Comparing Exercise Responses to High Intensity Interval Training between Adults With and Without Asthma

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The above committee determined that the thesis is acceptable in form and content and that a satisfactory knowledge of the field covered by the thesis was demonstrated by the candidate during an oral examination. A signed copy of the Certificate of Approval is available from the School of Graduate and Postdoctoral Studies.

ABSTRACT

Exercise induced bronchoconstriction (EIBC) occurs in response to high ventilations during exercise, which cools and dries the airways, triggering an inflammatory cascade. High intensity interval training (HIIT) is associated with reductions in inflammation, improvements in cardiorespiratory outcomes, and mental health in healthy adults; however, the impact of HIIT in adults with EIBC is unclear. The purpose of this dissertation was to determine the impact of a 6-week HIIT intervention on physiological (e.g. inflammation, ventilation, and cardiorespiratory fitness) and psychological (i.e. anxiety) domains of health among adults with EIBC and healthy adults, and the impact of HIIT on clinical outcomes (i.e. asthma control) among adults with EIBC. **METHODS:** A quasi-experimental study design was used. A 6-week HIIT intervention was implemented in adults (18-44 years) with EIBC and healthy controls. Sessions were conducted three times per week and consisted of cycling at 10% PPO for 1 minute followed by 90% PPO for 1 minute, repeated 10 times. Primary measures at pre (T1) and post-intervention (T2) included: 1) maximal exercise test 2) passive drool saliva samples 3) anxiety sensitivity index-3 4) asthma control questionnaire-7 (EIBC group only). **RESULTS:** Participants in the EIBC group (n=20; T1: 32.9 ± 8.0; T2: 38.6 ± 8.2 ml/kg/min, $p<0.01$) and control group (n=12; T1: 38.6 ± 8.2; T2: 38.9 ± 12.3 ml/kg/min, $p<0.01$) improved VO_2max. Adults with EIBC had lower levels of IL-1Ra at T2 when compared to healthy controls (EIBC T2: 0.2 ± 0.16pg/ug protein; Control T2: 0.8 ± 0.21pg/ug protein; $p<0.01$, $h_p^2 = 0.3$). Maximal ventilation in the EIBC group did not improve (EIBC T1: 97.8 ± 22.2; EIBC T2: 108.7 ± 29.5, p=0.7, Cohens d=0.4); however, the control group improved ventilation at the same absolute exercise workload (Control T1: 82.8 ± 20.1; Control T2:

101.8 ± 18.1, p=0.02). Reductions in anxiety sensitivity (EIBC T1: 17.9 ± 11.8; EIBC T2: 12.4 ± 13, p=0.002, Cohens d=0.4) and asthma control (EIBC T1: 0.8 ± 0.6; EIBC T2: 0.5 ± 0.4, p=0.02, Cohens d=0.5) from T1 to T2 occurred. **CONCLUSION:** A 6-week HIIT intervention leads to improvements in physiological, psychological, and clinical outcomes among adults with EIBC.

KEY WORDS: Exercise; Asthma; High Intensity Interval Training; Exercise Induced Bronchoconstriction

AUTHOR'S DECLARATION

I hereby declare that this thesis consists of original work of which I have authored. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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The research work in this thesis that was performed in compliance with the regulations of Research Ethics Board/Animal Care Committee under **REB Certificate number/Animal care certificate file number: #14611**

_____ Carley O'Neill

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I would like to dedicate this work to my Mom, Kelly O'Neill, who passed away unexpectedly during the first week of my PhD studies. Mom, I hope I've made you proud.

Statement of Contributions

This dissertation presents the research of Carley O'Neill in collaboration with her supervisor Dr. Shilpa Dogra and committee members Dr. Julia Green-Johnson and Dr. Holly Jones-Taggart. The sum of this research resulted in the following contributions to the literature:

Manuscript 1: O'Neill, C., Jeffrey, M., Jones-Taggart, H., Green-Johnson J., Dogra, S. (2020). The impact of HIIT on salivary markers of inflammation among adults with and without asthma. *In Preparation.*

Manuscript 2: O'Neill, C., Dogra, S. (2020). Comparing the pulmonary responses to high intensity interval training among adults with and without exercise induced bronchoconstriction. *In Preparation.*

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Manuscript 4: O'Neill, C., Dogra, S. (2020). Low volume high intensity interval training leads to improved asthma control in adults. *Journal of Asthma, Published.*

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List of Abbreviations

ACQ	Asthma control questionnaire
ASI	Anxiety sensitivity index
BSQ	Body sensations questionnaire
EVH	Eucapnic voluntary hyperpnea
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GAD-7	Generalized anxiety disorder 7
HIIT	High intensity interval training
IL-8	Interleukin-8
IL-1β	Interleukin 1-beta
IL-1RA	Interleukin 1 receptor antagonist
CXCL10/IP-10	Interferon (IFN)-gamma inducible protein
MICE	Moderate intensity continuous exercise
MVV	Maximal voluntary ventilation
PPO	Peak power output
RR	Respiratory rate
TNF-*a*	Tumor necrosis factor alpha
V_E	Ventilation
V_E/MVV	Breathing reserve
V_T	Tidal volume
VO_2	Volume of oxygen
VO_2max	Maximal oxygen consumption

Chapter 1 - General Overview

Asthma is defined as a respiratory condition characterized by chronic inflammation and acute bronchoconstriction [1]. Currently, the prevalence of asthma among Canadians is approximately 8% [2]. Of the almost three million Canadians with a diagnosis of asthma, approximately 90% experience ***exercise induced bronchoconstriction (EIBC)*** [3]. EIBC is triggered by the increase in ventilation that occurs during exercise, which increases the evaporative water and heat loss from the lungs and triggers an inflammatory response causing bronchoconstriction [4]. For the purpose of this dissertation the term asthma will be used when referring to the overall chronic condition, and EIBC will be used when specifically referring to the physiological response to exercise.

Asthma cannot be cured, therefore, the clinical goal is management of asthma symptoms. ***Asthma control*** is determined by assessing the frequency of asthma symptoms such as dyspnea, coughing, wheezing, chest tightness, and limitations of daily activities (e.g. exercise participation) [5]. It can range from complete (experiencing no symptoms during any activity) to not at all (experiencing symptoms all the time). Poor asthma control is associated with lower quality of life and an increased risk of developing anxiety, depression [6], and higher levels of systemic inflammation (assessed via serum) [7].

The aforementioned associations among asthma control, anxiety, depression, and inflammation point to the ***interconnectedness*** of these domains of health. Figure 1 illustrates this interconnectedness, beginning with higher levels of systemic and local (airway) inflammation among adults with asthma (Step 1). Regular exercise has been

shown to elicit a plethora of health benefits among adults with asthma and as such, is often recommended to patients (Step 2) When adults with asthma participate in an acute bout of exercise, ventilation increases to meet the increased oxygen demand of the working muscles (Step 3). This increase in ventilation could be misinterpreted as a precursor to an asthma attack, trigger a further anxiety related increase in ventilation adding to the cooling and drying of the airways and thus, exacerbate the bronchoconstriction [4]. The cooling and drying of the airways elicits an influx of inflammatory mediators to the airways (Step 4) and lead to a reduction in forced expiratory volume in 1 second (FEV_1), and trigger EIBC symptoms (Step 5). Bronchoconstriction and EIBC symptoms following acute exercise may lead to higher anxiety surrounding exercise participation in fear of experiencing an asthma attack and may lead to exercise avoidance (Step 6) [8]. Exercise avoidance leads to worse asthma control (e.g. increase in asthma symptoms) (Step 7).

Regular exercise training has been shown to reduce inflammation [9] and improve asthma management (i.e. reduce symptoms, improve asthma control) [10]. Therefore, it is pertinent that adults with asthma participate in exercise that allows them to do so without experiencing the negative symptoms described above and in Figure 1. Asthma control has been associated with various physiological outcomes in that, higher levels of inflammation and higher levels of anxiety have been associated with worse asthma control [11, 12]. It is clear that each domain of health contributes to the overall management of asthma therefore, the impact of HIIT within each domain of health will allow for a better understanding of the benefits of HIIT among this population.

Figure 1. Interconnectedness of EIBC on Physiological, Psychological, and Clinical Components of Health

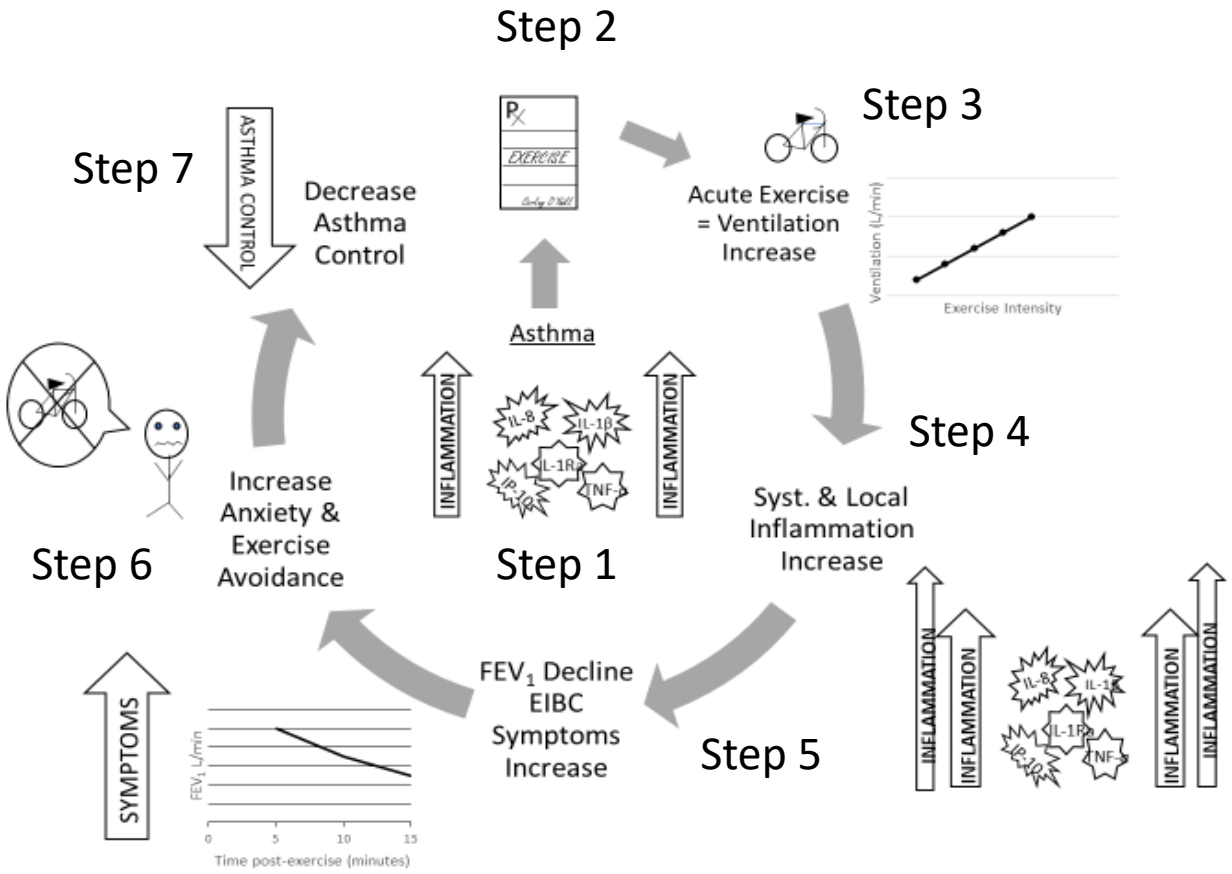


Figure 1. The multi-faceted responses to exercise and how these response can contribute to exercise avoidance and thus, poor clinical outcomes among adults with asthma. In response to an asthma diagnosis, exercise *should* be prescribed; however, the acute responses (ventilation increases, inflammation increases, reductions in FEV_1 lead to increases in anxiety and decreases exercise participation and thus, asthma control.

Exercise training leads to improved maximal oxygen uptake (VO_2max) [13], reduced risk of developing chronic disease [14], reduced systemic inflammation [15], and improved mental health [16]. Among adults with a chronic condition such as asthma, regular exercise has been shown to have clinical benefits such as improvements in asthma control [10]. Despite these benefits, many Canadians are not sufficiently active [17]. There are many possible reasons as to why Canadians are not meeting the minimum guidelines. In particular, perceived barriers such as lack of time, lack of motivation, lack of enjoyment, and poor health have been cited [18]. Due to the high prevalence of EIBC among adults with asthma, EIBC symptoms, and anxiety surrounding EIBC symptoms may serve as additional barriers.

My masters work showed that among adults with EIBC, an acute bout of HIIT led to a smaller reduction in lung function (i.e. smaller reductions in FEV_1 post-exercise) when compared to continuous exercise [19]. This smaller reduction in FEV_1 following HIIT was hypothesized to be due to the intermittent recovery intervals associated with HIIT which would allow for ventilation to recover intermittently and thus, reduce the amount of evaporative water and heat loss from the airways. This is of particular importance because a reduction in the amount of water and heat loss from the airways may contribute to a reduction in EIBC symptoms as a result of exercise participation [4]. One of the limitations of this work was that we did not monitor ventilation during the exercise sessions, thus, the role of ventilation remained unclear. Another limitation was that there was no control group so it remained unclear as to whether differences in ventilation responses occurs during HIIT between adults with and without EIBC [19]. Finally, this work also indicated that adults with EIBC experienced greater exercise enjoyment during HIIT when compared to

other exercise protocols. With these limitations in mind, questions surrounding the physiological adaptations (e.g. inflammation, lung function) and psychological changes (e.g. anxiety, enjoyment) to HIIT and the differences in these responses between adults with EIBC and healthy adults arose and as such, formed the basis for this dissertation.

The overarching goal of this body of work was twofold. First, this work sought to better understanding the impact of HIIT on physiological, psychological, and clinical outcomes in response to a low-volume 6-week HIIT among adults with EIBC and healthy adults. Second, this work sought to elucidate the interconnectedness between the physiological, psychological and clinical outcomes associated with asthma in response to low-volume HIIT.

2.0 REVIEW OF THE SCIENTIFIC LITERATURE

2.1 Introduction

The following literature review details the physiological variables (i.e. inflammation, lung function, ventilation, and cardiovascular), psychological variables (i.e. anxiety and enjoyment), and clinically relevant variables (i.e. asthma control) that were assessed during the 6-week HIIT intervention implemented among adults with and without EIBC.

For the purpose of this review, acute exercise is defined as a single bout of exercise; whereas, exercise training is defined as repeated bouts of exercise.

2.2 High Intensity Interval Training

HIIT is composed of brief bouts of high intensity activity followed by intermittent recovery periods. It is a time-efficient form of exercise and has been shown to be safe and effective among healthy populations as well as among those with chronic condition such as diabetes [20], cardiovascular disease [21], and chronic obstructive pulmonary disease (COPD) [22].

