Original Article

The Dietary Inflammatory Index and Current Wheeze Among Children and Adults in the United States

Yueh-Ying Han, PhD[a], Erick Forno, MD, MPH[a], Nitin Shivappa, PhD[b,c,d], Michael D. Wirth, PhD[b,c,d,e], James R. Hébert, ScD[b,c,d], and Juan C. Celedón, MD, PhD[a] *Pittsburgh, Pa; and Columbia, SC*

What is already known about this topic? Dietary patterns are associated with asthma and lung function, likely through proinflammatory pathways.

What does this article add to our knowledge? An overall proinflammatory diet, assessed by the Dietary Inflammatory Index (DII), increases the risk of current wheeze in adults and in children with high fractional exhaled nitric oxide. Moreover, the DII is associated with decreased forced expiratory volume in 1 second and forced vital capacity in adults without wheezing.

How does this study impact current management guidelines? A diet with higher proinflammatory components and lower anti-inflammatory components may have detrimental effects on asthma symptoms in adults and atopic children in the United States. Our findings further support studies of whole-diet interventions to reduce asthma burden.

BACKGROUND: A proinflammatory diet may increase allergic airway inflammation by affecting innate and adaptive immune responses.

OBJECTIVE: In this study, we examine the relation between the diet's inflammatory potential, measured by the Dietary Inflammatory Index (DII), and current asthma, current wheeze, and lung function in U.S. children and adults.

METHODS: We analyzed data from 8,175 children (aged 6-17 years) and 22,294 adults (aged 18-79 years) who participated in the 2007-2012 National Health and Nutrition Examination Survey. The DII was calculated by nutrient intake based on 24-hour dietary recalls, and normalized as per 1,000 calories of food consumed to account for total energy intake. Multivariable regression models were used for the analysis of the DII and current asthma, current wheeze, and lung function measures.

RESULTS: Higher DII (a proinflammatory diet) was associated with current wheeze among adults (eg, odds ratio [OR] for quartile 4 vs 1, OR = 1.41, 95% confidence interval [CI] = 1.17-1.70; $P_{trend} < .01$) and among children with high fractional exhaled nitric oxide (a marker of eosinophilic airway inflammation; OR = 2.38, 95% CI = 1.13-5.02; $P_{trend} = .05$). The DII also was associated with decreased forced expiratory volume in 1 second and forced vital capacity in adults without asthma or wheezing. The DII was not associated with lung function in children or current asthma in either age group.

CONCLUSIONS: Our findings suggest that a proinflammatory diet, assessed by the DII, increases the odds of current wheeze in adults and children with allergic (atopic) wheeze. These results further support testing dietary interventions as part of the management of asthma. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;■:■-■)

Key words: *Dietary Inflammatory Index; Asthma; Wheezing; Lung function; NHANES*

[a]Division of Pediatric Pulmonary Medicine, Allergy, and Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, Pa
[b]Department of Epidemiology and Biostatistics, University of South Carolina, Columbia, SC
[c]Cancer Prevention and Control Program, Arnold School of Public Health, University of South Carolina, Columbia, SC
[d]Connecting Health Innovations, Cancer Prevention and Control Program, University of South Carolina, Columbia, SC
[e]College of Nursing, University of South Carolina, Columbia, SC

E. Forno's contribution was supported by grants from the U.S. National Institutes of Health (NIH, HL125666), Children's Hospital of Pittsburgh, and the Klosterfrau Foundation. J. C. Celedón's contribution was supported by grants from the U.S. NIH (HL117191, HL119952, and MD011764) and by The Heinz Endowments. N. Shivappa, M. D. Wirth, and J. R. Hébert were supported by grant number R44DK103377 from the United States National Institute of Diabetes and Digestive and Kidney Diseases. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Y.-Y. Han and N. Shivappa had full access to all of the data and take responsibility for the integrity and accuracy of the analysis. None of the funding sponsors had any role in study design, data analysis, or manuscript preparation or approval.

Conflicts of interest: N. Shivappa and M. D. Wirth are employees of Connecting Health Innovations LLC (CHI). J. R. Hébert owns controlling interest in CHI, a company planning to license the right to his invention of the dietary inflammatory index (DII) from the University of South Carolina to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. J. C. Celedón received materials from Merck (inhaled steroids) and Pharmavite (vitamin D and placebo tablets), to provide medications at no cost to participants in 2 NIH-funded studies, unrelated to the current work. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 18, 2017; revised November 30, 2017; accepted for publication December 30, 2017.

Available online ■■

Corresponding author: Juan C. Celedón, MD, PhD, Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Pittsburgh, PA 15224. E-mail: juan.celedon@chp.edu.

2213-2198

https://doi.org/10.1016/j.jaip.2017.12.029

Abbreviations used
BDR- Bronchodilator response ([post-bronchodilator FEV_1 − pre-bronchodilator FEV_1]/pre-bronchodilator FEV_1) × 100)
BMI- Body mass index (weight [kg]/height [m]^2)
CDC- Centers for Disease Control and Prevention
COPD- chronic obstructive pulmonary disease
CRP- C-reactive protein
DII- Dietary inflammatory index
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
NHANES- National Health and Nutrition Examination Survey
PUFA- Polyunsaturated fatty acid
SCFA- Short chain fatty acid

Asthma is a chronic inflammatory airway disease that affects approximately 330 million people worldwide.[1] Temporal changes in environment and lifestyle, including diet, may partly explain the "asthma epidemic" in industrialized countries.[2,3] Whereas a Mediterranean diet (characterized by high intake of fruits, vegetables, and omega-3 polyunsaturated fatty acids [PUFAs]) has been associated with lower risk of asthma and wheeze,[4] a Westernized diet (characterized by low intake of fiber but high intake of saturated fats) has been associated with increased risk of asthma and wheeze.[5]

Dietary components can modulate immunity by regulating T-helper (Th)2 (proallergic) immune responses that lead to airway inflammation.[6] Dietary lipids can contribute to allergic diseases (such as atopic asthma) by enhancing inflammation,[7] whereas vitamin C and vitamin E have shown anti-inflammatory effects and potentially beneficial effects on asthma symptoms.[8] We previously reported that frequent consumption of vegetables and grains, coupled with less frequent consumption of dairy products and sweets, was associated with lower risk of asthma[9] but better lung function (higher forced expiratory volume in 1 second [FEV_1] and forced vital capacity [FVC])[10] in Puerto Rican children, a finding that may be mediated by IL-17F-dependent inflammatory pathways.[9,10]

Recent studies of diet and chronic diseases have focused on dietary patterns, as the combined and interacting effects of dietary components may have greater effects on disease pathogenesis than individual nutrients. The Dietary Inflammatory Index (DII) is a score that categorizes an individual's diet on a continuum from the most anti-inflammatory to the most proinflammatory. The DII was developed and validated to account for the whole diet of an individual, and not individual nutrients or food items.[11,12] A higher DII score, which reflects a proinflammatory diet, was recently associated with asthma and lower FEV_1 in a small case-control study of adults.[13]

We hypothesized that a proinflammatory diet is associated with increased asthma or wheeze, and worsened lung function. To test this hypothesis, we examined the relation between DII score and current asthma, current wheeze, and lung function in a large representative sample of U.S. children and adults. Because the proinflammatory effects of diet may vary by allergic status, we also examined whether the estimated effects of the DII on asthma or lung function are modified by the level of fractional exhaled nitric oxide (FeNO, a marker of eosinophilic airway inflammation).

