Dietary inflammatory index is related to asthma risk, lung function and systemic inflammation in asthma

Lisa G Wood[1], **Nitin Shivappa**[2,3], **Bronwyn S Berthon**[1], **Peter G Gibson**[1,4], and **James R Hebert**[2,3]

[1]Centre for Asthma and Respiratory Diseases, Hunter Medical Research Institute, University of Newcastle, NSW, Australia 2308

[2]Cancer Prevention and Control Program, University of South Carolina, Columbia, SC 29208 USA

[3]Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208 USA

[4]Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton, NSW, Australia 2305

Abstract

Background—Asthma prevalence has increased in recent years and evidence suggests that diet may be a contributing factor. Increased use of processed foods has led to a decrease in diet quality, which may be creating a pro-inflammatory environment, thereby leading to the development and/or progression of various chronic inflammatory diseases and conditions. Recently, the Dietary Inflammatory Index (DII) has been developed and validated to assess the inflammatory potential of individual diets.

Objective—This study aimed to examine the DII in subjects with asthma compared to healthy controls and to relate the DII to asthma risk, lung function and systemic inflammation.

Methods—Subjects with asthma (n=99) and healthy controls (n=61) were recruited. Blood was collected and spirometry was performed. The DII was calculated from food frequency questionnaires administered to study subjects.

Results—The mean DII score for the asthmatics was higher than the DII score for healthy controls (−1.40 versus −1.86, p=0.04), indicating their diets were more pro-inflammatory. For every 1 unit increase in DII score the odds of having asthma increased by 70% (OR: 1.70, 95% CI: 1.03, 2.14; p=0.040). FEV_1 was significantly associated with DII score (β=−3.44, 95% CI: −6.50,−0.39; p=0.020), indicating that for every 1 unit increase in DII score, FEV_1 decreased by 3.44 times. Furthermore, plasma IL-6 concentrations were positively associated with DII score (β=0.13, 95% CI: 0.05, 0.21;p=0.002).

Corresponding author: Dr Lisa Wood, Level 2 Hunter Medical Research Institute Building, Kookaburra Crt, New Lambton Heights, NSW, AUSTRALIA, 2305. Ph: +61 2 40420147, Fax +61 2 40420046, lisa.wood@newcastle.edu.au.

Conclusion and clinical relevance—As assessed using the DII score, the usual diet consumed by asthmatics in this study was pro-inflammatory relative to the diet consumed by the healthy controls. The DII score was associated with increased systemic inflammation and lower lung function. Hence, consumption of pro-inflammatory foods may contribute to worse asthma status and targeting an improvement in DII in asthmatics, as an indicator of suitable dietary intake, might be a useful strategy for improving clinical outcomes in the disease.

Introduction

Asthma is a chronic inflammatory disease of the airways, involving reversible airflow obstruction and characterised by symptoms such as coughing, breathlessness and wheezing. Both genetic and environmental factors, such as dietary intake, are believed to contribute to asthma development and progression. Consumption of a westernised dietary pattern may promote a pro-inflammatory environment [1]. Indeed, there are a number of studies that have shown that certain nutrients modify systemic inflammation. For example, high-fat meals have been shown to lead to increased circulating IL-6, TNFα [3] and CRP [3]. Other nutrients such as n-3 polyunsaturated fatty acids [4], fibre [5], moderate alcohol intake [6], vitamin E [7], vitamin C [7], β-carotene [7] and magnesium [8] also have been consistently associated with lower levels of systemic inflammation. Systemic inflammation has been shown to be clinically relevant in asthma, as lung function and asthma control have been shown to be worse in subjects with high circulating IL-6 levels [9].

