BMJ Open Respiratory Research

Reduced tidal volume-inflection point and elevated operating lung volumes during exercise in females with well-controlled asthma

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To cite: Brotto AR, Phillips DB, Rowland SD, *et al*. Reduced tidal volume-inflection point and elevated operating lung volumes during exercise in females with well-controlled asthma. *BMJ Open Respir Res* 2023;**10**:e001791. doi:10.1136/bmjresp-2023-001791

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2023-001791).

Received 24 April 2023
Accepted 1 December 2023

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ABSTRACT

Introduction Individuals with asthma breathe at higher operating lung volumes during exercise compared with healthy individuals, which contributes to increased exertional dyspnoea. In health, females are more likely to develop exertional dyspnoea than males at a given workload or ventilation, and therefore, it is possible that females with asthma may develop disproportional dyspnoea on exertion. The purpose of this study was to compare operating lung volume and dyspnoea responses during exercise in females with and without asthma.

Methods Sixteen female controls and 16 females with asthma were recruited for the study along with 16 male controls and 16 males with asthma as a comparison group. Asthma was confirmed using American Thoracic Society criteria. Participants completed a cycle ergometry cardiopulmonary exercise test to volitional exhaustion. Inspiratory capacity manoeuvres were performed to estimate inspiratory reserve volume (IRV) and dyspnoea was evaluated using the Modified Borg Scale.

Results Females with asthma exhibited elevated dyspnoea during submaximal exercise compared with female controls ($p<0.05$). Females with asthma obtained a similar IRV and dyspnoea at peak exercise compared with healthy females despite lower ventilatory demand, suggesting mechanical constraint to tidal volume (V_T) expansion. V_T-inflection point was observed at significantly lower ventilation and $\dot{V}O_2$ in females with asthma compared with female controls. Forced expired volume in 1 s was significantly associated with V_T-inflection point in females with asthma ($R^2=0.401$; $p<0.01$) but not female controls ($R^2=0.002$; $p=0.88$).

Conclusion These results suggest that females with asthma are more prone to experience exertional dyspnoea, secondary to dynamic mechanical constraints during submaximal exercise when compared with females without asthma.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Individuals with asthma report exercise avoidance to a greater extent compared with healthy controls, with exertional dyspnoea being cited as a major contributor. Further, in health, females are more likely to report higher dyspnoea then males due to airway size.

WHAT THIS STUDY ADDS

⇒ Females with asthma reported significant dyspnoea at matched workloads compared with controls due to earlier tidal volume-inflection and higher operating lung volumes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Females with asthma may be at a higher risk for symptom burden during exercise. Further research is needed to understand how this may affect perception around exercise and exercise avoidance in asthma.

INTRODUCTION

Asthma is a chronic airway disease characterised by recurrent episodes of wheezing and shortness of breath (commonly termed dyspnoea) brought on by pulmonary inflammation and bronchoconstriction.[1] Although physical activity has been shown to reduce symptom burden,[2] individuals with asthma perform less physical activity compared with individuals without asthma.[3] The reasons for exercise avoidance in people with asthma are multifactorial and complex,[4] and increased exertional dyspnoea has been cited as a major contributor to exercise avoidance in these individuals.[3 5]

During high-intensity exercise, increased ventilatory rate can result in expiratory flow limitation.[6] The presence of expiratory flow limitation can lead to a compensatory increases in operating lung volume, which is reflected by a reduction in inspiratory capacity (IC) and inspiratory reserve volume (IRV).[5 7–9] The increase in operating lung volume is advantageous as it facilitates greater airflow during high-intensity exercise. However, the elevated operating lung volume places tidal volume (V_T) on the non-compliant portion

of the sigmoidal pressure–volume curve, increasing the elastic load of the inspiratory muscles and ultimately heightening dyspnoea.[9–12] Previous work has shown that individuals with controlled asthma develop greater expiratory flow limitation, breathe at higher operating lung volumes and report greater dyspnoea during exercise compared with age-matched and fitness-matched healthy individuals.[5] Further, early V_T-inflection points can mark significant ventilatory mechanical constraints and are closely related to increased perceived exertion in individuals with asthma.[13–15]

Females typically have smaller lungs and lower maximal expiratory flow rates than males of the same height.[16 17] Healthy females have narrower airways, and during exercise they breathe at higher operating lung volumes, which increases the work of breathing and neural drive to breathe, when compared with males at similar ventilation rates.[7 18 19] When expressed relative to maximal ventilation, males and females demonstrate similar work of breathing,[7 18 19] suggesting the difference is predominantly driven by structure rather than function.[20] As a result, females report greater dyspnoea at a given ventilatory rate,[19 21] and female athletes typically report increased exertional dyspnoea compared with male athletes with asthma.[22] Despite research evaluating sex differences in the dyspnoea response to exercise in health,[19 21] the physiological underpinnings of increased exertional dyspnoea in females with asthma are poorly understood. Accordingly, the primary objective of the present study was to compare ventilatory and sensory responses during incremental exercise in females with and without asthma. It was hypothesised that females with asthma would experience greater dyspnoea compared with female controls and that the increased dyspnoea in females with asthma would be secondary to dynamic respiratory mechanical abnormalities, specifically elevated operating lung volumes, compared with female controls. As a comparison group, males with asthma and male controls were also examined in the study.

MATERIALS AND METHODS

Patient and public involvement

Patients were not involved in the concept, recruitment or design of the current trial.

Study design

This manuscript is part of a larger series of studies examining cardiopulmonary physiology in individuals with asthma, and some of the patient data has been published previously.[5 23]

The present study is a case–controlled observational study. The four sessions included: (1) a standardised pulmonary function test, including inhaled beta-agonist reversibility; (2) a methacholine challenge test; (3) an exercise challenge test and (4) an incremental cycle cardiopulmonary exercise test (CPET). On initial visit to the laboratory, each participant completed the Asthma Control Questionnaire (ACQ[24]) and the Physical Activity Readiness Questionnaire plus.[25] In addition, medical history and demographic data were obtained prior to a pulmonary function test and CPET. The CPET was completed on a separate day as the pulmonary function test to avoid interference of beta-agonist inhalers on the CPET outcomes. Each participant completed three separate screening days to determine eligibility for participating including bronchodilator response following inhaled beta-agonist, a methacholine challenge and exercise challenge test in accordance with American Thoracic Society (ATS) guidelines.[26]

Participants

In accordance with previously listed ATS criteria,[27] self-reported physician diagnosis of asthma was confirmed in 32 individuals (16 females with asthma, 16 males with asthma) by one of the following challenges: (1) ≥200 mL and 12% improvement in forced expired volume in 1 s (FEV_1) following a beta-agonist administration, (2) ≥10% reduction in FEV_1 following an exercise challenge test or (3) a 20% decrease in FEV_1 following ≤4.0 mg/mL methacholine (PC_{20}). For the control groups, 32 individuals (16 females and 16 males) without clinical history of asthma and who demonstrated no reversibility or hypersensitivity to the methacholine challenges were recruited. All individuals were free from any other known cardiovascular disease or lung disease. Patients with asthma were required to withhold inhaled corticosteroids for 48 hours prior to testing and short-acting beta-agonists 8 hours prior to testing. Participants were asked to abstain from physical activity, caffeine and alcohol 12 hours prior to testing. All participants who were identified as female reported contraception use and menstrual phase on the exercise day.

