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Resistin is a predictor of asthma risk and resistin: adiponectin ratio is a negative predictor of lung function in asthma

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ABSTRACT

Background: Adipokines, such as resistin and adiponectin, modify inflammation and may contribute to increased asthma risk and severity in obese people.

Objective: To examine plasma resistin and resistin: adiponectin ratio: (1) in asthmatics compared to healthy controls, (2) according to asthma severity, obesity and gender (3) following weight loss in obese asthmatics.

Methods: In a cross-sectional observational study of asthmatic adults (n=96) and healthy controls (n=46), plasma resistin and adiponectin were measured. In a separate intervention study, obese asthmatic adults (n=27) completed a 10-week weight-loss intervention and plasma resistin and adiponectin concentrations were analysed.

Results: Plasma resistin and resistin: adiponectin ratio were higher in asthma compared to controls and were higher again in subjects with a severe versus mild to moderate asthma pattern. Amongst asthmatic subjects, resistin was not modified by gender or obesity, while adiponectin was lower in males and obese subjects. As a result, resistin: adiponectin ratio was higher in obese males, non-obese males and obese females, compared to non-obese females. In a logistic regression model, plasma resistin concentration was a predictor of asthma risk. In a multiple linear regression model, plasma resistin: adiponectin ratio was a negative predictor of FEV₁ in asthma. Following weight loss, neither resistin, adiponectin nor resistin: adiponectin ratio were changed. However, the change (Δ) in %body fat was associated with Δ resistin: adiponectin ratio. Post intervention Δ resistin was negatively correlated with both Δ FRC and Δ RV.

Conclusion and clinical relevance: This study demonstrates that resistin and resistin: adiponectin ratio are higher in asthma and are higher again in subjects who have more severe disease. Resistin: adiponectin ratio is highest in obese male asthmatics. As resistin is a predictor of asthma risk and resistin:adiponectin is a predictor of FEV₁ in asthma, these adipokines may be contributing to the obese-asthma phenotype, thus providing a potential therapeutic target for obese asthma.

INTRODUCTION

Both obesity and asthma have increased in prevalence in recent decades. Cross-sectional studies suggest that obesity and asthma are associated, as the risk of asthma is higher in individuals who are overweight or obese (1-4). Obesity appears causally associated with asthma, as prospective studies demonstrate that obesity precedes asthma development and that weight gain is associated with onset of asthma (1, 2). Some studies suggest that this association is specific to women (1, 5). Obese asthmatics have worse severity of asthma symptoms and lung function and reduced response to asthma medications, such as inhaled corticosteroids (ICS) (6-9). The mechanisms linking obesity and asthma are unclear; both mechanical and inflammatory causes have been proposed.

Asthma is a chronic inflammatory airways disease characterised by recurrent episodes of wheezing, breathlessness, coughing, reversible or variable airway narrowing and hyperresponsiveness (10). Airway inflammation in asthma is heterogeneous and both T-helper type 2 (Th2) mediated eosinophilic inflammation and neutrophilic inflammation have been described (11). Some studies have shown that obese asthma involves airway neutrophilia; a relationship that appears to be stronger in females (12). Obese asthma is also

characterized by systemic inflammation, with higher levels of interleukin 6 (IL-6) and C-reactive protein (CRP) (13).

Adipokines have been proposed to provide a mechanistic link between obesity and asthma (14). Obesity is a chronic low-grade systemic inflammatory disorder, associated with an increased number of macrophages infiltrated in adipose tissue. Adipocytes and macrophages secrete biologically active cytokines, including IL-6 and tumor necrosis factor α (TNF- α), and adipokines, such as resistin, adiponectin and leptin, which are released into the circulation exerting systemic effects (14). While there is a substantial body of literature describing leptin and adiponectin levels in asthma, there is a paucity of data describing resistin and its relationship to clinical asthma markers. Resistin belongs to the family of resistin-like molecules (RELMs), also known as the FIZZ family (found in inflammatory zones). Resistin has pro-inflammatory effects involving activation of the NF- κ B pathway (15). Conversely adiponectin, an adipocyte-specific insulin sensitising hormone, has potent anti-inflammatory properties (5, 16) and interestingly, has been shown to inhibit the effects of resistin (17). It is likely that both the concentrations of resistin and the balance between resistin and adiponectin are important in asthma pathology (18). With receptors to these adipokines extensively dispersed throughout the body, including the lungs, they may be a contributing factor underlying the obese asthma phenotype (5).

