

ORIGINAL ARTICLE

Investigation of the association between dietary intake, disease severity and airway inflammation in asthma

BRONWYN S. BERTHON,¹ LESLEY K. MACDONALD-WICKS,² PETER G. GIBSON¹ AND LISA G. WOOD¹

¹Centre for Asthma and Respiratory Disease, Hunter Medical Research Institute, and ²Discipline of Nutrition and Dietetics, School of Health Sciences, University of Newcastle, Newcastle, New South Wales, Australia

ABSTRACT

Background and objective: Dietary intake is an important modifiable risk factor for asthma and may be related to disease severity and inflammation, through the effects of intake of anti-oxidant-rich foods and pro-inflammatory nutrients. This study aimed to examine dietary intake in asthma in relation to asthma severity, lung function, inhaled corticosteroid use, leptin levels and inflammation.

Methods: Food frequency questionnaires, spirometry and hypertonic saline challenge were completed by 137 stable asthmatics and 65 healthy controls. Plasma leptin was analysed by immunoassay. Induced sputum differential cell counts were determined.

Results: Subjects with severe persistent asthma consumed more fat and less fibre as compared with healthy controls (odds ratio 1.04 (95% confidence interval: 1.01–1.07), $P = 0.014$) (odds ratio 0.94 (95% confidence interval: 0.90–0.99), $P = 0.018$). Among asthmatics, higher fat and lower fibre intakes were associated with lower forced expiratory volume in 1 s and airway eosinophilia. Leptin levels were increased in both male and female asthmatics as compared with healthy controls. No association existed among asthmatics between corticosteroid use and dietary intake.

Conclusions: It was found that asthmatics within the subgroup of severe persistent asthma have a different pattern of dietary intake as compared with healthy controls, which was associated with lower lung function and increased airway inflammation.

Key words: asthma, corticosteroid, dietary fat, dietary fibre, leptin.

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroids; OCS, oral corticosteroids.

SUMMARY AT A GLANCE

This cross-sectional study investigated diet, inflammation, lung function and asthma symptoms in Australian asthmatics and healthy controls. Participants with severe persistent asthma showed a different dietary intake pattern compared with healthy controls, which was associated with lower lung function and increased airway inflammation. Asthmatics also had increased serum leptin levels.

INTRODUCTION

In asthma, dietary intake and weight gain are key environmental exposures that may contribute to the development and progression of the disease.¹ The significant morbidity associated with asthma may be ameliorated through addressing modifiable risk factors such as diet. The Western diet has shifted towards less fruit and vegetables, more refined and processed foods,¹ and convenience foods that are high in fat, salt and sugar and low in fibre and anti-oxidants. This increase in caloric density of the diet results in positive energy balance and subsequent increases in obesity. Several epidemiological studies support the hypothesis that a Western-style diet is associated with asthma.^{2–5} Western-style fast-food intake has been shown to increase asthma risk.³ Proposed mechanisms include the hypothesis that this eating pattern may worsen asthma through pro-inflammatory responses induced by various nutrients. Indeed, low anti-oxidant intake,⁶ high dietary fat intake⁷ and obesity⁸ have all been shown to augment airway inflammation in asthma.⁹ Hence, dietary intake may be important in the management of inflammation and clinical outcomes in asthma.

Studies describing the usual dietary intake of subjects with asthma are scarce. There is also very little objective information on how asthma pharmacotherapy such as oral (OCS) and inhaled corticosteroids (ICS), influences dietary intake. This study examines the hypotheses that: (i) Dietary intake is associated with disease severity in asthma; (ii) dietary

Correspondence: Lisa G. Wood, Respiratory Medicine, Level 2, Hunter Medical Research Institute, Lot 1 Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia. Email: lisa.wood@newcastle.edu.au

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intake of fat is positively associated with airway inflammation, and dietary intake of fibre and antioxidants is inversely associated with airway inflammation in asthma; and (iii) dietary intake is associated with corticosteroid use in asthma.

