observations between common conditions that frequently coexist. Such information could be of importance in formulating appropriate therapies and guiding future research.

In the present study, we reasoned that it might be possible to begin to differentiate between the above contingencies by examining the impact of each condition alone and in combination on multiple elements of pulmonary function. We hypothesized that if asthma and obesity altered a particular test through similar mechanisms, and if the individual abnormalities were submaximal, there should be synergistic changes in the comorbid state that would correlate with the magnitude of adiposity (20, 29). Alternatively, if the combination represented the concurrence of two prevalent illnesses, the overall physiologic consequences would derive from an algebraic admixture of the individual conditions (20, 29). To test this possibility, we examined the individual components that comprise pulmonary mechanics, airway responsivity and exercise performance, to determine how the different abnormalities associated. Our observations form the basis of this report.

METHODS

Our data were obtained in a prospective, cross-sectional study involving normal subjects (N), nonobese asthmatics (A), obese nonasthmatics (O), and individuals with both conditions (OA). The normal volunteers were obtained from advertisements in the local community and hospital. Participants with the illnesses of interest were outpatients who were identified by chart review and recruited sequentially during visits to the asthma, pulmonary, and/or sleep clinics. The clinic patients were placed into one of the three study groups based on the existing diagnosis in the medical records. No attempt was made to include or exclude asthmatic or obese individuals with a predetermined level of severity or with a particular set of abnormalities. All diagnoses were established before enrollment by caregivers who were not involved in recruitment, data acquisition, or analysis. After joining the study, all subjects prospectively underwent new measures of body mass index (BMI) and detailed assessments of pulmonary function. These data were then used to phenotype members of each group. Weights were measured on a Tanita balance (BWR-627A), and heights were recorded in stocking feet. BMI was calculated as weight (kg)/height (m²) (14).

The admission criteria consisted of physician-diagnosed asthma with and without obesity and obesity alone. Asthma was considered to be present if the medical records contained a diagnosis of such made by a pulmonary specialist based on a history of intermittent wheezing in combination with bronchodilator and/or methacholine responsiveness (27). Obesity was defined as a BMI ≥ 30 kg/m² (14). Normality was defined as the absence of cardiac and pulmonary disease in a person with a BMI ≤ 29 kg/m². The nonasthmatic obese subjects

Address for reprint requests and other correspondence: E. R. McFadden, Jr., Div. of Pulmonary, Critical Care, and Sleep Medicine, MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, OH 44109 (e-mail: erm2@case.edu).
were also free of heart and lung disease and were enlisted from individuals being evaluated and/or treated for sleep disorder breathing. Enrollment in each group was sequential. To limit the study to the effects of asthma and obesity, we excluded individuals with a history of lung disease other than asthma, coronary artery disease, congestive heart failure, or cor pulmonale. Both the normal and overweight asthmatics had recently experienced acute exacerbations, and all were stable at the time of study.

Airway resistance was measured in a constant volume plethysmograph by having the subjects pant at frequencies of 1–1.5 Hz with flows of 0.5–1.5 l/s (9, 16). Resistance was converted to its reciprocal, conductance, and expressed as a conductance-to-thoracic gas volume (TGV) ratio, termed specific conductance (sGaw) (9). Four to five measurements of each variable were averaged. The data were considered acceptable if the coefficients of variation were \( \leq 5\% \).

Static lung volumes were also determined plethysmographically (37). Immediately following the measurement of TGV, the subjects exhaled completely and then inhaled fully in a single maneuver while flow was integrated (37). The expired volume was subtracted from TGV to obtain residual volume (RV), and the inspired vital capacity was added to RV to derive total lung capacity (TLC) (37). Thoracic gas volume was determined at functional residual capacity (FRC).

Three to four complete maneuvers were performed. The FRC and the RV were reported from the trial with the largest TLC value. The coefficient of variation of the TGV maneuvers was \(<7\%\).

Maximum forced exhalations were performed in triplicate with a waterless spiroimeter (25). The curves with the largest 1-s forced expiratory volume (FEV\(_1\)) and forced vital capacity (FVC) were analyzed. The mean forced expiratory flows between 25 and 75% of the FVC (FEF\(_{25-75}\)) were taken from the exhalation with the largest sum of FEV\(_1\) and FVC (25). The static and dynamic lung volume data were expressed as a percentage of predicted normal using race-correction regression equations (4, 19).

