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Effects of short term oral corticosteroid intake on dietary intake, body weight and body composition in adults with asthma- a randomised controlled trial

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Condensed title: Adverse effects of oral corticosteroids in asthma

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Abstract

Background: Oral corticosteroids are an efficacious treatment for asthma exacerbations ,yet risk of adverse effects may decrease patient adherence to therapy. In particular, changes in

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appetite and dietary intake, that lead to weight gain and changes in body composition are considered undesirable.

Objective: To determine whether 10 days oral corticosteroid therapy in adults with asthma causes changes in leptin, appetite, dietary intake, body weight and body composition.

Methods: Double-blinded, placebo controlled randomised cross-over trial of 10 days prednisolone (50mg) in adults with stable asthma (n=55) (ACTRN12611000562976). Pre and post assessment included spirometry, body weight, body composition measured by dual energy x-ray absorptiometry and bioelectrical impedance analysis, appetite measured using a validated visual analogue scale and dietary intake assessed using 4-day food records. Leptin was measured as a biomarker of appetite and eosinophils as an adherence biomarker. Outcomes were analysed by generalised linear mixed models.

Results: Subject adherence was confirmed by a significant decrease in blood eosinophils ($\times 10^9/L$) following prednisolone compared to placebo (Coef. -0.29 95% CI: (-0.39, -0.19) $p < 0.001$). There was no difference in serum leptin (ng/ml) (Coef. 0.13 95% CI: (-3.47, 3.72) $p = 0.945$) or appetite measured by visual analogue scale (mm) (Coef. -4.93 95% CI: -13.64, 3.79) $p = 0.267$) following prednisolone vs. placebo. There was no difference in dietary intake (kJ/day) (Coef. 255, 95% CI: (-380, 891) $p = 0.431$), body weight (kg) (Coef. -0.38 95% CI: (-0.81, 0.05) $p = 0.083$) or body fat (%) (Coef. -0.31 95% CI: (-0.81, 0.20) $p = 0.230$). Symptoms including sleep and gastrointestinal disturbance were reported significantly more often during prednisolone vs placebo.

Conclusions & Clinical Relevance: Short term oral corticosteroids in stable asthma did not induce significant changes in appetite, dietary intake, body weight or composition, though other adverse effects may require medical management. This evidence may assist in increasing medication adherence of asthmatics prescribed oral corticosteroids for exacerbations.

Introduction

Oral corticosteroids (OCS) are an extremely effective anti-inflammatory medication, prescribed in various conditions, including asthma (1). Unfortunately their efficacy is shadowed by their adverse event profile, which includes minor to life-threatening adverse effects (1). Serious adverse effects of OCS include osteoporosis, arterial hypertension, diabetes, psychosis, lipodystrophy (morphological changes of fat accumulation in facial, dorsocervical and abdominal region), hypothalamic-pituitary-adrenal (HPA) axis suppression, cataracts, glaucoma, skin thinning, easy bruising, and myopathy (1, 2). Less serious effects may include anxiety or mood changes, nausea, vomiting, anorexia or increased appetite, weight gain or weight loss, stomach bloating or irritation and diarrhoea or constipation (3). While these effects are considered minor from a medical perspective, they are serious from a subjects perspective and may impact significantly on quality of life (4). In the literature the reporting of adverse events focuses on the more severe effects, is associated

with long-term (>3 months) use of OCS and is predominantly self-reported (5). Yet in asthma, OCS are often prescribed as occasional short courses to people experiencing acute, moderate to severe asthma exacerbations (6). Although there are more serious adverse events associated with OCS use, subjects are also concerned with body weight gain, increased appetite and lipodystrophy; these concerns may reduce adherence when OCS are prescribed (1, 7). There is a paucity of evidence for the relationship between OCS, weight gain and increased appetite. We have previously conducted a systematic literature review (5) on the effect of OCS on body weight, appetite and energy intake and concluded that it is unlikely that short-term OCS cause these adverse effects, however further investigation is required.

Despite significant advancements in pharmacotherapy treatment to control asthma, OCS remain the mainstay of treatment for moderate to severe exacerbations (6). An exacerbation of asthma is an amplified response of the lower airway to an environmental exposure, such as viral infection, allergen or pollutant (8). All subjects with asthma are at risk of exacerbation, whether their asthma is well or poorly controlled, though exacerbation frequency increases with disease severity (9). Evidence based practice guidelines currently recommend acute treatment with a fixed dose of OCS (50-100mg of prednisone equivalent) for 5-10 days (10). Latest Australian data from April 2007 to March 2010 indicate that OCS are prescribed for asthma by GP's at 13.5% [CI 12.4-14.7%] of all encounters where asthma is managed, and in 11.9% of encounters with adults. The majority (58%) of these OCS prescriptions were 'new' indicating they were for acute exacerbations (6).

Increased BMI and obesity appear to be risk factors for asthma (11), associated with poor response to controller medications (12, 13), increased hospitalisation rates (14), adverse lung mechanical effects (15) and increased airway inflammation (16). Thus weight gain as an adverse effect of asthma treatment would be deleterious. The mechanisms for the link between obesity and asthma are unclear; it is possible that increased leptin levels and leptin resistance may provide some explanation. Leptin is a pro-inflammatory satiety hormone primarily secreted by adipose tissue, though is also produced and has actions within the lung and immune cells (17). Paradoxically, leptin levels increase as a result of OCS therapy, while reportedly appetite and body weight also increase (18). Thus it is important to determine the likelihood and extent of OCS side effects during short-term treatment in asthma, to increase medication adherence and allow for development of strategies to manage increased appetite and prevent weight gain if they occur (1).

We hypothesised that the use of oral corticosteroids to treat asthma leads to increased body weight as a result of increased production of appetite control hormones. Therefore this study aimed to determine whether significant side effects, including changes in leptin, dietary intake and appetite occur as a result of short term OCS therapy in adults with stable asthma.

