

TITLE PAGE

Title: Association between Asthma and Serum Adiponectin Concentration in Women
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Authors: Akshay Sood, M.D., M.P.H., University of New Mexico Health Sciences Center
School of Medicine, Albuquerque, NM, U.S.A.

Xichun Cui, Ph.D., University of New Mexico Health Sciences Center School of
Medicine, Albuquerque, NM, U.S.A.

Clifford Qualls, Ph.D., University of New Mexico Health Sciences Center School of
Medicine, Albuquerque, NM, U.S.A.

William S. Beckett, M.D., M.P.H., University of Rochester School of Medicine and
Dentistry, Rochester, NY, U.S.A.

Myron D. Gross, Ph.D., University of Minnesota, Minneapolis, MN, U.S.A.

Michael W. Steffes, M.D., Ph.D., University of Minnesota Minneapolis, MN, U.S.A.

Lewis J. Smith, MD, The Feinberg School of Medicine, Northwestern University,
Chicago, IL, U.S.A.

David R. Jacobs, Jr., PhD, University of Minnesota, Minneapolis, MN, U.S.A. (also
affiliated with the University of Oslo, Oslo, Norway)

Corresponding author: Akshay Sood, M.D., M.P.H.

Associate Professor, Division of Pulmonary and Critical Care Medicine

University of New Mexico Health Sciences Center School of Medicine

Department of Medicine

1 University of New Mexico

MSC 10 5550, ACC 5

Albuquerque, NM 87131, U.S.A.

Telephone: (505) 272-4751

Fax: (505) 272-8700

Email: asood@salud.unm.edu

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ABSTRACT:

INTRODUCTION: The association of murine asthma with adiposity may be mediated by adiponectin, an anti-inflammatory adipokine with reduced serum concentrations in the obese. We studied whether serum adiponectin concentration was associated with human asthma and explained the association between adiposity and asthma, particularly in women and in pre-menopausal women. **METHODS:** A cross-sectional analysis of 2,890 eligible subjects at year 15 of the Coronary Artery Risk Development in Young Adults (CARDIA) cohort and its YALTA ancillary study, and had either current asthma or never asthma at that evaluation, was performed. Obesity was defined as body mass index (BMI) ≥ 30 kg/m². Multivariable logistic regression analysis was performed with dependent variable current asthma status. **RESULTS:** Women, but not men, with current asthma had lower mean unadjusted serum adiponectin concentration than those with never asthma ($p < 0.001$; p for sex interaction < 0.001). Similarly, current asthma was related to obese status only in women (OR 3.31, 95% CI 2.00, 5.46, p for sex interaction 0.004); this association was little affected by adjusting for serum adiponectin. Prevalence of current asthma in pre-menopausal women was reduced in the highest vs. lowest tertile of serum adiponectin concentration (OR 0.46, 95% CI 0.26, 0.84, p 0.03), after adjusting for BMI. However, the interaction between serum adiponectin concentration and BMI category on current asthma status was not significant in pre-menopausal women or women overall. **DISCUSSION:** High serum adiponectin concentration may protect against current asthma in pre-menopausal women, but does not explain the association between asthma and adiposity.

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INTRODUCTION:

The incidence of obesity is dramatically increasing in the United States and worldwide in both children and adults (1). Recently, it has been shown that adiposity is a risk factor for asthma, particularly in women (2-6). Mechanistic explanations that have been advanced to explain this association include mechanical effects (such as lack of tidal stretch leading to latching of airway smooth muscle), immunological effects of adiposity, as well as genetic, hormonal (particularly the effect of female sex hormones), and environmental effects (the latter including change in dietary factors and increased exposure to indoor allergens from increased sedentary habits) (7).

It has been recently demonstrated that adiposity is associated with chronic low-grade systemic inflammation (8). This inflammatory state is related to adipokines – proteins mainly produced by adipocytes – which may be pro-inflammatory, such as leptin, or anti-inflammatory, such as adiponectin. Our recent cross-sectional analysis has suggested that high serum concentrations of leptin may be an independent risk factor for asthma in pre-menopausal women (9). Similarly, it has been hypothesized that decreased serum concentrations of adiponectin observed in obese humans may also contribute to the propensity towards asthma in this population (10).

The study objective was to determine whether serum adiponectin concentration was associated with asthma and explained the association between adiposity and asthma, particularly in women and in pre-menopausal women. This was evaluated using the prospective Coronary Artery Risk Development in Young Adults (CARDIA) cohort and its Young Adult Longitudinal Trends in Antioxidants (YALTA) ancillary study. A better understanding of the role of adiponectin in asthma may suggest newer ways of treating asthma in the expanding obese population.

METHODS:**Study design:**

This is a cross-sectional analysis of the CARDIA and YALTA datasets. This longitudinal epidemiologic study focusing on development of cardiovascular disease risk is funded by the National Heart, Lung, and Blood Institute (NHLBI). During 1985 and 1986, CARDIA recruited 5,115 black and white men and women, aged 18 to 30 years from four clinical centers in Birmingham, AL, Chicago, IL, Minneapolis, MN, and Oakland, CA, with follow-up examinations completed 2, 5, 7, 10, and 15 years later. At the year 15 examination, 3,672 persons were reexamined, constituting nearly 74% of survivors.

Inclusion and exclusion criteria:

All participants with current or never asthma at the year 15 examination were included. Former asthma, pregnancy, not fasting for 8 hours, possible renal disease (men with serum creatinine > 1.8 mg/dL and women with serum creatinine > 1.5 mg/dL) were

exclusion criteria. Additionally, those with missing data for independent variables and covariates were excluded from the analysis.

