

Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial

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Summary

Background Obesity and asthma are associated conditions; however, the mechanisms linking the two remain unclear. Few studies have examined the effects of weight loss on inflammation and clinical outcomes in obese-asthma.

Objective To compare the effects of weight loss achieved by dietary restriction, exercise or combined dietary restriction and exercise on airway inflammation and clinical outcomes in overweight and obese adults with asthma.

Methods Participants ($n = 46$; 54.3% female, body mass index (mean $\pm$ SD) 33.7 ± 3.5 kg/m²) were randomized to complete a 10-week dietary, exercise or combined dietary and exercise intervention. Dual-energy x-ray absorptiometry was performed, the Juniper Asthma Control Questionnaire and Juniper Asthma Quality of Life Questionnaire completed and inflammatory markers, dietary intake and physical activity measured. The trial was registered with the Australian Clinical Trials Registry: ACTRN12611000235909.

Results Retention was 82.6%. Mean $\pm$ SD weight loss was $8.5 \pm 4.2\%$, $1.8 \pm 2.6\%$ and $8.3 \pm 4.9\%$ after the dietary, exercise and combined interventions respectively. Asthma control improved after the dietary (mean $\pm$ SD; -0.6 ± 0.5 , $P \leq 0.001$) and combined interventions (-0.5 ± 0.7 , $P = 0.040$), whereas quality of life improved after the dietary [median (IQR); 0.9 (0.4, 1.3), $P = 0.002$], exercise [0.49 (0.03, 0.78), $P = 0.037$] and combined [0.5 (0.1, 1.0), $P = 0.007$] interventions. A 5–10% weight loss resulted in clinically important improvements to asthma control in 58%, and quality of life in 83%, of subjects. Gynoid adipose tissue reduction was associated with reduced neutrophilic airway inflammation in women [β -coefficient (95% CI); 1.75 (0.02, 3.48), $P = 0.047$], whereas a reduction in dietary saturated fat was associated with reduced neutrophilic airway inflammation in males ($r = 0.775$, $P = 0.041$). The exercise intervention resulted in a significant reduction to sputum eosinophils [median (IQR); -1.3 (-2.0 , -1.0)%, $P = 0.028$]. **Conclusion and clinical relevance** This study suggests a weight-loss goal of 5–10% be recommended to assist in the clinical management of overweight and obese adults with asthma. The obese-asthma phenotype may involve both innate and allergic inflammatory pathways.

Keywords adipose tissue, asthma, body composition, eosinophil, exercise, low-energy diet, neutrophil, obesity, weight loss

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Introduction

Obesity is a risk factor for asthma, with asthma incidence being almost doubled in obese individuals compared with healthy-weight individuals [1]. Obese asthmatics experience more severe asthma symptoms,

reduced lung function, have a poorer quality of life [2–6] and a reduced response to inhaled corticosteroid (ICS) medication [4, 7, 8], the mainstay of asthma pharmacotherapy. This highlights the need for alternative treatment strategies to effectively manage asthma in this population.

Weight loss induced by either caloric restriction or bariatric surgery appears to improve asthma symptoms, lung function and quality of life [9–12]; however, most studies have not measured asthma objectively or as the primary outcome [10, 13–17]. The effect of weight loss on airway inflammation has been examined by Dixon et al. [18], who reported no change after surgically induced weight loss. To our knowledge, the effect of exercise has yet to be investigated as a weight-loss strategy in an asthmatic population. This is important because exercise is associated with reduced asthma exacerbations [19], asthma symptoms [20] and bronchial hyperresponsiveness in an asthmatic population. Furthermore, asthmatics are less likely to exercise than non-asthmatics [20], whereas obese individuals are less likely to exercise compared with those of a healthy weight [21]. These studies suggest that obese asthmatics generally have a low exercise level, which may have a role in the aetiology of the obese–asthma phenotype.

The mechanisms driving the obese–asthma phenotype are not well understood; however, it appears to involve a predominantly female population with a high symptom expression despite an absence of airway eosinophils [22]. We have proposed previously that this non-eosinophilic obese–asthma phenotype may in fact represent neutrophilic asthma, as we observed a positive association between body mass index (BMI) and sputum neutrophils in asthmatic women, but not men [23]. This observation is important because neutrophilic airway inflammation is associated with the most severe forms of asthma [24] and is resistant to ICS medication [25]. Others have since demonstrated an association between obesity and neutrophil concentrations in both the airways [26] and circulation [5, 26, 27] of adults with asthma.

It is uncertain whether weight loss reduces neutrophilic airway inflammation. We therefore sought to examine the effect of weight loss on the inflammatory and clinical outcomes of overweight and obese adults with asthma. Whether physical inactivity has a role in the aetiology of the obese–asthma phenotype is also uncertain. Therefore, we also sought to examine the effects of increased exercise on clinical asthma outcomes and airway inflammation. We hypothesized that weight loss induced both by caloric restriction and increased exercise would improve clinical asthma outcomes in overweight and obese asthma. We also hypothesized that weight loss would be associated with a reduction in airway neutrophils in women and significantly improve clinical asthma outcomes. The aim of this study was to compare the effects of weight loss and increased exercise achieved by a dietary intervention, exercise intervention and combined dietary and exercise intervention, on airway inflammation and the clinical asthma outcomes of overweight and obese men and women with asthma.

Methods

Study design

Participants were randomized between June 2009 and December 2010 to complete a 10-week dietary intervention, exercise intervention or combined dietary and exercise intervention (Fig. 1). Participants were overweight and obese (BMI 28–40 kg/m²) non-smoking adults with asthma. Asthma was defined by doctor's diagnosis and documented history of airway hyperresponsiveness (AHR); however, there were no entry criteria in relation to symptom severity or lung function. Exclusion criteria included: weight change > 5% in the preceding 3 months; pregnancy or breastfeeding; cardiac arrhythmia or angina; renal or hepatic failure; use of insulin or oral hypoglycaemic medication; gallstones, pancreatitis, cancer; or an orthopaedic problem that would impede physical activity. Participants were deemed medically fit for weight loss through a screening examination and written approval from their primary healthcare provider. All clinical measures were performed pre- and post-intervention at the John Hunter Hospital, NSW, Australia. Recruitment was conducted in blocks of up to five participants, who were blind to group allocation until completion of their baseline assessment. Computer-generated blocks of random numbers were generated by the statistician, which randomized participants within each block. These randomization codes were held by the statistician and concealed to study personnel. Once each block was scheduled and confirmed by study personnel, the study coordinator contacted the statistician by email. At this point, the statistician revealed the next block allocation. Once this was revealed, study personnel were not permitted to enrol additional participants to that particular block. Due to the nature of the interventions, it was not possible to blind the researchers or participants during the study intervention. Hence, to reduce risk of bias, objective outcomes measures were used, including lung function, anthropometry and inflammatory markers. This research was approved by the Hunter New England Human Research Ethics Committee (HREC/09/HNE/77) and all subjects provided written informed consent. The trial was registered with the Australian Clinical Trials Registry (<http://www.actr.org.au>), Registration Number: ACTRN12611000235909.