Among healthy adults, HIIT has been shown to improve physical fitness (i.e. maximal oxygen consumption (VO_2max)), physiological functions (i.e. reductions in inflammation), and cardiovascular disease factors [23, 24]. In addition to these improvements, HIIT is perceived as a more enjoyable form of exercise training when compared to moderate intensity and vigorous intensity continuous exercise training among adults with EIBC [25]. There are many possible reasons as to why HIIT is perceived as the more enjoyable choice of exercise training among healthy adults. One possible reason may be related to its' time-efficient nature paired with its success in

physiological changes (i.e. body weight reduction, improvements in physical fitness) when compared to traditional continuous exercise training [26]. Secondly, it is possible that HIIT offers an added mental stimuli (i.e. changes in intensity during exercise) that continuous exercise lacks, thus minimizing boredom during exercise [27].

Among adults with asthma, we have observed additional benefits of HIIT among adults with EIBC [19]. We have previously observed a reduction in FEV_1 following an acute bout of HIIT (FEV_1 reduction = -7.1% ± 8.3) compared to an acute bout of moderate intensity continuous exercise (FEV_1 reduction = -14.8% ± 12.2) was significantly less ($p = <0.001$) [19] among adults with EIBC [19]. The less severe reduction in FEV_1 may also lead to a reduction in EIBC related symptoms (i.e. perceived dyspnea) during and after exercise. A reduction in EIBC related symptoms during and following exercise offers another possible explanation for the preference for HIIT exercise among adults with EIBC.

2.3 Pathophysiology of Asthma and EIBC

The Immune Systems

The immune system can be categorized into two major units, the innate and the adaptive immune systems. The innate immune system is employed to offer fast general protection against pathogens [28]. The adaptive immune system is not as fast acting upon first exposure to an antigen but offers more precise protection against pathogens and is able to remember an antigen using memory cells, which allow for a more efficient and faster response against a known antigen than the innate immune system [29].

Asthma is a heterogeneous condition that occurs as a result of the interaction between genetic susceptibility and environmental influences. [30] Asthma is often considered a disease of the adaptive immune system, exemplified by the fast acting inflammatory response that occurs upon exposure to a trigger (e.g. exercise) [31]. Although primarily a condition of the adaptive immune system, research has shown a network of innate immune cells (e.g. mast cells, epithelial cells, and dendritic cells) that become activated in response to a trigger. [32] Taken together, it is clear that asthma can no longer be considered only a condition of the adaptive immune system, and the interaction between the innate and adaptive immune systems must be considered in order to fully comprehend the asthma immune response.

Asthma is one of the most prevalent conditions in Canada and continues to rapidly increase. One hypothesis that has been put forth to explain the increase in asthma prevalence that has gained considerable attention in the scientific literature, is the *hygiene* hypothesis. It is hypothesized that among those in industrialized nations (e.g. Canada) there is less exposure to microbes due to a variety of factors including better infection control, more immunizations, and better sanitation. [33] CD4+ helper T-lymphocytes have been divided into two sub-classes, Th1 and Th2, depending on the cytokines they secrete. The hygiene hypothesis suggests that exposure to microbes at a young age allows the immune response and immunological phenotype shift from a predominate Th2 to a Th1 phenotype as we age[34]; however, this exposure to microbes is reduced in more Westernized areas.

Inflammation is the immune system's response to harmful stimuli (i.e. damaged cells, pathogens) and serves to remove harmful stimuli and begin the healing process [35, 36]. The inflammatory immune response is therefore a vital defense mechanism for health and allows tissues to restore to homeostasis [37]. The inflammatory response occurs due to numerous inflammatory mediators that participate in intracellular signaling pathways to induce a target response (i.e. bronchoconstriction). Pro-inflammatory cytokines such as interelukin-1Beta (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor-a (TNF-*a*) mediate the inflammatory response by interacting with receptors such as, IL-1 receptor (IL-1R), and the TNF receptor [37]. The activation of these receptors furthers the inflammatory response via intracellular signaling. The innate immune response is designed to protect us from potentially dangerous invaders; however, when the inflammatory process is unnecessarily triggered, health issues arise.

Cytokines that are either pro or anti-inflammatory are responsible for facilitating or inhibiting the inflammatory response, respectively [38]. Cytokines are produced by cells to primarily recruit leukocytes to the site of injury (i.e. recruitment of leukocytes to the airways during an acute asthma exacerbation). IL-1 and TNF-*a* induce the release of various chemokines, which recruit different cell types (depending on the chemokine) to the site of injury., w[39]. Among adults without asthma or any respiratory condition, epithelial cells in the airways are the primary source of chemokines; however, among adults with asthma experiencing bronchoconstriction, infiltrated cells (e.g. mast cells, basophils, and macrophages) [40] within the submucosa become a major source of chemokines [41]. When there is excessive cytokine release, tissue damage, hemodynamic changes, organ failure, and death can occur [42]. When the acute

inflammatory response becomes uncontrolled, the inflammatory response becomes chronic and thus, contributes to the development of various chronic conditions, such as asthma.

The chronic inflammation associated with asthma results from various inflammatory cells, such as eosinophils, lymphocytes, and mast cells [43, 44]. These cells release various mediators of inflammation including cytokines, and additional mediators that can be classified into the following groups: pro-inflammatory cytokines, chemokines, growth factors, and eicosanoids [45]. The release of these inflammatory mediators contribute to bronchoconstriction, damage of the epithelium, and to the recruitment of additional leukocytes creating chronic inflammation, one of the key characteristics of asthma [45].

Eosinophils are white blood cells that are a key feature in asthma and found in increased levels in the sputum of patients with asthma [46]. These higher levels of eosinophils in the airways of patients with asthma have been associated with more severe disease and contributed to the inflammation in the airways [46]. It has been suggested that eosinophils may play more of a role in the late asthmatic response [46, 47]. Specifically, within the airways of patients with asthma following exposure to a trigger, eosinophilic chemotactic factors are released. In response to their release, eosinophils arrive to the airways by means of migration through the vascular endothelium, upregulation of eosinophils, and adhesion of eosinophils to airway epithelium. Once in the airways, eosinophils promote obstruction, injury, and bronchial hyper-responsiveness [46].

Lymphocytes are a type of white blood cell categorized as either B-cells or T-cells. T-cell are developed in the thymus gland and play an important role in asthma [48]. T-lymphocytes have been shown to be increased in the lungs of adults with asthma and

more so during an acute exacerbation [49, 50]. Lymphocytes activate the release of various cytokines from other inflammatory cells, which in turn stimulates eosinophils and mast cells, contributing to further bronchoconstriction [49, 51].

Mast cells mediate airway hypersensitivity, and were among the first cells to be associated with the pathogenesis of asthma [52]. Mast cells can be activated to release various mediators by multiple triggers (i.e. exercise as a trigger in EIBC). Mast cell activation occurs through the interaction between an antigen/allergen with its specific IgE antibody bound to its high affinity receptor on the membrane of a mast cell [53]. Once activated, the degranulation of mast cells release a variety of inflammatory mediators such as histamine and thus, in the context of asthma, contributes to furthering the bronchoconstriction of the airways. Histamine is well-known as an important chemical mediator for the immediate allergic reaction and is suggested to play a critical role in the pathophysiology of asthma [54]. There are four types of histamine receptors (H1, H2, H3, H4) in the airways and in the pulmonary tissue [55-57]. In a study of 18 adults with asthma and 18 controls, bronchial responsiveness was monitored during an increasing dosage of histamine challenge. Results showed that histamine induced bronchoconstriction is predominately meditated by the H1 receptors [58]. Histamine causes bronchoconstriction in response to exposure to a trigger by initiating contraction of the bronchial smooth muscle and the pulmonary peripheral tissue [59]. Anti-histamine medications are effective in reducing the decline in FEV_1 [60] and have also been shown to be effective in EIBC [61]. In a study of 10 adults with EIBC, participants inhaled an anti-histamine and placebo on separate days, followed by an 8-minute exercise bout on a cycle-ergometer and FEV_1 was assessed pre and post-exercise. Inhalation of the anti-

histamine resulted in a smaller reduction in FEV_1 suggesting that histamine plays an important role in EIBC as well as allergic asthma [61].

As described, the inflammatory cascade associated with asthma is complex and occurs in response to a trigger. Importantly, these triggers vary between individuals with asthma. For the purpose of this review and PhD work, the focus will be on the trigger of exercise.

Pathophysiology of EIBC

Approximately 90% of adults with asthma experience EIBC [3]. The exact mechanisms responsible for EIBC remain unclear; however two hypotheses known as the *osmotic* and *thermal* hypotheses, have been suggest to explain the EIBC response [4].

The osmotic hypothesis suggests that the increase in ventilation during exercise leads to an increase in evaporative water loss from the airways and thus, triggers an inflammatory response (described above). The thermal hypothesis suggests that it is the cooling of the airways as ventilation increases during exercise, and the subsequent rewarming of the airways when ventilation returns to normal post-exercise, that is responsible for triggering the inflammatory response associated with EIBC [4]. Table 1 contains a list of cytokines that have been shown to respond to acute bouts [62] and to regular exercise training [63, 64] among adults, and their respective functions. In a review of both of these hypotheses it has been suggested that the EIBC response likely occurs as a result of both evaporative water loss and airway cooling and rewarming, due to changes in ventilation during exercise [4].

Thus, it is clear that ventilation plays an integral role in triggering the inflammatory response associated with EIBC.

Table 1.1 Cytokines and their Functions

Cytokine	Family	Main sources	Function
IL-1β	IL-1	Macrophages, monocytes	Pro-inflammatory, proliferation, apoptosis, differentiation
IL-4	IL-4	Th-cells, mast cells	Anti-inflammatory, T-cell and B-cell proliferation, B-cell differentiation
IL-6	IL-6	Macrophages, T-cells, adipocyte	Pro-inflammatory, differentiation, anti-inflammatory
IL-8	CXCL8	Macrophages, epithelial cells, endothelial cells	Pro-inflammatory, chemoattractant for neutrophils, angiogenesis
IL-10	IL-10	Monocytes, T-cells, B-cells	Anti-inflammatory, key regulatory cytokine, decreases production of cytokines involved in macrophage activation
IL-12	IL-12	Dendritic cells, macrophages, neutrophils	Pro-inflammatory, cell differentiation, activates NK cell
IL-11	IL-6	Fibroblasts, neurons, epithelial cells	Anti-inflammatory, differentiation, induces acute phase protein
TNF-α	TNF	Macrophages, NK cells, $CD4^{+}$lymphocytes, adipocyte	Pro-inflammatory, , cell proliferation, apoptosis,

TGF-β	TGF	Macrophages, T cells, Epithelial cells	Anti-inflammatory, inhibition of pro-inflammatory cytokine production
IP-10	CXCL	Monocytes, neutrophils, endothelial cells	Pro-inflammatory, chemoattractant for macrophages, T cells, natural killer cells
IL-1Ra	IL-1	Monocytes, macrophages, neutrophils, epithelial cells	Anti-inflammatory, blocks binding of IL-1β and IL-1*a* to the IL-1 receptor

In summary, asthma is defined as a chronic respiratory condition characterized by chronic inflammation and acute bronchoconstriction. The development of asthma results in an inappropriate inflammatory response, primarily led by T-helper type (TH)-2 lymphocytes in response to various triggers. EIBC occurs in response to evaporative water and heat loss from the airways that occur as a result of changes in ventilation during and post-exercise

2.4 Diagnosis and Assessment of Asthma and EIBC

A diagnosis of asthma is based on a history of variable respiratory symptoms (i.e. wheeze, shortness of breath, cough) and confirmed variable expiratory airflow limitation [1]. Expiratory airflow limitation can be determined via a pulmonary function test (PFT)

using spirometry. A PFT is a non-invasive test to determine lung volume, lung capacity, and flow rates [65].

Variable expiratory airflow limitation can be confirmed using the following methods, positive bronchodilator reversibility test, excessive variability in twice-daily peak expiratory flow over 2 weeks, positive exercise challenge test, positive bronchial challenge test, or excessive variation in lung function [66]. Table 2.1 summarizes the criteria for each of the confirmatory expiratory airflow limitation assessments listed above.

Table 2.1 Methods and Diagnostic Criteria for the Confirmation of Variable Expiratory Airflow Limitation [66]

Method	**Diagnostic Criteria**
Positive bronchodilator reversibility test	Increase in FEV_1 >12% and >200mL from pre-medication to 10-15 minutes post-medication.
Excessive variability in twice-daily peak expiratory flow over 2 weeks	Increase in FEV_1 >12% and >200mL from pre corticosteriod treatment to 4 weeks of anti-inflammatory treatment
Positive exercise challenge test	Decline in FEV_1 of >10% and >200mL from pre to post-exercise
Positive bronchial challenge test	Decline in FEV_1 from baseline of >20% with standard doses of methacholine or histamine OR >15% decline with

	standardized hyperventilation, hypertonic saline or mannitol
Excessive variation in lung function between visits (less reliable)	Variation in FEV_1 of >12% and >200mL between visits, outside of respiratory infections

Exercise Challenge Tests

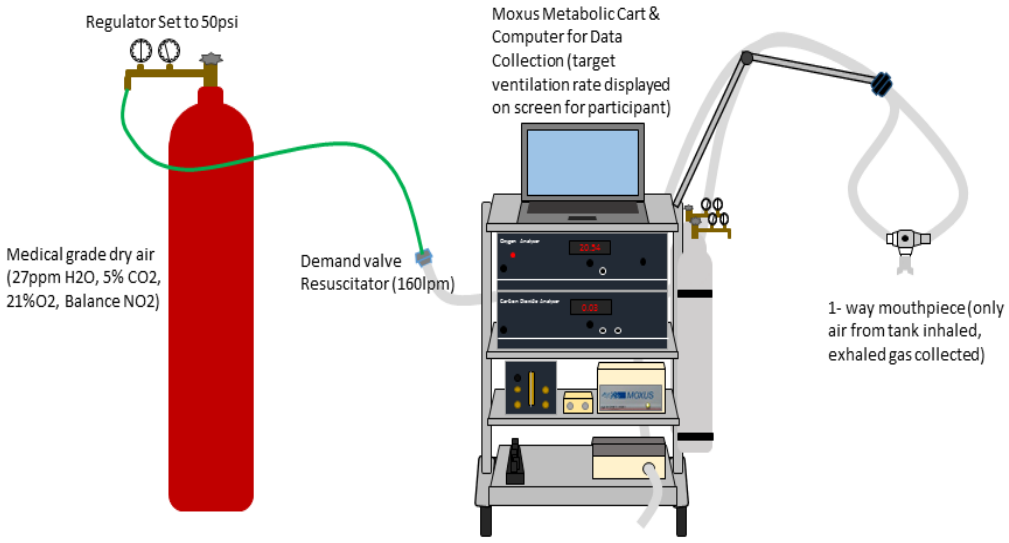
EIBC can be diagnosed in a laboratory setting by either an exercise challenge test or via bronchial provocation challenge. The laboratory based exercise challenge test can be completed on a treadmill or cycle ergometer; two standardized protocols exist for conducting an exercise challenge test on a cycle ergometer. The first protocol is a single load, at an exercise intensity of 45% to 60% of the predicted maximum voluntary ventilation (MVV) for 6 to 8 minutes [67]. The second protocol is an increasing protocol, which begins at an exercise intensity of 60% of the final load in the first minute, then 75% in the second minute, 90% in the third minute and 100% in the fourth minute. Once the target level is reached, the workload is held for 4 minutes [68]. The standardized treadmill protocol recommends a speed and grade to produce 4 to 6 minutes at near maximum heart rate, with a total exercise duration of 6 to 8 minutes. During the first 2 to 3 minutes, the treadmill speed and grade are rapidly increased until the participant achieves a heart rate of 80% to 90% of the maximum predicted. PFT is measured with regular intervals for up to 30 minutes following completion of either challenge [67]. As highlighted in Table 1, an exercise challenge test is deemed positive if there is a decline in FEV_1 of 15% or greater from pre to post-exercise.