Methods

Study design

The study was a double-blinded, randomised, placebo-controlled cross-over trial of prednisolone 25mg twice daily for 10 days. The intervention dosage and duration emulate the current treatment guidelines for asthma exacerbations (10). The trial was registered with the Australian and New Zealand Clinical Trials Registry, number: ACTRN12611000562976 prior to the study commencing. This study was conducted at the Hunter Medical Research Institute, Newcastle, Australia according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Hunter New England and University of Newcastle Human Research Ethics Committees (11/06/15/3.03). Written informed consent was obtained from all subjects.

Subjects

Subjects with stable asthma were recruited from the John Hunter Hospital Severe Asthma Clinic, NSW, Australia; an internal respiratory research volunteer outpatient database; Hunter Medical Research Institute (HMRI) research volunteer database; and by media releases in local newspapers and radio (n=60). Inclusion criteria were; age over 18 years, non-smoking status (ceased smoking for at least 6 months) and confirmed stable asthma. Asthma stability was defined as no exacerbation, respiratory tract infection or OCS use in the past 4 weeks. Asthma diagnosis was confirmed on the basis of either: current (past 12 months) episodic respiratory symptoms, doctor's diagnosis of asthma (ever) or airway hyper-responsiveness (AHR) to hypertonic saline. Exclusion criteria were: current smokers, pregnancy or breastfeeding, subjects under 18 yrs, uncontrolled diabetes mellitus (DM) or DM managed with medication, current respiratory disorders other than asthma, uncontrolled hypertension or blood pressure >190/100 mm/Hg, uncontrolled reflux, maintenance OCS therapy, current participation in other research study, currently taking medications known to interact with oral corticosteroids or allergy or intolerance to oral corticosteroids.

Clinical intervention

Eligibility screening was performed prior to randomisation. Eligible subjects attended the clinic at visit 1 for clinical and dietary assessment and were randomised to receive the active treatment (Prednisolone 25mg capsule) or identical placebo capsules (Richard Stenlake compounding Chemist, Bondi, Australia), to be taken twice daily with food for 10 days during phase A. Subjects were assessed after 10 days at visit 2 upon conclusion of phase A. All subjects completed a wash out period of 4 weeks between phase A and B to avoid carry over effects. Subjects' acted as their own control group by crossing over to the alternate treatment in phase B. At visit 3 subjects were provided with the alternate study medication and assessed again at visit 4.

Clinical Assessment

Blood pressure (Connex® Vital Signs Monitor, Welch Allyn Inc New York, USA), exhaled nitric oxide (FeNO) (Ecomedics CLD 88sp FENO, Ecomedics, Switzerland) and lung function (Medgraphics, PFS/D and BreezeSuite software, MedGraphics, Minnesota, USA) were measured. Predicted values for forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were calculated using NHANES III data, which accounts for gender, age, and height (19). Combined bronchial provocation and sputum induction with nebulised (ULTRA-NEB™ ultrasonic nebuliser, DeVilbiss, Model 2000) hypertonic saline (4.5%) were performed as previously described (20).

Blood collection and processing

Blood was collected from patients after >12hour fast. Samples were refrigerated immediately and within 30 minutes of collection blood samples were centrifuged at 4°C, 3000rpm, for 10 minutes and plasma aliquots were stored at -80°C. Centrifugation was repeated on thawing to clear samples of precipitate.

Plasma leptin was measured with commercial Quantikine ELISA human leptin immunoassay kits (R&D systems, MN, USA). A full blood count was performed using whole blood samples (Hunter Area Pathology Service, Coulter STKS Cell Analyzer, (Miami, FL, USA). The full blood count included determination of blood immune cells including eosinophils, neutrophils, lymphocytes and monocytes.

Anthropometry

At each study visit subjects were weighed in light clothing to the nearest 100g with NU WEIGH LOG842 scales, (NU Weigh Scales Inc, MI). Height was measured using the stretch stature method to the nearest 0.1cm using a wall mounted stadiometer. Height and weight measures were used to calculate BMI (kg/m²). Waist circumference (WC) was measured to the nearest 0.1cm at the midpoint between the lower costal edge and the iliac crest, using a non-extensible steel tape (Lufkin W606PM, Cooper Tools, Apex NC). Waist to height ratio (WHR) was calculated (waist circumference (cm) / height (cm)). Bioelectrical impedance analysis (BIA) (InBody720, Lookin'Body 3.0, Biospace, Korea) and total body composition using dual-energy x-ray absorptiometry (DXA) (DXA Lunar Prodigy; GE Medical Systems, encore 2007 software Version 11.40.004, Madison WI) were measured at each visit.

Questionnaires

Detailed medical & smoking history and history of inhaled and oral corticosteroid intake over 2 years were obtained. Asthma control was assessed using the validated 7-item Juniper Asthma Control Questionnaire (ACQ-7) at each visit (21). Severe asthma was defined by a subject demonstrating AHR, bronchodilator response $\geq 12\%$ (BDR) or documented peak flow

with $\geq 12\%$ variability and high dose ICS ($\geq 1000\text{mcg BDP Equiv}$) in combination with a long acting B₂-agonist (LABA), and at least one of the following; FEV₁ Post B₂: $<80\%$ predicted OR FEV₁/FVC: $<70\%$ predicted, ACQ-7 ≥ 1.5 or a severe exacerbation within previous 12 months with OCS use (22). Data was collected on adverse events at each visit.

Dietary intake and Appetite Assessment

Subjects completed 4-day food records prior to study commencement, on the last 4 days in each phase of the intervention and during the washout period. Food records were analysed using the Australian AusNut 1999 database (All Foods) Revision 17 and AusFoods (Brands) Revision 5, accessed through FoodWorks (version 4.00.1158, 2005; Xyris Software, Brisbane, Queensland, Australia). Subjects also completed the Food Cravings Inventory (23) (FCI) at each visit to indicate the occurrence of cravings for 28 foods over the previous 7 days.

Subject appetite was assessed using a validated satiety labelled intensity magnitude (SLIM) scale, a bi-directional visual analogue scale (VAS) that measures perceived satiety (24). The VAS contains phrases associated with hunger and fullness tested for meaning and given magnitude estimates ranging from +100 ('greatest imaginable fullness') to -100 ('greatest imaginable hunger'), with 0 labelled as 'neither hungry or full' (24).

