

Elevated atopy in healthy obese women^{1–5}

Victoria J Vieira, Anne M Ronan, Mark R Windt, and Anthony R Tagliaferro

ABSTRACT

Background: Allergic disorders, including asthma, have increased dramatically in the United States in the past 20 y. Epidemiologic studies have found body mass index (body weight in kg/height squared in m) to be a positive independent correlate of atopy in women but not in men.

Objective: We investigated the prevalence of atopy among healthy obese and nonobese women and its relation to fat mass (FM), insulin resistance, and plasma concentrations of 17 β -estradiol, interleukin 4 (IL-4), and leptin.

Design: A cross-sectional study of 21 obese ($\geq 30\%$ body fat) and 22 nonobese ($< 30\%$ body fat) women (18–41 y of age) was performed. The following measurements were taken: FM by plethysmography, total and specific immunoglobulin E (IgE) by automated immunosorbent analysis, and blood glucose, insulin, C-peptide, 17 β -estradiol, sex hormone-binding globulin, and IL-4. Insulin sensitivity was determined on the basis of the fasting insulin resistance index and with an oral-glucose-tolerance test.

Results: The frequency of specific IgE in the obese group was almost 3 times that in the nonobese group ($P = 0.008$). The total IgE concentration was not significantly different between groups. Plasma concentrations of 17 β -estradiol, the ratio of 17 β -estradiol to sex hormone-binding globulin, the fasting insulin resistance index, and C-peptide and leptin concentrations were higher in the obese than in the nonobese group ($P < 0.05$) after adjustment for oral contraceptive use. All factors correlated positively with FM. Logistic regression showed FM to be the only positive predictor of specific IgE ($P = 0.01$).

Conclusion: The findings confirm a direct relation between obesity and a T helper 2 cell immune response in women. *Am J Clin Nutr* 2005;82:504–9.

KEY WORDS Allergy, obesity, leptin, atopy, insulin resistance, 17 β -estradiol

INTRODUCTION

Atopy is a genetically determined state that is characterized by an elevation of circulating specific immunoglobulin E (IgE) antibodies to environmental allergens. Atopy is viewed as a major risk factor for asthma and other allergic diseases (1). Factors that may cause the development of an atopic state are not well understood. Some have hypothesized that vaccines, the frequent use of antibiotics, and the promotion of a pathogen-free environment may inadvertently cause a shift toward the T helper 2 (Th2)

cell immune response, or atopic state, rather than a T helper 1 cell immune response or nonatopic state (2). Not all evidence, however, supports this “hygiene hypothesis.” For example, inner cities, one of the least hygienic areas in our society, continue to have the greatest percentage of allergic asthmatics (3). Such observations have moved some researchers to look at other factors characteristic of westernized living that could cause allergic disorders.

In 1980, the prevalence of obesity [body mass index (BMI; in kg/m^2) > 30] in adult Americans was 14.5% (4). At the end of the past decade, 1 in 4 Americans was obese (5). An impressive body of experimental evidence strongly suggests a causal relation between obesity and asthma development (6). Recent clinical and epidemiologic investigations of men and women have reported BMI to be a positive and independent risk factor of allergy in sexually mature teenage girls (7, 8) and asthma in women (9–14), respectively. It is noteworthy that these effects are specific to females, which suggests that fat mass (FM) and hormonal changes associated with menarche promote atopy in women.

The major female sex hormone, 17 β -estradiol, has been found *ex vivo* to up-regulate the expression and secretion of interleukin 4 (IL-4) from CD4⁺ helper cells (15). IL-4 is one of the primary signals for activating an immune response toward atopy (16). Obesity also affects both the circulating concentration of 17 β -estradiol (17) and the biological availability of 17 β -estradiol (BAE) (18). With increased adiposity, a state of insulin resistance (IR) develops (19). IR suppresses the hepatic production of the transport protein, sex hormone-binding globulin (SHBG). A decrease in SHBG has been shown to increase free 17 β -estradiol (20). An increase in free estrogen would increase the likelihood

¹ From the Department of Animal and Nutritional Sciences, University of New Hampshire, Durham, NH (VJV, AMR, MRW, and ART).

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⁵ Address reprint requests to AR Tagliaferro, Department of Animal and Nutritional Sciences, University of New Hampshire, Durham, NH 03824. E-mail: anthonyt@cisunix.unh.edu.

