

Diet-induced weight loss in obese children with asthma: a randomized controlled trial

M. E. Jensen^{1,2}, P. G. Gibson^{1,2}, C. E. Collins³, J. M. Hilton⁴ and L. G. Wood^{1,2}

¹Centre for Asthma and Respiratory Diseases, University of Newcastle, Newcastle, NSW, Australia, ²Respiratory and Sleep Medicine, Hunter Medical Research Institute, Newcastle, NSW, Australia, ³School of Health Sciences, Faculty of Health and Priority Research Centre in Physical Activity and Nutrition, University of Newcastle, Newcastle, NSW, Australia and ⁴Paediatric Respiratory and Sleep Medicine, John Hunter Children's Hospital, Newcastle, NSW, Australia

Clinical & Experimental Allergy

Summary

Background Obesity is highly prevalent in asthmatic children and associated with worse clinical outcomes. Energy restriction to induce weight loss in asthmatic children has not been investigated in a randomized controlled trial (RCT).

Objective To assess if (1) weight loss can be achieved in obese asthmatic children using a dietary intervention; and (2) changes in asthma outcomes occur following diet-induced weight loss.

Methods In a 10-week pilot RCT, obese asthmatic children, aged 8–17 years, were randomized to a wait-list control (WLC) ($n = 15$) or dietary-intervention group (DIG) ($n = 13$). Lung function, Asthma Control Questionnaire (ACQ) score, and sputum and systemic inflammation were assessed at baseline and post-intervention. (Australian New Zealand Clinical Trials Registry: ACTRN12610000955011).

Results Body mass index (BMI) z-score reduced significantly in the DIG vs. the WLC ($-0.2 [-0.4, -0.1]$ vs. $0.0 [-0.1, 0.0]$, $P = 0.014$). Expiratory reserve volume (ERV) increased significantly within the DIG, but not compared to the WLC ($0.7 [0.0, 1.0]$ L vs. $0.3 [0.0, 0.8]$ L, $P = 0.355$). ACQ improved significantly in the DIG, compared to the WLC ($-0.4 [-0.7, 0.0]$ vs. $0.1 [0.0, 0.6]$, $P = 0.004$). Airway and systemic inflammation did not change within the DIG. In comparison, C-Reactive Protein (CRP) increased significantly in the WLC ($-0.4 [-0.5, 0.4]$ vs. $0.7 [-0.1, 1.9]$, $P = 0.037$). Change (Δ) in BMI z-score correlated with Δ CRP ($r = 0.47$, $P = 0.012$) and Δ exhaled nitric oxide (eNO) ($r = 0.46$, $P = 0.034$), and Δ ACQ was associated with Δ CRP ($r = 0.43$, $P = 0.029$).

Conclusion and Clinical Relevance Dietary intervention can induce acute weight loss in obese asthmatic children with subsequent improvements in static lung function and asthma control. Systemic and airway inflammation did not change following weight loss. However, changes in BMI z-score were associated with changes in airway and systemic inflammation and this requires further investigation in a larger RCT. This is the first weight loss RCT conducted in obese asthmatic children. Diet-induced weight loss can achieve significant improvements in clinical outcomes for obese children with asthma.

Keywords asthma, body composition, body mass index, child, diet, inflammation, obesity, paediatric, respiratory function tests, weight loss

Submitted 10 December 2012; revised 18 February 2013; accepted 20 February 2013

Correspondence:

L. G. Wood, Respiratory and Sleep Medicine, Level 2, Hunter Medical Research Institute, Locked Bag 1, Hunter Region Mail Centre, NSW, 2310, Australia.

E-mail: lisa.wood@newcastle.edu.au

Cite this as: M. E. Jensen, P. G. Gibson, C. E. Collins, J. M. Hilton and L. G. Wood, *Clinical & Experimental Allergy*, 2013 (43) 775–784.

Introduction

Obesity is highly prevalent in the asthmatic population, with almost one in two children with asthma carrying excess weight [1], compared to approximately one quarter of the general population [2]. Addressing the

high prevalence of obesity in children with asthma is of critical importance. Once a child becomes overweight or obese the risk of obesity tracking into adulthood is dramatically increased [3]. The detrimental effects of obesity upon adult respiratory status has been well documented [4], with significant lung restriction [5], steroid

resistance [6], altered airway inflammation [7, 8] and raised systemic inflammation [8] characterizing factors. There is also increasing evidence to suggest that excess weight in children with asthma is associated with worse asthma control and increased risk of exacerbations [4, 9], reduced static lung function [10, 11] and reduced steroid efficacy [12], complicating their management.

Despite the heterogeneity in interventions and measurement outcomes, weight loss in asthmatic populations consistently demonstrates a significant improvement in asthma outcomes [13, 14], notably lung function [15–18], asthma control and severity [15–18], airway responsiveness [15, 16, 18], medication use [16, 18] and quality of life [15, 18]. With the exception of one uncontrolled study [17], previous weight-loss interventions in the asthmatic population have been conducted in adults. The majority of these studies have investigated surgically induced weight loss [13], while few have used very low to low-calorie diets [14] or combination therapy [15, 17]. Surgical intervention has achieved up to 35–45% weight loss within 1- to 3-year follow-up in asthmatic adults [13, 16], with associated improvements in dynamic and static lung function, airway reactivity and medication usage [13, 16, 18]. Dietary interventions conducted in asthmatic adults have ranged from 8 to 26 weeks in duration and achieved approximately 8–19% weight loss, with associated improvements in asthma control, lung function, bronchodilator response, quality of life, self-reported dyspnoea and rescue medication use [14, 15].

Evidence suggests that interventions including a dietary component are effective in achieving weight loss in non-asthmatic children [19]. Only one weight loss study has been conducted in obese asthmatic adolescents, which used a 12-month combined dietary, physical activity, psychological and medical intervention [17]. This uncontrolled pre-post study reported significant improvements in lung function, asthma severity and symptoms, with approximately 13% weight loss [17]. However, whether an energy-restricted diet can induce acute weight loss in obese children with asthma and achieve significant improvements in asthma outcomes has not been investigated in a randomized controlled trial (RCT). Although the importance of physical activity is acknowledged, this study is designed to investigate the effects of dietary intervention alone on weight and asthma outcomes in children.