The dietary inflammatory index (DII) has recently been developed to provide an overall score for the inflammatory potential of the diet [10, 11]. The DII is based upon an extensive literature search incorporating cell culture, animal, and epidemiologic studies on the effect of diet on inflammation. The overall score is dependent on the whole diet, not just certain nutrients or foods. DII scoring is not dependent on population means or recommendations of intake; it is based on results published in the scientific literature. The DII is not limited to micronutrients and macronutrients, but also incorporates commonly consumed components of the diet including flavonoids, spices, and tea. Previously, the DII has been shown to predict CRP levels [11, 12]. We hypothesised that the DII is higher, indicating a more pro-inflammatory diet, in subjects with asthma and related to both increased systemic inflammation and worse clinical asthma outcomes. The aim of this study was to determine the DII in asthmatics compared to healthy controls and to examine associations between DII, lung function and systemic inflammation.

Materials and Methods

Subject group

Subjects with stable asthma were recruited from the John Hunter Hospital Asthma Clinic, NSW, Australia and by advertisement on noticeboards at the John Hunter Hospital and the University of Newcastle (n=99). Healthy controls were also recruited by advertisement at the University of Newcastle (n=61). Subjects were recruited between July 2006 and March 2010 and were matched on sex and age range. Results based on a subset of data from some of these subjects has previously been reported [13–15]. Inclusion criteria were; age over 18 years, non-smoking status (ceased smoking for at least 6 months) and confirmed stable

asthma. Asthma was diagnosed on the basis of current (past 12 months) episodic respiratory symptoms, doctor's diagnosis of asthma (ever) and airway hyper-responsiveness to hypertonic saline. Asthma stability was defined as no exacerbation, respiratory tract infection or OCS in the past 4 weeks. Healthy controls had normal lung function without airway hyper-responsiveness, no respiratory symptoms, never had a doctor's diagnosis of asthma, and were steroid naïve. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Hunter New England and University of Newcastle Human Research Ethics Committees, reference number 05/03/09/3.09 and 06/10/25/5.03. Written informed consent was obtained from all subjects.

Clinical assessment

Subjects' medication use was recorded, including inhaled corticosteroid (ICS) and oral corticosteroid (OCS) use in the previous 12 months and smoking history (pack years) was obtained. Asthma control was assessed using the validated Asthma Control Questionnaire (ACQ) [16]. Asthma severity was categorised as intermittent, mild persistent, moderate persistent and severe persistent using previously described Global Initiative for Asthma (GINA) criteria and ICS dose [17]. Atopy was tested by skin prick test using 5 common aero-allergens, prepared by Hollister-Stier (USA) (Aspergillus fumigataus, Alternaria tenius, Dust mite (DP), Cockroach mix and Grass mix). Histamine and saline were used as positive and negative controls, respectively. Wheals were measured after 15 min, a positive reaction was defined as wheal geometric mean diameter of at least 3mm. Spirometry (Minato Autospiro AS-600; Minato Medical Science, Osaka, Japan) was performed as previously described [18].

Anthropometry

Subjects were weighed in light clothing to the nearest 100g with NU WEIGH LOG842 scales, (NU Weigh Scales Inc, MI). Height was measured using the stretch stature method to the nearest 0.1cm using a wall mounted stadiometer. Height and weight measures were used to calculate BMI (kg/m^2).

Sputum collection and processing

Spirometry (Minato Autospiro AS-600; Minato Medical Science, Osaka, Japan) and combined bronchial provocation and sputum induction with hypertonic saline (4.5%) were performed as previously described [18]. Salbutamol 200ug was administered via pressurised inhaler and valve holding chamber if FEV_1 dropped below 15% of baseline. In subjects for whom FEV_1 did not decrease by 15% from baseline, salbutamol 200ug was administered at the maximum nebulisation time of 15 minutes. Lower respiratory sputum portions were selected from saliva, dispersed with dithiothreitol, and a total and differential cell count of leukocytes was performed, as previously described [18].

Blood collection and processing

Blood was collected in EDTA tubes, centrifuged at 4°C, 3000g, for 10 minutes and plasma was stored at −80°C. Plasma IL-6 and TNFα concentrations were analysed by commercial

ELISA (R&D systems, Minneapolis, MN, USA). CRP concentrations were analysed by commercial ELISA (MP-Biomedicals, Solon, OH, USA).