Adrenergic and cholinergic responsiveness were evaluated by employing consensus recommendations (3, 25). Bronchodilatation was assessed by recording the FEV\(_1\) before and 15 min after standard aerosols of albuterol (25). The magnitude of effect was expressed as a percentage change from the pretreatment value (\(\%\Delta\)FEV\(_1\)). Airway reactivity was measured by inhaling increasing concentrations of methacholine from a DeVilbis nebulizer (Somerset, PA) with a breath-synchronized trigger (Rosenthal Dosimeter; PDS Instrumentation, Louisville, CO) (3). The initial concentration of 1 mg/ml was progressively raised until the FEV\(_1\) fell \(\geq 20\%\) from control or until an amount of 25 mg/ml was reached. The provocative concentrations (PC\(_{20}\)meth) required to achieve this end point were determined by linear interpolation in the asthmatics and extrapolation in the nonasthmatic subjects. All of the normal and obese subjects received a maximum concentration of 25 mg/ml.

A subset from each group performed 6-min walks to assess the respiratory response to exercise. Selection was based entirely on interest and availability. Subjects moved at their own pace according to American Thoracic Society criteria (2). The intensity of dyspnea was measured before and immediately after exertion with a 10-point Borg scale (0, no symptoms; 10, severe). Arterial saturation was recorded continuously by pulse oximetry (SpO\(_2\)). The Institutional Review Board for human investigations approved the study, and written informed consent was obtained.

Statistical comparisons were performed with one- and two-factor analyses of variance, univariate analysis of variance, \(\chi^2\), regression analysis, and paired and unpaired \(t\)-tests. Post hoc analyses were made with Scheffe’s tests with Bonferroni corrections. Two-tailed \(P\) values \(\leq 0.05\) were considered significant. The study was powered to detect \(\geq 15\%\) differences in the spirometric measurements between N and OA subjects with an \(\alpha = 0.05\) and a \(\beta = 0.20\).

## RESULTS

### General

Two hundred ten adults (52 N, 53 A, 52 O, and 53 OA) participated (Table 1). There were 52 men and 158 women with a mean age of 45.8 ± 14.5 yr. There were no significant between group differences among populations with regard to age (\(P = 0.16\)) or sex distribution (\(P = 0.71\)). The BMI of the N and A subjects averaged 24.5 ± 0.5 and 25.3 ± 0.5 kg/m\(^2\) (\(P = 0.98\)), whereas those of O and OA subjects were 42.1 ± 1.4 and 40.3 ± 1.1 kg/m\(^2\) (\(P = 0.49\)). There was a greater percentage of non-Caucasians in the obese compared with the nonobese groups (\(P > 0.001\)), but there were no differences between O and OA subjects (\(P = 0.77\)).

### Specific conductance

The average values for sGaw (Table 2) ranged between 0.22 ± 0.02 s\(^{-1}\)cmH\(_2\)O\(^{-1}\) in the normal controls and 0.16 ± 0.01 s\(^{-1}\)cmH\(_2\)O\(^{-1}\) in the OA subjects (\(P = 0.001\)). Asthma was associated with a 22.7% reduction from control (\(\Delta\)Gaw = 0.05 s\(^{-1}\)cmH\(_2\)O\(^{-1}\), \(P = 0.001\) (Fig. 1)). Obesity, per se, had no significant impact on this variable (\(\Delta\)Gaw = 0.02 s\(^{-1}\)cmH\(_2\)O\(^{-1}\), \(P = 0.77\)). In the comorbid state, sGaw was 0.06 s\(^{-1}\)cmH\(_2\)O\(^{-1}\) lower than in the normal controls (\(P = 0.004\)). There was no statistical difference between the observed value for OA and the sum of the individual reductions in O and A subjects alone as shown by univariate analysis of variance (\(\Sigma\Delta O + \Delta A = 0.07 \text{s}^{-1}\text{cmH}_{2}\text{O}^{-1}, P = 0.65\) vs. OA) (Fig. 1).