Exercise challenge tests increase ventilation and thus, lead to evaporative water and heat loss from the airways triggering the inflammatory EIBC response. An exercise challenge assessment is time and cost-effective and has been shown to be specific for assessing EIBC. The disadvantage to this method however, is that it is not performed in the same environment that exercise is usually performed (i.e. no environmental stimuli) and can be improperly conducted if attention isn't given to the proper protocols and timing of FEV_1 assessment post-exercise.

Eucapnic voluntary Hyperpnea (EVH) challenge

The EVH challenge is a sensitive and specific diagnostic method that triggers EIBC by hyperventilation of safe concentrations of dry gases (5% CO_2, 21% O_2, and balance N2 that simulate ventilation for a period of 6 minutes [69]. The dry air is inhaled using a one-way mouthpiece and exhaled breath is analyzed using a metabolic cart. Figure 2 illustrates the EVH set-up.

Figure 2. Eucapnic Voluntary Hyperpnea Challenge



Prior to an EVH challenge participants are asked to refrain from taking short acting bronchodilators for 8 hours and to refrain from taking long acting or sustained release bronchodilators for 48 hours in order to maximize the airway response. Prior to the EVH challenge, FEV_1 is measured three times and the highest FEV_1 value obtained at baseline is used to determine target ventilation during the EVH challenge. Previous literature has shown that a ventilation rate of 21x FEV_1 at baseline is sufficient to elicit a positive

response among adults with asthma and a target ventilation rate of 30x FEV_1 at baseline is sufficient to elicit a positive response among those without a diagnosis of asthma[69]. Figure 3 provides a visual representation of a participant completing the EVH challenge. Following the 6-minute challenge, FEV_1 is assessed again following the challenge at minutes 5, 10, 15 and 20-post challenge [70]. The percent decline between the FEV_1 obtained pre-challenge and the FEV_1 obtained post-challenge is used to determine the airway response. Discrepancy exists regarding the FEV_1 decline criteria post-EVH to confirm EIBC. Previous studies have used a decline of 10%, 12%, 15%, and 20% as a diagnostic criteria. The EVH challenge has a very high sensitivity and is recommended by the International Olympic Committee-Medical Commission[67]. Thousands of EVH challenges have been performed without serious unwanted side effects, making it a safe and effective diagnostic tool[71].

Figure 3. Participant Completing the EVH Challenge

Although many methods exist for the diagnosis of EIBC, many adults are diagnosed via a history of respiratory symptoms only. As such, many adults with a prescription for an inhaled bronchodilator may not have a positive response to the EIBC diagnostic tests. In order to ensure an EIBC diagnosis, efforts should be made to conduct one if not two of

the confirmatory EIBC tests listed above. The EVH is considered the gold standard in a laboratory setting and as such, if equipment is available, this challenge should be conducted in order to confidently confirm EIBC. A second method of EIBC confirmation, such as the bronchodilator reversibility test, would add confidence to the EIBC diagnosis. The EVH challenge was conducted for the current PhD work in order to ensure that participants included in the EIBC group had a confirmed diagnosis of the condition. These confirmation assessments of EIBC added strength to the methodology and subsequent findings from this work.

2.5 Asthma and EIBC Management

Following an asthma or EIBC diagnosis, treatment and management options are discussed and implemented. The goal of asthma management as outlined by the Global Initiative for Asthma, is to achieve good symptom control, minimize risk of asthma related mortality, exacerbations, airflow limitation, and side-effects of treatment [72]. The pharmacological recommendations for the management of asthma among adults is inhaled corticosteroids (ICS) controller treatment either as-needed or daily, depending on the severity of the condition. The ICS controller treatment is used to reduce the risk of serious exacerbations and to control asthma related symptoms [73].

Asthma medications can be divided into two main categories, controller medications and reliever (rescue) medications [1]. Controller medications are used to reduce the chronic airway inflammation associated with asthma. As well, controller medication is used to control asthma related symptoms, reduce future risks of an asthma exacerbation, and reduce the decline in lung function. Reliever, or rescue medication, are used to provide adults with asthma with relief from asthma related symptoms on an as-needed basis,

either during worsening asthma or during an acute asthma exacerbation. During an acute exacerbation (i.e. following exercise participation), bronchoconstriction occurs due to the influx of various pro-inflammatory cytokines (described below). These cytokines trigger constriction of the bronchioles, which narrows the passageway for air to pass through thus, lowering FEV_1. Furthermore, these cytokines increase mucous production in the airways, which creates further obstruction for air to pass through and causes an increase in asthma symptoms such as coughing. To prevent an acute EIBC exacerbation, rescue medication should be taken 15 minutes prior to exercise participation [72].

Inflammatory Cytokines

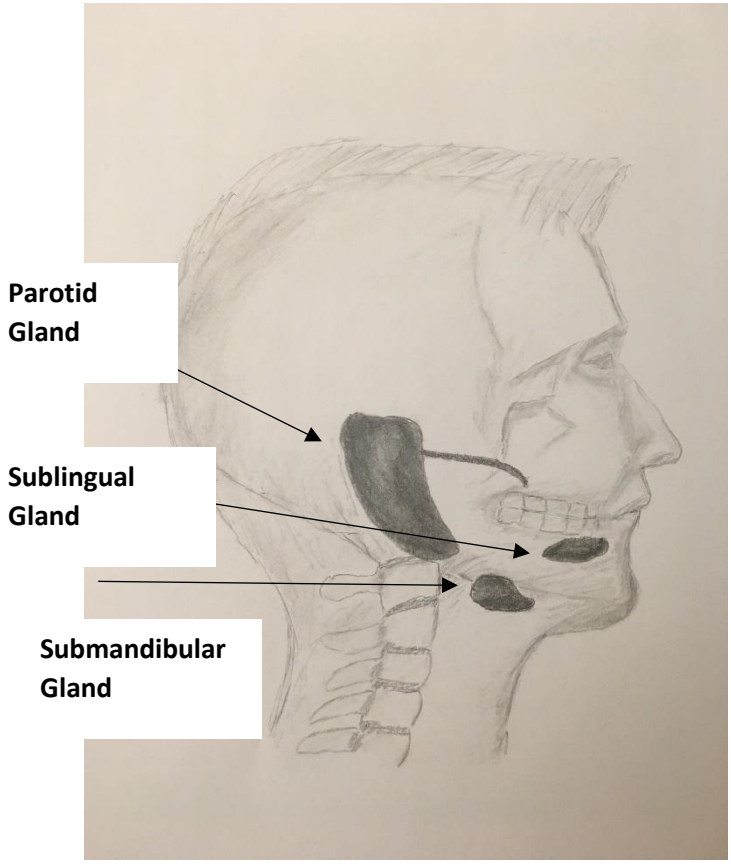
As highlighted above, EIBC occurs due to evaporative heat and water loss from the airways, which triggers an inflammatory cascade responsible for bronchoconstriction and asthma related symptoms (i.e. coughing, wheezing, chest tightness). Assessing inflammation via cytokines poses various difficulties. For example, circulating cytokines can be degraded by sample collection protocols (i.e. sample handling, processing and storage). Time of day in which the sample is collected has been shown to play an important role in obtaining accurate measures of inflammation, due to many immune systems experiencing oscillations within the 24-hour period [74, 75]. Cytokine samples are most commonly collected via serum or plasma samples. When assessing cytokines via serum samples, fibrinogen, platelets, and other circulating proteins must be removed. This removal and coagulation process can trigger the release of inflammatory mediators (e.g. histamine, eicosanoids) that may affect cytokine levels [76]. As such, plasma has been shown to produce the most consistent results for many cytokines [77, 78]. Furthermore, during acute exercise muscle cells release various cytokines that can be

detected via plasma [79]. Serum and plasma samples should be collected in sterile tubes, chilled, and processed quickly in order to maintain cytokine stability [77]. The stability of cytokines are further impacted by the short-half life, the production of cytokines by cells in the peripheral blood preparations, and the potential degradation. Although there are many factors that may negatively impact the integrity of the cytokines within serum and plasma, these methods of cytokine assessment are commonly used. Of note, the feasibility of these methods may be considered a disadvantage. Serum and plasma sample collection requires the skills of trained professionals (i.e phlebotomist) and require participants to consent to venous blood or arterial blood sampling. Therefore, many participants may not be willing or comfortable with needles, which has been shown to lead to health care avoidance and thus, may limit the use of this form of measurement [80]. Thus, research examining a non-invasive method of measuring cytokines is warranted.

Saliva is an exocrine secretion from the salivary glands and is composed of water (99%), electrolytes, proteins, and enzymes [81]. Whole saliva is composed of a mixture of fluids, secreted from the submandibular, sublingual, parotid, and the minor gland and mucous from the nasal cavity and pharynx (see Figure 1) [82]. Approximately 65% of unstimulated, or resting, saliva comes from the submandibular gland, 25% from the parotid gland, 4% from the sublingual gland, and 8% from other salivary glands [83]. The submandibular gland is considered to be a mucosal effector tissue and contains T cells, B cells, and dendritic cells [84]. These cells are all part of the oral immune system and are able to produce various cytokines, while the B cells produce antibodies [85]. Saliva secretion by the major and minor salivary glands is regulated through neurotransmitter

stimulation and secretion is often referred to as a two-step process [86]. Step one involves the secretion of an isotonic primary fluid by the acinar cells (water-permeable) and step two occurs in the duct system and involves the re-absorption of most sodium and potassium [87]. The acinar glands are also the site of the majority of protein secreted into the saliva (approximately 80%), with the remaining 20% of protein being secreted from the duct cells [88].

Figure 4. Salivary Glands



Salivary collection and analysis is a non-invasive method of assessing inflammation and easily allows for repeated measures per day over time. There are two collection methods for saliva: passive drool or oral swab. Many researchers consider the passive drool method the gold standard for collecting saliva samples for biological testing because it allows for the purest sample possible [89]. Samples collected using this method ensures that the saliva collected is a mixture of saliva secreted from all glands. The swab method of obtaining saliva, on the other hand, provides some degree of stimulation and thus, increases variability[90].

> Furthermore, the swab method is less representative of whole saliva given that it remains in the same area of the mouth and thus, the majority of the saliva collected results from secretion from the sublingual gland.

Cytokines can be reliably assessed via saliva and are responsive to exercise. In a study of 10 physically active males who completed a 60 minutes of cycling exercise stressor at 75% VO_2max and a resting control condition (reading or writing silently) on different days at least seven days apart, saliva samples were taken immediately before, immediately after, one hour after, and two hours after task completion [91]. TNF-α levels significantly increased during the exercise stress session compared to the control resting session ($p < .01$), with levels highest immediately after the completion of the 60-minute stressor [91]. As well, levels of IL-6 significantly increased during the exercise stress session compared to the control resting session ($p < .01$), with levels highest immediately after the completion of the 60-minute stressor. Levels of IL-1β significantly increased during the exercise stress session compared to the control resting session ($p < .01$), with levels highest immediately after the completion of the 60-minute stressor [91]. Similar findings were reported with IL-1β in a study of 30 participants (male n=20, female n=10) who completed a one-hour competitive rafting competition [92]. Saliva samples were obtained before and immediately after the competition. There was a significant increase ($p = .01$) in IL-1β concentrations before and after the exercise [92]. These findings suggest that TNF-*a*, IL-6, and IL-1β are responsive to exercise and can be assessed via saliva.

2.6 Inflammation, Exercise, and EIBC

The cytokines highlighted in the section below were chosen based on previous work highlighting their integral role in the acute and chronic inflammatory response to exercise, their role in exercise and acute bronchoconstriction (described above), and their successful assessment via saliva [93].

In the section below, the following 4 pro-inflammatory markers TNF-*a*, IL-1β, IL-8, and Interferon (IFN)-gamma inducible protein, (CXCL10/IP-10) and the following 2 anti-inflammatory markers, interleukin-1 Receptor antagonist (IL-1Ra) and TGF- β will be discussed as they relate to EIBC. Following the description of these cytokines, this section will summarize previous literature examining the response of these cytokines to acute and chronic exercise.

Pro-Inflammatory Markers

TNF-*a*: TNF-*a* is primarily produced by macrophages and is an important cytokine in the innate immune response, providing immediate defense against invading organisms [94]. It has been shown to contribute to the dysregulation of the inflammatory response among individuals with asthma [95]. TNF-*a* further contributes to the inflammation observed in bronchoconstriction by regulating early neutrophil infiltration and eosinophil recruitment into the airways, which serves to amplify the inflammatory response [96]. It also increases epithelial expression of intercellular adhesion molecule-1 (I-CAM) and vascular cell adhesion molecule-1 (V-CAM1) [97]. The increased expression of these molecules play an important role in the migration of T cells to the airways and in the development of airway hyper-responsiveness [98].

Among healthy adults, TNF-*a* has been shown to increase in response to acute exercise. Specifically, in a study of 10 adult males, salivary levels of TNF-*a* increased in response to a standardized treadmill test, using the standardized Bruce protocol. Levels of salivary TNF-*a* increased steadily at minutes 7 and 14 of exercise when compared to pre-exercise [99].

The aforementioned studies clearly illustrate the important and complex role that TNF-*a* plays in the inflammatory response of asthma. However, the response of TNF-*a* following a HIIT intervention among adults with EIBC has not been studied.