As obesity worsens asthma outcomes, weight loss may be able to reverse this, potentially via modulation of adipokine levels (19). Several studies have shown that weight loss improves asthma symptoms, lung function and quality of life, and reduces inhaled corticosteroid use (20-23). Our recent study demonstrated that as well as improving asthma control and quality of life, weight loss reduced plasma leptin levels in obese asthmatics (19). Here we

hypothesised that plasma resistin and resistin: adiponectin ratio would be higher in adults with asthma, and would be higher again due to disease severity, obesity and female gender. We also hypothesised that weight loss would reduce plasma resistin and resistin: adiponectin ratio in obese asthma. The aims of this study were to examine plasma resistin and resistin: adiponectin ratio: (1) in asthmatics compared to healthy controls, (2) according to asthma severity, obesity and gender (3) following weight loss in obese asthmatics.

MATERIALS AND METHODS

Subjects

Cross-sectional study

Participants were non-smoking adults with or without asthma, a subset of whom have previously been described (12). Asthma was defined by doctor's diagnosis of asthma and documented history of airway hyperresponsiveness, demonstrated by a fall in FEV₁ of 15% compared to baseline, in response to hypertonic (4.5%) saline solution. Asthma pattern was classified according to the Global Initiative for Asthma (GINA) guidelines, which categorises subjects as mild, moderate or severe persistent asthma, according to their frequency of symptoms, nature of exacerbations, nocturnal symptoms and lung function when stable (24). All subjects with asthma were stable, defined as no change in asthma medication use, no unscheduled doctor or emergency visits due to asthma and no respiratory tract infection or oral corticosteroids used 4 weeks prior. All subjects underwent spirometry, hypertonic (4.5%) saline challenge, blood collection and had an allergy skin prick test to assess atopy. Subjects with asthma completed the Juniper Asthma Control Questionnaire (ACQ) (25). Body weight was measured using calibrated electronic scales (Nuweigh EB8271; Newcastle Weighing Services, Wickham, Australia) measuring in 0.1kg increments. Height was measured to the

nearest millimeter using a wall-mounted stadiometer (Seca 220; Seca, Hamburg, Germany).

This research was approved by the Hunter New England Human Research Ethics Committee (approval no: 05/03/09/3.09). All subjects provided written informed consent.

Weight loss in asthma study

Participants (n=27) were overweight and obese (BMI 28-40 kg/m²) non-smoking adults with asthma who were randomised to complete a 10-week dietary restriction intervention or combined dietary restriction and exercise intervention at the John Hunter Hospital, NSW, Australia, as previously described (19). Asthma was defined by doctor's diagnosis of asthma and documented history of airway hyperresponsiveness, demonstrated by a fall in FEV1 of 15% compared to baseline, in response to hypertonic (4.5%) saline solution. All subjects were stable at baseline, defined as above. All subjects underwent spirometry, hypertonic (4.5%) saline challenge, blood collection and had an allergy skin prick test to assess atopy. Height, weight (Nuweigh LOG 842; NWS, Newcastle, NSW, Australia) and waist circumference were measured. ACQ was used to evaluate asthma control (25), while the Juniper Asthma Quality of Life Questionnaire (AQLQ) was used to assess asthma-related quality of life (26). Ethics approval for this research was provided by the Hunter New England Human Research Ethics Committee (approval number 09/03/18/5.05) and written informed consent was obtained from all subjects. The trial was registered with the Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/>), Registration Number: ACTRN12611000235909. The results of the primary analysis of this study have previously been reported (19).

Subjects were prescribed a dietary intake of 3700-4900 kJ/day (885-1170 kcal/day), including meal replacements for two meals per day (Optifast® Very Low Calorie Diet

(VLCD™); Nestle Nutrition, Notting Hill, Victoria, Australia; and/or KieStart™ VLCD; Prima Health Solutions, Frenchs Forest, NSW, Australia) and one main meal and snacks (900-1200 kJ) daily of their own choice. Subjects participated in weekly counselling with a dietitian, alternating between face-to-face and telephone consultations. A subset of study subjects (n=12) were also prescribed an exercise intervention. Subjects attended gymnasium sessions at least three times per week, which consisted of 1 hour sessions of aerobic physical activity and resistance training and included a group personal training session each week. Subjects wore a pedometer daily with the goal to increase daily steps by 10% each week to a target number of 10,000 steps per day.