METHODS

Subject recruitment and study procedures

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional nationwide survey designed to assess the health and nutritional status of the noninstitutionalized U.S. population. Study participants were selected by using stratified multistage probability sampling. By design, persons 60 years and older and ethnic minorities (African Americans and Hispanics) were oversampled to increase the statistical power for data analysis, and to represent the U.S. population across all ages. Both children (aged 6-17 years) and adults (aged 18-79 years) who participated in the 2007-2008, 2009-2010, and 2011-2012 NHANES cycles were included in this analysis. The NHANES interview includes questions on demographic, socioeconomic, dietary, and health-related factors. The examination component consists of medical and physiological measurements, as well as laboratory tests administered by highly trained medical personnel. NHANES was approved by the Institutional Review Board of the National Center for Health Statistics of the U.S. Centers for Disease Control and Prevention (CDC). Informed consent was obtained from all participants. A proxy provided information for survey participants who were less than 16 years of age and for subjects who could not answer the questions by themselves.

Survey participants aged 6 to 79 years were eligible for spirometry, except for those who were on supplemental oxygen or had painful ear infections, current chest pain or a physical problem with forceful expiration, surgery (of the eye, chest, or the abdomen) in the prior 3 months, heart disease, history of an aneurysm or a detached retina, hemoptysis, or history of a collapsed lung or tuberculosis exposure. Eligible participants performed spirometry following American Thoracic Society recommendations.[14] The best FEV_1 and FVC were selected for analysis. Participants whose baseline FEV_1/FVC ratio was below the lower limit of normal[15,16] and/or whose baseline FEV_1 was below 70% of the predicted value for their demographic characteristics underwent a repeat spirometry, 15 minutes after inhalation of albuterol. Participants were excluded from bronchodilator administration if they had recently used a short-acting inhaled β_2-agonist or had a previous adverse reaction to albuterol; had a history of congenital heart disease, hypertension, major arrhythmia, or an implanted defibrillator; or were pregnant or breastfeeding. Percent predicted FEV_1, FVC, and FEV_1/FVC in children and adults were calculated using Global Lung Initiative equations that account for age, sex, race/ethnicity, and height.[17] FeNO was measured using the Aerocrine NIOX MINO, a portable, hand-held nitric oxide analyzer (Aerocrine AB, Solna, Sweden). The NHANES protocol required 2 valid FeNO measurements that were reproducible. High FeNO was defined as $\geq$20 ppb in children and $\geq$25 ppb in adults.[18] Further details of the methods, protocols, and definitions used in NHANES can be found at http://www.cdc.gov/nchs/nhanes.htm.

The dietary inflammatory index

The development and validation of the DII has previously been reported.[11,12] Peer-reviewed literature published between 1950 and 2010 was evaluated, and 1943 articles linked to 45 individual nutrients, foods, or flavonoid intake parameters were identified. Points were assigned to each of these parameters according to whether they: (1) increased (+1), decreased (−1), or had no (0) effect on the 4 established proinflammatory biomarkers: IL-1β, IL-6, TNF-α, and C-reactive protein (CRP); or (2) decreased (+1), increased (−1), or had no (0) effect on the 2 established anti-inflammatory biomarkers:

IL-4 and IL-10. Based on the study designs and total number of research articles, the score for each of the food parameters was weighted. An overall inflammatory effect score was then calculated for each parameter, based on the ratio of the total weighted number of articles to the weighted pro- and anti-inflammatory articles for that parameter, followed by subtracting the anti- from the pro-inflammatory fraction. Parameters with a number of weighted articles greater than the median of 236 were assigned the full value of that score. Parameters with a total article weight less than 236 were adjusted by dividing it by 236, and then multiplying this fraction by the previously defined inflammatory effect score.

Our assessment of the DII included all of its 45 parameters. Dietary intake data were adjusted against a reference global daily mean and standard deviation intake for each parameter to obtain a *Z*-score and centered percentiles. The global intake data were based on consumption data from 11 countries in different parts of the world. In NHANES, 27 of the 45 DII food parameters were available, including carbohydrates, proteins, fats, alcohol, fiber, cholesterol, saturated fats, monounsaturated fats, PUFAs, omega-3 and omega-6 PUFAs, niacin, vitamins (A, B1, B2, B6, B12, C, D, and E), iron, magnesium, zinc, selenium, folic acid, beta carotene, and caffeine. The centered percentile for each intake parameter was multiplied by its respective parameter-specific inflammatory effect score, and then these 27 scores were summed to obtain an overall DII score for each participant. Higher (ie, more positive) scores indicate a more proinflammatory diet, and more negative scores indicate a more anti-inflammatory diet. To control for the effect of total energy intake, the DII was calculated per 1,000 calories of food consumed (using a calorie-adjusted version of the global database for comparison). Approximately 25% of the study participants reported intake of dietary supplements, and thus a separate DII score accounting for 24-hour dietary supplement was calculated. A sequence of steps in creating the DII for the NHANES 2007-2012 study is shown in Figure E1, available in this article's Online Repository at www.jaci-inpractice.org.

Statistical analysis

Current asthma was defined by a positive answer to both following questions: "Has a doctor or other health professional ever told you that you have asthma?" and "Do you still have asthma?" Participants who answered "no" to both questions were selected as control subjects. Current wheeze was defined by a positive answer to "In the past 12 months, have you had wheezing or whistling in your chest?" Bronchodilator response (BDR) was defined as follows: ([post-bronchodilator FEV_1 − pre-bronchodilator FEV_1]/pre-bronchodilator FEV_1) × 100.

Primary sampling units and strata for the complex NHANES survey design were taken into account for data analysis. Sampling weights, stratification, and clusters provided in the NHANES dataset were incorporated into the analysis to obtain proper estimates and their standard errors. All statistical analyses were conducted using the SAS SURVEY procedure and SAS 9.3 software (SAS Institute, Cary, NC). Wald χ^2 tests and *t* tests were used for bivariate analyses of binary and continuous variables, respectively. Logistic and linear regression was used for the multivariable analysis of the DII, current wheeze, current asthma, and lung function. BMI was calculated as weight (in kilograms) divided by height (in meters) squared. BMI *z*-scores in children were calculated based on the 2000 CDC growth charts.[19] All multivariate logistic regression models were adjusted for age, gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), annual household income, BMI (adult) or BMI *z*-score (children), family history of asthma, and smoking status (measured by serum levels of cotinine). In addition, models for BDR were adjusted for pre-bronchodilator FEV_1. Interaction terms were tested to explore potential modification of the estimated effect of the DII on current wheeze or current asthma by the covariates included in the multivariate models.

