Physical Deconditioning as a Cause of Breathlessness among Obese Adolescents with a Diagnosis of Asthma

Yun M. Shim1*, Autumn Burnette1*, Sean Lucas1*, Richard C. Herring1, Judith Weltman1, James T. Patrie2, Arthur L. Weltman3, Thomas A. Platts-Mills1

1 Department of Medicine, University of Virginia, Charlottesville, Virginia, United States of America, 2 Department of Public Health Sciences, University of Virginia, Charlottesville, Virginia, United States of America, 3 Department of Human Services and Department of Medicine, University of Virginia, Charlottesville, Virginia, United States of America

Abstract

Background: Obese children frequently complain of breathlessness. Asthma and obesity can both contribute to the symptoms during exercise, and this symptom can contribute to a diagnosis of asthma in these children. Despite the high prevalence of obesity few studies have investigated the cardiopulmonary physiology of breathlessness in obese children with a diagnosis of asthma.

Methods: In this case-control study, thirty adolescents between age 12 and 19 were studied with baseline spirometry and a cardiopulmonary exercise test. Ten adolescents were normal controls, ten had obesity without a diagnosis of asthma, and ten had obesity with a history of physician-diagnosed asthma.

Results: Baseline characteristics including complete blood count and spirometry were comparable between obese adolescents with and without a diagnosis of asthma. During exercise, obese asthmatic and obese non-asthmatic adolescents had significantly reduced physical fitness compared to healthy controls as evidenced by decreased peak oxygen uptake after adjusting for actual body weight (21.7±4.5 vs. 21.4±5.4 vs. 35.3±5.8 ml/kg/min, respectively). However, pulmonary capacity at the peak of exercise was comparable among all three groups as evidenced by similar pulmonary reserve.

Conclusion: In this study, breathlessness was primarily due to cardiopulmonary deconditioning in the majority of obese adolescents with or without a diagnosis of asthma.

Introduction

Over the last fifty years, there has been a steady increase in both asthma and obesity in children [1,2,3]. In parallel, there has been an increase in the proportion of overweight children who are diagnosed with asthma [4,5]. This has led to multiple studies on the mechanisms by which obesity might contribute to asthma [6,7]. Breathlessness is a cardinal symptom of asthma and is generally thought to be caused by a combination of obstructive lung physiology, inflammation, and/or deconditioning [8,9]. Even though cardiac failure, anemia, renal failure, and musculoskeletal abnormalities may also present with breathlessness, these chronic diseases are rare among adolescents and asthma becomes the prevailing diagnosis. However, several authors have also recognized the risk of misdiagnosing asthma in obese children [10,11]. Therefore, the more common problem in adolescent medicine is how to sort out breathlessness related to inflamed airways from other diseases, or as we will argue, obesity related cardiopulmonary deconditioning [12,13,14].

There are at least two distinct routes to the development of the combination of obesity and a diagnosis of asthma. First, there are children with inflamed airways causing bronchial reactivity who avoid exercise because it induces bronchospasm and who often require steroid treatment; some of these children will gain weight over time and become obese. Second, there are children who gain weight because of a poor diet and sedentary lifestyle who become progressively short of breath on exercise and receive a diagnosis of asthma because of complaint of breathlessness. Clearly, these two conditions are different, but in practice, they are not distinguished and often are treated in the same way.

Most epidemiological studies on the relationship between obesity and asthma assume that a physician diagnosis of asthma implies the same etiopathogenesis in obese and normal weight children [4,5,15,16]. Studies investigating the specific underlying
mechanisms of asthma in obese children or adults, however, have found that obese asthmatics are less allergic and/or less inflamed than normal weight subjects [17,18,19,20]. An important feature of the epidemiological studies is that most of them have used a “physician diagnosis of asthma” or a diagnosis of asthma “based on parental survey” to define which children have asthma [4,6,17,18,19]. In practice, a diagnosis of asthma is often based on reports of breathlessness and/or wheezing during exercise [4,6,17,18,19]. In practice, a diagnosis of asthma is often based on parental survey” to define which children have asthma “physician diagnosis of asthma” or a diagnosis of asthma “based on parental survey” to define which children have asthma [21,22,23]. We used cardiopulmonary exercise testing (CPET) because it: i) offers a testing modality in which the subject is challenged to replicate the subjective symptoms of breathlessness; and ii) provides objective information on the cardio-, pulmonary-, and metabolic- limitation at a time when subjective breathlessness is apparent. The results show that a large proportion of our obese teenage subjects with or without a diagnosis of asthma had no measurable cardiac or pulmonary deficit, and appeared to be limited by deconditioning alone.

