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Diet, Interleukin 17, and Childhood Asthma in Puerto Ricans

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INTRODUCTION

Childhood asthma continues to be a major public health problem worldwide(1). Changes in dietary patterns may partly explain the “asthma epidemic” in industrialized nations like the United States(2).

Because of the complexity of human dietary behavior, intake of certain food groups or overall dietary patterns may have greater influence on health than a single food item or nutrient(3). Whereas a “Mediterranean diet” (characterized by low intake of saturated fats but high in fruits, vegetables, grains and mono-/n-3 poly-unsaturated fatty acids [e.g. in olive

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oil]) has been associated with decreased risk of asthma or asthma symptoms(4, 5), a “Westernized” diet (low in fruits, vegetables, grains and mono/n-3 poly-unsaturated fats but high in refined grains, red meats, sweets and saturated fats) has been associated with asthma symptoms(6). Recent findings suggest that an unhealthy diet and obesity worsen airway inflammation and asthma severity through pathways mediated by T-helper 17 (TH17) cells, including production of cytokines like interleukin 17 (IL-17)(7, 8).

In the United States, Puerto Rican children have a disproportionate burden of asthma(9, 10). Although a recent study of 633 Puerto Rican adolescents showed a high frequency of unhealthy dietary patterns (e.g. low in fruits or vegetables but high in soda or fried foods(11)), no study has examined diet and asthma in Puerto Ricans.

We hypothesized that frequent intake of healthier food groups leads to lower risk of childhood asthma, and that this beneficial effect is mediated by down-regulation of T_H17 cytokines.

METHODS

Study population

Between March, 2009, and June, 2010, children were recruited from randomly selected households in the metropolitan area of San Juan, as previously described(12, 13). Households were selected by a multistage probability sampling design. Primary sampling units (PSU) were randomly selected neighborhood clusters based on the 2000 US census, and secondary units were randomly selected households within each PSU. A household was eligible if 1 resident was a child 6-14 years old. 7,073 households were selected and 6,401 (~91%) were contacted. Of these, 1,111 had 1 child within the study age range who met other inclusion criteria (four Puerto Rican grandparents, residence in the same household for 1 year). Of these 1,111 households, 438 (39.4%) had 1 eligible child with asthma (a case, defined as having physician-diagnosed asthma and at least one episode of wheeze in the previous year). From these 438 households, one child with asthma was selected (at random if there was more than one such child). Similarly, only one child without asthma (a control, defined as having neither physician-diagnosed asthma nor wheeze in the previous year) was randomly selected from the remaining 673 households. In order to reach a target sample size of ~700 children, we attempted to enroll a random sample (n=783) of these 1,111 children. Parents of 105 of these 783 households refused to participate or could not be reached. There were no significant differences in age, gender, or area of residence between eligible children who did (n=678 [86.6%]) and did not (n=105 [13.4%]) participate.

Written parental consent and assent were obtained for participating children. The study was approved by the Institutional Review Boards of the University of Puerto Rico (San Juan, PR), Brigham and Women's Hospital (Boston, MA), and the University of Pittsburgh (Pittsburgh, PA).

Study procedures

One of the child's caretakers (usually the mother) completed a questionnaire slightly modified from one used in the Collaborative Study of the Genetics of Asthma(14)

containing questions about demographics, the child's general and respiratory health, family history of asthma, breastfeeding, environmental tobacco smoke (ETS), and outdoor physical activity. Height and weight were measured to the nearest centimeter and kilogram, respectively. Dietary data were collected using a semi-quantitative food frequency questionnaire (FFQ) adapted from one developed and validated to measure intake of 75 food items in Costa Ricans(15).

Fifteen circulating T_H17 pathway-related cytokines (IL-1b, IL-4, IL-6, IL-10, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-25, IL-31, IL-33, interferon- γ , soluble CD40 ligand, and tumor necrosis factor- α) were measured in plasma samples using Bio-Plex Pro Human T_H17 cytokine panel on the BioPlex HTF system (Bio-Rad Laboratories Inc., Hercules, CA). Assays were designed on magnetic beads in a capture-sandwich immunoassay format. Levels are presented as pg/mL. Undetectable cytokine levels were assigned a constant (half the lowest limit of detection). All cytokine levels were log-transformed for data analysis.