METHODS

Study participants

Subjects with stable asthma were recruited from the John Hunter Hospital Asthma Clinic, NSW, Australia, and by advertisement ($n = 137$). Healthy controls were recruited by advertisement ($n = 65$). Subjects and controls were matched by gender and age range. A subset of data from some of these subjects has previously been reported.^{8,10} Inclusion criteria were age over 18 years, non-smoking status (ceased smoking for at least 6 months) and confirmed stable asthma. Asthma diagnosis was confirmed on the basis of current (past 12 months) episodic respiratory symptoms, doctor's diagnosis of asthma (ever) and airway hyperresponsiveness to hypertonic saline. Asthma stability was defined as no exacerbation, respiratory tract infection or OCS use in the past 4 weeks. Healthy controls had normal lung function without airway hyperresponsiveness, 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. Written informed consent was obtained from all subjects.

Clinical assessment

Subject medication use was recorded, including ICS and OCS use in the previous 12 months. Asthma control was assessed using the validated Asthma Control Questionnaire.¹¹ Asthma severity was categorized as intermittent, mild persistent, moderate persistent and severe persistent using previously described Global Initiative for Asthma criteria and ICS dose.¹² Atopy was tested by skin prick test using five common aero-allergens, prepared by Hollister-Stier (Chicago, IL, USA) (*Aspergillus fumigatus*, *Alternaria tenuis*, dust mite, cockroach mix and grass mix).

Anthropometry

Subjects were weighed in light clothing to the nearest 100 g with NU WEIGH LOG842 scales, (NU Weigh Scales, Inc, MI, USA). Height was measured using the stretch stature method to the nearest 0.1 cm using a wall-mounted stadiometer. Height and weight measures were used to calculate body mass index (BMI, kg/m²).

Sputum collection and processing

Exhaled nitric oxide (NIOX, Aerocrine, Solna, Sweden), 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.¹³ Lower respiratory sputum portions were selected from saliva, dispersed with dithiothreitol, and total and differential cell count of leucocytes was performed, as previously described.¹³

Blood collection and processing

Blood was collected in ethylenediaminetetraacetic acid tubes, centrifuged at 4°C, 3000 g, for 10 min and plasma was stored at -80°C. Plasma leptin was measured with commercial Bio-Plex Pro Human Diabetes capture sandwich Luminex immunoassay kits (Bio-Rad Laboratories, Hercules, CA, USA).

Dietary intake collection and analysis

Subjects completed a 186-item semi-quantitative food frequency questionnaire developed in Victoria, Australia, and modified in Western Sydney, NSW, Australia.¹⁴ The food frequency questionnaire has been validated using weighed food records within a female student population aged between 20–43 years.¹⁴ Data entry and analysis of the food frequency questionnaire were completed by a qualified dietitian (B.B.) using the Australian AusNut 1999 database (All Foods) Revision 17 and AusFoods (Brands) Revision 5, accessed through FoodWorks (version 4.00.1158, 2005; Xyris Software, Brisbane, Queensland, Australia). Average daily dietary intakes were computed from the reported frequency of consumption, the standard serving size (unless other serve specified) and the foods available in the nutrient composition software.

Statistical analysis

Data are reported as means $\pm$ standard deviation and median (interquartile range). Statistical comparisons of continuous outcomes were performed using one-way analysis of variance or Kruskal–Wallis test, both followed by Bonferroni post-hoc testing and chi-square analysis for categorical outcomes. Leptin levels in male and female asthmatics were compared with healthy controls using two-sample Wilcoxon rank sum tests. Multivariate logistic regression was used to analyse dietary intake and compare the intake of the subjects with severe persistent asthma with the healthy control subjects. Multiple linear regressions were used to assess associations between continuous variables. All logistic and linear regression models included age, gender and BMI as covariates to reduce confounding. All dietary data were adjusted for total energy before analysis using the residual method.¹⁵ Significance was accepted if $P < 0.05$.

RESULTS

Participant characteristics

While the age and BMI ranges for asthma and control subjects were similar, the mean age and BMI for

Table 1 Participant characteristics[†]