RESULTS

A total of 8,175 children aged 6 to 17 years and 22,294 adults aged 18 to 79 years had information on asthma status, underwent a 24-hour dietary recall interview and spirometry testing, and were thus included in the current analysis from NHANES 2007-2008 to 2011-2012. The main characteristics of study participants are shown in Table I. The overall prevalence of current asthma among children and adults was 11.3% and 7.9%, respectively (data not shown). Compared with children and adults without current wheeze, children and adults with current wheeze were more likely to be non-Hispanic black, and to have a lower annual household income, family history of asthma, lower FEV_1 and FEV_1/FVC, and higher BDR and FeNO. Compared with adults without wheeze, adults with current wheeze were more likely to be female, to lack private health insurance, to be current smokers, and to have higher BMI and higher serum cotinine levels. The DII was significantly higher in adults with current wheeze than in those without current wheeze. Table E1 in this article's Online Repository at www.jaci-inpractice.org shows the characteristics of study participants by current asthma, which yielded results similar to those for the comparison of subjects with and without current wheeze.

Results from the multivariable analysis of the DII, current asthma, and current wheeze are shown in Table II. After adjusting for age, gender, race/ethnicity, annual household income, BMI, family history of asthma, and serum cotinine, a one-point increment in the DII was significantly associated with 9% increased odds of current wheeze. In a multivariable analysis of quartiles of the DII, adults in the third and fourth quartile of the DII had significantly higher odds of current asthma than those in the first quartile (eg, quartile 4 vs quartile 1, the odds ratio = 1.41, 95% confidence interval [CI] = 1.17-1.70). The DII was not significantly associated with current asthma in children or adults, or with current wheeze in children. Similar results were found using the DII that accounted for 24-hour intake of dietary supplements. Because the interaction terms between the DII and gender, race/ethnicity, annual household income, BMI, and current smoking were significant on current wheeze among adults (data not shown), multivariate analyses stratified by these variables were conducted and are shown in Table III. The association between the higher DII and current wheeze was more pronounced among those who were male, current smokers, non-Hispanic white, and overweight or obese, as well as in those who had an annual household income of ≥$20,000.

To examine whether the estimated effect of the DII on current asthma or current wheeze is modified by allergic (eosinophilic) airway inflammation, an interaction term between the DII and level of FeNO was tested. Significant interactions between the DII and FeNO level on current wheeze were found in both children ($P = .04$) and adults ($P = .01$). We thus repeated the multivariable analysis in children and adults after stratification by level of FeNO (Figure 1 and Table E2 in this article's Online Repository at www.jaci-inpractice.org). In this analysis, children

TABLE I. Characteristics of participants by current wheeze, NHANES 2007-2012

Characteristics	Children 6-17 y		Adults 18-79 y	
	Current wheezing			
	No n = 6,343	Yes n = 744	No n = 15,313	Yes n = 2,204
Age (y)	11.7 ± 0.1	11.7 ± 0.3	44.0 ± 0.4	44.1 ± 0.7
Male gender	3,166 (48.7)	437 (51.8)	7,639 (49.5)	1,007 (44.3)*
Race/ethnicity				
Non-Hispanic white	1,914 (59.1)	221 (53.3)*	6,579 (67.9)	1,131 (72.1)*
Non-Hispanic black	1,428 (12.9)	248 (21.2)	3,081 (10.8)	528 (13.1)
Mexican American/other Hispanic	2,438 (21.6)	208 (16.7)	4,481 (14.9)	422 (8.9)
Other	563 (6.4)	67 (8.8)	1,172 (6.4)	123 (5.9)
Private health insurance coverage	2,155 (59.8)	240 (54.1)	6,360 (65.2)	769 (54.9)*
Annual household income <$20,000	1,304 (15.0)	175 (17.8)	2,819 (13.2)	614 (21.2)*
Family history of asthma	1,686 (26.6)	413 (53.5)*	2,709 (17.6)	801 (36.9)*
Current asthma	330 (4.7)	483 (59.1)*	526 (3.4)	787 (36.4)*
Body mass index (kg/m^2)	21.0 ± 0.1	21.5 ± 0.2	28.4 ± 0.1	30.7 ± 0.3*
BMI *z*-score	0.64 ± 0.03	0.76 ± 0.06	–	–
Current smoker	–	–	2,845 (18.8)	858 (42.1)*
Serum cotinine level (ng/mL)	5.5 ± 1.2	8.8 ± 3.2	50.0 ± 2.4	110.3 ± 6.9*
The dietary inflammatory index (DII)†	0.91 ± 0.05	1.01 ± 0.10	0.22 ± 0.04	0.77 ± 0.06*
Fractional exhaled nitric oxide (FeNO), ppb	15.0 ± 0.4	24.3 ± 1.6*	16.0 ± 0.3	21.2 ± 0.9*
% predicted pre-bronchodilator FEV_1	104.3 ± 0.4	100.6 ± 0.7*	98.6 ± 0.3	89.1 ± 0.7*
% predicted pre-bronchodilator FVC	105.9 ± 0.4	105.4 ± 0.9	101.8 ± 0.3	97.0 ± 0.5*
% predicted pre-bronchodilator FEV_1/FVC	98.0 ± 0.2	95.1 ± 0.5*	96.6 ± 0.2	91.3 ± 0.4*
Bronchodilator response (%)	9.3 ± 0.6	14.4 ± 1.5*	5.3 ± 0.2	8.9 ± 0.6*

BMI, Body mass index; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *NHANES*, National Health and Nutrition Examination Survey.
Results are shown as mean ± standard error (SE) for continuous variables, and as N (%) for binary variables.
*$P < .01$ for current wheezing vs no current wheezing (within each age group).
†The DII was calculated per 1,000 calories of daily food consumed.

with the DII in the second to fourth quartiles and who had a high FeNO had 2- to 3-fold significantly increased odds of current wheeze. In contrast, there was no significant association between the DII and current wheeze among children with low FeNO. Among adult participants, those in the fourth quartile of the DII had significantly higher odds of current wheeze than those in the first quartile of the DII, both in the low/normal FeNO group and in the high FeNO group. The DII was not significantly associated with current asthma in children or adults, regardless of their FeNO level (data not shown).

