High-intensity training improves airway responsiveness in inactive nonasthmatic children: evidence from a randomized controlled trial

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Submitted 27 May 2011; accepted in final form 27 December 2011


High-intensity training improves airway responsiveness in inactive nonasthmatic children: evidence from a randomized controlled trial. J Appl Physiol 112: 1174–1183, 2012. First published January 12, 2012; doi:10.1152/japplphysiol.00663.2011.—Purpose: The relationship between physical activity and airway health in children is not well understood. The purpose of this study was to determine whether 8 wk of high-intensity exercise training would improve airway responsiveness in prepubescent, nonasthmatic, inactive children. Methods: 16 healthy, prepubescent children were randomized [training group (TrG) n = 8, control group (ConG) n = 8]. Prior to and following 8 wk of training (or no training), children completed pulmonary function tests (PFTs): forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), forced expiratory flow at 25–75% of vital capacity (FEF25–75), and exhaled nitric oxide (FENO). Children completed an incremental cycle V˙O2max test, eucapnic voluntary hyperventilation (EVH), anthropometric tests, and blood tests to determine fasting blood glucose, total cholesterol, HDL, LDL, and triglycerides. Body fat percentage was determined using dual-energy X-ray absorptiometry pretraining and bioelectrical impedance posttraining. Results: there were no differences (P > 0.05) in anthropometric measures or PFTs between TrG and ConG at baseline. In the TrG, there was a significant increase in V˙O2max (~24%) and a decrease in total cholesterol (~13%) and LDL cholesterol (~35%) following training. There were improvements (P < 0.05) in ΔFEV1 both postexercise (pre: –7.60 ± 2.10%, post: –1.10 ± 1.80%) and post-EVH (pre: –6.71 ± 2.21%, post: –1.41 ± 1.58%) with training. The ΔFEF25–75 pre-post exercise also improved with training (pre: –16.10 ± 2.10%, post: –6.80 ± 1.80%; P < 0.05). Lower baseline body fat percentages were associated with greater improvements in post-exercise ΔFEV1 following training (r = –0.80, P < 0.05). Conclusion: these results suggest that in nonasthmatic prepubescent children, inactivity negatively impacts airway responsiveness, which can be improved with high-intensity training. Excess adiposity, however, may constrain these improvements. 

airway hyperresponsiveness; interval training; prepubescent; airway narrowing; asthma

Asthma is the most common chronic disease in childhood (26). Although many factors contribute to the development of asthma, the role of physical activity in airway health in children is not well understood, and inadequate moderate to vigorous physical activity (MVPA) may be contributing to the development of asthma or asthmalike symptoms (47).

Lack of physical activity, particularly at higher intensity levels (MVPA), may increase the risk of asthma development in multiple ways. First, it is well established that lack of physical activity is a potent risk factor for development of obesity, which is associated with asthma prevalence in children, as well as in adults (8). Second, low levels of MVPA are an independent risk factor for asthma development (47). Additionally, lung function has been observed to be the highest in physically active children compared with their less active peers (4). A few studies in children with asthma have also demonstrated improved lung function in addition to decreased use of medications following completion of a physical activity intervention program (5, 26). Similarly, low physical fitness during childhood is significantly associated with development of asthma in adolescence (40).

Healthy children undergoing an 8-wk high-intensity training protocol have shown significant pre- to post-training improvements in resting pulmonary function (35). However, in contrast to this beneficial effect of high-intensity training, the training group participants in this study by Nourry and colleagues (35) also showed decreases in pre- to posttraining pulmonary function when assessed following an exercise test (35). The authors speculated that changes in postexercise pulmonary function were due to heat and/or water loss from the airways triggering bronchoconstriction resulting from higher ventilation levels and increased exercise intensity posttraining. This study, however, did not control for previous levels of habitual physical activity.

In a previous study with an adult sample and controlling for physical activity levels, Shaaban and colleagues (47) found a negative association between physical activity and bronchial hyperresponsiveness to methacholine (47). In a sample of children with stable, mild asthma, Bonsignore and colleagues (5) showed a decrease in bronchial hyperresponsiveness following a 12-wk training protocol. Bonsignore and colleagues speculated that the decreased hyperresponsiveness could be due to repeated airway stretch associated with increased ventilation during regular training that modified the contractile mechanism of the airway smooth muscle (ASM). A lack of smooth muscle stretch in the airway that is obtained through MVPA may be a risk factor for asthmalike symptoms in childhood. It is recognized that ASM stretch relaxes the tone of muscle in the airway, which reduces airway reactivity (5), although the specific role of ASM in asthma remains unclear (2). It is possible that moderate to vigorous intensity training (and therefore, chronic airway stretch) will make the airway less susceptible to developing increased responsiveness and asthmalike symptoms.