Lung function testing

Lung function was measured according to American Thoracic Society and European Respiratory Society criteria (27, 28). Forced expiratory volume in one-second (FEV₁) and forced vital capacity (FVC) were measured using a Koko Spirometer [POS instrumentation, Inc, Louisville, KY, USA). Percentage of predicted values for FEV₁ and FVC were calculated using NHANES3 reference data and prediction equations from Hankinson et al (29).

In the weight loss study, total lung capacity (TLC), functional residual capacity (FRC), expiratory reserve volume (ERV) and residual volume (RV) were also measured via the volume body plethysmographic method (Vmax Encore; Sensormedics Corp., Yorba Linda, CA, USA). Predictions of normal values were obtained for all measures.

Hypertonic saline challenge

Bronchial provocation with hypertonic saline (4.5%) was performed as described previously (34). Following baseline spirometry, hypertonic saline was administered via an ultrasonic nebuliser (ULTRA-NEBe Model 2000; De Vilbiss Healthcare Inc., Somerset, PA, USA) with a Hans Rudolph two-way valve (Hans Rudolph Inc., Shawnee, KS, USA). If FEV₁ decreased by 15% from baseline, subjects were considered to have airway hyperresponsiveness (AHR). The response of subjects to hypertonic saline was described by the provocation dose required to induce a 15% fall in FEV₁ from baseline (known as PD₁₅), or the dose–response slope (DRS) which is calculated by dividing the percentage fall in FEV₁ from baseline by the amount of hypertonic saline inhaled (ml).

Serum inflammatory markers:

Venous blood was collected after a 12 hour overnight fast and centrifuged at 4°C for 10 minutes at 3000 g. Plasma and serum were separated and stored at -80°C until analysis. Commercial enzyme-linked immunosorbant assays (ELISA) were used to determine fasting plasma resistin (R&D Systems, Minneapolis, MN, USA) and adiponectin concentrations (Bio-Rad, Hercules, CA, USA).

Statistical analysis

Statistical analyses were performed using Graphpad Prism 6 (Graphpad Software Inc, La Jolla, CA, USA) and Intercooled Stata version 11.1 (Stata Corporation, College Station, TX, USA) with data reported as mean $\pm$ standard error of the mean (SEM) or median (interquartile range, IQR).

Cross-sectional study

Group comparisons of continuous outcomes were carried out using either student's unpaired t-test or one-way analysis of variance (ANOVA) with post hoc Tukey's multiple comparison test (parametric data) or the Mann Whitney or Kruskal–Wallis test with post hoc Dunn's multiple comparison test (non-parametric data). Group comparisons of categorical outcomes (proportions) were performed using Pearson's Chi Squared test. Adipokine data were normalized by log transformation, then evaluated by two-way ANOVA in subjects with asthma to test for interactions between obesity and gender. When comparing outcomes according to clinical asthma pattern, we observed no difference between the mild and moderate asthmatics for any of the biomarkers. Hence we combined these groups, which increased the power of the analysis to detect differences between the mild/moderate and severe persistent asthma groups. Associations between log transformed adipokine data, systemic inflammatory markers, BMI and lung function indices were examined in subjects with asthma using Pearson's correlation coefficient. Logistic regression analysis was used to determine the predictors of asthma risk. Multiple regression analysis was used to determine predictors of %predicted FEV₁; variables that were significantly associated with %FEV₁ in univariate analysis were included in the model. A *p*-value of ≤ 0.05 was considered to be statistically significant.

Weight-loss in Asthma study

Analysis of the primary weight loss study (19) revealed similar weight loss was achieved via the diet alone and diet combined with exercise groups (-8.4 ± 4.4 kg and -8.2 ± 5.1 kg respectively). Furthermore, there were no differences in lung function (including %FEV₁, %FVC, %ERV) or inflammatory mediators between groups. Hence, the groups were combined for further analysis. Wilcoxon signed rank tests or paired t-tests were used to

analyse change before and after the intervention. Associations between adipokines, body composition and lung function were analysed using the Spearman rank test.

