued wheezing symptoms later in childhood, and a

history of wheeze increases the probability that a child will have asthma.[50] Our findings were consistent across time points and outcomes. Our study calculated the E-DII from high-quality dietary and supplement intake data that was collected using a validated FFQ. While it is uncommon to have dietary intake data for all of the food parameters in the DII, we had data on a substantial number of the parameters (35 of 45), and as such, E-DII scores are more likely to reflect the inflammatory potential of diets. Furthermore, our study applied the E-DII in an underrepresented population in the United States (predominantly African American with lower educational status), where the inflammatory potential of diet may differ. Our study population is well-characterized and we were able to adjust for many established confounders of wheeze and asthma.

Our data suggest there is no association between the inflammatory potential of maternal diet during pregnancy, as assessed by the E-DII, and the development of respiratory outcomes in early childhood. This is consistent with the findings from the majority of other prospective observational studies examining maternal diet and childhood asthma outcomes. Studies assessing the association between maternal diet and asthma outcomes using E-DII scores are limited; thus, future studies in more representative populations are necessary in order to form more definitive conclusions.

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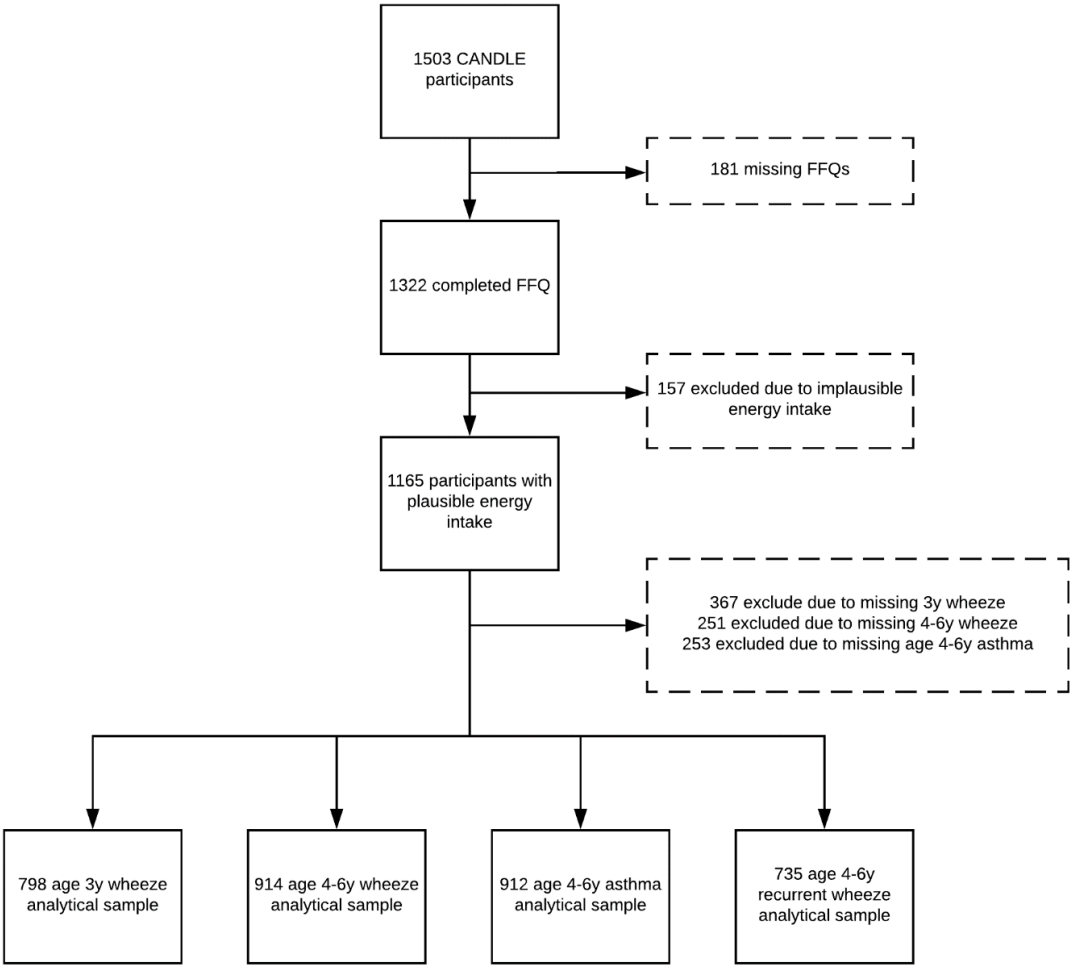

Figure 1. Analytical sample and reasons for exclusion, Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) Study, Memphis, Tennessee, 2006 to 2015.