Pulmonary function

FEV_1 and forced vital capacity (FVC) were evaluated using spirometry.[28] On a separate day from the CPET, reversibility following an inhaled beta-agonist (4×100 µg salbutamol) was performed using a space chamber to ensure uniform dosing. Lung volumes were determined using plethysmography.[29] Diffusing capacity was determined by measuring the single-breath diffusing capacity of carbon monoxide.[30] All measurements were assessed using the V62J Body Plethysmography (Encore229 Vmax, SensorMedics, Yorba Linda, California, USA), and values were expressed as a percentage of predictive values, using Global Lung Initiative predictive equations.[31–33]

Methacholine challenge

ATS guidelines for the administration of methacholine have been previously published.[34 35] In short, participants performed the tidal breathing method of administration and performed FEV_1 manoeuvres at 30 and 90 s intervals. Individuals with asthma diagnosis started

at a methacholine concentration of 0.125 mg/mL and doubling concentrations were administered until either a provocative concentration resulting in a 20% reduction in FEV_1 (PC_{20}) or a maximal concentration of 16 mg/mL was reached. Participants with no history of asthma (controls) performed the same procedure as above, though started at a concentration of 1.0 mg/mL as per recommendations.[34]

Exercise challenge test

ATS guidelines for the administration of an exercise challenge test have been previously published.[36] Briefly, participants performed a cycle ergometer protocol such that each participant reached an exercise intensity to elicit a minute ventilation equivalent to 18–21 times their respective FEV_1 within 3 min of initiating exercise and maintained that intensity for 6 min. During the entirety of the exercise session, participants breathed through a three-way, non-rebreathe mouthpiece which administered dry air (0% relative humidity) from a compressed gas cylinder through a Douglas bag apparatus (Hans Rudolph, Kansas, USA). Spirometry was conducted 1, 3, 5, 10, 15 and 20 min following the exercise session. A drop in FEV_1 greater than or equal to 10% was used as criteria for a positive test.

Cardiopulmonary exercise test

The CPET consisted of a 4 min steady state rest period for baseline measurements. Initial work rate was set to 50 W and was increased by 25 W every 2 min to the limits of exercise tolerance.[5 37] Participants rated their perceived breathing and leg discomfort using the modified Borg Scale[38] at rest, within the last 30 s of every 2 min exercise interval and at the end of exercise, followed by an inspiratory capacity manoeuvre. Inspiratory capacity manoeuvre was used to calculate operating lung volumes including end-expiratory lung volume (EELV= total lung capacity (TLC)−IC) and inspiratory reserve volume (IRV=IC−V_T).[34] Dynamic hyperinflation was defined by a reduction in inspiratory capacity of >150 mL during exercise.[39–41] Participants were asked to report the reason for exercise test termination immediately following completion of the protocol. The responses were broken down into four categories: breathing discomfort, leg discomfort, both breathing and leg discomfort, and other. All ventilatory and cardiovascular measurements were collected over the first 30 s of every second minute during the exercise test and were linked with the perceptual ratings and inspiratory capacity measurements collected in the final 30 s of the respective minute to avoid contamination of the expired gas data from the inspiratory capacity manoeuvre.[42 43] Post-exercise spirometry was completed within 5 min of exercise cessation. V_T-inflection points were derived using inverted Hey plots[14] and verified by two independent collaborators. Briefly, all breath-by-breath V_T data were averaged over 30 s and plotted relative to the corresponding minute ventilation (inverted Hey plot) for each participant. Consistent with previous work,[15 44 45] the V_T-inflection was then defined as the point at which the V_T inflected or plateaued in each individual, despite a continual increase in ventilation. The associated physiological (eg, V_E, IC, IRV) and sensory (eg, dyspnoea) data at this time point were compared between groups. Expiratory flow limitation was determined by placing the tidal breathing inside the maximal flow volume loop produced following the CPET.[46] The minute ventilation relative to $\dot{V}CO_2$ production ratio $(\dot{V}_E/\dot{V}CO_2)_{slope}$ was calculated from the initiation of exercise to the respiratory compensation point,[8] while $\dot{V}_E/\dot{V}CO_{2nadir}$ was determined as the lowest 30 s average observed by each individual.

All exercise tests were performed on an electronically braked cycle ergometer (Ergoselect II 1200 Ergoline) using a cardiorespiratory metabolic measurement system (Encore229 Vmax, SensorMedics). Arterial oxygen saturation (S_pO_2) was estimated using finger pulse oximetry (N-595; Nellcor OxiMax). Heart rate was measured using electrocardiography (CardioSoft, GE Medical Systems). CPET measurements were expressed as per cent of predicted normal values.[47]

Statistical analysis

The sample size was calculated from previous work examining dyspnoea observed in stable asthma compared with controls during incremental exercise[5] which found a 1.5 Borg unit (pooled SD of 1.4) difference between the two groups during submaximal exercise. An a priori sample size calculation determined that 16 females with asthma would be sufficient in detecting a difference in dyspnoea sensation compared with female controls (α=0.05, β=0.80) while accounting for a potential 5% drop-out. Thirty-two males (16 asthma and 16 controls) were also recruited as a comparison (total sample=64).

Baseline demographics and pulmonary function data were compared between controls and individuals with asthma using a one-way analysis of variance (ANOVA). A repeated measures ANOVA was used to evaluate physiological and sensory variables at standardised submaximal work rates. Additionally, a one-way ANOVA was used to analyse differences in peak exercise variables. A linear regression was used to determine associations between baseline pulmonary function and exercise outcomes. Reason for test termination was analysed using Fisher's exact test. All statistical tests were performed using SPSS Statistics V.26.0 (IBM, Armonk, New York, USA). Statistical significance was set at $p<0.05$ *a priori* for all comparisons.

RESULTS

Participant characteristics

Sixteen females with asthma were pairwise age, height and sex-matched to 16 healthy female controls (table 1). Sixteen males with asthma and matched controls were also recruited as a comparison group,

Table 1 Female participant characteristics

Variable	Control	Asthma	P value
n	16	16	
Age (years)	24±3	24±4	0.96
Height (m)	1.65±0.10	1.65±0.06	1.00
Weight (kg)	61.9±6.7	61.2±7.8	0.79
BMI (kg·m^{-2})	22.9±3.5	22.5±2.8	0.73
ACQ score	0.0±0.0	0.6±0.6	**0.01**
Allergies (%)	31	88	
Medications			
SABA (%)	0	50	
ICS (%)	0	38	
Combination (%)	0	0	
Airway evaluation			
Positive reversibility	0/16	8/16	
Mean FEV_1 change (%)	4±3	10±9	**0.02**
Positive MCT	0/16	9/16	
Mean FEV_1 change (%)	−6±5	−23±12	**0.01**
Positive ECT (%)	0/16	2/16	
Mean FEV_1 change (%)	0±2	−6±11	0.10

Values are expressed as mean±SD.
Note: Positive reversibility defined as a change in FEV_1 by 12% following bronchodilator.
Bolded value signifies p<0.05.
ACQ, Asthma Control Questionnaire; BMI, body mass index; ECT, exercise challenge test; FEV_1, forced expired volume in 1 s; ICS, inhaled corticosteroid; MCT, methacholine challenge test; SABA, short-acting beta-agonist.

and their characteristics and exercise data can be found in the supplement (online supplemental table 1). All participants were non-smokers and all participants with asthma were defined as well-controlled using the ACQ.[24] Pulmonary function results for females are reported in table 2. Male pulmonary function results are found in the supplement (online supplemental table 2).

Pulmonary responses to bronchial challenges are described in table 1 for females and online supplemental table 1 for males. The mean responses in FEV_1 to reversibility, methacholine and exercise challenge test (regardless of whether the tests were positive) were 10±9%, −23±12% and −6±11% in females with asthma, respectively.

All participants reached peak exercise criteria, meeting at least three of the four conditions: volitional exhaustion, a respiratory exchange ratio greater than 1.1, increases in oxygen consumption <100 mL·min^{-1} with further increase in power output and reaching age-predicted maximum heart rate[48] as shown in online supplemental table 3 and 4. Relative peak oxygen consumption ($\dot{V}O_{2peak}$) was not significantly different between female controls and females with asthma (p=0.07).