Independent and Dependent variables:

Independent variables measured at year 15 evaluation, included standard categories of body mass index (BMI < 18.5 kg/m² or underweight; BMI 18.5-24.9 kg/m² or normal weight; BMI 25-29.9 kg/m² or overweight; and BMI ≥ 30 kg/m² or obese), quartiles of waist circumference (which may correlate better with visceral adiposity than global adiposity), as well as three categories (tertiles) of serum adiponectin concentration.

The dependent variable measured at the same time was current asthma status, defined as 1) a subject report of taking a medication for asthma at year 15 evaluation or 2) a self-reported doctor or nurse asthma diagnosis along with asthma symptoms in the year previous to the year 15 evaluation. Those who denied both taking an asthma medication and a provider-given diagnosis of asthma at all evaluations (years 0, 2, 5, 7, 10, and 15) were classified as never asthma.

Covariates:

The following variables at year 15 were evaluated as covariates - diabetes mellitus, insulin resistance, self-reported smoking status, race, age, and physical activity level. The above listed covariates were selected since they have been shown to affect either asthma status or serum adiponectin concentration (11, 12). Further details about the covariates are available in the online data supplement.

Study Measurements:

At the year 15 evaluation, self-reported information was obtained from study subjects using standardized questionnaires. Certified technicians measured height (within 0.5 cm), weight (within 0.09 kg) and waist circumference (within 0.5 cm) using standardized techniques. Body mass index (BMI) was defined as weight/height² in kg/m². Blood samples were collected after at least 8 hours of fasting. Adiponectin was measured as part of the YALTA ancillary study in serum by radioimmunoassay at Linco Research, Inc. using a polyclonal antibody raised in a rabbit and purified recombinant adiponectin standards with an effective range of 0.2 to 40 mg/L (13). This assay measures total adiponectin and not the various molecular weight forms of adiponectin. Further details about the study measurements are available in the online data supplement.

Statistical Analysis:

We performed descriptive analyses (to calculate frequency distributions), univariate analyses (such as chi-square and t tests for categorical and continuous variables respectively), and multivariable logistic regression analyses using asthma status (current vs. never) as the categorical dependent variable. Consistent with our *a priori* hypothesis, we examined subgroups defined by sex and menopausal status and performed formal tests for interaction. Issues of confounding were resolved by including the above-described covariates to the models. A two-sided p-value of < 0.05 was considered statistically significant. All statistical analysis was done using the Statistical Analysis Software (SAS) package version 9.1 (Cary, NC). This study was approved by the University of New Mexico Human Research Review Committee, Albuquerque, NM.

RESULTS:

Among the 3, 672 participants in the CARDIA year 15 evaluation, 424 met the exclusion criteria, including 404 participants with former asthma. An additional 358 participants were excluded either because of missing serum adiponectin values (n = 317) or missing covariates (n = 41). Among the 2,890 eligible participants whose data was analyzed, 246 had current asthma, and 2,644 had never asthma. This population included 1,603 women (55%). Of the 1,554 women for whom these data were available, 1,391 (90%) were pre-menopausal. As shown in Table 1, participants with current asthma had significantly higher mean values for body mass index (BMI), waist circumference, and insulin resistance, lower mean values of FEV₁/FVC ratio (obtained 5 years prior to the year 15 evaluation), and were more likely to be women and diabetic, when compared to those with never asthma (p values for all comparisons < 0.05).

Table 1) Distribution of selected characteristics according to asthma status (all variables assessed at year 15, except where noted)

Characteristics	Current Asthma (n = 246)	Never Asthma (n = 2,644)	p value
Mean Age (in years)	40.1 ± 3.6	40.2 ± 3.6	0.61
Women	168/246 (68%)	1,435/2,644 (54%)	<0.001
Pre-menopausal women	132/163 (81%)	1,259/1,391 (91%)	<0.001
White race	119/246 (48%)	1,443/2,644 (55%)	0.06
Current Smokers	53/246 (22%)	555/2,644 (21%)	0.84
Mean FEV ₁ /FVC ratio 5 years prior	0.79 ± 0.18 (n = 210)	0.83 ± 0.11 (n = 2,308)	0.01
Geometric Mean Physical Activity Score (Exercise units)	186.4; 95% C.I. 51.6, 672.8	221.5; 95% C.I. 61.5, 797.7	0.04
History of Diabetes Mellitus	21/246 (9%)	141/2,644 (5%)	0.04
Geometric Mean Insulin Resistance	2.9; 95% C.I. 1.6, 5.3	2.5; 95% C.I. 1.3, 4.8	0.002
Use of Cholesterol Lowering Medication	9/246 (4%)	60/2,643 (2%)	0.17
Mean Body Mass Index (kg/m ²)	31.6 ± 8.3	28.4 ± 6.5	<0.001
Men	28.3 ± 5.3 (n = 78)	28.2 ± 5.3 (n = 1,209)	0.81
Women	33.2 ± 9.0 (n = 168)	28.6 ± 7.4 (n = 1,435)	<0.001
Pre-menopausal women	32.4 ± 9.2 (n = 132)	28.3 ± 7.2 (n = 1,259)	<0.001
Mean Waist Circumference (cm.)	93.8 ± 16.1	88.9 ± 14.8	<0.001
Men	93.6 ± 12.7 (n = 78)	93.8 ± 13.1 (n = 1,209)	0.91
Women	93.8 ± 17.4 (n = 168)	84.8 ± 14.9 (n = 1,435)	<0.001
Pre-menopausal women	92.3 ± 18.0 (n = 132)	84.2 ± 14.7 (n = 1,259)	<0.001
Geometric Mean Serum Adiponectin (mg/L)	8.9; 95% C.I. 4.9, 16.1	9.0; 95% C.I. 4.8, 16.8	0.77
Men	8.0; 95% C.I. 4.5, 14.3 (n = 78)	7.0; 95% C.I. 3.8, 12.9 (n = 1,209)	0.06
Women	9.3; 95% C.I. 5.1, 16.9 (n = 168)	11.1; 95% C.I. 6.3, 19.3 (n = 1,435)	<0.001
Pre-menopausal women	9.8; 95% C.I. 5.7, 16.8 (n = 132)	11.3; 95% C.I. 6.5, 19.7 (n = 1,259)	0.005

Note 1: For untransformed variables, the data are expressed as mean ± S.D (n); for geometric means, the data are expressed as mean; 95% confidence intervals (n).