IL-1β: IL-1β is an innate immune cytokine that plays an important role in the initiation and persistence of inflammation [100]. IL-1β has been shown to play a role in the early phase of asthma as well as the altered airway response [101]. IL-1β is elevated in individuals with stable and exacerbating asthma [100]. As well, airway IL-1β is associated with systemic inflammation among individuals with asthma [100, 102]. In a prospective cohort study assessing airway IL-1β among individuals with asthma (n=63), it was reported that an increase in airway IL-1β and systemic inflammation was associated with an increased risk for an asthma exacerbation. There was increased IL-1β gene and protein expression among individuals with asthma, although it failed to reach statistical significance [102]. These initial findings warrant further investigation to better determine the role of IL-1β in the systemic inflammatory pathway among individuals with asthma. Among adults without asthma, salivary levels of IL-1β have been shown to increase following an acute bout of exercise (60 minutes at 75% VO_2max) when compared to a resting condition [91]. To date, no study has compared the IL-1β response to exercise between adults with and without asthma. However, in a study examining

levels of IL-1β in sputum among adults with and without asthma, no differences were observed [103]. Research to understand the impact of exercise on salivary levels of IL-1β among adults with and without EIBC is warranted.

IL-8: IL-8 is produced by a variety of tissue and blood cells, and acts as a chemoattractant cytokine. IL-8 plays a key role in the attraction and activation of neutrophils to areas of inflammation [104]. Adults with asthma have greater levels of IL-8 when compared to adults without, and that higher levels of IL-8 are associated with worse asthma control [105]. IL-8 has been shown to be responsive to acute exercise, in that high intensity or exhaustive exercise with an eccentric component (e.g. motion of an active muscle while lengthening under load) elicits increases in systemic levels of IL-8 [106]. Among healthy adults, an acute bout of high intensity interval exercise decreases serum levels of IL-8 [107]. Interestingly, an acute bout of high intensity exercise among adults with asthma (n=39) increases plasma IL-8 immediately post-exercise and a return to baseline values 1 hour post-exercise [108]. A study examining the impact of moderate intensity aerobic exercise twice per week for 12-weeks versus no exercise among adults with asthma (n=58), found no differences in sputum IL-8 from pre to post-intervention or between groups [109]. The response of IL-8 to acute and chronic exercise among adults with asthma is inconclusive. Higher intensity exercise may allow for a more potent inflammatory stimulus and thus, elicit greater reductions in pro-inflammatory markers among adults with asthma when compared to those without. In summary, it appears that an acute bout of high intensity exercise may elicit different responses among those with and without asthma; however, the impact of adherence to chronic HIIT on IL-8 among adults with and without asthma remains unknown and warrants further investigation.

CXCL10/IP-10: CXCL10/IP-10 is a member of the CXC chemokine family with pro-inflammatory properties. CXCL10/IP-10 is secreted from leukocytes, neutrophils, eosinophils, monocytes, epithelia, and endothelial cells [110, 111]. CXCL10/IP-10 preferentially attracts activated Th1 lymphocytes and is up-regulated in the airways of adults with asthma [112]. Aerobic exercise training among healthy adults reduces plasma levels of CXCL10/IP-10. Specifically, in a study of healthy adults (n=413) participants were randomized into 8 weeks of aerobic exercise, mindfulness-based stress reduction, or a wait-list group. Those in the aerobic exercise group experienced the greatest reductions in CXCL10/IP-10, and those reductions remained after a 6-week follow-up [113]. To date, no study has examined the acute or chronic impact of HIIT among adults with asthma on salivary CXCL10/IP-10. It is possible that chronic HIIT would reduce CXCL10/IP-10 among adults with asthma; however, given that adults with asthma tend to have an up-regulation of CXCL10/IP-10 it is likely that they would experience reductions in this cytokine.

Anti-Inflammatory Markers

IL-1Ra –IL-1Ra is a specific inhibitor for the IL-1 family. Specifically, IL-1Ra acts by blocking the IL-1 receptor and therefore, stops the pro-inflammatory effects of cytokines in the IL-1 family [114]. T-helper cells 1 and 2 are responsible for regulating the ratio between IL-1β and IL-1Ra [115]. Among healthy adults, exercise has been shown to increase plasma levels of IL-1Ra. In a study of 19 well-trained athletes, plasma IL-1Ra was assessed pre and post a 6 hour endurance run. Plasma IL-1Ra increased from 188 pg/ml to 886 pg/ml [116]. Unfortunately, less is known about the acute and chronic response of IL-1Ra to exercise training among adults. However, the dysregulation of the

IL-1β /IL-Ra ratio is important for the inflammation observed among adults with asthma [117]. It is possible that during an asthma attack, such as following an acute bout of exercise, adults with EIBC would exhibit greater levels of IL-1Ra when compared to controls, in an attempt to reduce inflammation associated with bronchoconstriction. Furthermore, chronic HIIT may allow for an adaptation that may reduce acute inflammation following a single exercise bout and thus, adults with and without EIBC may exhibit similar IL-1Ra profiles.

TGF-β: TGF-β is produced by various cell types (i.e. epithelial cells, eosinophils, macrophages, and fibroblasts and plays a central role in airway smooth muscle remodeling and mucous production [118]. Strenuous exercise elicits increases in the plasma concentration of TGF-β among healthy, physically active adults [119]. Furthermore, moderate intensity (70% VO_2peak) acute exercise has also been shown to increase levels of salivary TGF-β among healthy adult males (n=10) [120]. Animal studies using diabetic mice have reported decreases in TGF-β following moderate intensity exercise training;[121] however, limited research exists on the impact of exercise training among adults with asthma and to date, no study has examined the impact of HIIT on salivary levels of TGF- β in adults with asthma. Strenuous exercise has a greater impact on circulating levels of TGF-β when compared to moderate intensity exercise [122]. Given the importance of TGF-β in the asthmatic response , it is important to better understand the chronic response of HIIT on salivary levels of TGF-β among adults with asthma.

Inflammation and Acute Exercise: Acute exercise has been shown to increase salivary levels of various pro- inflammatory cytokines such as TNF-*a*, IL-1β, and IL-8, and anti-

inflammatory cytokines such as IL-1Ra among adults both with and without asthma. Specifically, in a study of 10 physically active males (age: 23 ± 3years), a 60 minute exercise session was completed on a cycle ergometer at 75% of VO_{2max} [91]. Saliva samples were obtained before exercise, immediately post, 60 minutes post, and 120 minutes post-exercise. Levels of TNF-*a*, and IL-1β were significantly increased following the exercise session. The highest levels of TNF-*a* and IL-1β were observed 60 minutes post exercise [91]. Similar results were observed in IL-6 levels in a study of 15 male athletes, who completed an exercise test consisting of 15 minutes of warm-up cycling followed by 25 minutes of isometric exercise (160 contractions of the knee) [123]. Saliva samples were obtained via the passive drool and salivette methods immediately before, immediately after, and 30, 60, 90, and 120 minutes post-exercise test. Salivary levels of IL-6 were significantly elevated immediately post-exercise, but did not remain significantly elevated 30 minutes post-exercise [123]. Among adults with EIBC, an increase in the aforementioned inflammatory markers may result in bronchoconstriction post-exercise[4]. Furthermore, it is likely that the levels of pro-inflammatory cytokines obtained from adults with EIBC would be higher than that among adults without EIBC, due to the inflammatory nature of the condition.

Inflammation and Exercise Training: As opposed to acute exercise, exercise training reduces levels of systemic inflammation. Exercise training of continuous intensity improves airway inflammation among individuals with asthma as evidenced by reductions in fractional exhaled nitric oxide [124]. Similarly, exercise training of continuous intensity has been shown to reduce the expression of Th2 pro-inflammatory cytokines and increase the expression of IL-10 [125]. Reductions in pro-inflammatory

cytokines have been reported among individuals with allergic rhinitis with aerobic exercise training as well. Specifically, reductions in serum concentrations of TNF-*a* and IL-4 were reported following exercise training, which consisted of 40-60 minutes of moderate intensity continuous exercise, performed 3-4 days per week, for 6 months [15]. Similar reductions in serum concentrations of TNF-*a* were reported following an 8-week endurance exercise program, which consisted of running on a treadmill for 15-30 minutes, at 50-70% of maximum heart rate among healthy sedentary men [126]. Local concentrations of TNF-*a*, IL-6, and IL-1β decreased following a six month endurance exercise training intervention among males with chronic heart failure [127]. The anti-inflammatory properties of exercise have predominately been studied using *moderate intensity continuous exercise training*, with limited research available on the anti-inflammatory properties of HIIT.

Of the literature that is available, one study randomized 32 overweight/obese participants into three exercise conditions: 1) continuous exercise at 70% maximum heart rate 5 times per week, 2) HIIT sessions of 1x4 minutes at 90% maximum heart rate, and 3) 4x4 minutes at 90% maximum heart rate [64]. HIIT sessions were completed 3 times per week for a total of 16 weeks. Serum levels of TNF-*a*, IL-6, and IL-10 were assessed at baseline and post-intervention. Results showed that HIIT reduced levels of IL-6 but increased TNF-*a*, while the continuous exercise reduced TNF-*a* among participants [64]. These results suggest that exercise training can elicit improvements in serum levels of inflammatory markers; however, less is known about whether HIIT can elicit improvements in the salivary levels of these markers. A better understanding of the impact of HIIT on pro and anti-inflammatory markers, assessed non-invasively, may

allow for easier assessment and monitoring of inflammation levels among adults with EIBC.

Summary: Pro-inflammatory markers TNF-α, IL-8, and CXCL10/IP-10 have been shown to play an important role in the inflammatory cascade that occurs in response to acute exercise. Furthermore, these pro-inflammatory cytokines have been shown to play an integral role in bronchoconstriction. Circulating levels of IL-1Ra and TGF-β are responsive to acute exercise and increase as a result of exercise training. An increase in these anti-inflammatory cytokines may reduce the severity of EIBC by minimizing the pro-inflammatory effects.

Research Gap: The inflammatory response to an acute bout of HIIT and to regular participation in HIIT among adults with asthma and healthy adults requires further investigation. To date, no study has assessed the inflammatory response to HIIT among adults with EIBC, or compared the differences in the inflammatory response to HIIT among adults with asthma and healthy adults. Positive results from this work may allow for improved exercise prescription (i.e. HIIT) among adults with asthma.

Hypothesis: It is hypothesized that a 6-week HIIT intervention will lead to reductions in salivary concentrations of pro-inflammatory markers TNF- α, IL-1β, IL-8, and CXCL10/IP-10 and an increase in salivary concentrations of anti-inflammatory markers IL-1Ra and TGF-β among adults with EIBC and healthy adults; however, adults with EIBC would experience greater improvements. Greater improvements among the EIBC group were expected based on literature that indicates adults with asthma generally have higher levels of these cytokines.

2.7 FEV_1, Ventilation, Exercise, and EIBC

This next section outlines a review of the response of ventilation to acute exercise and how that triggers the inflammatory cascade outlined above, which ultimately reduces lung function, or FEV_1, among adults with EIBC. For the purpose of this dissertation, the term ***pulmonary outcomes*** will be used to encompass all pulmonary data collected.

As described in the preliminary sections of this dissertation, EIBC occurs due to evaporative water and heat loss from the lungs due to an increase in ventilation during exercise. This increase in ventilation is a normal physiological response to exercise and thus, occurs among adults with asthma and healthy adults. An increase in ventilation occurs as a result of an increase in breathing frequency (i.e. respiratory rate) and/or tidal volume (i.e. volume of air displaced between a normal inhalation and exhalation). Among healthy adults, the normal response of V_T and RR is to increase as exercise intensity increases; however, during high intensity exercise the ventilatory efficiency (V_E/ carbon dioxide output (VCO_2)) is often reduced due to an excessive increase in respiratory rate [128].

Ventilatory efficiency describes the relationship between ventilation and VCO_2 [129]. Among healthy adults, the most efficient lung is one where there is matching between ventilation to perfusion. When mismatching occurs, common among those with EIBC, the efficiency of the lung is reduced, which causes ventilation to increase for a given VCO_2. To date, no study has examined the chronic impact of HIIT on pulmonary outcomes among adults with asthma or examined the perfusion of oxygen to the working muscles. It is possible that the intermittent recovery periods associated with HIIT may

allow for intermittent recovery of respiratory rate and thus, ventilation. This may lead to less of a reduction in FEV_1 post-exercise.

Chronically, HIIT may improve cardiorespiratory fitness (VO_2max) and ventilatory efficiency. Among adults with and without EIBC, VO_2max is an important indicator of cardiorespiratory fitness and improvements in VO_2max correlate with overall health. Additional benefits have been reported among adults with EIBC, in that improvements in VO_2max correlate with improvements in asthma specific outcomes (i.e. asthma control) [14, 16]. Therefore, adherence to a 6-week HIIT intervention may lead to improvements in ventilatory variables during an acute bout of exercise, reducing the decline in FEV_1 post-exercise among adults with EIBC, and lead to improvements in VO_2max, thus improving overall health among adults with and without EIBC and improving asthma-specific outcomes among adults with EIBC.

FEV_1, Ventilation, and Acute Exercise:

As mentioned above, limited research exists on the acute ventilatory response to HIIT. Of the literature that is available, such as the results from my Masters work, it appears that an acute bout of HIIT leads to a smaller reduction in FEV_1 when compared to traditional continuous exercise among adults with EIBC [19]. Whether the ventilation patterns (i.e. V_T, RR) between adults with and without EIBC differs during HIIT remains to be elucidated. Previous research suggests that when comparing the ventilation response during exercise between adults with and without EIBC, despite variations in lung function at baseline between adults with and without EIBC (i.e. adults with EIBC having

a lower FEV_1 at baseline and/or experiencing bronchoconstriction), the exercise ventilatory response is remarkably similar between groups [130]. In a study of 8 adults with mild asthma and 9 healthy adults, participants completed constant work-rate cycling to exhaustion following four separate interventions, consisting of the following: a control trial; inhalation of a fast-acting B_2-agonist; eucapnic voluntary hyperpnea challenge; and sham to the hyperpnea. For each intervention, lung function was assessed pre and post-intervention, and ventilation data during exercise were compared between the four interventions between groups. Results indicated that baseline FEV_1 was significantly lower among adults with asthma when compared to adults without. Interestingly, despite variations in pre-exercise lung function, no differences were observed in ventilation during exercise between adults with and without asthma [130]. These findings suggest that despite the altered airway function associated with asthma, the ventilatory system during exercise among adults with and without EIBC appear to be similar.

Although the majority of research has reported that EIBC occurs post-exercise, [19, 130] there is evidence to suggest that some adults experience EIBC during exercise [131, 132]. Specifically, in a study of 6 adults with asthma, participants completed a short exercise session (6 minutes) and a long exercise session (20 minutes), and lung function was assessed throughout each exercise session. A reduction in FEV_1 during the long exercise session but not during the short exercise session was observed [131]. The reductions in FEV_1 reported in the aforementioned study may be due to sustained high ventilations associated with continuous exercise. As such, the intermittent recovery periods that are associated with HIIT may allow for ventilation to recover intermittently, ultimately

reducing the evaporative water and heat loss from the airways and thus, reducing the decline in FEV_1 post-exercise.