Dietary intake collection and analysis

Subjects completed a 186-item semi-quantitative food frequency questionnaire (FFQ) developed in Victoria, Australia, and modified for screening subjects for heart disease risk factors in Western Sydney, NSW, Australia to capture further information on fat intake, macronutrients and fibre intake [19]. The FFQ has been validated using weighed food records within a female student population aged 20–43 years [19]. Data entry and analysis of the FFQ's were completed by a qualified dietitian (B.B.) using the Australian AusNut 1999 database (All Foods) Revision 17 and AusFoods (Brands) Revision 5, both of which were accessed through FoodWorks (version 4.00.1158, 2005; Xyris Software, Brisbane, Queensland, Australia). Average daily intakes of energy, macro- and micronutrients and fibre were computed from the reported frequency of consumption, the standard serving size (unless other serving specified) and the foods available in the nutrient composition software.

Assignment of the Dietary Inflammatory Index

The DII provides a tool that categorizes individual diets on a continuum from maximally anti-inflammatory to maximally pro-inflammatory. The methods used in the construction of the DII have been published elsewhere [10, 11]. Briefly, to calculate DII for the participants of this study, the dietary data were first linked to the regionally representative world database that provided a robust estimate of a mean and standard deviation for each parameter. These then become the multipliers to express an individual's exposure relative to the "standard global mean" as a z-score. This is achieved by subtracting the "standard mean" from the amount reported and dividing this value by its standard deviation. To minimize the effect of "right skewing," this value is converted to a centered percentile score, which were then multiplied by the respective food parameter effect score that, in turn, is derived from extensive literature review to obtain a food parameter-specific DII score for an individual. All of the food parameter-specific DII scores are then summed up to create the overall DII score for every participant in the study [10]. In total there were 25 of 45 possible food parameters that were available from the dietary assessment method that could be used to calculate DII for this study. These included various macronutrients, such as carbohydrates and proteins, as well as various minerals such as zinc and magnesium, and vitamins such as B1, A, and thiamin.

Statistical analysis

SAS 9.3© software was used to carry out all analyses. Data are reported as means ± standard deviation. Comparisons of baseline characteristics by disease outcome were made using chi-square tests for categorical variables and 2-sample t-tests or Wilcoxon rank sum tests for continuous variables. Trends were also tested for key variables and pro- and anti-inflammatory food parameters across tertiles of DII score. Multivariate logistic regression was used to analyse DII with asthma as the outcome. Multiple linear regression was used to assess associations between DII and continuous outcomes such as FEV_1, IL-6, TNFα and CRP. All logistic and linear regression models were adjusted for age, sex, smoking status

and BMI as covariates in order to reduce confounding. A result was deemed significant if *P* < 0.05.

Results

DII value was calculated in subjects with stable asthma (n=99) and healthy controls (n=61). Baseline characteristics of the study population are described in Table 1. The mean DII score for the healthy control group was significantly lower than the mean DII score in the asthma group (−1.86 vs −1.40, p =0.04). The mean age, weight, BMI and the prevalence of atopy were lower in healthy controls compared to asthmatics and FEV_1 %, FVC % and FEV/FVC were significantly lower in asthma compared to healthy controls. When DII was converted into tertiles (Table 2) increasing trends across tertiles of DII were observed for BMI and IL-6, while significant decreasing trends were observed for FEV % (p=0.02) and FVC % (p=0.03). There also was a significantly higher number of asthmatics in tertile 3 compared to the number of healthy controls in tertile 3 (p-value=0.03). A significant increasing trend was observed across tertiles for saturated fat, a pro-inflammatory nutrient, and significant decreasing trends were observed for the anti-inflammatory nutrients, fibre, β-carotene and magnesium.