Ventilatory and metabolic responses to exercise

Metabolic and ventilatory responses at highest equivalent workload (125W), V_T-inflection point and peak exercise data for both female groups can be found in online supplemental table 4. Ventilation at submaximal exercise was significantly higher in females with asthma compared with female controls at matched workloads (100W: p=0.02, 125W: p=0.01) which was secondary to an increased breathing frequency (figure 1). Despite elevated ventilation at matched submaximal exercise intensities in females with asthma, the V_T-inflection was determined to be at a significantly lower minute ventilation in females with asthma compared with female controls (Control: 70.2±16.5 L·min^{-1} vs Asthma: 57.7±12.3 L·min^{-1}; (p=0.02). The V_T-inflection also occurred at significantly lower power output (Control: 163±33 W vs Asthma: 128±26 W; p<0.01) and relative $\dot{V}O_2$ (Control: 35.7±6.7 mL·kg^{-1}·min^{-1} vs Asthma: 30.6±6.2 mL·kg^{-1}·min^{-1}; p=0.03) in females with asthma as compared with controls. In contrast, males with asthma had similar minute ventilation at the V_T-inflection point as male controls (Control: 93.7±25.3 L·min^{-1} vs Asthma: 91.4±27.8 L·min^{-1}; p=0.81). Further, males with asthma reached similar relative $\dot{V}O_2$ and power output at V_T-inflection as compared with male controls (p=0.75 and p=0.39, respectively) which highlights the differential response in females with asthma.

V_T/inspiratory capacity and end inspiratory lung volume was not significantly different at the V_T-inflection point (p=0.07 and p=0.12, respectively) between females with asthma and female controls. These results are consistent with previous respiratory mechanics studies in health and disease that showed close association between the V_T-inflection and the mechanical load on the respiratory system (tidal oesophageal pressure swings, inspiratory elastic work of breathing).[15 49] Interestingly, relative $\dot{V}O_2$ at V_T-inflection was significantly associated with pre-bronchodilator FEV_1 in females with asthma (R^2=0.401; p<0.01) but not female controls (R^2=0.002; p=0.88) (figure 2B).

Lung mechanics

Inspiratory capacity throughout submaximal exercise and at peak exercise was significantly lower in females with asthma compared with female controls (75W p=0.01, 100W p=0.03, 125W p=0.01, V_T-inflection p=0.01, and peak p=0.04) (figure 1C); however, inspiratory capacity was not significantly different between groups when expressed as %TLC (online supplemental table 4). IRV was also significantly lower at matched workloads in females with asthma compared with controls (75W p=0.01, 100W p=0.01, 125W p=0.04), but no difference was detected at the V_T-inflection (p=0.72) or peak exercise (p=0.34) (figure 1D). Differentially, males with asthma demonstrated no differences in both inspiratory capacity and IRV (p=0.20 and p=0.81, respectively) during submaximal exercise. Males with asthma did have a significantly lower inspiratory capacity at peak exercise

Table 2 Pulmonary function with and without bronchodilator and following exercise in female control and asthma

	Control			Asthma		
	Pre-BD	Post-BD	Post-CPET	Pre-BD	Post-BD	Post-CPET
Spirometry						
FVC (L)	4.32±0.59	4.32±0.59	4.52±0.42	3.96±0.57	3.99±0.58	3.99±0.64
FVC (% predicted)	111±17	111±17	121±22	101±12	102±13	102±13
FEV_1 (L)	3.59±0.61	3.75±0.58	4.07±0.28	2.99±0.55†	3.19±0.48	3.04±0.61
FEV_1 (% predicted)	107±20	112±19	127±27	89±17†	95±14	90±17
FEV_1/FVC	83±7	87±6	90±6	76±10†	80±6	76±10
FEV_1/FVC (% predicted)	96±9	100±7	104±5	87±11†	92±7	88±11
Lung volumes						
TLC (L)	5.49±0.77			5.09±0.65		
TLC (% predicted)	106±15			98±9		
RV (L)	1.03±0.31			1.11±0.41		
RV (% predicted)	92±28			97±35		
IC (L)	2.62±0.39			2.31±0.36†		
IC (% predicted)	104±16			92±11†		
Diffusion capacity						
DLCO ($mL \cdot min^{-1} \cdot mm\ Hg^{-1}$)	24.5±3.3			23.8±3.9		
DLCO (% predicted)	108±10			105±16		

Values expressed as mean±SD.
*Signifies p<0.05 compared with pre-BD.
†Signifies p<0.05 compared with controls.
BD, bronchodilator; CPET, cardiopulmonary exercise test; DLCO, diffusing capacity of carbon monoxide; FEV_1, forced expired volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; RV, reserve volume; TLC, total lung capacity.

compared with male controls (control: 3.89±0.41 L vs asthma: 3.46±0.47 L; p=0.02) (online supplemental figure 1).

Consistent with previous literature in asthma,[5] expiratory flow limitation was also significantly greater in both females and males with asthma at peak exercise compared with their respective controls (p=0.04 and p=0.01, respectively) (online supplemental table 3 and 4).

Perceptual responses to exercise

Dyspnoea responses to exercise are shown in figure 3. Exertional dyspnoea was significantly higher in females with asthma compared with controls at matched submaximal workloads (figure 3A) but was not significantly different at the V_T-inflection point (p=0.64) or at peak exercise (p=0.75). Males with asthma however did not demonstrate significant differences in dyspnoea throughout submaximal (p=0.06) or peak exercise (p=0.34). Despite the significantly reduced IRV in females with asthma at submaximal workloads, the IRV/dyspnoea relationship to exercise was maintained in all four groups (figure 3B and online supplemental figure 2B).

DISCUSSION

The main findings from the study are threefold. First, females with asthma had elevated dyspnoea at submaximal workloads during incremental exercise, which was associated with decreased IRV compared with female controls. Second, females with asthma demonstrated a lower V_T-inflection point compared with female controls. Third, the V_T-inflection point was significantly associated with pre-bronchodilator FEV_1 in females with asthma but not in healthy female controls. Consistent with other respiratory conditions,[50] these findings demonstrate that dyspnoea is linked to reduced IRV in females with asthma and that the early V_T-inflection point observed in females with asthma is largely due to mechanical constraint on V_T expansion. Further, the above findings help to explain why females with controlled asthma consistently report greater dyspnoea during submaximal exercise compared with healthy females and males with asthma.

As previously mentioned, females have narrower conducting airways then males even when matched for lung size.[17] The relatively narrower airways predispose even healthy females to greater airway resistance when ventilation is increased during exercise.[6 51 52] In individuals with asthma, airway resistance may be further limited by baseline bronchoconstriction which further increases resistance and the prevalence of mechanical ventilatory constraint.[5 53] Although lung size was not significantly associated with the V_T-inflection point in females with asthma, baseline FEV_1 was found to be significantly associated with relative $\dot{V}O_2$ at the V_T-inflection point (figure 2B).