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of estrogen binding to target tissues. Furthermore, plasma leptin—the protein product of the *ob* gene—increases with adiposity (21). In vitro, leptin has been found to induce aromatase activity and to activate estrogen receptor α in MCF-7 cells (22).

The purpose of the present investigation was to examine the prevalence of atopy in healthy, obese, nonasthmatic women and its relation to FM, IR, and plasma concentrations of 17β -estradiol, IL-4, and leptin.

SUBJECTS AND METHODS

Subjects

Women were recruited from the University of New Hampshire community and surrounding towns. Subjects were recruited by posting flyers in Durham, NH; by posting advertisements in the university website's wanted section; and by word of mouth. Prospective subjects underwent a brief telephone screening and were excluded if they met the following criteria: medical history of asthma, high blood pressure, heart disease (atherosclerosis), type 1 or type 2 diabetes mellitus, cigarette smoking, current pregnancy or lactation, and eating disorders. Information about the subjects' weight, height, and date of last menstrual period was also collected. Before any testing procedure was performed, all study participants signed an informed consent form and completed a personal health questionnaire that addressed weight history, birth weight, known allergies, oral contraceptive (OC) use (including the amount of conjugated 17β -estradiol in the formulation, if known), and family history of disease.

The 43 women (18–41 y of age) in the present study were the control group of a larger ongoing experiment investigating the relation between obesity and asthma. The women had no history of asthma and had a normal result from a pulmonary function test without a bronchodilator response. The nonobese group consisted of 22 women ($<30\%$ body fat), and the obese group consisted of 21 women ($\geq 30\%$ body fat). The protocols used herein were approved by the University of New Hampshire Institutional Review Board of Human Subject Research.

Methods

At the time of admission to the study, a medical history was taken; pulmonary function was assessed by spirometry, pre- and postbronchodilator, to rule out asthma; body composition and blood lipids were measured; blood pressure readings were taken; and an OGTT was administered. At time 0 (baseline) of the OGTT, a fasting blood sample was taken to measure total IgE, specific IgE, glucose, insulin, C-peptide, 17β -estradiol, SHBG, IL-4, and leptin.

Body composition, blood lipids, and blood pressure

Percentage body fat and lean body mass were measured by plethysmography in a BOD POD (Life Measurement Inc, Concord, CA). Instrument calibration and subject testing were done according to the basic protocol of the manufacturer. Briefly, subjects fasted overnight or did not eat for ≥ 3 h before testing. To obtain the most accurate measurement, the subjects were tested while wearing minimal clothing (a swimsuit) and a bathing cap to contain hair. All accessories (eg, eyeglasses and jewelry) were removed before testing. Waist and hip circumferences were measured with a steel tape measure to assess the degree of abdominal adiposity. The measurement was made to the nearest 0.25 inch,

at the narrowest point between the last rib and the iliac crest. A hip circumference measurement was also taken by placing the measuring tape around the widest point of the buttocks.

After an overnight fast, triacylglycerol, total cholesterol (TC), HDL-cholesterol, LDL-cholesterol, and VLDL-cholesterol concentrations were measured enzymatically in a peripheral blood sample with the use of an automated blood analyzer (Cholestech Corp, Haywood, CA). Blood pressure was measured with an automated electronic blood pressure monitor (Omron HEM-704C; Omron Healthcare Inc, Vernon Hills, IL) while the subject was seated. Two measurements were taken: the first within the first 30 min of the subject's arrival and the second 1 h later, after resting metabolism (a 1-h test that was done as part of the larger study) was measured. The lower measurement was recorded.

Total and specific IgE

Serum concentrations of total IgE antibodies were measured with an automated immunosorbent analysis (UniCAP 100; Pharmacia & Upjohn Diagnostics, Uppsala, Sweden). The presence of atopy was determined by the presence of specific IgE with the use of the Phadiatop diagnostic system (Pharmacia & Upjohn Diagnostics). Phadiatop is an in vitro immunosorbent test that differentiates atopy and nonatopy by demonstrating the presence of specific IgE antibodies in response to a balanced mixture of common aeroallergens (cat dander, dog dander, grass pollen, rye pollen, birch pollen, artemisia pollen, house dust mite, and *cladosporium*) in a serum sample. The test quantitates the concentration of specific IgE in specific units, which are used to differentiate a negative from a positive test result. An IgE concentration <0.35 kU_A/L (kU_A = kilounits of specific antigen) is defined as a negative test result for atopy; a concentration ≥ 0.35 kU_A/L is defined as a positive test result for atopy. It has been reported that this method of assessing specific IgE is 90% reliable for patients older than 6 y. A series of clinical trials verified that this diagnostic system has a sensitivity of 93% and a specificity of 89% (Pharmacia & Upjohn, unpublished data). Moreover, an assessment of analytic precision and accuracy of commercial immunoassays for specific IgE found that the Pharmacia & Upjohn UniCAP system performed well in terms of both precision and accuracy when compared with the standard RAST test (23).