RESULTS

Cross-sectional study

Characteristics of the 142 subjects are presented in Table 1. There were no significant differences among the asthmatic and control groups with respect to age or gender. Asthmatic subjects had lower lung function, a higher rate of atopy and higher BMI. Resistin concentrations and resistin: adiponectin ratio were higher in asthma compared with control subjects (Table 1). Subjects with a severe persistent asthma pattern had higher levels of resistin and resistin: adiponectin ratio compared to those with a mild to moderate asthma pattern (Figure 1).

Amongst subjects with asthma, resistin was not different between obese and non-obese males and females (Figure 2a). Using 2 way ANOVA, resistin levels were not higher in obese subjects or according to gender. Adiponectin levels were higher in non-obese females compared to obese males and non-obese males. Adiponectin levels were also higher in obese females compared to obese males (Figure 2b). Using 2 way ANOVA, adiponectin was significantly lower in obese subjects ($p=0.005$) and males ($p<0.001$). Resistin: adiponectin ratio was higher in obese females, non-obese males and obese males compared to non-obese females and higher in obese males compared to obese females (Figure 2c). Using 2 way ANOVA, resistin: adiponectin ratio was higher in obese subjects ($p=0.004$) and males ($p<0.001$). There were no interactions between obesity and gender for resistin, adiponectin and resistin: adiponectin.

Using correlation analysis, we identified weak associations between BMI and log resistin ($r=0.175$, $p=0.037$), log adiponectin ($r=-0.304$, $p=0.001$) and log (resistin: adiponectin) ($r=0.327$, $p<0.001$) (Figure 3). We also observed a weak correlation between log resistin and %FVC ($r=-0.167$, $p=0.047$). In a logistic regression model, log resistin was a predictor of asthma after adjusting for BMI, age and sex (Table 2a); a one unit increase in log resistin increased the odds of asthma by 9.97 (odds ratio: 9.97, 95% confidence interval: 1.61-61.59, $p=0.010$). In a multiple regression model, log resistin: adiponectin ratio was a negative predictor of %predicted FEV1 (β -coefficient = -9.57, $p=0.049$) after adjusting for smoking, sputum neutrophils and eosinophils (Table 2b).

Weight loss intervention

Baseline demographics including age, gender, body composition, %predicted lung function, and asthma severity are reported in Table 3. Following the weight loss intervention, neither resistin, adiponectin or resistin: adiponectin ratio were changed (Table 4). However, the change (Δ) in %body fat following the intervention was positively associated with Δ resistin: adiponectin ratio ($r=0.479$, $p=0.024$). Post intervention Δ resistin was negatively correlated with both Δ FRC ($r = -0.536$, $p=0.005$) and Δ RV ($r=-0.459$, $p=0.018$). Furthermore, Δ adiponectin showed significant correlation with Δ FEV₁/FVC ($r = 0.467$, $p=0.019$) and Δ dose response slope (DRS) ($r= -0.546$, $p=0.009$).

DISCUSSION

In this study we have shown that resistin concentrations and resistin: adiponectin ratio were higher in asthma compared to healthy controls. In asthmatics with a severe asthma pattern these levels were higher again. Within the asthmatic group, resistin concentrations were not different according to gender or the presence of obesity. In contrast, adiponectin

concentrations were lower in asthmatic subjects who were obese or male. As a result, amongst the asthmatic subjects, obese males had the highest resistin: adiponectin ratio, while non-obese females had the lowest resistin: adiponectin ratio. In a logistic regression model, resistin was a predictor of asthma risk, while in a multiple regression analysis, resistin:adiponectin ratio was a negative predictor of %FEV₁ in asthma. In our pilot weight loss study, neither resistin, adiponectin nor resistin: adiponectin ratio were changed. However, Δ %body fat was positively associated with Δ resistin: adiponectin ratio. Furthermore, Δ resistin after weight loss was negatively correlated with some markers of lung function (Δ FRC and Δ RV).

