

Systemic inflammation and higher perception of dyspnea mimicking asthma in obese subjects

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Background: There are a variable number of obese subjects with self-reported diagnosis of asthma but without current or previous evidence of airflow limitation, bronchial reversibility, or airway hyperresponsiveness (misdiagnosed asthma). However, the mechanisms of asthma-like symptoms in obesity remain unclear. **Objectives:** We sought to evaluate the perception of dyspnea during bronchial challenge and exercise testing in obese patients with asthma and misdiagnosed asthma compared with obese control subjects to identify the mechanisms of asthma-like symptoms in obesity.

Methods: In a cross-sectional study we included obese subjects with asthma ($n = 25$), misdiagnosed asthma ($n = 23$), and no asthma or respiratory symptoms ($n = 27$). Spirometry, lung volumes, exhaled nitric oxide levels, and systemic biomarker levels were measured. Dyspnea scores during adenosine bronchial challenge and incremental exercise testing were obtained.

Results: During bronchial challenge, patients with asthma or misdiagnosed asthma reached a higher Borg-FEV₁ slope than control subjects. Moreover, maximum dyspnea and the Borg-oxygen uptake (V'O₂) slope were significantly greater during exercise in subjects with asthma or misdiagnosed asthma than in control subjects. The maximum dyspnea achieved during bronchial challenge correlated with IL-1 β levels, whereas peak respiratory frequency, ventilatory equivalent for CO₂, and IL-6 and IL-1 β levels were independent predictors of the Borg-V'O₂ slope during exercise ($r^2 = 0.853$, $P < .001$).

Conclusions: A false diagnosis of asthma (misdiagnosed asthma) in obese subjects is attributable to an increased perception of dyspnea, which, during exercise, is mainly associated with systemic inflammation and excessive ventilation for metabolic demands. (J Allergy Clin Immunol 2016;■■■:■■■-■■■.)

Key words: Obesity, dyspnea, asthma, inflammation

Asthma and obesity are common disorders with a prevalence that has increased substantially over recent decades. Obesity is a growing worldwide problem that has reached epidemic proportions. The World Health Organization estimates that more than

Abbreviations used

AMP: Adenosine-5'-monophosphate
FENO: Fraction of exhaled nitric oxide
HRR: Heart rate reserve
V'O₂: Oxygen uptake

600 million adults were obese in 2014.¹ Asthma is also a major health problem, which is estimated to affect about 300 million persons worldwide, with the global prevalence of asthma ranging from 1% to 18% of the general population.²

Several cross-sectional and prospective longitudinal studies have suggested a link between obesity and asthma.³⁻⁵ It has been reported that obesity is associated with a dose-dependent increase in the odds of incident asthma⁶ and that weight reduction leads to a significant improvement in asthma symptoms.⁷ Moreover, in adults with self-reported symptoms of asthma, obesity was associated with asthma severity indicators, such as respiratory symptoms, use of health care services, or medication requirements, after adjusting for potential confounders.⁸

However, most of these studies have used self-reported diagnosis of asthma with no confirmation based on objective measurements of variable airflow obstruction or bronchial hyperresponsiveness.^{9,10} This raises the possibility that asthma might not be adequately diagnosed (misdiagnosed asthma). In fact, analysis of 16,171 participants from the Third National Health and Nutrition Examination Survey showed that subjects in the highest body mass index quintile had the greatest risk of exercise-related dyspnea and self-reported asthma, despite having the lowest risk for airflow obstruction.¹¹ Moreover, other studies have not demonstrated associations between obesity and asthma severity.^{12,13} This is particularly relevant when we consider the possibility that obesity can cause dyspnea through other mechanisms, leading to a misdiagnosis of asthma.

Aside from airflow obstruction, obesity has been shown to adversely affect respiratory mechanics, decrease respiratory muscle function and lung volume, and increase the work and energy cost of breathing,^{9,14} which, either independently or in combination, could also cause asthma-like symptoms. Furthermore, the perception of dyspnea can be related to other factors that are common in obese subjects, such as deconditioning¹⁵ or psychological and emotional stress.¹⁶ An additional possible mechanism involves the effect of inflammation on perception of symptoms. Adipose tissue from obese subjects secretes several regulatory adipokines and proinflammatory cytokines,¹⁷ leading to a chronic mild systemic inflammatory state.¹⁸ Several reports suggest that some of these mediators contribute significantly to neuronal mechanisms of inflammatory hypernociception¹⁹ and that specific receptors have been localized in brainstem regions involved in respiratory control.²⁰

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On the basis of these observations, we hypothesized that an increased perception of dyspnea might be related to the misdiagnosis of asthma in obese subjects. Our objective was to evaluate the perception of dyspnea during bronchial challenge and exercise testing in obese subjects with asthma, misdiagnosed asthma, and no asthma or respiratory symptoms to identify the mechanisms of asthma-like symptoms in obesity.

METHODS

Study subjects

We selected obese subjects (body mass index >30 kg/m²) between the ages of 18 and 65 years from outpatient obesity clinics in the Endocrinology Department at La Paz University Hospital between January 2012 and December 2012. Exclusion criteria were the existence of a previous diagnosis of chronic obstructive pulmonary disease, bronchiectasis, sleep apnea, hypoventilation syndrome, heart disease, or psychiatric disorders; asthma exacerbation within the previous 3 months; use of oral glucocorticoids; contraindication for performing bronchial challenge or exercise testing; and the inability to comprehend or carry out the study procedures.

Selected obese subjects were classified as asthmatic, misdiagnosed asthmatic, or control subjects according to their clinical reports and current evaluation. Patients with a diagnosis of asthma established at least 6 months earlier, according to the Global Initiative for Asthma criteria,²¹ were considered asthmatic subjects. Subjects with self-reported asthma but no previous evidence of airflow limitation, bronchial reversibility, or airway hyperresponsiveness were considered to have misdiagnosed asthma. Moreover, these subjects were re-evaluated at the time of enrollment to confirm that they did not meet Global Initiative for Asthma criteria and were therefore included in the misdiagnosed asthma group. The remaining subjects were considered control subjects.

The study was approved by the La Paz Hospital Medical Ethics Committee (PI-795), and informed consent was provided by all subjects.

Clinical and functional evaluation

Height and body weight were recorded, and body mass index was calculated as body weight divided by the square of the calculated height (in kilograms per meter squared). Body composition was evaluated by using bioelectrical impedance analysis (Bodystat, Isle of Man, United Kingdom). Smoking history, age at asthma diagnosis, and current asthma treatment were recorded. Specific questionnaires for depression (Beck depression inventory)²² and anxiety (State-Trait Anxiety Inventory)²³ were administered to all patients.

Spirometry was performed with a pneumotachograph, and static lung volumes were measured with a constant-volume body plethysmograph (MasterLab Pro; Vyasis Healthcare, Hoechst, Germany), according to current recommendations.^{24,25} European Coal and Steel Community-predicted values were used.²⁶ Before testing, patients omitted short-acting inhaled bronchodilators for 8 hours and long-acting β -agonists for 12 hours.

