CHEST

Original Research

ASTHMA

Obesity-Asthma Association

Is It Explained by Systemic Oxidant Stress?

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Background: **The mechanism for the obesity-asthma association is unknown. This study evaluated the hypothesis that systemic oxidant stress explains this association.**

Methods: **This cross-sectional study used year-20 follow-up evaluation data of 2,865 eligible participants in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort. Current asthma was self-reported. Oxidant stress primarily was assessed by plasma F2-isoprostane concentrations. Obesity measures included categories of BMI and dual-energy x-ray absorptiometry-assessed fat mass index (FMI) and lean mass index (LMI). Logistic and linear regressions were used for analyses.**

Results: **Asthma was associated with higher plasma F2-isoprostane concentrations ($p = 0.049$); however, this association was not significant when adjusted for either gender or BMI. The BMI-asthma association was seen only among women ($p = 0.03$; gender-specific interaction, $p = 0.01$), and this association was not explained by plasma F2-isoprostane levels. Similarly, both FMI and LMI were positively associated with asthma in women ($p = 0.20$ and 0.01, respectively). These associations also were not explained by plasma F2-isoprostane levels. Similar results were obtained when plasma levels of oxidized low-density lipoprotein were used instead of F2-isoprostane levels to study the BMI-asthma association at the year-15 evaluation.**

Conclusions: **Systemic oxidant stress, primarily assessed by plasma F2-isoprostane concentrations, was not independently associated with asthma and, therefore, may not explain the obesity-asthma association in women. The asthma-oxidant stress association is confounded by gender and obesity. This study is limited by the inability to measure airway oxidant stress. It is possible that another (as yet undetermined) measure of systemic oxidant stress may be more relevant in asthma.**

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Abbreviations: CARDIA = Coronary Artery Risk Development in Young Adults; DEXA = dual-energy x-ray absorptiometry; FMI = fat mass index; LDL = low-density lipoprotein; LMI = lean mass index; OR = odds ratio

Obesity is a risk factor for asthma, particularly among women. The mechanism responsible for the obesity-asthma association is not understood and is considered a major research priority.[1] Systemic oxidant stress is increased in women,[2] obesity,[2–4] and asthma,[5–9] and with inhaled corticosteroid use.[9] Some investigators[10,11] have recently hypothesized that increased systemic oxidant stress may explain the obesity-asthma association. We sought to evaluate this hypothesis in a large epidemiologic study.

Oxidant stress represents a state of imbalance between the increased production of free radicals (*eg*, reactive oxygen species) and reduced antioxidant activity. Oxidant stress may be assessed by direct measurement of reactive oxygen species or indirect measurements of oxidized products of lipids, proteins, or DNA. One such indirect measure, and reportedly the most accurate *in vivo*, is the plasma concentration of F2-isoprostanes, which are products of lipid peroxidation.[2,6,12–14] Plasma F2-isoprostanes track other biomarkers of lipid peroxidation[15] and may be reduced by antioxidant supplementation.[16–20] Another indirect measure of oxidant stress is plasma oxidized low-density lipoprotein (LDL), which is a product of protein peroxidation.

Our objective was to evaluate the effect of systemic oxidant stress, primarily measured by plasma F2-isoprostane concentrations, on the association between obesity and asthma, particularly among women. If systemic oxidant stress explains the obesity-asthma association, augmentation of systemic antioxidant defenses, such as by use of antioxidants or weight loss, might be beneficial in the management of patients with obesity and asthma.

Materials and Methods

Study Design

This study was a cross-sectional analysis of a prospective Coronary Artery Risk Development in Young Adults (CARDIA) cohort. From 1985 to 1986, CARDIA study recruited 5,115 subjects, with follow-up examinations completed among 3,672 and 3,549 persons, respectively, 15 and 20 years later. A subset of 2,865 eligible subjects at the year-20 evaluation underwent plasma F2-isoprostane measurement. Another subset of 2,679 eligible subjects underwent plasma oxidized LDL measurement at the year-15 evaluation. Additional detail about the CARDIA cohort is provided in the online data supplement.

The primary analysis focused on the effect of plasma F2-isoprostane concentrations on the obesity-asthma association at the year-20 evaluation. The secondary analysis focused on the effect of plasma oxidized LDL levels on the obesity-asthma association at the year-15 evaluation.