Adiposity is a potential confounder when examining associations between physical activity and asthma or asthmalike symptoms. Although the focus of the current study is not on obesity, obesity may impact the relationship between physical activity and asthma.
activity and airway responsiveness. Previous research, while equivocal, has shown that obesity is often associated with increased asthma severity (37, 57). This relationship may also hold true for children who have increased airway responsiveness, but who have not been diagnosed with asthma. The mechanisms underlying this relationship are unclear, particularly in a pediatric population. However, potential mechanisms include a lack of airway stretch attributable to low physical activity levels at a moderate to vigorous intensity (5) and also altered breathing patterns in obesity that result in airway remodeling, which may also be driven by systemic inflammation created by excess adiposity. Inflammation from adipocytes may play a role that is closely linked to airway remodeling. Similar to asthma, obesity may increase the severity of the airway narrowing seen in children not getting adequate physical activity (53).

On the basis of the collection of evidence outlined above that illustrates the potential for chronic physical activity levels to positively impact on airway health, we were interested in determining whether a high-intensity running training program would improve airway health in nonasthmatic prepubescent children who were not meeting current physical activity guidelines. We hypothesized that in this population, 8 wk of high-intensity running training would reduce postexercise and post-tetrapolar bioelectrical impedance (discussed below), and blood pressure via stethoscope auscultation. Following the resting measurements, children performed standard pulmonary function and FENO tests. Children reported for their second visit following a 10- to 12-h overnight fast. A finger stick was used to determine fasting blood glucose (BG), total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. Following 5 min of quiet sitting, each child underwent assessment of waist circumference, tetrapolar bioelectrical impedance (discussed below), and blood pressure via stethoscope auscultation. Following the resting measurements, children performed standard pulmonary function and FENO tests. Children then performed a 6-min eucapnic voluntary hyperventilation (EVH) test at 30 times their best pretest FEV1 from that day’s testing. Two minutes following the EVH test, children performed standard pulmonary function and FENO measurements. Following the breathing testing, each subject underwent a DXA scan to determine body fat percentage.

Pulmonary-function measurement. Each child underwent standard pulmonary function tests (PFTs): forced expiratory volume in 1-s (FEV1), forced vital capacity (FVC), forced expiratory flow at 25–75% of vital capacity (FEF25–75%), sensorMedics 229 Metabolic Cart, SensorMedics, Yorba Linda, CA) following recommended protocols (discussed below). Total lung capacity (TLC) was determined via nitrogen washout technique. Children exhaled nitric oxide measurements (FENO; a marker of eosinophilic airway inflammation) via chemiluminescence (Sievers Nitric Oxide Analyzer 280, Sievers Instruments, Boulder, CO). Children then completed an incremental cycle exercise test to exhaustion to determine maximal oxygen uptake VO2max (discussed below). Two minutes following the maximal exercise test, standard pulmonary function tests and FENO measurements were repeated. A second exercise test at constant work load (105% VO2max) was performed following 15 min of rest to verify VO2max. The parent or guardian and the child completed a two-item questionnaire to determine previous 7-day physical activity and physical activity in a typical week (39). Children returned ~1 wk later for their second visit.

METHODS

Participants

Eighteen healthy prepubescent children (16 girls, 2 boys) ages 7–12 yr, with no diagnoses or history of acute or chronic diseases (determined via medical history questionnaire) volunteered as participants. Two children were excluded from data analyses because of interruption in training for greater than 1 wk. Sixteen children (14 girls, 2 boys) were included in the data analysis. All children demonstrated normal lung function, as determined by standard resting pulmonary function tests (22). According to parent- or guardian-completed questionnaires, children were prepubescent and were in the first stage of maturation, as defined by Tanner stage 1 (54). All children, with assistance from their parent or guardian, reported their current level of physical activity (within the past 6 mo) and were categorized as meeting US Department of Health and Human Services physical activity guidelines or not (36) (≥5 days/wk of 60 min or more MVPA). Physical activity levels were confirmed via accelerometry. Children had an Actigraph GT1M (MTI Actigraph, Shalimar, FL) accelerometer placed on their right hip for the next 7 days. Children were asked to complete a log for the accelerometers indicating time on and time off each day and any additional periods where the accelerometer was not worn. Raw count data for the 7 days of wear were uploaded to a customized data-processing software program. The MET prediction equation from Freedson and colleagues (12) was used to estimate time spent in moderate to vigorous (MVPA; ≥4 METs) physical activity. The age-specific counts per minute thresholds were divided by two to accommodate our 30-s epoch length. Non-wear time for each 24-h period was determined by summing the consecutive zero counts that were 10 min or longer. MVPA per day was determined only if total wear time reached a 10-h minimum. Participants met physical activity guidelines if their total daily accumulated MVPA time was equal to or exceeding 60 min/day on 5 or more days. Each subject had a parent or guardian present to provide medical history information and written informed consent. All research components were reviewed and approved by the Institutional Review Board of Human Subjects at Kansas State University, Manhattan, KS.