Randomisation and blinding

All subjects were randomly assigned to take either the prednisolone in phase A then placebo in phase B or placebo in phase A and prednisolone in phase B. Subjects were allocated a study number to which the intervention order was assigned through randomisation codes. Randomisation codes were developed and applied to study numbers by a senior biostatistician and sent to Richard Stenlake Compounding Chemists (Bondi, Australia) who manufactured, bottled and labelled the study medication. Study medication was labelled for each study number as bottle A and bottle B. The study was performed double-blinded, whereby both the participants and investigators were not aware of the intervention allocation. Study medication was dispensed by John Hunter Hospital pharmacy individually for each subject during each phase of the study. The hospital pharmacy that dispensed study medication, chief investigators and clinical trial officers did not have access to the randomisation codes.

Subject Adherence

Adherence was evaluated through both the use of a blood biomarker and analysis of study medication returns. Blood eosinophil concentration was measured before and after intervention and the change calculated. Peripheral blood eosinophils are an acceptable biomarker of OCS therapy due to the significant decrease or abolishment of blood

eosinophils after OCS (25-29). Blood eosinophil concentration significantly decreased in both males and females following prednisolone, confirming subject adherence to the intervention. No subjects were excluded on this basis. A pill count analysis on the medication returned by subjects after each phase of the study was performed to evaluate the percentage of study medication consumed. On average subjects consumed 95% of the placebo medication, with no subject consuming less than 80%. Subjects consumed on average 91% of prednisolone medication, though three subjects consumed less than 80%, 2 subjects consumed 67% and one subject consumed 78% of the prednisolone medication, these subjects were not excluded from analysis.

Statistical Analysis

Data are reported as mean $\pm$ standard deviation for parametric and median [interquartile range] for non-parametric data. Statistical comparisons of continuous outcomes were performed using Student t-tests and one-way ANOVA for groups where data was parametric and two-sample Wilcoxon rank-sum and Kruskal-Wallis tests where data was non-parametric data. Chi squared analysis was used for analysis of categorical outcomes. Multiple linear regressions, Pearson's correlation coefficients and Spearman's rank correlation coefficients were used to assess associations.

An intention to treat (ITT) analysis was performed, which included all observed data to test outcome variables for treatment effects. A mixed models analysis was conducted with the plausible assumption that data was missing at random, that is, subjects with missing data would have experienced a change in variables that was similar on average as other subjects in the study (30). A sensitivity analysis was conducted on all significant treatment variables with imputed data using the 'last observation carried forward' method. The results of this analysis showed no differences in significance to the original ITT analysis. The mean difference between treatment and placebo in intervention outcomes was tested by generalised linear mixed models using an independent t-test of the period differences by treatment sequence, which provided an estimate of the treatment effect independent of any period effect (31). An independent t-test of the period totals by treatment sequence was used to test the assumption of no carry over effects. Significance was accepted if $p < 0.05$.

With 49 subjects the study had $>80\%$ power to detect a significant difference of $p < 0.05$ in changes in serum leptin and $>90\%$ power to detect a 2000kJ difference in total dietary energy intake.

Results

Baseline

Sixty subjects were randomised, 55 completed phase A and 49 completed both phase A and B of the study (**Figure 1**). Subjects were aged from 21 to 78 years old, with a mean age of 53.6 years and mean BMI of 30.7 kg/m^2 (**Table 1 & Table 2**). The majority of subjects (58%)

were female ($p=0.086$). Males and females were of similar age, BMI and ACQ-7 score. Lung function was similar in males and females, except FEV₁/FVC which was lower in males, showing more airway obstruction. Forty per cent of subjects had severe asthma. There were significantly more males with severe asthma (61%) compared to females (25%).

Intervention Outcomes

As a biomarker of adherence, blood eosinophils indicate that both male (and female subjects were adherent to the intervention. After 10 days of prednisolone treatment blood eosinophils in males decreased from 0.3 (0.2,0.4) $10^9/L$ (med (IQR) by -0.36 ± 0.45 ($p<0.001$), and decreased from 0.2 (0.2,0.4) $10^9/L$ (med (IQR) by -0.25 ± 0.23 ($p<0.001$) in females.

There was no difference in serum leptin concentration in either males or females on prednisolone compared to placebo treatment (**Table 3, Figure 2**). Likewise the change in appetite before and after prednisolone treatment was not different to the placebo in both males and females as measured by the SLIM VAS (**Figure 2**). Dietary intake of total energy, macro (including alcohol and fibre) and micronutrients was not different between the prednisolone and placebo in both males and females.

Changes in body weight were not significantly different between the prednisolone and placebo phases, however there was a trend ($p=0.067$) for body weight in males to decrease during the prednisolone phase compared to the placebo phase (**Table 2, Figure 2**). Waist circumference increased significantly in women during the prednisolone phase compared to placebo (**Table 2**). There was no change in total body fat %, fat mass distribution or lean mass measured by DXA in either males or females in the prednisolone phase compared to placebo. When measured by BIA, there was a small decrease in intracellular water in females only, during the prednisolone phase.

Adverse Effects

Results from the adverse effects questionnaire showed there was a significantly higher incidence and severity of adverse effects reported by subjects during the prednisolone than placebo phase (**Figure 3**). Sleep disturbance was most commonly reported, occurring in 75% of subjects whilst taking prednisolone; half of these subjects experienced moderate to severe disturbance. Increased appetite was reported by over 50% of subjects whilst taking prednisolone compared to 17% of subjects on placebo. Almost 50% of subjects reported reflux symptoms during the prednisolone phase, which was predominantly mild, however 8% of subjects reported severe reflux. Gastrointestinal (GI) disturbance occurred more frequently during the prednisolone than placebo phase with constipation and bloating reported by over 25% of subjects. Mild muscle weakness and mild increase in urinating frequency were also reported more frequently in subjects whilst taking prednisolone versus placebo. Occurrence of mood changes, decreased appetite, fluid retention, nausea, vomiting, diarrhoea, changes in energy level, excess thirst and dry mouth did not differ between the prednisolone and placebo

phases. Upon examining adverse effect occurrence by gender, only females reported reflux and constipation more on prednisolone than placebo (**Table 4**). However decreased energy and appetite, excess thirst, dry mouth and muscle weakness were reported significantly more by females on prednisolone than males.