Statistical analysis

Asthma was defined as physician-diagnosed asthma and at least one episode of wheeze in the previous year. The frequency of consumption of each food item was measured using eight categories: never or <1 time/month, occasionally or 1-3 times/month, 1-2 times/week, 3-4 times/week, 1 time/day, 2-3 times/day, 4-5 times/day, or 6 times/day or more. Based on a food guidance system developed by the U.S. Department of Agriculture (USDA) Center for Nutrition Policy and Promotion(16), each FFQ item was assigned to one of six food groups: fruits, vegetables, grains, protein foods, dairy, and fats. A seventh group (sweets, soda, and snacks) was added for completion. To avoid misclassification, we utilized Pearson correlation analysis to assign complex foods (such as tacos, burritos, pizza, and soup) to one of the seven food groups (e.g., ham-and-cheese sandwich intake was most highly correlated with intake of grains, and thus was assigned to that group). This food grouping is shown in detail in eTable 1. In order to avoid bias from an individual's tendency to respond on the lower or higher ends of the scale, we calculated the "average frequency" reported for the 75 items for each individual, and each specific item was scored as a deviation from the mean.

Two-sample *t*-tests (for continuous variables) or chi-square tests (for categorical variables) were used to compare characteristics between cases and controls. Logistic regression was used for the analysis of quartiles of food group consumption and asthma. Logistic models were adjusted for age, gender, annual household income (<\$15,000 or \$15,000 [near the median household income for Puerto Rico in 2008-2009](17)), health insurance (private/ employer-based vs. others), parental history of asthma, early-life (*in utero* or before age 2 years) ETS exposure, body mass index (BMI) z-score (based on 2000 CDC growth charts(18)), moderate/intense outdoor physical activity vs. none/minimal, and breastfeeding (never, 6 or >6 months). Based on the results of this analysis, cut-off points were chosen to evaluate dichotomized intake (high vs. low) of each food group (we grouped quartiles that had odds ratios <1.0 vs >1.0; e.g. quartiles 2-3-4 vs 1 for grains, and quartiles 3-4 vs 1-2 for dairy).

Next, we built a logistic model including all food groups using a stepwise approach, and then created a food score to identify dietary patterns including food groups that were

significantly associated with lower (vegetables and grains, healthy food groups) or higher (dairy and sweets, unhealthy food groups) odds of asthma, as follows: individuals were assigned a score of +1 for high consumption of healthy food groups, or -1 for high consumption of unhealthy groups. The score thus ranged from -2 (most “unhealthy diet”) to +2 (most “healthy diet”). Finally, logistic regression was used to evaluate the relation between cytokine levels and asthma (as a binary outcome); linear regression was used to evaluate the association between food groups, the dietary patterns and cytokine levels (as a continuous outcome). SAS v9.3 (SAS Institute, Inc, Cary, NC) was used for all analyses.

RESULTS

Compared to children without asthma (n=327), those with asthma (n=351) were slightly younger and more likely to be male and have a history of parental asthma and early-life ETS exposure (Table 1).

Table 2 shows the prevalence of asthma according to consumption frequency quartile for each food group: a higher intake frequency of dairy products and a lower intake frequency of vegetables or grains were significantly associated with higher prevalence of asthma. In the logistic regression analysis (Table 3), increased consumption of vegetables or grains was significantly and linearly associated with reduced odds of asthma, and there was evidence of potential thresholds for the relation between fruits, dairy products and sweets, and asthma.

Cut-off points were chosen to dichotomize the consumption of each group as high or low (Table 4, **Model 1**) based on the quartile analyses (quartiles with adjusted odds ratios <1.0 vs. >1.0): high intake of dairy products or sweets was associated with higher odds of asthma (aOR=1.72, 95%CI=1.19, 2.49 and aOR=1.71, 95%CI=1.12, 2.62, respectively), while high consumption of grains or vegetables was associated with a reduction in the odds of asthma (aOR=0.58, 95 %CI=0.38, 0.89 and aOR=0.46, 95%CI=0.30, 0.71, respectively). When simultaneously accounting for other food groups (Table 4, **Model 2**), frequent consumption of grains was associated with decreased odds of asthma (aOR=0.52, 95%CI=0.33, 0.82), while frequent intake of dairy products and sweets were associated with higher odds of asthma, (aOR=1.93, 95%CI=1.32, 2.83 and aOR=1.72, 95%CI=1.08, 2.72, respectively). Finally, we evaluated the association between the dietary patterns and asthma. A healthier diet (each 1-point increment in the food score) was associated with 36% lower odds of asthma (aOR=0.64, 95%CI=0.53-0.77). The proportion of children with asthma decreased from 75% in the group with the most “unhealthy diet” (lowest food score) to 34% in the group with the most “healthy diet” (highest food score) (Figure 1, P for linear trend <0.01). These results remained the same after additionally adjusting for atopic status (aOR=0.60, 95%CI=0.49-0.73). We conducted a confirmatory analysis using quartiles based only on data from children without asthma (“healthy” quartiles), obtaining similar results; we also performed exploratory analyses stratifying by breastfeeding history, obtaining similar results (data not shown).