Intervention descriptions

Dietary intervention. Participants were prescribed an intake of 3700–4900 kilojoules (kJ)/day (885–1170 kcal/day), including two meal replacements per day provided free of charge (Optifast® VLCDTM; Nestle Nutrition, Nottingham Hill, Victoria, Australia; and/or KicStart™ VLCD;

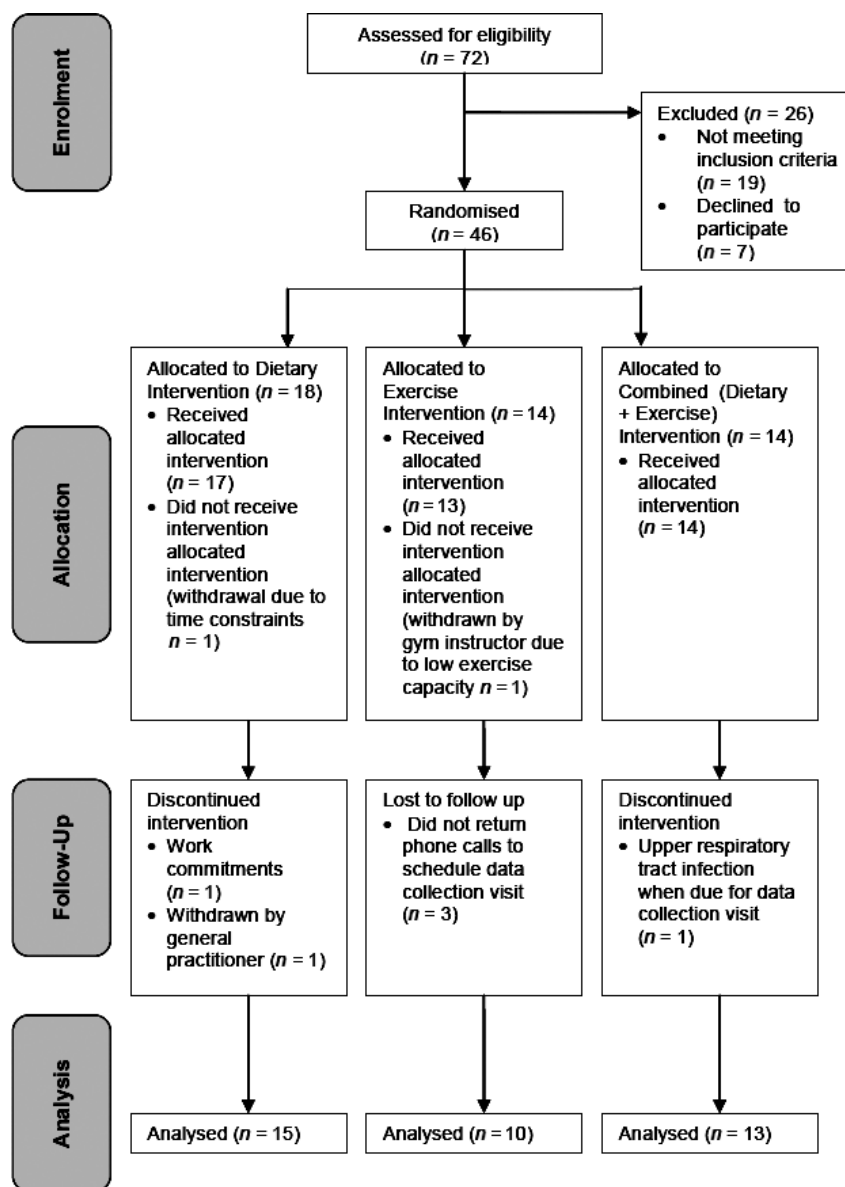


Fig. 1. Flowchart of study participants.

Prima Health Solutions, Frenchs Forest, NSW, Australia). Participants were also instructed to consume one main meal and snacks daily, and complete weekly counselling with a dietician: seven 1-h clinic visits and four 10-min phone consultations. These sessions focused on nutrition education, behaviour modification and motivational strategies. Participants maintained a daily food diary for the duration of the intervention, which included details on hunger perception, water intake and food habits, in addition to actual food eaten.

Exercise intervention. Participants received a 12-week gymnasium membership and a group personal training session for 1 h each week. All sessions were completed

at the same gymnasium to ensure that comparable exercise programmes were undertaken. Each programme was designed by an exercise physiologist, and included both aerobic activities and resistance training. Participants attended the gymnasium at least three times each week and wore a pedometer daily for the duration of the intervention, with the goal of increasing their daily steps by 10% each week to a target of 10 000 steps per day. Participants received educational materials regarding national physical activity recommendations, set goals with the study dietician and signed an informal contract prior to commencing their first gymnasium session. Participants also completed a daily physical activity diary throughout the intervention, which

included space to list activities completed each day, daily pedometer step goals and a section for comments and resolutions.

Combined (dietary + exercise) intervention. Participants completed both the dietary and exercise interventions concurrently.

Anthropometric measurements

Height, weight (Nuweigh LOG 842; NWS, Newcastle, NSW, Australia) and waist circumference [28] were measured by trained research assistants. A total body scan was performed using dual-energy x-ray absorptiometry (DXA; Lunar Prodigy Series, GE Medical Systems, Madison, WI, USA) after subjects removed unfixed metal objects. Percentage fat change was calculated as [(post-intervention fat mass (g) – pre-intervention fat mass (g))/pre-intervention fat mass (g)] × 100. DXA regions were defined as described previously [29]. Quality assurance and quality control measures were performed in accordance with the manufacturer's instructions.

Dietary intake and physical activity level

Four-day semi-quantitative food diaries were completed prior to randomization and during the final week of the intervention. Data were entered by a dietician and analysed using nutrient analysis software (FoodWorks Professional Edition Version 6.0; Xyris Software Pty Ltd, Kenmore Hills, Queensland, Australia). The short form of the International Physical Activity Questionnaire (IPAQ) was used to quantify physical activity levels and daily sitting time [30], and a categorical variable was generated according to IPAQ guidelines [31]. Participants wore a pedometer for 7 days and recorded their steps in a diary, prior to randomization and during the final week of the intervention (Yamax Digi-Walker SW 700, Tokyo, Japan).

Asthma symptoms, lung function testing, sputum induction and processing

Asthma control was quantified using the Juniper Asthma Control Questionnaire (ACQ) [32], whereas asthma-related quality of life was assessed by the Juniper Asthma Quality of Life Questionnaire (AQLQ) [33]. Clinically significant improvements in ACQ and AQLQ scores were defined by a reduction in the ACQ score of ≥ 0.5 [34] and an increase in the AQLQ score of ≥ 0.5 [35] respectively. Lung function was measured in accordance with American Thoracic Society and European Respiratory Society guidelines [36, 37]. Dynamic lung function [forced expiratory volume in one-second (FEV₁) and forced vital capacity (FVC)] was

measured using a Koko Spirometer (POS Instrumentation, Inc, Louisville, KY, USA) and static lung function [total lung capacity (TLC), functional residual capacity (FRC), expiratory reserve volume (ERV) and residual volume (RV)] using a computerized body-plethysmograph system (Vmax Encore; Sensormedics Corp., Yorba Linda, CA, USA). Sputum induction coupled with bronchial provocation using 4.5% hypertonic saline was performed over a standardized 15.5-min nebulizer time [38]. A decrease in FEV₁ $\geq 15\%$ from baseline was indicative of airway hyperresponsiveness. Provocation dose (PD₁₅) was calculated and β_2 -agonist (salbutamol 200 µg) administered [38]. Lower respiratory sputum portions were selected and dispersed using dithiothreitol. Total cell counts and cell viability were determined using haemocytometer. Differential cell counts were determined from cytopins, which were prepared, stained and counted from 400 non-squamous cells.