Discussion

This is the first RCT in asthma to objectively measure appetite, dietary intake and body composition during OCS therapy. This study investigated the effects of 10 day OCS therapy, in adults with stable asthma. Results demonstrate that short term OCS intervention has no effect on serum leptin or an objective measure of appetite, does not affect dietary intake and has no adverse effects on body weight and body composition. Our data provides evidence which fills a gap in the literature by showing that short term bursts of OCS, as commonly prescribed to adults with acute asthma, do not affect appetite, dietary intake or cause food cravings and body weight changes.

In this RCT, we confirmed that subjects were adherent with the intervention, by measuring peripheral blood eosinophils (25, 26). Peripheral blood eosinophil count significantly decreased following prednisolone therapy, which demonstrates that both male and female subjects were adherent with the intervention. Serum leptin was measured in a fasted state before and after 10 days of prednisolone therapy, and the change was not different from placebo. In agreement with our leptin findings, there was also no change in SLIM VAS appetite score. Other OCS intervention studies of similar dose and duration have reported increased leptin levels in healthy subjects (32-36). Serum leptin increased following short term high dose (≥ 40 mg/day prednisolone equivalent) OCS in healthy males (37) and females (38), after moderate dose (>10 mg & <40 mg prednisolone equivalent) OCS for 24 hours in healthy and obese males (39), in newly diagnosed subjects with diabetes mellitus (40) and in subjects with various autoimmune conditions on OCS for 1 and 3 months (41, 42). Conversely, leptin levels did not change significantly in healthy young males taking moderate dose OCS for 5 days (43) or high dose OCS for 4 days (44), or in subjects with chronic diabetes mellitus using moderate dose OCS for 24 hours (40). While there is some heterogeneity in the data, overall, the majority of studies suggest that OCS lead to an increase in serum leptin levels in healthy subjects and in some disease states. Considering the already increased leptin levels of subjects with asthma (45), it is possible that in our study, OCS did not further increase the expression of the *ob* gene and subsequent adipose tissue secretion of leptin. Other evidence suggests that glucocorticoid modulation of leptin occurs only in a fed state. An IV bolus (26mg prednisolone equivalent) administered to healthy subjects was unable to stimulate leptin in fasting subjects, suggesting that other factors regulating food ingestion, including insulin and GI hormones, were necessary, as glucocorticoids or feeding alone were unable to increase serum leptin (46). Blood samples in this study were obtained after OCS was last taken with the evening meal followed by overnight fast, when physiological leptin levels are at a nadir (47), which may have contributed to the lack of

response of leptin to the intervention. Further study of leptin levels in the fed and fasting state in asthma is warranted.

While appetite was not affected by OCS treatment when measured by the SLIM VAS appetite tool, subjects reported symptoms of increased appetite more during the prednisolone than placebo phase. It is important however to distinguish the SLIM VAS tool as an objective measure with a labelled magnitude scale, whereas the data from side effects were subjective and categorical, i.e. yes or no. The authors conclude that as appetite was not different following prednisolone to placebo or baseline measurements using the VAS tool, it is unlikely that a significant change in appetite occurred. The finding that neither dietary intake nor food cravings were different between treatment groups is also in agreement with the results of the SLIM VAS. This concurs with other studies using OCS interventions which found that appetite following OCS was not different to placebo (48, 49). Another study used a standard VAS to assess hunger and desire to eat before meals and fullness after meals and found no difference in scores between OCS and placebo groups (35).

Four day food records completed by subjects during each intervention phase showed that neither energy intake nor composition of food intake differed, which is concordant with no changes in food cravings. This finding is supported by other OCS intervention studies of similar dose and duration in healthy subjects that also showed no change in dietary energy intake (34-36). However the literature is not consistent in this area, an OCS intervention study in 15 young healthy males consuming food and drinks ad libitum from automated vending machines for 4 days reported increased energy intake compared to placebo (50). While a 24 hour OCS intervention in 6 young health subjects being fed as inpatients reported a decrease in energy intake compared to placebo (51).

This study also found that body weight, total fat mass and fat distribution, total lean mass and total body water were not affected by 10 days OCS treatment, which is in agreement with the results of dietary intake. These results agree with reports in the literature of similar OCS interventions where body weight and fat mass did not change in asthma (52) and in healthy subjects, (32-36, 50). Waist circumference increased in females following prednisolone, which may be explained by abdominal distension accompanying constipation and bloating. Self-reported symptoms of GI upset following prednisolone treatment concur with this finding. OCS are well known for their undesirable effects on muscle mass; including proximal skeletal muscle wasting and weakness (53), yet in this study there was no effect of prednisolone treatment on total lean mass or fat free mass. Our results are in agreement with other reports in the literature where there was no change in % lean mass in asthmatics after 12 months OCS therapy (54), and in healthy controls after 4 days high dose OCS in healthy subjects there was no difference in lean body mass between prednisolone and placebo (32). Short term moderate dose OCS in healthy subjects had no effect on whole body protein metabolism or muscle function after six days of 0.5mg/kg/day prednisone (55). Thus, it is

likely that the adverse effects of OCS on muscle mass occur with longer treatment periods and /or higher dosages.

Self-reported adverse effects were more frequent in subjects following prednisolone treatment, in particular GI symptoms and sleep disturbance. Education for patients with asthma and management of these symptoms by clinicians and health professionals may be important to aid with adherence to therapy when OCS are prescribed.

There is extensive data on adherence rates for ICS medication use in asthma, data on OCS adherence rates in adults are sparse, and predominantly relate to subjects with difficult to treat or severe asthma on maintenance OCS, not OCS for exacerbations. Poor adherence to prescribed doses of OCS following hospital discharge for severe asthma exacerbations, defined as using less than 50% of prescribed medication, is reported in 24% (56) and 27% (57) of subjects in two studies that used electronic monitoring devices. However these rates of non-adherence are thought to be lower than expected from a clinical setting where patients must fill and pay for their prescriptions themselves. In two studies using blood eosinophil suppression as an indirect measure of adherence to maintenance OCS, 45% and 50% of subjects were not considered adherent (27, 58). Data from this study, demonstrating a lack of effect of short-term OCS on body weight, may be useful in improving adherence rates in the future.