Table IV shows the multivariable analysis of the DII and lung function measures among study participants. In adults without current asthma or current wheeze, each unit increment in the DII was significantly associated with 0.22% to 0.35% decrements in % predicted FEV_1 ($\beta = -0.22$, 95% CI = −0.44, −0.01), and % predicted FVC ($\beta = -0.35$, 95% CI = −0.55, −0.15). In adults with current wheeze, there was no significant association between the DII and FEV_1 or FVC. The DII was significantly associated with higher BDR among children ($\beta = 2.17$, 95% CI = 1.91, 2.43) with current wheeze and adults without current asthma or wheeze ($\beta = 0.23$, 95% CI = 0.05, 0.41). The DII was not associated with FEV_1, FVC, or FEV_1/FVC in children.

DISCUSSION

To our knowledge, this is the first report of an association between a high DII score and wheeze or lung function in a large

TABLE II. The Dietary Inflammatory Index (DII), current wheeze, and current asthma by age group, NHANES 2007-2012

	Children (n = 8,175)	Adult (n = 22,294)
	Odds ratio (95% CI), *P* value	
Current wheeze		
DII (continuous)	1.01 (0.92, 1.10)	**1.09 (1.05, 1.13)**†
DII		
Quartile 1	1.0 (reference)	1.0 (reference)
Quartile 2	1.28 (0.85, 1.95)	0.98 (0.76, 1.27)
Quartile 3	1.16 (0.72, 1.89)	**1.22 (1.01, 1.47)***
Quartile 4	1.00 (0.67, 1.50)	**1.41 (1.17, 1.70)**†
	P trend = .89	***P* trend < .01**
Current asthma		
DII (continuous)	1.03 (0.93, 1.13)	1.01 (0.94, 1.08)
DII		
Quartile 1	1.0 (reference)	1.0 (reference)
Quartile 2	1.06 (0.72, 1.55)	0.90 (0.64, 1.27)
Quartile 3	1.09 (0.67, 1.79)	0.97 (0.66, 1.42)
Quartile 4	1.14 (0.73, 1.79)	0.94 (0.66, 1.33)
	P trend = .57	*P* trend = .81

CI, Confidence interval; *NHANES*, National Health and Nutrition Examination Survey.
All models adjusted for gender, race/ethnicity, annual household income, BMI *z*-score (children) or BMI (adults), family history of asthma, and serum level of cotinine.
*$P < .05$; †$P < .01$.

TABLE III. The Dietary Inflammatory Index (DII) and current wheeze, stratified by relevant covariates in adults

	Q1	Q2	Q3	Q4	
The DII			**Odds ratio (95 % confidence interval)**		***P* trend**
Gender					
Male	1.0	1.14 (0.83, 1.57)	**1.39 (1.04, 1.86)***	**1.64 (1.23, 2.18)†**	**<.01**
Female	1.0	0.87 (0.62, 1.23)	1.11 (0.87, 1.41)	1.24 (0.96, 1.61)	.05
Race/ethnicity					
Non-Hispanic white	1.0	1.05 (0.75, 1.45)	**1.45 (1.14, 1.84)†**	**1.58 (1.22, 2.05)†**	**<.01**
Non-Hispanic black	1.0	1.04 (0.61, 1.79)	0.99 (0.68, 1.45)	**1.48 (1.08, 2.02)***	**<.01**
Mexican American/other Hispanic	1.0	0.72 (0.42, 1.22)	0.80 (0.49, 1.32)	1.06 (0.68, 1.66)	.71
Other	1.0	0.96 (0.45, 2.08)	0.80 (0.35, 1.85)	0.59 (0.23, 1.52)	.29
Household income					
<$20,000/year	1.0	0.63 (0.43, 0.93)*	0.82 (0.55, 1.21)	1.03 (0.70, 1.52)	.43
≥$20,000/year	1.0	1.09 (0.79, 1.51)	**1.35 (1.10, 1.66)†**	**1.54 (1.23, 1.92)†**	**<.01**
BMI (kg/m^2)					
≤ 25 (kg/m^2)	1.0	0.71 (0.47, 1.10)	0.89 (0.56, 1.40)	1.15 (0.74, 1.49)	.38
> 25	1.0	1.13 (0.84, 1.54)	**1.46 (1.20, 1.78)†**	**1.67 (1.29, 2.15)†**	**<.01**
Current smoker					
No	1.0	0.99 (0.74, 1.35)	1.17 (0.92, 1.49)	**1.28 (1.01, 1.62)***	**.02**
Yes	1.0	0.79 (0.46, 1.36)	1.23 (0.76, 2.00)	**1.55 (1.07, 2.25)***	**<.01**

BMI, Body mass index.
All models adjusted for age, gender, race/ethnicity, annual household income, BMI, family history of asthma, and serum level of cotinine except for the covariate used for stratification in each model.
*$P < .05$; †$P < .01$.

sample of children and adults. Among adults, a higher DII (indicating a proinflammatory diet) was significantly associated with current wheeze, as well as with decreased FEV_1 and FVC in subjects without active wheezing. Among children, a higher DII was significantly associated with current wheeze, but only among those with a high FeNO (≥20 ppb).

Quality of dietary intake has been associated with socioeconomic disparities.[20] The association between the DII and current wheeze was found to be more pronounced among males, non-Hispanic whites and blacks, those who had a higher household income, and those who were overweight or obese. Identifying how these variables contribute to food patterns and the DII score may help improve respiratory health in underserved populations. Our negative findings for current asthma in children and adults may be due to underdiagnosis or misclassification of this disease. Current wheeze, which is not dependent on a physician's diagnosis, is highly correlated with asthma in children aged 6 years and older, but may be due to asthma or chronic obstructive pulmonary disease (COPD) in adults. However, misclassification of COPD as asthma is unlikely to fully explain our results, as we accounted for cigarette smoking in our multivariable analysis. Moreover, we obtained similar results in an analysis restricted to nonsmoking adults (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

The effect of dietary patterns on lung function is less clear. Consistent with our prior report that dietary patterns did not affect lung function among Puerto Rican children with asthma,[10] we found that the DII did not significantly affect FEV_1 and FVC among adults with current wheeze. Because subjects with asthma or active wheezing typically have lower lung function and greater airway inflammation, dietary intake might affect lung function differently among those with wheezing symptom and disease-free individuals. Because a repeated spirometry was only tested among those individuals who demonstrated airway obstruction, the BDR results should be interpreted with caution.

Among the food parameters included in the DII, saturated fat, trans fat, and cholesterol are the main proinflammatory contributors, whereas n-3 and n-6 fatty acids have anti-inflammatory properties.[11] A Westernized diet, including consumption of food rich in energy and fat, has been linked to airway inflammation,[21] respiratory symptoms,[22] and reduced lung function.[23] Mice fed a high-fat diet develop obesity and airway hyperreactivity through upregulation of the proinflammatory cytokine IL-17A.[24] N-3 fatty acids have shown stronger and more consistent anti-inflammatory effects on asthma than n-6 fatty acids; however, the ratio of n-3 to n-6 fatty acids is thought to be important.[25] A murine model reported that whereas a high-fiber diet leads to increased circulating levels of short chain fatty acids (SCFAs, which reduce allergic airway inflammation), a low-fiber diet leads to decreased levels of SCFAs (and increased severity of allergic airway inflammation).[26] Dietary intake of high fat and low fiber has been associated with lower FEV_1 and worsened airway inflammation among adults with asthma.[27] Consistent with proinflammatory effects of a Westernized diet on the airways, we show that a higher DII is significantly associated with higher BDR among individuals with obstruction of the lung in NHANES.