Our interest in adipokines in obese asthma stems from the fact that they are released by adipose tissue and receptors for leptin, adiponectin and resistin have all been identified in the lung. Hence we hypothesise that they may contribute to the obesity-asthma association. We, and others, have previously described levels of leptin in obese asthma (12) and following weight loss in obese asthma (19). In contrast, there are very few studies available to date examining resistin levels in obese asthma. Resistin is produced by adipocytes and macrophages and has been associated with inflammation (15, 30). For example, macrophages exposed to resistin *in vitro* have increased inflammatory cytokine production (TNF α and IL-12) (15) and *in vitro* exposure of macrophages to lipopolysaccharide induces increased resistin mRNA expression (30). In human studies, plasma resistin concentrations have been associated with circulating pro-inflammatory mediators, including CRP (31). Adiponectin is primarily considered to be anti-inflammatory due to its dual role in inhibiting the effects of pro-inflammatory cytokines (eg TNF α and IL-6) and inducing expression of anti-inflammatory cytokines (eg IL-10 and IL1RA)(18). In addition, a direct interaction between resistin and adiponectin has been previously observed, with adiponectin inhibiting resistin-

induced smooth muscle proliferation (17). Hence, in this study we were interested in both resistin concentrations and the balance between resistin and adiponectin levels (18).

In this study, we observed higher levels of resistin and resistin: adiponectin in asthma and this was exaggerated in those with more severe disease. Regression analysis also revealed that higher resistin concentrations were a predictor of asthma risk and that higher resistin: adiponectin ratio was a negative predictor of %FEV₁ in asthma. While there are few studies available examining the relationship between resistin and the lungs, evidence from murine models has suggested that resistin or RELMs induce effects in the airways that could contribute to asthma pathology. For example, RELM β administration caused a dose-dependent inflammatory response, with increased accumulation of macrophages in the airways of allergic mice (32). This study also reported that RELM β administration caused an increase in collagen deposition associated with increased fibroblast motility, highlighting a role for RELM β in airway remodeling (32). Human data describing the role of resistin or RELMs in asthma are also scarce. Our result is in agreement with studies conducted by Al Mutairi *et al.* and LaRochelle *et al.* (33, 34), which also found significantly higher plasma levels of resistin in asthmatic adults compared with healthy controls, higher resistin levels in subjects with acute asthma (33) and more severe disease (34) and an inverse correlation between plasma resistin and %FEV₁ and FEV₁/FVC (33). In contrast, one study in children found that atopic asthmatics had lower levels of resistin than non-atopic asthmatics and controls, possibly due to different biological effects of resistin in children compared to adults (35). Fang *et al* demonstrated that RELM β was overexpressed in the bronchial mucosa of asthmatics and correlated with impaired lung function and airway epithelial mucin production (36). Furthermore, in human epithelial cells, RELM β induced increased proliferation, mucin and growth factor production, suggesting a potential contribution to airway remodelling (36).

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Finally, in another human study RELM β expression was higher in asthmatics, higher again in more severe asthma and correlated negatively with lung function. In addition, RELM β expression within the epithelium increased following inhaled allergen or methacholine challenge and the increase correlated with an increase in airway thickening (37). As airway thickening has previously been shown to relate to lung function (38), we hypothesise that airway remodelling may be contributing to the association between resistin and resistin: adiponectin and lung function and asthma risk that we observed in our study.

The ability of circulating adipokines to modify lung health is plausible, as the involvement of systemic pro-inflammatory mediators in asthma pathology has previously been demonstrated. High plasma IL-6 concentrations have been associated with worse lung function and asthma control (13), and circulating TNF α (39) and IL-6 (40) levels have been shown to be elevated during asthma exacerbation. In addition, plasma CRP has been shown to be higher in non-allergic (41) and steroid-naïve asthmatics (42), and correlated with lung function and airway inflammatory cell counts (42). In murine models, leptin, another pro-inflammatory adipokine has been shown to augment airway inflammation (43, 44) and enhance airway hyperresponsiveness (45).

Interestingly, in our study, we did not detect a difference in resistin levels according to gender. This contrasts with other adipokines, as both leptin (46) and adiponectin (47) concentrations are lower in men compared to women, at least partly due to differences in testosterone levels and body fat distribution (18). Our data also show that in asthma, adiponectin levels were lower in males, as well as obese subjects. As a result, the resistin: adiponectin ratio was highest in obese males and lowest in non-obese female asthmatics. The functional consequence of this is uncertain, particularly in light of reports that serum

adipokines have differential effects in men and women with asthma (48). However, the association that we observed between resistin and asthma risk, as well as resistin: adiponectin ratio and FEV1 suggests that resistin and adiponectin may be clinically important and this warrants further investigation.