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Independent Variables

Plasma concentrations (in nanograms per liter) of F2-isoprostanes at the year-20 evaluation and of plasma oxidized LDL concentrations (in milligrams per deciliter) at the year-15 evaluation were the primary and secondary independent variables, respectively. Additional details about these variables are provided in the online data supplement.

Measures of obesity for the primary analysis included categories of BMI and tertiles of dual-energy x-ray absorptiometry (DEXA)-assessed fat mass index (FMI) and lean mass index (LMI) at the year-20 evaluation. The DEXA-assessed LMI includes skeletal muscle and viscera, and excludes physiologic fat depots and bone. LMI was defined by total lean mass divided by height squared (in kilograms per square meter); FMI similarly was defined by the total fat mass divided by height squared (in kilograms per square meter). Details about the DEXA examination are provided in the online data supplement. BMI category at the year-15 evaluation was similarly used for the secondary analysis involving plasma oxidized LDL levels.

Outcome Variables

Current asthma at the year-20 evaluation was the primary outcome variable and was defined as either a self-reported provider diagnosis of asthma, in the presence of asthma symptoms in the year prior to the year-20 evaluation, or a validated self-report of receiving a medication for the treatment of asthma at the year-20 evaluation. After excluding subjects with former asthma, those who never had asthma were treated as control subjects. Similar variables were defined at the year-15 evaluation for the secondary analysis.

Covariates

Potential covariates included age, race, and smoking at the year-15 and year-20 evaluations, as was done in a previous CARDIA study.[2] Smoking was treated as a categorical variable, including current smokers, former smokers, and never-smokers. Insulin resistance defined by the homeostasis model assessment,[21] history of diabetes mellitus, and menopausal status did not significantly contribute to the overall model and, therefore, were not included as covariates.

Statistical Analysis

Logarithmic transformation of plasma F2-isoprostane concentrations and square-root transformation of plasma oxidized LDL levels were used because these variables were not normally distributed. Multivariable logistic and linear regression analyses were used for categorical and continuous outcomes, respectively, including stepwise and best subset modeling. The comparison of baseline characteristics between asthma groups was done with the χ^2 test and t test for categorical and continuous variables, respectively. Consistent with our *a priori* hypothesis, we examined subgroups defined by gender. All analyses were performed with a statistical software package (SAS, version 9.1.3; SAS Institute; Cary, NC). This study was approved by the institutional review boards at the University of New Mexico (Albuquerque, NM) and the CARDIA study sites.

Results

Subject Characteristics

The primary analysis at the year-20 evaluation included 2,865 eligible subjects with completed

Table 1—*Distribution of Characteristics Among Groups*

Characteristics	Asthma Patients (n = 232)	Patients, No.	Control Subjects (n = 2,633)	Subjects, No.	p Value
Female gender, %	69.0	160	54.4	1,432	< 0.001
Age, yr	45.2 ± 3.7	232	45.2 ± 3.6	2,633	0.95
White race, %	47.8	111	56.1	1,477	0.02
Postmenopausal women, %	27.3	38/139	23.6	311/1,320	0.32
Self-reported current smoking, %	27.6	64	18.9	498	< 0.001
History of diabetes mellitus, %	8.3	19/229	7.5	197/2,612	0.68
Insulin resistance, HOMA units	3.2 (2.9–3.5)	232	3.0 (2.9–3.0)	2,630	0.17
BMI category, %*					0.06
Normal weight	25.4	59	29.0	763	
Overweight	29.7	69	34.1	898	
Obese	44.8	104	36.9	972	
BMI, kg/m^2†	30.9 ± 8.4	232	29.2 ± 6.7	2,633	0.003
Men (n = 1,273)	28.9 ± 6.9	72	28.9 ± 5.6	1,201	0.99
Women (n = 1,592)	31.8 ± 8.9	160	29.4 ± 7.5	1,432	0.001
FMI, kg/m^2	9.8 ± 4.7	167	8.7 ± 4.2	2,074	0.003
Men (n = 999)	6.3 ± 2.8	52	6.6 ± 2.6	947	0.50
Women (n = 1,242)	11.3 ± 4.5	115	10.4 ± 4.4	1,127	0.04
LMI, kg/m^2	18.8 ± 2.7	167	18.7 ± 3.0	2,072	0.82
Men (n = 998)	20.0 ± 2.2	52	20.4 ± 2.5	946	0.31
Women (n = 1,241)	18.2 ± 2.6	115	17.3 ± 2.7	1,126	0.001
Plasma F2-isoprostane concentration, ng/L	51.6 (48.5–54.9)	232	48.1 (47.3–48.9)	2,633	0.03
Men (n = 1,273)	45.2 (40.7–50.1)	72	43.3 (42.5–44.2)	1,201	0.45
Women (n = 1,592)	54.8 (50.8–59.0)	160	52.5 (51.2–53.8)	1,432	0.29

Values are given as the mean ± SD or geometric mean (95% CI), unless otherwise indicated. All measurements were performed at the same time at the year-20 evaluation. HOMA = homeostasis model assessment.

