Cover Page

Official Title: Asthma and childhood obesity: Understanding potential mechanisms and identifying strategies to improve respiratory symptoms

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The 2013 American Thoracic Society guidelines strongly recommend interval warm-up exercise[1] to reduce EIB severity. This recommendation is based on studies of warm-up exercise protocols that reduce EIB severity in nonobese asthmatic children [2]. However, no empirical data on the effects of interval warm-up exercise on EIB severity are available in *obese asthmatic children*, where excess fat exerts such an unfavorable burden on the respiratory system, particularly during exercise. Investigation of the effectiveness of *simple* EIB reduction strategies, such as interval warm-up exercise, in obese asthmatic children is urgently needed. Therefore, **the objective of this study is to investigate the effects of interval warm-up exercise on EIB in obese and nonobese asthmatic children.**

Our approach will be to investigate EIB after an exercise challenge test (ECT) preceded by a no-treatment control and two randomized conditions: (1) 8x30s interval warm-up and (2) pretreatment with a bronchodilator (short-acting beta agonist [SABA]). We will test the following aims in obese asthmatic children (n=12) compared with nonobese asthmatic children (n=12):

Aim: To investigate the effects of interval warm-up exercise on EIB severity

Hypothesis: Interval warm-up exercise will reduce EIB severity after an ECT to a similar extent as SABA and better than control.

RESEARCH STRATEGY

Study design and participants: This is a cross-sectional study. We will complete testing in 9 – 12 yr old nonobese and obese children with a physician diagnosis of mild asthma with a Tanner pubertal stage of ≤3. This approach will enable us to study and compare obese and nonobese boys and girls of similar maturation while pubertal effects on lung function and exercise responses are minimized. For adequate power to test the stated hypotheses, 12 nonobese and 12 obese asthmatic children will need to complete all five visits in this study. We may need to enroll up to 50 children considering possible attrition, to reach a final sample of 12 obese and 12 nonobese asthmatic children.

All participants will have no history of smoking, no history or evidence of heart disease, no history of uncontrolled hypertension, no documented and/or diagnosed sleep disorders, no diagnosed diabetes, no metabolic disorders, no history of significant mental illness, no dietary restrictions, no serious health conditions, or no musculoskeletal abnormality that would preclude exercise. Children who have been hospitalized for an asthma exacerbation or who have taken oral glucocorticoids for asthma in the past year and children who have been admitted to an intensive care unit or been intubated because of their asthma in the past five years, will be excluded to reduce the risk of exacerbation during the study[3].

BMI criteria: We will study nonobese children with a BMI between the 16th and 84th percentile and obese children with a BMI > 95th percentile but less than 170% above the 95th percentile and less than an absolute BMI of 40 $kg \cdot m^{-2}$. Recently, there has been a shift towards classifying child BMI over the 95th percentile as a percent above the 95% percentile because the statistical procedures used to generate percentile curves are not accurate at the extreme tails of BMI distribution[4]. We have chosen 170% above the 95th percentile as a reasonable cut-off or upper-limit because it will exclude children with an average age and sex specific BMI of approximately > 40 $kg \cdot m^{-2}$ (BMI Range 36 – 43 in boys and 37 – 45 in girls 9 – 12 yr), which roughly corresponds to Class III obesity in adults. Since this BMI percentile range also includes children with a BMI > 40 $kg \cdot m^{-2}$, we will further exclude any children with an absolute BMI > 40 $kg \cdot m^{-2}$.

Lung function criteria: We will study children with 1) FVC ≥ 80% predicted, 2) FEV_1 ≥ 75% predicted, and TLC ≥ 80% predicted, consistent with normal pulmonary function and including participants with mild obstructive airway disease. Since the risk of severe EIB increases in children with moderate or severe obstructive airway disease, children with FEV_1 < 75% predicted will be excluded from the study[5]. Diagnosis of asthma (i.e., airway responsiveness with reversible obstruction) will be established by spirometry (i.e., improvement of FEV_1 of ≥8% after administration of SABA[6]). Children without reversible airway obstruction will also be excluded from the study.