Note 2: The total n value for various comparisons is not uniform because of missing data. The n value for a specific cell is listed in parenthesis when it differed from the n value at the top of the column.

As has been shown previously, serum adiponectin concentration correlated better with waist circumference than with BMI (Spearman correlation coefficient of – 0.42 vs. – 0.31 respectively) (11). Women had higher mean serum adiponectin concentrations than men (geometric means 10.9 mg/L vs. 7.1 mg/L; p <0.001). Among women, pre-menopausal women had higher mean serum adiponectin concentration than post-menopausal women (geometric mean 11.2 mg/L vs. 8.9 mg/L; p < 0.001). Although there was no

difference in mean serum adiponectin concentrations between the current asthma and never asthma groups in men and women combined, women with current asthma had lower mean serum adiponectin concentrations compared to women with never asthma (geometric means 9.3 vs. 11.1 mg/L; $p < 0.001$, Table 2). This association between current asthma and low serum adiponectin concentration was not seen in men (p for interaction between sex and serum adiponectin in estimation of current asthma < 0.001).

Further, since this population included only 42 underweight participants (1%) and since initial evaluation showed a linear and not a bowl-shaped relationship between BMI categories and asthma risk, underweight and normal weight subjects were combined to form the referent category for subsequent analyses in Tables 2 and 4. As shown in Table 2, current asthma was associated with overweight and obese status for women with odds ratio of 1.68 (95% C.I. 1.01, 2.79) and of 3.31 (95% C.I. 2.00, 5.46) respectively. The formal test for interaction between sex and BMI category in estimation of current asthma was significant ($p = 0.004$). Similarly, current asthma was associated with the third and fourth quartiles of waist circumference for women with odds ratio of 2.58 (95% C.I. 1.52, 4.38) and of 3.09 (95% C.I. 1.77, 5.37) respectively (expanded Table 2, online data supplement). The formal test for interaction between sex and waist circumference category in estimation of current asthma was similarly significant ($p = 0.02$). However, the association between the risk for current asthma and adiposity (BMI or waist circumference) was not affected by adjusting for the serum adiponectin concentration in women. Similar results were obtained when the analysis was limited to pre-menopausal women alone (expanded Table 2, online data supplement).

Table 2: Association between risk for current asthma and adiposity with and without adjustment for serum adiponectin concentration

Models for adiposity measure		Women		Men	
		n with current asthma/ Total n	Odds Ratio (95% C.I.)	n with current asthma/ Total n	Odds Ratio (95% C.I.)
BMI	Under & Normal weight	31/585	1	18/356	1
	Over weight	37/420	1.68 (1.01, 2.79)	39/559	1.54 (0.84, 2.80)
	Obese	100/598	3.31 (2.00, 5.46)	21/372	1.33 (0.61, 2.89)
	p-value for Wald χ^2	<0.001		0.37	
BMI adjusted for Adiponectin	Under & Normal weight	31/585	1	18/356	1
	Over weight	37/420	1.63 (0.98, 2.74)	39/559	1.64 (0.89, 3.02)
	Obese	100/598	3.19 (1.91, 5.32)	21/372	1.45 (0.66, 3.17)
	p-value for Wald χ^2	<0.001		0.28	

Note 1: Covariates adjusted in each logistic regression model include age, race, smoking status, ln(physical activity), history of diabetes, and ln(insulin resistance). In addition, when indicated, group-specific tertiles of serum adiponectin concentration were also adjusted.

Note 2: The interaction between sex and BMI on current asthma was significant (p value 0.004 in both models).

Note 3: Adiponectin tertile cut points are 1.2-9, 9-14.4, and 14.4–94.8 mg/L for women and 1-6, 6-9.6, and 9.6-64 mg/L for men.

Note 4: Similar results were obtained when the underweight and normal weight categories were analyzed separately with the latter serving as the referent category.

Note 5: BMI categories are defined as follows - Underweight - BMI < 18.5 kg/m²; Normal weight - BMI 18.5-24.9 kg/m²; Overweight - BMI 25-29.9 kg/m²; Obese - BMI ≥ 30 kg/m².

Since the associations between adiposity and asthma (Table 2) and between serum adiponectin and asthma (Table 1) were seen only in women and since most women in this study were pre-menopausal (90%), further analyses in Tables 3 and 4 were focused on pre-menopausal women. Analyses related to all women and men are presented in the expanded Tables 3 and 4 in the online data supplement. Uniform adiponectin cut points generated from the pre-menopausal group were used for these analyses.

Table 3 shows that high serum adiponectin concentration was associated with reduced odds of current asthma in pre-menopausal women. After adjusting for BMI and other covariates, the highest tertile of serum adiponectin concentration in pre-menopausal women was associated with reduced odds of current asthma, with an O.R. of 0.46 (95% C.I. 0.26, 0.84) compared to the lowest tertile ($p = 0.03$). Similar results were obtained after adjusting for waist circumference in the analysis instead of BMI (expanded Table 3 in online data supplement).

The interaction between menopausal status and serum adiponectin category on current asthma status in women was not significant (the range of p values in the unadjusted pair wise comparisons was 0.32 -0.92, expanded Table 3). However, this analysis was limited by the small number of participants in the post-menopausal group ($n = 163$).