*The normal-weight category was defined as a BMI < 25 kg/m^2; overweight was defined as BMI 25 to < 30 kg/m^2; and obese was defined as BMI ≥ 30 kg/m^2. Because the number of underweight (BMI < 18.5 kg/m^2) subjects was very small (n = 25) and because they showed a similar relationship to asthma as normal-weight subjects, they were included in the normal-weight category. The higher BMI in the CARDIA population, relative to the US national average, reflects the sampling technique that was stratified to obtain a larger number of blacks.

†One man and one woman each had DEXA assessment of fat mass but not lean mass.

F2-isoprostane measurements, including 232 subjects (8.1%) with asthma. Subgroup analysis included 2,241 eligible subjects (78.2%) with completed DEXA measurements. Women, blacks, and current smokers were more likely to have asthma than men, whites, and noncurrent smokers, respectively ($p < 0.05$ for each analysis) [Table 1], which is consistent with previous reports.[22–24] Women with asthma had higher BMIs, FMIs, and LMIs than women without asthma (all $p \leq 0.04$) [Table 1]. Women also had greater plasma F2-isoprostane concentrations than did men (effect size, approximately 22% higher; 95% CI, 18 to 26%; $p < 0.001$); the further addition of BMI to the model did not change the effect size.

Obesity Is Positively Associated With Plasma F2-Isoprostane Concentrations

BMI, FMI, and LMI were all significant predictors for plasma F2-isoprostane concentrations; correlations were 0.24, 0.09, and 0.24, respectively, in men, and 0.37, 0.22, and 0.40, respectively, in women (all $p < 0.002$). However, the mean increase in plasma F2-isoprostane concentration per unit increase in BMI and LMI was significantly higher in women than in men (gender-specific interaction, both $p < 0.009$).

Association of Asthma With BMI Is Not Explained by Plasma F2-Isoprostane Concentrations

Asthma was significantly associated with greater plasma F2-isoprostane concentration among all subjects ($p = 0.049$) [Table 2]. However, when also adjusted for either gender or BMI, asthma was no longer associated with plasma F2-isoprostane concentrations ($p = 0.31$ and 0.15, respectively). This finding suggests that the relationship between asthma and systemic oxidant stress may be explained by gender-related and BMI-related differences in plasma F2-isoprostane concentration. Gender-specific stratified analysis confirmed the absence of an association between asthma and plasma F2-isoprostane concentrations in both men and women (Table 2). Further, we found that neither the use of inhaled corticosteroids (alone or in combination with long-acting β_2-agonists) nor the number of asthma medications used (a surrogate marker for disease severity) was

Table 2—*Association of Asthma on Plasma F2-Isoprostane Concentration at Year-20 Evaluation*

Plasma F2-Isoprostane Concentration Model	Men (n = 1,273)		Women (n = 1,592)		All (n = 2,865)	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Adjusted for covariates	1.35 (0.70–2.59)	0.37	1.13 (0.79–1.60)	0.50	1.35 (1.00–1.83)	0.049
Adjusted for BMI and covariates	1.49 (0.76–2.93)	0.24	0.96 (0.66–1.40)	0.84	1.26 (0.92–1.73)	0.15

All measurements were done at the same time at the year-20 evaluation. OR represents a one-unit change in the natural log of plasma F2-isoprostane concentration. Covariates adjusted include age, race, and smoking status. BMI was a categorical variable after including 25 underweight (BMI < 18.5 kg/m^2) subjects in the normal-weight category. Similar results were obtained when analysis was redone after excluding underweight subjects. There was no significant interaction between gender and F2-isoprostane concentration on asthma (p = 0.83) after adjustment for covariates.

associated with plasma F2-isoprostane concentrations (p = 0.64 and 0.40, respectively).