In the logistic regression analysis, several cytokines were associated with asthma (data not shown): IL-1b (OR=0.64, 95%CI=0.44-0.94) and IL-22 (OR=0.70, 95%CI=0.56-0.88) were associated with lower odds of asthma, and IL-17F (OR=1.34, 95%CI=1.11-1.62) and IL-23

(OR=1.65, 95%CI=1.14-2.38) with higher odds. When we analyzed the relation between food groups and those four cytokines, IL-17F was consistently associated with all four significant food groups: consumption of vegetables or grains was associated with lower levels of IL-17F, while consumption of dairy or sweets was associated with higher IL-17F (eTable 2). Finally, we tested the association between IL-17F and the dietary patterns: IL-17F decreased from a geometric mean of 22.9pg/ml in the group with most “unhealthy diet” to 4.8pg/ml in the group with the most “healthy diet” (Figure 1). In addition to lower odds of asthma, a “healthier” diet was also associated with lower IL-17F levels (adjusted β = -1.48pg/ml, 95%CI= -1.78 to -1.20, $p<0.001$ [after Bonferroni correction for multiple comparisons], eTable 3). This association remained significant after additionally adjusting for atopic status (data not shown).

DISCUSSION

We found that frequent consumption of vegetables and grains, but low consumption of dairy products and sweets, is associated with lower plasma levels of IL-17F and decreased risk of childhood asthma. To our knowledge, this is the first report of an association between dietary intake patterns, IL-17F, and asthma.

Although vegetable and fruit intake has been associated with lower levels of serum C-reactive protein (CRP, a marker of systemic inflammation) in Puerto Rican adults(19), only 14.5% meet recommendations for daily fruit and vegetable intake (and ~91% were not even aware of such recommendations)(20). A recent study reported that, on average, Puerto Rican children in New York City consume less fruits and vegetables but more sweetened beverages than children from other ethnic minority groups(21). Consistent with this, the mean daily fruit and vegetable intakes in our study were only 1.9 and 1.3 servings per day, respectively. Moreover, only 18.6% of children met the recommended 5 servings of fruits and vegetables per day (data not shown).

Our findings for vegetable consumption are supported by previous studies among children in Canada(22), and Greece(23), as well as those participating in Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC), which did not include the U.S. or Puerto Rico(24). Our study provides further evidence that more frequent vegetable consumption, a proxy for antioxidant intake, may protect against asthma.

Even though whole grains may lower the risk of chronic diseases like coronary heart disease, diabetes, and cancer, and may contribute to body weight management and digestive health(25), few studies have examined whether intake of whole grains is associated with respiratory health. Similarly, a higher intake of whole grain products was associated with 54% lower odds of asthma in a study of Dutch school-aged children(26). Whole grains may protect against asthma through the anti-oxidant and anti-inflammatory effects of their contents (vitamins, minerals, and phytonutrients)(27). In support of this hypothesis, consumption of whole grains was inversely associated with CRP serum levels in a study of 13,811 adults in the US(28).

Few studies have reported on dairy product consumption and asthma. We found that consumption of dairy products (including pasteurized milk and cheese) was associated with increased odds of asthma. A community-based cross-sectional study of Australian young adults found that cheese intake was inversely associated with asthma but that intake of whole milk was positively associated with increased odds of asthma(29). Our study did not distinguish types of dairy products (whole, low fat or fat free); whether each type of dairy products affects asthma differently requires further investigation. In a study of Central European children living in farm environments, consumption of raw (but not boiled) milk was associated with lower odds of asthma and atopy, a finding attributed to whey protein in raw milk –which would be rarely consumed by children in urban San Juan(30).