### Spirometry

The spirometric data are presented in Table 2 in both absolute and relative terms. The value for FEV\(_1\) ranged between a mean of 3.19 ± 0.13 liters in the N and 2.08 ± 0.09 liters in the OA subjects (\(P < 0.001\)). Asthma and obesity were associated with reductions of 0.67 (\(P = 0.001\)) and 0.62 liter (\(P = 0.001\)) from normal, respectively (Fig. 1). With OA subjects, there was a 1.11-liter decrement from control (\(P < 0.001\)). This value equaled the sum of both individual changes (\(\Sigma\Delta O + \Delta A = -1.29\) liters, \(P = 0.22\) vs. OA) (Fig. 1).

The value for FEF\(_{25-75}\) varied from 3.33 ± 0.19 l/min in the N to 1.82 ± 0.13 l/min in the OA subjects (\(P < 0.001\)). Asthma was associated with a 1.39-liter decrease from normal (\(P < 0.001\)) (Fig. 1). The change with obesity was −0.93 liter (\(P = 0.001\)). The effect of comorbidity was a decrement of 1.51 liters (\(P < 0.001\)). This value was significantly less than the sum total of obesity and asthma in isolation (\(\Sigma\Delta O + \Delta A = -2.32\) liters, \(P = 0.003\) vs. OA) (Fig. 1). Correcting the FEF\(_{25-75}\) value for the volume expelled by dividing by the FVC did not influence the findings (N, 0.75, A, 0.55, O, 0.72, and AO, 0.65 l/min (\(\Sigma\Delta O + \Delta A = 0.23\) l/min, \(P = 0.001\) vs. OA).

The FVC value fluctuated between 3.98 ± 0.15 liters in the N and 2.82 ± 0.11 liters in OA subjects (\(P < 0.001\)). Asthma

### Table 1. Demographic data

<table>
<thead>
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<th>Variable</th>
<th>N</th>
<th>A</th>
<th>O</th>
<th>OA</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>52</td>
<td>53</td>
<td>52</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>42.1±2.0</td>
<td>46.1±2.2</td>
<td>48.4±1.9</td>
<td>46.4±1.7</td>
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<tr>
<td>Sex, M/F</td>
<td>16/36</td>
<td>13/40</td>
<td>14/38</td>
<td>9/44</td>
<td>0.71</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>24.5±0.5</td>
<td>25.3±0.5</td>
<td>42.1±1.3</td>
<td>40.3±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>C/N/C</td>
<td>40/12</td>
<td>37/16</td>
<td>26/26</td>
<td>28/25</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Data for age and body mass index (BMI) are means ± SD for \(n\) subjects in each of the following groups: N, normal; A, asthmatic; O, obese; OA, both obese and asthmatic. M, male; F, female; C, Caucasian; NC, non-Caucasian. \(P\) values are derived from between-group comparisons.
and obesity were associated with individual reductions of 0.46 ($P = 0.001$) and 0.72 liter ($P = 0.004$) from control, respectively (Fig. 1). In OA subjects, the observed difference from N subjects was $-1.16$ liters ($P < 0.001$) and represented the sum of the effects of both conditions ($\Sigma \Delta O + \Delta A = -1.18$ liters, $P = 0.004$) from control, respectively (Fig. 1). The latter was statistically identical to the sum of obesity and asthma alone ($\Sigma \Delta O + \Delta A = -0.92$ liter, $P = 0.72$ vs. OA) (Fig. 2).

FRC varied from $3.16 \pm 0.12$ liters in A to $2.29 \pm 0.10$ liters in O subjects ($P < 0.001$). With asthma, the FRC rose insignificantly ($\Delta FRC = +0.10$ liter, $P = 0.94$) (Fig. 2). Obesity produced a 0.77-liter reduction ($P < 0.001$). The FRC in OA subjects was 0.72 liter smaller than in N subjects ($P < 0.001$) and statistically equaled the algebraic sum of the findings with obesity and asthma ($\Sigma \Delta O + \Delta A = -0.67$ liter, $P = 0.98$ vs. OA) (Fig. 2).

The RV ranged from $2.30 \pm 0.10$ liters in A to $1.83 \pm 0.09$ liters in O subjects ($P = 0.003$). Asthma and obesity had opposite effects. Asthma was associated with mild hyperinflation ($\Delta RV = +0.30$ liter, $P = 0.03$), whereas obesity caused a small decrement ($\Delta RV = -0.17$ liter, $P = 0.18$). Comorbidity represented the algebraic combination of the two events ($\Delta RV = -0.04$ liter). In this case, the RV fell between the changes with obesity and asthma ($\Sigma \Delta O + \Delta A = +0.13$ liter, $P = 0.40$ vs. OA) and was similar to the value in the controls ($P = 0.98$) (Fig. 2).