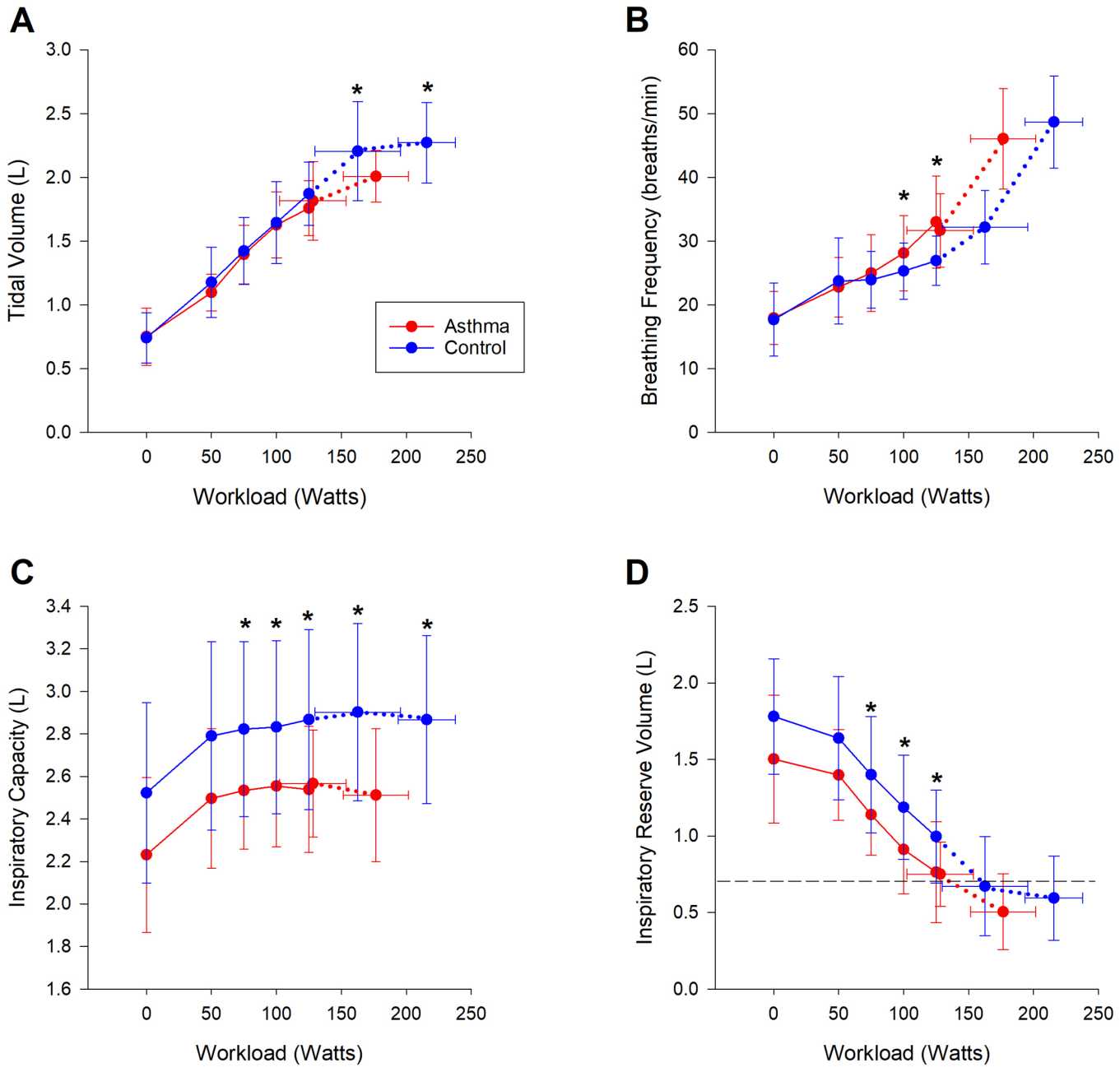

Figure 1 (A) Tidal volume (B) breathing frequency (C) inspiratory capacity (D) inspiratory reserve volume responses to exercise in females with asthma and female controls. Dotted line represents critical inspiratory reserve volume.[44] This graph shows data means±SD. *Signifies p<0.05 between female controls and females with asthma.

These findings are consistent with Lougheed *et al*[54] which similarly demonstrated a relationship between FEV_1 and hyperinflation during bronchial challenges in asthma. The significantly early V_T-inflection in females with asthma could be an attempt to minimise further increases in elastic work of breathing which is associated with large respiratory efforts during exercise. Altering breathing patterns by maintaining the V_T and increasing breathing frequency allows for maintenance of minute ventilation without encroaching on maximal expiratory flow. In the current study, no between-group differences were observed in peak V_E/VCO_2 and end-tidal PCO_2 was below 35 mm Hg at peak exercise in females with asthma (online supplemental table 4), suggesting sufficient compensatory alveolar hyperventilation at maximal exercise. Despite relative VO_{2peak} not being significantly different between females with and without asthma, females with asthma had a lower absolute aerobic fitness compared with controls, and therefore, it is possible that the difference in V_T-inflection point could be explained by fitness. However, a subanalysis conducted using the females with asthma who have the greatest aerobic fitness (ie, the top 50% VO_{2peak} of females with asthma) were compared with controls, there is no difference between these two groups in VO_{2peak} (control: 44.0±5.3 mL·kg^{-1}·min^{-1} vs higher 50%: 44.6±4.1 mL·kg^{-1}·min^{-1}; p=0.76); however,

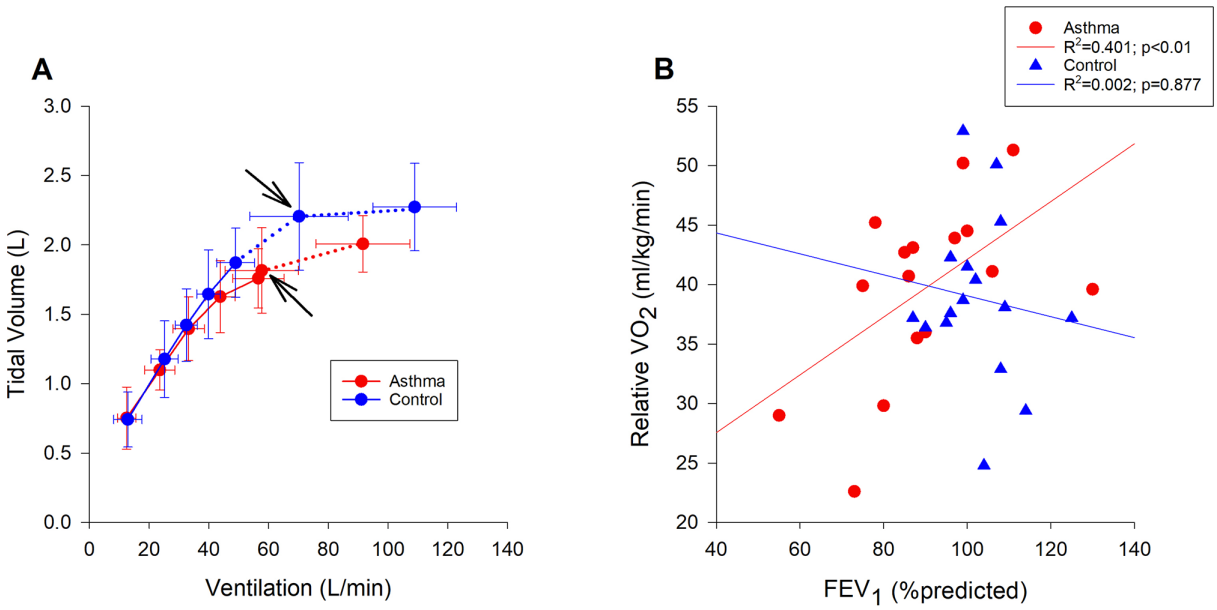

Figure 2 (A) Tidal volume (V_T) as a function of minute ventilation depicting the reduced V_T-inflection point in females with asthma compared with female controls. Arrows indicate V_T-inflection point of both groups. (B) The association between V_T-inflection point and pre-bronchodilator forced expired volume in 1 s (FEV_1) (p<0.05).

the minute ventilation at V_T-inflection was still lower in the females with asthma (control: 70.2±16.5 L·min^{-1} vs higher 50%: 56.3±11.8 L·min^{-1}; p=0.03), suggesting the difference is not explained by fitness. The current study was observational, and future work examining interventions to improve respiratory mechanics, which presumably would positively affect V_T-inflection, dyspnoea and exercise capacity, is required.