Methods

Subjects

Prior to enrolment all subjects and their parents signed informed consent documents. The consent procedure and study were approved by the institutional review board of the University of Virginia. Thirty adolescents aged 12 to 19 years were enrolled in three groups: a healthy, non-asthmatic, normal weight control group (controls; n = 10), obese group without history of asthma (OB-CTL; n = 10), and an obese group with a diagnosis of asthma (OB-Asthma; n = 10). Subjects in the latter group had to have been diagnosed with asthma by a physician. Obesity was defined as body mass index (BMI) > 95th percentile for age [24]. Anthropomorphic measurement was assessed based on published methods [25,26]. Subjects were asked to discontinue asthma controller medications 24 hours and short acting beta agonists 6 hours prior to physiologic testing. Additional details are provided in an online supplement.

Baseline assessment and cardiopulmonary stress test (CPET)

Body composition was measured using air displacement plethysmography as described previously [27]. Levels of each subject’s physical activity and metabolic rate were calculated by Previous Daily Activity Recall tool (PAR) [28]. Baseline complete blood count (CBC) with differential was obtained before administering CPET. Spirometry (KoKo Spirometry, nSpire Health, Inc.) was obtained before administering CPET and immediately after completing CPET. Exhaled nitric oxide (eNO) and serum total IgE were measured as previously described [29,30,31]. Participants completed a modified Balke protocol [32]. At the peak of the exercise each subject’s perceived breathlessness was measured by the children’s OMNI scale [33]. Data was continuously analyzed to allow interval calculations of spirometry values, including minute ventilation (Ve), oxygen consumption (Vo2), carbon dioxide production (VCO2), and O2 pulse (Vo2/HR). Maximal voluntary ventilation (MVV) was calculated by multiplying forced expiratory volume in 1 second (FEV1) by a factor of 40. Pulmonary reserve (%PR) was calculated as (1-Ve/ MVV)×100 [34]. Additional detail is provided in the online supplement.

Table 1. Demographic and anthropomorphic characteristics of the study population.

|                      | CTL (n = 10) | OB-CTL (n = 10) | OB-Asthma (n = 10) | P value (CTL vs OB-CTL) | P-value (CTL vs OB-Asthma) | P-value (OB-CTL vs OB-Asthma) |
|----------------------|-------------|-----------------|--------------------|-------------------------|---------------------------|-------------------------------|
| Age (yr)             | 15.1±2.8*   | 13.2±1.7        | 14.7±2.0           | 0.09 (0.27)             | 0.72 (1.00)               | 0.09 (0.23)                   |
| Gender M/F           | 5/5         | 5/5             | 4/6                | 1.00 (1.00)             | 1.00 (1.00)               | 1.00 (1.00)                   |
| Race:                |             |                 |                    |                         |                          |                               |
| Caucasian            | 5           | 7               | 3                  | 0.35 (1.00)             | 0.65 (1.00)               | 0.07 (0.14)                   |
| African American     | 5           | 2               | 7                  |                         |                          |                               |
| Native American      | 0           | 1               | 0                  |                         |                          |                               |
| Weight (kg)          | 55±14       | 96±22           | 115±19             | <0.01 (<0.01)           | <0.01 (<0.01)             | 0.05 (0.16)                   |
| Height (cm)          | 161±12      | 162±5           | 169±8              | 0.74 (1.00)             | 0.11 (0.33)               | 0.07 (0.20)                   |
| Mean BMI             | 20.7±3.0    | 36.3±8          | 40.2±6             | <0.01 (<0.01)           | <0.01 (<0.01)             | 0.24 (0.72)                   |
| Lean Body Weight (kg)| 43.9±10.4   | 55.4±6.1        | 62.7±10.4          | 0.01 (0.03)             | 0.01 (0.01)               | 0.08 (0.23)                   |
| Fat Mass (kg)        | 10.6±6.0    | 42.6±17.8       | 47.5±11.0          | <0.01 (<0.01)           | <0.01 (<0.01)             | 0.48 (1.00)                   |
| % Body Fat           | 18.6±7.3    | 42.0±8.2        | 45.2±4.6           | <0.01 (<0.01)           | <0.01 (<0.01)             | 0.29 (0.87)                   |
| Waist Umbilicus (cm) | 72.6±8.2    | 110.3±13.5      | 130.3±28.1         | <0.01 (<0.01)           | <0.01 (<0.01)             | 0.06 (0.19)                   |
| Sagittal Diameter (cm)| 18.3±1.2   | 30.2±7.3        | 35.0±5.1           | 0.01 (0.01)             | <0.01 (<0.01)             | 0.10 (0.31)                   |
| PAR Met Rate (kcal/kg/min) | 69.0±24.7 | 54.0±14.0       | 60.3±11.6          | 0.09 (0.12)             | 0.74 (0.33)               | 0.12 (0.29)                   |