	Healthy controls (<i>n</i> = 65)	Intermittent, mild and moderate persistent asthma (<i>n</i> = 46)	Severe persistent asthma (<i>n</i> = 64)	<i>P</i>
Age, years (range)	46.7 ± 17.4 ^a (20,78)	54.5 ± 15.5 ^b (21,78)	57.8 ± 14.4 ^b (23,78)	<0.001***
Weight, kg (range)	73.4 ± 13.6 ^a (49.6,109)	77.9 ± 15.3 ^{ab} (48.9,108.6)	80.3 ± 15.9 ^b (55.1,119.6)	0.031*
BMI, kg/m ² (range)	25.4 ± 3.9 ^a (18.5,35.5)	27.7 ± 4.6 ^b (18,36)	28.4 ± 4.3 ^b (17.3,35.4)	<0.001***
Men, <i>n</i> (%)	27 (42)	18 (40)	27 (42)	0.946
Women, <i>n</i> (%)	38 (58)	28 (60)	37 (58)	
Atopic, <i>n</i> (%)	16 (37)	27 (59)	47 (74)	0.001**
Ex-smokers, <i>n</i> (%)	16 (25)	17 (37)	32 (50)	0.027*
Pack years, median (IQR)	7.5 (1,28)	11 (5,19)	18 (7.5, 30)	0.359
FEV ₁ % predicted	102.9 ± 14.1 ^a	91.5 ± 12.8 ^b	68.9 ± 20.6 ^c	<0.001***
FVC % predicted	107.8 ± 14.9 ^a	103.6 ± 12.4 ^a	86.3 ± 17.9 ^b	<0.001***
#FEV ₁ /FVC %	78.0 ± 5.8 ^a	72.2 ± 7.9 ^b	63.4 ± 10.8 ^c	<0.001***
Inhaled steroids, µg/day [†]	N/A	400 ± 627	1059 ± 911	<0.001***
Oral steroids in 12 months, <i>n</i> (%)	N/A	2.0 (4)	14.0 (23)	0.009**

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[†] Where the P -value is significant, values within a row with the same superscript letter are not significantly different.

[‡] Beclomethasone equivalent dose.

Data are mean ± standard deviation unless otherwise indicated.

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; N/A, not applicable.

Table 2 Airway and systemic inflammation in participants with asthma and healthy controls[†]

	Healthy controls (<i>n</i> = 52)		Intermittent, mild and moderate persistent asthma (<i>n</i> = 41)		Severe persistent asthma (<i>n</i> = 56)		<i>P</i>
	Median	IQR	Median	IQR	Median	IQR	
Cell count (×10 ⁶ /mL)	2.3	1.5, 4.3	2.5	1.8, 4.8	2.9	1.8, 5.4	0.513
% eosinophils	0.3 ^a	0, 1.4	0.8 ^a	0.3, 2.0	3.1 ^b	0.8, 9.0	<0.001***
% neutrophils	33.6	20.9, 55.4	36.8	22.8, 54.8	44.4	28.5, 62.3	0.108
% macrophages	57.8 ^a	39.5, 69.8	55.5 ^{ab}	35.0, 69.5	39.9 ^b	26.9, 57.0	0.003**
% lymphocytes	1.25 ^a	0.1, 2.4	0.5 ^{ab}	0, 1.5	0.5 ^b	0.1, 1.3	0.035*
eNO (ppb)	17.2 ^a	12.0, 24.0	21.4 ^{ab}	14.7, 31.9	22.9 ^b	16.0, 40.7	0.019*
Leptin (pg/mL)	1025 ^a	419, 1817	3539 ^b	2246, 8088	5050 ^b	2689, 8088	<0.001***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

[†] Where the P -value is significant, values within a row with the same superscript letter are not significantly different.

eNO, exhaled nitric oxide; IQR, interquartile range.

subjects with asthma were higher than healthy controls (Table 1). Hence, all comparisons were adjusted for age and BMI. Asthmatics had a higher prevalence of atopy. Severe persistent asthmatics had worse lung function and were more likely to be ex-smokers than controls and intermittent, mild and moderate persistent asthmatics. ICS doses were significantly higher in severe compared with intermittent, mild and moderate asthmatics. OCS were used by 15% of asthmatic subjects over the previous 12 months; the majority (88%) of these were severe asthmatics.

Systemic and airway inflammation

Airway inflammation was increased in asthmatics, with higher exhaled nitric oxide compared with

healthy controls. Compared with healthy controls, sputum % eosinophils and % macrophages were higher in subjects with severe asthma, but not in intermittent, mild or moderate disease severity ($P = 0.001$; $P = 0.003$) (Table 2). Serum leptin concentrations in all subjects with asthma were increased compared with healthy controls ($P < 0.001$). Women had significantly higher leptin levels than men in both the asthmatic and healthy control groups ($P < 0.001$) (Fig. 1). Leptin was positively associated with BMI in both male ($r = 0.74$, $P < 0.001$, $n = 37$) and female ($r = 0.71$, $P < 0.0001$, $n = 53$) asthmatics (Fig. 2). Leptin levels were associated with the presence of asthma in both men and women ($P < 0.001$). In a logistic regression model, a 1000 pg/mL increase in leptin increased the odds of asthma by 2.35 (odds