A handful of studies have shown an association between sugar intake and asthma. A recent analysis of ecologic data from 53 countries participating in Phase III of ISAAC found a positive relationship between *per capita* sugar consumption and severe asthma symptoms in children(31). Daily consumption of soda or soft drinks has been associated with increased risk of asthma among high school students in the U.S.(32) and Australian adults(33). Intake of soft drinks and salty snacks may lead to asthma through sensitivity to food preservatives such as sulfites(34) or increased sodium content (which has been linked to airway hyper-responsiveness [AHR] in children with asthma)(35). A recent study indicates that non-caloric artificial sweeteners alter microbial metabolic pathways linked to host susceptibility to dysbiosis and glucose intolerance(36); dysregulation of these pathways through diet has been linked to AHR and allergic airway inflammation(7, 37). In our study, children with a “healthy” diet would have, on average, ~83% lower odds of asthma than children with “unhealthy” diet. These findings underscore the importance of assessing overall dietary patterns and not only specific nutrients.

Ours is the first study to report that a healthier diet is associated with lower IL-17F levels in children with and without asthma. T_H17 cells, IL-17A and IL-17F (which may regulate adipogenesis and glucose homeostasis(38)) correlate with asthma severity(39, 40), eosinophilic inflammation(41) and airway smooth muscle contraction(42). Kim *et al.*(7) recently reported that diet-induced obesity leads to AHR in mice, and that this is mediated by IL-17. A handful of studies have suggested that foods rich in energy and lipids produce metabolic stress leading to higher IL-17, whereas n3 (omega-3) PUFAs and fruit juice inhibit IL-17 production(43-46). Thus, we postulate that the healthier diet measured by our food score may lead to reduced IL-17 levels, consequently reducing the risk of asthma. Our findings were significant for IL-17F but not for IL-17A, which is consistent with some prior reports(47, 48). In our cohort, as well as in other studies of asthma(48) and other inflammatory conditions(49), IL-17A serum levels are markedly lower than those of IL-17F, and thus differences may be more difficult to detect.

Our study has considerable strengths, including a study sample representative of children living in the largest city in Puerto Rico, detailed phenotyping, and the ability to account for a number of potential confounders. We also recognize some limitations. A cross-sectional design does not allow determination of a temporal relationship between dietary intake, cytokine levels, and asthma. However, dietary patterns at school age are likely to be correlated with those in early life. Some complex foods such as pizza, hamburgers or

burritos are difficult to categorize. However, we performed a sensitivity analysis removing complex foods (each one separately, and all at once) from their assigned groups, without significant changes in our results. In our cohort, the frequency of food allergy by ~10% of participants; our analyses remained unchanged after additional adjustment for presence of food allergies. Further studies are needed to identify food allergies in relation to dietary patterns in Puerto Rico. Data for food consumption were reported by parents and thus recall bias, social desirability bias and inaccurate reporting are possible. This is unlikely, however, as FFQs completed by parents of young children have been shown to be accurate (50). Finally, our findings may not be generalizable to non-Puerto Rican children. However, recent studies have found that unhealthy dietary patterns are common in under-served populations and ethnic minorities in the U.S. mainland (10).

In summary, our findings suggest that a dietary pattern including frequent consumption of dairy products and sweets/sodas/snacks but infrequent grain or vegetable intake leads to increased odds of asthma in Puerto Rican children. This may be mediated through an IL-17F-dependent inflammatory pathway. Our results further emphasize ongoing public health efforts to foster positive dietary habits (e.g. through education and access to food sources) among the poor and ethnic minorities in the U.S.(10).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Dietary pattern, IL-17F plasma levels, and proportion of children with current asthma (n=578)

[†] Individuals who had high consumption of vegetables or grains were assigned a score of +1 for each. Individuals who had higher consumption of dairy products or sweets were assigned a score of -1 for each. The overall dietary pattern is represented by the sum of the four individual scores (range -2 for the most “unhealthy diet” to +2 for the most “healthy diet”)

*P-trend < 0.01. **P-trend = 0.01

Table 1Characteristics of study participants[§]