**Bronchial responsiveness.** The bronchodilator response to albuterol varied from a $2.3 \pm 0.07\%$ increase in FEV$_1$ over baseline in the N subjects to an $11.6 \pm 1.3\%$ improvement in OA subjects ($P < 0.001$) (Table 4). Albuterol had no effect in N subjects ($P = 0.35$) but produced significant improvements in FEV$_1$ in A subjects ($P < 0.001$). The differences between the N and A groups equaled 6.0% ($P = 0.009$). The obese subjects did not have a bronchodilator response (%$\Delta$FEV$_1$ vs. baseline = $2.6 \pm 0.06\%$, $P = 0.72$; $\Delta$FEV$_1$ O vs. N = $0.3\%$, $P = 0.99$). In the combination, the FEV$_1$ rose $11.6 \pm 1.3\%$ over pretreatment baseline ($P = 0.001$), a difference of $9.3\%$ from N subjects ($P = 0.001$). The latter was statistically equivalent to the sum of the individual elements ($\Sigma \Delta O + \Delta A = 6.3\%$, $P = 0.09$ vs. OA) (Fig. 3).

### Table 2. Specific conductance and spirometry

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>A</th>
<th>O</th>
<th>OA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sGaw, s$^{-1}$·cmH$_2$O$^{-1}$</td>
<td>0.22±0.02</td>
<td>0.17±0.01</td>
<td>0.20±0.01</td>
<td>0.16±0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>FEV$_1$, liters</td>
<td>3.19±0.13 (97.4±2.4)</td>
<td>2.52±0.12 (83.0±2.7)</td>
<td>2.57±0.13 (83.8±2.7)</td>
<td>2.08±0.09 (74.2±2.6)</td>
<td>&lt;0.001 (&lt;0.001)</td>
</tr>
<tr>
<td>FEF$_{25-75}$, l/min</td>
<td>3.33±0.19 (90.6±4.1)</td>
<td>1.94±0.14 (58.1±3.2)</td>
<td>2.40±0.16 (77.7±5.3)</td>
<td>1.82±0.13 (60.6±3.9)</td>
<td>&lt;0.001 (0.001)</td>
</tr>
<tr>
<td>FVC, liters</td>
<td>3.98±0.15 (100.2±2.8)</td>
<td>3.52±0.16 (91.2±2.5)</td>
<td>3.26±0.15 (86.9±2.6)</td>
<td>2.82±0.11 (81.1±2.5)</td>
<td>&lt;0.001 (&lt;0.001)</td>
</tr>
</tbody>
</table>

Data are means ± SE. sGaw, specific airway conductance; FEV$_1$, 1-s forced expiratory volume; FEF$_{25-75}$, forced expiratory flow in the mid vital capacity; FVC, forced vital capacity. Percentages of predicted normal values are in parentheses. $P$ values are derived from between-group comparisons.
The PC_{20}meth ranged from 160.8 ± 22.3 mg/ml in N to 4.7 ± 0.6 mg/ml in A subjects (P < 0.001). The extrapolated threshold dose of methacholine in the normal subjects was 160.8 ± 22.3 mg/ml. The PC_{20}meth in A subjects was significantly smaller at 4.7 ± 0.6 mg/ml (P < 0.001). The between-group difference was 156.1 mg/ml (Fig. 3). The methacholine responsiveness in O subjects mirrored that in N subjects (165.6 vs. 160.8 mg/ml, P = 0.99). The PC_{20}meth in the combined illnesses was 5.4 ± 0.7 mg/ml. This value equaled that in A subjects (P = 0.92). It was 155.4 mg/ml less than control (P < 0.001) and represented the algebraic sum of the individual components (ΣΔΔ + ΔA = 151.3 mg/ml, P = 0.99 vs. OA) (Fig. 3).

**BMI vs. lung function.** The associations between pulmonary mechanics and BMI for all of the asthmatics (n = 106) are presented in Figs. 4–6. As shown, significant relationships were only recorded between the degree of adiposity and those indexes dependent on the volume of gas in the thorax [i.e., FEV₁ and FVC (Fig. 4) and TLC, FRC, and RV (Fig. 5)]. No correlations were found between BMI and airway geometry or bronchial responsiveness [i.e., sGaw and FEF_{25-75} (Fig. 4) or \%ΔFEV₁ and PC_{20}meth (Fig. 6)].