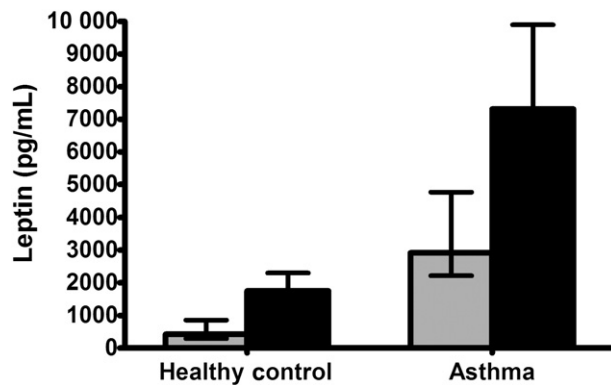


Figure 1 Leptin levels in asthmatics and healthy controls by gender. Leptin levels of asthmatic subjects were higher than healthy controls in both (□) male and (■) female subjects ($P \leq 0.001$, adjusted for age, gender and BMI).

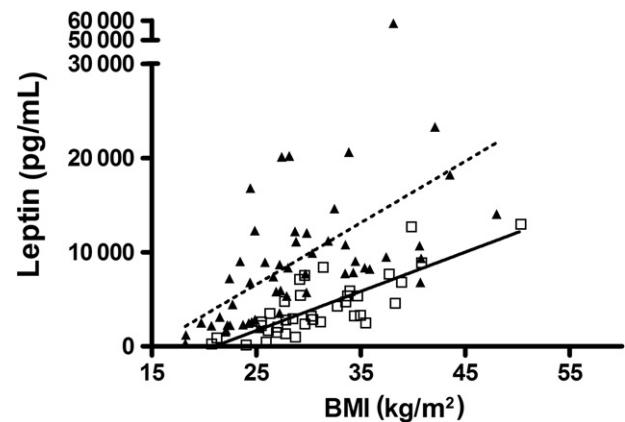


Figure 2 Relationship of leptin and body mass index (BMI) in (□) male and (▲) female asthmatics. Leptin and BMI were significantly and positively related in men ($r = 0.74$, $P < 0.001$) (solid line) and women ($r = 0.71$, $P < 0.0001$) (dashed line) with asthma.

Table 3 Logistic regression analysis of dietary intake in subjects with severe persistent asthma compared with healthy controls[†]

	Healthy controls ($n = 61$)		Severe persistent asthmatics ($n = 59$)		Odds ratio [‡]	P	95% CI
	Mean	SEM	Mean	SEM			
TEE (kJ)	11 211.0	330.0	11 115.0	389	0.99	0.470	0.99–1.00
Fat (g/day)	98.0	4.0	103.0	4.0	1.04	0.014*	1.01–1.07
PUFA (g/day)	17.0	1.0	16.0	1.0	1.04	0.359	0.95–1.14
MUFA (g/day)	37.0	2.0	40.0	2.0	1.09	0.011*	1.02–1.16
SFA (g/day)	36.0	2.0	38.0	2.0	1.04	0.162	0.99–1.09
Protein (g/day)	117.0	4.0	118.0	7.0	0.99	0.909	0.99–1.01
Carbohydrate (g/day)	295.0	9.0	281.0	12.0	0.99	0.167	0.98–1.00
Fibre (g/day)	37.0	13.0	32.0	11.0	0.94	0.018*	0.90–0.99
Sodium (g/day)	2924.0	105.0	3139.0	156.0	2.73	0.019*	1.18–6.33
Potassium (g/day)	4680.0	141.0	4182.0	144.0	0.99	0.002**	0.99–0.99
Calcium (mg/day)	1292.0	51.0	1172.0	66.0	0.99	0.155	0.99–1.00
Magnesium (mg/day)	498.0	22.0	452.0	21.0	0.99	0.193	0.99–1.00
Phosphorous (mg/day)	2094.0	59.0	1953.0	98.0	0.99	0.208	0.99–1.00
Iron (mg/day)	18.0	0.8	17.0	0.7	0.91	0.085	0.82–1.01
Zinc (mg/day)	18.0	0.8.0	17.0	0.8	0.95	0.286	0.87–1.04
Vitamin C (mg/day)	250.0	27.0	230.0	49.0	0.99	0.791	0.99–1.00
Retinol (µg)	623.0	79.0	634.0	44.0	1.00	0.646	0.99–1.00

* $P < 0.05$, ** $P < 0.01$.