The association of asthma with increased BMI was seen only among women (odds ratio [OR], 1.79; 95% CI, 1.16 to 2.76 [in obese women]; p = 0.03 for trend) [Table 3], as has been described in previous analyses of CARDIA study data.[25,26] This finding was confirmed by the presence of a significant interaction between gender and BMI in asthma patients (p = 0.01). The association between asthma and BMI in women, however, was not statistically explained by plasma F2-isoprostane concentrations; adjustment for this measure did not affect the strength of the association (Table 3).

Associations of Asthma on DEXA Measures of Obesity Are Not Explained by Plasma F2-Isoprostane Concentrations

Subgroup analyses of 2,241 subjects with DEXA measurements at year 20 showed a positive relationship of FMI with asthma in women, similar to BMI, although it was not statistically significant (p = 0.20 for trend) [Table 4]. There was a significant association between asthma and higher LMI in women (OR, 2.03; 95% CI, 1.19 to 3.48 in women with highest LMI tertile; p = 0.01 for trend). Interestingly, increased lean mass may be negatively associated with asthma in men, although this association was not statistically significant (p = 0.11 for trend). However, there was a significant gender-specific interaction of LMI with asthma (p = 0.004). These associations also were not affected when adjusted for plasma F2-isoprostane concentrations.

Sensitivity Analyses and Alternate Analytical Approaches

Similar results were obtained when the entire analysis was redone after including subjects with former asthma (n = 158) among either control subjects or among case patients. Similar results also were obtained when the analysis was redone after excluding ever-smokers (n = 1,133 excluded) or subjects who were underweight (n = 25 excluded). Further, the addition of atopic status (defined by the self-reported presence of hay fever) at baseline evaluation (year 0) as a covariate did not change the results. Atopic status at year 20 was not available. When the pre-bronchodilator therapy FEV_1/FVC

Table 3—*Association of Asthma on Obesity (as Defined by BMI Category) After Adjusting for Plasma F2-Isoprostane Concentration*

BMI Model	Men (n = 1,273)		Women (n = 1,592)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Adjusted for covariates				
Normal weight	1.0	0.20	1.0	0.03
Overweight	0.63 (0.35–1.11)		1.31 (0.81–2.11)	
Obese	0.62 (0.34–1.15)		1.79 (1.16–2.76)	
Adjusted for plasma isoprostanes and covariates				
Normal weight	1.0	0.15	1.0	0.03
Overweight	0.62 (0.35–1.10)		1.32 (0.81–2.13)	
Obese	0.57 (0.30–1.07)		1.81 (1.15–2.87)	

All measurements were done at the same time at the year-20 evaluation. Covariates adjusted include age, race, and smoking. BMI was studied in the following three categories: normal weight (BMI < 25 kg/m^2), overweight (BMI 25 to < 30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). Twenty-five underweight (BMI < 18.5 kg/m^2) subjects were included in the normal-weight category. There was a significant interaction between gender and the BMI category on asthma (p = 0.01) after adjustment for covariates. Similar results were obtained when BMI was studied as a continuous variable and when analysis was redone after excluding underweight subjects.

Table 4—*Association of Asthma on Tertiles of DEXA-Assessed FMI and LMI After Adjusting for Plasma F2-isoprostane Concentration*

Obesity Measures	Men (n = 999)		Women (n = 1,242)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
FMI model*				
Adjusted for covariates				
Tertile 1	1.0	0.17	1.0	0.20
Tertile 2	0.53 (0.27–1.03)		1.52 (0.78–2.97)	
Tertile 3	0.90 (0.38–2.10)		1.78 (0.95–3.35)	
Adjusted for plasma isoprostanes and covariates				
Tertile 1	1.0	0.16	1.0	0.25
Tertile 2	0.53 (0.27–1.02)		1.52 (0.78–2.96)	
Tertile 3	0.87 (0.36–2.13)		1.74 (0.91–3.35)	
LMI model†				
Adjusted for covariates				
Tertile 1	1.0	0.11	1.0	0.01
Tertile 2	0.42 (0.18–1.01)		1.79 (1.13–2.83)	
Tertile 3	0.43 (0.18–0.99)		2.03 (1.19–3.48)	
Adjusted for plasma isoprostanes and covariates				
Tertile 1	1.0	0.11	1.0	0.02
Tertile 2	0.42 (0.17–1.00)		1.77 (1.11–2.82)	
Tertile 3	0.42 (0.18–0.98)		2.00 (1.16–3.47)	