Expiratory flow limitation can be alleviated through increasing operating lung volumes (as demonstrated by reduced IRV).[7 55] While reducing airflow resistance, breathing at higher operating lung volumes forces breathing to occur on the less compliant portion of the pressure–volume curve, which has been shown to increase elastic work of breathing and heighten dyspnoea sensation.[15 56] Previous work in obstructive pulmonary diseases (ie, COPD and asthma) has shown that increased dyspnoea sensation with exercise is associated to reduced IRV.[5 44 54] A reduced IRV reflects a decrease in the operating limit for V_T expansion, as end-inspiratory lung volume approaches TLC, where further increase in volume is constrained. Further, a greater ventilation in the setting of a reduced resting and dynamic inspiratory capacity accelerates the decline in IRV to its critically low value, which would be corroborated by an earlier V_T-inflection at a low work rate and onset of severe exertional dyspnoea.[15 44 57] In the current study, females with asthma were found to experience more dyspnoea at matched absolute submaximal exercise intensities than healthy female controls. Exertional dyspnoea was associated with reduced IRV (figure 3A), which was consistent with previous work in health and other obstructive diseases.[19 21 44 58] Further, the trajectory of perceived dyspnoea increases in both female groups as IRV approaches ~0.7 L which is consistent with previous work demonstrating the association between mechanical critical constraint (ie, a critically low IRV) and dyspnoea sensation.[44 59]

Dyspnoea is a distressing sensation that can have dramatic impact on quality of life. Previous work has suggested that females with obstructive lung disease report more dyspnoea during activities of daily living than their male counterparts.[60–62] To our knowledge, no study to date has evaluated the lung mechanics and exertional dyspnoea responses in female patients with asthma. In the current study, females with asthma were found to experience more dyspnoea at matched absolute submaximal exercise intensities (figure 3A). Females with asthma had similar dyspnoea ratings at the V_T-inflection point as female controls, despite breathing at significantly lower ventilation rate. These findings are consistent with Laveneziana *et al*[13] which found a significant increased inflection of dyspnoea sensation at the V_T-inflection point regardless of IRV in individuals with asthma. The observed reduced IRV during submaximal exercise coupled with the early onset of V_T-inflection in females with asthma provides an explanation to the significantly elevated dyspnoea experienced in this group during exercise.

Although the primary focus of the study was to investigate ventilatory and dyspnoea responses in females with asthma, as a comparison, males with asthma and matched controls were also recruited for the current study and results can be found in online supplemental file. Despite similar asthma control to females, the V_T-inflection was not significantly different between males with asthma and male controls. Further, operating lung volumes (IRV and inspiratory capacity) were not different between the

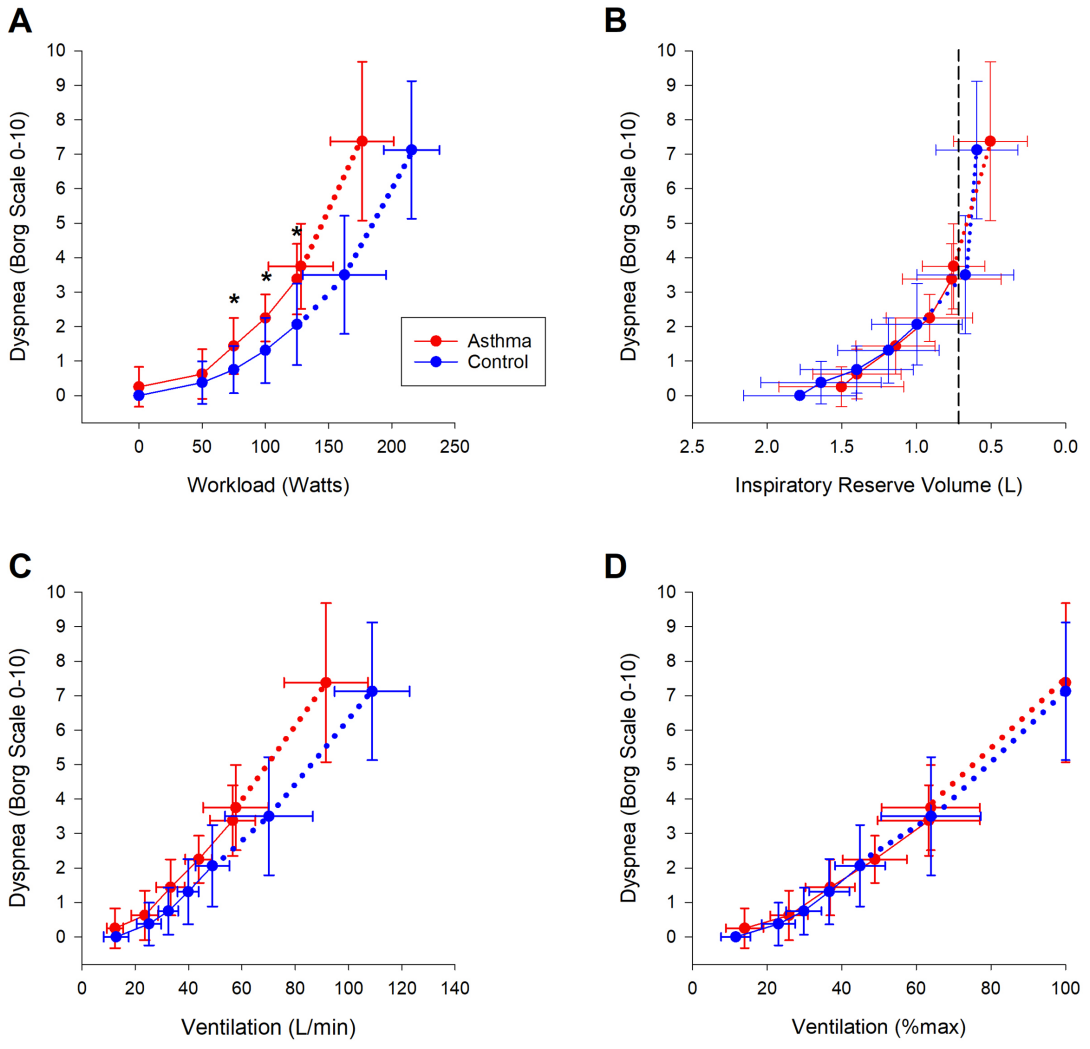

Figure 3 Dyspnoea response to workload (A) inspiratory reserve volume (B) ventilation (C) and ventilation as a percentage of maximum (D) in females with asthma and female controls. Dotted line represents critical inspiratory reserve volume.[44] This graph shows data mean±SD. *Signifies p<0.05 between female controls and females with asthma.

two male groups during submaximal exercise. Similar to females with asthma, males with asthma demonstrated an adequate ventilatory response to exercise as V_E/VCO_2 and end-tidal PCO_2 were not different compared with male controls. Lastly, males with asthma did not demonstrate significantly greater dyspnoea at submaximal exercise compared with controls which is in contrast to what was observed in females with asthma. These findings demonstrate that compared with males with asthma, females with asthma tend to demonstrate greater mechanical constraint during submaximal exercise as indicated by an earlier V_T-inflection point and significantly reduced IRV compared with controls, contributing to increased dyspnoea sensation.

LIMITATIONS

The current study did not evaluate invasive measurements of diaphragmatic muscle effort,[12 63] electrical activation of the diaphragm (reflecting inspiratory neural drive)[19 64] or discriminate between qualitative descriptors of dyspnoea.[21] Rather, the current study focused on non-invasive measurements of operating lung volumes and breathing pattern in females with asthma compared with female controls and its relationship to dyspnoea.

Asthma is a heterogeneous disease with varying severity and phenotypes. A much larger study would be required to describe the exercise responses across varying asthma phenotypes including those individuals with asthma who may demonstrate significant bronchodilation[53] or bronchoconstriction[65] during exercise. Although the current study tested individuals with asthma while withholding inhaler medications, previous work has demonstrated that administration of a short-acting inhaler prior to an incremental exercise test did not significantly alter operating lung volumes nor dyspnoea perception in individuals with mild to moderately controlled asthma.[5] The current study included all patients with asthma as defined by ATS criteria; however, only 2 of the 16 females with asthma demonstrated evidence of exercise-induced

bronchoconstriction. The low percentage of females with asthma who demonstrated significant exercise-induced bronchoconstriction most likely reflects a bias of recruitment to an exercise-based research study. Therefore, this small subsample size did not allow for further subanalysis.