CTL = healthy normal weight subjects; OB-CTL = obese subjects without a diagnosis of asthma; OB-Asthma = obese subjects with a diagnosis of asthma; PAR Met Rate = Metabolic rate calculated by recall of the previous 24 hour activity in kcal/kg/min. Between-group comparison of means based on the Welch’s modified version of the Students t-test. Between-group comparison of frequencies based on the Fisher’s exact test. Data are presented as Mean ± SD.

*Mean ± standard deviation,

Unadjusted p value,

1Bonferroni adjusted p value assuming 3 hypothesis tests.

doi:10.1371/journal.pone.0061022.t001
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Table 2. Spirometry results.

|                | CTL (n = 10) | OB-CTL (n = 10) | OB-Asthma (n = 10) | P value (CTL vs OB-CTL) | P-value (CTL vs OB-Asthma) | P-value (OB-CTL vs OB-Asthma) |
|----------------|-------------|-----------------|--------------------|-------------------------|---------------------------|-----------------------------|
| FEV1 (Liters)  | 3.01 ± 0.96*| 2.80 ± 0.36     | 3.17 ± 0.60        | 0.55 (1.002)            | 0.65 (1.00)                | 0.12 (0.36)                 |
| FEV1 % predicted| 95 ± 15     | 95 ± 10         | 89 ± 17            | 0.93 (1.00)             | 0.39 (1.00)                | 0.37 (1.00)                 |
| FVC (Liters)   | 3.53 ± 1.07 | 3.38 ± 0.43     | 4.07 ± 0.93        | 0.64 (1.00)             | 0.24 (0.72)                | 0.05 (0.15)                 |
| FVC % predicted| 102 ± 15    | 105 ± 12        | 103 ± 18           | 0.90 (1.00)             | 0.70 (1.00)                | 0.83 (1.00)                 |
| FEV1/FVC       | 0.85 ± 0.07 | 0.83 ± 0.09     | 0.79 ± 0.09        | 0.59 (1.00)             | 0.10 (0.29)                | 0.28 (0.83)                 |

 ctl = healthy normal weight subjects. OB-CTL = obese subjects without a diagnosis of asthma. OB-Asthma = obese subjects with a diagnosis of asthma. Between-group comparison of means based on the Welch’s modified version of the Students t-test. Data are presented as Mean ± SD.

*Mean ± standard deviation,
Unadjusted p value,
Bonferroni adjusted p value assuming 3 hypothesis tests. FEV1 = Forced Expiratory Volume in 1 second. FVC = Forced Vital Capacity.
doi:10.1371/journal.pone.0061022.t002

Statistical analysis

Data were analyzed using One-Way ANOVA and Welch’s version of the Student’s t-test. The degrees of freedom associated with the Welch’s t-test were determined via the Satterwaite approximation method, and a Bonferroni multiple comparison type I error rate corrected rejection rule was implemented in order to restrict the overall probability of falsely rejecting one or more null hypotheses to be no greater than 0.05. The software, MIXED procedure of version 9.1.2 EAS (SAS Institute Inc. Cary, NC) was utilized to conduct statistical analyses.

Results

Baseline demographics

The subjects were 14.3 ± 2.4 years old (mean age ± SD) and included 15 males and 15 females. Lean body weight, BMI, fat mass, percent body fat, waist circumference, and sagittal diameter were significantly higher in OB-CTL and OB-Asthma subjects as compared to controls (Table 1). There was no significant difference in baseline spirometry or eosinophils among the three groups (Table 2, Table S1). There was no significant difference in the levels of previous 24 hour-activities quantified by PAR and of estimated metabolic rates among three groups (Table 1).