Therefore, the aim of this pilot study was to investigate whether: (1) the pilot dietary intervention induces acute weight loss in obese children with asthma in a 10-week RCT; and (2) changes in asthma outcomes (systemic and airway inflammation, lung function and asthma control) occur following diet-induced weight loss, which may inform the design of a larger RCT, powered to detect significant changes in these outcomes.

Methods

Study design

Participants. Obese children [Body mass index (BMI) z-score ≥ 1.64 standard deviation score (SDS)], aged 8–17 years, with a physician diagnosis of asthma were recruited from the John Hunter Children's Hospital (JHCH) outpatients, local medical centres and the general community in Newcastle, Australia. Participants were reviewed by a paediatric respiratory physician. Participants were randomized to one of two groups: (1) Dietary intervention (DIG); or (2) Wait-list control (WLC), who received the intervention after the initial 10-week control period (Fig. 1). Block randomization was performed by a statistician, using a block size of four. The participant's group allocation was given to the research officer on the day prior to the scheduled baseline assessment. The participant and the research officer who performed the baseline assessments were not blinded to group allocation. Exclusion criteria included unexplained weight change during the past 3 months, inflammatory or endocrine disorders, and respiratory disorders other than asthma. Participant assent and guardian consent were obtained. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000955011) and approved by the Hunter New England and University of Newcastle Human Research Ethics Committees (09/05/20/5.08).

Intervention. Participants randomized to the intervention group underwent a 10-week dietary intervention, which targeted a 500-kilocalorie/day energy reduction from individually calculated age- and gender-appropriate energy requirements (Schofield equation to estimate basal metabolic rate using activity factor of 1.55) [20]. Participants were required to attend counselling sessions with an Accredited Practising Dietitian (MEJ) in weeks 0, 1, 2, 4, 6, 8 and 10 and were contacted via

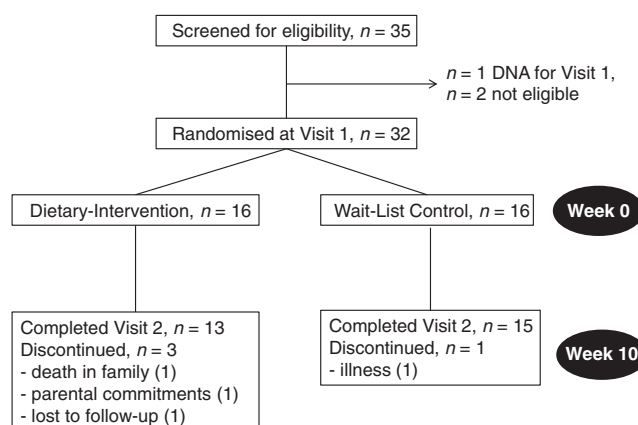


Fig. 1. Participant flow through study.

telephone in alternate weeks. Sessions involved theoretical and practical education on selection of foods and appropriate serving sizes to optimize macronutrient and micronutrient intakes within an energy-restricted diet; identification and resolution of barriers to dietary change; and goal-setting. Materials included individually adapted meal plans and a commercial calorie counter. Participants were encouraged to self-monitor energy intake using a food diary throughout the study period. These sessions were directed at the child and therefore the information provided was at a child's reading level. However, parents were invited to participate in the sessions by helping with suggestions to facilitate dietary change and monitoring of progress for reporting back to the dietitian, including assistance with dietary recall.

Clinical visits

Clinical assessment. At baseline and following the 10-week intervention period, participants attended JHCH after an overnight fast (≥ 12 h) and withholding antihistamines and asthma medications (≥ 24 h). Asthma stability was confirmed, defined as no exacerbation, respiratory tract infection or oral corticosteroid use in the past 4 weeks. Clinical asthma pattern was assessed at baseline using Global Initiative for Asthma (GINA) guidelines [21]. Atopy was determined at baseline by positive skin prick test to common allergen(s) (*Aspergillus fumigatus*, *Alternaria tenuis*, *Dermatophagoides Pteronyssinus*, Cockroach mix, Grass mix). The following were assessed at baseline and post-intervention: current asthma status (Juniper Asthma Control Questionnaire (ACQ) [22]); quality of life (Paediatric Asthma Quality of Life Questionnaire (standardized) (PAQLQ(s)) [23]); tobacco exposure by measuring urinary cotinine (NicAlert; Nymox Pharmaceutical Corp, Hasbrouck Heights, NJ, USA); and dynamic and static lung function via spirometry (Windows KoKo PFT System Version 4.9 2005, PDS Inc., Louisville, KY, USA) and plethysmography (MedGraphics Elite Series Plethysmograph, St. Paul, MN, USA; Breeze Suite 6.4.1.14 Version 510 2008, MedGraphics Corp., St. Paul, MN, USA). Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) values were expressed as a percentage of the predicted values [24], and obstruction as FEV_1 /total lung capacity (TLC) (%) [25].

Anthropometry. Weight and height were measured at baseline and post-intervention using 150 kg max scales (EB8271 NuWeigh, Newcastle Weighing Services, Newcastle, NSW, Australia) and 2 m wall-suspended measuring tape with wall stop (Surgical and Medical Supplies Pty Ltd, Rose Park, SA, Australia). BMI was calculated [weight (kg)/height (m^2)] and converted to

BMI z-scores [26]. Total body and thoracic fat and lean mass were measured as a percentage (%) of total body weight using dual energy X-ray absorptiometry (DEXA) (GE Lunar Prodigy, Medtel, Madison, WI, USA; GE Healthcare encore 2007 software Version 11.40.004, Madison, WI, USA) at baseline and post-intervention.