Tables

Table 1. Demographic characteristics of CANDLE mother-child dyads by quartiles (Q1-4) of maternal energy adjusted diet inflammatory index (E-DII) + supplements, Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) Study, Memphis, Tennessee, 2006 to 2015.*

		More anti-inflammatory <- E-DII quintiles -> More pro-inflammatory			
		Q1	**Q2**	**Q3**	**Q4**
	N=	234	227	222	231
	Range:	(-6.3, -3.4)	(-3.4, -1.8)	(-1.8, 0.004)	(0.01, 4.9)
Characteristic	N (%)	N (%)	N (%)	N (%)	N (%)
Current child wheeze, age 3					
Yes	161 (21.9)	46 (23.2)	35 (18.6)	43 (23.2)	37 (22.6)
No	574 (78.1)	152 (76.8)	153 (81.4)	142 (76.8)	127 (77.4)
Current child wheeze, age 4-6					
Yes	183 (20.0)	37 (15.8)	48 (21.2)	43 (19.4)	55 (23.8)
No	731 (80.0)	197 (84.2)	179 (78.8)	179 (80.6)	176 (76.2)
Recurrent child wheeze, age 4-6					
Yes	82 (11.2)	18 (9.1)	18 (9.6)	22 (11.9)	24 (14.6)
No	653 (88.8)	180 (90.9)	170 (90.4)	163 (88.1)	140 (85.4)
Current child asthma, age 4-6					
Yes	135 (14.8)	27 (11.6)	28 (12.4)	31 (14.0)	49 (21.2)
No	776 (85.2)	206 (88.4)	198 (87.6)	190 (86.0)	182 (78.8)
Child Sex					
Male	458 (50.2)	115 (49.1)	110 (48.5)	112 (50.7)	121 (52.4)
Female	455 (49.8)	119 (50.9)	117 (51.5)	109 (49.3)	110 (47.6)
Maternal education					
≤High school diploma/GED	79 (8.6)	9 (3.9)	11 (4.9)	15 (6.8)	44 (19.1)
Technical school	499 (54.6)	82 (35.0)	114 (50.2)	144 (64.9)	159 (68.8)
Completed college	336 (36.8)	143 (61.1)	102 (44.9)	63 (28.3)	28 (12.1)
Maternal race					
White	323 (35.3)	138 (59.0)	96 (42.3)	62 (27.9)	27 (11.7)
Black	576 (63.0)	89 (38.0)	128 (56.4)	155 (69.8)	204 (88.3)
Other	15 (1.6)	7 (3.0)	3 (1.3)	5 (2.3)	0 (0.0)

Rec Medicaid at enrollment					
Yes	488 (53.4)	66 (28.2)	94 (41.4)	139 (62.6)	189 (81.8)
No	426 (46.6)	168 (71.8)	133 (58.6)	83 (37.4)	42 (18.2)
Maternal asthma history					
Yes	113 (12.5)	28 (12.0)	28 (12.5)	28 (12.8)	29 (12.6)
No	794 (87.5)	205 (88.0)	196 (87.5)	192 (87.3)	201 (87.4)
Maternal smoking history					
Ever smoke	94 (11.0)	19 (8.5)	19 (8.8)	24 (11.8)	32 (15.1)
Never smoke	760 (89.0)	204 (91.5)	197 (91.2)	179 (88.2)	180 (84.9)
Maternal age, years	26.0 ± 5.4	29.2 (5.0)	27.2 (5.3)	26.0 (5.2)	24.3 (5.3)
Maternal pre-pregnancy BMI, kg/m^2	27.5 ± 7.5	26.6 (6.8)	28.3 (7.5)	29.3 (8.9)	27.4 (7.5)
Child Birthweight	3227.8 ± 567.8	3355.6 ± 449.2	3313.0 ± 550.1	3252.7 ± 589.4	3133.3 ± 757.0

*Descriptive characteristics are presented using age 4 y current wheeze analytical sample (N=914). Samples sizes for other outcomes are as follows: age 3 y current wheeze N=798, age 4 y recurrent wheeze N = 735, age 4 asthma N= 912.
*Values are n (%) categorical variables or mean ± SD for continuous variables.