This is the first study, to our knowledge, to examine the effects of weight loss on resistin levels in asthmatic subjects. We did not observe any changes in resistin or resistin: adiponectin ratio with weight loss, which likely reflects our observation that resistin is only weakly associated with BMI. Weight loss in asthmatics has previously been shown to lead to a reduction in leptin, by us (19) and others (49), in studies of similar sample size. Thus, it appears that leptin concentrations are more sensitive to weight change than resistin and a greater degree of weight loss, or a larger sample size, may be required to detect a significant reduction in resistin levels. Nonetheless, strategies for achieving this need to be explored, considering the role of resistin and resistin: adiponectin as predictors of asthma risk and negative predictors of lung function, respectively.

A limitation of the first analysis in this paper is that the study was cross-sectional in design, which is able to detect associations but cannot prove causality. Furthermore, in each of our analyses, there is significant overlap in data collected from the clinical groups of interest, such as BMI category and gender. This is reflective of the heterogeneity of individuals and highlights the complexity of understanding the obese-asthma phenotype. The analysis of samples from our previously conducted weight loss study (19) was included to confirm the findings of the cross-sectional study. However, it appears that the relatively small size did not provide enough power to detect changes in adipokine levels in these subjects. Nonetheless, we did observe some significant associations between change in fat mass, adipokine levels

and lung function in the weight loss intervention, which need to be confirmed in future studies.

In conclusion, this study has demonstrated that asthma is associated with higher levels of resistin and resistin: adiponectin ratio, and that these biomarkers are higher again in asthmatics who have more severe disease. Furthermore, resistin: adiponectin ratio is higher in obese male asthmatics. As resistin was a predictor of asthma risk and resistin: adiponectin was a negative predictor of %FEV₁ in asthma, our data suggest resistin may be contributing to the obese-asthma phenotype, thus providing a potential therapeutic target for the management of obese asthma. The correlation between reduction in body fat mass and reduction in resistin: adiponectin ratio also reinforces the potential for weight loss to improve clinical outcomes in obese asthma.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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Table 1: Subject characteristics and systemic inflammation

	Asthma	Healthy controls	p-value
Subjects, n	96	46	
Age, yrs	49.5 ± 1.6	50.2 ± 2.7	0.118
BMI, kg/m ²	30.8 ± 0.7	27.2 ± 0.7	0.001
Females, %	65.6	71.7	0.317
FEV ₁ %, predicted	83.7 ± 1.9	102.3 ± 2.2	<0.001
FVC%, predicted	97.0 ± 1.6	108.1 ± 2.0	<0.001
FEV ₁ /FVC, %	70.4 ± 1.0	77.6 ± 0.9	<0.001
Atopy, %	61.3	41.3	<0.001
ICS dose [#] , µg/day	500 (0 – 1000)	NA	NA
ACQ Score, units	0.9 (0.4 – 1.4)	NA	NA
GINA pattern, %Intermittent/ Mild/ Moderate/ Persistent	31/15/38/16	NA	NA
PD ₁₅ [¶] , mL	0.62 ± 0.70	NA	NA
Resistin, ng/mL	7.2 (4.8-9.6)	4.8 (3.7-7.3)	0.005
Adiponectin, µg/mL	4.86 (2.33-7.93)	4.45 (3.05-7.69)	0.669
Resistin: Adiponectin (x10 ⁻³)	3.04 ± 0.58	1.55 ± 0.23	0.019

Data are presented as median (quartile 1 – quartile 3) or mean ± SEM, unless stated. FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity; BMI: body mass index; ICS: inhaled corticosteroid; ACQ: Asthma Control Questionnaire; GINA: Global Initiative for Asthma; PD₁₅: provocation dose of 4.5% hypertonic saline required to induce a drop in FEV₁ of 15% from baseline; NA: not available; [#]beclomethasone equivalents; [¶]presented as geometric mean ± log SD.