Oral-glucose-tolerance test

A 2-h OGTT was administered at the University Health Services Center in the morning while the subjects were in a fasted state (at least 12 h with no food or drink, except water). Five blood samples were collected in evacuated tubes from the antecubital vein of each subject at baseline, and 2 blood samples were taken 30, 60, and 120 min after the consumption of a 75-g glucose beverage (SUN-DEX; Fisher Scientific, Houston, TX). Glucose samples were collected in tubes containing a glycolytic inhibitor (potassium oxalate and sodium fluoride). All other blood samples were collected and prepared for the serum or plasma analysis of blood substrates. The samples were placed on ice during the OGTT, centrifuged at $827 \times g$ at 5°C for 30 min, and then frozen at -80°C until the assay was conducted. In the event that the blood samples hemolyzed, samples were deproteinized before assay conduction. Concentrations of glucose, insulin, and C-peptide were also measured 30, 60, and 120 min after the glucose load. The area under the curve for blood substrates was determined by using the trapezoid method.

Blood assays

Plasma glucose concentrations were measured enzymatically according to the glucose oxidase method with the use of a commercial diagnostic kit (no. 510; Sigma Diagnostics, St Louis, MO). Insulin and C-peptide were measured by competitive binding radioimmunoassay (RIA) with commercial diagnostic kits (Diagnostic Systems Laboratories, Webster, TX). The fasting insulin concentration was used to determine insulin sensitivity. C-peptide was used to assess insulin secretion under fasting and postglucose challenge conditions. Commercial RIA assay kits were used to measure plasma leptin (Linco Research Inc, St Charles, MO) and 17β -estradiol and SHBG (Diagnostic Systems Laboratories, Webster, TX). Serum IL-4 concentrations were measured by a quantitative sandwich enzyme immunoassay with the use of a commercial diagnostic kit (Quantikine; R&D Systems Inc, Minneapolis, MN).

Insulin resistance

IR was assessed by using an empirical fasting insulin resistance index (FIRI) according to the calculations of Duncan et al (24). The FIRI method compares fasting insulin and glucose concentrations with an expected reference range centered around unity. FIRI has been shown to be comparable with well-known reliable methods of assessing insulin sensitivity, such as the minimal model of Bergman et al and the HOMA-R (homeostasis model assessment) model. FIRI was calculated as follows:

$$\text{FIRI} = \text{fasting glucose (mmol/L)} \times \text{fasting insulin (mU/L)} / 25 \quad (1)$$

Biological availability of 17β -estradiol

In this study, the ratio of total circulating 17β -estradiol (pg/mL) was expressed relative to SHBG (nmol/L) to serve as an index of free 17β -estradiol or BAE. For this purpose, estradiol units were converted to nmol/L by multiplying by 0.0037.

Statistics

Chi-square analyses were used to compare categorical variables (atopy, OC use, and reported allergies) between groups. All other comparisons between groups were done by analysis of variance (ANOVA) with the use of a general linear model (GLM). Because OC use affects female sex hormone concentrations and has been reported to reduce insulin sensitivity in women (25), all analyses of carbohydrate metabolism and hormone concentrations were reported both with and without adjustment for OC use. Because of the variability in insulin concentrations, the insulin and FIRI values were log transformed. Differences between groups in glucose, insulin, and C-peptide during the OGTT were analyzed by using an ANOVA GLM for repeated measures, both with and without adjustment for OC use. Areas under the curve (AUCs) for glucose, insulin, and C-peptide were analyzed by using an ANOVA GLM. Simple Pearson's pairwise correlations of adiposity (FM and waist circumference), IR, C-peptide, BAE, and leptin were done by using uncorrected probability values. Logistic regression techniques were used to determine significant predictors of atopy. Unless otherwise stated, P values ≤ 0.05 were considered significant. All statistical analyses were done by using SYSTAT (version 10.0; Systat Inc, Richmond, CA).