Fraction of exhaled nitric oxide (FENO) values were measured immediately before spirometry by using a chemiluminescence analyzer (CLD88sp, Eco Medics, Dürnten, Switzerland), according to American Thoracic Society/European Respiratory Society recommendations.²⁷

Systemic biomarkers

Quantitative determination of C-reactive protein was done by using a latex agglutination turbidimetric immunoassay on the ADVIA 2400 analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany), with a lower detection limit of 0.003 mg/dL and an intra-assay coefficient of variation of 1.2%. Fibrinogen was assessed by using a coagulation analyzer (Roche, Mannheim, Germany) according to the Clauss method and calculated from EDTA to citrate plasma values. The detection range was 0.5 to 12.0 g/L, and the intra-assay variability was 2.8%.

Serum levels of IL-1 β , IL-6, IL-8, TNF- α , leptin, and adiponectin were determined by using a Milliplex MAP immunoassay by Millipore (Merck KGaA, Darmstadt, Germany) with a Luminex xMAP analyzer (Luminex, Austin, Tex). The lower detection limits were 0.5 pg/mL for IL-1 β , 0.4 pg/mL for IL-6, 0.1 pg/mL for IL-8, 0.1 pg/mL for TNF- α , 4.7 pg/mL for leptin, and 6.0 pg/mL for adiponectin. The intra-assay coefficients of variation ranged from 2% for adiponectin to 16% for leptin.

8-Isoprostane levels were measured by using an enzyme immunoassay (Cayman Chemical Company, Ann Arbor, Mich) with a detection limit of 2.7 pg/mL and an intra-assay coefficient of variation of 11.7%. Neuropeptide Y levels were measured by using a competitive enzyme immunoassay (Abnova, Taipei City, Taiwan) with a detection limit of 0.18 ng/mL and an intra-assay coefficient of variation of less than 10%.

Adenosine bronchial challenge

Adenosine-5'-monophosphate (AMP) bronchial challenge was performed after a short dosimeter protocol²⁸ by using a bronchial aerosol provocation system (APS; Jaeger, Würzburg, Germany) with a Medic Aid SideStream nebulizer (Medic-Aid, Bognor Regis, United Kingdom). Each subject was instructed to inhale the aerosols by taking slow deep breaths from functional residual capacity to total lung capacity without breath holding. The first aerosol was 0.9% saline, followed by quadrupling doses of AMP from 0.02 to 36.86 mg. FEV₁ was measured 2 minutes after each dose, and the highest of 3 acceptable measurements within 150 mL was retained to create dose-response curves. Just before the spirometric measurements, intensity of dyspnea was assessed by using a modified Borg scale,²⁹ which is a categorical scale scored from 0 to 10 with specific descriptors of dyspnea, where 0 represents the sensation of normal breathing (absence of dyspnea) and 10 corresponds with the most severe (maximal) difficulty breathing that the subject had previously experienced or could imagine. Each subject was instructed to record the degree of dyspnea they felt at that moment.

The test was discontinued when there was a decrease in FEV₁ of 20% or greater compared with the control inhalation (0.9% saline solution) or until the maximum dose was inhaled. When FEV₁ had decreased by 20% or greater from postdiluent baseline values, the challenge result was considered positive and the PD₂₀ value was determined by means of linear extrapolation on a semilogarithmic scale. The bronchial reactivity index was defined as the log of the percentage decrease in FEV₁/log final AMP dose after adding 10 to eliminate negative values.³⁰ We also recorded the maximum Borg score, the perception of breathlessness at a 20% decrease in FEV₁, and the Borg score change divided by the cumulative AMP dose and by the change in FEV₁ over the postdiluent value (Δ Borg/ Δ FEV₁).

Exercise testing

A week after the AMP bronchial challenge, a symptom-limited incremental exercise test was performed on an electronically braked cycle ergometer (Ergobex, Bexen, Spain), according to the standards of the American Thoracic Society/American College of Chest Physicians statement.³¹ The initial 2 minutes consisted of resting data collection followed by 1 minute of unloaded cycling. Subsequently, workload was increased by 15 W/min until maximal symptom-limited exercise was achieved. Pedaling rates were maintained between 50 and 60 revolutions per minute. Expired gases and ventilation were measured on a metabolic cart by using a pneumotachograph positioned at the mouth with O₂ and CO₂ analyzers (Oxycon Alpha, Jaeger). This allowed for breath-by-breath measurements of oxygen uptake (V'O₂), carbon dioxide production (V'CO₂), minute ventilation, respiratory rate (*f*), and tidal volume. The predicted values of Jones et al³² were used for the exercise measurements. In all patients heart rate, heart rhythm, blood pressure, and oxygen saturation were continuously monitored. In addition, full 12-lead electrocardiograms were monitored during each minute of exercise and recovery. Oxyhemoglobin saturation was continuously monitored by using a finger Oscar II pulse oximeter (Datex, Helsinki, Finland). Maximal work rate was defined as the highest work rate that the subject was able to maintain for at least 30 seconds. Anaerobic threshold was estimated by using the V-slope method.³¹

TABLE I. Demographic data and clinical characteristics of the study subjects*

Characteristic	Control group	Misdiagnosed asthma group	Asthma group	P value
Subjects, n	27	23	25	—
Male/female sex				.435
Male, no. (%)	16 (59)	10 (44)	11 (44)	
Female, no. (%)	11 (41)	13 (56)	14 (56)	
Age (y)	41 ± 12	42 ± 11	43 ± 11	.798
Height (m)	1.69 ± 0.09	1.67 ± 0.09	1.66 ± 0.09	.496
Weight (kg)	119 ± 28.9	112 ± 26	114 ± 17	.619
BMI (kg/m ²)	41.4 ± 7.7	40.0 ± 7.1	41.2 ± 5.2	.751
Fat body mass (kg)	50 ± 19	47 ± 12	53 ± 9	.462
Fat-free body mass (kg)	69 ± 16	64 ± 18	61 ± 12	.257
FFMI (kg/m ²)	23.8 ± 3.8	22.8 ± 5.3	22.1 ± 2.6	.320
Smoking status				.705
Current smoker, no. (%)	11 (41)	6 (26)	8 (32)	
Former smoker, no. (%)	11 (41)	8 (35)	9 (36)	
Never smoker, no. (%)	5 (19)	9 (39)	8 (32)	
Smoking history (pack years)	16 ± 16	15 ± 14	14 ± 6	.881
Asthma diagnosis in relatives, no. (%)	13 (48)	7 (30)	9 (36)	.416
Self-reported asthma, no. (%)	0	23 (100)	25 (100)	<.001
Age at asthma diagnosis (y)	—	28 ± 12	28 ± 11	.969
Asthma treatment				
SABA, no. (%)	1 (4)	13 (57)	15 (60)	<.001
LABA, no. (%)	0	7 (30)	7 (28)	.006
IC, no. (%)	0	6 (26)	11 (44)	<.001
History of anxiety or depression diagnosis, no. (%)	7 (26)	8 (35)	7 (29)	.790
State anxiety-STAI score	15.6 ± 11.6	26.7 ± 17.4	18.9 ± 12.9	.081
Trait anxiety-STAI score	19.1 ± 13.2	30.9 ± 13.9†	23.6 ± 9.5	.042
Beck Depression Inventory score	8.6 ± 7.4	14.1 ± 10.5	10.9 ± 7.8	.184

BMI, Body mass index; FFMI, fat-free mass index; IC, inhaled corticosteroids; LABA, long-acting β -agonists; SABA, short-acting β -agonists; STAI, State-Trait Anxiety Inventory.