Inflammatory markers

Venous blood was collected after a 12-h overnight fast. High-sensitivity C-reactive protein (CRP) was measured in heparinized plasma using the CRP Flex[®] reagent cartridge (Siemens Healthcare Diagnostics Inc., Newark, DE, USA) and automatically analysed by the Dimension Vista[®] System (Siemens Healthcare Diagnostics Inc.). A commercial ELISA was used to measure plasma IL-6 (R&D Systems, Minneapolis, MN, USA), and commercial assays used to measure serum leptin and adiponectin (Bio-Rad, Hercules, CA, USA).

Statistical analysis

Data were analysed using Intercooled Stata version 11.1 (Stata Corporation, College Station, TX, USA) with results reported as median (IQR), mean $\pm$ SD or the percentage of subjects with the specified variable. Per-protocol analysis of covariance (ANCOVA) was used to compare pre- and post-intervention data, rather than intention-to-treat analysis. Change was also examined using Wilcoxon signed rank test or a paired *t*-test, divided by intervention group. The associations between changes in airway inflammation and exercise were determined by partial correlations, adjusted for the effects of age and ICS use. Sex-specific associations between airway inflammation, body composition, dietary fat intake and systemic inflammation were determined by partial correlations, adjusted for age and ICS use. Dietary fat intake was also adjusted for total kilojoule intake. Change in gynoid fat (%) was examined by multiple linear regression, as a predictor of sputum neutrophils in men and women with asthma. These models were adjusted for age and ICS use. Change in neutrophilic airway inflammation was analysed by two-

factor ANOVA after adjustment for age and ICS use to determine the interactions between sex, and body composition and dietary fat. The robust variance estimator was applied to non-parametric variables to account for the outcome being skewed. P -values ≤ 0.05 were considered statistically significant.

Results

Participant demographics

Forty-six participants were randomized and 38 completed the trial (82.6% retention; Fig. 1). All groups had a similar baseline age, sex, body composition, asthma status and sputum inflammatory profile (Table 1). The mean ACQ score was 1.2 ± 0.6 , indicative of partially controlled asthma [39]. Almost 25% of participants reported hypertension; 25% reported back, knee or shoulder pain; 25% depression or anxiety; and 8% reported having previously had a cholecystectomy (Table 1).

Anthropometric characteristics

Subjects had a mean weight reduction of $8.5 \pm 4.2\%$ after the dietary intervention, $1.8 \pm 2.6\%$ after the exercise intervention and $8.3 \pm 4.9\%$ after the combined intervention (Fig. 2a). Exercise was less effective at reducing body weight, waist circumference, total body fat and fat within the thoracic, gynoid and leg regions relative to the other interventions (Table 2). All interventions resulted in a significant reduction in waist circumference (Fig. 2b) and android fat mass (Table 2). Fat mass was decreased in all regions after the dietary and combined interventions (Fig. 2c, Table 2), whereas lean mass was conserved as a result of the exercise and combined interventions (Fig. 2d).

Nutrient intake

The dietary and combined interventions resulted in a significantly lower kilojoule, dietary fat and carbohydrate intake, relative to the exercise intervention (Table 2). Macronutrient intake was not altered after the exercise intervention (Table 2).

Physical activity

At baseline, 29% of participants had a low physical activity level and 24% had a moderate physical activity level, determined by IPAQ. After the exercise and combined intervention, 80% ($P = 0.025$ vs. baseline) and 92% ($P = 0.063$ vs. baseline) of participants, respectively, were classified as having a high physical activity level. Physical activity was also examined as a continu-

ous variable. The exercise group had a significant increase in physical activity ($P = 0.022$) and significant reduction in physical inactivity (sitting time; $P = 0.031$; Table 2). Pedometer step counts did not significantly change after the exercise or combined interventions; however, step counts were already close to the 10 000 steps/day target prior to intervention commencement (Table 2).

Clinical asthma status change with weight loss

Effect of diet and/or exercise on clinical asthma status.

Total lung capacity was significantly improved after the exercise and combined interventions relative to the dietary intervention (Table 3), whereas ERV was improved after the dietary intervention (Table 3). All three interventions improved AQLQ score (Fig. 3a), with clinical improvements in 73% of subjects after the dietary intervention and 50% of subjects after both the exercise and combined interventions ($P = 0.365$ for between-group comparison; Fig. 3b). ACQ was improved after the dietary and combined interventions (Fig. 3c), with clinically significant improvements in 53% and 42% of subjects respectively ($P = 0.250$ for between-group comparison; Fig. 3d). Men and women experienced a similar degree of improvement to ACQ and AQLQ ($P > 0.05$). The proportion of subjects with AHR [measured as PD_{15} (mL)] decreased significantly from pre- to post-intervention in the combined group (100% vs. 66.7% respectively, $P = 0.027$), with a non-significant trend for the dietary (66.7% vs. 40.0% respectively, $P = 0.143$) and exercise groups (60.0% vs. 30.0% respectively, $P = 0.178$).

Impact of degree of weight loss on clinical asthma status. A modest (5–10%) weight loss resulted in significant improvements to FVC, AQLQ and ACQ (Table 4), with clinically important improvements to AQLQ (Fig. 3e) and ACQ (Fig. 3f) in 83% and 58% of participants respectively. A greater weight loss ($> 10\%$) did not confer additional benefit to AQLQ or ACQ, despite a greater improvement to lung function (Table 4). While weight loss $< 5\%$ significantly improved ACQ and AQLQ (Table 4), the proportion of subjects who had a clinically significant improvement to their ACQ and AQLQ was substantially lower compared with subjects who lost between 5% and 10% body weight (Figs 3e and f). Furthermore, there was no significant change to lung function with a weight loss $< 5\%$ (Table 4). Seven subjects who lost 5–10% body weight had poorly controlled asthma at baseline; five became partially controlled (71%) and one well controlled (14%) after weight loss. Four subjects who lost $> 10\%$ body weight had poorly controlled asthma at baseline; 75% became well controlled and 25% partially controlled. Only one