Cardiovascular capacities & physical fitness

During exercise testing, the comparable maximum heart rates were achieved among all groups, and each group reached greater than 90% of the percent predicted target heart rate. At the point of volitional fatigue, children’s OMNI scores were increased to more than 90% of the percent predicted target heart rate. At the point of volitional fatigue, children’s OMNI scores were increased to more than 90%

Table 3. Comparison of cardiopulmonary stress test (CPT) results.

|                | CTL (n = 10) | OB-CTL (n = 10) | OB-Asthma (n = 10) | P value (CTL vs OB-CTL) | P-value (CTL vs OB-Asthma) | P-value (OB-CTL vs OB-Asthma) |
|----------------|-------------|-----------------|--------------------|-------------------------|---------------------------|-----------------------------|
| Total Exercise Time (sec) | 919 ± 215* | 515 ± 127       | 489 ± 149          | <0.01 (<0.01)           | <0.01 (<0.01)             | 0.53 (0.67)                 |
| Children’s OMNI Scale | 7.7 ± 1.9  | 7.2 ± 2.6       | 7.7 ± 1.8          | 0.80 (0.63)             | 1.00 (1.00)               | 0.85 (0.62)                 |
| Maximum Heart Rate | 188.3 ± 14 | 186.5 ± 11      | 184 ± 11           | 0.75 (1.00)             | 0.44 (1.00)               | 0.60 (1.00)                 |
| % Target Heart Rate | 91.9 ± 7.0 | 90.2 ± 5.4      | 89.6 ± 5.4         | 0.54 (1.00)             | 0.42 (1.00)               | 0.81 (1.00)                 |
| Maximum RER | 1.06 ± 0.06 | 1.02 ± 0.07     | 1.07 ± 0.05        | 0.14 (0.43)             | 0.79 (1.00)               | 0.07 (0.20)                 |
| VO2-Peak(L/min) | 1.93 ± 0.7 | 2.06 ± 0.4      | 2.53 ± 0.7         | 0.64 (1.00)             | 0.07 (0.19)               | 0.08 (0.25)                 |
| VO2-Peak/ABW(L/min/kg) | 35.3 ± 5.8 | 21.4 ± 5.4      | 21.7 ± 4.5         | <0.01 (<0.01)           | <0.01 (<0.01)             | 0.69 (1.00)                 |
| VO2-Peak/IBW(mL/min/kg) | 31.4 ± 6.3 | 33.4 ± 6.7      | 36.6 ± 5.9         | 0.51 (1.00)             | 0.07 (0.22)               | 0.27 (0.80)                 |
| O2 pulse (mL/min) | 10.3 ± 3.5 | 11.0 ± 2.1      | 13.8 ± 3.5         | 0.56 (1.00)             | **0.04 (0.11)**          | **0.05 (0.15)**            |
| VO2-Peak/IBW(mL/min/kg) | 2.08 ± 0.79 | 2.01 ± 0.46    | 2.60 ± 0.67        | 0.83 (1.00)             | 0.13 (0.39)               | 0.04 (0.11)                 |
| Vj(L/min) | 63.5 ± 24.2 | 62.4 ± 14.5     | 79.0 ± 21.4        | 0.91 (1.00)             | 0.15 (0.44)               | 0.06 (0.18)                 |
| Pulmonary Reserve (%) | 46.8 ± 12.7 | 43.2 ± 16.0     | 37.4 ± 12.4        | 0.59 (1.00)             | 0.11 (0.33)               | 0.37 (1.00)                 |

ctl = healthy normal weight subjects. OB-CTL = obese subjects without a diagnosis of asthma. OB-Asthma = obese subjects with a diagnosis of asthma.

OMNI = Children’s OMNI scale of perceived exertion. VO2-peak = Maximum VO2 detected during the CPT. ABW = actual body weight in kg. IBW = ideal body weight in kg (male: 50+(2.3 × height in inches – 60)); female: 45+(2.3 × height in inches – 60)). VO2 = Maximum VO2 detected during the CPT. RER = Respiratory Exchange Ratio. Vj = Maximum minute ventilation detected during the CPT. Between-group comparison of means based on the Welch’s modified version of the Students t-test. Data are presented as Mean ± SD.

*Mean ± standard deviation,
Unadjusted p value,
Bonferroni adjusted p value assuming 3 hypothesis tests.
doi:10.1371/journal.pone.0061022.t003
controls, but there was no significant difference between the OB-CTL and OB-Asthma subjects (Table 3). Maximum oxygen consumption normalized with actual body weight (VO$_2$-Peak/ABW) was significantly lower in the OB-CTL and OB-Asthma subjects as compared to the controls, but no significant difference in the VO$_2$-Peak/ABW was detected between the OB-CTL and OB-Asthma subjects (Table 3, Figure 1A). VO$_2$-Peak normalized for ideal body weight (VO$_2$-Peak/IBW) was not significantly different among the three groups (Table 3, Figure 1B). The O$_2$ pulse and the maximum VCO$_2$ (VCO$_2$-Peak) were not significantly different among all groups in adjusted comparison (Table 3, and online Figure 1).

Pulmonary capacities

The OB-Asthma subjects demonstrated higher levels of V$_E$ at the peak of exercise; however, these differences were not statistically different as compared to the controls and OB-CTL subjects (Table 3, Figure 2A). Pulmonary reserve fell below 30% in a comparable number of subjects in each group; two among the controls, two among the OB-CTL, and three among the OB-Asthma (underlined in Table 4). Averages of the %PR among the three groups were not statistically different (Table 3, Figure 2B). The results suggest that only three out of ten OB-Asthma children were restricted by pulmonary capacity, while the same was true for two of the ten in the OB-CTL group. Spirometry was performed before and after exercise, and relative changes in the FEV$_1$ from the values pre to post exercise were calculated. The changes in FEV$_1$ were not significantly different among the three groups (Figure 3). Two among the controls, three among the OB-CTL, and three among the OB-Asthma experienced greater than 12% relative reduction in FEV$_1$ after exercise (data points below the thick dotted line in Figure 3).

eNO, total serum IgE, and pulmonary capacity at exercise

In order to assess the relationship between pulmonary capacity at the peak of exercise and markers related to inflammation, values for %PR were reviewed with corresponding eNO and IgE in each patient (Table 4). Based on previously published observations [30,31,35,36,37], levels of eNO greater than 25 ppb were considered abnormal, and subjects with eNO greater than 25 ppb were marked together with V$_E$ and %PR (bold and underlined in Table 4). Levels of eNO were elevated in one control, two OB-CTL, and three OB-Asthma subjects. Two of the three OB-Asthma subjects with elevated levels of eNO had %PR less than 30%. None of the controls or OB-CTL subjects with elevated levels of eNO had %PR less than 30%. Based on usual clinical reference values, levels of total serum IgE greater than 150 IU/mL were considered abnormal, and subjects with IgE greater than 150 IU/mL were marked together with %PR (bold and underlined in Table 4). Levels of eNO were elevated in one control, two OB-CTL, and three OB-Asthma subjects. Three of the three OB-Asthma subjects with elevated levels of IgE had %PR less than 30% (25%, 25%, and 25%, respectively). None of the controls or OB-CTL subjects with elevated levels of IgE had %PR less than 30%.

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Figure 1. Exercise physiology of O$_2$ Uptake. Panel A: Maximum VO$_2$ (VO$_2$-Peak/ABW) normalized with actual individual weight in kg. Panel B: Maximum VO$_2$ (VO$_2$-Peak/IBW) normalized with individual ideal body weight in kg. CTL = healthy normal weight subjects. OB-CTL = obese subjects without a diagnosis of asthma. OB-Asthma = obese subjects with a diagnosis of asthma. N = 10 in each group. n.s. indicates p value not significant. † unadjusted p value significant, ‡ Bonferroni adjusted p value assuming 3 hypothesis tests significant. doi:10.1371/journal.pone.0061022.g001

Figure 2. Pulmonary Physiology. Panel A: VE = maximum minute ventilation achieved and measured by continuous spirometry circuit during the exercise. Panel B: Pulmonary Reserve = percentage of unused MVV at the peak of exercise by a formula [%PR = (1 - V$_E$-Peak/MVV) x 100]. CTL = healthy normal weight subjects. OB-CTL = obese subjects without a diagnosis of asthma. OB-Asthma = obese subjects with a diagnosis of asthma. N = 10 in each group. n.s. indicates p value not significant. † unadjusted p value significant, ‡ Bonferroni adjusted p value assuming 3 hypothesis tests significant. doi:10.1371/journal.pone.0061022.g002
None of the controls or OB-CTL subjects with elevated IgE had %PR less than 30%.