TABLE 1

Descriptive characteristics of the obese and nonobese women¹

	Obese (n = 21)	Nonobese (n = 22)	P ²
Age (y)	21.6 $\pm$ 0.8	21.4 $\pm$ 0.8	0.40
Birth weight (kg)	3.4 $\pm$ 0.15	3.4 $\pm$ 0.15	0.78
BMI (kg/m ²)	26.6 $\pm$ 0.5	21.1 $\pm$ 0.5	< 0.001
Fat mass (%)	35.4 $\pm$ 0.8	22.9 $\pm$ 0.8	< 0.001
WC (cm)	30.7 $\pm$ 0.5	26.6 $\pm$ 0.4	< 0.001
WHR	0.76 $\pm$ 0.01	0.73 $\pm$ 0.01	0.027
SBP (mm Hg)	118.5 $\pm$ 2.2	114.2 $\pm$ 2.2	0.166
DBP (mm Hg)	76.9 $\pm$ 2.2	72.4 $\pm$ 2.2	0.149
OC users (%)	28	77	< 0.001
Reported allergies (%)	43	41	0.897

¹ All values are least-squares means $\pm$ least-squares errors. WC, waist circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; OC, oral contraceptive.

² Differences between groups were determined by using a general linear model ANOVA for all variables except OC and allergies, which were analyzed by using Pearson's chi-square.

RESULTS

Characteristics of the subject population

Characteristics of the women in the obese and nonobese groups are presented in **Table 1**. The obese women had a greater percentage of body fat, had a greater waist circumference, and were significantly heavier than the nonobese women. The prevalence of OC use was significantly lower in obese than in the nonobese women. Of the total 23 OC users (6 obese and 17 nonobese), the most common formulation used in obese (33%) and nonobese (50%) women was 35 μ g 17β -estradiol:0.25 μ g progesterin. There were no significant differences in the history of allergies between the 2 groups of women. No significant differences in fasting blood triacylglycerols or in total cholesterol or its subfractions were observed between groups.

IgE, IL-4, sex hormones, and leptin

There were no significant differences in circulating concentrations of total IgE antibodies between the obese and nonobese women (87.1 $\pm$ 43.5 and 110.8 $\pm$ 44.3 kU/L, respectively). The presence of specific IgE in the obese women, however, was almost 3 times that in the nonobese women (**Figure 1**). The obese women had higher circulating 17β -estradiol and lower SHBG concentrations than did the nonobese women. After adjustment for OC use, the differences in SHBG between the obese and nonobese women were no longer significant. BAE was significantly higher in the obese than in the nonobese women (**Table 2**).

Plasma concentrations of leptin in the obese women were >2 times those in the nonobese women (**Table 2**). The differences in leptin remained after adjustment for OC use. Circulating concentrations of IL-4 could not be detected.

Carbohydrate metabolism and insulin resistance

Fasting concentrations of glucose, insulin, and C-peptide and the FIRI were greater in the obese than in the nonobese women after adjustment for OC usage (**Table 3**). In the same analysis, with OC as an independent factor, OC users had higher FIRI values than did nonusers ($P = 0.051$). The interaction between

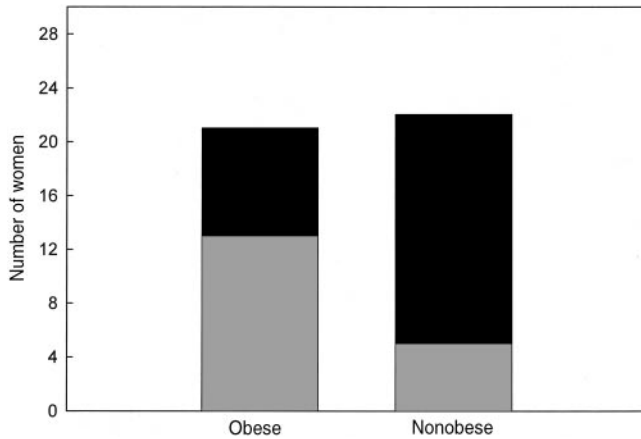


FIGURE 1. Number of obese ($n = 21$) and nonobese ($n = 22$) women who tested positively for the presence of circulating specific immunoglobulin E antibodies (gray shading). Black shading represents the total number of women. Differences were determined by Pearson's chi-square analysis, $P = 0.008$.

body fat status and OC use was not significant, which indicated that the effect of OC use on the FIRI was independent of obesity.