*Data are expressed as means $\pm$ SDs or numbers (percentages).

†Comparisons versus control group: $P < .05$.

By pointing to the Borg scale, subjects rated dyspnea at rest, every minute during exercise, and at peak exercise. The Borg dyspnea scores were related to work rate and $\dot{V}O_2$ to standardize for stimulus intensity. The exercise response slopes expressed as means of slopes from linear regression analysis of individual subjects' data were used as indices of exertional dyspnea. Dyspnea thresholds were expressed as the x-intercepts of the relationships between Borg ratings and work intensity or $\dot{V}O_2$.

Statistical analysis

The minimum sample size for detection of an effect difference was calculated from a previous analysis about perception of dyspnea in nonsmoking and nonobese healthy subjects, reporting a slope for a Borg- $\dot{V}O_2$ score of 0.238 ± 0.038 Borg/L/min.³³ Accepting an α risk of .05 and a β risk of .2 in a 2-sided test, 23 subjects were necessary in each group to recognize as statistically significant a minimum difference of 0.038 units between any pair of groups, assuming that 3 groups existed (dropout rate, 10%).

Continuous variables were expressed as means $\pm$ SDs or medians (interquartile ranges), depending on their distribution. Categorical variables were reported as absolute numbers and percentages. Comparisons between groups were performed by using ANOVA, followed by the Bonferroni *post hoc* test for continuous variables and the χ^2 test for categorical variables.

Variables related to perception of dyspnea were determined by using Pearson correlation. Those significant contributors were then introduced in a stepwise multiple linear regression analysis to identify determinants of the perception of dyspnea after verifying the assumptions of multiple regression. Skewness and kurtosis were used to assess whether selected variables were normally distributed, whereas partial regression plots between the independent and dependent variables were visually inspected to check for linearity. Moreover, homoscedasticity was explored by using scatter plots of the standardized residuals on the standardized predicted values and by using

the Levene test for equality of variances. In the multiple linear regression analysis predictor variables were retained only if their addition significantly improved ($P < .05$) the fraction of explained variability (r^2). A P value of less than .05 was deemed statistically significant throughout. Statistical analysis was performed with SPSS software for Windows (version 13; SPSS, Chicago, Ill).

RESULTS

Included in the study were 25 obese asthmatic subjects, 23 subjects with misdiagnosed asthma, and 27 obese control subjects. The demographic and clinical characteristics of the 3 study groups are presented in Table I. We found no significant differences between groups for anthropometric characteristics or smoking status. However, obese subjects with misdiagnosed asthma had higher trait anxiety scores (a measurement of chronic anxiety) than control obese subjects ($P = .028$).

Lung function and systemic biomarker measurements are summarized in Table II. Of the 25 asthmatic subjects, 14 had mild persistent asthma ($FEV_1 \geq 80\%$ of predicted value), and 11 had moderate persistent asthma (FEV_1 60% to 80% of predicted value). The asthmatic subjects had significantly lower FEV_1 and FEV_1 /forced vital capacity ratio and higher residual volume and FENO values compared with the other 2 groups. Interestingly, lung volumes and FENO values were similar between subjects with misdiagnosed asthma and control subjects (Table II). There were no significant differences in baseline biomarker levels among the 3 study groups, although the log-adjusted IL-1 β level was higher in subjects with misdiagnosed asthma than in control subjects (1.06 ± 0.41 vs 0.53 ± 0.30 , $P = .026$).

TABLE II. Baseline lung function and serum levels of biomarkers in the study subjects*

Variable	Control group	Misdiagnosed asthma group	Asthma group	P value
FVC (% predicted)	105 ± 15	99 ± 13	100 ± 15	.352
FEV ₁ (% predicted)	101 ± 14	94 ± 15	86 ± 17‡	.006
FEV ₁ /FVC ratio	0.81 ± 0.05	0.80 ± 0.05	0.73 ± 0.11‡¶	<.001
PEF (% predicted)	97 ± 16	91 ± 14	87 ± 18	.065
FEF _{25-75%} (% predicted)	79 ± 20	79 ± 23	58 ± 19‡¶	.001
FIF _{50%} (L/s)	4.74 ± 0.93	3.17 ± 1.07	3.32 ± 1.52‡¶	.007
FEF _{50%} /FIF _{50%} (%)	83 ± 21	86 ± 17	56 ± 39	.074
Raw (% predicted)	134 ± 36	155 ± 33	170 ± 63†	.024
TLC (% predicted)	92 ± 16	97 ± 11	94 ± 12	.521
FRC (% predicted)	86 ± 19	92 ± 12	101 ± 23†	.025
RV (% predicted)	77 ± 21	99 ± 26	111 ± 33§	<.001
FENO (ppb)	16.7 ± 8.4	14.1 ± 6.1	29.9 ± 12.0§#	<.001
hsCRP (mg/dL)	6.4 ± 7.7	11.2 ± 9.7	8.4 ± 4.8	.525
Fibrinogen (g/L)	480.3 ± 86.5	508.2 ± 155.4	471.5 ± 121.1	.833
8-Isoprostane (pg/mL)	8.5 ± 5.5	65.8 ± 99.9	48.8 ± 80.0	.403
Neuropeptide Y (ng/mL)	8.9 ± 4.4	7.1 ± 5.4	11.1 ± 3.2	.261
Leptin (ng/mL)	1.87 ± 1.43	4.25 ± 3.43	4.21 ± 1.89	.181
Adiponectin (ng/mL)	329 ± 400	363 ± 372	551 ± 548	.619
IL-1β (pg/dL)	0.41 ± 0.27	1.76 ± 1.96	0.76 ± 0.47	.136
IL-6 (pg/mL)	6.6 ± 8.4	8.6 ± 7.1	7.7 ± 6.5	.873
IL-8 (pg/mL)	5.3 ± 2.8	11.3 ± 8.3	11.2 ± 14.8	.495
TNF-α (pg/mL)	3.5 ± 1.8	6.9 ± 5.8	9.7 ± 16.1	.550

FEF_{25-75%}, Forced expiratory flow between 25% and 75% of forced vital capacity; FEF_{50%}, forced expiratory flow at 50% of forced vital capacity; FIF_{50%}, forced inspiratory flow at 50% of forced vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; hsCRP, high-sensitivity C-reactive protein; PEF, peak expiratory flow; Raw, airway resistance; RV, residual volume; TLC, total lung capacity. Comparison versus the control group: † $P < .05$, ‡ $P < .01$, and § $P < .001$. Comparison versus the misdiagnosed asthma group: || $P < .05$, ¶ $P < .01$, and # $P < .001$.