Table 2. Characteristics of maternal diet by quartiles (Q1-4) of energy adjusted dietary inflammatory index (E-DII) + supplements reported as mean ± SD or N (%), Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) Study, Memphis, Tennessee, 2006 to 2015.

		More anti-inflammatory <- E-DII quintiles -> More pro-inflammatory			
		Q1	**Q2**	**Q3**	**Q4**
	Range:	(-6.3, -3.4)	(-3.4, -1.8)	(-1.8, 0.004)	(0.01, 4.9)
	N=	234	227	222	231
Characteristic	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Maternal dietary intake					
Total energy, kcal	2401.7 ± 928.3	1930.8 ± 683.1	2167.5 ± 806.1	2486.2 ± 921.9	3027.9 ± 901.4
Protein, % kcal	14.9 ± 2.5	15.7 ± 2.3	15.0 ± 2.5	14.7 ± 2.4	14.3 ± 2.4
Carbohydrate, % kcal	50.8 ± 6.6	53.2 ± 5.8	51.5 ± 2.5	50.2 ± 6.0	48.1 ± 7.0
Fat, % kcal	36.3 ± 5.1	33.9 ± 4.8	35.5 ± 5.0	36.7 ± 4.3	38.8 ± 5.1
Supplement use					
Yes	860	233 (99.6)	226 (99.6)	215 (96.9)	186 (80.5)
No	54	1 (0.4)	1 (0.4)	7 (3.1)	45 (19.5)
Nutrients†					
Dietary Alpha-carotene, mcg	190.7 ± 224.7	360.3 ± 318.6	195.5 ± 185.7	120.4 ± 106.8	81.6 ± 82.2
Total Beta-carotene, mcg	2051.5 ± 1421.1	3608.7 ± 1528.3	2169.9 ± 913.1	1421.6 ± 637.4	963.6 ± 623.6
Total Vitamin A, RAE	1079.3 ± 415.0	1440.4 ± 342.7	1191.7 ± 310.3	995.8 ± 298.0	683.2 ± 274.2
Total Vitamin C, mg	112.5 ± 48.7	149.4 ± 56.2	119.9 ± 39.0	104.2 ± 32.7	75.9 ± 28.8
Total Alpha-tocopherol, mg	6.4 ± 2.8	8.5 ± 3.7	6.8 ± 2.4	5.8 ± 1.3	4.5 ± 1.2
Total Selenium, mcg	73.1 ± 16.7	82.6 ± 14.5	76.1 ± 15.5	71.8 ± 14.9	61.7 ± 14.5
Total avg daily omega-3 FA, g	0.9 ± 0.2	0.9 ± 0.03	0.9 ± 0.2	0.8 ± 0.2	0.8 ± 0.2
Total avg daily omega-6 FA, g	7.3 ± 1.5	7.3 ± 1.5	7.3 ± 1.4	7.3 ± 1.4	7.4 ± 1.5
E-DII (with supplements)	-1.6 ± 2.3	-4.4 ± 0.6	-2.6 ± 0.5	-0.9 ± 0.5	1.4 ± 1.2
E-DII (no supplements)	0.6 ± 2.3	-2.3 ± 1.0	-0.1 ± 0.8	1.6 ± 1.1	3.2 ± 1.0

*Values are n (%) categorical variables or mean ± SD for continuous variables

†Micronutrients are energy-adjusted per 1000 kcal

Table 3. Adjusted associations between quartiles of maternal energy-adjusted dietary inflammatory index and age 3y current child wheeze, age 4-6y current child wheeze, age 4-6y recurrent wheeze, and age 4-6y asthma, Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) Study, Memphis, Tennessee, 2006 to 2015