Table 3: Association between current asthma status and serum adiponectin concentration in pre-menopausal women, with and without adjusting for adiposity

Adiponectin models		Pre-menopausal women	
		n with current asthma/total n	Odds Ratio (95% C.I.)
Adiponectin	1 st Tertile	62/495	1
	2 nd Tertile	51/487	0.87 (0.57, 1.33)
	3 rd Tertile	19/409	0.38 (0.21, 0.69)
	p-value for Wald χ^2	0.004	
Adiponectin adjusted for Body Mass Index	1 st Tertile	62/495	1
	2 nd Tertile	51/487	0.93 (0.61, 1.42)
	3 rd Tertile	19/409	0.46 (0.26, 0.84)
	p-value for Wald χ^2	0.03	

Note 1: Covariates adjusted in each logistic regression model include age, race, smoking status, ln(physical activity), history of diabetes, and ln(insulin resistance).

Note 2: Adiponectin tertile cut points used in the above analysis were derived from pre-menopausal women (1.2-9, 9-15, and 15-94.8 mg/L mg/L).

Note 3: Further, when the third tertile of adiponectin was further split into two halves, the more extreme half had the lowest odds ratio. Additionally, similar trends were obtained when ln (adiponectin) was used as a continuous (instead of categorical) independent variable in the above analysis.

A stratified analysis suggested that the odds ratio of the association between current asthma and obese status may be the highest in those with the lowest tertile of serum adiponectin concentration, both in pre-menopausal women and in women overall (Table 4 below and Expanded Table 4 in data supplement), although the formal test of interaction between BMI and adiponectin in estimation of current asthma was not statistically significant in either group (the range of p values in the unadjusted pair wise comparisons was 0.45-0.99). Similar results were obtained after adjusting for waist circumference in the analysis instead of BMI (data not shown).

Table 4: Stratified analysis of the association between current asthma and Body Mass Index (BMI) categories in pre-menopausal women, according to the various tertiles of serum adiponectin concentration

Tertiles of adiponectin	BMI Category	Pre-menopausal women	
		n with current asthma/ total n	n with current asthma/ total n
Tertile 1	Under & Normal weight	5/88	1
	Over weight	10/130	1.82 (0.58, 5.72)
	Obese	47/277	5.77 (1.96, 17.01)
	p-value for Wald χ^2	0.001	
Tertile 2	Under & Normal weight	15/186	1
	Over weight	14/145	1.21 (0.56, 2.62)
	Obese	22/156	1.93 (0.87, 4.24)
	p-value for Wald χ^2	0.24	
Tertile 3	Under & Normal weight	8/259	1
	Over weight	8/98	2.30 (0.80, 6.63)
	Obese	3/52	1.11 (0.24, 5.14)
	p-value for Wald χ^2	0.26	

Note1: All models were adjusted for age, race, smoking status, ln(physical activity), history of diabetes, and ln(insulin resistance).

Note 2: The interactions between BMI categories and serum adiponectin on current asthma status were not significant ($p = 0.45$). Similar results were obtained when BMI and ln(adiponectin) were used as continuous variables ($p = 0.75$).

Note 3: Adiponectin tertile cut points used in the above analysis were 1.2-9, 9-15, and 15-94.8 mg/L mg/L.

Note 4: Similar results were obtained when the underweight and normal weight categories were analyzed separately with the latter serving as the referent category.

Note 5: BMI categories are defined as follows - Underweight - BMI < 18.5 kg/m²; Normal weight - BMI 18.5-24.9 kg/m²; Overweight - BMI 25-29.9 kg/m²; Obese - BMI ≥ 30 kg/m².

DISCUSSION:

This study demonstrates three possible and important results. First, lower serum adiponectin concentration is associated with current asthma only in women in an unadjusted analysis. Second, the serum adiponectin concentration does not appear to explain the adiposity-asthma association in women. Third, high serum adiponectin concentration may be associated with reduced odds of asthma in pre-menopausal women, an effect that may be independent of adiposity. In addition, we confirm results from other studies that showed that asthma is associated with adiposity only in women.

In 2005, more than 21 million people in the United States were estimated to be affected by asthma, amounting to 7.6% of the total population (14). Between 1980 and 1996, the prevalence of and morbidity trends related to asthma increased in the United States (15). Paralleling the rise in prevalence of asthma has been a rise in the prevalence of obesity in the United States (1). In 1999-2002, 65.1% of adults in the United States were either overweight or obese and 30.4% were obese (16). The somewhat contemporaneous course of the two epidemics has sparked interest in adiposity as a risk

factor for asthma. Some (but not all) studies have also shown that adiposity is a stronger risk factor for asthma in women than in men (2-6).

Adipose tissue produces and releases a variety of pro-and anti-inflammatory factors (17). Some of these substances may play a role in the development of a variety of inflammatory conditions such as cardiovascular disease, type II diabetes, and possibly asthma, although their pathogenic role is far from proven. One of the anti-inflammatory adipokines is adiponectin. Although central (visceral) adipocytes are the most important source of adiponectin (11), serum adiponectin concentration does not increase with obesity as serum leptin concentration does. On the contrary, there is a tendency for reduced serum adiponectin concentration among obese subjects (18).

Obesity is associated with high rates of necrosis of adipocytes, exposing naked lipid droplets to the interstitium (19). Macrophages gather around the necrosing adipocytes and become functionally activated, forming syncytia (19). Macrophages in the adipose tissue produce tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) which in turn may directly inhibit the local production of adiponectin in a paracrine fashion (20). This may explain the reduced systemic adiponectin concentration seen in obesity.