Table 1. Subject baseline characteristics, by intervention

	Dietary	Exercise	Combined
<i>N</i>	15	10	13
Sex (% Female)	53.3	50.0	53.9
Age (years)	44.7 ± 14.7	42.2 ± 11.5	33.9 ± 11.5
BMI (kg/m ²)	34.7 ± 4.0	32.8 ± 2.5	32.7 ± 3.4
Waist circumference (cm)	112.9 ± 11.4	108.6 ± 8.0	109.2 ± 10.7
Total body fat (%)	44.1 (40.7, 52.6)	42.6 (33.6, 48.7)	47.9 (36.7, 51.8)
FEV ₁ % predicted	80.8 ± 18.5	87.7 ± 16.0	78.4 ± 16.8
FVC % predicted	92.1 ± 14.7	96.8 ± 12.3	94.0 ± 13.5
FEV ₁ /FVC (%)	73.2 (58.7, 77.0)	73.2 (66.9, 80.4)	68.2 (64.0, 78.4)
TLC % predicted	100.5 (87.5, 106.6)	98.7 (87.9, 102.5)	95.6 (93.1, 96.7)
FRC % predicted	94.5 (73.8, 115.0)	85.6 (71.7, 116.0)	90.6 (83.2, 105.8)
ERV % predicted	109.6 ± 27.3	113.8 ± 45.0	114.2 ± 27.3
RV % predicted	85.6 (57.3, 105.1)	62.7 (47.5, 94.1)	61.7 (49.0, 80.7)
Atopy (%)	86.7	77.8	92.3
ICS dose (µg/day)*	1000 (0, 1000)	1000 (500, 1000)	1000 (0, 1000)
Ever smokers (%)	33.3	30.0	30.8
Pack years of ever smokers	8 (3, 15)	2 (1, 27)	5 (1, 8)
Age at asthma diagnosis (years)	8 (2, 40)	5 (2, 32)	9 (6, 16)
ACQ score	1.24 ± 0.57	1.00 ± 0.71	1.36 ± 0.63
AQLQ score	5.8 (5.4, 6.1)	6.1 (5.0, 6.3)	5.8 (4.8, 6.1)
GINA classification (%) (intermittent/mild/moderate/severe)	27/27/27/20	30/30/40/0	8/23/54/15
Systemic inflammatory markers			
Leptin (µg/L)	13.8 (7.1, 22.8)	11.8 (6.2, 20.0)	19.7 (5.6, 33.4)
Adiponectin (mg/L)	5.9 (4.7, 9.2)	4.3 (2.9, 7.1)	7.9 (2.9, 28.5)
CRP (mg/L)	3.6 (1.2, 8.0)	2.3 (1.0, 7.1)	3.6 (1.9, 5.8)
IL-6 (pg/mL)	1.6 (0.8, 2.1)	1.0 (0.7, 1.3)	1.4 (1.1, 2.0)
Airway inflammatory markers			
Total cell count (× 10 ⁶ /mL)	4.1 (2.4, 5.0)	2.3 (1.6, 6.2)	1.5 (1.2, 5.9)
Neutrophils (%)	34.7 ± 24.0	37.6 ± 19.5	27.1 ± 23.7
Eosinophils (%)	2.3 (0.3, 6.8)	2.8 (1.3, 4.3)	4.3 (2.0, 15.3)
Macrophages (%)	57.9 ± 22.1	55.1 ± 18.1	56.8 ± 17.5
Lymphocytes (%)	1.3 (0.5, 1.5)	0.9 (0.3, 2.0)	0.8 (0.6, 2.0)
Comorbidities (%)			
Gastro-oesophageal reflux	0	20.0	15.4
Hypertension	20.0	30.0	46.2
Hypercholesterolaemia	13.3	10.0	23.1
Depression/anxiety	26.7	20.0	15.4

Data presented as mean ± SD, median (IQR) or % the percentage of subjects with the specified variable.

*Beclomethasone equivalents. Comorbidities were determined by self-report, medication usage and measurement of blood pressure and total fast-ing cholesterol.

BMI, body mass index; FEV₁, forced expiratory volume in one-second; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; ERV, expiratory reserve volume; RV, residual volume; ICS, inhaled corticosteroid; ACQ, asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire; GINA, global initiative for asthma; Mild, mild persistent; Moderate, moderate persistent; Severe, severe persistent; CRP, C-reactive protein; IL-6, interleukin-6.

subject losing < 5% body weight was poorly controlled at baseline, and remained so after the intervention.

Inflammatory changes after weight loss. Serum leptin was significantly reduced after the dietary and combined interventions, whereas IL-6 was reduced after the combined intervention (Table 3). Sputum samples were successfully obtained both pre- and post-intervention from 76% of participants. Percentage sputum eosinophils were significantly reduced in subjects who

completed the exercise intervention ($P = 0.028$; Table 3) and, consequently, the effect of exercise was examined in the overall cohort. An increase in moderate-intensity exercise correlated with a reduction in sputum percentage eosinophils, while there was a trend between increased walking and reduced sputum percentage eosinophils ($P = 0.071$; Table 5).

There was a positive correlation between change in sputum percentage neutrophils and percentage weight change in women (Table 6). This was confirmed by

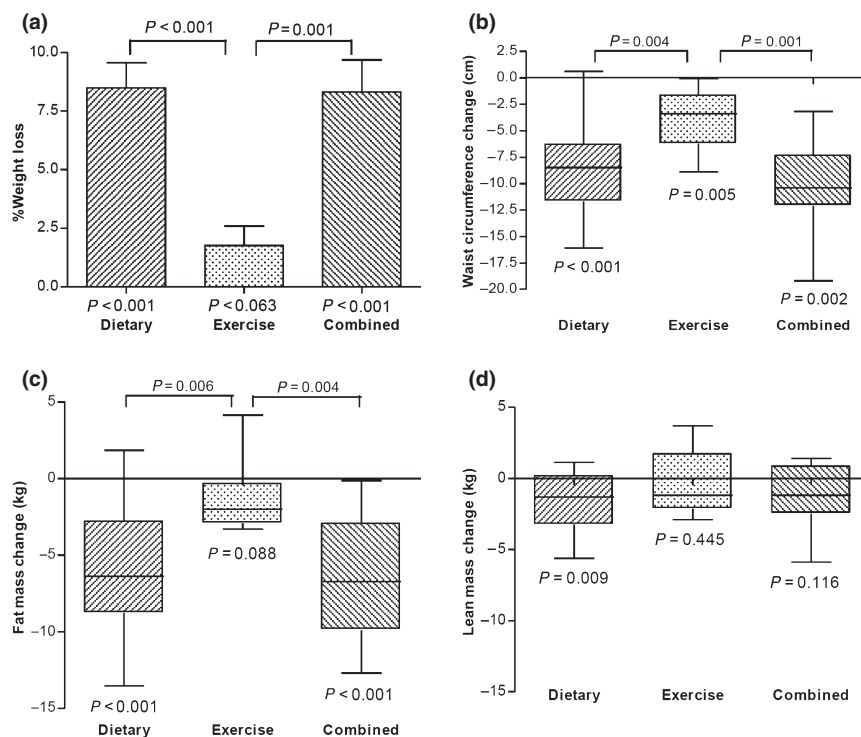


Fig. 2. (a) Mean $\pm$ SD percent weight loss, (b) median (IQR) waist circumference change, (c) median (IQR) fat mass change and (d) median (IQR) muscle mass change, by intervention. Within-group changes are shown below each figure; significant between-group differences are shown above each figure.

DXA, which demonstrated a positive correlation between change in sputum percentage neutrophils and change in total percentage fat and percentage fat within the gynoid, leg and arm regions (Table 6). Linear regression was performed, illustrating an association between change in sputum percentage neutrophils and change in percentage gynoid body fat in women [β -coefficient (95% CI) = 1.75 (0.02, 3.48), $P = 0.047$]. In this model, for every 1% fat loss from the gynoid region, there was a corresponding reduction in sputum percentage neutrophils of 1.7%. This relationship was not observed in men ($P = 0.831$); however, there was an association between reductions in saturated fat intake and absolute counts of sputum neutrophils ($r = 0.775$, $P = 0.041$; data not shown) and a trend towards reduced sputum percentage neutrophils ($r = 0.472$, $P = 0.286$; Table 6). The results of two-factor ANOVA demonstrate an interaction between sex and weight loss (% weight loss, % android fat loss, % arm fat loss), whereby being female resulted in a significantly greater reduction in sputum percentage neutrophils compared with being male ($P < 0.05$ for each, data not shown). There was not an interaction between sex and dietary fat intake in relation to neutrophilic airway inflammation (data not shown).