Airway biomarkers. At baseline and post-intervention, participants underwent exhaled Nitric Oxide (eNO) measurement (NiOX chemiluminescent Detector, Aerocrine, Australian Supplier Zynergy Medical) and combined bronchial provocation testing and sputum induction with hypertonic saline (4.5%) (ULTRA-NEB™ ultrasonic nebulizer, DeVilbiss, Model 2000) [27]. Airway hyperresponsiveness (AHR) was defined as a fall in $FEV_1 \geq 15\%$ of their baseline FEV_1 . The dose-response slope (DRS) and the log-transformed provocation dose ($LogPD_{15}$) were calculated. Opaque mucocellular sputum portions were selected from saliva, processed using dithiothreitol [27, 28], and a total cell count of leucocytes and viability performed [27, 28]. Cytospins were prepared, stained (May-Grunwald Geimsa) and a differential cell count obtained from 400 non-squamous cells.

Systemic biomarkers. Baseline and post-intervention fasting blood samples were centrifuged at 17 230 g, 4°C for 10 min. All samples underwent duplicate testing. Plasma interleukin (IL)-6 (R&D Systems, Minneapolis, MN, USA), and serum leptin and adiponectin (Bio-Rad, Hercules, CA, USA) were measured using commercial ELISAs, with respective sensitivity of 0.039 pg/ml, 3.1 pg/mL and 32.7 pg/mL. Serum high sensitivity C-Reactive Protein (CRP), and plasma cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride and glucose were measured using commercial assays (CRP Flex reagent cartridge, CHOL Flex reagent cartridge, HDLC Flex reagent cartridge, TRIG Flex reagent cartridge & GLU Flex reagent cartridge, Dimension Vista System, Siemens Healthcare Diagnostics Inc. 2008, Newark, NJ, USA). Plasma insulin was measured using commercial immunoassay (Access Ultrasensitive Insulin assay; Beckman Coulter Inc. 2008, Brea, CA, USA). Low-density lipoprotein cholesterol (LDL-C) [total cholesterol-(HDL-C)-(0.4545*triglycerides)] and homeostasis model assessment of insulin resistance (HOMA-IR) [glucose (mmol/L)*insulin (mIU/L)/22.5] were calculated.

Statistical analysis

Data are presented as mean (standard deviation, SD), median [interquartile range, IQR], or proportion [n , (%)]. Outcome data are reported as change (Δ) from baseline. Continuous data were assessed using a paired

mean-comparison *t*-test or Wilcoxon sign-rank test for within-group comparisons, and a two-group mean-comparison *t*-test or Wilcoxon rank-sum test for between-group comparisons. Associations between Δ BMI z-score and 5 key pathways were explored using spearman rank correlation coefficients: mechanical function (Δ ERV), airway inflammation (Δ %sputum inflammatory markers, Δ eNO), systemic inflammation (Δ CRP), endocrine function (Δ leptin) and metabolic function (Δ HOMA). All tests were of size $\alpha = 0.05$ and unadjusted for multiple comparisons. Statistical analysis was performed using Intercooled Stata Version 11.0 for Windows (StataCorp, College Station, TX, USA 1984–2005). No adjustments were made for multiple testing.

Results

Group characteristics were similar at baseline (Table 1), except for a significantly higher ACQ score in the DIG compared to the WLC. The mean age of asthma diagnosis was 3.7 (3.0) years. Following the intervention period, a significant reduction in all adiposity indicators occurred in the DIG (Table 2), with a clinically important reduction in BMI z-score (Fig. 2a) and a reduction in %body fat (Fig. 2b). However, metabolic markers remained unchanged in the DIG. No significant change in anthropometric or metabolic markers was observed for the WLC, except for a statistically significant increase in body weight and fasting glucose levels (Table 2). The change in BMI z-score and %body fat was significantly different between groups (Figs 2a and b). The change in weight was also significantly different between groups, while changes in metabolic markers were not significantly different (Table 2).

There was no significant change in dynamic lung function, within or between groups (Table 3). Static lung function, including expiratory reserve volume (ERV) (Fig. 3a), was significantly different within the DIG compared to baseline. However, the difference between groups was not statistically significant. ACQ score improved significantly within the DIG, compared to the WLC (Fig. 3b). PAQLQ symptom (Baseline 5.1 [4.4, 6.2]; Δ 0.6 [−0.1, 1.2] $P = 0.038$) and emotional (Baseline 5.8 [4.6, 6.6]; Δ 0.4 [0.3, 1.7] $P = 0.020$) domain scores significantly improved within the DIG, but PAQLQ symptom (Baseline 6.0 [5.4, 6.4]; Δ 0.1 [−0.4, 0.6] $P = 0.593$) and emotional (Baseline 6.6 [5.4, 6.9]; Δ −0.1 [−0.4, 0.8] $P = 0.572$) scores remained unchanged within the WLC. However, the change in PAQLQ symptom ($P = 0.142$) and emotional ($P = 0.121$) scores were not significantly different between the DIG and WLC. The change in PAQLQ total (Baseline 5.5 [4.7, 6.3]; Δ 0.7 (1.2) $P = 0.071$) and activity domain (Baseline 5.6 [5.0, 6.2]; Δ 0.6 [−0.3, 1.7] $P = 0.195$) scores were not statically significant in the DIG. PAQLQ total

Table 1. Subject characteristics at baseline, randomized to dietary intervention or wait-list control group for ten weeks

Subject characteristics	Dietary intervention	Wait-list control
Number; <i>n</i>	13	15
Age (years); mean (SD)	11.5 (2.1)	12.4 (2.4)
Gender (%females); %	3 (23.1)	8 (53.3)
Height (cm); mean (SD)	1.6 (0.1)	1.6 (0.1)
Weight (kg); median [IQR]	59.9 [56.1, 78.6]	71.2 [66.5, 82.4]
BMI z-score (SDS); median [IQR]	2.1 [1.9, 2.3]	2.2 [1.8, 2.4]
Total body fat mass (%); mean (SD)	44.7 (5.9)	44.8 (7.3)
Total body lean mass (%); mean (SD)	53.3 (5.6)	53.3 (6.8)
Atopic (Y/N); <i>n</i> (%Y)	9 (69.2)	10 (66.7)
FEV ₁ %predicted (%); mean (SD)	90.5 (13.6)	96.0 (7.6)
FVC%predicted (%); mean (SD)	100.8 (10.2)	101.4 (6.9)
FEV ₁ /TLC (%); mean (SD)	59.1 (9.0)	64.0 (9.0)
ACQ Score; median [IQR]	1.14 [0.43, 1.57]*	0.57 [0.29, 0.86]
PAQLQ; median [IQR]	5.52 [4.65, 6.26]	6.00 [5.65, 6.52]
Airway hyperresponsiveness (%true) [†] ; <i>n</i> (%)	8 (72.7)	10 (76.9)
logPD ₁₅ (mL); mean (SD)	1.4 [0.4, 2.0]	1.1 [−0.3, 2.4]
Dose–response slope (%fall/mL); median [IQR]	2.6 [1.4, 9.2]	1.8 [0.5, 14.3]
SABA (true) [†] ; <i>n</i> (%)	11 (84.6)	13 (86.7)
ICS (true) [†] ; <i>n</i> (%)	7 (53.9)	3 (20.0)
Beqs; median [IQR]	400 [275, 400]	400 [233, 400]