Table 2a: Logistic regression model describing plasma resistin as a predictor of asthma (n=142)

Outcome		Asthma		
Overall Model		r ² = 0.099		
		p = 0.001		
Predictors	Coefficient	SE	p-value	Odds ratio (95% CI)
	Coefficient			
Log Resistin (ng/mL)	2.299	0.929	0.010	9.97 (1.61, 61.59)
BMI (kg/m ²)	0.093	0.035	0.005	1.10 (1.03, 1.17)
Age (years)	-0.006	0.012	0.604	0.99 (0.97, 1.02)
Sex (female=0)	0.127	0.422	0.762	1.14 (0.50, 2.60)

BMI: body mass index

Table 2b: Multiple linear regression model describing resistin: adiponectin ratio as a predictor of lung function in asthma (n=96)

Outcome	%predicted FEV ₁ *		
Overall Model	r² = 0.149		
	p = 0.049		
Predictors	Coefficient	SE Coefficient	p-value
Log Resistin: Adiponectin (x10 ⁻³)	-9.57 (0.049)	11.30	-9.57 (0.049)
Smoking history (Never=0/ Ex=1)	-2.44 (0.591)	4.50	-2.44 (0.591)
Log Sputum Neutrophils (x10 ⁶ /mL)	-4.79 (0.281)	4.40	-4.79 (0.281)
Log Sputum Eosinophils (x10 ⁶ /mL)	-4.46 (0.253)	3.86	-4.46 (0.253)

FEV₁: forced expiratory volume in 1 second. *Data are expressed as the percentage of the expected value for age, sex and height.

Table 3: Weight loss study: Subject baseline characteristics

	Subjects (n = 27)
Age, yrs	40.38 ± 2.7
Females, %	51.9
BMI, kg/m ²	33.74 ± 0.7
Atopy %	88.9
ICS dose, ug/day [#]	759.3 ± 131.7
Ever smokers, %	33.3
Pack years of ever smokers	8 (1 – 11.5)
Age at asthma diagnosis, years	8 (3 – 18)
GINA classification, % (Intermittent/Mild/Moderate/Severe)	18.5/26/37/18.5
FEV1, %predicted	79.3 ± 3.5
FVC, %predicted	92.7 ± 2.8
FEV1/ FVC, %	68.9 ± 2.0
Dose-response slope (DRS) (%/mL)	1.93 (0.89 – 3.59)
ACQ Score	1.29 ± 0.12

Data are presented as mean ± SEM, median (quartile 1 – quartile 3) or % the percentage of subjects with the specified variable. BMI: body mass index; ICS: inhaled corticosteroid; GINA: global initiative for asthma; Mild: mild persistent; Moderate: moderate persistent; Severe: severe persistent; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; ACQ: Asthma Control Questionnaire; #: beclamethasone equivalents.

Table 4: Change in systemic inflammatory mediators following weight loss

	Baseline	Change	p-value
Weight (kg)	99.1 ± 14.5	-8.5 ± 4.7	<0.0001
BMI (kg/m ²)	33.7 ± 3.8	-2.8 ± 1.4	<0.0001
%Body fat	43.5 ± 9.1	-3.9 ± 3.3	<0.0001
Resistin (ng/mL)	6.47 ± 0.57	0.22 ± 0.39	0.918
Adiponectin (µg/mL)	6.03 (4.35 – 11.73)	-0.20 (-0.84 – 0.54)	0.345
Resistin: Adiponectin (x10 ⁻³)	0.89 (0.47-1.54)	0.09 (-0.20-0.31)	0.300

Data are presented as median (quartile 1 – quartile 3) or mean ± SEM. BMI: body mass index.

FIGURE LEGENDS

Figure 1: a) Resistin concentration, b) Adiponectin concentration and c) Resistin: Adiponectin ratio in subjects with a persistent asthma pattern; Mild and Moderate Persistent Asthma versus Severe Persistent Asthma, according to GINA classification. Horizontal bars represent median concentrations.

Figure 2: a) Resistin concentration, b) Adiponectin concentration and c) Resistin: Adiponectin ratio, in subjects with asthma, according to gender and presence of obesity. Horizontal bars represent median concentrations. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 3: Correlation between BMI and Log (Resistin:Adiponectin), $r = 0.327$, $p < 0.001$. The line of best fit and the 95% confidence band of the line of best fit are shown.