Aim: To investigate the effects of interval warm-up exercise on EIB severity

Introduction: The *working hypothesis* is that interval warm-up exercise will reduce EIB severity to a similar extent as a SABA and a greater extent than control in obese asthmatic children. Furthermore, we propose that reduction of EIB severity in obese asthmatic children after interval warm-up exercise and/or SABA may be to a lesser extent than in nonobese asthmatic children. The *rationale* behind the proposed research centers on the fact that

EELV will be forced to even lower levels during exercise in an obese asthmatic child creating the potential for increased airway hyperresponsiveness and EIB. In this context, interval warm-up exercise and SABA may improve EIB as it does in nonobese asthmatic children[2], but obesity-related changes in respiratory function may reduce the effectiveness of interval warm-up exercise and SABA in obese asthmatic children.

Sample size estimation: Our primary variable is maximum % fall in FEV_1 after interval warm-up exercise vs. no-treatment control. Schnall and Landau[7] reported maximum % fall in FEV_1 after an exercise challenge preceded by interval warm-up of 6.9±5.2% compared to control 23.0±5.2%. Based on these data[7], we would be able to detect a significant mean reduction in maximum % fall in FEV_1 between the control and interval warm-up at greater than 95% power in 12 nonobese asthmatic children. While effect sizes may be lower in obese asthmatic children, we can detect a maximum 9.9% fall in FEV_1 difference between control and interval warm-up at 80% power with a sample size of 12 obese asthmatic children. A sample size calculation to detect a significant group x treatment interaction was not possible for this aim without preliminary/published data. Nevertheless, testing the effectiveness of interval warm-up exercise on EIB in obese asthmatic children is itself of considerable clinical value and an important clinical outcome in the proposed project.

METHODS: Over five separate visits (1.5 – 2.5 h each), we will measure respiratory function, exercise tolerance, and EIB after an ECT that is preceded by a no-treatment control and two randomized conditions: (1) 8 x 30 s interval warm-up, and (2) pretreatment with a bronchodilator (SABA). Testing that requires physician oversight (e.g., exercise tests) will be conducted at the Sunrise Health and Medical Center (SHMC). Testing that does not require physician oversight, such as plethysmography measurements for lung volumes, will be conducted at UNLV.

Visit 1: We will conduct spirometry and airway resistance measurements (using FOT) before and after SABA (Albuterol 4 puffs, 90mcg per actuation) to assess airway hyperresponsiveness. Participants with an FEV_1 < 75% predicted will be excluded from the study to reduce risk of severe EIB after exercise[5]. Lung volumes (i.e., TLC, FRC, RV) will be measured by plethysmography. Maximal voluntary ventilation (MVV) will be determined from a 10 s test extrapolated to 1 min. Height, weight, circumference measurements (chest, waist, hip, and neck), and BMI percentile will be used to characterize body size and fat distribution.

Visit 2: Participants will undergo maximal graded cycle ergometry to exhaustion to measure exercise tolerance. Graded cycle ergometry will be performed using 1-min increments of 10W on an electronically braked cycle ergometer (VIAsprint™, Vyaire Medical, Yorba Linda, CA). During cycle ergometry, we will measure ventilation and gas exchange to assess minute ventilation ($\dot{V}_E$), $\dot{V}O_2$, $\dot{V}CO_2$, respiratory exchange ratio, and ventilatory equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$. During cycle ergometry we will also measure exercise tidal flow-volume loops and participants will perform inspiratory capacity maneuvers by inhaling to TLC every minute to assess end-expiratory lung volume (EELV). Expiratory flow limitation (EFL) will be assessed by comparing overlap of exercise tidal flow-volume loops with the maximal flow-volume loop. For patient safety and to monitor progress during the test, we will also record ratings of perceived breathlessness (RPB: 0–10 scale), ratings of perceived exertion (RPE: 6–20 scale), blood pressure, heart rate, breathing frequency, tidal volume, pulse oximetry (SpO_2), and $P_{ET}CO_2$. $\dot{V}O_{2max}$ will be confirmed by a supramaximal verification test at 105% of maximal work rate to exhaustion. Maximal exercise capacity will be evidenced by $\dot{V}O_{2max}$ (highest $\dot{V}O_2$ obtained during maximal or verification test)[8].