**Exercise performance.** Twenty-three N, 15 A, 13 O, and 20 OA subjects completed the 6-min walks. There were significant differences between groups in the lengths ambulated (P = 0.002) (Table 5). The N and A subjects went statistically similar distances (P = 0.62). The O subjects ambulated less than N subjects (P = 0.001), but there were no differences between them and A (P = 0.18) or OA subjects (P = 0.38). All participants were asymptomatic before exercise. Borg scores increased between 0.7 and 1.2 units over control with exertion (P < 0.001), but there were no significant differences among O, A, and OA subjects and no significant interactions in the combination of OA. No significant alterations in SpO₂ were observed.

**Symptoms and medication use.** To determine whether the presence of obesity influenced the clinical features of asthma, we contrasted the symptoms and medication use in the obese and nonobese asthmatics. As shown in Table 6, no significant between-group differences were found for any variable.

**DISCUSSION**

The results of the current study provide an in-depth physiological assessment of how obesity and asthma combine to influence lung function. By examining the impact of both conditions on multiple traditional tests of pulmonary performance, we could sequentially deduce the unique interactions that existed in each. Once this was established, combining those parameters that reflected specific areas such as pulmonary mechanics, airway responsibility, and exercise performance permitted us to draw a composite picture of the manner in which the illnesses associated. We readily acknowledge that this approach may not provide a complete description of all the potential events transpiring in comorbidity and that complex interactions could be occurring in systems that we did not examine. Nevertheless, we believe it provides valuable insights into the areas studied.

Our data demonstrate that each illness in isolation produces a specific set of abnormalities in pulmonary mechanics that coalesce in an algebraic fashion when the diseases coexist. As
a result, the derangements that are unique to a given condition remain unchanged in comorbidity, whereas shared ones either add or subtract depending on the directional changes in the components. Synergistic interactions do not occur. These observations strongly suggest that asthma and obesity influence the respiratory system through different pathways. Asthma impacts bronchial tone and evokes the sequela of airway obstruction (8, 27). Obesity reduces lung volumes and interferes with chest movement. It does not appear to alter bronchial smooth muscle activity (7, 21, 23, 32).

The asthmatic patients demonstrate the usual physiological alterations seen during remission. They have hypersensitivity to adrenergic and cholinergic agonists, reduced flows in the mid vital capacity range, and hyperinflated RV (8, 27). The attenuated sGaw and FEV₁ values coupled with normal values for FVC, TLC, and FRC are also typical (8, 27). Their PC₂₀meth values are well within diagnostic norms, and the bronchodilator effect size for albuterol is appropriate for the magnitude of the prechallenge FEV₁ (8, 27). In composite, these findings nicely match the published phenotype for chronic asthma and support the representative nature of the subjects in this group.

Adiposity mainly compresses the chest, limiting the expansion of the lungs, and only secondarily influences the airways (21, 26, 31, 35, 38). Functionally, the thorax acts as though it were immersed in water, and the obese participants have reduced values for TLC, FRC, and FVC and a normal RV. Their small thoraxes also produce low forced expiratory volumes and flows. Like asthma, these physiological derangements mirror previous findings (7, 21, 22, 30, 33, 42) and demonstrate the similarities between our subjects and those in the literature.

In our experiments, sGaw and the indexes of bronchial responsiveness in obesity are not different from normal. Such phenomena have been noted previously (15, 18, 30, 33, 42). Airway resistance, as an isolated measurement, can indeed be high in this situation (30, 42), but only because of the small lungs and not because of intrinsic bronchial pathology. When corrected for volume, as in our case, and those of others (30, 42), airway sizes are appropriately normal. A critical evaluation of the data concerning the association of obesity and airway hyperreactivity follows below.

Comorbidity joins the above patterns in a noninteractive fashion. As a result, the combined state has the heightened airway reactivity and diminished sGaw that adiposity lacks and the reduced TLC and FRC that asthma lacks. The low lung volumes of obesity combine with the delayed emptying of asthma to cause the forced expiratory volumes in the union to be smaller than with either alone. Finally, the air trapping of asthma appears to be opposed by the diminished chest expansion of obesity, causing the FRC and RV in the combination to lie between the individual extremes. The only exception to simple combination effects is the FEF₂⁵-₇⁵ value. In this case, the flows in the comorbid state are better preserved than expected and principally reflect the presence of asthma even when corrected for expired volume.