While the short duration (10 days) of the trial could be considered a limitation of the study, this time period was specifically chosen, as our aim was to examine the effects of an OCS dose that would typically be used to treat an asthma exacerbation. This time period may not have been sufficient to see changes in body weight or fat mass and fat distribution, yet it is the most clinically relevant for patients with acute asthma.

Both the subjects and research staff were blinded to the study allocation. However the presence of symptoms commonly associated with OCS use may have un-blinded some subjects to randomisation. However, as adherence to the intervention was confirmed and many subjects were OCS naïve and reported presence of such symptoms during the placebo phase, it is unlikely that un-blinding significantly affected the study results.

Further limitations to be acknowledged are that not all subjects were naïve to OCS treatment affects and that subject selection may have been affected by subjects being reluctant to participate in the study due to known side effects of OCS. Notwithstanding the study design including random allocation, blinding and placebo controls, which adds to the credibility to the study results.

This novel study has addressed whether a 10 day course of OCS affect leptin levels, appetite, dietary intake, body weight and body composition of subjects with stable asthma and concludes that there were no significant adverse effects in relation to these outcomes. Minor adverse effects associated with OCS use were common and highlight the need for patient education and symptom management. These outcomes apply to all adults with asthma, as

acute exacerbations requiring short term OCS can occur in all asthma phenotypes and levels of severity. Furthermore this study provides clinicians and health professionals with the evidence needed to assure adults prescribed short term OCS for acute asthma that increases in appetite, dietary intake or body weight are unlikely to occur, which may facilitate increased adherence to treatment.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Figure Legends

Figure 1. Consort participant flow diagram

Figure 2. Effect of OCS treatment on Blood Eosinophils Leptin, Appetite – Satiety Labelled

Intensity Magnitude (SLIM) Score and Body weight by gender

(A) Reduced blood eosinophils following prednisolone (*triangles*) versus no change following placebo (*circles*). No difference in the change in leptin (B), appetite (B) or body weight (C) following prednisolone (*triangles*) and placebo (*circles*).

Figure 3 Frequency of self reported adverse events by treatment

*Difference in number of adverse events reported between prednisolone and placebo phases, $P < 0.05$