FEV_1, Ventilation, and Exercise Training: Conflicting evidence exists regarding the effectiveness of exercise training to improve pulmonary function among adults with asthma. In a study of 36 individuals with asthma, participants were randomized into two groups as follows: an 8-week aerobic exercise group, and a control group of no exercise. Results showed an increase in FEV_1, forced vital capacity, peak expiratory flow, and maximal voluntary ventilation following exercise training [133]. In contrast, following a 12-week aerobic exercise training program among adults with asthma, no changes in pulmonary function as measured by FEV_1, forced vital capacity, and FEV_1 percent predicted were observed from pre to post-training [10]. Although no improvements in FEV_1 post-exercise were observed, a trend towards significant improvements were reported in ventilatory efficiency (i.e. V_E/VCO_2). Furthermore, Cochrane reviews have consistently reported exercise training does not improve FEV_1 among adults with asthma. The discrepancies in changes in FEV_1 between studies may be due to improper spirometry technique and/or improvements in spirometry technique due to a learning effect. There are three key factors to consider in obtaining a valid and reliable measure [134]. These factors include the operator, the equipment, and the patient/participant. Those studies reporting contrasting evidence of improvements in FEV_1 following exercise training may have included participants who were unskilled at spirometric maneuvers, who were uninterested in ensuring a maximal effort, or who improved based on practice from pre to post-intervention testing [134]. In order to reduce the impact of a training effect in participants who were included as part of this dissertation,

familiarization, practice maneuvers, and video tutorials were sent to participants prior to attending the laboratory sessions.

Of note, many adults with asthma experience hyperventilation [135], which may be due to anxiety surrounding the potential of experiencing an asthma attack [136]. Hyperventilation among adults with EIBC may lead to greater reductions in ventilatory efficiency and thus, increase the evaporative water and heat loss from the lungs, leading to a greater decline in FEV_1. It is possible that a reduction in anxiety during before and/or during exercise (i.e. repeated exposure to feared stimuli or improvements in physical fitness) may aid in improving ventilatory efficiency, breathing frequency, tidal volume, and FEV_1 post-exercise among adults with EIBC. To date, the majority of research has focused on *continuous exercise training*; however, the impact of HIIT on V_E, tidal volume, respiratory rate, and FEV_1 is unclear. It is possible that repeated exposure to HIIT may reduce ventilation during acute exercise and thus, reduce post-exercise FEV_1. Furthermore, reductions in inflammation as a result of reducing evaporative water and heat loss through ventilation may ultimately reduce the decline in FEV_1 post-exercise.

Summary: Among those with EIBC, FEV_1 is generally lower at rest when compared to healthy adults, and decreases in response to an acute bout of exercise. Despite these differences, the ventilatory response to acute exercise is similar between those with asthma and healthy adults. The bronchoconstriction associated with EIBC is triggered by the ventilation *during* acute exercise; however, the bronchoconstriction (i.e. decline in FEV_1) generally occurs *post*-exercise. As such, the oxygen perfusion to the working muscle theoretically, should be similar between adults with asthma and healthy adults.

Research Gap: Although ventilation during exercise appears to be similar between adults with and without EIBC, the ventilatory response during HIIT has not been compared between these groups. Intermittent recovery periods associated with HIIT may for allow for ventilation (i.e respiratory rate and tidal volume) to recover intermittently, improving ventilatory efficiency and reducing the amount of water and heat loss from the lungs; thus, reducing the decline in FEV_1 post-exercise. Chronic HIIT may further improve the ventilatory response by reducing hyperventilation due to improvements in fitness (i.e. VO_2max) and in improvements in anxiety surrounding exercise and EIBC among adults with EIBC. If this is the case, HIIT may be a safer and more preferred form of exercise than traditional continuous exercise for adults with EIBC.

Hypothesis: It is hypothesized that a 6-week HIIT intervention will improve post-exercise FEV_1, when exercising at the same absolute workload, among adults with EIBC. It is also hypothesized that improvements in fitness (i.e. VO_2max) following 6-weeks of HIIT, will lead to improvements in breathing frequency, tidal volume, and ventilatory efficiency among adults with and without EIBC. It is further hypothesized that adults with EIBC will have a more dynamic ventilatory response to HIIT when compared to adults without EIBC.

2.8. VO_2max, Heart Rate, Exercise, and EIBC

Monitoring ventilation, RR, and V_T during exercise is particularly important among adults with EIBC. In addition to providing a better understanding of the mechanisms responsible (i.e. increases in RR and V_T leading to airway cooling and dehydrating) for the decline in FEV_1 post-exercise, monitoring ventilation during exercise also allows for the measurement of VO_{2max}; an important indicator of the efficiency and effectiveness of the cardiorespiratory system to deliver oxygen to the working muscles among adults with and without EIBC [137]. During exercise, there is an increased requirement for oxygen from the working muscles, which leads to an increase in heart rate and to an increase in tissue oxygen saturation. Improvements in any and/or all outcomes of cardiorespiratory fitness can improve exercise performance [138-140].

VO_2, Oxygen Saturation, Heart Rate, and Acute Exercise: During exercise, increases in VO_2 and heart rate occur in response to the demand of exercise. Among adults with EIBC, ventilation does not appear to limit exercise performance [130]. Given that EIBC is a condition of the respiratory system, the cardiovascular response to exercise among those with and without EIBC *should* be similar. However, many adults with EIBC use bronchodilators prior to exercise in order to prevent the EIBC response. These inhaled bronchodilators increase heart rate and thus, may alter the cardiovascular response to exercise among adults with EIBC when compared to those without EIBC [141]. As well, the ventilatory limitations adults with EIBC may experience at rest (e.g. MVV) could reduce peripheral oxygen saturation during exercise when compared to adults without EIBC. Of the limited literature that is available, studies have reported that tissue oxygen saturation (TSI) does not differ during acute exercise (continuous) between adults with

EIBC and healthy adults [142]. However, the TSI response to HIIT has not been examined between these groups.

VO_2, Oxygen Saturation, Heart Rate, and Exercise Training: HIIT is an effective form of exercise for improving VO_2max [26]. In a meta-analysis, a mean increase of 0.51 L-min^{-1} has been reported following HIIT of 6-13 weeks, with higher HIIT volumes resulting in greater improvements (0.8-0.9 L.min^{-1}) in VO_2max. [13]. Similar findings were reported in a systematic review and meta-analysis comparing HIIT to continuous exercise training among healthy adults. Results showed that HIIT elicited greater improvements in VO_2max (5.5ml/kg/min ± 1.2 ml/kg/min) when compared to continuous exercise (1.2ml/kg/min ± 0.9ml/kg/min) [143]. Literature on the HIIT-mediated improvements in VO_2max among adults with EIBC is sparse and as such, it is likely that the response between adults with EIBC and healthy adults would be similar. It is expected that adults with EIBC and healthy adults with a similar fitness level at baseline, would experience similar improvements in VO_2max following a HIIT intervention.

Among adults with EIBC, an increased heart rate may occur as a result of bronchodilator use; however, reduced need for bronchodilators following exercise participation has been observed. Therefore, it is possible that the cardiovascular profile during HIIT among adults with EIBC would not differ when compared to those without EIBC. Furthermore, it is expected that HIIT would lead to similar improvements in TSI between adults with EIBC and healthy adults due to the expected similar improvements in fitness.

Summary: Exercise training improves parameters of cardiorespiratory fitness. Adults with EIBC may experience a higher heart rates and reduced tissue oxygen saturation when compared to healthy adults as a result of EIBC medication.

Research Gap: To date, no study has examined the impact of a 6-week HIIT intervention between adults with EIBC and healthy adults on cardiorespiratory and cardiovascular outcomes. Therefore, it remains unclear as to whether the cardiovascular adaptations associated with HIIT among healthy adults would be similar among adults with EIBC.

Hypothesis: It is hypothesized that adults with EIBC will exhibit a more dynamic heart rate response during exercise, as a result of medication use. It is further hypothesized that adults with EIBC will experience similar improvements in VO_2max as healthy adults.

2.9 Psychological Outcomes of EIBC

As alluded to in the introduction, asthma and EIBC impact various domains of the individual including not only the physiological, but the psychological as well. Psychological variables play an important role in exercise participation and the exercise response among adults both with and without EIBC, and are often considered a barrier to regular exercise [144]. The psychological variables addressed in the current review and in this PhD work will focus on anxiety and enjoyment.

Anxiety is a common problem among adults with asthma and may serve as a barrier to regular exercise, due to the fear of experiencing an asthma attack and/or asthma related symptoms. Exercise enjoyment is a strong predictor of future exercise engagement and thus, if exercise is not perceived as enjoyable there is a greater likelihood that adults will not participate in exercise. The section below discusses general anxiety and anxiety sensitivity among adults with and without EIBC and highlights their responses to acute and chronic exercise.

General Anxiety & Anxiety Sensitivity

Anxiety refers to a feeling of worry, nervousness, or unease about an event or about something with an unknown outcome. Among adults with asthma, anxiety is more prevalent when compared to those without [144]. One possible explanation for the higher prevalence of anxiety among adults with asthma may be due to unease around experiencing an asthma attack and the potential of an unknown outcome (i.e. medication

needs, hospital admittance). General anxiety is a common health problem among young Canadians; approximately 12% of young Canadians have been reported to have been diagnosed with anxiety or an anxiety disorder [145]. Importantly, many adults with and without asthma have symptoms of anxiety that may interfere with their every lives, despite not having a clinical diagnosis of an anxiety disorder. Therefore, strategies to reduce symptoms of anxiety, such as exercise training, may have major implications in improving the lives of many Canadians with and without EIBC.

Anxiety sensitivity differs from general anxiety in that anxiety sensitivity refers to fear related to anxiety sensations, such as an increase in heart rate, sweating, and difficulty breathing [146]. Research suggests that prevalence rates of anxiety sensitivity among adults with asthma ranges from 3.3 to 16% [147, 148]. This high prevalence of anxiety sensitivity among this population is of particular concern given that the presence of a psychiatric diagnosis, in particular panic-related psychopathology, is associated with poor asthma control [149, 150]. Furthermore, anxiety sensitivity may pose a significant problem for adults with EIBC given that sensations of anxiety sensitivity (i.e. increased heart rate, sweating) are also normal physiological responses to exercise. Therefore, adults with EIBC may experience heightened anxiety during exercise or at the thought of exercise due to the misinterpretation of normal physiological responses as an imminent threat. Heightened anxiety sensitivity often leads to avoidance of the feared stimuli (i.e. fear of physiological responses to exercise leads to the avoidance of exercise) [151], and the avoidance of exercise creates a multitude of health issues for adults with and without asthma.

Anxiety and Acute Exercise: The aforementioned anxiety sensations are a normal physiological response to exercise; however, these responses pose a significant issue among those with greater levels of anxiety sensitivity. An inverse relationship between anxiety sensitivity and exercise participation has been reported due to avoidance of the physiological sensations of exercise, which may be interpreted as anxiety and panic related sensations [152]. Therefore, reducing levels of anxiety sensitivity may contribute to improving exercise participation rates by reducing anxiety-related barriers to regular exercise.

Anxiety and Exercise Training: Fortunately, exercise training has been shown to improve anxiety sensitivity [16]. Improvements in anxiety sensitivity were observed following six 20-minute exercise sessions at 70% of maximum heart rate over a two week period [16]. Furthermore, the meaningful improvements observed in anxiety sensitivity tended to precede meaningful improvements in levels of general anxiety symptoms. The exact mechanisms responsible for the reductions in anxiety sensitivity observed following exercise training remains unclear; however, various theories purport to explain this improvement. For example, exposing someone with high anxiety sensitivity to the feared physiological sensations (i.e. increased heart rate), in the context of exercise can reduce their anxiety surrounding those sensations [152]. The exposure to the feared physiological sensations associated with exercise exemplifies to the individual, that although these sensations may be uncomfortable they do not pose a serious threat, and repeated exposure to exercise may facilitate habituation of the feared sensations [153, 154].

It is unknown as to whether the same improvements in anxiety sensitivity can be achieved through HIIT among adults with EIBC and healthy adults. Anxiety sensitivity surrounding the feared physiological sensations associated with HIIT are expected to reduce over time, as a result of repeated exposure to the feared stimuli (i.e. HIIT). Reductions in anxiety sensitivity among adults with EIBC and healthy adults may serve to increase motivation to exercise as not only a means of improving physical health, but as an effective way to improve their psychological health. Taking into consideration the research suggesting that adults with asthma may have higher levels of anxiety [144], it is possible that a 6-week HIIT intervention will reduce general anxiety and anxiety sensitivity to a greater extent among adults with EIBC, given that they are more likely to experience higher anxiety and anxiety sensitivity at baseline. An acute bout of HIIT has been shown to preserve lung function; [19] therefore, chronic HIIT may reduce anxiety sensitivity to a greater extent among adults with EIBC, by not only exposing them to repeated HIIT, but by also allowing them to exercise without experiencing EIBC related symptoms (i.e. without experiencing feared EIBC related sensations).

Summary: Adults with asthma are at an increased risk of developing an anxiety disorder. Among adults with and without asthma, elevated levels of anxiety and anxiety sensitivity may serve as a barrier to regular exercise; however, repeated exposure to anxiety provoking sensations through exercise training improves anxiety as well as anxiety sensitivity.

Research Gap: Limited research exists on the anti-anxiety properties of HIIT among adults with and without EIBC. Given the prevalence of anxiety among adults with and without EIBC, non-pharmacological anxiety management or treatment tools such as HIIT, could have a major impact on the mental health of Canadian adults.

Hypothesis: It is hypothesized that adults with EIBC will have higher levels of general anxiety and anxiety sensitivity when compared to adults without EIBC. Furthermore it is hypothesized that adults with EIBC will experience greater improvements in general anxiety and anxiety sensitivity when compared to adults without following a 6-week HIIT intervention. Lastly, it is hypothesized that adults with EIBC will experience a reduction in asthma specific exercise anxiety following a 6-week HIIT intervention, as a result of repeated exposure to HIIT and EICB symptoms.

Perceptual Feedback and Exercise Enjoyment

Exercise participation rates remain suboptimal which may be in part, be due to exercise affect and/or exercise enjoyment. Among those with EIBC specifically, perceptions of dyspnea may contribute to an increase in perceptual levels of effort, affecting overall exercise enjoyment, and thus adherence to exercise.