Experimental Design

All children reported to the lab on four separate occasions. A parent or guardian was present at each session. Sessions 1 and 2 were completed prior to group randomization via random number generator. Children either completed 8 wk of training or were asked to continue their usual physical activity and dietary habits for the 8-wk duration. Sessions 3 and 4 were completed at the conclusion of the 8-wk period of training or no training. Sessions 1 and 3, Procedures in sessions 1 and 3 were identical. Height and weight were recorded using a calibrated eye-level physical scale with height rod (Detecto, Webb City, MO). Children were then familiarized with the equipment and procedures. After several practice trials and demonstrations, standard pulmonary function measurements were performed using an automated pulmonary function testing system (SensorMedics 229 Metabolic Cart, SensorMedics, Yorba Linda, CA) following recommended protocols (discussed below).

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residual volume without breath holding. Three successive FENO measurements of the plateau phase were obtained, with less than five percent variation, and the average value was used in statistical analyses. TLC and MFVLs were assessed prior to exercise testing (SensorMedics 229 Metabolic Cart). TLC was determined using the nitrogen wash-out technique. MFVLs were performed in triplicate, with the best value of each PFT used in analysis.

Eucapnic voluntary hyperventilation. In addition to the postexercise airway narrowing assessment, eucapnic voluntary hyperventilation (EVH) was used to determine the changes in airway function following voluntary hyperventilation. The target ventilation for EVH was 30 × FEV1, which is intended to be ~85% of predicted maximal voluntary ventilation (51). The child then hyperventilated while breathing on a bag containing 5% carbon dioxide dry gas mixture for 6 min. Children wore a nosepiece and looked at a computer monitor indicating their ventilation level to maintain target ventilation throughout the 6-min test.

Maximal oxygen uptake. VO2max, heart rate, and an estimate of arterial oxygen saturation (SpO2) were determined during a maximal exercise test on an electronically braked cycle-ergometer (Ergometer 800S, SensorMedics). Children were given consistent instructions explaining the protocol of the test to ensure maximal volitional effort. Prior to testing, known gas concentrations spanning the range of expected measurements were used to calibrate gas analyzers. Flow sensor calibration was also performed using a 3-liter calibration syringe. Resting metabolic measurements were taken for 3 min. Children then began with a warm-up for ~2 min at a work rate of 20 W, pedaling between 50 and 60 revolutions/min (rev/min). Children were instructed to remain seated and maintain this pedaling speed while the work rate was increased by 10 W each minute. Metabolic and ventilatory data were assessed continuously through breath-by-breath analysis (SensorMedics 229 Metabolic Cart). Heart rate (HR) was monitored throughout the test via a four-lead electrocardiograph (ECG) interfaced to the metabolic software. The sensor from a pulse oximeter (Datex-Ommeda, 3900P, Madison, WI), calibrated before each test, was secured to the left earlobe to estimate arterial SpO2. Children continued to exercise until reaching volitional exhaustion (<16 min). Verbal encouragement was provided throughout the test. The VO2max test concluded when children could not maintain a pedal frequency of ≥50 rev/min for five consecutive revolutions.

Following the VO2max test, children performed pulmonary function tests and then rested for the remainder of a 15-min period. At the end of the 15-min period, a constant load (105% VO2max) exercise test was performed until exhaustion to verify VO2max (38). Work rate for the test was determined from the final work rate (watts) during the incremental test. Children were given a warm-up period of 90 s pedaling 50 rev/min at 20 W. Work rate was increased until reaching calculated work rate (~30 s), and children were instructed to maintain 50 rev/min until volitional fatigue.

Body Fat Percentage

Dual energy X-ray absorptiometry. During the pretest week, body composition was measured by use of a whole body DXA system (v5.6, GE Lunar, Milwaukee, WI) as the criterion measure of body fat percentage. Children removed shoes and any metal objects prior to scanning and lay in a supine position with arms separated from trunk and legs slightly spaced apart. Children were asked to lie as still as possible during the scanning procedure. DXA has previously been validated and uses two X-ray beams with differing energy levels to find differences in absorption and therefore lean body mass, body fat percentage, and fat mass (27). Additionally, DXA is considered to be safe and valid for use in the pediatric population (19).