Discussion

This study demonstrates that modest weight loss (5–10% body weight) is sufficient to improve lung function, asthma control and quality of life in overweight and obese adults with asthma. Dietary restriction, with or without exercise, resulted in a greater weight loss than exercise alone, and provided greater benefit in terms of asthma control. There was a correlation between a reduction in neutrophilic inflammation and weight loss in women and saturated fat reduction in men, whereas exercise resulted in a significant reduction in sputum eosinophils. Furthermore, while dietary restriction achieved a greater weight loss compared with exercise, exercise improved lung function (ERV) to a greater degree than dietary restriction.

This is the first study to demonstrate that dietary restriction using meal replacements and exercise are efficacious strategies for improving body composition and clinical outcomes of overweight and obese adults with asthma. A modest weight loss of 5–10% is recommended for overweight and obese individuals, as it is a realistic weight-loss goal [40] and favourably modifies cholesterol, triglycerides, insulin resistance and blood pressure [41, 42]. We have demonstrated that this degree of weight loss also alleviates asthma symptoms.

Table 2. Change in body composition, dietary macronutrient intake and physical activity by treatment group

Characteristic	Dietary (n = 15)		Exercise (n = 10)		Combined (n = 13)		Group effect (P-value)
	Baseline	Change	Baseline	Change	Baseline	Change	
Weight (kg)	101.0 ± 17.6	-8.4 ± 4.4 ^{†***}	97.6 ± 9.1	-1.8 ± 2.7	96.7 ± 9.3	-8.2 ± 5.1 ^{†***}	0.001
Waist circumference (cm)	112.9 ± 11.4	-8.5 (-11.7, -6.3) ^{†***}	109.4 (106.0, 114.2)	-3.4 (-5.8, -2.1) ^{**}	107.3 (103.2, 116.6)	-10.4 (-11.6, -7.5) ^{†**}	0.001
Fat (kg)							
Total	42.7 ± 12.6	-6.0 ± 4.1 ^{†***}	39.1 ± 6.4	-1.3 ± 2.2	40.3 ± 9.3	-6.5 ± 4.0 ^{†***}	0.002
Android	4.5 ± 1.4	-0.7 (-1.2, -0.6) ^{†***}	3.8 (3.5, 4.4)	-0.4 (-0.6, -0.2) ^{**}	3.9 (3.1, 4.8)	-0.5 (-1.0, -0.4) ^{**}	0.045
Gynoid	7.2 (5.1, 9.2)	-1.1 (-1.4, -0.9) ^{†**}	7.2 (5.8, 8.9)	-0.2 (-0.3, 0)	7.0 (5.9, 8.4)	-1.0 (-1.6, -0.8) ^{†***}	0.002
Thoracic	10.9 (9.4, 14.1)	-2.6 (-4.0, -0.4) ^{**}	10.5 (9.2, 11.2)	-1.0 (-1.6, -0.8)	10.6 (9.0, 12.7)	-2.7 (-3.2, -0.7)	0.147
Arms	3.7 (2.5, 4.5)	-0.6 (-1.0, -0.2) [*]	3.4 (2.7, 4.3)	-0.1 (-0.3, 0)	4.1 (3.3, 4.4)	-0.8 (-1.1, -0.4) ^{†**}	0.098
Legs	14.9 (10.6, 17.9)	-1.9 (-2.8, -1.2) ^{†**}	13.7 (10.3, 19.2)	-0.5 (-0.8, 0.4)	12.4 (10.9, 19.1)	-1.5 (-2.9, -1.4) ^{†**}	0.017
Lean (kg)							
Total	47.5 (45.6, 63.6)	-1.3 (-2.4, -0.5) ^{**}	56.3 (44.1, 65.5)	-1.2 (-1.9, 1.7)	55.2 (44.0, 60.8)	-1.2 (-2.3, 0.7)	0.382
Android	3.8 (3.6, 4.6)	-0.1 (-0.4, -0.1) [*]	3.9 (3.1, 4.6)	-0.3 (-0.3, 0.1)	3.8 (3.1, 4.2)	0.1 (-0.3, 0.1)	0.724
Gynoid	7.1 (6.5, 9.7)	-0.2 (-0.5, -0.1) [*]	7.9 (6.6, 9.3)	-0.1 (-0.2, 0.2)	7.8 (6.5, 9.4)	-0.5 (-0.6, 0.1) [†]	0.111
Thoracic	15.0 (12.0, 20.9)	-1.1 (-2.3, 0.2) ^{**}	17.3 (12.4, 18.9)	-0.8 (-1.2, -0.1)	15.9 (12.5, 17.4)	-0.5 (-1.9, 0.9)	0.437
Arms	4.9 (4.6, 8.6)	-0.2 (-0.9, 0.3)	6.1 (4.3, 7.4)	0.1 (-0.2, 0.5)	5.8 (4.6, 8.2)	-0.3 (-0.4, 0) [*]	0.172
Legs	16.7 (15.2, 22.6)	-0.4 (-1.0, 0.2)	19.1 (15.6, 24.3)	0.3 (-0.6, 0.6)	18.7 (15.7, 21.5)	-0.5 (-0.9, 0.2)	0.467
Energy (kJ)	8961 (7137, 11 616)	-4261 (-5896, -2632) ^{†**}	9825 (8749, 11 874)	-232 (-3254, 464)	11 449 (10 000, 12 432)	-5584 (-7386, -4624) ^{†**}	< 0.001
Fat (g)	84 (77, 113)	-46 (-83, -38) ^{†**}	80 (68, 87)	0 (-40, 9)	121 (110, 136)	-90 (-94, -63) ^{†**}	< 0.001
SFA (g)	35 (28, 50)	-24 (-35, -13) ^{†**}	36 (30, 39)	-7 (-22, 7)	46 (43, 47)	-30 (-37, -25) ^{†**}	< 0.001
MUFA (g)	34 (26, 45)	-19 (-30, -13) ^{†**}	30 (26, 35)	2 (-13, 6)	48 (45, 59)	-37 (-38, -25) ^{†**}	0.001
PUFA (g)	12 (10, 16)	-5 (-9, -2) ^{†**}	11 (9, 11)	1 (-4, 1)	17 (15, 22)	-11 (-13, -8) ^{†**}	0.020
Carbohydrate (g)	213 (191, 293)	-120 (-162, -85) ^{†**}	302 (196, 365)	-26 (-104, -15)	224 (200, 312)	-95 (-142, -64) ^{†**}	< 0.001
Sugars (g)	109 (83, 131)	-46 (-70, -26) ^{†**}	90 (89, 146)	13 (0, 18)	102 (76, 164)	4 (-90, 10) [†]	0.001
Protein (g)	100 (84, 132)	-1 (-34, 14)	108 (103, 144)	-9 (-10, -8)	128 (108, 156)	-36 (-70, -21) [*]	0.407
Total physical activity	2347 (1188, 4176)	495 (-825, 3473)	3079 (2382, 6120)	2651 (389, 7428) [*]	3333 (2217, 8052)	2267 (691, 4812)	0.720
Vigorous activity	320 (0, 1574)	480 (0, 3120)	80 (0, 360)	1200 (720, 3840) ^{**}	960 (480, 2160)	480 (160, 1440)	0.494
Moderate Activity	240 (0, 1680)	0 (-120, 1440)	180 (0, 3600)	1200 (720, 3840)	960 (360, 1440)	360 (-60, 1320)	0.696
Walking	495 (297, 3465)	0 (-693, 347)	2608 (792, 3960)	74 (-215, 4356)	1386 (462, 4752)	231 (-132, 1089)	0.124
Sitting time (min/day)	300 (180, 420)	0 (-120, 60)	330 (180, 540)	-120 (-180, 0) [*]	240 (210, 300)	-30 (-120, 30)	0.516
Step Count (steps/day)	7239 ± 2969	1000 ± 3063	8335 ± 3607	1867 ± 2190	10 186 ± 3328	1958 ± 3117	0.147

Data presented as median (IQR) or mean ± standard deviation.