The regression data offer further insights into the interplay between obesity and asthma. BMI correlated weakly with lung volumes and related indexes but not with sGaw or airway reactivity. If obesity and asthma influenced lung function through a similar mechanism, stronger associations would have been expected and would have involved all variables.

The exercise studies were designed to explore potential limitations that could interfere with daily activities and not to examine detailed cardiopulmonary function (2). The expectation was that the combined illness would cause more respiratory distress than either alone. This did not appear to be the case. It needs to be noted that the number of participants in this

Table 4. Bronchial responsiveness

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>A</th>
<th>O</th>
<th>OA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFEV₁, %</td>
<td>2.3±0.7</td>
<td>8.3±1.1</td>
<td>2.6±0.6</td>
<td>11.6±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PC₂₀meth, mg/ml</td>
<td>160.8±22.3</td>
<td>4.7±0.6</td>
<td>165.6±31.7</td>
<td>5.4±0.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are means ± SE. ΔFEV₁, percentage improvement in FEV₁ following albuterol; PC₂₀meth, provocative concentration of methacholine required to reduce the FEV₁ 20% from control. P values are derived from between-group comparisons.
phase is relatively small, and type II statistical errors are possible. It is also possible that those who volunteered had better exercise tolerance.

Benthal et al. (6) have postulated that corpulence is associated with a pattern of rapid shallow breathing at lung volumes near closing volume, which produces limited lung distension. This, in turn, purportedly leads to a perturbed equilibrium of myosin binding in airway smooth muscle, causing an increase in airway reactivity. Although this is an appealing hypothesis, it lacks supporting data. Prevention of deep inhalations during a methacholine challenge amplifies airway responsiveness, but this is only seen in normal subjects (36). It is not observed in asthmatics (36) and has never been reported in obesity. Although respiratory system compliance and lung volumes are lowered in obesity (26, 35), affected individuals can still take deep breaths. As shown in Table 3, TLC, although reduced from control, remained within predicted norms (22).

Furthermore, if the Benther et al. hypothesis (6) were correct, obese subjects would be expected to show an augmented sense of dyspnea at rest that worsens with exertion. None of this was observed experimentally. Neither was there an interaction with asthma. Like the data of Dixon et al. (15), our observations in Tables 5 and 6 do not demonstrate differences in the sensation of breathlessness between obese and nonobese asthmatics. Moreover, if the airways are truly smaller in obesity because of an abnormal latch state of myosin, rather than a passive loss of volume, and if the former augmented the asthma diathesis, then the responses to albuterol and methacholine should have exceeded normal. They also should have exceeded, or at least equaled, the effect sizes in the comorbid group. Neither of these events occurred.

Our observations regarding the lack of concordance between adiposity and airway hyperreactivity are part of a growing body of evidence (1, 15, 18, 32, 33, 36, 37, 39). In early positive studies, Litonjua et al. (24) and Chinn et al. (12) reported that methacholine responsiveness correlates with BMI, but a reevaluation of their data raises important concerns. In the first investigation, individuals with both high and low BMI were found to be at increased risk for the development of bronchial hypersensitivity, thereby raising issues about the selectivity and sensitivity of the findings (24). Interestingly, a subsequent study in asthmatic children by the same investigative group (39) failed to find any relationship between BMI and methacholine susceptibility. In the second investigation, hyperresponsivity could only be detected in males and not females. Such observations have no apparent clinical corollary. In fact, several studies suggest that obesity is a risk factor for asthma in women and not men (5, 10, 18). It is pertinent to note that the magnitude of the difference in reactivity in the Chinn et al. study between the obese and normal subjects is only 0.3 of a doubling dose of agonist (12). Changes greater than or equal to two doubling doses are usually considered meaningful (3, 27).