Bioelectrical impedance. Whole body resistance and reactance were measured using a tetrapolar bioelectrical impedance analyzer (RJL systems, Quantum II, Detroit, MI) and used to determine change in body fat percentage from baseline to posttest. Calibration was performed using the 500-ohm resistor provided by the manufacturer. Electrodes were placed at the ankle and wrist as indicated by the manufacturer. Body fat percentage, fat-free mass, and body water were determined via the NHANES III algorithm included in the manufacturer-provided body composition software.

Physical Activity Status

To determine whether the children were meeting current physical activity guidelines, children were asked to report on the previous week and a normal or usual week how many days per week they accumulated at least 60 min of moderate to vigorous physical activity, not including physical education or gym class (36). This two-item physical activity screening tool has been previously validated in a similar age group for determining whether physical activity guidelines are met (39). Physical activity status was confirmed with 7 days of accelerometer assessment at baseline.

Training Protocol

A modified version of the training protocol reported by Nourry and colleagues (35) was used for the current study. Training group participants participated in two weekly training sessions spaced at least 48 h apart for 8 wk in addition to their usual activities. To determine appropriate distances for each interval, prior to the first training session, children performed a multistage 20 m PACER run test to determine their maximal aerobic speed (MAS) (3, 35). Exercise sessions were performed on an indoor track, and each session lasted ~30 min, including ~8–9 min of vigorous activity. Each training session began with a standardized warm-up performed at 100% MAS. The warm-up set was followed by four sets of 10 × 10 s or, later in the 8-wk progression, 5 × 20-s intervals at 100–130% of MAS. Rest intervals were performed at a one to one work-to-rest ratio and were passive recovery rest periods. Adherence to appropriate MAS was encouraged by having a research assistant run alongside the child and encouragement from the timekeeper to complete each interval in the correct timeframe.

Statistics

SigmaStat 3.5 statistical software (Jandel Scientific Software) was used for data analysis. Data are expressed as mean ± SD. All parametric statistical assumptions were checked and the appropriate statistics were chosen. Differences between groups and conditions were determined using mixed factorial ANOVA. Relationships were determined by Pearson product-moment correlation. Significance was set at P < 0.05 for all analyses.

RESULTS

Subject Characteristics

Subject characteristics are presented in Table 1. There were no significant differences between ConG and TrG for anthropometric data or body fat percentage. Additionally, anthropometric data and body fat percentage did not change (P > 0.05) over the course of the study. Total cholesterol decreased in the TrG (pre: 171.9 ± 26.0, post: 149.9 ± 20.5, P < 0.05) following training. LDL cholesterol also decreased in the TrG (pre: 97.5 ± 18.8, post: 62.7 ± 20.2, P < 0.05).

On the basis the two-item questionnaire at baseline, the ConG indicated meeting PA guidelines 2.7 ± 0.5 days/wk, whereas the TrG reported meeting guidelines 1.4 ± 0.8 days/wk (P < 0.05). Accelerometer data at baseline, however, indicated no differences between groups with the control group achieving MVPA guidelines on 1.4 ± 1.3 days and the TrG meeting guidelines on 1.8 ± 1.8 days/wk [F(1,14) = 0.24, P = 0.64].
Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Reference values</th>
<th>Acceptable range</th>
<th>ConG (n = 8)</th>
<th>Mean ± SD</th>
<th>TrG (n = 8)</th>
<th>Mean ± SD</th>
<th>P = 0.05</th>
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<tbody>
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<td>Age, yr</td>
<td>9.00–12.00</td>
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<td>Height, cm</td>
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<td>139.9 ± 7.0</td>
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<td>BMI, kg/m²</td>
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<td>Systolic blood pressure, mmHg</td>
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<td>106 ± 5.5</td>
<td>106 ± 5.5</td>
<td>106 ± 5.5</td>
<td>0.41</td>
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<tr>
<td>Total cholesterol, mg/dl</td>
<td>150–200</td>
<td>189 ± 14.9</td>
<td>189 ± 14.9</td>
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<td>0.41</td>
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</tbody>
</table>

Resting Pulmonary Function

Resting pulmonary function values at baseline and following training are shown in Table 2. Baseline PFTs were not significantly different from predicted values for prepubescent children (22). Baseline PFTs were also not significantly different between the ConG and TrG. There were no significant differences in PFTs, including TLC and FENO within groups pre-post training.