Physical activity level was calculated as Metabolic Equivalent Task (MET) minutes/week. METs are multiples of the resting metabolic rate. MET-minutes were calculated by multiplying the MET score of the level of activity by the minutes it was performed [31].

Group effect analysed by ANCOVA. Significant effects highlighted in bold.

†Significant difference in change from baseline vs. the exercise group. There was no significance in change between the dietary and combined interventions.

*P ≤ 0.05 vs. pre-intervention; **P ≤ 0.01 vs. pre-intervention; ***P ≤ 0.001 vs. pre-intervention.

SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Table 3. Change in clinical asthma outcomes and airway and systemic inflammatory markers, by treatment group

Characteristic	Dietary (<i>n</i> = 15)		Exercise (<i>n</i> = 10)		Combined (<i>n</i> = 13)		Group effect (<i>P</i> -value)
	Baseline	Change	Baseline	Change	Baseline	Change	
FEV ₁ (L)	2.80 ± 0.98	0.08 ± 0.31	3.23 ± 1.00	0.07 ± 0.16	2.96 ± 0.81	0.07 ± 0.30	0.999
FVC (L)	4.00 ± 1.19	0.12 ± 0.10	4.41 ± 1.06	0.13 ± 0.32	4.34 ± 1.14	0.18 ± 0.31	0.923
FEV ₁ /FVC (%)	73.2 (58.7, 77.0)	-0.5 (-2.3, 3.0)	73.2 (66.9, 80.4)	0.2 (-2.2, 1.0)	68.2 (64.0, 78.4)	-0.7 (-3.6, 0.7)	0.735
TLC (L)	5.31 (4.68, 7.44)	-0.03 (-0.33, 0.14)	5.79 (5.36, 6.71)	0.13 (-0.02, 0.28) [†]	5.17 (4.89, 6.97)	0.06 (-0.06, 0.33) [†]	0.037
FRC (L)	2.69 (2.04, 3.55)	0.07 (-0.23, 0.28)	2.63 (2.46, 3.10)	0.09 (0.04, 0.26)	2.86 (2.32, 3.34)	0.11 (-0.15, 0.420)	0.922
ERV (L)	1.33 ± 0.53	0.28 ± 0.43*	1.44 ± 0.58	0.12 ± 0.32	1.59 ± 0.53	0.12 ± 0.39	0.456
RV (L)	1.53 (0.90, 2.01)	-0.12 (-0.57, 0.01)	1.06 (0.71, 2.06)	0.07 (-0.13, 0.12)	1.12 (0.71, 1.69)	-0.04 (-0.30, 0.39)	0.560
Dose-response slope [‡]	1.2 (0.5, 3.2)	0.1 (-0.7, 0.7)	1.0 (0.5, 1.7)	-0.6 (-0.9, 0.2)	2.3 (1.7, 3.4)	-0.7 (-1.6, 1.0)	0.295
ACQ score	1.2 ± 0.6	-0.6 ± 0.5***	1.2 ± 0.6	-0.3 ± 0.5	1.4 ± 0.6	-0.5 ± 0.7*	0.343
AQLQ score	5.8 (5.4, 6.1)	0.9 (0.4, 1.3)**	5.8 (5.4, 6.1)	0.49 (0.03, 0.78)*	5.8 (4.8, 6.1)	0.5 (0.1, 1.0)**	0.212
Airway markers							
Total cell count (× 10 ⁶ /mL)	4.1 (2.4, 5.0)	0.9 (-1.1, 1.6)	2.3 (1.6, 6.2)	2.2 (-0.2, 4.2)	1.5 (1.2, 5.9)	1.8 (0.4, 0)	0.986
Neutrophils (%)	29.4 (22.3, 40.8)	4.5 (-5.8, 18.0)	32.4 (28.8, 58.3)	2.0 (-18.3, 9.0)	23.8 (3.0, 39.0)	2.8 (-3.8, 18.0)	0.754
Eosinophils (%)	2.3 (0.3, 6.8)	0.3 (-1.5, 1.8)	2.8 (1.3, 4.3)	-1.3 (-2.0, -1.0)*	4.3 (2.0, 15.3)	-0.5 (-15.3, 8.9)	0.763
Macrophages (%)	57.9 ± 22.1	-3.7 ± 17.7	55.1 ± 18.1	3.9 ± 23.0	56.8 ± 17.5	8.0 ± 29.1	0.581
Lymphocytes (%)	1.3 (0.5, 1.5)	0.4 (-0.9, 1.1)	0.9 (0.3, 2.0)	-0.5 (-1.3, 0)	0.8 (0.6, 2.0)	0.5 (-1.8, 1.5)	0.074
Systemic markers							
Leptin (µg/L)	13.8 (7.1, 22.8)	-5.3 (-8.6, -3.5)**	11.8 (6.2, 20.0)	-1.2 (-4.8, 1.7)	19.7 (5.6, 33.4)	-6.2 (-9.7, -2.7)**	0.425
Adiponectin (mg/L)	5.9 (4.7, 9.2)	0.02 (-0.83, 1.13)	4.3 (2.9, 7.1)	-0.27 (-0.71, 0.03)	7.9 (2.9, 28.5)	-0.44 (-0.54, 0.46)	0.716
CRP (mg/L)	3.6 (1.2, 8.0)	-0.6 (-2.1, 0.5)	2.3 (1.0, 7.1)	-0.7 (-1.1, 0)	3.6 (1.9, 5.8)	-0.4 (-0.8, 0)	0.280
IL-6 (pg/mL)	1.6 (0.8, 2.1)	-0.02 (-0.59, 0.32)	1.0 (0.7, 1.3)	0.23 (-0.09, 0.31)	1.4 (1.1, 2.0)	-0.18 (-0.56, 0.01)*	0.300

Data presented as median (IQR) or mean ± standard deviation.

Group effect analysed by ANCOVA. Significant effects highlighted in bold.

[†]Significant difference in change from baseline vs. the dietary group. There was no significance in change between the exercise and combined interventions.**P* ≤ 0.05 vs. pre-intervention; ***P* ≤ 0.01 vs. pre-intervention; ****P* ≤ 0.001 vs. pre-intervention.[‡]Provocation fall (%) ÷ provocation dose of 4.5% hypertonic saline (mL), after hypertonic saline challenge.FEV₁, forced expiratory volume in one-second; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; ERV, expiratory reserve volume; RV, residual volume; ACQ, asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire; CRP, C-reactive protein; IL-6, Interleukin-6.