After the glucose test load, there were no significant differences in glucose or insulin concentrations between the obese and nonobese women over the time points studied, regardless of whether OC was unadjusted or adjusted for. Plasma concentrations of C-peptide in the obese women, however, remained

TABLE 2

Hormone and leptin concentrations adjusted for oral contraceptive use in obese and nonobese women¹

	Obese ($n = 21$)	Nonobese ($n = 22$)	P^2
17 β -Estradiol (pg/mL) ³	57.4 $\pm$ 6.2	35.4 $\pm$ 6.2	0.024
SHBG (nmol/L)	71.3 $\pm$ 8.9	76.4 $\pm$ 9.0	0.7
BAE (nmol/L)	0.009 $\pm$ 0.001	0.003 $\pm$ 0.002	0.01
Leptin (ng/mL)	24.5 $\pm$ 2.0	11.2 $\pm$ 2.0	< 0.001

¹ All values are least-squares means $\pm$ least-squares errors. SHBG, sex hormone-binding globulin; BAE, biologically available 17 β -estradiol (estimated by the ratio of 17 β -estradiol to SHBG).

² Differences were determined by using a general linear model ANOVA.

³ For women not using oral contraceptives, blood concentrations were measured during the luteal phase of the menstrual cycle.

TABLE 3

Fasting blood values and insulin resistance adjusted for oral contraceptive use in obese and nonobese women¹

	Obese ($n = 21$)	Nonobese ($n = 22$)	P^2
Glucose (mg/dL)	88.1 $\pm$ 1.5	81.7 $\pm$ 1.5	0.007
Insulin (μ U/mL) ³	8.6 + 9.8/–7.5	5.4 + 6.1/–4.7	0.025
C-peptide (ng/mL)	2.3 $\pm$ 0.1	1.5 $\pm$ 0.1	0.001
FIRI ³	1.68 + 1.9/–1.5	–1.03 + 1.1/–1.2	0.01

¹ All values are least-squares means $\pm$ least-squares errors. FIRI, fasting insulin resistance index.

² Differences were determined by using a general linear model ANOVA.

³ Values were log transformed.

TABLE 4

Pearson's multiple correlation analysis (r values)¹

	FM	WC	FIRI ²	C-peptide	BAE
WC	0.76 ³				
FIRI ²	0.30 ⁴	0.26 ⁵			
C-peptide	0.36 ⁴	0.30 ⁴	0.55 ³		
BAE	0.55 ³	0.55 ³	0.23 ⁵	0.30 ⁴	
Leptin	0.77 ³	0.77 ³	0.45 ³	0.30 ⁴	0.45 ³

¹ FM, fat mass; WC, waist circumference; FIRI, fasting insulin resistance index; BAE, biologically available 17 β -estradiol.

² Values were log transformed.

³ $P \leq 0.01$.

⁴ $P \leq 0.05$.

⁵ $P \leq 0.1$.

greater than those in the nonobese women over the course of the OGTT. On average, the C-peptide concentrations of the obese women were 22% higher ($P < 0.05$) than those in the nonobese women across the 4 time points.

A comparison of the AUCs of glucose, insulin, and C-peptide between groups showed that only plasma glucose, after adjustment for OC, was greater in the obese than in the nonobese women (7044 ± 267 compared with 5944 ± 271 mg $\cdot$ min/dL, respectively; $P = 0.01$).

Multiple correlations

A simple Pearson's multiple correlation analysis showed that several hormonal and metabolic variables tested were interrelated (Table 4). Percentage FM correlated positively and significantly with waist circumference, FIRI, C-peptide, BAE, and leptin. FIRI was positively associated with fasting concentrations of C-peptide and leptin. BAE was significantly related to C-peptide and leptin. Logistic regression analysis with FM, BAE, and leptin as independent variables showed FM to be a positive predictor of specific IgE. Leptin tended toward a negative correlation with specific IgE (Table 5).

DISCUSSION

The prevalence of an atopic state, as indicated by the presence of specific IgE, was greater in the obese than in the nonobese women in this study. Although the frequencies of self-reported allergies and total IgE antibody concentrations were similar between the 2 groups of women, the test for the presence of specific IgE showed that 62% of the obese women, in contrast with 28% of the nonobese women, tested positively for atopy. To our knowledge, this is the first evidence of a direct relation between adiposity and a Th2 immune response in women. The present findings are an extension of previous investigations that reported

TABLE 5

Logistic regression analysis of specific immunoglobulin E antibodies¹

Parameter	Estimate	SE	P^2
Constant	–6.58	2.37	0.005
Fat mass	0.28	0.11	0.008
BAE	–26.81	52.38	0.609
Leptin	–0.11	0.06	0.059

¹ BAE, 17 β -estradiol.