The Hedonic Theory refers to human motivation and suggests that humans are motivated to experience pleasure and avoid pain, which has great implications in the context of affect during exercise [155]. Specifically, the way one feels during exercise, or their

affective response to exercise, may have a predictive role in future exercise engagement, and play a role in exercise behavior [156]. Exercise intensity is an important contributor to exercise affect and overall exercise enjoyment. Specifically, a negative relationship exists between exercise intensity and affect. For example, as exercise intensity increases above ventilatory threshold, the affective response during exercise becomes more negative [157, 158]. In a study that sought to determine the affective response to vigorous intensity exercise (80% of VO_{2max} for 30 minutes) and moderate intensity exercise (50% of VO_{2max}), participants reported greater psychological distress and lower exercise enjoyment during the vigorous intensity exercise [157]. The dual-model theory has been proposed as an explanation of the negative relationship observed between exercise intensity and affect. According to this theory, affect experienced during exercise is partly influenced by metabolic cost associated with exercise intensity [159].

Interestingly, HIIT is associated with higher levels of exercise enjoyment when compared to moderate intensity continuous training [27, 160]. An acute bout of HIIT elicits a more positive mood and greater exercise enjoyment than an acute bout of moderate intensity continuous exercise among adults with EIBC [161, 162]. One possible explanation for the higher affect observed during HIIT among adults with EIBC, may be due to the intermittent recovery periods associated with HIIT. These intermittent recovery periods may allow adults with EIBC to intermittently reduce ventilation and thus, reduce water and heat loss from the airways, contributing to an attenuated EIBC response [4]. A second explanation that may be contributing to the higher affect during HIIT among adults with EIBC, may be related to the reduced time commitment associated with HIIT. Lack of time is consistently cited as the primary barrier to regular physical activity

regardless of age, sex, or health status [163]. Therefore, the time-efficient nature of HIIT may lead to greater affect during exercise. The critical role exercise enjoyment plays in regular exercise participation requires further investigation in order to reduce barriers to regular exercise and improve exercise rates among adults with and without EIBC.

Research Gap: The affective and enjoyment response to chronic HIIT among adults with and without EIBC has not yet been determined.

Hypothesis: It is hypothesized that affect during exercise and exercise enjoyment will improve following a 6-week HIIT intervention among adults with and without EIBC, with the greatest improvements being observed among adults with EIBC due to a reduction in EIBC symptoms during exercise.

2.10 EIBC Specific Variables and Exercise

The following EIBC specific variables need to be taken into consideration when monitoring and prescribing exercise among this population in order to better understand the impact of exercise on this condition.

Asthma Symptoms, Asthma Control & Asthma Related Quality of Life

Dyspnea, or shortness of breath, is a common symptom among adults with asthma and a common response during exercise. Dyspnea has been shown to be a strong barrier to exercise participation and thus, adults with asthma often avoid exercise in an effort to avoid dyspnea [164]. The problem with this is that without exercise dyspnea becomes

worse over time and eventually dyspnea occurs during activities of daily living. The frequency of dyspnea, as well as additional asthma symptoms such as coughing, wheezing, and chest tightness is used to determine asthma control [5]. Asthma control can range from completely controlled (experiencing no symptoms during any activity) to not at all controlled (experiencing symptoms all the time). Poor asthma control has been associated with a lower perception of health related quality of life [165]. Despite various treatment options, many individuals with asthma continue to report symptoms of poorly controlled asthma[166]. Poor asthma control can reduce quality of life and has been associated with an increased risk of developing anxiety, depression, and hyperventilation [7]. Therefore, reducing asthma symptoms (i.e. dyspnea) can lead to improvements in asthma control and as such, have major implications in the quality of life among adults with asthma.

Asthma Control and Exercise Training: Exercise training has been shown to improve asthma control;[10] however, the mechanisms responsible for the improvements in asthma control are unknown. In a study of 18 adults with asthma, participants completed a 12-week aerobic exercise training program and experienced improvements in asthma control from pre to post- intervention, and these improvements were maintained 12-weeks following the intervention. The improvements in asthma control were also accompanied by improvements in quality of life among participants [10]. Similar findings in improvements in quality of life were reported in a 16-week aerobic training intervention among children with asthma [167].

Improvements in health related quality of life among adults with asthma following a 12-week HIIT intervention (2 times per week for 40 minutes) [168] have been observed.

These findings paired with the benefits of HIIT described above, illustrate that HIIT is a promising form of exercise among adults with EIBC. Unfortunately, limited research exists regarding the benefits of a low volume HIIT intervention among this population. The low volume HIIT intervention that was implemented within this dissertation lends itself to a more real-world application, in that many adults with and without EIBC perceive time as a significant barrier to exercise. Therefore, a HIIT intervention that offers a shorter time commitment than traditional exercise training may be more attractive among many adults. Furthermore, long-term compliance to exercise training is difficult to attain and thus, having a better understanding of the EIBC-specific adaptations that occur over 6-weeks of HIIT will provide valuable insight into exercise prescription and disease management among this population.

Summary: Exercise training has been associated with improvements in perceptions of dyspnea, asthma control, and health related quality of life among adults with asthma.

Research Gap: To date, no study has examined the impact of a 6-week HIIT intervention on asthma control and quality of life among adults with EIBC.

Hypothesis: It is hypothesized that adults with EIBC will experience improvements in asthma control and asthma related quality of life following a 6-week HIIT intervention as a result of improvements in fitness.

2.11 Chapter Summary:

In this chapter HIIT, the pathophysiology of asthma, treatment options for asthma and EIBC, and the impact of exercise on the inflammatory, ventilatory, cardiovascular, and psychological variables were described. By examining previous literature within these areas, it is clear that evidence surrounding the physiological, psychological, and clinical impact of HIIT among adults with EIBC and evidence is greatly lacking.

The overarching goals outlined in Chapter 1 were sub-divided into four distinct research questions. The research questions outlined below were addressed by implementing a 6-week high intensity interval training (HIIT) intervention and assessing outcomes pre (T1) and post (T2) intervention among adults with asthma and healthy controls.

2.11 RESEARCH QUESTIONS:

1. Does a 6-week HIIT intervention lead to a reduction in salivary concentrations of IL-8, TNF-*a*, IL-1β, and IP-10 and an increase in IL-1Ra and TGF- β from T1 to T2 among adults with and EIBC and healthy controls?
2. Does a 6-week HIIT intervention alter the acute response in pulmonary outcomes among adults with EIBC and healthy controls?
3. Does a 6-week HIIT intervention improve general anxiety, anxiety sensitivity, and asthma specific exercise anxiety among adults with EIBC?
4. Does a 6-week HIIT intervention improve asthma control, perceptions of dyspnea, and exercise enjoyment, among adults with EIBC?

The subsequent chapters of this dissertation have been organized to highlight the key findings for each research question outlined above.

Chapter 3: The impact of HIIT on salivary markers of inflammation among adults with and without asthma

TITLE: The Impact of HIIT on Salivary Markers of Inflammation among Adults with and without Asthma

ABSTRACT

INTRODUCTION: The chronic airway inflammation associated with asthma occurs due to the release of a variety of cells, such as eosinophils, lymphocytes, and mast cells. Interleukin-8 (IL-8), IL-1beta (β) and interferon-gamma-inducible-protein (CXCL10/IP-10)) are pro-inflammatory markers that contribute to the acute and chronic inflammation associated with asthma. Exercise training reduces various pro-inflammatory markers and increases anti-inflammatory markers (e.g. interleukin-1 receptor antagonist (IL-1Ra)) in the serum; however, limited research exists on the impact of exercise training on reducing salivary levels of IL-8 and IL-1Ra among adults with asthma and healthy controls. METHODS: A 6-week exercise intervention was conducted among adults with asthma and healthy controls. Exercise-induced bronchoconstriction was confirmed using the eucapnic voluntary hyperpnea challenge. Saliva samples were collected at the beginning and end of the first (T1) and last (T2) exercise sessions. RESULTS: Independent samples t-test revealed a trend towards the asthma group (n=20) having higher levels of IL-8 at T1 (Asthma: 0.2 ± 0.1 pg/ug protein; Control: 0.1 ± 0.1 pg/ug protein, p=0.07) when compared to the control group (n=12). Results from the ANCOVA revealed that adults with asthma had significantly lower levels of IL-1Ra at T2 when compared to healthy controls ($F(11.7, 1)$ $p<0.01$, $h_p^2 = 0.3$). No between group differences in IL-8 were observed at T2. CONCLUSIONS: A 6-week exercise intervention does not lead to reductions in salivary levels of IL-8 in adults with EIBC and healthy adults; however, adults with EIBC experience a reduction in salivary levels of IL-1Ra. These findings suggest that HIIT may play an important role in reducing the IL-1β /IL-1Ra ratio that contributes to the chronic inflammation associated with EIBC.

INTRODUCTION

Approximately 8.1% of Canadians are living with asthma, [169]characterized by chronic inflammation and acute bronchoconstriction [170]. The chronic airway inflammation associated with asthma results from various cells, such as eosinophils, lymphocytes, and mast cells [43, 44]. These inflammatory cells release inflammatory markers including cytokines, chemokines, and mediators (i.e. interleukin-8 (IL-8), IL-1beta (β), interferon-gamma-inducible-protein (CXCL10/IP-10)) that contribute to local inflammation and systemic inflammation among adults with asthma [30, 44]. In order to combat this inflammatory cascade various anti-inflammatory cytokines are released and have been shown to play an important role in asthma, such as IL-1receptor antagonist (IL-1Ra) [117]. IL-1Ra is a specific inhibitor for IL-1 receptor pro-inflammatory cytokines and thus, plays an important role in combating the inflammatory response; unfortunately, adults with asthma have lower levels (assessed via serum) of IL-1Ra when compared to controls [117].

It has been suggested that the local lung inflammation associated with asthma contributes to an increase in systemic inflammation (e.g. higher levels of IL-8 and IL-1β) [171]. Increased systemic inflammation among adults with asthma is evident by an increase in circulating pro-inflammatory cytokines and neutrophils [172, 173]. For example, IL-8 has been shown to be upregulated among adults with asthma and plays an important role in the inflammatory cascade associated with asthma [104]. Furthermore, higher levels of IL-8 among adults with asthma has been associated with worse asthma control [105].

Investigating the impact of various treatment strategies that lead to reductions in local and systemic inflammation among adults with asthma is warranted.

One such strategy that may serve to reduce local and systemic inflammation among adults with asthma may be through exercise training. Previous research has found that aerobic exercise can reduce inflammation among adults with asthma [109]. Specifically, following a 12-week intervention, adults with asthma in the exercise group experienced a greater reduction in serum levels of cytokines interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) when compared to the non-exercise control asthma group (n=23). Interestingly, the exercise group and non-exercise group did not experience a significantly different reduction in IL-8 from pre to post-intervention [109]. Serum IL-8 has been shown to be upregulated among adults with asthma [105] and as such, strategies to reduce IL-8 levels may have important implications among this population. Among healthy adults, exercise training has been shown to increase plasma levels of anti-inflammatory cytokines, including IL-1Ra [116]. Unfortunately, less is known about the response of IL-1Ra to exercise training among adults with asthma.

Despite the benefits of exercise training noted above, acute activity triggers exercise induced asthma (EIA) in approximately 90% of adults with asthma [3]. Higher levels of IL-8 among adults with asthma have been associated with worse asthma control (15) (i.e. increased coughing, wheezing, greater declines in forced expiratory volume in 1 second (FEV_1)). As such, it is possible that those with a more severe EVH response (i.e. greater decline in FEV_1 following the challenge) may exhibit higher inflammation; however, this has yet to be determined.

To date, the majority of literature on inflammation and exercise training has been assessed via invasive methods such as blood draws and as such, requires highly trained personnel and a willingness of participants to allow such invasive measures. In recent years, assessment of inflammation assessed non-invasively via saliva has grown in popularity [174].

Thus, the purpose of this study was to determine if a 6-week exercise intervention would lead to a reduction in pro-inflammatory salivary markers of inflammation IL-8 and IL-1β, and anti-inflammatory marker IL-1Ra and CXCL10/IP-10. It was hypothesized that adults with asthma would experience greater reductions in IL-8 and IL-1β and greater increases in salivary concentrations of IL-1Ra following exercise training when compared to healthy adults, given the up-regulation of inflammation associated with asthma [105]. Secondly, it was hypothesized that adults with asthma who experienced the greatest reduction in FEV_1 following the EVH challenge would exhibit higher levels of pro-inflammation when compared to those with a smaller FEV_1 decline [175, 176].

METHODS

Study Design

A 6-week HIIT intervention using a quasi-experimental study design was conducted among adults with and without asthma. Adults with asthma and healthy controls completed a 6-week high intensity interval training (HIIT) intervention, 3 times per week. Measurements were taken pre-exercise and post-exercise during the first HIIT (T1) and last HIIT (T2) sessions to determine the overall effect of the intervention as well as the the ***acute*** inflammatory response to exercise.

Participants

Inclusion in the ***control group*** was limited to adults aged 18-44 years, self-reported as moderately active, and non-smoking. Inclusion in the ***asthma group*** was further limited to those who had a self-report physician diagnosis of asthma, those with a current prescription for a short-acting bronchodilator, and to those who had a positive response to the EVH challenge (described elsewhere) [69]. All participants provided written informed consent prior to participation in the study. This study was approved by the Research Ethics Board at the University of Ontario Institute of Technology.

Experimental Procedure

Participants completed a maximal exercise test to determine baseline cardiorespiratory fitness and peak power output (PPO) to establish the workload of the HIIT protocols. A warm up at 25 Watts (W) for 4 minutes preceded the test, which included a ramp protocol in which the intensity increased by 1 W every 2 seconds, until volitional exhaustion. On a separate day, participants began the HIIT intervention consisting of a 4-minute warm up at 25 W followed by 10% PPO for 1 minute, 90% PPO for 1 minute, repeated 10 times. Participants completed the training 3 times per week for 6-weeks. Following the 6-week intervention, participants completed a second maximal exercise test.

Saliva Collection and Analysis

Unstimulated whole saliva was collected via the passive drool method. Two saliva samples were collected at two time points. A sample was collected pre- and 15 minutes post-exercise at T1 and T2 until the 2mL vial was full. Twenty-four hours prior to collection, participants were asked to refrain from consuming caffeinated beverages at least 4 hours

prior to testing, and to refrain from consuming a heavy meal at least 2 hours prior to testing. Upon arrival to the laboratory, participants rinsed their mouths with water, in order to discard of any debris in the mouth. Saliva was then collected and samples were immediately stored at -80^{o}C until analysis.

Saliva samples were thawed and centrifuged for 15 minutes at 1500 x *g* to pellet mucins and other debris. Prior to cytokine analysis, total protein content within each saliva sample was determined using the Coomassie PLUS Protein Assay Reagent (Thermo Fisher Scientific, MA, USA). Levels of IL-8 (R&D Systems), IL-1Ra (R&D Systems, Catalog), and tumor necrosis factor (TNF) α (R&D Systems) were determined in both healthy and asthma groups, while levels of IL-1β (R&D Systems) and CXCL10/IP-10 (R&D Systems) were also determined in the asthma group using enzyme-linked immunosorbent assays (ELISA) following manufacturer's protocols (R&D Systems, MN, USA). IL-1β and CXCL10/IP-10 were assessed in the asthma group only due to funding restraints. ELISAs were processed in 96-well high-binding microplates (Greiner Bio-One, Frickenausen, Germany) and plates were read at a wavelength of 450 nm using a Synergy HTTR microplate reader (Bio-Tek Instrumentation, VT, USA). Cytokine data was standardized with the amount of total protein found within each saliva sample and expressed as pg/mL and pg/μg of protein.