### Discussion

Investigation of cardiopulmonary exercise response among obese adolescents found major differences from non-obese controls but no significant differences between those with or without a history of physician-diagnosed asthma. Only a minority of subjects had evidence of respiratory compromise and such individuals were present in all groups. We anticipated that obese children with a diagnosis of asthma would be significantly limited by respiratory abnormalities. Our results suggest that the connection between the activity intolerance and respiratory limitations due to a history of asthma diagnosis was weak in our subjects. Therefore, we believe that breathlessness on exercise should not be taken on its own as evidence of asthma in obese children. The implications as far as management is concerned, however, are more complex than currently appreciated in clinical practice.

Although it is easy to argue that the obese adolescents in our study did not have asthma, we would counter that this is exactly the point. Much of the evidence about an association between asthma and obesity has been based on physician diagnosis or statements such as "asthma was diagnosed using guideline based criteria." [15,16,17,18] A recent population based study of 17,000 children reported a significant increase of asthma among obese and morbidly obese children. In that study, asthma was defined as following:

Asthma status (yes/no) was determined by the parent-completed item, "Did a doctor ever say that (child's name) had asthma?" [4] Where patients have been studied in detail, there exists an increasing body of evidence that obese subjects with a diagnosis of asthma are phenotypically different; they demonstrate

### Table 4. Comparison of $V_e$, %PR, eNO, and IgE results.

| Group       | Study ID | FEV$_1$/FVC | %FEV$_1$ | %FVC | PAR Met Rate | OMNI | $V_e$ | %PR | eNO | IgE |
|-------------|----------|-------------|----------|------|--------------|------|-------|-----|-----|-----|
| CTL         | 1        | 0.89        | 106      | 102  | 50.5         | 10   | 114.6 | 40.68 | 8   | 741 |
|             | 2        | 0.87        | 89       | 94   | 102.3        | 5    | 48.6  | 61.55 | 9.3 | 28.6 |
|             | 4        | 0.83        | 87       | 96   | 88.7         | 7    | 74.5  | 28.37 | 23.5 | 60.4 |
|             | 5        | 0.83        | 74       | 81   | 69.2         | 6    | 33.6  | 48.78 | 25.6 | 299 |
|             | 6        | 0.89        | 82       | 84   | 62.1         | 8    | 38.5  | 48.80 | 12  | 9.2  |
|             | 7        | 0.69        | 83       | 110  | 119.9        | 9    | 82.7  | 26.94 | 9   | 4.78 |
|             | 8        | 0.88        | 105      | 107  | 40.6         | 8    | 43.6  | 59.78 | 5.8  | 26.4 |
|             | 9        | 0.94        | 99       | 100  | 52.9         | 10   | 65    | 57.01 | 18  | 8.48 |
|             | 10       | 0.85        | 106      | 117  | 47.6         | 5    | 66.6  | 38.56 | 18  | 634  |
|             | 11       | 0.85        | 123      | 130  | 61.7         | 9    | 67.2  | 57.03 | 6.7  | 27   |
| OB-CTL      | 14       | 0.85        | 84       | 88   | 66.9         | 8    | 76.8  | 13.90 | 22  | 31.7 |
|             | 15       | 0.81        | 98       | 112  | 52.0         | 10   | 71.8  | 38.53 | 41  | 445  |
|             | 18       | 0.72        | 83       | 106  | 47.2         | 7    | 87.5  | 24.05 | 10  | 101  |
|             | 19       | 0.90        | 100      | 106  | 42.7         | 9    | 39.7  | 68.29 | 14  | 125  |
|             | 27       | 0.88        | 87       | 89   | 86.1         | 8    | 63.8  | 44.81 | 9   | 35.9 |
|             | 29       | 0.89        | 101      | 103  | 43.2         | 10   | 58.9  | 40.86 | 11  | 624  |
|             | 30       | 0.87        | 68       | 91   | 48.5         | 8    | 67.1  | 47.90 | 10  | 19.8 |
|             | 32       | 0.75        | 100      | 120  | 43.8         | 2    | 63    | 44.15 | 11  | 27.8 |
|             | 33       | 0.96        | 116      | 109  | 60.2         | 4    | 47.8  | 62.30 | 58  | 182  |
|             | 35       | 0.70        | 92       | 121  | 46.9         | 6    | 47.8  | 47.59 | 24  | 103  |
| OB-Asthma   | 13       | 0.78        | 80       | 97   | 54.2         | 10   | 65.3  | 36.48 | 24  | 858  |
|             | 16       | 0.78        | 83       | 91   | 48.4         | 8    | 97    | 32.64 | 20  | 9.41 |
|             | 17       | 0.92        | 105      | 109  | 48.4         | 6    | 61.4  | 56.27 | 11  | 81.5 |
|             | 20       | 0.84        | 68       | 75   | 63.9         | 7    | 60.8  | 41.31 | 55  | 355  |
|             | 21       | 0.83        | 88       | 97   | 76.1         | 6    | 75.4  | 33.63 | 23  | 1370 |
|             | 22       | 0.60        | 72       | 111  | 81.6         | 10   | 74.7  | 25.30 | 72  | 182  |
|             | 24       | 0.88        | 125      | 130  | 53.6         | 9    | 53.1  | 61.52 | 9   | 13.1 |
|             | 25       | 0.72        | 83       | 101  | 50.7         | 5    | 86.6  | 30.61 | 15  | 679  |
|             | 26       | 0.70        | 104      | 131  | 59.7         | 9    | 124.6 | 29.84 | 110 | 79.3 |
|             | 31       | 0.83        | 82       | 88   | 66.0         | 7    | 91    | 25.90 | 20  | 157  |