Quartiles of DII Score	Age 3y Current Wheeze				Age 4-6y Current Wheeze				Age 4-6y Recurrent Wheeze				Age 4-6y Asthma			
	aOR*	(95% CI)	aOR†	(95% CI)	aOR*	(95% CI)	aOR†	(95% CI)	aOR*	(95% CI)	aOR†	(95% CI)	aOR*	(95% CI)	aOR†	(95% CI)
E-DII+S‡[1]																
Q1 (N= 291)	Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Q2 (N= 291)	1.41	(0.86, 2.30)	1.45	(0.87, 2.40)	0.77	(0.48, 1.24)	0.73	(0.44, 1.21)	1.05	(0.52, 2.10)	0.99	(0.48, 2.05)	1.1	(0.61, 1.94)	0.99	(0.54, 1.81)
Q3 (N= 292)	1.28	(0.78, 2.11)	1.31	(0.79, 2.17)	0.79	(0.50, 1.27)	0.85	(0.52, 1.40)	1.11	(0.56, 2.17)	1.19	(0.60, 2.38)	0.9	(0.54, 1.66)	0.88	(0.49, 1.60)
Q4 (N= 291)	1.17	(0.69, 1.99)	1.12	(0.70, 2.06)	0.90	(0.56, 1.44)	0.93	(0.57, 1.53)	1.32	(0.67, 2.61)	1.38	(0.69, 2.76)	1.3	(0.78, 2.26)	1.39	(0.80, 2.43)
E-DII+S‡ (continuous)	0.98	(0.90, 1.07)	0.98	(0.90, 1.07)	1.01	(0.94, 1.10)	1.02	(0.94, 1.11)	1.04	(0.93, 1.17)	1.06	(0.94, 1.19)	1.02	(0.93, 1.11)	1.04	(0.95, 1.15)
E-DII‡[2]																
Q1 (N= 291)	Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Q2 (N= 291)	0.90	(0.56, 1.44)	0.96	(0.59, 1.56)	0.75	(0.47, 1.22)	0.74	(0.45, 1.22)	0.84	(0.43, 1.65)	0.85	(0.42, 1.73)	1.2	(0.67, 2.07)	1.09	(0.60, 1.97)
Q3 (N= 292)	0.79	(0.49, 1.28)	0.82	(0.50, 1.34)	0.93	(0.59, 1.47)	1.00	(0.62, 1.61)	1.12	(0.59, 2.09)	1.27	(0.67, 2.43)	1.2	(0.70, 2.04)	1.18	(0.67, 2.07)
Q4 (N= 291)	0.65	(0.39, 1.09)	0.69	(0.41, 1.15)	0.82	(0.52, 1.29)	0.86	(0.53, 1.40)	0.83	(0.42, 1.62)	0.90	(0.45, 1.79)	1.0	(0.59, 1.71)	1.09	(0.63, 1.91)
E-DII‡ (continuous)	0.96	(0.88, 1.04)	0.96	(0.88, 1.04)	1.01	(0.93, 1.09)	1.02	(0.94, 1.11)	1.01	(0.91, 1.13)	1.02	(0.91, 1.14)	0.98	(0.90, 1.07)	1.00	(0.91, 1.10)

*Adjusted for maternal education level and Medicaid status at enrollment

†Adjusted for maternal education level, Medicaid status at enrollment, age, self-reported pre-pregnancy BMI, history of ever smoking, maternal self-reported asthma history, birthweight, and sex of CANDLE child

‡Energy-adjusted dietary inflammatory index

[1]E-DII+S quartile cut-points: Q1 (-6.3, -3.4); Q2 (-3.4, -1.8); Q3 (-1.8, 0.004); Q4 (0.01, 4.9)

[2]E-DII quartile cut-points: Q1 (-5.4, -1.2); Q2 (-1.2, 0.6); Q3 (0.6, 2.5); Q4 (2.5, 5.4)

Table 4. Adjusted associations between quartiles of maternal energy-adjusted dietary inflammatory index and age 3y current child wheeze, stratified by maternal smoking history, Conditions Affecting Neurocognitive Development in Early Childhood (CANDLE) Study, Memphis, Tennessee, 2006 to 2015.

	Minimally Adjusted			Fully Adjusted		
	N	**aOR***	**95% CI**	**N**	**aOR†**	**95% CI**
E-DII+S‡						
Non-Smokers	699	0.96	(0.87, 1.05)	693	0.95	(0.86, 1.04)
Smokers	81	1.46	(1.03, 2.06)	78	1.50	(1.03, 2.19)
E-DII‡						
Non-Smokers	699	0.95	(0.87, 1.04)	693	0.94	(0.86, 1.03)
Smokers	81	1.15	(0.86, 1.54)	78	1.18	(0.85, 1.63)

*Adjusted for maternal education level and Medicaid status at enrollment

†Adjusted for maternal education level, Medicaid status at enrollment, age, self-reported pre-pregnancy BMI, history of ever smoking, maternal self-reported asthma history, birthweight, and sex of CANDLE child

‡Energy-adjusted dietary inflammatory index

**P-value for interaction between E-DII+S and maternal smoking was 0.03