Statistical Analyses

All data are presented as means and standard errors of the mean. Data were tested for normality using the Shapiro-Wilk test. IL-8, IL-1Ra, CXCL10/IP-10, and IL-1β concentrations were transformed for normality. Transformed data showed consistent results with the non-transformed data and as such, non-transformed data are reported. For

some samples, cytokine concentrations were below the limit of quantification (LoQ). In such cases, the value was imputed using the following equation:

Below Limit of Quantification (BLQ) = LOQ/$\sqrt{2}$ x dilution factor

An independent samples t-test was conducted to determine between group differences in IL-8 and IL-1Ra concentrations at T1. Analyses could not be conducted for the acute response to exercise at T1 and T2 due to insufficient data. A paired samples t-test was conducted to determine within group differences in IL-8 and IL-1Ra from T1 to T2. A one-way analysis of covariance (ANCOVA) was conducted to determine between group differences in IL-8 and IL-1RA at T2, while controlling for values of IL-8 and IL-1Ra at T1. Effect sizes were reported using partial eta squared (h_p^2) values from the ANCOVA.

Among the asthma group, a Pearson correlation was conducted to determine the relationship between the decline in FEV_1 post-EVH to levels of IL-8, IL-1Ra, CXCL10/IP-10, and IL-1β at T1.

All statistics were completed in IBM SPSS statistics 26.0 (Armonk, NY) and statistical significance was declared at $p<0.05$.

RESULTS

Participants in the asthma group (n=20) had an average age of 22 years ± 3.3 and 11/20 were female. Participants in the control group (n=12) had an average age of 21 years ± 1.9 and 8/12 were female. Participants did not differ in height, weight, or VO_2max. Participant characteristics are displayed in Table 1.

TABLE 3.1 Participant Characteristics at T1

Characteristic	**Asthma n=20**	**Healthy Control n=12**
M/F	9/11	4/8
Age	22 ± 3.3	21 ± 2.0
Height (cm)	169.5 ± 7.2	165.5 ± 8.1
Weight (kg)	73.8 ± 12.8	69.9 ± 11.8
Maximal Oxygen Consumption (VO_2max) (ml/kg/min)	32.9 ± 8	34.5 ± 11.8

Independent samples t-test revealed a trend towards the asthma group having higher levels of IL-8 at T1 (Asthma: 0.2 ± 0.1; Control: 0.1 ± 0.1, p=0.07).

Chronic Response to Exercise

Results from the ANCOVA revealed that adults with asthma had significantly lower levels of IL-1Ra at T2 when compared to healthy controls ($F(11.7, 1)$ $p<0.01$, $h_p^2 = 0.3$). No between group differences in IL-8 were observed at T2. Figures 1a-b illustrate between group differences in IL-8 and IL-1Ra concentrations at T1 and T2.

Figure 1a. IL-8 at T1 and T2 between adults with asthma and healthy controls

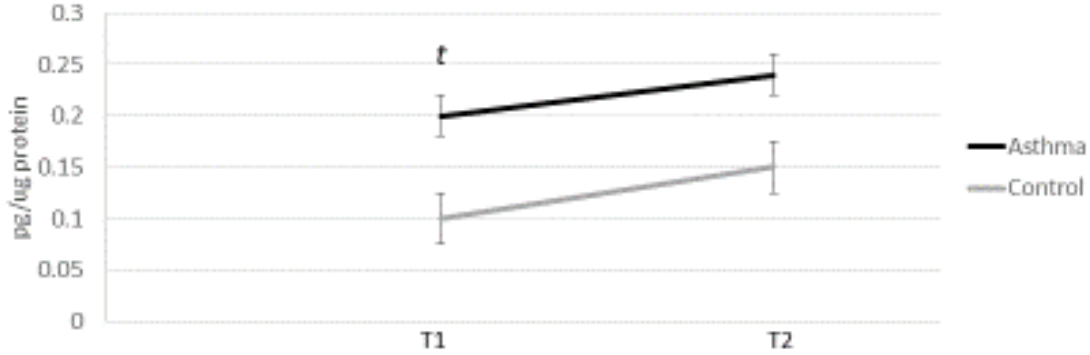
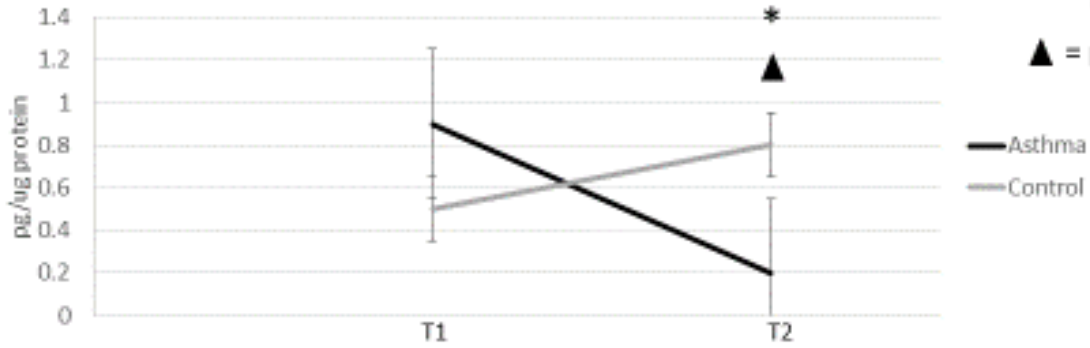


Figure 1b. IL-1Ra at T1 and T2 between adults with asthma and healthy controls



* = p<0.05 between T1 and T2 between groups

t = p<0.1 between T1 and T2 between groups

▲ = p<0.05 between T1 and T2within asthma group

Figure 1a. IL-8 at T1 and T2 between adults with asthma and healthy controls

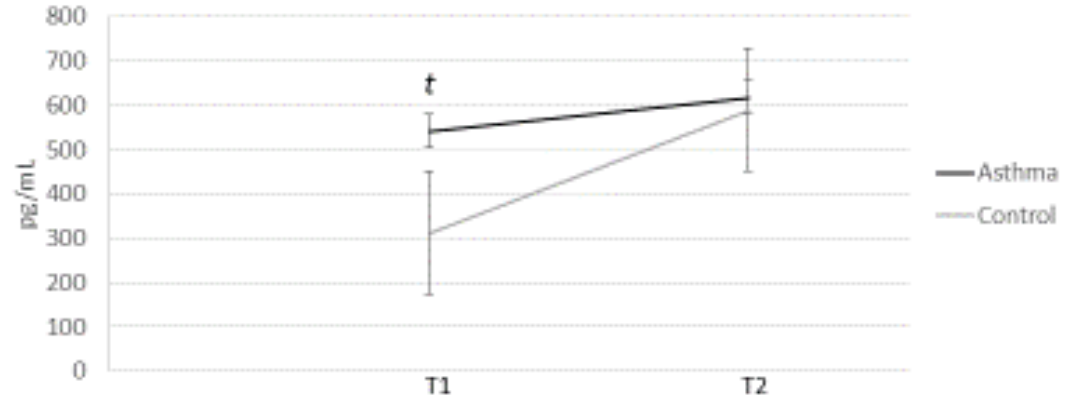
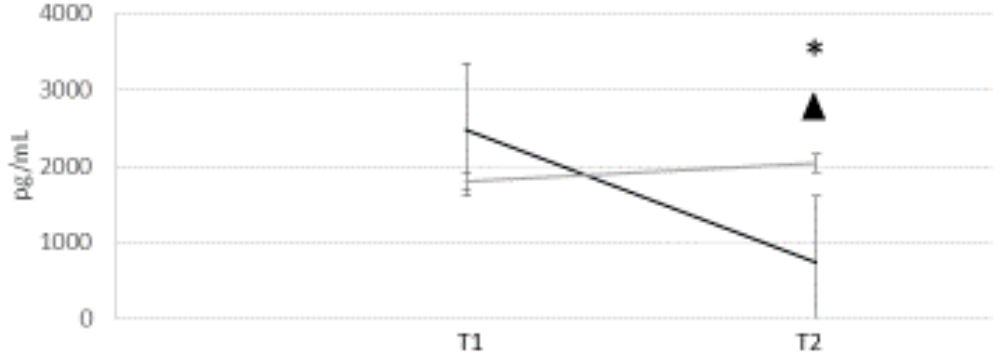


Figure 1b. IL-1Ra at T1 and T2 between adults with asthma and healthy controls



* = p<0.05 between T1 and T2 between groups

t = p<0.1 between T1 and T2 between groups

▲ = p<0.05 between T1 and T2within asthma group

No within group differences in IL-8 or IL-1Ra concentrations were observed among the healthy control group from T1 to T2.

Within the asthma group, a significant reduction in IL-1Ra concentration (Asthma T1: 0.9 ± 0.6pg/ug protein; Asthma T2: 0.2 ± 0.16pg/ug protein, $p<0.01$) and a significant reduction in IL-1β concentration (Asthma T1: 0.05 ± 0.046pg/ug protein; Asthma T2: 0.01 ± 0.016pg/ug protein, $p=0.01$) was observed from T1 to T2. No within group differences in CXCL10/IP-10 from T1 to T2 were observed. Figures 2a-b illustrate changes in CXCL10/IP-10 and IL-1β concentrations among the asthma group from T1 to T2.

Figure 2a. IP-10 at T1 and T2 among adults with asthma

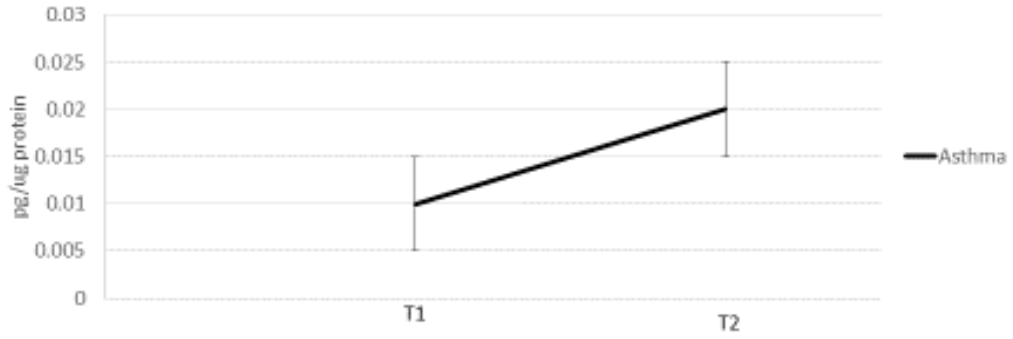
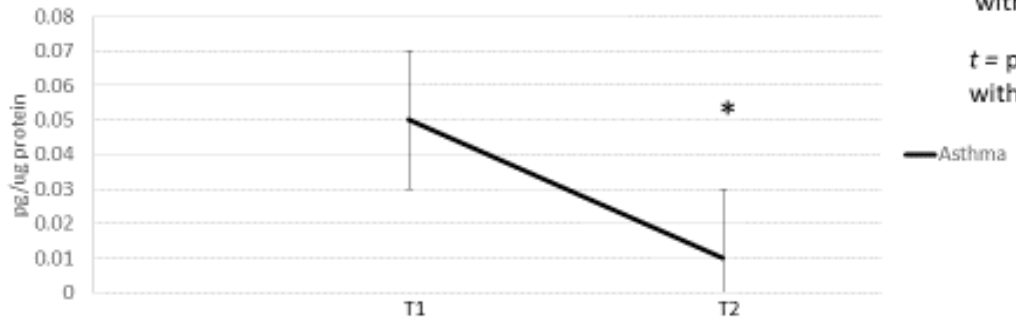


Figure 2b. IL-1B at T1 and T2 among adults with asthma



* = p<0.05 between T1 and T2 among a
with asthma

t = p<0.1 between T1 and T2 among adu
with asthma

Figure 2a. IP-10 at T1 and T2 among adults with asthma

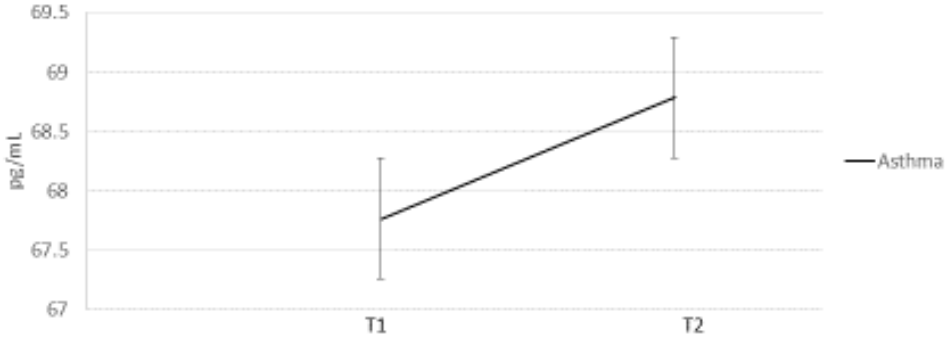
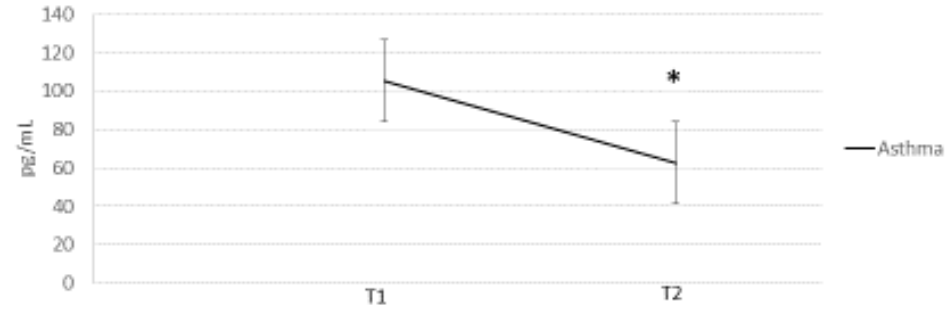


Figure 2b. IL-1B at T1 and T2 among adults with asthma



* = p<0.05 between T1 and T2 among adult with asthma

t = p<0.1 between T1 and T2 among adults with asthma

Among the asthma group, a moderate positive correlation ($r(18) = 0.33$, $p=0.1$) was observed between FEV_1 decline post-EVH and IL-8 at T1, suggesting greater bronchoconstriction following the EVH challenge was moderately positively correlated with higher levels of IL-8.