Change in Pulmonary Function

Resting pulmonary function values at baseline and following training as well as pre-post exercise and pre-post EVH percent change in pulmonary function at baseline and following training are shown in Table 3. Figure 1 shows individual and mean percent change in FEV\textsubscript{i} at baseline and following training for the ConG vs. TrG from pre- to postexercise, indicating that the TrG showed a decreased ΔFEV\textsubscript{i}% (indicating improved airway responsiveness) following training. Six out of eight children in the TrG showed a decreased postexercise ΔFEV\textsubscript{i}% from pre- to posttraining (6.50 ± 2.10%). The two children who did not show a decrease in postexercise ΔFEV\textsubscript{i}% were the children with the smallest decreases in postexercise FEV\textsubscript{i}% at baseline (0.5% increase and 0.7% decrease). There was no change in the ConG pre-to postexercise ΔFEV\textsubscript{i}% following training (pre: −3.01 ± 1.72%, post: −4.22 ± 1.86%; P = 0.85). Similar results (P < 0.05) were observed with the EVH test. The pre- to post-EVH ΔFEV\textsubscript{i}% was significantly decreased in the TrG (pre: −6.71 ± 2.21%, post: −1.41 ± 1.58%; 5.30 ± 1.90% decrease). From pre- to post-EVH, seven out of eight of the TrG participants decreased ΔFEV\textsubscript{i}% following training, and the child who did not show a decrease showed an increased post-pre ΔFEV\textsubscript{i}% with EVH at baseline. In the ConG, the pre-to post-EVH ΔFEV\textsubscript{i}% was not significantly different (pre: −3.03 ± 4.71%, post: −4.12 ± 5.17%; P = 0.37).

Figure 2 shows individual and mean percent change in FEF\textsubscript{25–75} at baseline and following training for the ConG vs. TrG from pre- to postexercise, indicating that the TrG showed a decreased ΔFEF\textsubscript{25–75}% (indicating improved airway responsiveness) following training. Pre- to postexercise ΔFEF\textsubscript{25–75}% decreased (−16.10 ± 2.10% to −6.80 ± 1.80%, P < 0.05) in the TrG following the training program, but did not change in the ConG (pre: −6.60 ± 5.90, post: −4.50 ± 4.70; P = 0.32). There were no differences between the ConG or TrG for FEF\textsubscript{25–75}% from pre-to post-EVH following training. Significant improvement from baseline to posttraining in postexercise ΔPEF% was also seen for the TrG only (pre: −14.26 ± 2.00%, post: −2.94 ± 1.40%; P < 0.05).

The change in FVC% from pre- to post-EVH was significantly decreased following training (pre: −3.76 ± 4.34, post: 2.42 ± 4.02; P = 0.03). However, the pre- to postexercise change in FVC% was not significant following training (pre: −1.02 ± 5.56, post: −4.41 ± 1.35; P = 0.41).

Exercise Test Data Pre-Post 8-wk Training Program

Data collected during the incremental cycle ergometer test at \( V_{O2\text{max}} \) are shown in Table 4. There was no difference (P > 0.05) in \( V_{O2\text{max}} \) between the incremental test and the constant load test at 105% \( V_{O2\text{max}} \). \( V_{O2\text{max}} \) was significantly (P < 0.05)
lower in the TrG vs. the ConG at baseline. Children in the TrG increased \( \dot{V}O_{2\text{max}} \) by an average of \(-24.5\% \) (4.4–69.1\%). Heart rate also increased significantly (4.8\%; 0.0–5.6\%, \( P < 0.05 \)) in the TrG.

**Body Fat Percentage and Airway Responsiveness**

Figure 3 shows there was a significant relationship between body fat percentage at baseline and the percent change in pre- to postexercise \( \Delta FEV_1 \) from pre- to posttraining (\( r = -0.80, P < 0.05 \)). When controlling for \( \dot{V}O_{2\text{max}} \), this relationship was unchanged. Children in the TrG with higher body fat percentages showed less of a decrease in postexercise \( \Delta FEV_1 \% \) from baseline to posttraining (indicating less improvement) than children with lower body fat percentages.

**DISCUSSION**

The results of the current study suggest that insufficient MVPA negatively impacts airway health in nonasthmatic prepubescent children, and high-intensity training can ameliorate these negative airway health outcomes. Our first hypothesis was supported by the finding that postexercise airway narrowing was reduced following training. Our data did not support our second hypothesis; i.e., at baseline, body fat percentage was not associated with airway narrowing. In fact, children with the highest levels of body fat experienced less of an improvement in airway narrowing following training compared with leaner children. Also, children in the training group who did not improve pulmonary function were the children with the least amount of airway narrowing prior to training.