[†] Logistic regression analysis for each dietary nutrient included the following covariates in the model: age, gender and BMI.

[‡] Indicates change in risk per unit of dietary intake.

CI, confidence interval; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SEM, standard error of the mean; SFA, saturated fatty acids; TEE, total energy intake.

ratio: 2.35, 95% confidence interval: 1.65–3.35, $P < 0.001$). In male asthmatics, ICS dose was significantly associated with leptin levels, (Coef.: 0.59, 95% confidence interval: 0.02–1.17, $P = 0.045$).

Dietary intake

Dietary intake in subjects with intermittent, mild and moderate persistent asthma was not different with

healthy controls. Total energy, protein and carbohydrate intakes of healthy controls and subjects with severe asthma were similar, although intake of total fat, fibre, sodium and potassium in the severe asthma subgroup was significantly different with the intake of healthy control subjects. Severe asthmatics had a higher total fat intake than healthy controls ($P = 0.014$), with a mean difference of 5 g/day in fat intake. For each extra 10 g of fat consumed, the odds

Table 4 Coefficients for multiple linear regression models of the relationships between dietary intake of fat and fibre and lung function and airway inflammation in asthmatic participants[†]

Explanatory variables	Outcome variables				
	FEV ₁ (L) <i>n</i> = 110	FVC (L) <i>n</i> = 110	FEV ₁ /FVC <i>n</i> = 110	% eosinophils <i>n</i> = 107	% neutrophils <i>n</i> = 107
	Coef. (<i>P</i>)				
Total fat intake	−0.004 (0.311)	−0.003 (0.451)	−0.0004 (0.479)	0.18 (0.039)*	−0.25 (0.092)
Fibre intake	0.02 (0.001)**	0.02 (0.002)**	0.002 (0.035)*	−0.36 (0.026)*	0.26 (0.330)
Age	−0.03 (0.001)	−0.04 (0.001)	−0.001 (0.039)	4.90 (0.082)	−1.56 (0.737)
Women [‡]	−0.71 (0.001)	−1.23 (0.001)	0.034 (0.085)	−0.22 (0.227)	0.55 (0.078)
BMI	−0.004 (0.583)	−0.02 (0.026)	0.003 (0.015)	0.24 (0.022)	0.15 (0.391)
R ²	0.4440	0.5564	0.1593	0.1509	0.0930

* $P < 0.05$ indicates that the dietary variable is significantly related to the outcome. ** $P < 0.01$.

[†] Coefficients indicate the change in the outcome variable per unit increase in the explanatory variable (adjusted for energy intake using residual method).

[‡] Gender coded: men = 0 and women = 1.

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

of severe persistent asthma were increased by 48% after adjusting for energy intake (Table 3). Fibre intake was an average of 5 g/day lower in the severe asthma group compared with the controls ($P = 0.018$). Sodium intake was higher and potassium intake was lower in severe asthmatics than healthy controls ($P = 0.020$, $P = 0.002$), with no difference in other micronutrient intakes. In subjects with asthma, there was no difference in energy or fat intake according to ICS dosage and no difference in dietary intake between those who had taken OCS in the last 12 months ($n = 16$) and those who had not ($n = 94$) ($P = 0.728$, $P = 0.912$ respectively).

Relationship of dietary intake, clinical and inflammatory indicators

In multiple linear regression, dietary fibre intake in asthmatics was positively associated with forced expiratory volume in 1 s (L) ($P = 0.001$), forced vital capacity (L) ($P = 0.002$) and forced expiratory volume in 1 s/forced vital capacity ($P = 0.035$) (Table 4) (Fig. 3). Fat intake was positively associated and fibre intake was negatively associated with airway % eosinophils ($P = 0.005$) (Table 4). Saturated fat intake was positively associated with sputum % eosinophils ($R^2 = 0.1460$, $P = 0.001$). Neither leptin nor airway hyperresponsiveness was associated with dietary intake.