*Data are expressed as means ± SDs.

Perception of dyspnea during bronchial challenge

Airway hyperresponsiveness was only identified in the obese asthmatic subjects. Moreover, these patients had a higher bronchial reactivity index than the misdiagnosed asthma or control groups (Table III). From similar baseline dyspnea scores and in the absence of acute bronchoconstriction, the subjects with misdiagnosed asthma reached maximum dyspnea levels and a Δ Borg/ Δ FEV₁ slope greater than those of control subjects and similar to those of asthmatic subjects (Table III). In comparison with the control group, the asthmatic subjects showed a higher increase in Borg scores compared with the cumulative AMP dose. A similar tendency was noted in subjects with misdiagnosed asthma (0.054 mg [interquartile range, 0.000-0.095 mg] vs 0.000 mg [interquartile range, 0.000-0.027 mg], $P = .051$).

Perception of dyspnea during exercise testing

Physiologic responses and dyspnea perception during exercise are presented in Table IV. The asthmatic subjects showed lower exercise tolerance than subjects from the other 2 groups, although there were no significant alterations in respiratory parameters. No difference was found in exercise response between subjects with misdiagnosed asthma and control subjects. During exercise, the patients with misdiagnosed asthma had more dyspnea than

control subjects (Fig 1). The maximum Borg score and the slopes of Borg ratings over V'O₂ (Borg/V'O₂) were higher in the asthma and misdiagnosed asthma groups than in the control group (Table IV). Moreover, the onset or threshold of dyspnea occurred at a much lower V'O₂ or work rate in subjects with asthma or misdiagnosed asthma than in control subjects (see Fig E1 in this article's Online Repository at www.jacionline.org).

Parameters related to perception of dyspnea in obese subjects

In all obese subjects of the study, the ratio between the Borg score increase and the AMP cumulated dose correlated with age ($r = 0.407$, $P = .001$, see Fig E2 in this article's Online Repository at www.jacionline.org) and the adiponectin level ($r = 0.487$, $P = .040$), whereas maximum dyspnea reached during the bronchial challenge significantly correlated with the IL-1β level ($r = 0.506$, $P = .027$, Fig 2). No other correlations between dyspnea indices and anthropometric, clinical, or functional parameters were identified.

In turn, the Borg-V'O₂ slope correlated significantly with residual volume ($r = 0.577$, $P < .001$), peak respiratory frequency ($r = 0.282$, $P = .041$), peak ventilatory equivalent for CO₂ ($r = 0.447$, $P = .001$), and log-adjusted levels of TNF-α ($r = 0.498$, $P = .022$), IL-6 ($r = 0.472$, $P = .031$), and IL-1β ($r = 0.739$, $P < .001$, Fig 3).

Interestingly, IL-1β levels also inversely correlated with the dyspnea threshold ($r = -0.486$, $P = .025$) and directly correlated with the maximal dyspnea load ($r = 0.543$, $P = .011$). Similarly, leptin levels were related to the dyspnea threshold ($r = -0.468$, $P = .032$) and maximal dyspnea load ($r = 0.457$, $P = .037$, see Fig E3 in this article's Online Repository at www.jacionline.org). None of the demographic and clinical variables, including body composition or anxiety-depression scores, correlated with any index of exercise dyspnea.

The stepwise multiple regression model for the Borg-V'O₂ slope only retained peak respiratory frequency, peak ventilatory equivalent for CO₂, and log IL-6 and log IL-1β levels as independent variables (Table V). The model that included the 4 variables accounted for 85% of the explained variance in perception of exercise dyspnea.

DISCUSSION

The main results of our study are the following: (1) the main difference between obese subjects with misdiagnosed asthma and obese control subjects lies in a higher perception of dyspnea (during bronchial challenge and exercise) to such an extent that this perception is similar to that of asthmatic subjects; (2) perception of dyspnea during bronchial challenge in obese subjects was related to adiponectin and IL-1β levels; and (3) in obese subjects peak respiratory frequency, peak ventilatory equivalent of CO₂, and serum IL-6 and IL-1β levels were independent determinants of perception of dyspnea during exercise, as assessed based on the slope of Borg ratings over V'O₂.

The presence of asthma-like symptoms in the absence of any functional evidence of asthma, which is known as misdiagnosed asthma in the present study, is not uncommon. Several studies report that asthma could be excluded after extensive testing in 30% of cases of physician-diagnosed asthma,^{34,35} even after

TABLE III. Comparisons of perception of dyspnea during AMP bronchial challenge among the 3 study groups*

	Control group	Misdiagnosed asthma group	Asthma group	P value
PD ₂₀ (mg)	—	—	12.2 ± 13.4	—
BRI	10.00 (9.99-10.02)	10.01 (9.82-10.40)	12.0 (10.09-15.83)‡§	.003
Basal Borg score	0 (0-1)	0 (0-1)	0 (0-2)	.705
Maximal Borg score	0.57 ± 1.12	1.95 ± 1.66†	2.33 ± 1.74‡	.001
ΔBorg/ΔFEV ₁ (1/mL)	0.0 (0.0-3.0)	5.3 (0.0-21.7)†	8.9 (0.0-20.3)†	.012
ΔBorg/cumulative AMP dose (1/mg)	0.000 (0.000-0.027)	0.054 (0.000-0.095)	0.109 (0.034-0.623)†	.020
PS ₂₀	—	—	3.70 ± 1.34	—

BRI, Bronchial reactivity index; PD₂₀, provocative dose of adenosine causing a 20% decrease in FEV₁; PS₂₀, perception of breathlessness at 20% decrease in FEV₁.

Comparisons versus the control group: †P < .05 and ‡P < .01. Comparison versus the misdiagnosed asthma group: §P < .01.

*Values represent means ± SDs or medians (interquartile ranges), depending on their distribution.

TABLE IV. Comparisons of exercise responses and dyspnea perception between the study groups*