**Pulmonary Adaptations and Physical Activity**

Excessive airway narrowing that occurs due to contraction of ASM is known to be a risk factor for future development of asthma and asthmalike symptoms (23). A low level of physical activity is also associated with the future development of asthma in otherwise healthy children (40, 47). One previous study in nonasthmatic children undergoing a similar 8-wk high-intensity training protocol showed significant decrements in pre- to posttraining pulmonary function (35). Our data, however, indicate that in children not meeting current physical activity guidelines, an 8-wk high-intensity training protocol can improve airway responsiveness. There are important distinctions between our participant population and the previously studied participant population that may account for this discrepancy. For example, the average \( \dot{V}O_{2\text{max}} \) from the training group from Nourry et al. (35) was nearly 60% higher than our group’s baseline average. By design, our recruited participant population was inactive (none were meeting guidelines for physical activity). Whereas Nourry and colleagues did not account for physical activity levels in their study, it is likely that their population would have been more physically active than ours. Nourry and colleagues (35) also showed a 16% increase in ventilation following training in their participants, reaching levels that were much higher than the average ventilation of our participant population following training. The authors attributed changes in postexercise airway function to heat or water loss in the airway due to increases in ventilation (35). Greater ventilation may also lead to increased ASM stretch, which may affect airway function (see below). The mean body fat percentage of Nourry’s training group was \(-7\% \) less than the mean among our participants. This is potentially another important difference that could help to explain mechanisms responsible for disparate results between studies.

**Airway Smooth Muscle Stretch**

We speculate that the reason for improved airway function following training in our study was increased ASM stretch and lung inflation associated with high-intensity training. Under normal conditions, ASM has reduced tone, allowing it to maintain the stiffness of the airways when there are large swings in transmural pressure, such as in exercise (52). Many pathology studies have documented an increased ASM mass in asthmatic airways along with faster proliferation, producing more chemokines and cytokines, and extracellular matrix proteins that are different from nonasthmatic ASM (9). Further, Skloot and Togias (49) reported that the differential effect of deep inhalation on induced bronchoconstriction in asthmatic vs. normal participants might be caused by different velocities of smooth muscle shortening in asthmatic airways. Although our participant population was not asthmatic, it is possible that similar mechanisms could account for the observed changes in airway responsiveness.

Lung inflation is known to have a beneficial effect on the airways of healthy participants, but the mechanisms through which it exerts its beneficial role in healthy participants and the factors impairing such an effect in those with airway hyperresponsiveness remain unclear (45). Lung inflation, or deep
Values are mean ± SD. PEF, peak expiratory flow. *Significantly different between pre- and posttest within group (P < 0.05). †Significantly different between groups (P < 0.05).

Table 3. Percent change in pulmonary function

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<th>Parameter</th>
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<th>% Change</th>
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Impact of Body Fat on Airway Health

It is well established that obesity is associated with asthma (48) and obesity has also been associated with asthmalike symptoms in otherwise healthy adults (55), but the mechanisms for these relationships are unclear. In a review by Shore (48), 16 of 17 potential prospective studies involving more than 200,000 adults and children indicated that obesity precedes asthma, and obesity also worsens asthma control (48). Although studies examining the relationship between obesity and AHR in children have shown inconsistent results, when exercise was the method of provocation, results have consistently indicated that obese children have more exercise-induced bronchoconstriction than nonobese children, even in nonasthmatics (48). The majority of our TrG participant population (n = 7) was not obese according to BMI standards; however, the fact that body fat was associated with airway responsiveness suggests that similar mechanisms may be involved. Our trained participants with higher body fat percentages had less of an improvement in ΔFEV1 than leaner participants, suggesting that excess adiposity places children at risk for asthmalike symptoms and acts to diminish potential benefits derived from engaging in a vigorous physical training program. The mechanistic basis for increased body fat contributing to diminished airway health benefits may be greater systemic inflammation. Further research is necessary to explore the relationship between adiposity and training-derived airway health benefits, as well as potential mechanisms.

Adipose tissue acts as an endocrine organ, generating pro-inflammatory cytokines and creating inflammation systemically as well as in the airways (29). Changes in many adipose-derived inflammatory markers, including TNF-α, leptin, and adiponectin, have the capacity to promote AHR and may thus contribute to asthma in the obese (41). In addition to adipocytes, ASM may produce multiple inflammatory mediators (prostanoids, cytokines, and chemokines) (20), contributing to the exacerbation of the inflammatory process in the airway wall. Related to the above discussion of AHR, in response to stretch, the contractile myocytes of the ASM have a mechanical plasticity that is thought to be directly influenced by...
inflammation (15). Chronic inflammation is likely to be one possible mechanism by which airway remodeling occurs, eventually leading to airway hyperresponsiveness. In agreement with this hypothesis, a recent study from Lowder and colleagues (25) indicated that moderate intensity aerobic exercise training may attenuate airway inflammation within the asthmatic airway via regulatory T cells. It is possible that in our study, training led to increased ventilation and, therefore, also to stretch in the airway smooth muscle. In our higher body fat children, however, systemic inflammation persisted, not allowing improvement in airway narrowing to the extent of the leaner children. Physical inactivity, as well as adiposity, may have contributed to the hyperresponsiveness seen in the higher body fat children. Therefore, through training, improvement was seen in one contributing factor, but not the other, diminishing the overall improvement in airway function.