Figure 1:

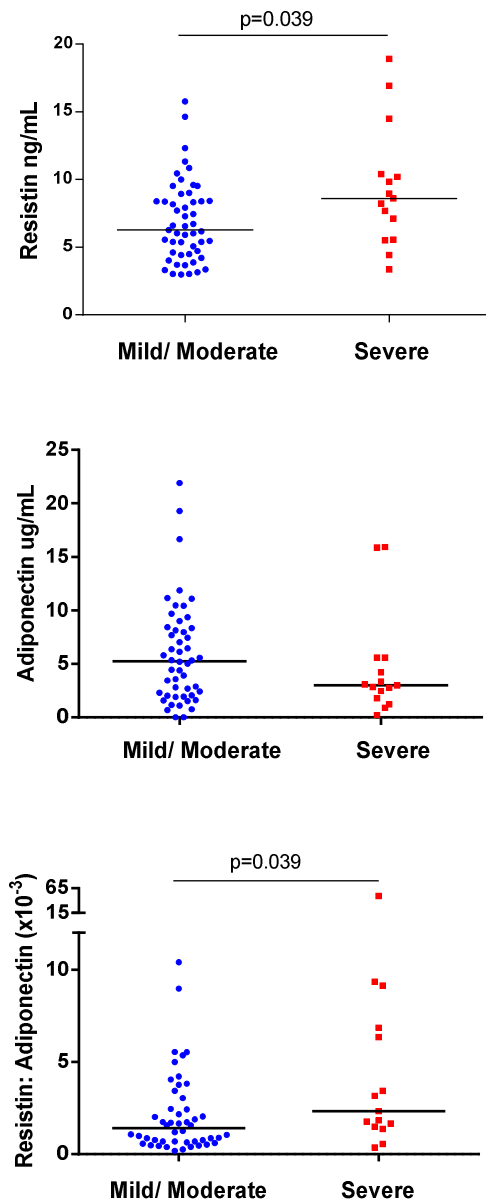


Figure 2:

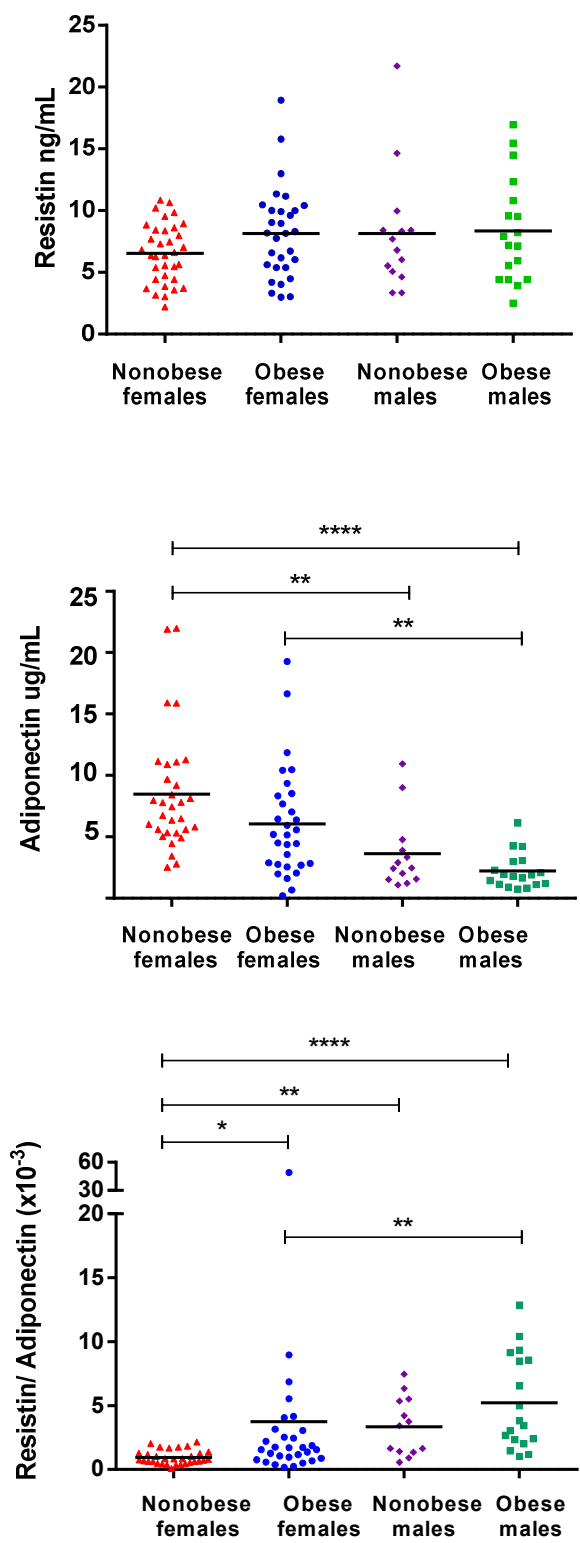


Figure 3:

