
Leptin, adiponectin, and asthma: findings from a population-based cohort study

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Background: Obesity is thought to increase the risk of asthma, especially in women. It has been proposed that this association could be due to the immune-modulating effect of adipokines secreted by adipose tissue.

Objective: To investigate whether aspects of the asthma phenotype are associated with higher levels of the proinflammatory adipokine leptin and lower levels of the anti-inflammatory adipokine adiponectin in a cross-sectional analysis of a group of young adults.

Methods: Associations between leptin and adiponectin and a diagnosis of asthma, symptoms of wheeze, bronchodilator response, airflow obstruction, and exhaled nitric oxide were evaluated by logistic or linear regression in a population-based birth cohort of approximately 1,000 men and women aged 32 years. Further analyses adjusted for smoking and body fat.

Results: There were no significant associations between leptin and any of the markers of the asthma phenotype in either men or women. In men, higher levels of adiponectin were associated with lower levels of exhaled nitric oxide but an increased risk of bronchodilator responsiveness. The inverse association with exhaled nitric oxide remained significant after adjustment for body fat, but the association with bronchodilator responsiveness did not. Adiponectin levels were not associated with any markers of asthma in women.

Conclusions: The inverse association between adiponectin and exhaled nitric oxide in men warrants further investigation. However, the findings indicate that levels of leptin and adiponectin are unlikely to mediate the previously observed association between obesity and asthma.

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INTRODUCTION

There is increasing evidence to support an association between obesity and asthma, but the mechanisms for this have yet to be elucidated.^{1,2} Adipose tissue is now known to be an active metabolic tissue that secretes the adipokines leptin and adiponectin, as well as a number of nonspecific inflammatory cytokines, such as interleukin 6 and tumor necrosis factor α .³ A number of researchers have suggested that the link between obesity and asthma could be explained by the immunomodulation of these adipokines,^{1,4,5} although there is currently little empirical evidence to support this.

The proinflammatory adipokine leptin has been shown to have an intricate role in energy metabolism and neuroendocrine function, depending on nutritional status and energy

storage.⁶ Leptin synthesis is regulated by a number of different mechanisms, including insulin secretion, glucocorticoids, and the process of lipogenesis,⁶ and is secreted in a circadian rhythm, with the lowest levels at around 8 AM.⁷ Leptin is increased in obesity,⁸ and there are some reports of a positive association with asthma, although these are not consistent. In children, leptin was higher in asthmatic compared with non-asthmatic boys, even after adjusting for body mass index (BMI), but there was no association in girls.⁹ In contrast, the Third National Health and Nutritional Examination Survey found an association between leptin and asthma in women, independently of obesity, but not in men.¹⁰ Leptin has also been demonstrated to be inversely associated with the forced expiratory volume in 1 second (FEV₁) in BMI-matched groups of both sexes¹¹ and in a mouse model of asthma; the administration of exogenous leptin has been shown to augment the airway response to methacholine and increase serum IgE levels after exposure to ovalbumin.¹²

Adiponectin is the most abundant protein specific to adipose tissue and is reduced in patients with type 2 diabetes mellitus and the metabolic syndrome.¹³ Like leptin, adiponectin also demonstrates a circadian rhythm, with the lowest levels early in the morning. However, unlike leptin, adiponectin is inversely related to obesity¹⁴ and has been demonstrated to have anti-inflammatory properties.¹⁵ In mouse models of asthma, adiponectin has been shown to reduce the level of T_H2 cytokines and eosinophils in bronchoalveolar lavage fluid and decrease airway responsiveness,¹⁶ which

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would suggest a protective role of adiponectin in the allergic inflammation of the airways. However, there is little evidence in humans to corroborate these experimental findings. One cross-sectional analysis found that women with asthma had lower mean adiponectin levels than those who had never had asthma but that this appeared to add little to the association between BMI and asthma.¹⁷

We have previously reported an association between obesity and asthma in a population-based cohort.^{18,19} In the present study, we explored the cross-sectional associations between leptin and adiponectin and asthma in this cohort at the age of 32 years. Rather than focus on one aspect of the asthma phenotype, as in other investigations, we considered a number of variables, including a diagnosis of asthma, symptoms of wheeze, exhaled nitric oxide as a measure of airway inflammation, FEV₁/forced vital capacity (FVC) ratio as a measure of airway obstruction, and bronchodilator response to β -agonist as a measure of airway variability. We hypothesized that these markers of asthma would be associated with higher levels of leptin and lower levels of adiponectin.

METHODS

The Dunedin Multidisciplinary Health and Development Study is a longitudinal investigation of health and behavior in a population-based birth cohort.^{18,20,21} Study members were born in Dunedin, New Zealand, between April 1972 and March 1973. A total of 1,037 children (91% of eligible births, 52% male) participated in the first follow-up at 3 years, constituting the base sample for the study. The cohort represents the full range of socioeconomic status in New Zealand's South Island and is mostly of New Zealand European ethnicity. Of 1,015 living study members, 972 (96%) participated in the evaluation at the age of 32 years. The study was approved by the Otago Ethics Committee, and written informed consent was obtained from each study member.

Study members answered questions selected from the European Community Respiratory Health Study and American Thoracic Society questionnaires.^{22,23} *Current asthma* was defined as a diagnosis of asthma with episodes of asthma, wheezing, or medication use within the previous year, and *current wheeze* was defined as recurrent episodes of wheezing in the previous year, excluding those with only 1 or 2 episodes lasting less than 1 hour. *Current smoking* was defined as smoking at least 1 cigarette a day for a month in the previous year. Cumulative smoking was updated at each evaluation and is measured in pack-years (20 cigarettes a day for 1 year = 1 pack-year). Women were asked about pregnancy and the number of days from the start of their last menstrual period.

Weight and height were measured in light clothing without shoes to calculate BMI (calculated as weight in kilograms divided by height in meters squared). A body composition analyzer (model BC-418MA; Tanita, Tokyo, Japan) was used to measure percentage body fat by bioelectrical impedance analysis.

Fractional exhaled nitric oxide (FE_{NO}) levels were measured on a chemiluminescence analyzer (Logan LR2000; Logan Research Ltd, Rochester, England), using a flow rate of 50 mL/s.²⁴ Plateau levels were read from the exhalation curves, and the mean of 2 acceptable exhalations was used. Tests on the first 44 study members were performed at a flow of 250 mL/s and converted to 50 mL/s using a locally validated conversion factor.²⁵

Spirometry measurements were performed using a plethysmograph (model 6200; SensorMedics, Yorba Linda, California) before and 15 minutes after the administration of 200 μ g of salbutamol (albuterol) via a metered-dose inhaler and volumetric spacer device (Allen & Hanburys, Stockley Park, Middlesex, United Kingdom). A 10% increase in FEV₁ over baseline was considered a significant bronchodilator response. A portable spirometer (Spiropro; SensorMedics) was used for study members ($n = 27$) who declined to sit in the plethysmograph or were unable to visit the research unit. Measurements were reviewed by a senior technician to ensure acceptable and reproducible results were entered for analysis.²⁶

Nonfasting blood samples were obtained at the same time of day for each study member, approximately 4 hours after lunch, for measurement of leptin and adiponectin by radioimmunoassay (Linco Research, St Charles, Missouri).

Leptin, adiponectin, and FE_{NO} were log-transformed to approximate normal distributions. Differences in log leptin and log adiponectin levels between men and women and between smokers and nonsmokers were analyzed with t tests.

Associations between asthma diagnosis, wheeze, bronchodilator responsiveness, log FE_{NO}, and prebronchodilator FEV₁/FVC ratio were analyzed by logistic or linear regression using either log leptin or log adiponectin as the independent variables. These analyses adjusted for sex and further analyzed the sexes separately because there were several significant sex by adipokine interactions. Because of the potential confounding effect of smoking and adiposity on symptoms of asthma, lung function, and FE_{NO}, analyses were repeated with adjustments for current smoking status and percentage body fat. To investigate possible nonlinear associations, analyses were also repeated with quadratic terms for log leptin and log adiponectin.

Pregnant women ($n = 31$) were excluded from the analyses to avoid the potential influence of adipokine changes associated with pregnancy. Analyses were performed using Stata 9.1 (Stata Corp, College Station, Texas).

RESULTS

The prevalence of current asthma and current wheeze, the presence of a significant bronchodilator response, and the mean FEV₁/FVC ratio and level of exhaled nitric oxide are presented in Table 1.

Leptin

Leptin values were available for 858 nonpregnant study members. Geometric mean leptin levels were higher in

Table 1. Markers of Asthma in Men and Women

Variables	Women	Men
Current asthma ^a	64/407 (15.7)	87/454 (19.2)
Current wheeze ^a	109/407 (26.8)	133/454 (29.3)
Bronchodilator response ^a	24/397 (6.1)	57/444 (12.8)
FEV ₁ /FVC ratio, % ^{b,c}	79.7 (79.1 to 80.3)	76.8 (76.2 to 77.4)
Exhaled nitric oxide, ppb ^{b,d,e}	11.7 (11.0 to 12.5)	15.3 (14.3 to 16.4)

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

^a Data are given as number/total (percentage).