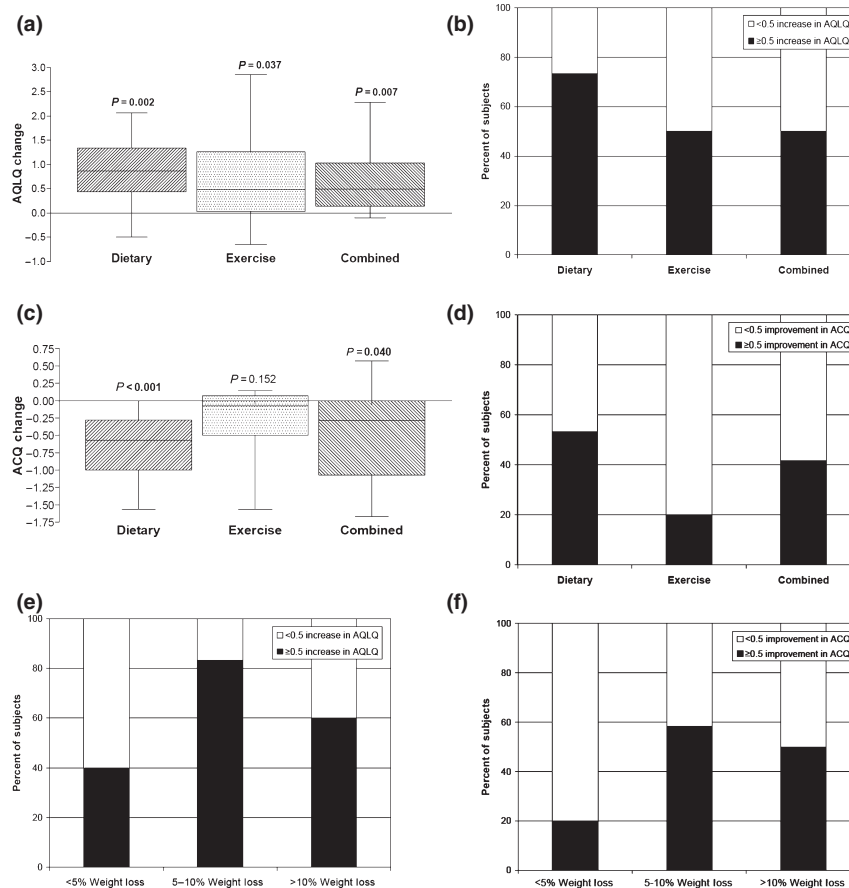


Fig. 3. (a) Change to asthma-related quality of life (AQLQ) – pre- vs. post-intervention. Data are presented as median (interquartile range). (b) Clinically significant improvement to asthma-related quality of life (AQLQ) – pre- vs. post-intervention, by intervention. A clinically significant improvement to AQLQ score was defined as an increase in the overall score of ≥ 0.5 [35]. (c) Change to asthma control questionnaire (ACQ) – pre- vs. post-intervention. (d) Clinically significant improvement to ACQ – pre- vs. post-intervention, by intervention. A clinically significant improvement to ACQ score was defined as a decrease in the total score of ≥ 0.5 [34]. Data are presented as median (interquartile range). (e) Clinically significant improvement to asthma-related quality of life (AQLQ) – pre- vs. post-intervention, by weight loss. (f) Clinically significant improvement to ACQ – pre- vs. post-intervention, by weight loss.

Therefore, a weight-loss goal of 5–10% may aid in the clinical management of overweight and obese individuals with asthma.

This study has advanced our understanding of obese-asthma in women, as fat reduction within the gynoid, leg and arm regions correlated with a reduction in sputum neutrophils. This is an important finding and supports our previous observation, where BMI and neutrophilic airway inflammation were positively associated in women [23]. The current study extends on this, by demonstrating that neutrophilic airway inflammation can be reduced with adipose tissue reduction. Neutrophils are more highly activated in the circulation [43] and adipose tissue vasculature [44] of obese individuals, and our work suggests that this inflammation extends to the airways of women with asthma. The mechanism by which this occurs is uncertain; however, it is possible that the relationship is mediated by leptin.

Leptin is highly correlated with adiposity, particularly with subcutaneous adiposity, which is abundant within the gynoid region of women [45]. Leptin enhances the Th1 response and increases the activation of neutrophils via TNF- α [46, 47]. Our study demonstrates a non-significant correlation between changes in circulating leptin and airway neutrophils. Investigation in a larger population powered to perform this analysis is warranted.

Reduced saturated fat intake was associated with a reduction in neutrophilic airway inflammation in men. Again, this supports our previous work, where plasma saturated fatty acids and neutrophilic airway inflammation were positively associated in men [23]. Men have a significantly higher rate of fatty acid uptake and lipolysis within the visceral abdominal region [48, 49]. These fatty acids are primarily transported to the liver where they encounter Kupffer cells, which are potently acti-

Table 4. Change in clinical asthma characteristics (pre- vs. post-intervention), by weight loss

Variable change	< 5% Weight Loss	5–10% Weight Loss	> 10% Weight Loss	P-value
N	16	12	10	
FEV ₁ (L)	−0.02 ± 0.18	0.2 ± 0.3	0.1 ± 0.3	0.124
FVC (L)	0.02 ± 0.20	0.25 ± 0.36 [†]	0.20 ± 0.32	0.108
FEV ₁ /FVC (%)	−1.3 (−2.3, 1.0)	0.1 (−2.0, 3.8)	−0.7 (−3.3, 0.7)	0.691
TLC (L)	0 (−0.1, 0.2)	0 (−0.2, 0.3)	0 (−0.2, 0.4)	0.993
FRC (L)	0.1 (0, 0.3)	0 (−0.3, 0.1)	0.4 (0.2, 0.5) ^{†§}	0.018
ERV (L)	0.11 ± 0.31	0.02 ± 0.32	0.49 ± 0.42 ^{†§}	0.008
RV (L)	0 (−0.1, 0.1)	−0.1 (−0.4, 0.2)	−0.1 (−0.8, 0.2)	0.792
ACQ	−0.30 ± 0.46 [†]	−0.64 ± 0.49 [†]	−0.54 ± 0.77	0.277
AQLQ	0.43 (0.03, 0.60) [†]	0.83 (0.60, 1.36) [†]	0.80 (0.40, 1.34) [†]	0.063

Data presented as mean ± SD or median (IQR).

FEV₁, forced expiratory volume in one-second; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; ERV, expiratory reserve volume; RV, residual volume; ACQ, asthma control questionnaire; AQLQ, asthma-related quality of life questionnaire.

P-value represents between group differences. Significant differences highlighted in bold.

[†]Significant difference between pre-intervention vs. post-intervention.

[‡]Significantly different change vs. < 5% weight loss.

[§]Significantly different change vs. 5–10% weight loss.

Table 5. The relationship between the change in airway inflammation and change in physical activity in all subjects pre- vs. post-intervention (*n* = 29)

	Neutrophils (%)	Eosinophils (%)
Total physical activity	0.286	−0.398*
Vigorous physical activity	0.091	0.008
Moderate physical activity	0.216	−0.444*
Walking	0.277	−0.353
Sitting time (min/day)	−0.394*	0.133
Step count (steps/day)	0.040	−0.254

Partial correlations adjusted for age and inhaled corticosteroid use.