The anti-inflammatory properties of adiponectin include inhibition of pro-inflammatory cytokines such as TNF- α and IL-6 (21, 22) and endothelial adhesion molecules such as ICAM-1, VCAM-1 and p-selectin (23) as well as induction of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (22, 24, 25). Therefore, adiponectin may modulate the activation, proliferation, cytotoxicity, and cytokine production by inflammatory cells as well as affect interactions of T-cells with other T-cells, target cells, and B-cells. Since ICAM-1 is the receptor for most rhinoviruses (the most important cause of asthma exacerbations) (26) and p-selectin-mediated adhesion of leukocytes to the vascular endothelium is a key early event in the initiation of inflammatory response, it is conjectured that the effects of adiponectin on endothelial adhesion molecules may play a role in asthma causation. Additionally, adiponectin inhibits proliferation and migration of cultured vascular smooth muscle cells induced by mitogens (27-29) and may have similar effects on murine airway smooth muscle (Figure 1) (10). Given that adiponectin receptors are expressed in cultured human airway smooth cells (30), it has been hypothesized that a decline in serum adiponectin concentration in the obese may contribute to the increased airway smooth muscle mass seen with remodeling in chronic asthma (31).

Murine models have also shown that subcutaneous injection of adiponectin in ovalbumin-sensitized mice prevents the subsequent development of increased airway responsiveness on exposure to ovalbumin (10, 31). Taken together, the known anti-inflammatory effects of adiponectin in both mice and humans, and the prevention of both allergen-induced airway responsiveness and airway smooth muscle proliferation in murine models has led to the hypothesis that the decreased serum concentrations of adiponectin in obese humans may contribute to the propensity towards asthma in this population (30).

This study suggests that higher serum adiponectin concentration may be a protective factor for current asthma in women, particularly those who are pre-menopausal. The observed association was independent of adiposity. These results are consistent with a previous cross-sectional study from a different population that suggested that high serum concentrations of leptin, another adipokine, are an independent risk factor for

asthma in pre-menopausal women and that this effect may also be independent of adiposity (9). These results suggest that there may be interplay of female sex hormones, selected adipokines, and asthma, although this remains to be proven.

Despite the strong biological plausibility cited above, this study fails to convincingly demonstrate that serum adiponectin concentration modifies the association between adiposity and asthma. There are three possible explanations. First, human asthma and murine asthma have different pathophysiologic pathways (32) and therefore, adiponectin may not play the same pathogenic role in the association between adiposity and human asthma as it does in the murine asthma model. Second, human cross sectional studies may not be able to show clear associations, because of the presence of multiple confounding factors and the lack of knowledge of temporal sequencing of the variables. For instance, it may be necessary to replicate the mouse intervention study design in human subjects in order to better understand the role of adiponectin on the human airway. This may be possible by studying either the effect of factors that affect serum adiponectin (such as exercise, weight reduction, and peroxisome proliferator-activated receptor (PPAR) γ agonists) on asthma outcome measures or the effect of specific allergen inhalation on serum adiponectin concentration in subjects with asthma. Third and most important, it is likely that the association between adiposity and a complex disease trait such as asthma is mediated not by one adipokine but a balance of several pro-inflammatory and anti-inflammatory adipokines, and adiponectin is only a part of the larger puzzle. On the same line of reasoning, it is possible that other mechanistic pathways such as the mechanical effect of adiposity, and genetic, hormonal, and environmental pathways are more important than the immunologic effects of adiposity, in the asthma-adiposity association in humans.

The strengths of the study include its relatively large sample size and its clinical translational character, based on the recently published data on the role of adiponectin in asthma in the mouse model by Shore *et al.* (10, 31). The study however, has some limitations. Asthma diagnosis was self-reported, and this may result in misclassification bias, particularly among the obese population (33). Further, this is an observational cross sectional study which can only allow for hypothesis generation but does not prove causality or the direction of causation. The number of post-menopausal subjects in this relatively young cohort is small (about 10%), making it difficult to compare with pre-menopausal women. Additionally, the observed lack of association among men may be due to relatively smaller number of asthmatics among men, compared to women, rather than a true lack of association. Further, in order to confirm definitively that adiponectin has a different effect on asthma status in various groups, a statistically significant interaction is required. This exploratory analysis lacks the power to detect a statistically significant interaction. Finally, adiponectin is present in serum in hexameric low molecular weight and multimeric high molecular weight forms, which were not separately measured in this study. Debate exists as to whether the various forms have the same *in vivo* activity (34).

In summary, high serum adiponectin concentration may exert a protective effect against asthma in pre-menopausal women and this effect may be independent of adiposity. However, the adiposity-asthma association seen among women subjects in the CARDIA study can not be explained by serum adiponectin concentration. Future studies will need to expand on these observations to improve our understanding of the association between asthma and adiposity. A better understanding of the role of adiponectin in asthma may suggest newer ways of treating asthma in the obese population.

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COMPETING INTERESTS:

None

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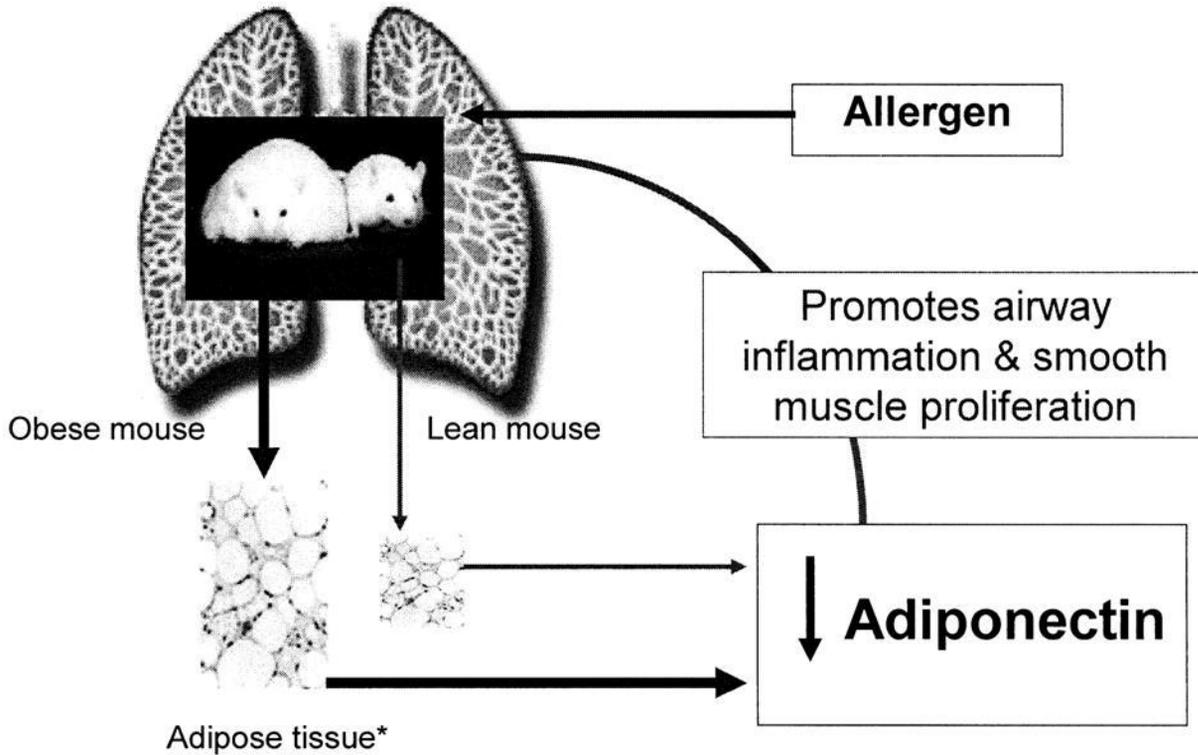
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Figure Legend

Figure 1: A schematic representation of the suggested role of adiponectin in murine asthma, based on work by Shore et al. (10, 30, 31).

Footnote for Figure 1 -

* Adipocytes and stromal macrophages are both hypertrophic and hyperplastic in obese mice, as compared to lean mice.



ONLINE DATA SUPPLEMENT

Title: Association between Asthma and Serum Adiponectin Concentration in Women
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Article type: Full paper

Authors: Akshay Sood, M.D., M.P.H., University of New Mexico Health Sciences Center
School of Medicine, Albuquerque, NM, U.S.A.

Xichun Cui, Ph.D., University of New Mexico Health Sciences Center School of
Medicine, Albuquerque, NM, U.S.A.

Clifford Qualls, Ph.D., University of New Mexico Health Sciences Center School of
Medicine, Albuquerque, NM, U.S.A.

William S. Beckett, M.D., M.P.H., University of Rochester School of Medicine and
Dentistry, Rochester, NY, U.S.A.

Myron D. Gross, Ph.D., University of Minnesota, Minneapolis, MN, U.S.A.

Michael W. Steffes, M.D., Ph.D., University of Minnesota Minneapolis, MN, U.S.A.

Lewis J. Smith, MD, The Feinberg School of Medicine, Northwestern University,
Chicago, IL, U.S.A.

David R. Jacobs, Jr., PhD, University of Minnesota, Minneapolis, MN, U.S.A. (also
affiliated with the University of Oslo, Oslo, Norway)

Corresponding author: Akshay Sood, M.D., M.P.H.

Associate Professor, Division of Pulmonary and Critical Care Medicine

University of New Mexico Health Sciences Center School of Medicine

Department of Medicine

1 University of New Mexico

MSC 10 5550, ACC 5

Albuquerque, NM 87131, U.S.A.

Telephone: (505) 272-4751

Fax: (505) 272-8700

Email: asood@salud.unm.edu

METHODS:

Independent and Dependent Variables:

Those with former asthma (*i.e.* those admitting to taking an asthma medication on any evaluation other than year 15 or having a provider-given diagnosis of ever having had asthma at any evaluation but not having asthma symptoms in the year previous to the year 15 evaluation) were excluded from the analysis. The characteristics of the group with former asthma were more similar to the group with never asthma than to the group with current asthma. The exclusion of this middle group allowed for a better discrimination between current asthma and never asthma.

Of note, we were able to validate self-report of asthma medication use by carefully analyzing lists of medications provided (mostly by direct examination of pill containers) and found a very strong correlation between self-report and confirmed use of asthma medications (Kappa of 0.91, 95% C.I. 0.89, 0.94).

In addition, women were classified as post-menopausal if they met the criteria for either surgical menopause (having a hysterectomy or both ovaries removed) or natural menopause (not menstruating within last 12 months not due to medication, chemotherapy, pregnancy, breast-feeding or severe weight loss).

Covariates:

The following variables at year 15 were evaluated as covariates –

- 1) Diabetes mellitus (defined as fasting glucose concentration ≥ 126 mg/dL or receiving medication for diabetes);
- 2) Insulin resistance (defined by the homeostasis model assessment (1, 2), calculated as $[\text{insulin} \times \text{glucose}] / 22.5$ (with fasting insulin expressed as mU/L and fasting glucose mmol/L);
- 3) Self-reported smoking status (classified as never smokers, former smokers, and current smokers);
- 4) Race was self-reported. Only blacks and whites were included in this study;
- 5) Age;
- 6) Physical activity - The frequency of participation in a range of specific heavy and moderate intensity physical activities in the previous year was obtained from a validated questionnaire (3). Duration of each activity was however, not queried. Data was converted into a weighted physical activity score, using the methods described by Taylor *et al* (4) and Folsom *et al* (5). Since the average number of minutes of performance of various activities in any week was not obtained, no interpretation as caloric expenditure (or METS) per unit of time was available. Therefore, the Physical Activity History score was used unaltered in 'Exercise Units'.

Because the distributions of insulin resistance and activity level were skewed, we analyzed natural logarithms (ln) of these variables. The above listed covariates were selected since they have been shown to affect either asthma status or serum adiponectin concentration (6, 7).

Study Measurements:

At the year 15 evaluation, self-reported information was obtained from study subjects using standardized questionnaires. Certified technicians measured height (within 0.5 cm)

and weight (within 0.09 kg) using standardized equipment with participants wearing light clothing, but without shoes. Body mass index (BMI) was defined as weight/height² in kg/m². Waist circumference was measured laterally midway between the iliac crest and the lowest lateral portion of the rib cage, and anteriorly midway between the xiphoid process of the sternum and the umbilicus to the nearest 0.5 cm. Blood samples were collected from seated participants after at least 8 hours of fasting, with tourniquet use limited to 2 minutes to prevent hemoconcentration. Samples were then centrifuged, aliquoted, and frozen at –70°C within 90 minutes of the collection with aliquots stored locally for a month and then shipped on dry ice for analysis or long-term storage. Serum glucose was measured using a Cobas Mira Plus chemistry analyzer (Roche Diagnostic Systems) with the hexokinase method. Serum insulin was measured by radioimmunoassay (Linco Research Inc., St. Charles, MO). Both assays were performed at Linco Research, Inc. Adiponectin was measured as part of the YALTA ancillary study in serum by radioimmunoassay at Linco Research, Inc. using a polyclonal antibody raised in a rabbit and purified recombinant adiponectin standards with an effective range of 0.2 to 40 mg/L (8). This assay measures total adiponectin and not the various molecular weight forms of adiponectin.

EXPANDED TABLES

Expanded Table 2: Association between risk for current asthma and adiposity with and without adjustment for serum adiponectin concentration

Models for adiposity measure		Pre-menopausal Women		All Women		Men	
		n with current asthma/ Total n	Odds Ratio (95% C.I.)	n with current asthma/ Total n	Odds Ratio (95% C.I.)	n with current asthma/ Total n	Odds Ratio (95% C.I.)
BMI	Under & Normal weight	28/533	1	31/585	1	18/356	1
	Over weight	32/373	1.74 (1.01, 2.99)	37/420	1.68 (1.01, 2.79)	39/559	1.54 (0.84, 2.80)
	Obese	72/485	3.26 (1.89, 5.65)	100/598	3.31 (2.00, 5.46)	21/372	1.33 (0.61, 2.89)
	p-value for Wald χ^2	<0.001		<0.001		0.37	
BMI adjusted for Adiponectin	Under & Normal weight	28/533	1	31/585	1	18/356	1
	Over weight	32/373	1.56 (0.90, 2.70)	37/420	1.63 (0.98, 2.74)	39/559	1.64 (0.89, 3.02)
	Obese	72/485	2.82 (1.61, 4.91)	100/598	3.19 (1.91, 5.32)	21/372	1.45 (0.66, 3.17)
	p-value for Wald χ^2	<0.001		<0.001		0.28	
Waist Circumference	1 st Quartile	16/319	1	36/612	1	8/109	1
	2 nd Quartile	25/364	1.43 (0.74, 2.74)	32/376	1.44 (0.87, 2.40)	18/325	0.77 (0.32, 1.86)
	3 rd Quartile	38/368	2.30 (1.21, 4.38)	39/268	2.58 (1.52, 4.38)	27/444	0.87 (0.37, 2.09)
	4 th Quartile	53/340	3.77 (1.87, 7.61)	61/347	3.09 (1.77, 5.37)	25/409	0.94 (0.35, 2.48)
	p-value for Wald χ^2	<0.001		<0.001		0.92	
Waist Circumference adjusted for Adiponectin	1 st Quartile	16/319	1	36/612	1	8/109	1
	2 nd Quartile	25/364	1.28 (0.66, 2.46)	32/376	1.39 (0.83, 2.33)	18/325	0.81 (0.34, 1.98)
	3 rd Quartile	38/368	1.91 (0.99, 3.69)	39/268	2.47 (1.44, 4.24)	27/444	0.97 (0.40, 2.34)
	4 th Quartile	53/340	3.01 (1.47, 6.16)	61/347	2.92 (1.65, 5.17)	25/409	1.04 (0.39, 2.79)
	p-value for Wald χ^2	0.01		<0.001		0.91	

Note 1: Covariates adjusted in each logistic regression model include age, race, smoking status, ln(physical activity), history of diabetes, and ln(insulin resistance). In addition, when indicated, group-specific tertiles of serum adiponectin concentration were also adjusted.

Note 2: The interaction between sex and adiposity on current asthma was significant, with adiposity modeled as either BMI (p value 0.004 in both models) or waist circumference (p value 0.02 in both models).

Note 3: Adiponectin tertile cut points are 1.2-9, 9-14.4, and 14.4–94.8 mg/L for women and 1-6, 6-9.6, and 9.6-64 mg/L for men.

Note 4: Similar results were obtained when the underweight and normal weight categories were analyzed separately with the latter serving as the referent category.

Note 5: BMI categories are defined as follows - Underweight - BMI < 18.5 kg/m²; Normal weight - BMI 18.5-24.9 kg/m²; Overweight - BMI 25-29.9 kg/m²; Obese - BMI ≥ 30 kg/m². Waist circumference quartile cut points are 33.5-73, 73-82, 82-95, and 95-172.5 cms. for pre-menopausal women, 33.5-73.5, 73.5-83, 83-96, and 96-172.5 cms. for all women, and 38.5-85, 85-92, 92-100.5, and 100.5-250 cms. for men.

Expanded Table 3: Association between current asthma status and serum adiponectin concentration in women, with and without adjusting for adiposity

Adiponectin models		Pre-menopausal women		All Women		Men	
		n with current asthma/ total n	Odds Ratio (95% C.I.)	n with current asthma/ total n	Odds Ratio (95% C.I.)	n with current asthma/ total n	Odds Ratio (95% C.I.)
Adiponectin	1 st Tertile	62/495	1	84/602	1	47/851	1
	2 nd Tertile	51/487	0.87 (0.57, 1.33)	58/551	0.86 (0.59, 1.26)	23/318	1.32 (0.77, 2.26)
	3 rd Tertile	19/409	0.38 (0.21, 0.69)	26/450	0.50 (0.30, 0.84)	8/118	1.21 (0.54, 2.71)
	p-value for Wald χ^2	0.004		0.03		0.59	
Adiponectin adjusted for Body Mass Index	1 st Tertile	62/495	1	84/602	1	47/851	1
	2 nd Tertile	51/487	0.93 (0.61, 1.42)	58/551	0.92 (0.62, 1.35)	23/318	1.39 (0.81, 2.39)
	3 rd Tertile	19/409	0.46 (0.26, 0.84)	26/450	0.62 (0.37, 1.05)	8/118	1.33 (0.59, 2.99)
	p-value for Wald χ^2	0.03		0.19		0.45	
Adiponectin adjusted for Waist Circumference	1 st Tertile	62/495	1	84/602	1	47/851	1
	2 nd Tertile	51/487	0.96 (0.63, 1.47)	58/551	0.92 (0.63, 1.36)	23/318	1.32 (0.77, 2.27)
	3 rd Tertile	19/409	0.49 (0.27, 0.89)	26/450	0.62 (0.36, 1.05)	8/118	1.22 (0.54, 2.75)
	p-value for Wald χ^2	0.04		0.19		0.59	

Note 1: Covariates adjusted in each logistic regression model include age, race, smoking status, ln(physical activity), history of diabetes, and ln(insulin resistance).

Note 2: The interactions between menopausal status and adiponectin on current asthma in women were not significant – the range of p values in the unadjusted pair wise comparisons was 0.32-0.92.

Note 3: Adiponectin tertile cut points used in the above analysis were derived from pre-menopausal women (1.2-9, 9-15, and 15-94.8 mg/L mg/L).

Note 4: Similar trends were obtained when the groups were compared using group-specific cutpoints for adiponectin tertiles. Further, when the third tertile of adiponectin, using uniform (pre-menopausally generated) cutpoints, was further split into two halves, the more extreme half had the lowest odds ratio. Additionally, similar trends were obtained when ln(adiponectin) was used as a continuous (instead of categorical) independent variable in the above analysis.

Expanded Table 4: Stratified analysis of the association between current asthma and Body Mass Index (BMI) categories in women, according to the various tertiles of serum adiponectin concentration

Tertiles of adiponectin	BMI Category	Pre-menopausal women		All Women		Men	
		n with current asthma/total n	Odds Ratio (95% C.I.)	n with current asthma/total n	Odds Ratio (95% C.I.)	n with current asthma/total n	Odds Ratio (95% C.I.)
Tertile 1	Under & Normal weight	5/88	1	5/99	1	6/165	1
	Over weight	10/130	1.82 (0.58, 5.72)	14/158	2.06 (0.70, 6.07)	26/384	2.09 (0.83, 5.29)
	Obese	47/277	5.77 (1.96, 17.01)	65/345	5.47 (1.96, 15.28)	15/302	1.65 (0.55, 4.90)
	p-value for Wald χ^2	0.001		<0.001		0.28	
Tertile 2	Under & Normal weight	15/186	1	16/203	1	8/130	1
	Over weight	14/145	1.21 (0.56, 2.62)	14/158	1.18 (0.55, 2.51)	9/129	1.19 (0.42, 3.39)
	Obese	22/156	1.93 (0.87, 4.24)	28/190	2.27 (1.07, 4.81)	6/59	1.75 (0.49, 6.18)
	p-value for Wald χ^2	0.24		0.07		0.68	
Tertile 3	Under & Normal weight	8/259	1	10/283	1	4/61	1
	Over weight	8/98	2.30 (0.80, 6.63)	9/104	2.01 (0.76, 5.27)	4/46	1.24 (0.22, 7.10)
	Obese	3/52	1.11 (0.24, 5.14)	7/63	1.89 (0.62, 5.79)	0/11	*
	p-value for Wald χ^2	0.26		0.32		0.97	

* - Model unstable due to small sample size

Note 1: All models were adjusted for age, race, smoking status, ln(physical activity), history of diabetes, and ln(insulin resistance).

Note 2: The interactions between BMI categories and serum adiponectin on current asthma status were not significant in any of the three groups above – the range of p values in the unadjusted pair wise comparisons was 0.45-0.99. Similar results were obtained when BMI and ln(adiponectin) were used as continuous variables (the range of p values was 0.61-0.99).

Note 3: Adiponectin tertile cut points used in the above analysis were derived from pre-menopausal women (1.2-9, 9-15, and 15-94.8 mg/L mg/L). Similar results were obtained when the groups were compared using group-specific cutpoints for adiponectin tertiles.

Note 4: Similar results were obtained when the underweight and normal weight categories were analyzed separately with the latter serving as the referent category.

Note 5: BMI categories are defined as follows - Underweight - BMI < 18.5 kg/m²; Normal weight - BMI 18.5-24.9 kg/m²; Overweight - BMI 25-29.9 kg/m²; Obese - BMI ≥ 30 kg/m².

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