When analysis was carried out with asthma as the outcome (Table 3), for every unit increase in DII score the odds of being asthmatic increased by 70% (OR: 1.70, CI: 1.03, 2.14, p=0.020). Significant odds ratios also were observed for age and smoking status (Table 3). In a model incorporating FEV_1 as the outcome, FEV_1 was significantly inversely associated with DII score (β= −3.44, 95% CI: −6.50, −0.39; p=0.040), which means that for every 1 unit increase in DII, FEV_1 decreased by 3.44 times. In the same model maleness and age showed significant associations (Table 4). In a model incorporating IL-6 as the outcome, logIL-6 was significantly positively associated with DII (β= 0.13, 95% CI: 0.05, 0.21; p=0.002) (Table 5). In the same model significant associations were observed between IL-6 and age, smoking and BMI. None of the other inflammatory markers showed any significant associations.

Discussion

This is the first study to apply the DII score to the diets of subjects with asthma. We found that asthmatics had a higher DII score than healthy controls, indicating their diets were more pro-inflammatory. We also determined that both plasma IL-6 and FEV_1 were associated with DII score, suggesting that the diet-induced systemic inflammation may contribute to impaired lung function.

Data on dietary intakes of people with asthma is scarce. However, the higher DII that we observed in asthma compared to controls, is consistent with two other reports of reduced diet quality in asthmatics. One group reported a higher fat intake in subjects with asthma [20]. We have also recently reported that subjects with severe asthma consume more fat and less fibre than healthy controls [13]. Saturated fat can activate cell surface receptors such as TLR4, thereby stimulating an nfκB-driven inflammatory cascade [21]. Conversely, soluble fibre can be fermented in the gut to produce short chain fatty acids, which activate GPR43

receptors, thereby stimulating production of anti-inflammatory mediators [22]. Hence the altered dietary patterns that have been previously reported could potentially contribute to the inflammatory milieu in asthmatics.

The negative association between DII and lung function that we observed concurs with a previous study that we conducted in another cohort from the general population in Australia, where plasma IL-6 and %total energy as dietary fat were found to be negative predictors of FEV_1 in males [23]. A number of other studies have suggested that dietary intake of foods known to have pro- or anti-inflammatory effects may be related to altered respiratory outcomes. For example, a high total fat intake has been shown to be related to bronchial hyperresponsiveness (Soutar et al., 1997) and incidence of asthma in men (Strom et al., 1996). Plasma triglycerides have been shown to be elevated in subjects with adult-onset wheeze (Bodner et al., 1999). A 'western' versus 'prudent' dietary pattern, which included higher intake of saturated and trans fatty acids, was associated with a higher risk of COPD (Varraso et al., 2007). A 'meat–dim sum' versus 'vegetable–fruit–soy' dietary pattern, was associated with increased risk of developing cough with phlegm (Butler et al., 2006). Furthermore, we also have shown that a low-fruit/low-vegetable diet, which is also low in antioxidants, leads to increased circulating CRP and increased risk of asthma exacerbations [15].

The association between DII and IL-6 suggests a mechanism through which DII may impair lung function. Plasma CRP has been shown to be elevated in non-allergic [24] and steroid-naïve asthmatics [25], and correlated with lung function and airway inflammatory cell counts [25]. We have also shown that high plasma IL-6 associated with worse lung function and asthma control [9]. The causes of systemic inflammation in asthma are likely to be multiple. Systemic dissemination of local lung inflammation may occur, leading to an 'overspill' effect [26]. Systemic inflammation also may result from subclinical respiratory tract infection [27], tissue hypoxia [28] and smoking, as well as host factors such as aging and obesity [29]. This study suggests that consumption of foods with an inflammatory potential is another predictor of systemic inflammation. Subjects with the highest DII in this study have the highest IL-6 levels and this also puts them at increased risk of comorbidities involving a systemic inflammatory component. For example, elevated CRP increases cardiovascular disease (CVD) risk [30] and circulating IL-6 levels predict risk of mortality from myocardial infarction [31]. Hence, modification of dietary composition to improve the DII may be beneficial from a whole body perspective.