	Control group	Misdiagnosed asthma group	Asthma group	P value
W peak (w)	97 ± 27	95 ± 27	76 ± 17†	.013
V _E peak (L/min)	67.6 ± 18.4	67.6 ± 14.4	72.2 ± 27.7	.746
Breathing reserve (%)	38 ± 14	39 ± 11	33 ± 12	.334
V _T peak (L)	1.92 ± 0.48	1.94 ± 0.46	2.00 ± 0.59	.889
f peak (min ⁻¹)	35 ± 5	36 ± 5	37 ± 6	.498
t _I /t _{TOT} peak	0.44 ± 0.04	0.45 ± 0.04	0.42 ± 0.03	.042
ΔV _E /ΔV'CO ₂ peak	30.6 ± 9.3	32.0 ± 3.3	30.2 ± 3.5	.594
V _D /V _T peak	16 ± 2	15 ± 2	16 ± 2	.358
HR peak (min ⁻¹)	133 ± 19	145 ± 11	141 ± 19	.135
HRR (min ⁻¹)	44 ± 21	35 ± 8	39 ± 12	.196
HR slope (1/mL/kg)	8.1 ± 1.7	8.5 ± 1.5	8.0 ± 1.2	.401
ΔV'O ₂ /HR peak (mL)	14.2 ± 3.0	14.6 ± 3.2	13.8 ± 2.2	.711
V'O ₂ peak (mL/min/kg)	19.5 ± 3.9	19.5 ± 4.3	15.9 ± 2.6†	.004
V'O ₂ peak (% predicted)	93 ± 12	94 ± 14	83 ± 11†	.015
V'O ₂ /W (mL/min/w)	17.1 ± 3.9	16.0 ± 3.1	15.8 ± 2.7	.488
AT (% VO ₂ max)	62 ± 14	61 ± 10	57 ± 17	.559
Dyspnea slopes				
Borg-V'O ₂	0.413 ± 0.183	0.703 ± 0.294‡	0.716 ± 0.215‡	.001
Borg-W	0.068 ± 0.033	0.095 ± 0.034	0.099 ± 0.055¶	.071
Dyspnea thresholds (x-intercept)				
V'O ₂ (mL/kg/min)	7.0 ± 1.1	4.8 ± 1.3§	4.2 ± 1.6§	<.001
W (w)	30.5 ± 10.7	13.7 ± 11.6§	12.5 ± 6.7§	<.001
Maximal dyspnea load	5 ± 1	8 ± 1§	8 ± 2§	<.001

AT, Anaerobic threshold; f, respiratory frequency; HR, heart rate; HRR, heart rate reserve; t_I, inspiratory time; t_{TOT}, total respiratory time; V_D/V_T, ratio of physiologic dead space to tidal volume; V_E, minute ventilation; ΔV_E/ΔV'CO₂, ventilatory equivalent for carbon dioxide; V_T, tidal volume; W, work intensity.

Comparisons versus the control group: †P < .05, ‡P < .01, and §P < .001. Comparisons versus the misdiagnosed asthma group: ||P < .05. ¶Asthma versus control groups: P = .096.

*Values represent means ± SDs or medians (interquartile ranges), depending on their distribution.

having withdrawn asthma medication.³⁵ This frequency is even greater in obese subjects. In subjects with emergency department visits in the past year, the odds ratio for being misdiagnosed with asthma for obese versus normal-weight subjects was 4.08 (95% CI, 1.23-13.5).³⁶ In fact, among 32 morbidly obese subjects with physician-diagnosed asthma, reversible airway obstruction or bronchial hyperresponsiveness was only detected in 19 patients, whereas in 13 (41%; 95% CI, 0.24-0.50) patients the diagnosis of asthma could not be confirmed.³⁷ Therefore an asthma diagnosis based on symptoms alone is particularly unreliable in obese subjects, and the need for objective measurements of variable airflow obstruction or bronchial hyperresponsiveness is even greater than in the general population. Otherwise, a misdiagnosis will lead to inappropriate treatment, with an increased risk of side effects and increased costs.³⁸

By definition, the patients of the misdiagnosed asthma group in our study had neither airflow limitation nor bronchial

hyperresponsiveness, and therefore the presence of respiratory symptoms cannot be attributed to these alterations. This finding concurs with previous studies confirming that obesity increases the risk for exertional dyspnea and self-reported asthma but not for airflow limitation.¹¹

The mechanisms of dyspnea in obesity remain controversial. Obesity has been shown to cause a reduction in respiratory mechanics, as well as an increase in the work of breathing.¹⁴ In obese subjects excess soft tissue weight compressing the rib cage, fatty infiltration of the chest wall, and an increase in pulmonary blood volume contribute to a reduction in respiratory system compliance.⁹ When morbidly obese patients are compared with nonobese subjects, the decrease in respiratory muscle function, as well as the reduction in respiratory system compliance, results in decreased static lung volumes (particularly functional residual capacity),¹⁴ higher oxygen cost of breathing, and a subjective increase in dyspnea.⁹ The contribution of these factors to the symptoms of our subjects with misdiagnosed

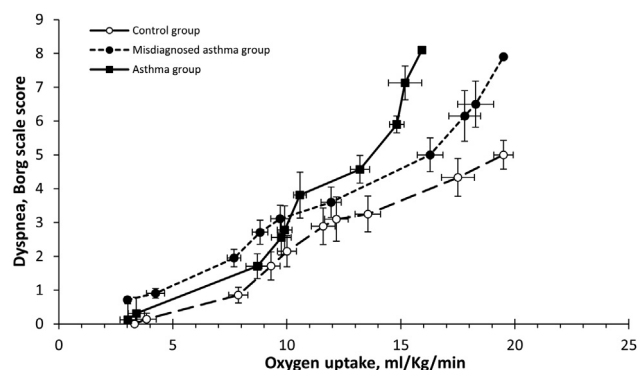


FIG 1. Dyspnea during exercise in the 3 study groups. Values are means $\pm$ SEMs. The Borg/ $\dot{V}O_2$ slopes are significantly greater ($P < .01$) in subjects with asthma or misdiagnosed asthma than in nonasthmatic subjects.

asthma does not seem to be a determinant because they have a degree of obesity that is similar to that of control subjects. Furthermore, the lack of differences in lung volumes or expiratory flows between the subjects with misdiagnosed asthma and control subjects supports this point.

Our results confirm the hypothesis posed by identifying that the main difference between obese subjects with misdiagnosed asthma and obese control subjects lies in a higher perception of dyspnea both during the bronchial challenge and exercise to such an extent that it is similar to that of asthmatic subjects.

The main determinants of dyspnea during exercise in our obese subjects are peak ventilatory equivalent of CO_2 , peak respiratory frequency, and baseline IL-6 and IL-1 β levels. The 2 former factors highlight the importance of the ventilatory response to exercise and agree with previous studies in nonasthmatic women, which observed that the perception of dyspnea in obese subjects at any given $\dot{V}O_2$ correlated significantly with ventilatory equivalent of CO_2 .³⁹ This indicates that an excessive ventilatory response for metabolic demands might be involved in the breathing discomfort of these subjects. These data are also in line with the results of Mahler et al,⁴⁰ who presented the high predictive value of breathing pattern variables, including respiratory frequency, on Borg ratings during exercise.

Nonetheless, the most striking finding of our study is the contribution of IL-6 and especially IL-1 β to the perception of dyspnea during exercise in all our obese subjects. Some prior reports suggest that asthma-like symptoms are more frequent in obese subjects who present a more proinflammatory state because of the presence of metabolic syndrome.⁴¹ This finding demonstrates the potential role of neuroinflammation in the symptomatic perception of obese subjects. In addition to the local effects of airway inflammation, release into the bloodstream of IL-1 β , TNF- α , IL-6, or IL-8 caused by an increase in numbers of classically activated macrophages of obese subjects might have direct effects on the central nervous system and modify the ventilatory pattern and perception of symptoms themselves.