Among the DII food parameters, nutrients mainly derived from fruits and vegetables (such as fiber, β-carotene, riboflavin, flavones, and vitamins A, C, D, and E) exhibit anti-inflammatory effects. Fruits and vegetables may have protective effects against allergic diseases such as asthma through downregulation of Th2 immune responses, airway inflammation, and oxidative stress.[8] A pooled study recently reported that dietary intake of fruits and vegetables was associated with 14% to 46% decreased risk of wheeze and asthma in both children and adults.[28] Higher intake

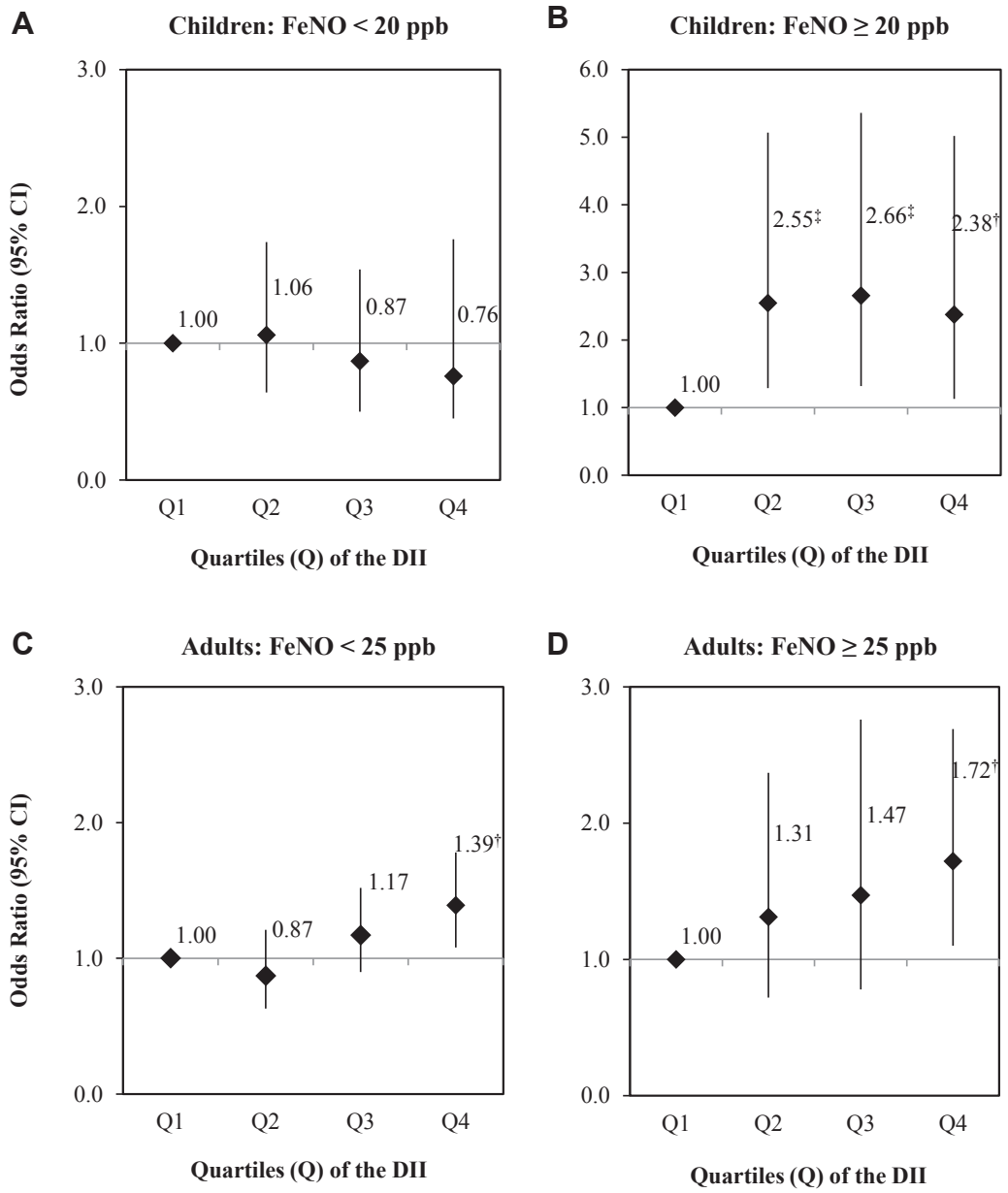

FIGURE 1. The dietary inflammatory index (DII) and current wheeze by fractional exhaled nitric oxide (FeNO) level, NHANES 2007-2012. All models were adjusted for age, gender, race/ethnicity, household income, BMI *z*-score (children) or BMI (adults), and family history of asthma. $^{\dagger}P < .05$; $^{\ddagger}P < .01$. *BMI*, Body mass index; *CI*, confidence interval.

of fruit and vegetables has been positively associated with FEV_1 and FVC but inversely associated with IL-8 levels in nasal lavage in asthmatic children.[29] In a study of adults in NHANES, participants in the highest quartile of fiber intake had 80 mL to 130 mL higher FEV_1 and FVC than those in the lowest quartile.[30] A higher Alternative Healthy Eating Index score (greater compliance to dietary guidelines) was associated with a slower FEV_1 decline in American men. Moreover, consuming 1 additional serving of vegetables or fruit per day could attenuate lung function decline among smoking men.[31]

FeNO is a sensitive marker of eosinophilic airway inflammation, with low FeNO levels (<20 ppb in children or <25 ppb in adults) denoting low likelihood of eosinophilic airway inflammation or corticosteroid responsiveness.[18] Our finding of an association between the DII and current wheeze in children with high FeNO suggests that children with predominantly allergic (atopic) asthma are more susceptible to the proinflammatory effects of their diet. Moreover, this association does not show a dose-response trend, suggesting a potential threshold effect. Among adults, higher DII was associated with wheeze in those with or without eosinophilic airway inflammation, while the effect size of the DII on wheeze was higher among those with eosinophilic airway inflammation.