Recently, there has been some renewed interest regarding the impact of oxidized LDL on airway and lung function (17, 50). In the current study, we found that change in LDL cholesterol was associated with improvements in ΔFEV1 for the entire group of participants (data not shown). LDL cholesterol improved ~35% in the TrG, providing potential insight into mechanisms for change in ΔFEV1.

Limitations

Because asthma is characterized by airway inflammation as well as airway hyperresponsiveness and because acute as well as chronic inflammation can affect airway hyperresponsiveness (32), we chose to assess airway inflammation previously, but its use has been primarily in asthmatics (21, 42). In our study, because of the fact that our subjects were nonasthmatic, no subjects had significant levels of airway inflammation evidenced as exhaled nitric oxide. Additionally, no differences were found in exhaled nitric oxide following training. These discordant inflammation and airway narrowing values lend support to previous findings that in nonasthmatic individuals, airway inflammation and airway hyperresponsiveness are only loosely related to one another (6, 13, 18). It would be useful in future studies to include other markers of inflammation to determine whether changes in airway responsiveness were occurring in concert with systemic changes in inflammation.

Unfortunately, despite group randomization, the ConG and TrG were not equal at baseline with regard to VO2max, Ve, and maximal workload achieved during the exercise test. Additionally, our primary outcome measure of ΔFEV1 was different between groups, indicating more airway responsiveness in the training group at baseline. We did statistically control for these group differences in our analyses; however, ideally the groups would have been equivalent at baseline.

In our study, we used two methods of airway perturbation (exercise and EVH) to make certain that children who may have responded to only one method and not to the other would not be misclassified. Previous literature has indicated that it is common for children to have inconsistent results for airway hyperresponsiveness depending on the method of perturbation (16). The results of the EVH perturbation were much less consistent than the exercise condition for pulmonary function measures other than FEV1, perhaps indicating inadequate airway irritation. For this reason, we chose to focus on exercise as the primary method of assessment. However, our participants experienced airway narrowing under both perturbation conditions and also posttraining improvements under both condi-

Fig. 1. Effect of training on postexercise airway narrowing. Percent change in postexercise forced expiratory volume in 1 s (ΔFEV1) from pre- to postraining is shown. •, Individual data; ○, means ± SD. In the training group (TrG) there was significant improvement from pre to post in ΔFEV1, with 6 of 8 participants in the TrG showing improvement in ΔFEV1 following training. *Significantly different from pre- to postraining (P < 0.05).

Fig. 2. Effect of training on postexercise forced expiratory flow at 25–75% of vital capacity (FEF25–75). Percent change in postexercise ΔFEF25–75 from pre- to postraining is shown. •, individual data; ○, means ± SD. Training led to significant improvement in ΔFEF25–75, with 6 of 8 participants in the TrG showing improvement in ΔFEF25–75 following training. *Significantly different from pre- to postraining (P < 0.05).
tions, indicating that the response to airway stretch is positive for multiple methods of perturbation and not just exercise.

We did not specifically recruit children who were overweight or obese for this study, and as a group the TrG children did not show an unhealthy airway response to exercise. A previous cross-sectional study from our laboratory indicated that not meeting physical activity guidelines and being overweight places children at risk for postexercise airway hyper-responsiveness (43). Whereas the majority of the children in the current study did not achieve a decrease in FEV1 % indicative of exercise-induced bronchoconstriction (≥10%), three children from the training group did decrease >10% and one was borderline at 9.58% postexercise. Following training, these children all had postexercise ΔFEV1 % values well below the 10% cut point.

Public Health Implications

Our recruitment methodology resulted in a population made up primarily of girls, with only two boys participating. We did not anticipate this would happen, as it was not our intention to recruit one sex over the other. The negative impact of insufficient activity at higher intensities may, however, be of particular importance to young girls, as physical activity literature indicates that girls tend to be less active than boys and, perhaps more importantly, less active at moderate and vigorous intensities (44, 56). Although asthma prevalence rates are higher in preadolescent boys than girls, in adulthood, women have a higher prevalence of asthma (31). This trend may be attributable in part to women becoming less active and engaging in inadequate MVPA. Further investigations should track children through adolescence to determine whether physical activity levels, specifically at higher intensities, provide the same benefit as in preadolescence. Additionally, the role of physical activity in airway health for preadolescent boys should be examined to determine whether the findings of this study are applicable.