These issues may not just represent methodological shortcomings. Schachter et al. (33) were unable to find any relationship between BMI and airway hyperreactivity in a survey of over 1,900 adults, whereas Hancox et al. (18) could not detect any association between obesity and either cholinergic or adrenergic sensitivity in their cohort of 1,000 subjects. At the opposite end of the spectrum, weight reductions ≥20 kg, although improving lung function and reducing symptoms, do not have any influence on airway responsiveness (1). Finally, since there is general agreement that cholinergic and sympathomimetic sensitivity occur concomitantly (27), one would expect bronchodilator responsiveness to be part of the obesity syndrome. This does not seem to be the case. Our obese subjects, like those of Hancox et al. (18), did not respond any
differently than normal individuals to albuterol. Furthermore, our obese asthmatics, again like those of Dixon et al. (15), reacted identically to the nonobese, suggesting that adiposity did not add anything to asthma with regard to this phenomenon.

We do not believe that our results are adversely influenced by protocol design or the choice of measurements. Since our investigation is not a longitudinal study or an epidemiological survey, it is limited in sample selection. Because it was not possible to observe temporally how obesity and asthma merged to form the combined condition, we characterized each population separately and computed the relative contributions. This analysis is only valid if the effect in each subgroup is established and representative of patients with the illnesses in question and if clinical features (symptoms and medication use) are similar between the obese and nonobese asthmatics. We believe that these conditions have been fully met (Tables 1–4 and 6) (7, 8, 21, 27, 30, 34).

A salient feature of the current work is that, unlike many population-based trials that involve individuals with self-reported diagnoses that may or may not account for their symptoms (17, 41), our subjects were well defined and documented to have the conditions of interest. Eighteen obese (34.6%) and 14 obese asthmatics (26.4%) also had obstructive sleep apnea (OSA) diagnosed by polysomnography. The existence of this illness did not influence our results. There was no significant difference in the distribution among groups ($P = 0.83$). Moreover, subgroup analysis demonstrated that the subjects with OSA had statistically higher BMI values, but there were no other differences among groups. All of our subjects were under the care of pulmonary specialists who used standard diagnostic criteria, and we did not make any of the diagnoses of the study illnesses in our participants. All of the functional observations reported were prospectively obtained. The clinical diagnoses in the chart at the time of enrollment were the sole criteria used to place individuals into the various groups, and the population assignments were done before testing. Once placed into a

Table 5. Exercise performance

<table>
<thead>
<tr>
<th>Variable</th>
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<th>A</th>
<th>O</th>
<th>OA</th>
<th>P Value</th>
</tr>
</thead>
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<td>15</td>
<td>13</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Distance, ft</td>
<td>1595±55</td>
<td>1451±65</td>
<td>1233±68</td>
<td>1409±63</td>
<td>0.002</td>
</tr>
<tr>
<td>Borg score</td>
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<td>1.5±0.4</td>
<td>1.9±0.4</td>
<td>2.0±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SpO₂, %</td>
<td>97.1±0.3</td>
<td>97.4±0.4</td>
<td>96.5±0.7</td>
<td>96.8±0.4</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Data are means ± SE for n subjects in each group. Distance is the length walked by subjects, and the Borg score indicates the intensity of dyspnea during exertion. SpO₂, average percent arterial oxygen saturation measured by pulse oximetry during the last minute of exercise. P values are derived from between-group comparisons.

Fig. 5. Association between body mass index (BMI) and lung volumes in asthmatics. These data were derived from the 106 subjects in the A and OA groups.

Fig. 6. Association between BMI and airway responsiveness in asthmatics. These data were derived from 106 subjects in the A and OA groups.

Fig. 5. Association between body mass index (BMI) and lung volumes in asthmatics. These data were derived from the 106 subjects in the A and OA groups.
specific population, membership therein remained inviolate irrespective of the subsequent physiological results. No attempt was made to include or exclude asthmatic or obese patients of a predetermined level of severity or with a particular set of abnormalities.

The assessments of lung function employed were all standard, and we have long experience in their use. The variety of indexes examined was intended to explore a broad range of potential impairments so that subtle interactions could be detected where present. We realize that extrapolating the PC_{20} values in the normal and obese participants did not produce physiological data, and this was not our intent. This procedure was undertaken solely to have continuous numeric values to make statistical comparisons between populations, rather than having to deal with cutoff limits. Such an approach had no impact on the results.

In summary, the findings in the current work indicate that asthma and obesity seem to influence the respiratory system through different pathways. Coexistence produces an algebraic summation of the individual abnormalities and not synergistic interactions. These observations indicate that the published epidemiological associations need to be supplemented by definitive mechanistic explanations so that advances can be made in the pathogenesis and therapy of comorbidity.

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REFERENCES