Covariate	Control (n=327)	Cases (n=351)
Age (years)	10.5 (2.7)	10.0 (2.6) *
Sex (male)	159 (48.6%)	201 (57.3%) *
Breastfed		
Never	142 (47.2%)	159 (52.8%)
6 months	152 (51.4%)	144 (48.7%)
> 6 months	26 (8.0%)	46 (13.1%)
Annual household income < \$15,000	196 (62.8%)	225 (65.4%)
No private or employer-based health insurance	205 (62.7%)	239 (68.1%)
Parental asthma	103 (31.7%)	232 (66.3%) *
Early-life exposure to environmental tobacco smoke	131 (40.2%)	174 (49.6%) *
BMI, z-score	0.5 (1.1)	0.7 (1.2)
Outdoor activity [†]	240 (73.4%)	268 (76.4%)

[§]Data are presented as number (percentage) for categorical variables or mean (SD) for continuous variables. Percentages were calculated for children with complete data.

BMI: Body mass index.

[†] At least a moderate amount of outdoor activity including playing, practicing sports and walking

* P< 0.05 for the comparison between groups (conducted using two-sample t tests or chi-square tests, as appropriate).

Table 2Proportion of children with asthma per quartile[§] of food group consumption among study participants (n=678)

Food group	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Fruits	55.6%	48.2%	50.6%	52.7%
Vegetables	60.6%	52.4%	47.0%	47.1% *
Grains	63.5%	41.2%	56.9%	45.6% *
Protein foods	54.4%	47.1%	49.7%	55.9%
Dairy	50.6%	42.9%	56.8%	56.8% *
Fats	56.8%	55.0%	47.7%	47.6%
Sweets, sodas, snacks	52.1%	47.3%	48.5%	59.2%

[§]Quartile 1 is the least consumption and Quartile 4 is the most consumption

* P for linear trend <0.05

Table 3Logistic regression analysis of quartiles[§] of food group consumption and asthma

Food group	Q1	Q2	Q3	Q4
Odds ratio (95% confidence interval)				
Fruits	1.0	0.56 (0.34, 0.95) *	0.79 (0.48, 1.32)	0.80 (0.48, 1.34)
Vegetables	1.0	0.73 (0.43, 1.22)	0.48 (0.28, 0.81) *	0.56 (0.34, 0.95) * †
Grains	1.0	0.36 (0.21, 0.61) *	0.69 (0.41, 1.18)	0.40 (0.23, 0.67) * †
Protein foods	1.0	0.76 (0.46, 1.26)	0.73 (0.44, 1.22)	0.76 (0.45, 1.26)
Dairy	1.0	0.64 (0.39, 1.06)	1.42 (0.84, 2.39)	1.31 (0.78, 2.22)
Fats	1.0	0.93 (0.55, 1.57)	0.67 (0.40, 1.12)	0.82 (0.48, 1.37)
Sweets, sodas, snacks	1.0	0.82 (0.49, 1.36)	0.80 (0.48, 1.35)	1.49 (0.89, 2.50)

All models adjusted for age, sex, household income, parental asthma, body mass index, outdoor physical activity, early-life ETS, and breastfeeding.

[§]Quartile 1 is the least consumption and Quartile 4 is the most consumption

* P<0.05 for comparison to lowest (first) quartile

† P<0.05 for linear trend

Table 4

Logistic regression analysis of high vs. low food group consumption and asthma

Food group	Low	Model 1	Model 2 [†]
		High [§]	High [§]
Fruits	1.0	0.71 (0.47, 1.08)	-
Vegetables	1.0	0.58 (0.38, 0.89) *	-
Grains	1.0	0.46 (0.30, 0.71) **	0.52 (0.33, 0.82) **
Protein foods	1.0	0.75 (0.50, 1.13)	-
Dairy	1.0	1.72 (1.19, 2.49) **	1.93 (1.32, 2.84) **
Fats	1.0	0.79 (0.52, 1.22)	-
Sweets, sodas, and snacks	1.0	1.71 (1.12, 2.62)	1.72 (1.08, 2.72) *

All models adjusted for age, sex, household income, parental asthma, body mass index, outdoor physical activity, early-life ETS, and breastfeeding.

[§]High vs. low = Q2-3-4 vs Q1, except for dairy (Q3-4 vs Q1-2) and sweets (Q4 vs Q1-2-3).

[†]Model 2 was built using all food groups (from Model 1) in a stepwise selection approach; thus each group is additionally adjusted for the other food groups listed (e.g. grains are adjusted for all covariates and also for consumption of dairy and sweets).

* P<0.05.

** P<0.01