BMI, body mass index; SDS, standard deviation score; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; ACQ, Asthma Control Questionnaire (Juniper); PAQLQ, Paediatric Asthma Quality of Life Questionnaire (Juniper); logPD₁₅, log-transformed provocation dose; SABA, short acting β -agonist; ICS, inhaled corticosteroid; Beqs, beclomethasone equivalents.

* $P = 0.026$ vs. control group; [†]Pearson's Chi-squared test.

(Baseline 6.0 [5.7, 6.5]; Δ 0.1 (0.7) $P = 0.615$) and activity domain (Baseline 5.8 [5.6, 6.2]; Δ 0.1 [−0.2, 0.4] $P = 0.326$) scores remained unchanged in the WLC. The change in PAQLQ total ($P = 0.119$) and activity ($P = 0.148$) scores were not significantly different between the DIG and WLC.

Airway & systemic inflammation

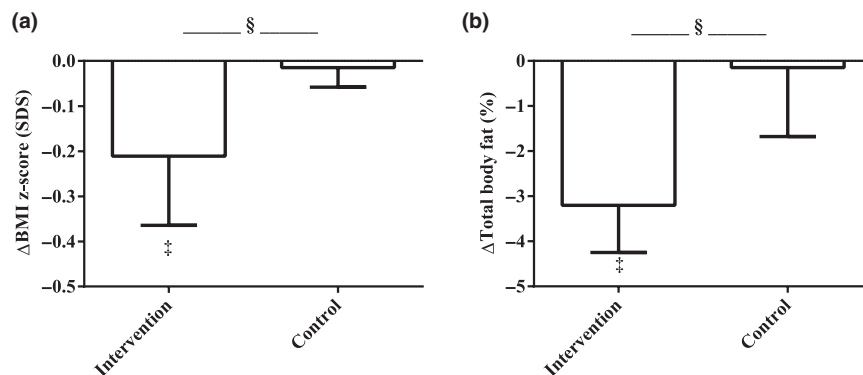
There was no change in the number or proportion of eosinophils or neutrophils, within or between groups (Table 4). However, a non-significant trend towards a reduction in % neutrophils in the DIG was observed. A statistically significant difference in both absolute and %lymphocytes was observed between groups. However, the change within groups was non-significant. A significant increase in CRP levels was detected in the WLC

Table 2. Change in anthropometric and metabolic variables in obese children with asthma, following randomization to diet-induced weight-loss intervention or no intervention for ten weeks

Anthropometric & metabolic markers	Intervention group		Control group		Change (Δ) between groups: <i>P</i> -value
	Baseline	Change (Δ) vs. Baseline	Baseline	Change (Δ) vs. Baseline	
Weight (kg); median [IQR]	59.9 [56.1, 78.6]	−3.4 [−4.8, −2.9]*	71.2 [66.5, 82.4]	1.3 [0.7, 2.2]*	0.003
Total body lean mass (%); mean (SD)	53.3 (5.6)	2.1 (3.0)*	53.3 (6.8)	0.2 (2.5)	0.083
Glucose (mmol/L); median [IQR]	4.3 [3.9, 4.4]	0.0 [−1.0, 0.3]	4.4 [4.0, 4.7]	0.4 [−0.2, 0.5]*	0.174
Insulin (mIU/L); median [IQR]	7.3 [5.3, 12.0]	−0.7 [−6.4, 3.7]	10.1 [7.1, 16.2]	0.9 [−2.3, 8.1]	0.356
Total cholesterol (mmol/L); median [IQR]	3.9 [3.8, 4.1]	−0.1 [−0.3, 0.2]	4.1 [3.8, 4.7]	0.1 [−0.3, 0.3]	0.437
LDL-C (mmol/L); median [IQR]	2.2 [2.0, 2.7]	−0.1 [−0.3, 0.2]	2.2 [1.9, 2.8]	0.1 [−0.1, 0.2]	0.423
HDL-C (mmol/L); median [IQR]	1.3 (0.2)	−0.0 [−0.1, 0.0]	1.1 (0.2)	0.1 [0.0, 0.1]	0.254
Triglycerides (mmol/L); median [IQR]	1.0 [0.7, 1.2]	0.0 [−0.4, 0.2]	1.3 [0.8, 2.0]	0.0 [−0.4, 0.2]	0.923
HOMA-IR; median [IQR]	1.4 [0.9, 2.0]	−0.2 [−1.0, 1.2]	2.0 [1.8, 3.2]	0.3 [−0.4, 1.6]	0.317

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance.

**P* < 0.05 vs. baseline value.

**Fig. 2.** Change from baseline in (a) BMI z-score, and (b) Total %body fat. **P*-value < 0.05 within group; §*P*-value < 0.05 between groups.

compared to the DIG, while no change was observed in IL-6, leptin or adiponectin levels, within or between groups (Table 4).

Correlations

Table 5 presents correlations between Δ BMI z-score and key outcomes. Change in BMI z-score was associated with Δ CRP and Δ eNO (Table 5). Change in CRP was positively associated with Δ %body fat ($r = 0.64$, $P = 0.001$) and negatively associated with Δ %lean mass ($r = -0.61$, $P = 0.001$) and Δ %thoracic lean mass ($r = -0.41$, $P = 0.043$). Change in eNO was negatively associated with Δ %thoracic lean mass ($r = -0.56$, $P = 0.011$) only. In addition, Δ HOMA-IR was positively associated with Δ %body fat ($r = 0.57$, $P = 0.003$) and Δ %thoracic fat ($r = 0.47$, $P = 0.020$), while negatively associated with Δ %lean mass ($r = -0.61$, $P = 0.001$) and Δ %thoracic lean mass ($r = -0.51$, $P = 0.012$). Only Δ CRP was associated with Δ ACQ ($r = 0.43$, $P = 0.029$).