SUMMARY

This study examined the differences in breathing patterns, operating lung volumes and dyspnoea responses to exercise between females with asthma and healthy female controls. This is the first study to show that during submaximal exercise, females with asthma experience greater dyspnoea than female controls secondary to mechanical constraint. Further, our findings show that in females with asthma, but not female controls, baseline bronchoconstriction is strongly associated with V_T-inflection point, further emphasising the importance of the mechanical ventilatory constraint on dyspnoea sensation in this group. Elevated exertional dyspnoea at submaximal intensities in females with asthma can lead to increased exercise avoidance and increased symptom burden.[2] A more targeted approach is needed in females with asthma to help manage exertional dyspnoea, as physical activity is a crucial part of asthma management.[1 3]

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Contributors ARB, DBP, LEM and MKS conceived the project. ARB, SR, LEM and EW acquired data set. ARB and DBP did the statistical analyses and drafted the initial manuscript. MKS obtained the funding. All authors participated in the interpretation of the results, edited and reviewed the manuscript. MKS is responsible for the overall content as guarantor.

Funding This work was supported by Canadian Institute of Health Research (grant number 407589). The corresponding author MKS obtained funding.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Human Research Ethics Board of the University of Alberta (Biomedical Panel: Pro00047054). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

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Supplement: Reduced tidal volume inflection point and elevated operating lung volumes in well-controlled females with asthma

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Running title: Supplement: V_T-inflection and dyspnea in females with asthma

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Supplement: V_T-inflection and dyspnea in females with asthma

Results

Male participant characteristics can be found in Supplementary Table 1. Pulmonary function pre-bronchodilator, post-bronchodilator, and following cardiopulmonary exercise test (CPET) can be found in Supplementary Table 2. Males with and without asthma had a significant increase in forced expired volume in 1 second following CPET due to exercise induced bronchodilation (1).

Ventilatory and metabolic responses to exercise

Male metabolic and ventilatory responses at highest equivalent workload (150W), the tidal volume (V_T)-inflection point, and peak exercise can be found in Supplementary Table 3. Ventilation during submaximal exercise was not significantly different between males with asthma and male controls (p=0.56) as both breathing frequency and V_T were not significantly different between the two groups (p=0.07 and p=0.16, respectively) (Supplementary Figure 1A and 1B).

When V_T-inflection is expressed as a percent of $\dot{V}O_{2peak}$, there was no significant difference between female controls and females with asthma (Control: 81 ± 9% vs. Asthma: 77 ± 10%; p= 0.155). However, a post-hoc analysis of the data suggests the current study was underpowered to find significance (β=0.42) and future exploration could be beneficial.

Females with asthma did not demonstrate ventilatory efficiency impairments as compared with female controls as $\dot{V}_E/\dot{V}CO_2$ at peak exercise and the lowest 30-seconds (Nadir) were not significantly different between females with asthma and controls (p=0.595 and p=0.312, respectively). Further, the $\dot{V}_E/\dot{V}CO_{2slope}$ was not significantly different between conditions (p=0.708), and the y-intercept showed no significant group differences (p=0.934). Lastly, end-tidal PCO_2 at peak exercise was not different between females with asthma and controls (p=0.336).

Brotto AR, *et al. BMJ Open Respir Res* 2023; 10:e001791. doi: 10.1136/bmjresp-2023-001791

Supplement: V_T-inflection and dyspnea in females with asthma

Similar to females with asthma, $\dot{V}_E/\dot{V}CO_2$ in males with asthma were not different between groups at peak exercise (p=0.29) or the lowest 30-seconds (Nadir) (p=0.23). Further, $\dot{V}_E/\dot{V}CO_{2slope}$ was not significantly different between males with asthma and male controls (Control: 23.1 ± 2.7 vs. Asthma: 22.4 ± 3.0; p=0.48). End-tidal PCO_2 at peak exercise was also not different between the two groups (p=0.61).

Perceptual responses to exercise

The dyspnea-ventilation slope was not significantly different between females with asthma and female controls (Control: 0.07 ± 0.03 vs. Asthma: 0.08 ± 0.02; p=0.13) (Figure 2C). Similarly, the dyspnea-ventilation slope was not different between males with asthma and male controls (Control: 0.06 ± 0.02 vs. Asthma: 0.06 ± 0.01; p=0.46) (Supplementary Figure 2C).

In females with asthma, 13 participants terminated the test due to “leg discomfort”, while 3 participants terminated the test due to “both leg and breathing discomfort”. In comparison, 14 female control participants terminated the test due to “leg discomfort” and 2 participants terminated the test due to “both leg and breathing discomfort”. The selection frequency of the reason for termination was not significantly different (p=0.50). In males with asthma, 12 participants terminated the test due to “leg discomfort”, while 4 participants terminated the test due to “breathing discomfort”. In comparison, 13 male control participants terminated the test due to “leg discomfort” and 3 participants terminated the test due to “both leg and breathing discomfort”. The selection frequency of the reason for termination was significantly different (p=0.02).

Supplement: V_T-inflection and dyspnea in females with asthma

1. Rossman MJ, Petrics G, Klansky A, Craig K, Irvin CG, Haverkamp HC. Exercise-induced Bronchodilation Equalizes Exercise Ventilatory Mechanics despite Variable Baseline Airway Function in Asthma. Med Sci Sports Exerc. 2022;54(2):258-66. doi: 10.1249/MSS.0000000000002793. PubMed PMID: 34559730.

Supplement: V_T-inflection and dyspnea in females with asthma

Figure Captions

Supplementary Figure 1. Ventilatory and lung mechanic responses to exercise in males with asthma and male controls. This graph shows data means ± standard deviation. *Signifies $p<0.05$ between male controls and males with asthma.

Supplementary Figure 2. Dyspnea response to exercise in males with asthma and male controls. This graph shows data means ± standard deviation. *Signifies $p<0.05$ between male controls and males with asthma.

Brotto AR, *et al. BMJ Open Respir Res* 2023; 10:e001791. doi: 10.1136/bmjresp-2023-001791

Supplement: V_T-inflection and dyspnea in females with asthma

Supplementary Table 1. Male participant characteristics

Variable	Control	Asthma	p-value
n	16	16	
Age (years)	24 ± 3	24 ± 5	0.77
Height (m)	1.78 ± 0.05	1.78 ± 0.08	0.32
Weight (kg)	79.5 ± 14.0	77.8 ± 11.9	0.26
BMI ($kg \cdot m^{-2}$)	24.9 ± 3.1	24.5 ± 3.0	0.44
ACQ Score	0.0 ± 0.0	0.7 ± 0.8	**0.01**
Allergies (%)	20	63	
Medications			
SABA (%)	0	50	
ICS (%)	0	31	
Combination (%)	0	13	
Airway Evaluation			
Positive Reversibility	0/16	10/16	
Mean FEV_1 Change (%)	6 ± 3	10 ± 5	**0.02**
Positive MCT (%)	0/16	6/16	
Mean FEV_1 Change (%)	3 ± 2	14 ± 8	**0.00**
Positive ECT (%)	0/16	1/16	
Mean FEV_1 Change (%)	2 ± 1	4 ± 4	0.18

Values are expressed as mean ± SD. BMI: body mass index; ACQ: asthma control questionnaire; SABA: short-acting beta agonist; ICS: inhaled corticosteroid; MCT: methacholine challenge test; ECT: exercise challenge test; FEV_1: forced expired volume in 1-second. Note: positive reversibility defined as a change in FEV_1 by 12% following bronchodilator

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Supplement: V_T-inflection and dyspnea in females with asthma

Supplementary Table 2. Pulmonary function with and without bronchodilator and following exercise in male control and asthma