All measurements were done at the same time at the year-20 evaluation. Covariates adjusted in all models include age, race, and smoking.
*The tertile cut points for FMI, as assessed by the year-20 DEXA, were 1.40 to 6.31 kg/m^2, 6.31 to 9.79 kg/m^2, and 9.79 to 34.17 kg/m^2. There was no significant interaction between gender and FMI tertiles with asthma (p = 0.09) after adjustment for covariates. Results similar to those described in this table were obtained when FMI was studied as a logarithmically transformed continuous variable.
†The tertile cut points for LMI, as assessed by the year-20 DEXA, were 2.14 to 17.22 kg/m^2, 17.22 to 19.99 kg/m^2, and 19.99 to 45.36 kg/m^2. There was a significant interaction between gender and LMI tertile with asthma (p = 0.004) after adjustment for covariates. When LMI was used as a logarithmically transformed continuous variable, there was a significant association between asthma and greater LMI in women (OR, 5.48; 95% CI, 1.43 to 20.96; p = 0.01) after adjusting for covariates. Additional adjustment for F2-isoprostane concentrations had little effect on the association (OR, 5.25; 95% CI, 1.34 to 20.61; p = 0.02). LMI was a better predictor for asthma than FMI in women, based on goodness-of-fit considerations.

ratio at year 20 was used instead of self-reported asthma as an outcome measure, again no significant associations were seen with plasma F2-isoprostane concentrations in the minimally adjusted model or after adjustment for BMI among men or women.

When incident asthma in women was analyzed (n = 50), associations analogous to those with current asthma were unchanged in Tables 2 and 4 but were weakened in Table 3, although in the same direction. Incident asthma analysis in men was limited by sample size (n = 17).

Association of Asthma With BMI Is Not Explained by Plasma Oxidized LDL Levels at Year-15 Evaluation

Additional analysis was performed in 2,679 eligible subjects at the year-15 evaluation, using plasma oxidized LDL level as the independent variable instead of F2-isoprostane concentration. Similar results again were noted in that plasma oxidized LDL level was not independently associated with asthma, inhaled corticosteroid use, and the number of asthma medications used, and did not statistically explain the BMI-asthma association at the year-15 evaluation (see Tables 1 and 2 in the online data supplement).

Discussion

Greater systemic oxidant stress, primarily measured by plasma F2-isoprostane concentration, although associated with obesity and female gender, is not independently associated with asthma or inhaled corticosteroid use. As a result, systemic oxidant stress may not adequately explain the association between excess mass (*ie*, total body mass, fat mass, or lean mass) and asthma in women.

Some studies have suggested that asthma is associated with increased systemic oxidant stress. In mice, systemic oxidant stress may modify asthma-related airway changes.[27,28] Nadeem et al[29] demonstrated increased concentrations of multiple markers of systemic oxidant stress among 38 patients with asthma compared to 23 control subjects. Another study[30] showed decreased systemic superoxide dismutase activity in 115 subjects with asthma compared to 20 control subjects, and yet another[9] showed increased plasma F2-isoprostane concentrations among subjects with asthma compared to control subjects (n = 15 in each group), with a relationship to both clinical disease severity and inhaled corticosteroid use. Further, a 2007 uncontrolled

study[31] showed that weight reduction in 10 subjects with obesity and asthma was associated with a decrease in systemic F2-isoprostane concentrations. Some studies[9,32,33] also suggested that inhaled corticosteroid use in subjects with asthma may suppress inflammation but not oxidant stress (as measured by F2-isoprostane concentrations in plasma or exhaled breath). Additionally, randomized controlled trials[34] of dietary antioxidant supplements have been largely ineffective in the treatment of asthma.

Systemic oxidant stress during acute asthma exacerbations also has not been well studied. Whereas one study[8] showed no change in systemic oxidant stress when subjects with asthma were challenged with platelet-activating factor, another study[35] showed an increase in systemic oxidant stress in patients during acute asthma exacerbations compared with stable patients with asthma.