Discussion

This study was a pilot RCT aimed at investigating the efficacy of dietary energy restriction to induce acute weight loss in obese children with asthma, and the subsequent effect on asthma outcomes. Results demonstrate that a dietary intervention can induce acute weight loss in asthmatic children within 10 weeks. Importantly, acute dietary-induced weight loss was associated with a significant improvement in static lung function, asthma control, and self-reported quality of life in this group of children.

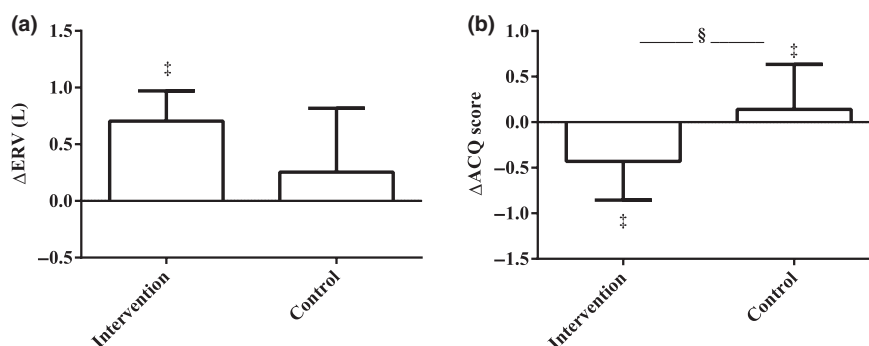
Our data demonstrate that statistically significant acute weight loss can be achieved in children with asthma, compared to controls, using a simple dietary intervention. The presented dietary intervention achieved a median 5.7% reduction in body weight within 10-weeks, comparable with the 5.4% weight loss achieved at 6-months using interdisciplinary therapy in a previous study [17]. Notably, in this study, the dietary

Table 3. Change in lung function & clinical asthma outcomes in obese children with asthma, following randomization to diet-induced weight-loss intervention or no intervention for ten weeks

Lung function variables	Intervention group		Control group		Change (Δ) between groups: <i>P</i> -value
	Baseline	Change (Δ) vs. baseline	Baseline	Change (Δ) vs. baseline	
FEV ₁ (L); median [IQR]	2.4 [2.0, 2.9]	0.0 [−0.2, 0.1]	2.6 [2.2, 2.9]	0.0 [−0.2, 0.1]	0.489
FVC (L); median [IQR]	3.4 [2.7, 3.5]	0.1 (0.2)	3.3 [2.9, 3.5]	0.0 (0.2)	0.191
FEV ₁ /TLC (%); mean (SD)	59.1 (9.0)	2.3 [−1.3, 14.1]	64.7 (8.9)	−0.5 [−4.6, 4.8]	0.217
TLC (L); median [IQR]	4.4 [3.4, 4.8]	0.0 [−0.5, 0.0]	4.0 [3.6, 4.7]	−0.1 [−0.2, 0.1]	0.471
FRC (L); median [IQR]	1.9 [1.7, 2.1]	0.2 (0.5)	1.6 [1.5, 2.1]	0.2 (0.4)	0.905
RV (L); median [IQR]	0.9 [0.8, 1.6]	−0.4 (0.5)*	0.9 [0.7, 1.1]	−0.1 (0.4)	0.237
RV/TLC (%); mean (SD)	25.8 (9.3)	−6.9 (9.2)*	20.5 (9.0)	−1.7 (10.2)	0.188
Dose–response slope (%fall/mL); median [IQR]	2.6 [1.4, 9.2]	0.4 [−0.4, 1.7]	1.8 [0.5, 14.3]	0.1 [−4.7, 0.6]	0.271
logPD ₁₅ (mL); mean (SD)	1.4 [0.4, 2.0]	−0.4 [−0.8, 0.3]	1.1 [−0.3, 2.4]	0.6 [−0.2, 1.2]	0.391

FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; logPD₁₅, log-transformed provocation dose.

**P* < 0.05 vs. baseline value.

**Fig. 3.** Change from baseline in (a) Expiratory Reserve Volume (ERV) and (b) Juniper's Asthma Control Questionnaire (ACQ) score. **P*-value < 0.05 within group; \$*P*-value < 0.05 between groups.**Table 4.** Change (Δ) in airway & systemic inflammatory markers in obese children with asthma, following randomization to diet-induced weight-loss intervention or no intervention for ten weeks