² Overall chi-square P value = 0.009.

a significant correlation between positive skin test results to common aeroallergens (8) or asthma-like symptoms (7) and BMI in adolescent girls. Furthermore, in those studies, the positive relation between overweight status and atopic state was observed only among sexually mature females. Those results suggest that the predisposition toward a humoral-mediated immune response is related to menarche and to an increased production of 17β -estradiol (8). In the present investigation, plasma concentrations of 17β -estradiol and BAE were higher in the obese than in the nonobese women.

Adipose tissue has been reported to contain the full complement of steroidogenic enzymes for synthesizing estrogens (18). Adipogenic synthesis and aromatization of testosterone to estradiol has been shown to be elevated in female obesity. Moreover, abdominal obesity in women has been shown to be associated with greater plasma concentrations of free estradiol (18) and IR (26). Waist circumference, a close correlate measure of abdominal obesity (27), was greater in the obese than in the nonobese women in the present study. The higher FIRI values and fasting C-peptide and glucose concentrations during the OGTT all indicated that the obese women were more insulin resistant than were the nonobese women.

Estradiol has been shown to be a modulator of IL-4 secretion from CD4⁺ T helper cells. Peripheral blood mononuclear cells, isolated ex vivo from women who were sensitized to mite allergen, were found to increase IL-4 secretion in a dose-response fashion (relative to phosphate buffer control) when different physiologic concentrations of estradiol were added to the incubation medium (15). In a related study, IL-4 release from peripheral blood mononuclear cells, in response to mitogenic provocation, was shown to parallel closely plasma estradiol concentrations measured during the follicular (low) and luteal (high) phases of the menstrual cycle of healthy women (28). In the present study, we measured the nonstimulated release of IL-4, which may explain our failure to detect circulating concentrations of this cytokine (29).

Although 17β -estradiol and BAE were greater in the obese than in the nonobese women, we found that neither of these factors, nor FIRI (data not shown), correlated directly with specific IgE. FM was the only positive predictor, and leptin tended to be a negative predictor of atopy.

Leptin concentrations in the present study were greater in the obese than in the nonobese women. Leptin correlated positively with plasma concentrations of 17β -estradiol and BAE and tended to correlate negatively with atopy (Table 5). The directionality of the correlation was unexpected, given that leptin is directly related to adiposity. This inverse relation may suggest that leptin could have a homeostatic function in immunity, analogous to that for energy balance (for a review see reference 30). One hypothesis is that leptin may down-regulate the Th2 response in obese women by facilitating estrogen binding to up-regulate receptors, thereby reducing estrogen availability to influence Th2 immunity.

Our failure to observe a stronger relation between atopy and either IR or estradiol could have been the result of the confounding influence of OC use by the women. The OC users had higher FIRI values than did the nonusers; 77% of the nonobese women and 28% of the obese women reported using OCs. The possible direct biological effect that synthetic steroids may have had on the Th2 immune response was not assessed. The relatively small

sample size and cross-sectional design of the present study limited our ability to resolve this issue. It will be necessary to control for this factor in future studies related to the present experimental question. Alternatively, it is possible that the strong relation that we found between FM and atopy may indicate the involvement of other chemical mediators, such as IL-18, which has been reported to be elevated in obesity (31) and also has been linked to Th2 immunity (32).

The prevalence of asthma has increased >50% in the United States since 1980 (33), with a greater incidence in adolescent and adult females than in males. Allergic disorders, particularly asthma, cost Americans >6 billion dollars annually in health care and lost productivity in the workplace (34). The findings of the present investigation strongly indicate that obesity, a preventable nutritional condition, is a risk factor for atopy. Although IR was not shown in this study to correlate with a Th2 immune response, obesity and IR have been shown to up-regulate a Th2 response in animal models (35). In view of our present findings and those of others, additional investigations of the mechanism by which adiposity is related to the Th2 immune response should be pursued.



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MRW and ART were responsible for the conceptualization of the research hypothesis and experimental design. ART was responsible for the overall execution of the study. VJV was responsible for the recruitment of subjects, collection of data, statistical analysis, biochemical assays, and preparation of the manuscript. AMR was responsible for the management of all laboratory testing, biochemical assays, and data management. None of the authors had a conflict of interest relative to the study.

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