Interestingly, in this study, maleness was a significant modifier of the association between DII and FEV_1. This is in agreement with the data from the cohort of the general population where we also observed a relationship between dietary intake and lung function that was specific to males. Plasma IL-6 and %total energy as dietary fat were found to be negative predictors of FEV_1, in males only [23]. It is unclear why the relationship between inflammatory foods and FEV_1 would be confined to males. In relation to dietary fat intake, there may be a link to the higher rates of lipogenesis and lipolysis that occur in the visceral abdominal depot of males [13], resulting in a greater flux of fatty acids that could render males to being more sensitive to fatty acid-induced inflammation. Further work is needed to understand the gender differences in relation to other nutrients.

In the present study, no relationship was observed between airway inflammatory markers and DII. There are a few studies that have demonstrated that dietary factors can directly affect the airway inflammation, as both a high fat load [14] and an antioxidant withdrawal diet [32] have been shown to increase airway neutrophilia, which is increased in the most severe forms of asthma [33]. It may be that the inflammatory effect of nutrients in the airways is somewhat different to what occurs systemically. This might argue for an airways-specific DII. However, very many more studies are needed to provide the data for developing such as index.

Interestingly, the mean DII for both asthmatics and healthy controls in this study was negative. This can be interpreted to mean that both diets had anti-inflammatory potential. It is possible that this has occurred because of the quality of food that is available in the Australian setting. Nonetheless, relative to the healthy controls, asthmatics had a more inflammatory diet.

As both healthy controls and subjects with asthma volunteered for this study there is a potential for selection bias in that the dietary intakes of these subjects may not be completely representative. However the subject characteristics of the participants are typical of these populations. The DII is a validated tool based upon an extensive literature search of cell culture, animal and epidemiologic studies. The whole diet is taken into account in deriving the DII - including micronutrients, macronutrients and commonly consumed bioactive compounds including flavonoids, spices, and tea - not just individual nutrients or foods. DII scoring is not dependent on specific population means or recommendations of intake; it is based on results published in the scientific literature. A potential limitation of the DII is that it does not include foods, nutrients or non-nutritive compounds with anti or pro-inflammatory properties, which are not yet established scientifically. The sample size in this study is relatively small in comparison to other population cohorts; nonetheless the study had sufficient power to detect significant associations. While this study design can detect associations, a limitation of the study is its cross-sectional design, which does not allow determination of cause and effect. Thus we are not able to conclude whether the presence of asthma leads to a more pro-inflammatory diet and higher DII, or if a pro-inflammatory diet and higher DII leads to asthma development. Hence intervention trials that could modulate the DII thus are recommended to more firmly establish the role of diet as a cause of asthma.

In conclusion, the DII has provided a useful tool for assessing inflammatory potential of the diets of asthmatics compared to controls in this study. The DII makes sense from a biological perspective, as it is correlated with systemic inflammation, in the form of IL-6. The DII also negatively predicts FEV_1, adding to its clinical relevance. Hence targeting an improvement in DII in asthmatics might be a useful strategy for improving clinical outcomes in the disease.

Acknowledgments

References

1. Wood LG, Gibson PG. Dietary factors lead to innate immune activation in asthma. Pharmacology & Therapeutics. 2009; 123(1):37–53. [PubMed: 19375453]

2. Nappo F, Esposito K, Cioffi M, Giugliano G, Molinari AM, Paolisso G, Marfella R, Giugliano D. Postprandial endothelial activation in healthy subjects and in Type 2 diabetic patients: role of fat and carbohydrate meals. J Am Coll Cardiol. 2002; 39:1145–1150. [PubMed: 11923038]

3. Aljada A, Ghanim H, Abdo T, Tripathy D, Chaudhuri A, Dandona P. Increase in intracellular nuclear factor κB and decrease in inhibitor κB in mononuclear cells after a mixed meal: evidence for a proinflammatory effect. Am J Clin Nutr. 2004; 79:682–690. [PubMed: 15051615]

4. Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, Martin A, Andres-Lacueva C, Senin U. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. J Clin Endocrinol Metab. 2006; 91:439–446. [PubMed: 16234304]

5. King DE, Egan BM, Woolson RF, Mainous AGI, Al-Solaiman Y, Jesri A. Effect of a high-fiber diet vs a fiber-supplemented diet on C-reactive protein level. Arch Intern Med. 2007; 167:502–506. [PubMed: 17353499]

6. Sierksma A, van der Gaag MS, Kluft C, Hendriks HFJ. Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels; a randomized, diet-controlled intervention study. Eur J Clin Nutr. 2002; 56:1130–1136. [PubMed: 12428180]

7. van Herpen-Broekmans WM, Klopping-Ketelaars IA, Bots ML, Kluft C, Princen H, Hendriks HF, Tijburg LB, van Poppel G, Kardinaal AF. Serum carotenoids and vitamins in relation to markers of endothelial function and inflammation. Eur J Epidemiol. 2004; 19:915–921. [PubMed: 15575349]

8. King DE, Mainous AGI, Geesey ME, Woolson RF. Dietary magnesium and C-reactive protein levels. J Am Coll Nutr. 2005; 24:166–171. [PubMed: 15930481]

9. Wood LG, Baines KJ, Fu J, Scott HA, Gibson PG. The neutrophilic inflammatory phenotype is associated with systemic inflammation in asthma. Chest. 2012; 142(1):86–93. [PubMed: 22345378]

10. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hebert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr. 2013; 14:1–8.

11. Cavicchia PP, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, Hébert JR. A new dietary inflammatory index predicts interval changes in high-sensitivity c-reactive protein. J Nutr. 2009; 139(12):2365–2372. [PubMed: 19864399]

12. Shivappa N, Steck SE, Hurley TG, Hussey JR, Ma Y, Ockene IS, Tabung F, Hebert JR. A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). Public Health Nutr. 2013; 10:1–9.

13. Berthon BS, Macdonald-Wicks LK, Gibson PG, Wood LG. An investigation of the association between dietary intake, disease severity and airway inflammation in asthma. Respirology. 2012 Epub ahead of print.

14. 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(5):1133–1140. [PubMed: 21377715]

15. Wood LG, Garg ML, Smart JM, Scott HA, Barker D, Gibson PG. Manipulating antioxidant intake in asthma: a randomized controlled trial. Am J Clin Nutr. 2012; 96(3):534–543. [PubMed: 22854412]

16. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999; 14:902–907. [PubMed: 10573240]

17. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2010 Available from: http://wwwginasthmaorg.

18. Wood LG, Powell H, Gibson PG. Mannitol challenge for assessment of airway responsiveness, airway inflammation and inflammatory phenotype in asthma. Clin Exp Allergy. 2009; 40(2):232–241. [PubMed: 19878195]

19. Gelissen IC, Roberts DCK. Comparison of estimated nutrient intake by two methods: validation of a food frequency questionnaire. J Hum Nutr Diet. 1992; 5:215–223.

20. Misso NLA, Brooks-Wildhaber J, Ray S, Vally H, Thompson PJ. Plasma concentrations of dietary and nondietary antioxidants are low in severe asthma. Eur Respir J. 2005; 26(2):257–264. [PubMed: 16055873]

21. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest. 2006; 116:3015–3025. [PubMed: 17053832]

22. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Nature. 2009; 461:1282–1286. [PubMed: 19865172]

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(8): 818–825. [PubMed: 20531437]

24. Olafsdottir IS, Gislason T, Thjodleifsson B, Olafsson I, Gislason D, Jogi R, Janson C. C reactive protein levels are increased in non-allergic but not allergic asthma: a multicentre epidemiological study. Thorax. 2005; 60:451–454. [PubMed: 15923243]