^b Data are given as mean (95% confidence interval).

^c n=404 for women, and n=452 for men.

^d n=396 for women, and n=445 for men.

^e Data are given as geometric means (95% confidence interval).

women than in men. Leptin tended to be lower in smokers, but this was only statistically significant among men (Table 2). Leptin levels were higher in overweight and obese men and women, and were strongly correlated with body fat percentage (Table 3). There were no significant associations between leptin levels and a diagnosis of current asthma, current wheeze, bronchodilator response, FEV₁/FVC ratio, or FE_{NO} in either sex (Table 4). This lack of association persisted after adjustment for smoking and body fat percentage (Table 5). Adjusting for cumulative smoking (pack-years) rather than current smoking made no material difference to the analyses. The quadratic term for log leptin was significant for the bronchodilator response and FEV₁/FVC ratio in men only. On further analysis by leptin quartiles, men with the

lowest leptin levels were more likely to have a significant bronchodilator response and had a lower mean FEV₁/FVC ratio (data not shown).

Adiponectin

Adiponectin results were available for 861 nonpregnant study members. Geometric mean adiponectin levels were higher in women than in men (Table 2). Male smokers had higher adiponectin levels than nonsmokers, but this difference was not seen in females. Adiponectin levels were lower in overweight and obese men and women (Table 2) and were negatively correlated with body fat percentage in both sexes (Table 3). There were no significant associations between adiponectin levels and a diagnosis of current asthma, current wheeze, or FEV₁/FVC ratio in either sex. In men, adiponectin levels were significantly associated with bronchodilator responsiveness and lower levels of exhaled nitric oxide (Table 4). These associations were not found in women. After adjustment for smoking and body fat percentage, the association between bronchodilator response and adiponectin in men was no longer apparent, but the inverse association between FE_{NO} and adiponectin in men remained (Table 5). Adjusting for cumulative smoking (pack-years) rather than current smoking made no material difference to the analyses. The quadratic term for log adiponectin was not significant.

DISCUSSION

In this unselected cohort of young adults, we found no evidence of an association between blood leptin levels and a

Table 2. Mean Leptin and Adiponectin Levels in Men and Women and in Smoking and BMI Subgroups

Variables	Women		Men	
	No. of participants	Geometric mean (95% confidence interval)	No. of participants	Geometric mean (95% confidence interval)
Leptin, $\mu\text{g/L}$ (n = 858)				
All values ^a	404	15.72 (14.78 to 16.71)	454	5.24 (4.93 to 5.57)
Smoker ^a	134	15.12 (13.58 to 16.82)	167	4.40 (3.95 to 4.91)
Nonsmoker	270	16.03 (14.86 to 17.28)	287	5.80 (5.40 to 6.22)
BMI				
<25	218	10.48 (9.81 to 11.20)	187	3.37 (3.12 to 3.63)
≥ 25 but <30	109	20.97 (19.71 to 22.32)	199	5.92 (5.56 to 6.31)
≥ 30	77	32.92 (30.72 to 35.27)	68	12.37 (11.04 to 13.86)
Adiponectin, $\mu\text{g/mL}$ (n = 861)				
All values ^b	407	8.60 (8.21 to 9.00)	454	5.75 (5.48 to 6.03)
Smoker ^b	137	8.37 (7.72 to 9.08)	167	6.18 (5.72 to 6.68)
Nonsmoker	270	8.71 (8.23 to 9.22)	287	5.51 (5.19 to 5.86)
BMI				
<25	220	9.85 (9.32 to 10.41)	187	6.81 (6.37 to 7.28)
≥ 25 but <30	110	7.87 (7.22 to 8.59)	199	5.29 (4.91 to 5.68)
≥ 30	77	6.61 (5.88 to 7.42)	68	4.61 (4.06 to 5.23)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^a The difference in leptin between the sexes was significant ($P < .001$), and the difference between male smokers and nonsmokers was significant ($P < .001$).

^b The difference in adiponectin between the sexes was significant ($P < .001$), and the difference between male smokers and nonsmokers was significant ($P = .02$).