Airway & systemic inflammatory markers	Intervention group		Control group		Change (Δ) between groups: <i>P</i> -value
	Baseline	Change (Δ) vs. baseline	Baseline	Change (Δ) vs. baseline	
Exhaled nitric oxide (ppb); median [IQR]	13.1 [8.4, 41.8]	−2.6 [−11.3, 0.39]	27.2 [10.5, 46.7]	−1.9 [−4.0, 0.3]	0.673
Total cell count ($\times 10^6$ /mL); median [IQR]	3.2 [1.3, 4.6]	0.5 [−0.5, 2.4]	2.8 [1.9, 5.5]	0.7 [0.3, 2.4]	0.596
Neutrophils (%); median [IQR]	10.5 [8.0, 18.8]	−4.8 [−7.5, −0.6]	10.3 [2.8, 27.5]	1.0 [−4.5, 14]	0.355
Eosinophils (%); median [IQR]	0.8 [0.5, 5.3]	−0.1 [−0.5, 5.1]	0.8 [0.3, 8.5]	0.0 [−0.8, 2.3]	0.938
Macrophages (%); mean (SD)	78.8 [71.3, 83.5]	3.4 [−3.6, 8.6]	78.0 [42.5, 84.8]	3.5 [−14.5, 4.0]	0.537
Lymphocytes (%); median [IQR]	2.3 [0.3, 7.0]	−2.4 [−4.9, −1.0]	1.0 [0.0, 1.3]	0.8 [0.0, 2.0]	0.025
Neutrophils ($\times 10^6$ /mL); median [IQR]	0.53 [0.15, 1.50]	−0.09 [−0.88, 0.48]	0.49 [0.14, 1.39]	0.16 [−0.24, 0.36]	0.497
Eosinophils ($\times 10^6$ /mL); median [IQR]	0.02 [0.01, 0.12]	−0.01 [−0.02, 0.24]	0.03 [0.01, 0.12]	0.01 [−0.01, 0.43]	0.396
Macrophages ($\times 10^6$ /mL); median [IQR]	2.48 [1.25, 4.03]	0.22 [−1.69, 3.92]	2.05 [1.71, 4.93]	0.41 [−0.49, 1.22]	1.00
Lymphocytes ($\times 10^6$ /mL); median [IQR]	0.12 [0.05, 0.40]	−0.04 [−0.35, 0.00]	0.04 [0.02, 0.07]	0.05 [0.01, 0.07]	0.042
C-Reactive Protein (mg/L); median [IQR]	2.1 [1.5, 3.3]	−0.4 [−0.5, 0.4]	2.1 [0.7, 4.0]	0.7 [−0.1, 1.9]*	0.037
Interleukin-6 (pg/mL); median [IQR]	1.2 [0.7, 2.7]	0.3 [−0.3, 0.4]	1.4 [0.7, 2.0]	−0.1 [−0.5, 0.4]	0.907
Leptin (ng/mL); median [IQR]	6.4 [0.5, 27.4]	−0.3 [−1.8, 0.2]	3.1 [0.7, 18.0]	−0.5 [−8.1, 0.1]	0.419
Adiponectin (ug/L); median [IQR]	4.4 [3.6, 6.0]	0.7 [−0.5, 2.4]	4.8 [4.1, 7.2]	1.1 [−1.3, 2.3]	0.954

**P* < 0.05 vs. baseline value.

Table 5. Spearman rank correlation coefficients between change (Δ) in BMI z-score, lung function and airway and systemic biomarkers[†]

H ₀ MOA	Key variable of interest	Δ BMI z-score	
		r^*	P-value
Mechanical	Δ ERV	0.12	0.568
Systemic inflammation	Δ CRP	0.47	0.012
Airway inflammation	Δ %eosinophils	-0.49	0.093
	Δ %neutrophils	0.05	0.873
	Δ %macrophages	0.16	0.591
	Δ %lymphocytes	0.05	0.865
	Δ eNO	0.46	0.034
Endocrine	Δ leptin	0.31	0.136
Metabolic	Δ HOMA-IR	0.33	0.104

H₀ MOA, hypothesized mechanism of action; Δ , change; BMI, body mass index; ERV, expiratory reserve volume; CRP, C-Reactive Protein; eNO, exhaled nitric oxide; HOMA-IR, homeostasis model assessment of insulin resistance.

*Spearman's rank correlation coefficient, [†]correlations include all participants (DIG and WLC, $n = 28$).

intervention was effective in reducing BMI z-score by a statistically significant 0.2 BMI-SDS, which is comparable to previous studies. Of previous weight-loss interventions in non-asthmatic children which included a dietary component and reported standardized BMI, reductions of approximately 0.2–0.4 BMI-SDS have been reported over time frames ranging from 4 to 6 months [29–32], while others have found no significant change [33, 34]. Hence, the weight loss achieved in this study, a median BMI z-score reduction of 0.2 SDS, suggests our intervention was effective. This may be due to the frequency of dietetic contact and/or the delivery of the dietary intervention. Participants were required to focus on one aspect of lifestyle modification which may make adjusting to beneficial changes easier than addressing multiple aspects simultaneously. Perhaps, a graduated approach to introducing lifestyle changes, including dietary and physical activity changes, may be more acceptable to participants and is worth investigating in future trials. Participation in a weight-loss study designed to evaluate the effect upon asthma outcomes may also have motivated adherence to the dietary prescription. Investigation of whether greater weight loss can be achieved with a longer intervention, and follow-up to evaluate weight-loss maintenance, is a consideration for future studies.

We recently reported that obesity in children with asthma is associated with a reduced ERV [35]. A recent uncontrolled weight-loss study did not measure static lung function, but did demonstrate significant improvements in %predicted spirometry values at 6-month and 12-month post-intervention in asthmatic adolescents [17]. In contrast to this study, our participants had relatively normal baseline %FEV₁ and %FVC, which may

explain why a change in spirometry measurements was not observed following acute weight loss. However, similar to adult studies [15, 16], a significant improvement in ERV for the intervention group was detected, following weight loss. In addition, there was a significant reduction in RV and %RV/TLC, suggesting a reduction in obstruction.

Importantly, the improvement in asthma control in the intervention group approached clinical significance. There was also a clinically significant improvement in self-reported quality of life for the intervention group. However, only the change in the PAQLQ symptom and emotion domains reached statistical significance. Improved quality of life and asthma control has been demonstrated in asthmatic adults 10 weeks following dietary-induced weight loss [15]. Our results demonstrate that acute weight loss can achieve clinically significant improvements in static lung function, and significant improvements in asthma control and quality of life in obese children. Follow-up studies, powered to detect significant changes, are needed to investigate the effect of long-term weight-loss intervention on lung function and asthma control in this group of children.

This study is the first paediatric weight-loss trial to report airway inflammation. No significant change in eNO or induced sputum inflammatory cells was detected within groups. However, there was a non-significant trend towards a reduction in %neutrophils in the intervention group. Likewise, there was no significant difference in the change in airway inflammatory markers between groups, with the exception of absolute and % lymphocytes. However, it is recognized that changes in airway inflammation following diet-induced weight loss in asthmatic children need to be investigated in a larger RCT, adequately powered to detect changes in this outcome.