DISCUSSION

In this study, severe asthmatics consumed a different diet as compared with healthy controls that consisted of higher fat and sodium intakes and lower fibre and potassium intakes. We have shown for the first time, to our knowledge, that high fat intake and low fibre intake are associated with worse airway inflammation and lung function in subjects with asthma. Plasma

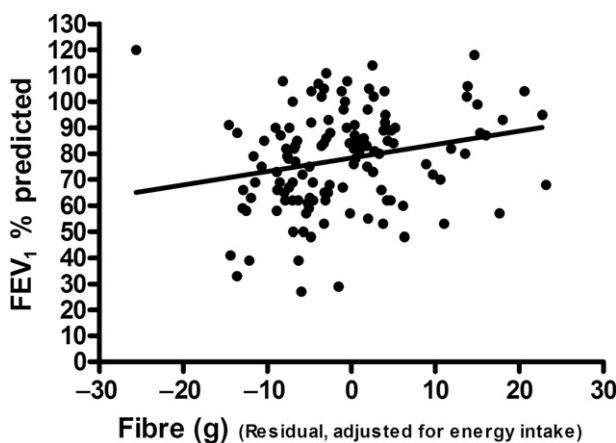


Figure 3 Relationship of forced expiratory volume in 1 s (FEV₁) and daily fibre intake adjusted for energy intake in subjects with asthma. Average daily fibre intake was significantly associated with FEV₁ % predicted in all subjects with asthma ($R^2 = 0.1698$ ($P \leq 0.001$)). Model adjusted for energy intake and body mass index.

leptin levels were significantly higher in asthma than healthy controls; however, dietary intake was not directly related to corticosteroid use in this study.

This study suggests that fibre has a protective role in asthma, a finding supported by recent work in chronic obstructive pulmonary disease where lower fibre intakes were associated with risk of chronic obstructive pulmonary disease diagnosis in women.¹⁶ Dietary fibre exerts anti-inflammatory effects due to the production of butyrate, a short-chain fatty acid, by microbiota in the gut that ferment soluble fibre. Butyrate activates the peroxisome proliferator-activated receptor- α which then inhibits NF κ B activity; a pro-inflammatory transcription factor.¹⁷ Short-chain fatty acids have also recently been shown to activate a family of G protein-coupled receptors,

reducing inflammatory responses in mice models of airway inflammation.¹⁸ It is also possible that other nutrients found in fibre-rich foods, such as fruit and vegetables, cereals and legumes, may be contributing to the inverse association between fibre and lung function. Many fibre-rich foods are also sources of anti-oxidants and other micronutrients, such as polyphenolic compounds and flavonoids, which may counteract oxidative stress in asthma.¹⁰ The nutrient database that was used to analyse the food frequency questionnaire only included vitamin C and retinol as anti-oxidant nutrients, and these were not associated with lung function. However, it is possible that other nutrients that we have not analysed may have contributed to the inverse association between fibre and airway inflammation.

The lower potassium and higher sodium intake seen in severe asthmatics in this cohort has been previously reported. Dietary sodium intake has been shown to be positively related to airway responsiveness¹⁹ and it has been proposed that high sodium intake may lead to hyperpolarization of bronchial smooth muscle, causing asthma exacerbation.²⁰ More recent evidence suggests that a low sodium diet has no therapeutic benefit for bronchial reactivity in adults with asthma.²¹ In addition, another study demonstrated that airway responsiveness and urinary sodium excretion, a direct indicator of dietary sodium intake, had no relationship.²² Hence, it appears that while a low sodium diet may not have additional benefits to lung function and bronchial reactivity, a higher sodium intake has the negative effects originally proposed.²³ Low dietary potassium intake has also been associated with bronchial hyperreactivity and lung function,²⁴ and although low serum potassium may be present in some people with asthma, it is postulated this is related to use of β_2 agonist medication.²⁵