Consistent with its ability to assess the proinflammatory effects of diet, the DII is associated with serum CRP, IL-6, and homocysteine levels.[12,32] Moreover, a high DII score has been

TABLE IV. The Dietary Inflammatory Index (DII) and lung function measures, NHANES 2007-2012

Lung function measures	Children (n = 5,796)	Adults (n = 15,791)
All participants		
% predicted pre-bronchodilator FEV_1	−0.25 (−0.67, 0.18)	**−0.27 (−0.47, −0.08)**‡
% predicted pre-bronchodilator FVC	−0.21 (−0.63, 0.21)	**−0.36 (−0.55, −0.18)**‡
% predicted pre_bronchodilator FEV_1/FVC	−0.05 (−0.28, 0.19)	0.07 (−0.03, 0.18)
Bronchodilator response (%)*	0.62 (−0.09, 1.32)	0.18 (−0.01, 0.38)
Participants without asthma or wheeze	n = 4,892	n = 13,303
% predicted pre-bronchodilator FEV_1	−0.22 (−0.64, 0.20)	**−0.22 (−0.44, −0.01)**†
% predicted pre-bronchodilator FVC	−0.20 (−0.61, 0.22)	**−0.35 (−0.55, −0.15)**‡
% predicted re-bronchodilator FEV_1/FVC	−0.04 (−0.29, 0.22)	0.12 (−0.01, 0.24)
Bronchodilator response (%)*	0.60 (0.00, 0.20)	**0.23 (0.05, 0.41)**†
Participants with current wheeze	n = 629	n = 2,001
% predicted pre-bronchodilator FEV_1	−0.33 (−1.65, 0.99)	0.07 (−0.60, 0.73)
% predicted pre-bronchodilator FVC	0.12 (−1.22, 1.45)	−0.12 (−0.70, 0.47)
% predicted re-bronchodilator FEV_1/FVC	−0.38 (−1.10, 0.35)	0.09 (−0.31, 0.50)
Bronchodilator response (%)*	**2.17 (1.91, 2.43)**‡	−0.20 (−0.43, 0.03)

BMI, Body mass index; *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 s; *FVC*, forced vital capacity; *NHANES*, National Health and Nutrition Examination Survey.

Data presented as β (95% CI), *P* value. All models adjusting for annual household income, BMI *z*-score (children) or BMI (adults), family history of asthma, serum level of cotinine and current asthma (in all participants).

*In addition adjusting for age, gender, race/ethnicity, and pre-bronchodilator FEV_1.

†$P < .05$; ‡$P < .01$.

linked to inflammatory conditions such cardiovascular disease,[33] colorectal cancer,[34] and glucose intolerance.[35] Consistent with some of our findings, Wood et al[13] reported that a higher DII is associated with asthma, decreased FEV_1, and increased IL-6 in a small case-control study of nonsmoking Australian adults.

Randomization of overweight or obese adults to a plant-based diet resulted in improved DII scores,[36] but whole-diet interventions on asthma or lung function are scarce. Current studies of dietary interventions or weight loss and asthma control have mostly focused on "obese asthma,"[37] but our findings for wheeze or lung function were independent of obesity. Prospective studies are needed to evaluate whether changes of dietary intake toward anti-inflammatory patterns improve wheezing and lung function in both children and adults.

The present study has considerable strengths, including a large sample representative of the U.S. population, performance of standardized procedures by uniformly trained personnel, and the ability to account for several potential confounders. We must also acknowledge several limitations. First, we cannot determine a temporal relationship between the DII and wheeze or lung function in a cross-sectional study. However, most children or adults with wheeze or worsened lung function are unlikely to differentially adopt a proinflammatory dietary pattern. Second, dietary intake was based on one 24-hour dietary recall, which does not account for day-to-day or seasonal variability in diet patterns. However, a longitudinal study recently found that the DII stays relatively constant over a period of years.[38] Third, few nutrients (ie, flavones, anthocyanidins) were not included in the DII calculation because of the lack of information from NHANES. Fourth, the study did not account for other potential confounders, including allergic sensitization, use of asthma medications, and exposure to air pollution.

In summary, our study suggests the detrimental effects of a proinflammatory diet on wheeze in adults and in atopic children (who have allergic airway inflammation). These results further support studying whole-diet interventions to improve asthma and respiratory health in the United States.

Acknowledgments

Conception and study design were given by Y.-Y. Han, E. Forno, and J. C. Celedón; data were analyzed and interpreted by Y.-Y. Han, E. Forno, N. Shivappa, M. D. Wirth, and J. R. Hébert; and Y.-Y. Han, E. Forno, N. Shivappa, M. D. Wirth, J. R. Hébert, and J. C. Celedón drafted the manuscript for intellectual content. All authors approved the final version of the manuscript before submission.

REFERENCES

1. Global Asthma Network. The Global Asthma Report 2014. Auckland: New Zealand; 2014.
2. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? Lancet 2015;386:1075-85.
3. Han YY, Forno E, Holguin F, Celedon JC. Diet and asthma: an update. Curr Opin Allergy Clin Immunol 2015;15:369-74.
4. Garcia-Marcos L, Castro-Rodriguez JA, Weinmayr G, Panagiotakos DB, Priftis KN, Nagel G. Influence of Mediterranean diet on asthma in children: a systematic review and meta-analysis. Pediatr Allergy Immunol 2013;24:330-8.
5. Thorburn AN, Macia L, Mackay CR. Diet, metabolites, and "western-lifestyle" inflammatory diseases. Immunity 2014;40:833-42.
6. Julia V, Macia L, Dombrowicz D. The impact of diet on asthma and allergic diseases. Nat Rev Immunol 2015;15:308-22.
7. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol 2005;115:1109-17.
8. Han YY, Blatter J, Brehm JM, Forno E, Litonjua AA, Celedón JC. Diet and asthma: vitamins and methyl donors. Lancet Respir Med 2013;1:813-22.
9. Han YY, Forno E, Brehm JM, Acosta-Perez E, Alvarez M, Colon-Semidey A, et al. Diet, interleukin-17, and childhood asthma in Puerto Ricans. Ann Allergy Asthma Immunol 2015;115:288-293.e1.
10. Han YY, Forno E, Alvarez M, Colón-Semidey A, Acosta-Perez E, Canino G, et al. Diet, lung function, and asthma exacerbations in Puerto Rican children. Pediatr Allergy Immunol Pulmonol 2017;30:202-9.
11. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr 2014;17:1689-96.

12. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, et al. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). Public Health Nutr 2014;17:1825-33.
13. Wood LG, Shivappa N, Berthon BS, Gibson PG, Hebert JR. Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma. Clin Exp Allergy 2015;45:177-83.
14. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.
15. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179-87.
16. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. Pediatr Pulmonol 1993;15:75-88.
17. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324-43.
18. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011;184:602-15.
19. Centers for Disease Control and Prevention National Center for Health Statistics. 2000 CDC Growth Charts for the United States: Methods and Development. Hyattsville, Md: Department of Health and Human Services; 2002.
20. Darmon N, Drewnowski A. Does social class predict diet quality? Am J Clin Nutr 2008;87:1107-17.
21. Wood LG, Garg ML, Gibson PG. A high-fat challenge increases airway inflammation and impairs bronchodilator recovery in asthma. J Allergy Clin Immunol 2011;127:1133-40.
22. Tromp II, Kiefte-de Jong JC, de Vries JH, Jaddoe VW, Raat H, Hofman A, et al. Dietary patterns and respiratory symptoms in pre-school children: the Generation R Study. Eur Respir J 2012;40:681-9.
23. Wood LG, Attia J, McElduff P, McEvoy M, Gibson PG. Assessment of dietary fat intake and innate immune activation as risk factors for impaired lung function. Eur J Clin Nutr 2010;64:818-25.
24. Kim HY, Lee HJ, Chang YJ, Pichavant M, Shore SA, Fitzgerald KA, et al. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. Nat Med 2014;20:54-61.
25. Wendell SG, Baffi C, Holguin F. Fatty acids, inflammation, and asthma. J Allergy Clin Immunol 2014;133:1255-64.
26. Trompette A, Gollwitzer ES, Yadava K, Sichelstiel AK, Sprenger N, Ngom-Bru C, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med 2014;20:159-66.
27. Berthon BS, Macdonald-Wicks LK, Gibson PG, Wood LG. Investigation of the association between dietary intake, disease severity and airway inflammation in asthma. Respirology 2013;18:447-54.
28. Seyedrezazadeh E, Moghaddam MP, Ansarin K, Vafa MR, Sharma S, Kolahdooz F. Fruit and vegetable intake and risk of wheezing and asthma: a systematic review and meta-analysis. Nutr Rev 2014;72:411-28.
29. Romieu I, Barraza-Villarreal A, Escamilla-Nunez C, Texcalac-Sangrador JL, Hernandez-Cadena L, Diaz-Sanchez D, et al. Dietary intake, lung function and airway inflammation in Mexico City school children exposed to air pollutants. Respir Res 2009;10:122.
30. Hanson C, Lyden E, Rennard S, Mannino DM, Rutten EP, Hopkins R, et al. The relationship between dietary fiber intake and lung function in the National Health and Nutrition Examination Surveys. Ann Am Thorac Soc 2016;13:643-50.
31. Rettig SA, Xu J, Karr AR, Tang W, Guertin KA, Goodman PJ, et al. Dietary patterns and lung function: assessment of the Alternative Health Eating Index-2010 (AHEI-2010) and rate of change in forced expiratory volume in the first second (FEV1). FASEB J 2017;31(Suppl 1). Abstract 167.8.
32. Shivappa N, Hebert JR, Rietzschel ER, De Buyzere ML, Langlois M, Debruyne E, et al. Associations between dietary inflammatory index and inflammatory markers in the Asklepios study. Br J Nutr 2015;113:665-71.
33. Wirth MD, Shivappa N, Hurley TG, Hebert JR. Association between previously diagnosed circulatory conditions and a dietary inflammatory index. Nutr Res 2016;36:227-33.
34. Tabung FK, Steck SE, Ma Y, Liese AD, Zhang J, Caan B, et al. The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the Women's Health Initiative. Cancer Causes Control 2015;26:399-408.
35. Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, et al. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. J Occup Environ Med 2014;56:986-9.
36. Turner-McGrievy GM, Wirth MD, Shivappa N, Wingard EE, Fayad R, Wilcox S, et al. Randomization to plant-based dietary approaches leads to larger short-term improvements in Dietary Inflammatory Index scores and macronutrient intake compared with diets that contain meat. Nutr Res 2015;35:97-106.
37. Forno E, Celedon JC. The effect of obesity, weight gain, and weight loss on asthma inception and control. Curr Opin Allergy Clin Immunol 2017;17:123-30.
38. Tabung FK, Steck SE, Zhang J, Ma Y, Liese AD, Tylavsky FA, et al. Longitudinal changes in the dietary inflammatory index: an assessment of the inflammatory potential of diet over time in postmenopausal women. Eur J Clin Nutr 2016;70:1374-80.