Visit 3: CONTROL VISIT We will ask participants to hold SABA for 8h, corticosteroid for 24h, and long acting asthma medications for 24h prior to the exercise challenge test (ECT) visits. Participants will also be asked to avoid exercise for 24h prior to the visit. We will measure FEV_1 using spirometry, airway function using FOT and FeNO before starting the ECT (see **Fig. 1** for timeline of ECT visits). The ECT will be performed in accordance with the American Thoracic Society guidelines[5]. Target work rate (W) will be calculated as [(53.76 × measured FEV_1) – 11.07] [5]. Work rate will be increased from 60% of target work rate in the first minute, to 75% in the second minute, 90% in the third minute, and 100% in the fourth minute[9]. We will measure HR, SpO_2%, RPB,

and RPE during 6 minutes of cycling at 80-90% of HR_{max}. We will measure FEV_1 using spirometry and airway function using FOT at 2, 5, 10, 15, and 30min after completing the ECT (see **Fig. 1**). SABA will be administered to any patient with exercise-related respiratory symptoms and the test will be stopped. Spirometry and FOT measurements will be conducted every 5min after SABA administration to determine whether SABA effectively reversed the bronchoconstriction. A decision of whether to exclude the participant from the study will be made after consulting the pediatric pulmonologist.

Visits 4 and 5: ECT will completed 15 min after two randomized conditions: (1) 8 x 30 s interval warm-up and (2) pretreatment with a SABA. We will conduct spirometry and airway function measurements at baseline prior to after interval warm-up exercise or SABA administration. We will also conduct spirometry and airway function measurements at 2, 5, and 10 min after interval warm-up exercise or SABA administration and prior to the ECT to assess bronchodilation or bronchoconstriction resulting from interval warm-up and SABA. FeNO will only be measured at baseline. ECT will be performed exactly as described in Aim 2. Details regarding interval warm-up and SABA administration are given below.

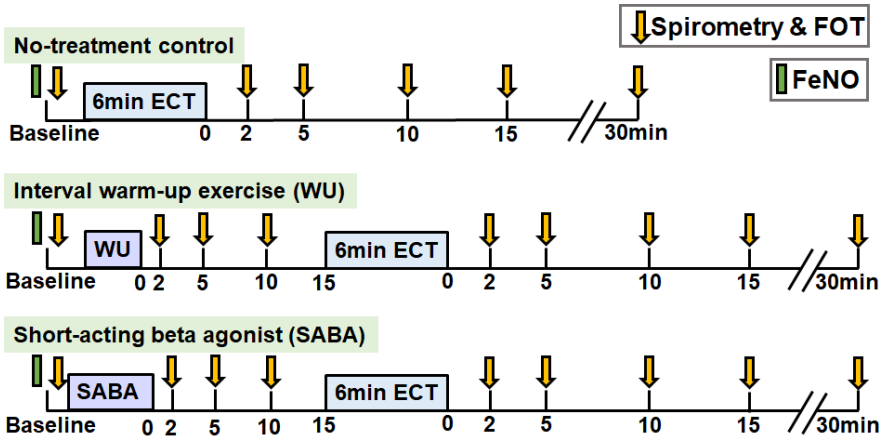

Figure 1. A timeline of testing for the exercise challenge tests (ECT) in visits 3-5. FOT, forced oscillation technique; FeNO, fractional expired nitric oxide

- Interval warm-up: eight 30 s intervals of cycling at 100% of the target work-rate calculated as [(53.76 × measured FEV_1) – 11.07][5]. 45 s of active recovery at 20W will be performed between two intervals. The interval warm-up protocol selected for the proposed study was based on published research by Mickleborough *et al* [10] comparing the effects of interval warm-up, SABA and no warm-up on EIB in nonobese asthmatic adults. We will monitor HR and SpO_2 during the test.
- SABA: 4 puffs of Albuterol (90mcg per actuation). Participants will actuate the medication into the spacer, inhale slowly from FRC and hold their breath for 10 s before exhaling. This procedure will be repeated four times with 1 min between actuations.

Statistical analysis plan: Comparisons in maximum % fall in FEV_1 from baseline will be made using a mixed ANOVA (between effect: obese, nonobese; within effect: control, SABA, interval warm-up). Pearson product-moment correlations will be utilized to examine associations between maximum % fall in FEV_1 and airway function (resistance and reactance) and FeNO, measures of body composition, and fat distribution.

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