Conclusions

These research findings provide information regarding the importance of lifestyle factors including physical activity and body fat percentage for prepubescent girls at risk for development of asthma. These results suggest that physical inactivity negatively impacts airway health in nonasthmatic prepubescent girls, which can be improved with high-intensity training. Increased body fat, however, may diminish these improvements. There are many factors contributing to the rapid increase in asthma and asthmalike symptoms in children over the past few decades, but early intervention relevant to lifestyle factors may be one potential way to reverse the trend of increasing asthma prevalence rates in children.

ACKNOWLEDGMENTS

We acknowledge and thank Dr. Mark Haub for assistance with this study. We also acknowledge Jenna Ediger, Gregory Tanquary, and Cali Dunham for assistance with completing the training sessions.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


Table 4. Ventilatory and metabolic data at peak exercise

<table>
<thead>
<tr>
<th></th>
<th>Pretest</th>
<th>Training</th>
<th>Pretest</th>
<th>Training</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 8)</td>
<td></td>
<td>Control (n = 8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>VO2, l/min</td>
<td>1.20 ± 0.34</td>
<td>0.64–1.83</td>
<td>0.80 ± 0.27†</td>
<td>0.31–1.25</td>
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<tr>
<td>VCO2, l/min</td>
<td>33.1 ± 6.2</td>
<td>20.9–40.9</td>
<td>23.6 ± 7.7†</td>
<td>14.2–34.4</td>
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<tr>
<td>VE/VO2</td>
<td>1.29 ± 0.36</td>
<td>0.68–1.91</td>
<td>0.84 ± 0.29†</td>
<td>0.32–1.33</td>
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<td>VE, l/min</td>
<td>55.1 ± 13.6</td>
<td>36.0–78.6</td>
<td>40.0 ± 10.2†</td>
<td>19.3–52.3</td>
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<td>VO2/VE</td>
<td>47.1 ± 6.8</td>
<td>39–60</td>
<td>52.8 ± 10.8</td>
<td>42–73</td>
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<tr>
<td>RER</td>
<td>44.0 ± 6.0</td>
<td>37–55</td>
<td>50.4 ± 9.6</td>
<td>40–66</td>
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<tr>
<td>HR, beats/min</td>
<td>1.08 ± 0.02</td>
<td>1.05–1.12</td>
<td>1.06 ± 0.06</td>
<td>0.97–1.13</td>
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<tr>
<td>O2, Sp%</td>
<td>190.4 ± 13.7</td>
<td>165–205</td>
<td>176.1 ± 14.9</td>
<td>147–192</td>
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<tr>
<td>VCO2, l/min</td>
<td>13.6 ± 3.6</td>
<td>36.0–78.6</td>
<td>6.6 ± 3.6</td>
<td>54.1</td>
</tr>
<tr>
<td>RER</td>
<td>1.00 ± 0.13</td>
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<td>1.00 ± 0.06</td>
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<tr>
<td>HR, beats/min</td>
<td>188.8 ± 10.3</td>
<td>172–199</td>
<td>184.5 ± 10.6*</td>
<td>169–196</td>
</tr>
<tr>
<td>Energy, W</td>
<td>98 ± 1</td>
<td>97–99</td>
<td>98 ± 1</td>
<td>96–100</td>
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<tr>
<td>Workload, W</td>
<td>102.5 ± 26.6</td>
<td>60–150</td>
<td>66.7 ± 20.0†</td>
<td>40–110</td>
</tr>
<tr>
<td>VO2, oxygen uptake</td>
<td>1.12 ± 0.32</td>
<td>0.66–1.65</td>
<td>0.92 ± 0.31</td>
<td>0.37–1.38</td>
</tr>
<tr>
<td>VCO2, carbon dioxide</td>
<td>30.4 ± 7.5</td>
<td>21.5–46.8</td>
<td>29.4 ± 8.2*</td>
<td>15.6–36.7</td>
</tr>
</tbody>
</table>

Values are mean ± SD. VO2, oxygen uptake; VCO2, carbon dioxide output; VE, minute ventilation; RER, respiratory exchange ratio; SpO2, arterial oxygen saturation; *Significantly different between pre and posttest within group (P < 0.05); †Significantly different between groups (P < 0.05).
1. American Diabetes Association. Standards of Medical Care in Diabetes—