Inflammatory cytokines play an important role in neuro-immune interactions and participate in intercellular communication as neuromodulators,⁴² and therefore they seem to be involved in the central regulation of various physiologic functions. In particular, IL-1 β displays multiple regulatory functions, including modulation of the physiologic response to stress and infection, fever, lymphocyte activation, enhanced release of

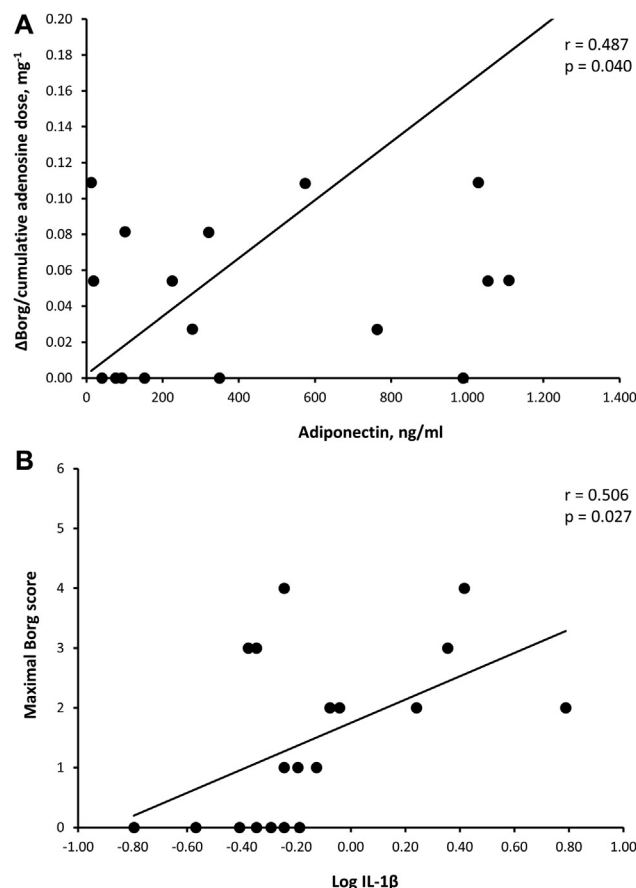


FIG 2. Correlation between the perception of dyspnea during the bronchial challenge and serum levels of adiponectin (A) and IL-1 β (B).

acute-phase protein reactants, increase in plasma epinephrine levels, and stimulation of adrenocorticotrophic hormone release.⁴³ Although little is known about interactions between systemic inflammatory and ventilatory control, several reports suggest that certain cytokines, especially IL-1 β , can have an effect on the generation of the respiratory pattern, as well as the perception of breathing discomfort, by the central nervous system.

The topographic location of IL-1 β receptors includes several brainstem regions that play an integral role in cardiovascular and respiratory control,^{20,44} and IL-1 β -responsive cells have been detected in the nucleus of the solitary tract.⁴⁵ In animal models it has been reported that systemic administration of IL-1 β induces a monophasic increase in ventilation,⁴³ suggesting that IL-1 β evokes prostanoid release in brainstem respiratory control centers and the hypothalamus, where it exerts an excitatory effect. A recent study provides evidence for participation of IL-1 β in the mechanisms of ventilatory control and central chemoreception. The intracerebroventricular administration of IL-1 β to rats increases their minute ventilation, tidal volume, and mean inspiratory flow and decreases their slope of the ventilatory response to carbon dioxide stimulation.⁴⁶ Thus IL-1 β enhances basal ventilation and reduces the sensitivity to hypercapnia, limiting the capacity for a natural compensatory reaction, which might be perceived as a sensation of respiratory discomfort.

Because IL-1 β is involved in the immune response and signal transduction in both the periphery and the central nervous system, it could also play a role in the perception of symptoms. In fact,

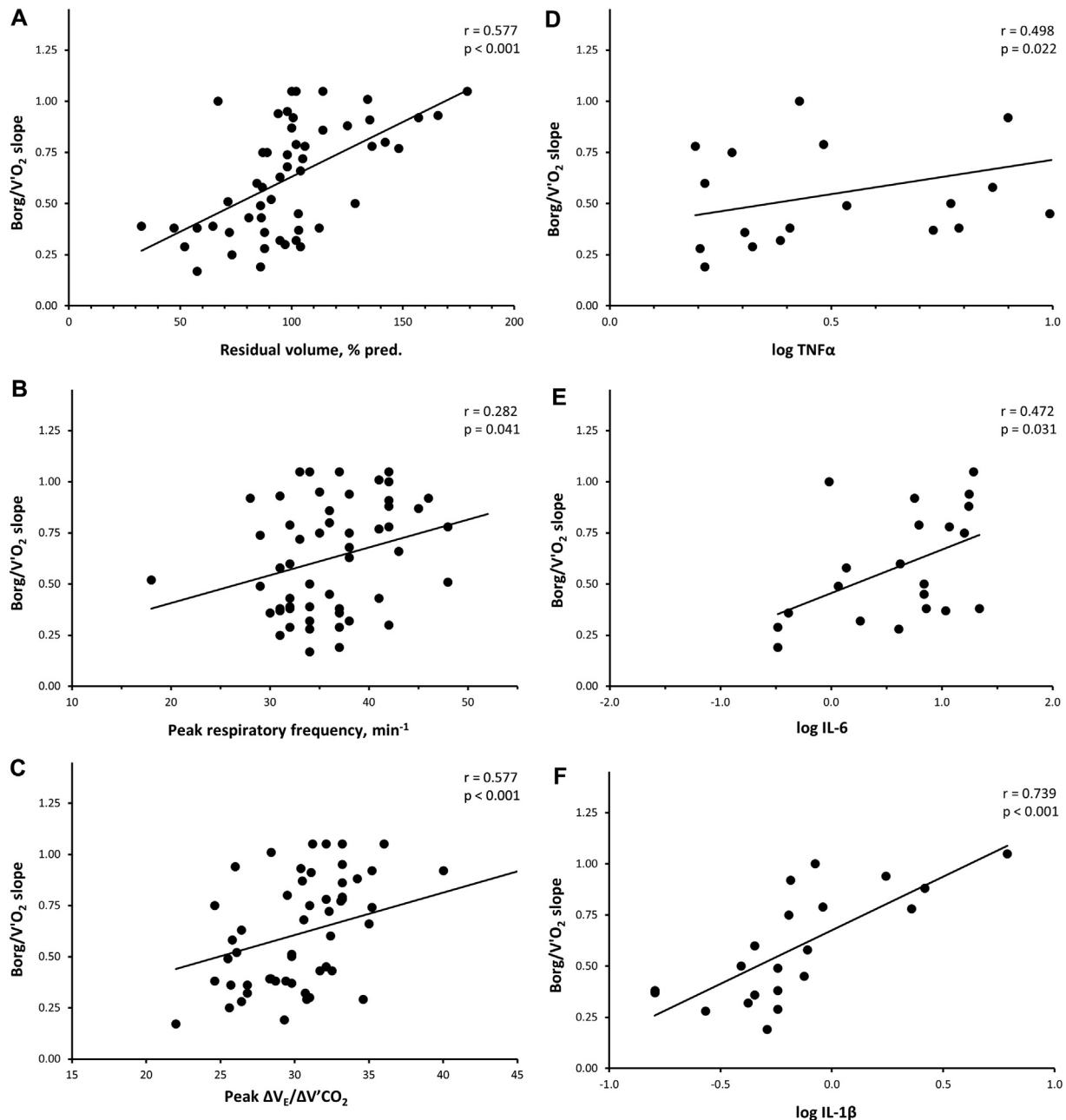


FIG 3. Correlation between exertional dyspnea (evaluated by the slope of Borg ratings over $V'O_2$ [Borg/ $V'O_2$ slope]) and residual volume (A), peak respiratory frequency (B), peak ventilatory equivalent of CO_2 ($\Delta V_E/\Delta V'CO_2$; C), and serum levels of inflammatory biomarkers (D-F).