25. Takemura M, Matsumoto H, Niimi A, Ueda T, Matsuoka H, Yamaguchi M, Jinnai M, Muro S, Hirai T, Ito Y, Nakamura T, Mio T, Chin K, Mishima M. High sensitivity C-reactive protein in asthma. Eur Respir J. 2006; 27(5):908–912. [PubMed: 16707391]

26. Wouters EF. Local and systemic inflammation in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2005; 2:26–33. [PubMed: 16113466]

27. Wilkinson TM, Donaldson GC, Johnston SL, Openshaw PJ, Wedzicha JA. Respiratory syncytial virus, airway inflammation, and FEV1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006; 173(8):871–876. [PubMed: 16456141]

28. Maclay JD, McAllister DA, MacNee W. Cardiovascular risk in chronic obstructive pulmonary disease. Respirology. 2007; 12:634–641. [PubMed: 17875049]

29. Wood LG, Gibson PG. Dietary factors lead to innate immune activation in asthma. Pharmacol Ther. 2009; 123(1):37–53. [PubMed: 19375453]

30. de Ferranti S, Rifai N. C-reactive protein and cardiovascular disease: a review of risk prediction and interventions. Clinica Chimica Acta. 2002; 317:1–15.

31. Tan J, Hua Q, Li J, Fan Z. Prognostic value of interleukin-6 during a 3-year follow-up in patients with acute ST-segment elevation myocardial infarction. Heart & Vessels. 2009; 24:329–334. [PubMed: 19784814]

32. Wood LG, Garg ML, Powell H, Gibson PG. Lycopene-rich treatments modify noneosinophilic airway inflammation in asthma: proof of concept. Free Radical Research. 2008; 42:94–102. [PubMed: 18324527]

33. Ordonez CL, Shaughnessy TE, Matthay MA, Fahy JV. Increased neutrophil numbers and IL-8 levels in airway secretions in acute severe asthma. Am J Respir Crit Care Med. 2000; 161:1185–1190. [PubMed: 10764310]

Table 1

Participant characteristics of both continuous and categorical variables

	Healthy Controls (n=61)	Asthma (n=99)	P-value
DII	−1.86±0.4	−1.40±0.23	0.04[*]
Age (years)	46.4±4.5	57.2±2.8	<0.0001[**]
Weight (kg)	73.3±3.5	79.3±3.1	0.01[*]
Height (m)	1.7±0.02	1.68±0.02	0.11
BMI (kg/m2)	25.7±4.3	28.0±4.1	0.007[*]
Gender			
Men, n %	25 (41)	40 (40.4)	0.94
Women, n%	36 (59)	49 (59.6)	
Atopic, n%	15 (37.5)	66 (66.7)	0.002[*]
Ex-smokers, n%	15 (25.4)	45 (44.4)	0.04[*]
Smoking pack years, yrs[***]	7.5 (1, 28)	15 (6, 25)	0.359
FEV$_1$ % predicted	102.6 ±14.3	77.9±20.1	<0.0001[**]
FVC % predicted	107.6±15.1	93.2±17.2	<0.0001[**]
FEV/FVC %	77.9±2	67.0± 2	<0.0001[**]

[*] $p<0.05$,

[**] $p<0.001$

Data are mean ± standard deviation unless otherwise indicated;

[***] Data are Median (Interquartile range).

DII, dietary inflammatory index, BMI, body mass index, FEV1, forced expiratory volume in 1s; FVC, forced vital capacity.