Table 3. Pearson Correlation Coefficients Among Log Leptin, Log Adiponectin, BMI, and Body Fat Percentage in Women and Men^a

Variable	Women			Men		
	Adiponectin	BMI	Body fat percentage	Adiponectin	BMI	Body fat percentage
Leptin	−0.24	0.78	0.86	−0.24	0.73	0.82
Adiponectin		−0.33	−0.32		−0.31	−0.32
BMI			0.89			0.80

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

^a All correlations were statistically significant ($P < .001$).

diagnosis of asthma, symptoms of wheeze, airflow obstruction, bronchodilator responsive, or exhaled nitric oxide in either men or women. Similarly, there were no associations between adiponectin levels and any of these markers of asthma in women. There were also no significant associations between adiponectin levels and asthma, wheeze, or airflow obstruction in men. Although adiponectin levels were associated with a positive bronchodilator response and lower levels of FE_{NO} in men, these associations were in the opposite direction to our hypothesis. Taken together, these data provide little support for the hypothesis that the obesity-asthma association is mediated by the immune effects of these adipokines.

Our data appear to conflict with a large cross-sectional survey indicating an association between asthma and leptin in adult women.¹⁰ This apparent difference may be due to our smaller sample size. There was a trend toward an association between leptin and an asthma diagnosis in women ($P = .08$), and analyzing our data using a similar method as the one used by Sood et al¹⁰ provides an odds ratio of 1.67 (95% confidence interval, 0.8–3.4) for asthma in the highest compared with the lowest quartile of leptin. This is similar to the odds ratio of 1.85 found by Sood et al, and our findings are consistent with an association between leptin and an asthma diagnosis in women of this magnitude. Indeed, leptin was so strongly correlated with percentage body fat (Table 3) that an association between an asthma diagnosis and leptin would be expected because there are known associations between asthma and adiposity in women in this cohort.¹⁹ Of greater interest is the finding that there were no trends to associations between leptin and symptoms of wheeze, airflow obstruction, bronchodilator responsiveness, or airway inflammation (measured by exhaled nitric oxide). Thus, it seems very unlikely that the proinflammatory effects of leptin explain the association between obesity and asthma in women.

There was some evidence of a nonlinear association between lower leptin levels and increased risk of bronchodilator responsiveness and airflow obstruction in men. These findings are in the opposite direction to that which we had hypothesized and reflect those from a previous analysis of this cohort in which thinner men were found to have more bronchodilator responsiveness and lower FEV₁/FVC ratios.¹⁹ They are also consistent with other studies reporting a relationship between extreme thinness and asthma in men.^{27–29}

To our knowledge, this is only the second study to investigate the association between adiponectin and adult asthma in a population-based cohort. Although most of the associations were not significant, higher adiponectin levels were associated with a trend to a lower risk of asthma in women but a significantly higher risk of a bronchodilator response in men. In contrast, there was an inverse association between FE_{NO} and adiponectin in men independently of percentage body fat. On further subgroup analysis, the significant inverse association between adiponectin and FE_{NO} was only significant in nonasthmatic men. It is difficult to be certain of the significance of these findings because the literature on adiponectin and asthma is sparse. Sood et al¹⁷ found lower adiponectin levels in women with a history of asthma, but they found no association in men. Two studies on children found no significant association between adiponectin levels and asthma, although in one of these studies there was a significant association between low adiponectin levels and nonatopic asthma.^{30,31} Our findings may represent spurious associations (type I errors) in view of the large number of analyses that we have conducted. However, the inverse association between adiponectin and exhaled nitric oxide is consistent with findings in a murine model, in which the infusion of adiponectin decreased levels of T_H2 inflammatory cells and cytokines in the airway after exposure to ovalbumin.¹⁶ Given that adiponectin is regarded as anti-inflammatory in nature,³² perhaps higher levels are in some way protective against the development of airway disease in men.

This analysis was prompted by the suggestion that adipokines may mediate the link between obesity and asthma.^{1,5,33,34} Obesity is associated with increased levels of C-reactive protein, the proinflammatory cytokines interleukin 6 and tumor necrosis factor α , and other immune-modulating proteins.^{1,35} Some of these markers of inflammation have been investigated in the context of respiratory diseases. C-reactive protein, for example, has been found to be associated with chronic obstructive pulmonary disease,³⁶ poor lung function,³⁷ and airway hyperresponsiveness³⁸ but not exhaled nitric oxide.³⁹ Tumor necrosis factor α is increased in asthma and increases the production of T_H2 cytokines in the airways.³⁴ We hypothesized that leptin and adiponectin would be associated with aspects of the asthma phenotype but found little evidence to support this.