Previous weight-loss interventions in non-asthmatic children have produced variable changes in systemic inflammation [14]. Both short (3–6 weeks) and long-term (3–12 months) weight-loss studies have observed significant reductions in CRP, IL-6 and leptin, and increases in adiponectin [14], while other studies have reported no difference in CRP, TNF- α or adiponectin levels over a 6–12 month period, despite weight loss of up to 0.4BMI-SDS [14, 29, 31]. These studies also failed to detect a significant change in metabolic markers [29, 31]. A recent weight-loss intervention reported modest but statistically significant improvements in CRP, leptin and adiponectin in obese asthmatic and non-asthmatic adolescents at 12 months, where there was no significant change at 6-months [17]. Furthermore, a 12-month longitudinal study in non-asthmatic children demonstrated that improvements in TNF- α , CRP, leptin and adiponectin levels did not occur in children with weight loss < 0.5BMI-SDS compared to children with weight

loss ≥ 0.5 BMI-SDS [36, 37]. Although this study achieved a statistically significant reduction in BMI z-score in 10 weeks, the median reduction of 0.2 BMI-SDS may not have been sufficient to achieve favourable changes in systemic biomarkers. Systemic inflammatory and metabolic biomarkers remained stable in this group of children, despite acute weight loss. However, moderate but significant increases in glucose and CRP were observed in the control group, even in this short period of time. This may suggest that although this group of children appeared metabolically healthy at baseline, changes in body weight, specifically body composition, may have adverse effects upon the metabolic profile. This is supported by the positive correlations between Δ CRP and Δ HOMA-IR vs. fat mass and negative associations vs. lean mass.

In an endeavour to understand the mechanism of weight loss in asthma, we explored the associations between Δ BMI z-score and key outcomes. Previous reports have suggested that obesity adversely impacts asthma outcomes via mechanical restriction of the chest wall and diaphragm [38]. It is also suggested that obesity alters the airway inflammatory phenotype in asthma, altering management needs [7, 8]. Our results indicate that weight change after 10 weeks is associated with airway and systemic inflammation, as indicated by Δ CRP and Δ eNO. This may suggest that weight loss, and more specifically, reductions in adiposity and increases in lean mass, can lead to reductions in both systemic and airway inflammation. However, increased systemic inflammation was the only outcome associated with poorer asthma control, supported by a positive association between Δ CRP and Δ ACQ. This may suggest that the adverse effect of obesity may operate via alterations in systemic inflammation, and that body composition is an important consideration, as previously hypothesized [4, 14]. However, further investigation is required. Although not statistically significant, there was an inverse relationship between %eosinophils and BMI z-score, which contrasts the positive relationship between eNO and BMI z-score. This may reflect the relative importance of airway cells other than eosinophils (such as neutrophils) as BMI increases. This is what is observed in adult obese asthma [8] and requires further investigation in children.

This was the first RCT, designed as a pilot study, to investigate whether: (1) the pilot dietary intervention induced acute weight loss in obese children with asthma; and (2) improvements in asthma outcomes are observed with acute weight loss, which can inform the design of a larger RCT powered to detect significant changes in these outcomes. The external validity of the results is limited by the small sample size and uneven randomization of several baseline characteristics across the groups, which may have also reduced the likelihood of detecting a change in outcome measures. In addition,

statistical analysis was not adjusted for multiple comparisons and the strength of the results is likely to have been impacted by this limitation. A potential source of bias is improved patient-directed asthma awareness (e.g. medication adherence), purely due to enrolment in a study in which the primary end-points are asthma outcomes. Although there was no significant change in reported medication use during the course of the study in either group, the reliability of this information is subject to the limitations of self-report. Furthermore, the nature of the intervention precluded blinding of participants and research officers to group allocation. However, the key outcomes of the study were objective measurements, which would have minimized bias. Lastly, the intervention was short term and did not include a follow-up period, an important limitation to the results. Further investigation into the efficacy of diet-induced weight loss in asthmatic children is needed, which includes an adequate follow-up period. Although dietary intake can make the greatest difference to energy balance, the importance of physical activity cannot be ignored. Future studies are required to investigate the effect of an exercise intervention alone and in combination with dietary intervention to induce weight loss and the subsequent impact on asthma outcomes in this group of children.

This study demonstrates that rapid weight loss can be achieved safely in obese asthmatic children with dietary intervention alone, resulting in improvements in static lung function, asthma control and quality of life. On the other hand, changes in airway and systemic inflammation were not detected following acute dietary-induced weight loss in this group of children. However, exploratory analysis suggests that body composition changes, specifically greater adiposity and lesser lean mass, are associated with adverse changes in systemic and airway inflammation. In addition, systemic inflammation was associated with poorer asthma control in children, indicating that the role of inflammation should not be discounted and further investigation in larger trials is needed. Our data indicate that short-term weight loss can be achieved following dietary intervention and may produce beneficial changes in childhood asthma outcomes. This supports the need for future larger RCTs to further investigate the efficacy of weight-loss intervention in asthmatic children. Future trials should include appropriate intervention and follow-up periods, and be adequately powered to detect changes in relevant asthma outcomes.

Acknowledgements

The study is supported by a Hunter Medical Research Institute Gastronomic Society Donor Grant. CEC is supported by an Australian National Health and Medical

Research Council Career Development Fellowship. MEJ is supported by a University of Newcastle Priority Research Centre (Asthma) RHD Scholarship. The Authors thank Respiratory Research (Hunter Medical Research Institute) laboratory and clinical staff members for assistance with sample collection and processing, Majella Maher (John Hunter Children's Hospital) for performing lung plethysmography, and Patrick

McElduff (University of Newcastle) for statistical consultation and assistance. Australian New Zealand Clinical Trials Registry (ACTRN12610000955011).

Conflict of interest

The authors declare no conflict of interest and financial relationships relevant to this article to disclose.