TABLE V. Independent predictors of perception of dyspnea during exercise, as assessed by the slope of Borg ratings over $V'O_2$, in a multivariate linear regression analysis

	Unstandardized regression coefficients		95% CI for B		Standardized regression coefficients		P value	R^2	R^2 change
	B	SE	Lower limit	Upper limit	B				
Constant	0.0311	0.189	0.033	0.916	—	—	—	—	—
Log IL-1 β	0.444	0.075	0.285	0.602	0.626	<.001	0.546	0.546	
$\Delta V_E/\Delta V'CO_2$ peak	0.0163	0.003	0.009	0.023	0.512	<.001	0.664	0.118	
Log IL-6	0.199	0.046	0.101	0.297	0.444	.001	0.811	0.146	
f_{peak} (min^{-1})	-0.0128	0.006	-0.025	0.000	-0.235	.046	0.853	0.043	

f , Respiratory frequency; $\Delta V_E/\Delta V'CO_2$, ventilatory equivalent for carbon dioxide.

IL-1 β is released during inflammatory and nociceptive conditions,⁴⁷ and the cascade of events involved in the genesis of inflammatory hypernociception has been extensively researched in animal models.⁴⁸ Several lines of evidence have demonstrated that local injection of this cytokine increases nociception through an IL-1 β /prostaglandin pathway.⁴⁹ In addition, IL-1 β has also been proved to be involved in the pathophysiology of several pain-related symptoms.⁵⁰

Although the contribution of IL-6 to the perception of dyspnea during exercise seems to be smaller in magnitude than that of IL-1 β , it could also participate in the neuroinflammatory pathway. In fact, this cytokine, which is mainly produced in response to TNF- α , plays an important role in the physiology of nociception and pain pathophysiology as one of the most powerful stimulants of the hypothalamic-pituitary-adrenal axis.^{51,52}

Our study has different limitations. Despite reaching the estimated sample size, the size of our study group is limited, and the study is based on a single center. Although an effort was made to control the majority of risk factors for dyspnea, some were not, such as small airway function or respiratory muscle strength. Because it is a cross-sectional study, it cannot establish a causal relationship but rather one of association. The sample of obese subjects that we have studied might not be representative of the entire population of obese subjects because the exclusion of several comorbidities (exclusion criteria) limits its extrapolation. Finally, the small sample size does not enable us to accurately assess the effect of inhaled corticosteroids. However, a comparison of the 3 study groups excluding patients treated with inhaled corticosteroids showed similar results (see Table E1 in this article's Online Repository at www.jacionline.org).

In conclusion, our study shows that false diagnoses of asthma (misdiagnosed asthma) in obese subjects are attributable to an increase in the perception of dyspnea. In these subjects exertional dyspnea is mainly determined by the development of an excessive ventilatory response for metabolic demands, as well as a higher level of systemic inflammation. Among the different cytokines that could potentially be involved, IL-1 β stands out because it could contribute to respiratory pattern alterations, as well as greater perception of breathing discomfort.

Key messages

- In addition to the known relationship between asthma and obesity, there are a variable number of obese subjects with self-reported diagnosis of asthma but without current or previous evidence of airflow limitation, bronchial reversibility, or airway hyperresponsiveness (misdiagnosed asthma). The causes of these asthma-like symptoms in obese subjects are not well defined.
- The main difference between obese subjects with misdiagnosed asthma and obese control subjects lies in a higher perception of dyspnea (during bronchial challenge and exercise) to such an extent that this perception is similar to that of asthmatic subjects.
- In obese subjects peak respiratory frequency, peak ventilatory equivalent of CO₂, and serum IL-6 and IL-1 β levels are independent determinants of perception of dyspnea during exercise.

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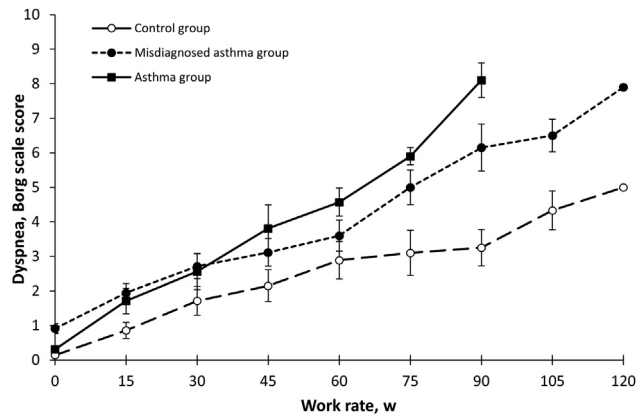


FIG E1. Borg/work rate slopes during exercise in the 3 study groups. Values are means $\pm$ SEMs. The dyspnea threshold (x-intercept) was significantly greater ($P < .001$) in subjects with asthma or misdiagnosed asthma than in nonasthmatic subjects.

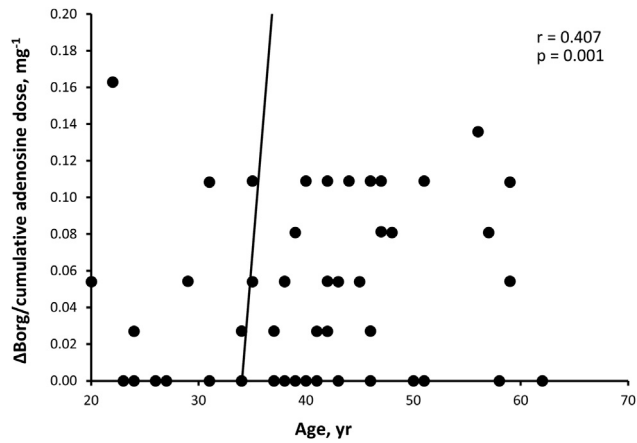


FIG E2. Correlation between the perception of dyspnea during the bronchial challenge and age.