ONLINE REPOSITORY

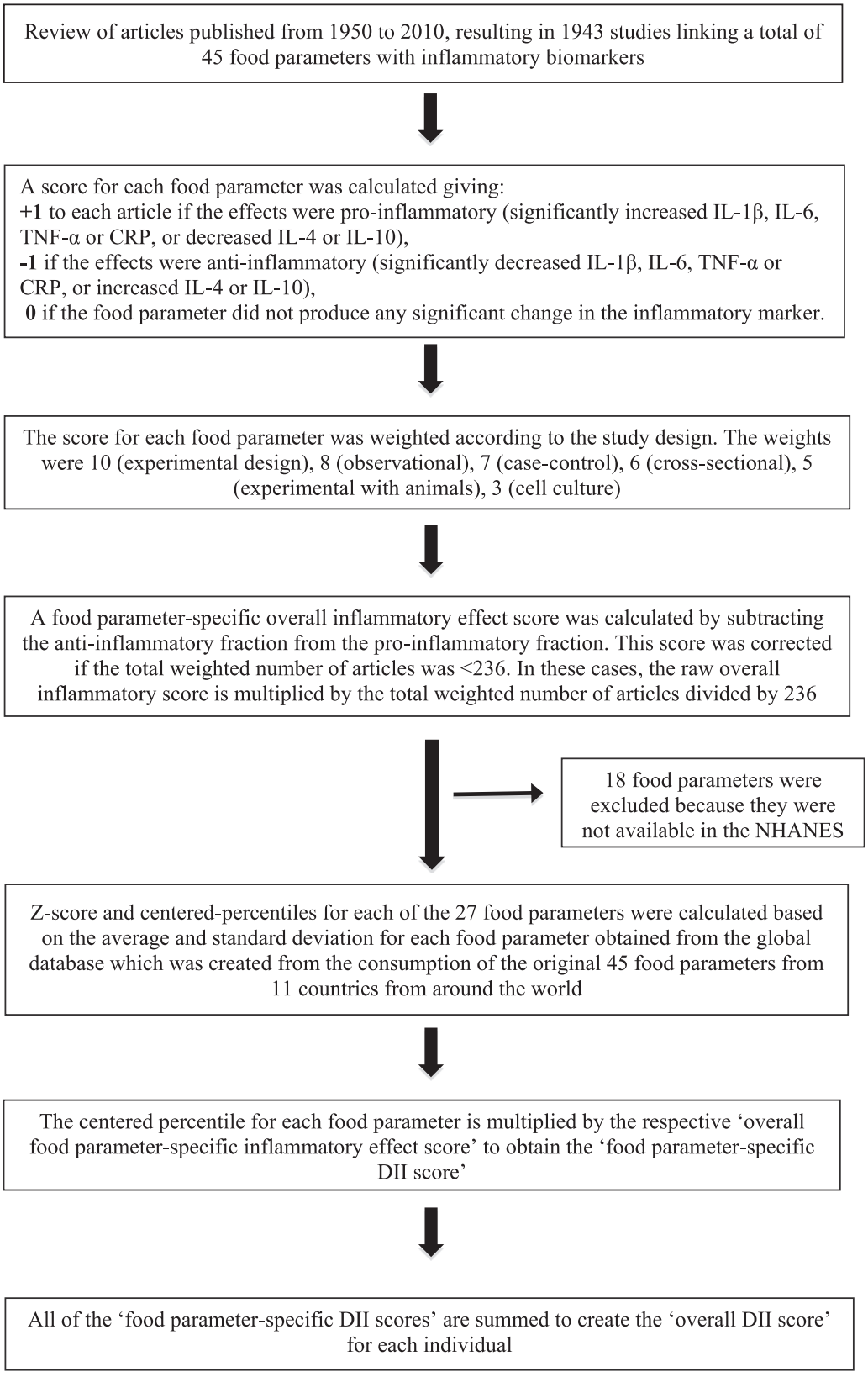

FIGURE E1. Sequence of steps in creating the Dietary Inflammatory Index (DII) for the National Health and Nutrition Examination Survey 2007-2012 study. *CRP*, C-reactive protein; *NHANES*, National Health and Nutrition Examination Survey.

TABLE E1. Characteristics of participants by current asthma, NHANES 2007-2012

	Children (6-17 y old)		Adults (18-79 y old)	
	Current asthma			
Characteristics	No n = 7,204	Yes n = 971	No n = 20,522	Yes n = 1,772
Age (y)	11.5 ± 0.1	11.7 ± 0.2	46.1 ± 0.4	45.8 ± 0.8
Male gender	3,643 (48.7)	538 (51.8)	10,199 (48.8)	659 (36.4)*
Race/ethnicity				
Non-Hispanic white	2,192 (59.1)	248 (47.8)*	9,190 (68.1)	879 (69.7)*
Non-Hispanic black	1,619 (12.9)	360 (25.3)	4,151 (10.1)	461 (15.2)
Mexican American/other Hispanic	2,753 (21.2)	275 (18.8)	5,659 (14.3)	324 (9.3)
Other	640 (6.8)	88 (8.1)	1,522 (6.5)	108 (5.8)
Private health insurance coverage	2,459 (59.5)	287 (47.7)*	8,324 (62.9)	586 (53.8)*
Annual household income <$20,000	1,486 (15.4)	257 (20.7)	4,323 (15.5)	556 (24.6)*
Family history of asthma	1,834 (26.2)	598 (60.2)*	3,530 (17.5)	766 (45.4)*
Wheeze in the past 12 mo	355 (5.3)	580 (59.8)*	1,865 (9.0)	1,088 (61.6)*
Body mass index (kg/m^2)	20.7 ± 0.1	22.4 ± 0.2*	28.4 ± 0.1	30.7 ± 0.3*
BMI *z*-score	0.60 ± 0.03	0.90 ± 0.05*	–	–
Current smoker	–	–	3,984 (20.2)	490 (28.2)*
Serum cotinine level (ng/mL)	5.4 ± 1.2	8.8 ± 2.6	55.0 ± 2.6	71.9 ± 6.5*
The dietary inflammatory index (DII)†	0.90 ± 0.04	0.95 ± 0.10	0.24 ± 0.04	0.43 ± 0.10
Fractional exhaled nitric oxide (FeNO), ppb	14.9 ± 0.4	23.8 ± 1.4*	16.0 ± 0.3	21.2 ± 1.0*
% predicted pre-bronchodilator FEV_1	104.3 ± 0.4	100.7 ± 0.7*	98.2 ± 0.3	88.9 ± 0.9*
% predicted pre-bronchodilator FVC	105.4 ± 0.4	105.3 ± 0.8	101.3 ± 0.3	96.8 ± 0.08*
% predicted pre-bronchodilator FEV_1/FVC	98.1 ± 0.2	94.7 ± 0.5*	96.3 ± 0.2	91.0 ± 0.5*
Bronchodilator response (%)	9.2 ± 0.6	14.2 ± 1.5*	5.6 ± 0.2	9.3 ± 0.6*

FEV_1, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *NHANES*, National Health and Nutrition Examination Survey.
Results are shown as mean ± standard error (SE) for continuous variables, and as N (%) for binary variables.
*$P < .01$ for current asthma vs no current asthma (within each age group).
†The DII was calculated per 1,000 calories of daily food consumed.

TABLE E2. The Dietary Inflammatory Index (DII) and current wheeze by the fractional exhaled nitric oxide (FeNO) level, NHANES 2007-2012

	Low FeNO	High FeNO
	Current wheezing, Odds ratio (95% CI), *P* value	
Children	FeNO < 20 ppb	FeNO ≥ 20 ppb
DII		
Quartile 1	1.0 (reference)	1.0 (reference)
Quartile 2	1.06 (0.64, 1.74)	**2.55 (1.29, 5.07)**†
Quartile 3	0.87 (0.50, 1.54)	**2.66 (1.32, 5.36)**†
Quartile 4	0.76 (0.45, 1.76)	**2.38 (1.13, 5.02)***
	P for trend = .28	*P* for trend = .05
Adults	FeNO < 25 ppb	FeNO ≥ 25 ppb
DII		
Quartile 1	1.0 (reference)	1.0 (reference)
Quartile 2	0.87 (0.63, 1.21)	1.31 (0.72, 2.37)
Quartile 3	1.17 (0.90, 1.52)	1.47 (0.78, 2.76)
Quartile 4	**1.39 (1.08, 1.78)***	**1.72 (1.10, 2.69)***
	P for trend ≤ .01	*P* for trend = .02

CI, Confidence interval; *NHANES*, National Health and Nutrition Examination Survey.
All models adjusted for age, gender, race/ethnicity, annual household income, BMI *z*-score (children) or BMI (adults), family history of asthma, and serum level of cotinine.
*$P < .05$; †$P < .01$.

TABLE E3. The Dietary Inflammatory Index (DII) and current wheeze by smoking status in adults, NHANES 2007-2012

	Nonsmoker	Current smoker
	Odds ratio (95% CI), *P* value	
The DII		
Quartile 1	1.0 (reference)	1.0 (reference)
Quartile 2	1.05 (0.74, 1.48)	0.55 (0.31, 0.98)*
Quartile 3	1.16 (0.87, 1.54)	0.94 (0.57, 1.55)
Quartile 4	1.28 (0.99, 1.64)	1.23 (0.82, 1.86)
	P for trend = .04	*P* for trend < .01

CI, Confidence interval; *NHANES*, National Health and Nutrition Examination Survey.
All models adjusting for adjusted for age, gender, race/ethnicity, annual household income, body mass index, and family history of asthma.
*$P < .05$.