The higher fat intake that we observed in severe asthma agrees with several other reports that have shown an increased total fat intake in severe asthma.²⁶ High dietary fat intake has been associated with airway hyperresponsiveness and asthma diagnosis.²⁷ Furthermore, plasma triglyceride levels have been reported to be elevated in subjects with adult-onset wheeze;²⁸ trans polyunsaturated fatty acids have been associated with increased asthma prevalence²⁹ and margarine intake, a source of trans fats, has been related to increased asthma risk.^{30,31} There are a variety of mechanisms by which dietary fat modulates inflammatory responses. Dietary fat consumption can modify inflammation due to alterations in eicosanoid synthesis, including leukotrienes and prostaglandins.³² Dietary fat intake affects cell membrane composition, which can induce changes in gene expression.^{33–35} Furthermore, fatty acids can activate innate immune receptors such as toll-like receptors, leading to the altered activity of transcription factors such as NF- κ B. We have previously demonstrated in an acute model in adults with asthma that a single high-fat meal leads to increased airway neutrophilia and increased gene expression of the innate immune receptor, toll-like receptor 4.⁷ The data presented in the current study suggest

that in a chronic model, a high fat intake may contribute to the development of eosinophilic airway inflammation.

Interestingly, asthmatic subjects had higher BMI than healthy controls yet did not consume more energy (kJ). In a similar study, asthmatic subjects had lower energy intakes than healthy controls, although their BMI were not different.³⁶ This may be due to reduced energy expenditure in asthmatics due to disease-induced limitation of physical activity or metabolic abnormalities associated with the disease process.³⁶

The reason for the association between altered dietary intake and severe asthma is not known. We examined whether corticosteroid use was related to dietary intake, and no direct association was found. Patients perceive that corticosteroids lead to weight gain, yet evidence supporting this concept in airway diseases is scarce and inconclusive.^{37,38} Reports of dietary intake in adult asthmatics on OCS therapy are contradictory. Misso *et al.* reported a higher fat intake for 28 severe asthmatics taking either OCS or ICS compared with control subjects.²⁶ However, Picado *et al.* reported asthmatic subjects on either OCS or ICS had significantly lower fat and total energy intake than healthy controls.³⁶ It is plausible that ICS may affect dietary intake, as high doses of ICS in subjects with mild asthma can exert a systemic response, by suppressing the hypothalamic-pituitary-adrenal axis, demonstrated by decreased serum cortisol secretion.³⁹ In this study, asthma severity was associated with both higher ICS doses and higher fat intake; however, ICS dose and fat intake were not directly associated.

One mechanism by which corticosteroids are suggested to contribute to increased appetite, dietary intake and weight gain is via modification of leptin levels. Leptin is a hormone secreted by adipocytes, signalling levels of cellular fat stores to the hypothalamus to influence energy intake and expenditure through regulation of other neuropeptides and hormones.⁴⁰ OCS use causes amplification of acute leptin levels.⁴¹ As well as regulating appetite, leptin has a role in the immune and respiratory systems. Leptin receptors are widely expressed throughout the airway and in vitro experiments have shown that leptin modulates expression of adhesion molecules that may lead to eosinophil infiltration into the lungs.⁴² Systemically, pro-inflammatory cytokines such as interleukin-6, tumour necrosis factor- α and interleukin-12 are upregulated by leptin, which may also contribute to asthma pathology.⁴² The leptin levels of healthy controls in our study were similar to other reports.⁴¹ In subjects with asthma, leptin levels were increased independent of BMI. Women had higher leptin levels than men, which agrees with results from a paediatric study showing asthmatic children had higher leptin levels than healthy controls,⁴³ and leptin was higher in healthy girls than in healthy boys.⁴³ This may be due to increased leptin expression by ovarian hormones.⁴² While we did not observe an association between leptin levels and dietary intake in our study, leptin levels were associated with ICS dose in men, suggesting that the link

between appetite, leptin and corticosteroid use in asthma needs to be further investigated.

A limitation of this study is the cross-sectional design, which is able to detect associations, but not determine causality. Hence, we are not able to conclude whether the presence of severe asthma leads to altered dietary intake, or if altered dietary intake leads to more severe disease. Investigation of OCS use within this cohort was limited as only a small number of subjects were prescribed OCS on an infrequent basis.

The results from this study suggest that asthmatics with severe disease have an altered pattern of dietary intake, with increased fat and reduced fibre intake, which is related to worsened lung function and airway inflammation. The relationships between dietary intake and asthma outcomes highlight the potential role for nutritional counselling in asthma management and suggest that dietary fibre and fat may be important nutrients to target. Asthmatics also had increased circulating leptin levels. Dietary intake of asthmatic subjects in this cohort was not directly driven by ICS or OCS use; however, altered leptin levels may indicate a link between appetite, leptin and corticosteroid use in asthma.

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