	Control			Asthma		
	Pre-BD	Post-BD	Post-CPET	Pre-BD	Post-BD	Post-CPET
Spirometry						
FVC (L)	6.06 ± 1.03	6.16 ± 0.99	6.31 ± 1.15	5.62 ± 0.86	5.65 ± 0.92	5.53 ± 0.70
FVC (% predicted)	107 ± 12	109 ± 11	110 ± 17	105 ± 15	107 ± 16	107 ± 16
FEV_1 (L)	4.83 ± 0.72	5.10 ± 0.74$^{\$}$	5.20 ± 0.56$^{\$}$	4.03 ± 0.62*	4.41 ± 0.67$^{\$}$	4.15 ± 0.71$^{\$}$
FEV_1 (% predicted)	101 ± 13	108 ± 9$^{\$}$	109 ± 10$^{\$}$	90 ± 18*	99 ± 17$^{\$}$	96 ± 17$^{\$}$
FEV_1/FVC	80 ± 4	83 ± 4$^{\$}$	84 ± 9$^{\$}$	72 ± 9*	79 ± 9$^{\$}$	75 ± 9$^{\$}$
FEV_1/FVC (% predicted)	95 ± 5	99 ± 5$^{\$}$	99 ± 11$^{\$}$	85 ± 9*	92 ± 9$^{\$}$	89 ± 10$^{\$}$
Lung Volumes						
TLC (L)	7.69 ± 1.14			7.76 ± 1.33		
TLC (% predicted)	107 ± 15			113 ± 21		
RV (L)	1.32 ± 0.50			1.43 ± 0.28		
RV (% predicted)	86 ± 32			95 ± 15		
IC (L)	3.88 ± 0.74			3.57 ± 0.67		
IC (% predicted)	104 ± 16			100 ± 16		
Diffusion Capacity						
DLCO ($ml \cdot min^{-1} \cdot mmHg^{-1}$)	37.6 ± 4.2			35.3 ± 5.7		
DLCO (% predicted)	110 ± 10			107 ± 11		

Values expressed as mean ± standard deviation. FVC: forced vital capacity; FEV_1: forced expired volume in 1 second; TLC: total lung capacity; RV: reserve volume; IC: inspiratory capacity; DLCO: diffusing capacity of carbon monoxide; BD: bronchodilator; CPET: cardiopulmonary exercise test. *Signifies $p<0.05$ as compared to controls. $^{\$}$Signifies $p<0.05$ as compared to Pre-BD.

Supplement: V_T-inflection and dyspnea in females with asthma

Supplementary Table 3. Metabolic and ventilatory responses in males at 150W, tidal volume inflection point, and peak exercise.

	150 Watts		V_T-Inflection Point		Peak	
	Control	Asthma	Control	Asthma	Control	Asthma
$\dot{V}O_{2peak}$ (L/min)	2.20 ± 0.24	2.28 ± 0.25	3.21 ± 0.69	3.07 ± 0.72	3.90 ± 0.68	3.78 ± 0.60
$\dot{V}O_{2peak}$ (ml/kg/min)	26.8 ± 3.0	29.8 ± 4.4	38.9 ± 7.0	40.0 ± 7.6	47.4 ± 7.0	49.0 ± 8.4
$\dot{V}O_{2peak}$ (% predicted)	---	---	---	---	134 ± 19	133 ± 19
$\dot{V}_E$ (L/min)	56.2 ± 9.6	62.4 ± 10.4	93.7 ± 25.3	91.4 ± 27.8	139.6 ± 26.6	141.7 ± 32.4
Power Output (W)	150 ± 0	150 ± 0	220 ± 44	206 ± 47	278 ± 43	258 ± 50
RER	1.01 ± 0.08	1.04 ± 0.07	1.09 ± 0.06	1.08 ± 0.08	1.17 ± 0.06	1.15 ± 0.07
$\dot{V}_E/\dot{V}CO_2$	25 ± 2	26 ± 2	27 ± 3	27 ± 3	32 ± 4	33 ± 4
$\dot{V}CO_2$ (L/min)	2.21 ± 0.23	2.38 ± 0.28	3.50 ± 0.73	3.33 ± 0.86	4.40 ± 0.64	4.25 ± 0.71
$P_{ET}CO_2$ (mmHg)	42.6 ± 3.1	40.8 ± 3.3	40.5 ± 4.2	39.4 ± 4.3	34.6 ± 3.5	33.8 ± 4.6
fb (breaths/min)	24 ± 5	29 ± 7	31 ± 6	34 ± 8	46 ± 9	52 ± 11
V_T (L)	2.44 ± 0.43	2.30 ± 0.36	3.05 ± 0.58	2.78 ± 0.65	3.10 ± 0.51	2.74 ± 0.43*
IC (L)	3.82 ± 0.77	3.61 ± 0.54	3.95 ± 0.73	3.68 ± 0.63	3.89 ± 0.41	3.46 ± 0.47*
IC (%TLC)	49 ± 5	47 ± 6	51 ± 5	49 ± 7	51 ± 6	45 ± 6
EELV (%TLC)	51 ± 5	53 ± 6	49 ± 5	51 ± 7	49 ± 6	55 ± 6
IRV (%TLC)	16 ± 4	17 ± 4	11 ± 5	12 ± 4	11 ± 6	9 ± 5
V_T/IC (%)	67 ± 8	64 ± 8	78 ± 10	76 ± 12	80 ± 11	80 ± 10
EILV (%TLC)/ $\dot{V}_E$	1.55 ± 0.32	1.36 ± 0.20	1.04 ± 0.28	1.06 ± 0.33	0.67 ± 0.11	0.73 ± 0.16
EFL (%)	0 ± 0	13 ± 28*	10 ± 23	23 ± 28	28 ± 27	54 ± 28*
HR (beats/min)	137 ± 13	145 ± 14	167 ± 14	165 ± 22	186 ± 7	181 ± 15
SpO_2 (%)	95 ± 4	96 ± 4	95 ± 2	95 ± 4	94 ± 4	96 ± 2
Dyspnea	2.1 ± 1.3	2.9 ± 1.1	4.1 ± 1.6	4.8 ± 1.5	7.1 ± 1.8	7.7 ± 1.5
Leg Discomfort	3.3 ± 1.4	3.8 ± 1.1	5.9 ± 2.1	5.9 ± 1.6	9.0 ± 1.3	9.1 ± 1.2

Values are expressed as mean ± standard deviation. $\dot{V}O_2$: rate of oxygen consumption; $\dot{V}E$: minute ventilation; RER: respiratory exchange ratio; $\dot{V}CO_2$: rate of carbon dioxide production; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; fb: breathing frequency; V_T: tidal volume; IC: inspiratory capacity; EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; IRV: inspiratory reserve volume; EFL: expiratory flow limitation; HR: heart rate; SpO_2: arterial oxygen saturation. *Signifies $p<0.05$ between asthma and control.