Generally speaking, many previous human studies of the association between asthma and systemic oxidant stress were limited by a lack of adjustment for the confounding effects of gender and obesity[9,29,30] and relatively small sample size.[9,29] Additionally, most studies[7,22,35] used markers other than plasma F2-isoprostane concentrations to measure systemic oxidant stress. Our study used plasma F2-isoprostane concentrations and has shown that they were not independently associated with either asthma or inhaled corticosteroid use. Our *post hoc* power analysis suggests that our results are not explained by type II error (see the online data supplement). It is unlikely that overadjustment with BMI has falsely obscured a possibly significant association between asthma and plasma isoprostane concentrations because BMI is not tightly linked with plasma isoprostane concentrations (correlation coefficient, < 0.37), and the BMI-asthma association is not meaningfully altered by plasma isoprostane concentrations. It is possible that increased systemic oxidant stress only becomes manifest at the initial diagnosis or during an acute asthma exacerbation and not under stable baseline conditions (as was the case in our study). It is also possible that asthma is associated with increased airway oxidant stress and not systemic oxidant stress. However, several studies[11,36,37] have not shown an association of asthma with airway oxidant stress, as measured by exhaled breath and induced sputum F2-isoprostane concentrations, although one study[11] did show higher exhaled F2-isoprostane concentrations in subjects who were obese. Finally, it is possible that the association between asthma and oxidant stress may vary with the type of oxidant stress marker studied. Although plasma oxidized LDL level analysis showed results that were similar to those seen with F2-isoprostane concentrations, it is possible that yet another measure of oxidant stress may be affected in asthma patients.

Obesity is a risk factor for asthma among women. Our study suggests that body mass and its fat and lean components are associated with increased risk for asthma in women. The basis for the gender-related difference is not known. A possible explanation is that IM fat, which DEXA assesses as lean mass and that is more pronounced in women than in men,[38,39] may be associated with asthma in women. This explanation is consistent with a previous observation by Sutherland et al[40] in their study of lung function that, although lean mass in men was a measure of muscle bulk, excess lean mass in women was a further measure of obesity.

The mechanisms for the obesity-asthma association remain unknown, and increased systemic oxidant stress has been hypothesized[10,11] as one possible mechanism. However, for systemic oxidant stress to explain the obesity-asthma association, it needs to be associated with both predictor and outcome variables. Because systemic oxidant stress was not associated with asthma in our study, it may not explain the obesity-asthma association. Alternative explanations[41,42] may include various mechanical, genetic, immunologic, hormonal, and environmental mechanisms.

The strengths of this study include its large sample size, gender-specific stratified analysis, well-defined study population set within a cohort structure, and the use of DEXA-assessed fat and lean mass measures and state-of-the-art measurements of oxidant stress. The limitations are our inability to evaluate airway oxidant stress or asthma exacerbation. Data on atopic status at year 20 was not collected; however, atopy at the year-0 evaluation did not influence the association. The cross-sectional study design does not establish the direction of association. Plasma F2-isoprostane concentrations at a specific time point may not reflect past oxidant stress status, which is an issue that can only be addressed by a prospective study. Selection bias may occur if those subjects in whom F2-isoprostane concentrations were measured were not representative of the 3,549 subjects studied at year 20. However, our *ad hoc* analysis did not demonstrate that those subjects measured were different from those who were not measured with respect to both obesity and asthma. The use of self-reported asthma diagnosis may result in misclassification; however, misclassification recently has been shown[43] to be nondifferential between obese and normal-weight subjects with self-reported asthma. In addition, self-report may include those with early COPD. The latter is an unlikely explanation because similar results were obtained when analyses were restricted to nonsmokers. Although we found no association between

systemic oxidant stress and number of asthma medications used, we did not have good measures of asthma control and severity. It is possible that the asthma-oxidant stress association may be seen only among subjects with greater disease severity or poorer control. Further, despite reportedly being the state of the art, the measurement of plasma F2-isoprostane concentrations by gas chromatography mass spectrometry method is difficult and could have contributed to a measurement error, although this would be nondifferential.

To summarize, the results from this large study suggest that systemic oxidant stress, primarily measured by plasma F2-isoprostane concentrations, is not independently associated with asthma and, therefore, may not explain the association of asthma with excess body mass, fat mass, or lean mass in women. Alternative explanations, therefore, should be considered to explain the obesity-asthma association. In addition, studies of the association between asthma and oxidant stress need to adjust for the confounding effects of gender and obesity. This study is limited by the inability to measure airway oxidant stress. It is also possible that another (as yet undetermined) measure of systemic oxidant stress may be more relevant in asthma patients.

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