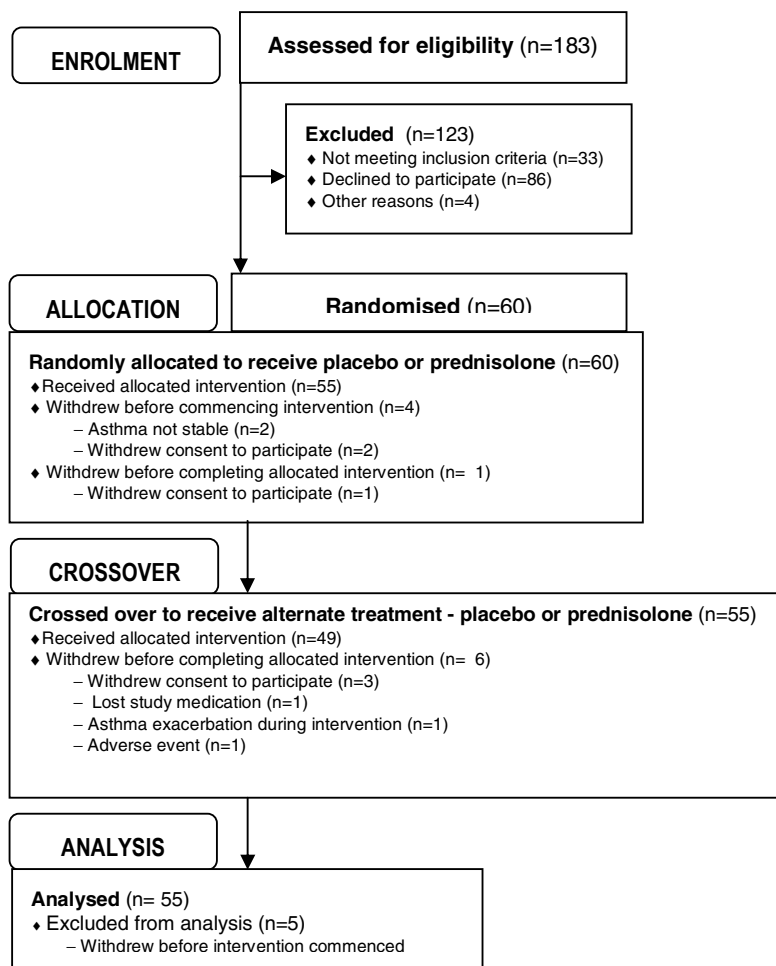


Figure 1 Consort participant flow diagram

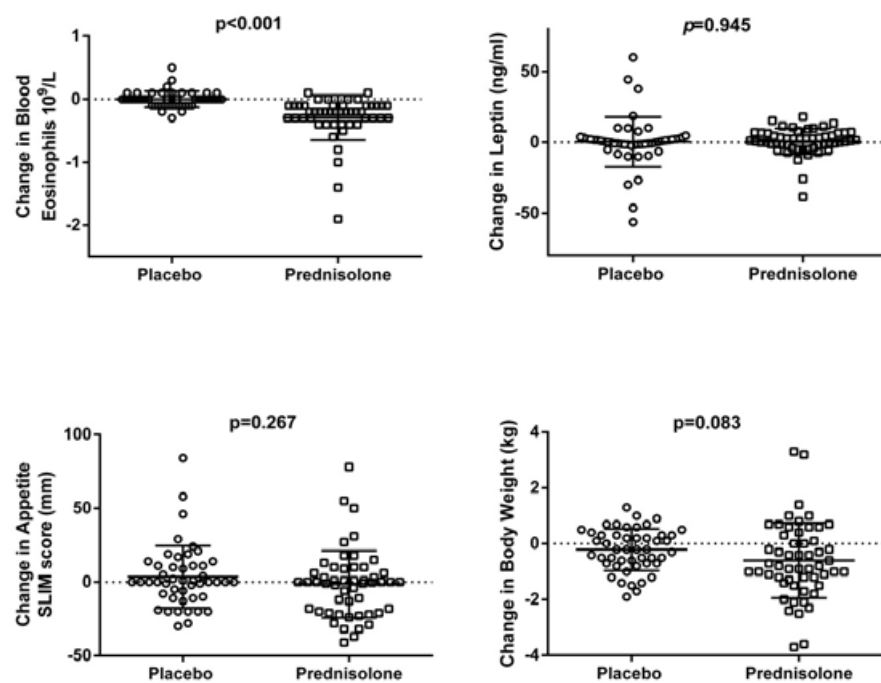


Figure 2. Effect of OCS treatment on Blood Eosinophils Leptin, Appetite – SLIM Score and Body weight by gender

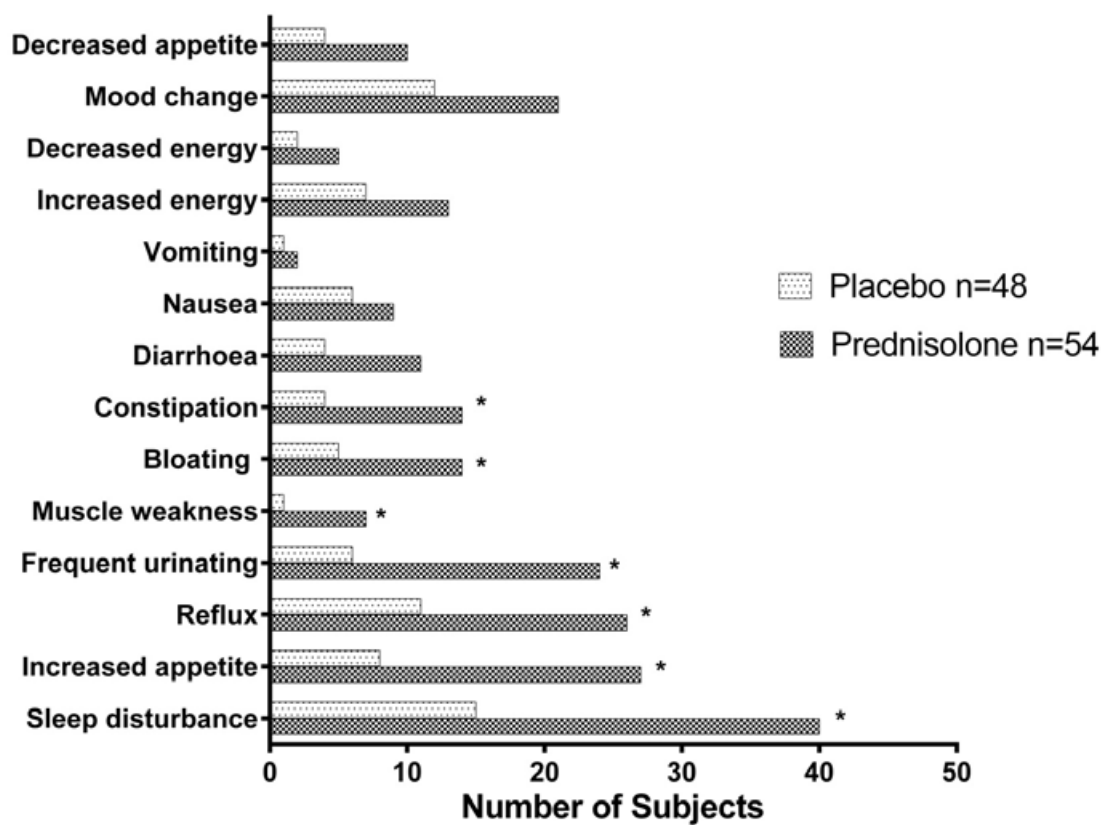


Figure 3 Frequency of self reported adverse events by treatment

Table 1: Clinical characteristics at baseline, by gender

	All asthma (n=55)	Male (n=23)	Female (n=32)	<i>P</i> [#]
Age (years) (range)	53.6 (21-78)	56.5 (27-28)	51.5 (21-71)	0.233
FEV₁ (% predicted)	79 ± 16.5	77.2 ± 17.4	80.9 ± 15.9	0.419
FVC (% predicted)	88 ± 14	89.9 ± 13.7	87.1 ± 14.9	0.479
FEV₁/FVC (%)	70 ± 10	65.0 ± 10.3	73.9 ± 9.7	0.002
ACQ 7 med [IQR]	1.1 [0.6, 1.7]	1.1 [0.8, 1.9]	0.9 [0.5, 1.6]	0.270
AHR n (%)	30 (55)	14 (61)	16 (50)	0.425
PD₁₅ (ml) med [IQR]	4.9 [2.9, 10.5]	6.2 [4.7, 10.5]	3.7 [0.9, 8.6]	0.109
Dose response slope (%fall/ml) med [IQR]	1.4 [0.5, 3.7]	1.4 [0.7, 2.5]	1.4 [0.5, 3.8]	0.854
Severe asthma n (%)	22 (40)	14 (61)	8 (25)	0.007
Ex-smokers n (%)	21 (38)	7 (30)	14 (43.8)	0.147
Pack years med [IQR]	3 [1, 20]	20 [1, 35]	1.8 [0, 4]	0.114
ICS use n (%)	43 (78)	18 (78)	23 (72)	0.592
ICS dose [#] (µg/d) mean (SD)	1025 ± 738	1195 ± 835	869 ± 615	0.146
OCS cumulative dose [^] in 2 yrs (mg) med [IQR]	400 [238, 675]	350 [238, 675]	450 [269, 625]	0.939

Data are mean±SD unless otherwise stated. FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ACQ 7, 7-item Asthma Control Questionnaire (Juniper); AHR, airway hyperresponsiveness; PD₁₅, provocation dose; ICS, inhaled corticosteroid; OCS, oral corticosteroid. [#]Beclomethasone equivalents, [^]Prednisone equivalents. [#]Difference between males and females.