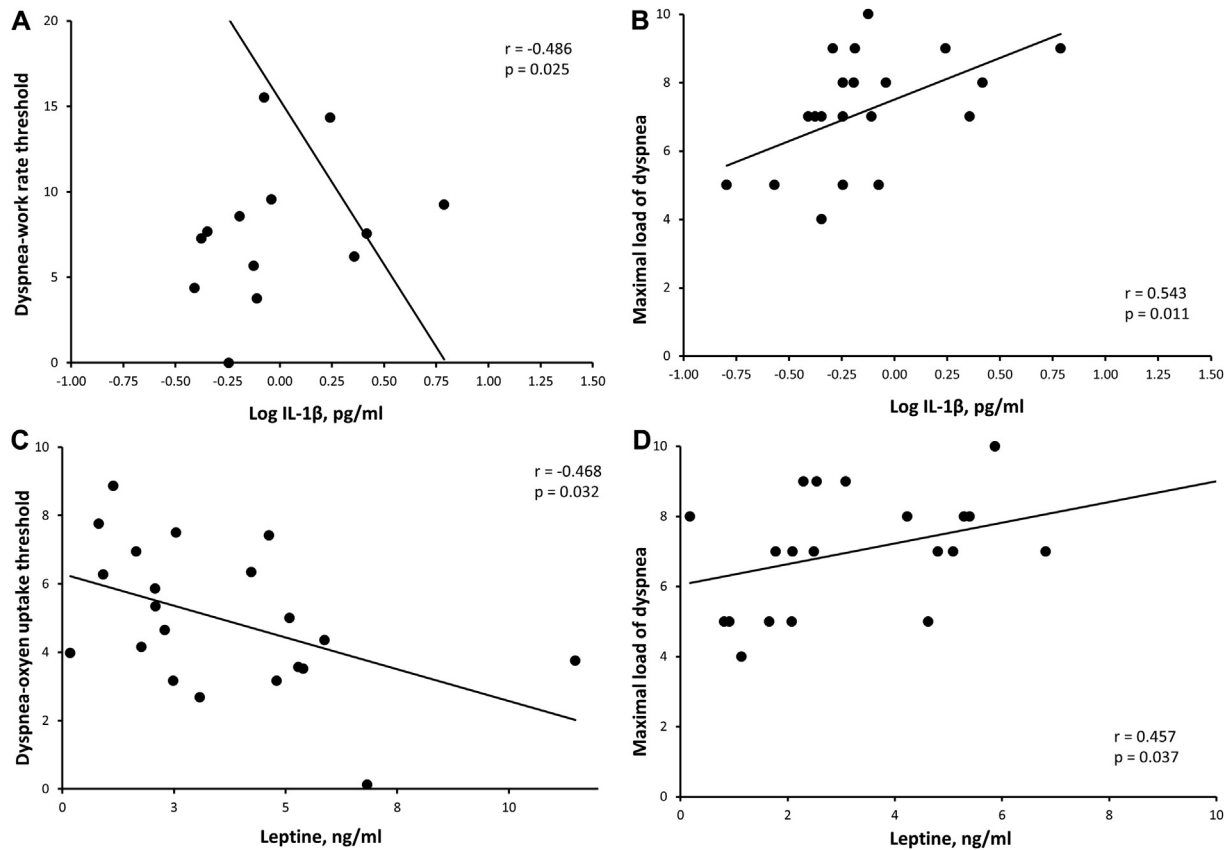


FIG E3. Correlations of IL-1 β and leptin levels with the dyspnea threshold (A and C) and maximal dyspnea load (B and D, respectively).

TABLE E1. Comparison of lung function, biomarker levels, and perception of dyspnea during bronchial challenge and exercise testing among the 3 study groups in subjects without inhaled corticosteroids*

Variable	Control group (n = 27)	Misdiagnosed asthma group (n = 17)	Asthma group (n = 14)	P value
Trait anxiety-STAI score	19.1 ± 13.2	29.3 ± 14.2	25.0 ± 11.3	.183
FENO (ppb)	16.7 ± 8.4	14.4 ± 4.8	28.9 ± 12.5‡¶	<.001
FVC (% predicted)	105 ± 15	100 ± 12	98 ± 17	.305
FEV ₁ (% predicted)	101 ± 14	94 ± 14	87 ± 15†	.021
FEV ₁ /FVC ratio	0.81 ± 0.05	0.79 ± 0.05	0.76 ± 0.10	.057
PEF (% predicted)	97 ± 16	91 ± 15†	88 ± 19†	.184
FEF _{25-75%} (% predicted)	79 ± 20	80 ± 23	58 ± 18‡	.007
Raw (% predicted)	134 ± 36	149 ± 30	166 ± 54	.060
TLC (% predicted)	92 ± 16	96 ± 10	92 ± 12	.558
FRC (% predicted)	86 ± 19	94 ± 6	97 ± 23	.147
RV (% predicted)	77 ± 21	102 ± 19†	111 ± 40‡	<.001
BRI	10.2 ± 0.9	10.3 ± 1.2	15.7 ± 8.3‡¶	.001
Maximal Borg score	0.6 ± 1.1	2.0 ± 1.5‡	2.0 ± 1.7†	.003
ΔBorg/cumulative AMP dose (1/mg)	0.018 ± 0.035	0.054 ± 0.040	1.623 ± 3.317‡	.016
ΔBorg/ΔFEV ₁ (mL ⁻¹)	0.001 ± 0.003	0.003 ± 0.004	0.014 ± 0.011	<.001
Borg-V'O ₂ slope	0.413 ± 0.183	0.736 ± 0.294‡	0.714 ± 0.233†	.001
V'O ₂ dyspnea threshold (mL/kg/min)	7.0 ± 1.1	4.8 ± 1.2#	4.7 ± 1.4§	<.001
Borg-W slope	0.068 ± 0.033	0.091 ± 0.035	0.105 ± 0.072	.124
W dyspnea threshold (w)	30.5 ± 10.7	13.4 ± 11.1§	11.6 ± 8.2§	<.001
Maximal dyspnea load	4.9 ± 1.4	8.2 ± 1.4§	7.5 ± 1.7§	<.001
8-Isoprostane (pg/mL)	8.5 ± 5.5	80.2 ± 113.1	79.1 ± 125.9	.350
Neuropeptide Y (ng/mL)	8.9 ± 4.4	5.2 ± 4.9	9.1 ± 3.8	.325
Leptin (ng/mL)	1.87 ± 1.43	4.16 ± 4.05	4.29 ± 1.56	.333
Adiponectin (ng/mL)	329 ± 400	224 ± 288	394 ± 551	.807
IL-1β (pg/dL)	0.41 ± 0.27	2.16 ± 2.15	0.60 ± 0.20	.114
IL-6 (pg/mL)	6.55 ± 8.44	10.23 ± 7.32	8.06 ± 7.35	.722
IL-8 (pg/mL)	5.32 ± 2.79	12.26 ± 9.16	3.30 ± 2.14	.102
TNF-α (pg/mL)	3.54 ± 1.84	8.41 ± 5.95	5.04 ± 2.82	.165

BRI, Bronchial reactivity index; FEF_{25-75%}, forced expiratory flow between 25% and 75% of forced vital capacity; FRC, functional residual capacity; FVC, forced vital capacity; PEF, peak expiratory flow; Raw, airway resistance; RV, residual volume; STAI, State-Trait Anxiety Inventory; TLC, total lung capacity.

Comparisons versus the control group: †P < .05, ‡P < .01, and §P > .001. Comparisons versus the misdiagnosed asthma group: ||P < .05, ¶P < .01, and #P < .001.

*Data are means ± SDs.