References

- Peters JI, McKinney JM, Smith B, Wood P, Forkner E, Galbreath AD. Impact of obesity in asthma: evidence from a large prospective disease management study. *Ann Allergy Asthma Immunol* 2011; 106:30–5.
- Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *Int J Pediatr Obes* 2006; 1:11–25.
- Lee W. An overview of pediatric obesity. *Paediatr Diabetes* 2007; 8(Suppl. 9):76–87.
- Jensen ME, Wood LG, Gibson PG. Obesity and childhood asthma – mechanisms and manifestations. *Curr Opin Allergy Clin Immunol* 2012; 12:186–92.
- Sin D, Sutherland E. Obesity and the lung: 4 Obesity and asthma. *Thorax* 2008; 63:1018–23.
- Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DYM. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 2008; 178:682–7.
- Halder P, Pavord ID, Shaw DE *et al.* Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008; 178:218–24.
- Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. *Eur Respir J* 2011; 38:594–602.
- Quinto KB, Zuraw BL, Poon K-YT, Chen W, Schatz M, Christiansen SC. The association of obesity and asthma severity and control in children. *J Allergy Clin Immunol* 2011; 128:964–9.
- Rastogi D, Canfield SM, Andrade A *et al.* Obesity-associated asthma in children: a distinct entity. *Chest* 2012; 141:895–905.
- Ruppel GL. What is the clinical value of lung volumes? *Respir Care* 2012; 57:26–35.
- Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedón JC. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J Allergy Clin Immunol* 2011; 127:741–9.
- Eneli IU, Skybo T, Camargo CA Jr. Weight loss and asthma: a systematic review. *Thorax* 2008; 63:671–6.
- Jensen ME, Collins CE, Gibson PG, Wood LG. The obesity phenotype in children with asthma. *Paediatr Respir Rev* 2011; 12:152–9.
- Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. *J Allergy Clin Immunol* 2011; 127:724–33, e30.
- Boulet L-P, Turcotte H, Martin J, Poirier P. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. *Respir Med* 2012; 106:651–60.
- da Silva PL, de Mello MT, Cheik NC *et al.* Interdisciplinary therapy improves biomarkers profile and lung function in asthmatic obese adolescents. *Pediatr Pulmonol* 2012; 47:8–17.
- Dixon AE, Pratley RE, Forgione PM *et al.* Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011; 128:508–15, e2.
- Collins C, Warren J, Neve M, McCoy P, Stokes B. Systematic review of interventions in the management of overweight and obese children which include a dietary component. *Int J Evid Based Healthc* 2007; 5:2–53.
- Mahut B, Beydon N, Delclaux C. Overweight is not a comorbidity factor during childhood asthma: the GrowthOb study. *Eur Respir J* 2012; 2012(39):1120–6.
- Global Initiative for Asthma. Pocket Guide for Asthma Management and Prevention in Children. USA: NIH, 2005, Contract No.: 02–3659.
- Juniper E, O'Byrne P, Guyatt G, Ferrie P, King D. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; 14:902–7.
- Seid M, Limbers CA, Driscoll KA, Opiari-Arrigan LA, Gelhard LR, Varni JW. Reliability, Validity, and Responsiveness of the Pediatric Quality of Life Inventory (PedsQL) Generic Core Scales and Asthma Symptoms Scale in Vulnerable Children With Asthma. *J Asthma* 2010; 47:170–7.
- Hankinson J, Odencrantz J, Fedan K. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159:179–87.
- Ruppel GL, Enright PL. Pulmonary function testing: conference summary. *Respir Care* 2012; 57:165–75.
- Division of Nutrition Physical Activity & Obesity, National Center for Chronic Disease Prevention & Health Promotion. A SAS Program for the CDC Growth Charts. Centre for Disease Control and Prevention. Available at: <http://www.cdc.gov/nccdphp/dnpao/growth-charts/resources/sas.htm>. (accessed on 27th June 2011).
- Gibson PG, Wlodarczyk J, Hensley M *et al.* Epidemiological association of airway inflammation with asthma symptoms and airway hyperresponsiveness in childhood. *Am J Respir Crit Care Med* 1998; 158:36–41.
- Gibson PG, Henry RL, Thomas P. Non-invasive assessment of airway inflammation in children: induced sputum, exhaled nitric oxide, and breath condensate. *Eur Respir J* 2000; 16:1008–15.
- Okely AD, Collins CE, Morgan PJ *et al.* Multi-site randomized controlled trial of a child-centred physical activity program, a parent-centred dietary-modification program, or both in

- overweight children: The HIKCUPS study. *J Pediatr* 2010; **157**:388–94.
- 30 Gunnarsdottir T, Njardvik U, Olafsdottir AS, Craighead LW, Bjarnason R. The role of parental motivation in family-based treatment for childhood obesity. *Obesity* 2011; **19**:1654–62.
- 31 Vos R, Wit J, Pijl H, Houdijk E. Long-term effect of lifestyle intervention on adiposity, metabolic parameters, inflammation and physical fitness in obese children: a randomised controlled trial. *Nutrition and Diabetes* 2011; **1**:e9.
- 32 Golley RK, Magarey AM, Baur LA, Steinbeck KS, Daniels LA. Twelve-month effectiveness of a parent-led, family-focused weight-management program for prepubertal children: a randomized controlled trial. *Pediatrics* 2007; **119**:517–25.
- 33 McCallum Z, Wake M, Gerner B *et al*. Outcome data from the LEAP (Live, Eat and Play) trial: a randomized controlled trial of a primary care intervention for childhood overweight/mild obesity. *Int J Obes* 2006; **31**:630–6.
- 34 Hughes AR, Stewart L, Chapple J *et al*. Randomized, controlled trial of a best-practice individualized behavioral program for treatment of childhood overweight: Scottish childhood overweight treatment trial (SCOTT). *Pediatrics*; 2008(121):e539–46.
- 35 Jensen ME, Gibson PG, Collins C, Wood LG. Airway and systemic inflammation in obese children with asthma. *Eur Respir J* 2013; doi: 10.1183/09031936.00124912. [Epub ahead of print].
- 36 Reinher T, Roth C, Menke T, Andler W. Adiponectin before and after weight loss in obese children. *J Clin Endocrinol Metab* 2004; **89**:3790–4.
- 37 Reinher T, Stoffel-Wagner B, Roth C, Andler W. High-sensitive C-reactive protein, tumour necrosis factor α , and cardiovascular risk factors before and after weight loss in obese children. *Metabolism* 2005; **54**:1155–61.
- 38 Farah CS, Salome CM. Asthma and obesity - a known association but unknown mechanism. *Respirology* 2011; **17**:412–21.