Table 2. Effect of treatment on body weight and body composition

Outcome	Baseline Value med [IQR]	Change on Placebo mean±SD n=48	Change on Prednisolone mean±SD n=54	Coef [#]	CI [^]	P-value
Weight (kg) n=102	86.5 ± 19.6	-0.21 ± 0.75	-0.59 ± 1.35	-0.38	-0.81, 0.05	0.083
Males n=44	92.9 ± 20.7	-0.24 ± 0.69	-0.77 ± 1.15	-0.53	-1.10, 0.04	0.067
Females n=58	82.4 ± 17.9	-0.19 ± 0.81	-0.46 ± 1.48	-0.27	-0.89, 0.36	0.396
Gender interaction				0.26	-0.62, 1.13	0.561
BMI (kg/m²) n=102	30.7 ± 6.4	-0.09 ± 0.30	-0.19 ± 0.51	-0.10	-0.26, 0.07	0.266
Males n=44	29.9 ± 5.9	-0.10 ± 0.25	-0.25 ± 0.40	-0.15	-0.35, 0.05	0.152
Females n=58	31.2 ± 6.8	-0.09 ± 0.34	-0.14 ± 0.58	-0.06	-0.31, 0.19	0.668
Gender interaction				0.09	-0.25, 0.44	0.590
Waist (cm) n=90	99.6 ± 17.6	-1.6 ± 3.8	0.1 ± 3.9	1.69	0.18, 3.21	0.028
Males n=47	105.0 ± 18.1	-1.44 ± 3.21	-1.26 ± 3.74	0.19	-1.98, 2.36	0.863
Females n=43	95.4 ± 16.2	-1.63 ± 4.27	1.22 ± 3.81	2.85	0.79, 4.90	0.006
Gender interaction				2.64	-0.39, 5.67	0.088
Total Lean (%)	58.1 ± 10.5	-0.15 ± 1.6	0.21 ± 1.6	0.36	-0.31, 1.03	0.292
Males n=39	65.3 ± 10.2	-0.35 ± 0.94	0.07 ± 1.60	0.42	-0.41, 1.25	0.319
Females n=51	52.7 ± 6.9*	0.01 ± 1.93	0.31 ± 1.71	0.31	-0.70, 1.32	0.551
Gender interaction				-0.11	-1.47, 1.24	0.869
Total fat (%) n=90	39.6 ± 10.7	0.16 ± 0.95	-0.15 ± 1.43	-0.31	-0.81, 0.20	0.230
Males n=39	32.3 ± 10.5	0.24 ± 0.77	-0.05 ± 1.19	-0.29	-0.92, 0.34	0.365
Females n=51	45.1 ± 6.9*	0.10 ± 1.08	-0.22 ± 1.62	-0.32	-1.08, 0.43	0.403
Gender interaction				-0.03	-1.06, 0.99	0.953
Android fat (%) n=90	45.9 ± 10.4	-0.06 ± 1.5	-0.51 ± 2.3	-0.45	-1.25, 0.36	0.275
Males n=39	41.9 ± 11.7	-0.21 ± 1.20	-0.57 ± 1.70	-0.36	-1.29, 0.56	0.442
Females n=51	48.9 ± 8.2*	0.05 ± 1.67	-0.46 ± 2.71	-0.51	-1.75, 0.73	0.421
Gender interaction				-0.15	-1.78, 1.49	0.862
Gynoid fat (%) n=90	43.7 ± 11.5	-0.08 ± 1.17	0.05 ± 1.62	0.13	-0.47, 0.72	0.676
Males n=39	34.2 ± 9.9	-0.23 ± 1.00	0.45 ± 1.49	0.69	-0.06, 1.44	0.072
Females n=51	50.9 ± 5.9*	0.04 ± 1.29	-0.25 ± 1.76	-0.29	-1.14, 0.56	0.498
Gender interaction				-0.97	-2.17, 0.22	0.112
Thoracic fat (%) n=88	36.1 ± 11.4	-0.09 ± 2.9	0.11 ± 3.7	0.20	-1.18, 1.58	0.780
Males n=39	31.5 ± 11.7	0.38 ± 1.82	0.32 ± 1.79	-0.10	-1.21, 1.00	0.855
Females n=51	39.5 ± 10.1	-0.42 ± 3.44	-0.05 ± 4.72	0.36	-1.89, 2.62	0.754
Gender interaction				0.43	-2.40, 3.26	0.767
Intracellular water (L) n=99	24.62 ± 4.77	0.11 ± 0.52	-0.08 ± 0.99	-0.20	-0.51, 0.12	0.219
Males n=44	28.62 ± 3.53	0.09 ± 0.49	0.07 ± 1.29	-0.02	-0.60, 0.55	0.933
Females n=55	21.55 ± 2.94*	0.13 ± 0.55	-0.21 ± 0.64	-0.34	-0.66, 0.02	0.036
Gender interaction				-0.31	-0.95, 0.32	0.330
Extracellular water (L) n=99	15.20 ± 2.95	-0.3 ± 0.5	0.2 ± 2.03	-0.05	-0.29, 0.20	0.719
Males n=44	17.62 ± 2.31	0.005 ± 0.35	-0.004 ± 0.70	-0.01	-0.34, 0.32	0.957
Females n=55	13.35 ± 1.82*	-0.06 ± 0.61	0.29 ± 2.70	-0.09	-0.43, 0.25	0.612
Gender interaction				-0.05	-0.55, 0.45	0.851

Data is mean ± SD. BMI: body mass index; WHR: waist to hip ratio. [#]Coefficient showing change in outcome as a result of treatment with prednisolone and difference in males vs females in outcome as a result of prednisolone treatment. [^]Confidence interval for coefficient. *Difference between males and females at baseline. P<0.05.