Table 2

Characteristics of the participants according to the tertiles of Dietary Inflammatory Index (DII)

Variables	Tertile 1[*]	Tertile 2[**]	Tertile 3[***]	P-value[a]
Age (years)	55 ± 15.1	59± 13	50± 17.3	0.38
BMI (kg/m^2)	26.7±3.7	27.6±4.4	27.9±4.8	0.21
IL-6 (pg/mL)	1.4±4.6	1.8±1.6	2.3±4.2	0.10
TNFα (pg/mL)	1.4±0.8	1.7±1.4	1.6±0.9	0.40
CRP (mg/L)	4.1±6.2	3.1±3.8	3.7±3.9	0.17
Sputum %neutrophils	43.8±23.8	39.4±20.5	36.7±20.0	0.09
Sputum %eosinophils	2.3±6.5	8.7±19.2	6.4±11.2	0.10
FEV1	91.1±22.8	83.3±18.5	82.2±19.7	0.02
FVC %	102.7±17.6	94.7±15.8	95.9±16.5	0.03
FEV/FVC %	71.5±10.4	70.6±8.0	69.8±9.7	0.26
Sex				0.72
Females	16 (42.1)	15 (44.1)	16 (38.1)	
Males	22 (57.9)	19 (55.9)	26 (61.9)	
Asthma				0.03
Yes	23 (60.5)	29 (85.3)	34 (80.9)	
No	15 (39.5)	5 (14.7)	8 (19.1)	
Food parameters				
Pro-inflammatory nutrients				
Total fat (g)	93.8±30.6	115.9±28.6	92.5±25.8	0.83
Cholesterol (mg)	291.1±106.1	453.7±429.1	331.2±119.1	0.48
Saturated fat (g)	31.6±11.3	44.6±12.5	36.9±11.0	0.03
Anti-inflammatory nutrients				
Fibre (g)	40.1±10.5	39.7±12.1	24.7±7.5	<0.0001
Beta carotene (ug)	8116.6±2196.2	7893.1±3020.9	3829.4±1958.7	<0.0001
Magnesium (mg)	549.6±221.5	523.8±136.9	345.0±95.7	<0.0001

[*] Tertile 1= <−2.12,

[**] Tertile 2= −2.12- (−) 1.29,

[***] Tertile 3 −1.30

[a]P-value determined through t-test for continuous variables and chi-square for categorical variables.

DII, dietary inflammatory index, BMI, body mass index, FEV1, forced expiratory volume in 1s; FVC, forced vital capacity.

Table 3

Summary of logistic regression analysis with asthma status as outcome

Variables	Odds Ratio	95% CI	P-value[*]
DII	1.70	1.03,2.14	0.020
Sex (referent = female)			
Males[+]	1.7	0.67, 4.26	0.26
Age (years)	1.05	1.02, 1.08	0.003
Smoking (pack years)	0.99	0.97, 1.03	0.94
BMI (kg/m^2)	1.12	0.99, 1.25	0.06

[*] p<0.05

DII, dietary inflammatory index, BMI, body mass index

Table 4

Summary of linear regression analysis based on FEV_1 as outcome

Variables	Estimate	95% CI	P-value
DII	−3.44	−6.50, −0.39	0.04
Sex (referent = female)			
Males	0.17	−7.18, 7.52	0.96
Age (years)	−0.39	−0.62, −0.15	<0.001
Smoking (pack years)	−0.23	−0.44, −0.01	0.04
BMI (kg/m^2)	−0.62	−1.48, 0.24	0.15

[*]
p<0.05

DII, dietary inflammatory index, BMI, body mass index, FEV1, forced expiratory volume in 1s; FVC, forced vital capacity.

Table 5

Summary of linear regression analysis based on log IL-6 as outcome

Variables	Estimate	95% CI	P-value[*]
DII	0.13	0.05, 0.21	0.002
Sex (referent = female)			
Males	0.009	−0.18, 0.20	0.93
Age (years)	0.01	0.01, 0.02	<0.0001
Smoking (pack years)	0.004	−0.002, 0.01	0.16
BMI (kg/m^2)	0.04	0.02, 0.06	0.001

[*] p<0.05

DII, dietary inflammatory index, BMI, body mass index