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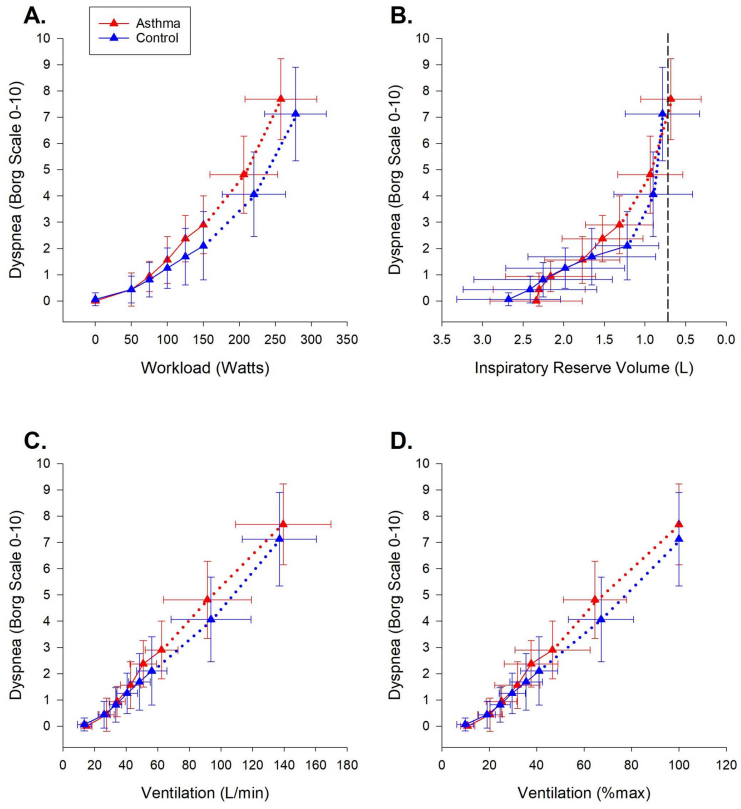
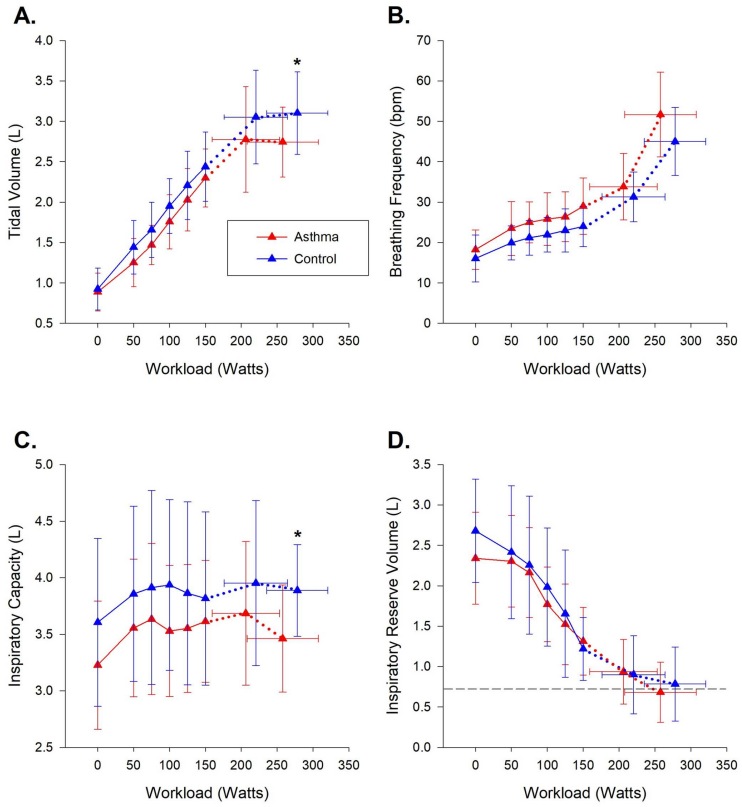
Supplement: V_T-inflection and dyspnea in females with asthma

Supplementary Table 4. Metabolic and ventilatory responses in females at 125W, tidal volume inflection point, and peak exercise.

	125 Watts		V_T-inflection Point		Peak	
	Control	Asthma	Control	Asthma	Control	Asthma
$\dot{V}O_{2peak}$ (L/min)	1.71 ± 0.12	1.84 ± 0.19	2.19 ± 0.42	1.85 ± 0.35*	2.70 ± 0.29	2.40 ± 0.35*
$\dot{V}O_{2peak}$ (ml/kg/min)	27.9 ± 3.3	30.6 ± 5.6	35.7 ± 6.7	30.6 ± 6.2*	44.0 ± 5.3	39.8 ± 7.1
$\dot{V}O_{2peak}$ (% predicted)	---	---	---	---	156 ± 18	139 ± 20*
$\dot{V}_E$ (L/min)	48.9 ± 6.3	56.6 ± 8.6*	70.2 ± 16.5	57.7 ± 12.3*	110.1 ± 14.2	91.6 ± 15.7*
Power Output (W)	125 ± 0	125 ± 0	163 ± 33	128 ± 26*	216 ± 22	177 ± 25*
RER	1.03 ± 0.07	1.07 ± 0.07	1.11 ± 0.07	1.07 ± 0.06	1.21 ± 0.05	1.17 ± 0.08
$\dot{V}_E/\dot{V}CO_2$	28 ± 2	29 ± 3	28.8 ± 2.0	29.2 ± 2.1	34 ± 3	33 ± 3
$\dot{V}CO_2$ (L/min)	1.75 ± 0.17	1.95 ± 0.17*	2.43 ± 0.50	1.98 ± 0.41*	3.25 ± 0.26	2.77 ± 0.38*
$P_{ET}CO_2$ (mmHg)	38.7 ± 2.6	37.0 ± 3.3	37.1 ± 2.6	36.9 ± 2.5	31.9 ± 2.5	32.7 ± 2.4
fb (breaths/min)	27 ± 4	33 ± 7*	32 ± 6	32 ± 6	49 ± 7	46 ± 8
V_T (L)	1.87 ± 0.25	1.76 ± 0.21	2.21 ± 0.39	1.82 ± 0.31*	2.27 ± 0.32	2.01 ± 0.20*
IC (L)	2.87 ± 0.42	2.54 ± 0.30*	2.90 ± 0.42	2.57 ± 0.25*	2.87 ± 0.40	2.51 ± 0.31*
IC (%TLC)	53 ± 7	51 ± 5	52 ± 7	51 ± 7	53 ± 7	51 ± 6
EELV (%TLC)	47 ± 7	49 ± 5	48 ± 7	49 ± 7	47 ± 7	50 ± 7
IRV (%TLC)	18 ± 5	15 ± 5*	12 ± 6	15 ± 4	11 ± 5	10 ± 4
Vt/IC (%)	66 ± 7	71 ± 10	77 ± 10	71 ± 8	80 ± 8	79 ± 7
EILV (%TLC)/ $\dot{V}_E$	1.70 ± 0.24	1.56 ± 0.24	1.34 ± 0.36	1.53 ± 0.30	0.83 ± 0.11	1.01 ± 0.17*
EFL (%)	0 ± 0	14 ± 27*	3 ± 10	28 ± 21*	16 ± 25	39 ± 33*
HR (beats/min)	151 ± 15	162 ± 14*	169 ± 15	162 ± 17	185 ± 10	182 ± 12
SpO_2 (%)	96 ± 2	97 ± 2	97 ± 3	97 ± 2	96 ± 4	96 ± 2
Dyspnea	2.1 ± 1.2	3.4 ± 1.0*	3.5 ± 1.8	3.8 ± 1.2	7.1 ± 2.0	7.4 ± 2.3
Leg Discomfort	2.9 ± 0.8	4.6 ± 1.2*	4.5 ± 1.7	4.9 ± 1.9	8.7 ± 1.7	9.1 ± 1.0

Values are expressed as mean ± standard deviation. $\dot{V}O_2$: rate of oxygen consumption; $\dot{V}E$: minute ventilation; RER: respiratory exchange ratio; $\dot{V}CO_2$: rate of carbon dioxide production; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; fb: breathing frequency; V_T: tidal volume; IC: inspiratory capacity; EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; IRV: inspiratory reserve volume; EFL: expiratory flow limitation; HR: heart rate; SpO_2: arterial oxygen saturation. *Signifies $p<0.05$ between asthma and control.


A.
Asthma
Control
Dyspnea (Borg Scale 0-10)
Workload (Watts)
B.
Dyspnea (Borg Scale 0-10)
Inspiratory Reserve Volume (L)
C.
Dyspnea (Borg Scale 0-10)
Ventilation (L/min)
D.
Dyspnea (Borg Scale 0-10)
Ventilation (%max)


A.
B.
C.
D.
Tidal Volume (L)
Breathing Frequency (bpm)
Inspiratory Capacity (L)
Inspiratory Reserve Volume (L)
Workload (Watts)
Asthma
Control
*