Table 3. Effect of treatment on Blood Eosinophils, Leptin, Appetite & Dietary Intake

Outcome	Baseline Value med [IQR]	Change on Placebo mean±SD n=49	Change on Prednisolone mean±SD n=52	Coef [#]	CI [^]	P-value
Eosinophils (10⁹/L) n=97	0.3 [0.2,0.4]	-1.52x10 ⁻⁹ ± 0.13	-0.29 ± 0.36	-0.29	-0.39, -0.19	<0.001
Males n=41	0.3 [0.2,0.4]	-0.005 ± 0.15	-0.36 ± 0.48	-0.35	-0.56, -0.14	0.001
Females n=56	0.2 [0.2,0.4]]	0.004 ± 0.11	-0.25 ± 0.23	-0.25	-0.35, -0.16	<0.001
Gender interaction				0.09	-0.12, 0.31	0.377
Leptin (ng/ml) n=101	21.4 [11.2,42.4]	0.19 ± 9.57	0.31 ± 8.85	0.13	-3.47, 3.72	0.945
med [IQR] Males n=35	9.66 [3.9,21.9]	0.79 ± 2.96	-0.24 ± 9.79	-1.03	-5.49, 3.44	0.652
Females n=54	28.97 [17.9,46.6]*	-0.23 ± 12.27	0.71 ± 8.24	0.95	-4.37, 6.26	0.727
Gender interaction				1.97	-4.37, 6.26	0.598
Appetite (SLIM) score n=98	-23.2± 18.9	3.51 ± 21.11	-1.42 ± 22.78	-4.93	-13.64, 3.79	0.267
Males n=41	-26.1 ± 18.9	2.11 ± 19.31	-7.23 ± 19.67	-9.03	-20.46, 2.39	0.121
Females n=57	-21.3 ± 18.8	4.46 ± 22.54	2.99 ± 24.28	-1.47	-13.65, 10.69	0.812
Gender interaction				7.86	-9.75, 25.46	0.382
Energy Intake (kJ/day) n=95	8877 ± 2022	-237 ± 1639	25 ± 1737	255	-380, 891	0.431
Males n=41	10270 ± 1894	107 ± 1807	-11 ± 1646	-166	-1078, 745	0.720
Females n=54	7810 ± 1376*	-502 ± 1478	52 ± 1832	556	-319, 1342	0.213
Gender interaction				707	-570, 1984	0.278
Energy Intake (kJ/day/kgBW)	106.5 ± 31.3	-2.69 ± 21.02	0.78 ± 20.63	3.46	-4.50, 11.43	0.394
Males n=41	116.7 ± 33.9	1.66 ± 20.03	1.80 ± 19.06	-0.03	-11.14, 11.07	0.995
Females n=54	98.7 ± 27.1*	-6.31 ± 21.56	0.01 ± 22.04	6.40	-4.89, 17.69	0.266
Gender interaction				6.42	-9.66, 22.50	0.434
Total fat (g/day) n=95	80.9± 26.1	-3.03 ± 20.64	1.13 ± 22.86	4.16	-4.27, 12.59	0.334
Males n=41	91.8 ± 30.8	-1.41 ± 22.95	-2.42 ± 16.86	-1.28	-11.97, 9.41	0.815
Females n=54	72.7 ± 18.4*	-4.28 ± 19.06	3.79 ± 26.48	8.09	-4.28, 20.45	0.200
Gender interaction				9.27	-7.66, 26.20	0.285
Total fat (g/day/kgBW)	0.97 ± 0.37	-0.03 ± 0.26	0.01 ± 0.28	0.45	-0.06, 0.15	0.417
Males n=41	1.05 ± 0.46	-0.001 ± 0.26	-0.11 ± 0.20	-0.12	-0.14, 0.14	0.849
Females n=54	0.91 ± 0.29	-0.06 ± 0.27	0.03 ± 0.33	0.09	-0.08, 0.25	0.293
Gender interaction				0.10	-0.12, 0.32	0.368

Data is mean ± SD. SLIM: satiety labelled intensity magnitude. [#]Coefficient showing change in outcome as a result of treatment with prednisolone. [^]Confidence interval for coefficient. *Difference between males and females at baseline. p<0.05.

Table 4. Side effects reported during treatment by gender

Side Effect	Males		P [#]	Females		P [^]
	Placebo (n=21)	Prednisolone (n=28)		Placebo (n=23)	Prednisolone (n=28)	
Mood change n(%)	3 (14)	8 (29)	0.236	9 (39)	13 (46)	0.601
Increased appetite n(%)	3 (14)	13 (46)	0.018	5 (22)	14 (50)	0.035
Decreased appetite n(%)	0	1 (4)	0.382	4 (17)	9 (32)*	0.229
Reflux n(%)	7 (33)	12 (43)	0.498	4 (17)	12 (43)	0.051
Sleep disturbance n(%)	5 (24)	19 (68)	0.002	10 (44)	21 (75)	0.022
Fluid retention n(%)	1 (5)	1 (4)	0.835	0	2 (7)	0.191
Nausea n(%)	3 (14)	2 (7)	0.414	3 (13)	7 (25)	0.285
Vomiting n(%)	1 (5)	0	0.243	0	2 (7)	0.191
Diarrhoea n(%)	1 (5)	4 (14)	0.276	3 (13)	7 (25)	0.285
Constipation n(%)	2 (10)	5 (18)	0.409	2 (9)	9 (32)	0.043
Bloating n(%)	2 (10)	5 (18)	0.409	3 (13)	9 (32)	0.110
Muscle weakness n(%)	0	0		1 (4)	7 (25)*	0.044
Increased energy n(%)	2 (10)	7 (25)	0.116	5 (22)	6 (21)	0.979
Decreased energy n(%)	1 (5)	0	0.243	1 (4)	5 (18)*	0.136
Frequent urinating n(%)	3 (14)	12 (43)	0.032	3 (13)	12 (43)	0.020
Excess thirst n(%)	0	2 (7)	0.211	5 (22)	8 (29)*	0.578
Dry mouth n(%)	4 (19)	3 (11)	0.409	11 (48)	14 (50)*	0.877

[#]Difference in the number of males reporting side effect between prednisolone and placebo treatment.

[^]Difference in the number of females reporting side effect between prednisolone and placebo treatment. *P<0.05 indicating difference in the number of males and females reporting side effect during prednisolone treatment