CTL = healthy normal weight subjects. OB-CTL = obese subjects without a diagnosis of asthma. OB-Asthma = obese subjects with a diagnosis of asthma. FEV$_1$ = Forced Expiratory Volume 1 second. FVC = Functional Vital Capacity. %FEV$_1$ = Percent predicted FEV$_1$. %FVC = Percent predicted FVC. PAR Met Rate = Calculated metabolic rate based on recall of previous 24 hour activity (kcal/kg/min). OMNI = Children’s OMNI scale of perceived exertion. $V_e$ = Maximum minute ventilation detected during the CPT. %PR = Percent pulmonary reserve. eNO = exhaled nitric oxide (ppb). IgE = Immunoglobulin E (IU/mL). Subjects with eNO greater than 25 ppb and or IgE greater than 150 IU/mL are highlighted with underline and bold font. Subjects with %PR less than 30% are highlighted with underline font.
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In conclusion, our results would not change the obvious truth that obese and overweight children need an exercise regime. Some of these children may need pulmonary rehabilitation if difficulty breathing is the perceived reason for not exercising. Based on our results, we propose that cardiopulmonary deconditioning should be considered as an important differential diagnosis for breathlessness among obese adolescents. In addition, we suggest that all studies on the relationship between obesity and asthma that are based on "physician diagnosis," or even on "guideline-based diagnosis," should be evaluated knowing that, in as many as 50% of the participants with a diagnosis of asthma, breathlessness on exercise may not reflect a condition of the airways.

Supporting Information

Figure S1 Exercise physiology of O₂ pulse and CO₂ production. Panel A: Maximum O₂-Pulse. Panel B: Maximum VCO₂ (VCO₂-Peak). N = 10 in each group. CTL = healthy normal weight subjects. OB-CTL = obese subjects without a diagnosis of asthma. OB-Asthma = obese subjects with a diagnosis of asthma. n.s. indicates p value not significant.
diagnosis of asthma. OB-Asthma = obese subjects with a diagnosis of asthma. n.s. indicates p value not significant. † unadjusted p value significant, ‡ Bonferroni adjusted p value assuming 3 hypothesis tests significant.

**Table S1** Complete blood counts with leukocyte differential percentages and cell counts. CTL = healthy normal weight subjects. OB-CTL = obese subjects without a diagnosis of asthma. OB-Asthma = obese subjects with a diagnosis of asthma. Between-group comparison of means based on the Welch’s modified version of the Students t-test. Data are presented as Mean ± SD.

**Author Contributions**
Conceived and designed the experiments: YMS TAP. Performed the experiments: YMS AB SL RCH JW JTP ALW TAP. Analyzed the data: YMS JTP ALW TAP. Contributed reagents/materials/analysis tools: YMS JTP ALW TAP. Wrote the paper: YMS JTP TAP.

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**Text S1** More detailed description of method related to subject recruitment with detailed inclusion and exclusion criteria, protocol for CPET, exhaled NO and IgE measurement, and statistical analysis.

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