Table 4. Unadjusted Analyses Showing the Associations Among the Dependent Variables, Leptin, and Adiponectin in Men and Nonpregnant Women Using Logistic and Linear Regression

Variable	Leptin				Adiponectin			
	Women		Men		Women		Men	
	N	OR or coefficient (95% CI) ^a	P value	OR or coefficient (95% CI) ^a	N	OR or coefficient (95% CI) ^a	P value	OR or coefficient (95% CI) ^a
Current asthma	404	1.49 (0.96 to 2.32)	.08	1.07 (0.75 to 1.53)	407	0.60 (0.35 to 1.04)	.07	1.26 (0.80 to 2.00)
Current wheeze	404	0.95 (0.67 to 1.35)	.79	0.97 (0.71 to 1.31)	407	0.81 (0.51 to 1.27)	.36	0.89 (0.60 to 1.31)
Bronchodilator response	394	0.90 (0.46 to 1.76)	.76	0.69 (0.45 to 1.06)	397	1.42 (0.57 to 3.52)	.45	1.85 (1.05 to 3.25)
FEV ₁ /FVC ratio ^b	401	-0.406 (-1.38 to 0.57)	.41	0.85 (-0.08 to 1.78)	404	0.96 (-0.30 to 2.23)	.14	-0.52 (-1.70 to 0.66)
Exhaled nitric oxide	393	-0.015 (-0.12 to 0.09)	.77	0.06 (-0.04 to 0.16)	396	0.03 (-0.11 to 0.16)	.69	-0.193 (-0.32 to -0.06)

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; N, number of participants; OR, odds ratio.

^a For current asthma, current wheeze, and bronchodilator response, the OR is given; for FEV₁/FVC ratio and exhaled nitric oxide, the coefficient is given.

^b The FEV₁/FVC ratio (%) is prebronchodilator.

Table 5. Adjusted Analyses Showing the Association Among the Dependent Variables, Leptin, and Adiponectin in Men and Nonpregnant Women Using Logistic and Linear Regression^a

Variable	Leptin				Adiponectin			
	Women		Men		Women		Men	
	N	OR or coefficient (95% CI) ^b	P value	OR or coefficient (95% CI) ^b	N	OR or coefficient (95% CI) ^b	P value	OR or coefficient (95% CI) ^b
Current asthma	402	1.46 (0.61 to 3.50)	.40	1.32 (0.71 to 2.45)	405	0.67 (0.38 to 1.20)	.18	1.29 (0.79 to 2.08)
Current wheeze	402	1.74 (0.84 to 3.61)	.13	1.18 (0.68 to 2.03)	405	0.76 (0.46 to 1.25)	.27	0.82 (0.54 to 1.24)
Bronchodilator response	392	1.32 (0.33 to 5.23)	.70	1.25 (0.59 to 2.64)	395	1.90 (0.69 to 5.17)	.21	1.57 (0.87 to 2.83)
FEV ₁ /FVC ratio ^c	399	0.87 (-1.04 to 2.78)	.37	-0.38 (-2.01 to 1.25)	402	0.77 (-0.57 to 2.12)	.26	-0.03 (-1.27 to 1.21)
Exhaled nitric oxide	391	0.11 (-0.08 to 0.30)	.24	-0.01 (-0.18 to 0.15)	394	-0.02 (-0.15 to 0.12)	.80	-0.16 (-0.29 to -0.04)

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; N, number of participants; OR, odds ratio.

^a Analyses were adjusted for smoking and percentage body fat.

^b For current asthma, current wheeze, and bronchodilator response, the OR is given; for FEV₁/FVC ratio and exhaled nitric oxide, the coefficient is given.

^c The FEV₁/FVC ratio (%) is prebronchodilator.

This study has a number of strengths. The study members come from a population-based cohort with high follow-up, providing information on a large sample of people of the same age. We investigated associations between both leptin and adiponectin and an asthma diagnosis, wheeze, airflow obstruction, bronchodilator response, and exhaled nitric oxide, providing a wide range of information on the different aspects of the asthma phenotype. Although none of these is a perfect marker for asthma, it seems unlikely that an important association has been missed. We were unable to measure airway hyperresponsiveness at the age of 32 years evaluation because it could not be performed at the same time as the bronchodilator response. Hence, we cannot exclude an association between adipokines and airway hyperresponsiveness, although the overlap between airway hyperresponsiveness and wheeze, bronchodilator responsiveness, and airway inflammation suggests that this is unlikely. A potential weakness is that leptin and adiponectin were not measured in a fasting state. However, blood samples were obtained at the same time of day and 4 hours after the last meal to minimize the influence of circadian rhythm and food intake on adipokine levels.

In summary, we found little evidence that either leptin or adiponectin is associated with the asthma phenotype. The inverse relationship between exhaled nitric oxide and adiponectin in men warrants further investigation. However, it seems unlikely that adipokines explain the previously observed association between obesity and asthma.

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