**P* ≤ 0.05.

vated by saturated fatty acids leading to the release of TNF- α [50]. This significantly larger flux of fatty acids likely results in a greater sensitivity to fatty acid-induced inflammation compared with women, providing a plausible explanation for this association. Interestingly, despite the lack of association between changes in weight and airway neutrophils in men, both sexes had a similar improvement to their asthma control and asthma-related quality of life after weight loss. This suggests that clinical asthma improvement operates via a different mechanism in men. Although reduction of adipose tissue may be important in women, it is plausible that the dietary fat restriction that often accompanies weight loss is more important in men.

Of interest was the decrease in sputum eosinophils after exercise. Mendes *et al.* [51] recently found that 3 months of aerobic training significantly reduced sputum eosinophils and exhaled nitric oxide levels in adults with asthma. In addition, OVA-sensitized mice exercised on a treadmill at a moderate intensity for 45

min have a significant reduction in eosinophils in bronchoalveolar lavage [52]. The effect of exercise on airway inflammation appears to occur independent of weight loss, as we observed a significant reduction to airway eosinophils despite no significant weight change after the exercise intervention. The mechanism requires further investigation; however, murine models suggest that moderate-intensity exercise increases the expression of the anti-inflammatory cytokine IL-10 and reduces IL-5 and IL-4 [52, 53]. While these models demonstrate that exercise of a low–moderate intensity reduces airway eosinophilia, vigorous activity appears to enhance Th2 responses [54]. Our study is the first to demonstrate that moderate-intensity exercise is associated with reduced eosinophilic airway inflammation in humans. It is plausible that physical inactivity may have a role in the aetiology of the obese–asthma phenotype.

This group of asthmatics participated in a greater amount of physical activity at baseline than previous cross-sectional research has suggested. For example, Ford *et al.* [20] found those with asthma partake in less physical activity and are more sedentary than those without asthma, while Westermann *et al.* [55] found that obese asthmatics are less likely to participate in vigorous- and moderate-intensity exercise compared with asthmatics of a healthy weight. In the study by Westermann *et al.* [55], only 37% of overweight and 19% of obese asthmatics reported participating in vigorous exercise. However, in our study, 61% of subjects reported participating in vigorous activity at baseline. Each of these studies utilized questionnaires to calculate physical activity levels; however, the questionnaire used varied across studies, which may account for some of the differences observed. In addition, it is plausible that

Table 6. The relationship between the change in airway inflammation and changes to body composition, dietary fat intake and systemic inflammation pre- vs. post-intervention in men and women

	Males (<i>n</i> = 14)		Females (<i>n</i> = 15)	
	Neutrophils (%)	Eosinophils (%)	Neutrophils (%)	Eosinophils (%)
Weight (%)	−0.259	0.049	0.640*	0.049
Waist circumference (cm)	−0.166	−0.050	0.183	0.390
Fat mass (%)				
Total	−0.003	−0.320	0.579*	0.136
Android	−0.380	−0.106	0.546	−0.008
Gynoid	−0.070	−0.196	0.561*	0.029
Thoracic	−0.107	−0.425	0.411	−0.023
Arms	−0.069	−0.337	0.648*	−0.285
Legs	−0.016	−0.197	0.571*	0.094
Lean mass (%)				
Total	−0.133	0.490	0.261	−0.357
Android	−0.580*	0.688*	0.264	−0.347
Gynoid	−0.234	0.455	−0.175	−0.227
Thoracic	−0.175	0.626*	0.273	−0.569*
Arms	−0.103	−0.049	0.392	−0.493
Legs	0.047	−0.193	0.064	0.024
Energy (kJ)	−0.526	0.426	−0.437	0.346
Fat (g)	0.417	−0.681	−0.001	0.316
SFA (g)	0.472	−0.561	−0.246	0.237
MUFA (g)	0.547	−0.795*	0.119	0.233
PUFA (g)	−0.357	−0.042	0.149	0.404
Linoleic acid	−0.309	−0.053	0.165	0.405
Linolenic acid	−0.200	−0.307	0.620	−0.106
Leptin (µg/L)	−0.368	0.288	0.196	0.144
Adiponectin (mg/L)	0.205	−0.062	0.083	−0.079
CRP (mg/L)	−0.249	0.534	0.109	0.030
IL-6 (pg/mL)	−0.176	−0.005	−0.168	0.104

Values reported are partial correlations adjusted for age and inhaled corticosteroid use. Dietary fat intake also adjusted for energy intake (kJ).

* $P \leq 0.05$.

the nature of the intervention may have been more appealing to those with a higher baseline level of physical activity, which may explain why the increase in physical activity after the combined intervention did not reach statistical significance.

A limitation of this study was the relatively small number of participants enrolled, and as such it may have been underpowered to detect changes in some outcome measures. To address this, a per-protocol analysis was performed rather than intention-to-treat analysis, which may also be a limitation. Despite this, some novel findings were observed, thus providing direction for future research. Another limitation is that a non-intervention control group was not recruited. Each of the interventions has been tested previously against

placebo, and in this study we sought to compare the comparative efficacy of known interventions. A previous randomized controlled weight-loss trial in asthmatic adults demonstrated lung function and asthma symptoms remained stable in control subjects, while these measures were significantly improved after weight loss. This suggests that the improvements we observed are due to the intervention rather than a chance effect resulting from the variability of asthma outcomes. In addition, we saw differential responses in these outcome measures, indicating that the observed changes are more likely to be specific to the interventions rather than chance effects. In addition, while DXA is an accurate and reliable measure of body composition, it does not distinguish visceral from subcutaneous adipose tissue and therefore the possible independent effects of these adipose depots could not be determined. Lastly, adjustments were not made for multiple comparisons and it is plausible that some of the observed associations may have arisen by chance. However, the prime motive of this study was to form hypotheses for later confirmation.

In conclusion, this study has demonstrated that both caloric restriction and increased exercise improves clinical asthma outcomes in overweight and obese asthmatics. The aetiology of the obese-asthma phenotype is multi-factorial, as a reduction in adipose tissue, dietary fat restriction and increased moderate-intensity exercise exerted independent effects. Weight loss and dietary fat restriction appear to reduce activation of innate immune pathways, while increased moderate-intensity exercise appears to down-regulate allergic pathways. Our findings suggest a weight-loss goal of 5–10% should be recommended for the clinical management of overweight and obese adults with asthma, while moderate-intensity exercise may be a useful adjunct therapy.

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Conflict of interest

PG has participated in the development of educational material and as a speaker in educational symposia sponsored by GlaxoSmithKline, Pharmaxis, Novartis,

AstraZeneca and Boehringer Ingelheim. All other authors declare no conflicts of interests.

Authors' contributions

HS participated in the design of the study, conducted participant visits, analysed and interpreted the data and drafted the manuscript. PG participated in the design of the study, assisted in interpretation of the data and helped to draft the manuscript. MG participated in the

design of the study and drafting the manuscript. JP assisted with acquisition and interpretation of the data and helped to draft the manuscript. PM participated in the design of the study and helped to draft the manuscript. RC participated in the design of the study, interpretation of the data and helped to draft the manuscript. LW participated in the design and coordination of the study, interpretation of the data and helped to draft the manuscript. All authors have read and approved the final manuscript.

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