Acute Response to Exercise

Between group differences in the acute response in IL-8 and IL-1Ra could not be analyzed due to >50% of values were BLQ[177].

DISCUSSION

The primary purpose of this study was to determine if a 6-week exercise intervention was effective in reducing salivary concentrations of the pro-inflammatory marker IL-8 and increasing salivary concentrations of the anti-inflammatory marker IL-1Ra among adults with asthma and healthy controls. Our primary finding is that, contrary to our hypothesis, no changes occurred in the salivary concentrations of IL-8 from T1 to T2 and that adults with asthma experience a decrease in salivary concentrations of the anti-inflammatory marker IL-1Ra from T1 to T2, while controls experienced no changes. Our secondary finding is that the decline in FEV_1 following the EVH challenge is moderately positively correlated with levels of IL-8.These findings suggest that HIIT may play an important role in the inflammatory profile of adults with asthma by improving the IL-1β /IL-1Ra ratio, despite no changes in IL-8.

In the present study, salivary IL-8 concentrations did not change from T1 to T2 among adults with asthma and healthy controls. One possible explanation for the lack of change observed post-intervention in IL-8 may be related to the timing of which IL-8 was

collected. Although all participants were instructed to provide a saliva sample 30 minutes post-exercise, saliva flow rate varied greatly among participants and as such, IL-8 levels could have been restored by the time the sample was collected. For example, an acute bout of high intensity exercise among adults with asthma (n=39) led to an increase plasma IL-8 immediately post-exercise but levels returned to baseline values 1 hour post-exercise [108]. This suggests that the timing of assessment of IL-8 ay be key in understanding its' response to acute and chronic exercise. The lack of changes in salivary markers of IL-8 following HIIT in the present study is in line with previous research that compared the impact of a 12-week continuous exercise program (twice per week) on serum levels of IL-8, in which no changes were observed between an asthma exercise and an asthma control group [109]. Participants in the study by Franca-Pinto and colleagues (2015) had moderate to severe asthma [109] whereas, participants in the present study had well-controlled asthma, suggesting that IL-8 may not be responsive to exercise training regardless of asthma control. Future research is required in order to determine the optimal timing of IL-8 assessment in order to better understand the impact of exercise training on this cytokine.

Contrary to our hypothesis, adults with asthma experienced a reduction in salivary concentrations of IL-1Ra following 6-weeks of exercise training. These findings differ from previous research reporting that in mouse models of asthma, aerobic exercise training leads to an increase in IL-1Ra expression in the bronchials [178]. Of note, our findings of a reduction in salivary IL-1Ra levels following exercise training may be related to the reduction observed in salivary IL-1β levels. IL-1β is elevated in the sputum of individuals with stable and exacerbating asthma [100] and the dysregulation between

the IL-1β /IL-Ra ratio is important for the inflammation observed among adults with asthma [117]. As such, it is possible that a reduction in IL-1β following exercise training may explain the reduction in IL-1Ra given the dampened pro-inflammatory profile. Thus, exercise training may reduce levels of the pro-inflammatory marker IL-1β and in turn reduce levels of the anti-inflammatory marker IL-1Ra. Our data suggest that the response of salivary concentrations of IL-1Ra differ between adults with asthma and healthy adults and as such, future research should be conducted to determine the mechanisms responsible for this difference to better tailor treatment options for adults with asthma.

. CXCL10/IP-10 increases the hyper-reactivity in the airways in asthma thus, options that may lead to a reduction in this cytokine are key in improving bronchoconstriction among adults with asthma [112]. This study is the first, to our knowledge, to determine the impact of exercise training on CXCL10/IP-10 among adults with asthma Previous research among healthy adults (n=413) has reported that an 8-week aerobic exercise training program leads to a reduction in serum CXCL10/IP-10 [113]. These discrepancies may be due to a variety of factors. First, it may be that our study was too short to detect a difference in CXCL10/IP-10 (i.e. 6 weeks vs 8 weeks). Second, it could be that exercise training among adults with asthma may not have the same effect on salivary CXCL10/IP-10 levels when compared to healthy controls. Discrepancies may also be due to the different methods of assessing CXCL10/IP-10 (i.e. serum vs saliva). The present study did not compare CXCL10/IP-10 between adults with asthma and healthy controls due to funding limitations and as such, we are unable to determine potential differences in CXCL10/IP-10 following exercise training between groups.

Results of the present study should be interpreted in light of the following limitations. First, the optimal timing for assessing cytokines via the saliva varies among cytokines and as such, it is possible that our assessment time point of 30 minutes post-exercise may have not been optimal for some cytokines assessed. As well, saliva flow rate varies greatly among individuals which may have led to greater variability in timing of assessments and may explain why some cytokines were BLQ (e.g. cytokine levels had restored to normal by the time measurement was completed). , Second, the homogeneity of our sample in regards to age and asthma control limits the generalizability of our findings. Future research should aim to determine the impact of HIIT among adults with varying levels of asthma control and among adults of different ages. Finally, the lack of an asthma control group confines the generalizability of our findings. Future larger scale randomized control trials should be conducted in order to better understand the impact of exercise training among adults with asthma.

In conclusion, it appears that a 6-week exercise intervention elicits a reduction in IL-1Ra among adults with asthma and elicits no changes in IL-8 among adults with asthma and healthy controls. Furthermore, it appears that the decline in FEV_1 following the EVH challenge is associated with levels of IL-8 among adults with asthma and thus, may lend additional benefits to the EVH challenge. These findings provide novel insight into the impact of exercise training on salivary pro and anti-inflammatory cytokines among adults with asthma and healthy controls.

Connecting Statement I

In the previous chapter, we found that a 6-week HIIT intervention does not improve the salivary concentrations of IL-8 among adults with asthma or among healthy adults. Furthermore, we observed that adults with EIBC experience a reduction in the salivary concentrations of anti-inflammatory IL-1Ra.. The dysregulation of the IL-1β /IL-Ra ratio is an important contributor in the systemic inflammation observed among adults with asthma and our findings suggest that regulation of this ratio may be improved through HIIT. The lack of changes in the salivary concentrations of IL-8 and may suggest that a 6-week HIIT intervention is not long enough to see reductions in this cytokine. In the following chapter we analyze data related to the changes in ventilation that occur as a result of HIIT to further elucidate this possible relationship.

Chapter 4: Comparing the pulmonary responses to high intensity interval training among adults with and without exercise induced bronchoconstriction

Title: Comparing the pulmonary responses to high intensity interval training among adults with and without exercise induced bronchoconstriction

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Abstract

PURPOSE: To determine if the response of ventilation, respiratory rate (RR), tidal volume (V_T), breathing reserve ((V_E/MVVmax), and peak tissue oxygen desaturation index (TSI) differs during maximal exercise pre (T1) and post (T2) a 6-week high intensity interval training (HIIT) intervention between adults with exercise induced bronchoconstriction (EIBC) and healthy adults. **METHODS:** A 6-week HIIT intervention was conducted. Participants completed a maximal exercise test at the beginning and end of the intervention to determine improvements in maximal oxygen consumption (VO_2max), $V_E$max, RRmax, $V_T$max, (V_E/MVVmax), and TSI. **RESULTS:** A total of 20 adults with EIBC (age: 21.4 ± 2.4) and 12 healthy controls (age: 22.5 ± 3.4), completed the 6-week HIIT intervention. Results from the one-way analysis of covariance (ANCOVA) revealed no improvements in $V_E$max, RRmax, $V_T$max, or V_E/MVV among the asthma group from pre to post-intervention; whereas, the control group did experience such improvements. Adults with asthma had a higher RRmax (asthma: 49.8 ± 17.5, control: 42.9 ± 8.5, p=0.04) and $V_T$max (asthma: 2.4 ± 0.3 mL, control: 1.8 ± 0.5 mL, p=0.02) when compared to healthy adults at T1; however, these differences were no longer evident at T2. Adults with asthma did not experience improvements in $V_E$max, $V_T$max, RRmax, or peak TSI from T1 to T2; whereas, healthy adults experienced significant improvements in $V_E$max, $V_T$max, and RRmax, **CONCLUSION:** A 6-week HIIT intervention does not elicit improvements in ventilation among adults with asthma; however, healthy adults are able to improve the ventilation response following 6-weeks of HIIT.

INTRODUCTION

During aerobic exercise, ventilation (V_E) increases in response to the increased requirement for oxygen (O_2) and increased production of carbon dioxide (CO_2). The increase in V_E occurs as a result of an increase in respiratory rate (RR) and/or tidal volume (V_T) [179]. In healthy, normal adults, V_T and RR increase with increasing exercise intensity. At higher intensities of exercise, ventilatory efficiency (V_E/ VCO_2) is reduced due to greater increases in RR than V_T. Many adults with asthma experience hyperventilation [135], which further increases RR leading to even greater reductions in ventilatory efficiency during exercise. Despite a reduction in efficiency, exercise performance is not typically limited by ventilation among adults with asthma [180].

The breathing reserve (V_E/maximal voluntary ventilation (MVV)), determined by assessing maximal ventilation during exercise (i.e. ventilatory demand) and maximal voluntary ventilation at rest (i.e. ventilatory capacity) is lower among those with obstructive lung conditions such as asthma [181]. Ventilatory demand is dependent on the metabolic demand of the exercise as well as individual differences (i.e. body weight, behavioural factors) [182]. Ventilatory capacity, is dependent upon mechanical factors such as airflow limitation, a common characteristic among adults with asthma [182]. As such, the lower breathing reserve observed among adults with obstructive lung conditions may be explained by the altered variable airflow limitation (i.e forced expiratory volume in 1 second (FEV_1)) experienced at rest (i.e. ventilatory capacity) [183]. Among healthy adults, improvements in ventilatory capacity following 3 weeks of high intensity exercise have been observed [184] and among adults with asthma improvements in ventilatory capacity following a 10-week continuous exercise program have been observed

[185].The impact HIIT on ventilatory capacity and breathing reserve between adults with asthma and healthy controls has not yet been determined.. It is possible that a higher exercise stimulus (e.g. high intensity intervals) may allow for improvements in ventilatory capacity among adults with asthma, similar to what has been observed in healthy adults [184].

High intensity *interval* training (HIIT) is composed of brief bouts of high intensity activity followed by intermittent recovery periods and is well-tolerated among adults with asthma, as evidenced by a smaller reduction FEV_1 pre and post-HIIT compared to continuous exercise [19]., The V_E response to acute HIIT remains unclear and the adaptations associated with chronic HIIT among adults with asthma has not been determined. Various studies have reported that exercise training does not improve FEV_1 among adults with asthma [10, 186]; however the impact of chronic HIIT on V_E, V_T, RR, MVV, and ventilatory efficiency is unclear and could provide novel insight into the similarities and/or differences of the ventilatory profile between adults with asthma and healthy controls. It is possible that the high intensity nature of HIIT may result in a lower breathing reserve among adults with asthma acutely due to the intermittent recovery periods; however, as fitness improves (i.e. VO_2max) through chronic training, V_E, V_T, RR, and the breathing reserve may also improve among adults with asthma.

The high intensity nature of HIIT may allow for substantial improvements in fitness (i.e. VO_2max) while experiencing less asthma related symptoms (e.g. reduced dyspnea) due to the intermittent recovery periods [162]. The primary purpose of this study was to determine if a 6-week HIIT intervention leads to improvements in ventilation (i.e. higher maximal ventilation) and its components (e.g. V_T, RR) among adults with asthma when

compared to healthy adults. It was hypothesized that adults with asthma would experience higher V_E during acute exercise due to the likelihood of hyperventilation and that both groups would experience improvements in V_E, V_T, and RR from pre to post-exercise training; however, healthy adults would experience greater improvements in V_E/MVV (i.e. breathing reserve), due to the ventilatory limitations (i.e. MVV at baseline) associated with asthma. The secondary purpose of this study was to determine whether differences in ventilatory efficiency at baseline was associated with differences in tissue saturation in the periphery, and whether HIIT would lead to improved efficiency and thus improved tissue saturation acutely and chronically. It was hypothesized that adults with EIBC would exhibit lower tissue saturation due to lower ventilatory efficiency among those with asthma.

METHODS

Study Design

A 6-week HIIT intervention using a quasi-experimental study design was conducted to compare changes in ventilatory measures of $V_E$max, $V_T$max, MVV, V_E/MVV, and RRmax to HIIT at pre (T1) and post (T2) intervention between adults with asthma and healthy adults (control).

Participants

Inclusion was limited to adults between the ages of 18-44 years, non-smokers, and those who were currently meeting the minimum physical activity guidelines of 150 minutes of moderate-vigorous intensity physical activity per week. For the ***asthma group***, inclusion was further limited to those who had physician diagnosed asthma, a current prescription

for a short-acting bronchodilator, and those who had a positive response to the eucapnic voluntary hyperpnea (EVH) challenge (described below). Inclusion in the ***control group*** was limited to those who were free of any chronic conditions.

All participants provided written informed consent prior to participation in the study. This study was approved by the Research Ethics Board at the University of Ontario Institute of Technology.

Overview of Sessions

Familiarization & Pre-Screening

All participants who met the eligibility criteria were familiarized with hand-held spirometry, the head-set and mouthpiece, near infrared spectroscopy (NIRS) probe placed on each quadriceps muscle, and the cycle ergometer.

Participants who self-reported having a physician diagnosis of asthma also completed the EVH challenge to confirm exercise induced bronchoconstriction. This procedure has been previously described [69]. Briefly, participants were asked to refrain from taking their short-acting bronchodilator 8 hours prior to the challenge. Upon arrival to the laboratory, participants completed three repeatable lung function measurements using a hand-held spirometer (EasyOne, Medizintechnik AG, Zurich, Switzerland) and the highest FEV_1 value obtained was used to determine the target ventilation for the EVH challenge. Participants completed a single stage 6-minute challenge at a target ventilation of 25-30x FEV_1. Participants inhaled room temperature dry air composed of 5% CO_2, 21% O_2 and balance N_2. Following the 6-minute challenge lung function was re-assessed in duplicate at 5, 10, 15, and 20 minutes post to determine the decline in FEV_1. A positive

response to the EVH challenge was considered as a 12% or greater decline in FEV_1 from pre to post-EVH. The decline in EVH was calculated as follows:

% Fall in FEV_1 = 100 [FEV_1 pre-challenge – FEV_1 post-challenge] / FEV_1 pre-challenge

First and Last HIIT Sessions: During the first and last HIIT session participants were fitted with the headset, mouthpiece, and NIRS probe. Participants completed the exercise protocol (described below) and post-exercise measures of lung function using hand-held spirometry was assessed at minutes 5, 10, 15, and 20 to determine the decline in FEV_1 post-exercise.

Maximal Exercise Test: Participants completed a ramp to maximal exercise test pre (T1) and post (T2) 6-week HIIT intervention. The protocol for the maximal exercise tests were as follows: 4-minute warm up at 25 W followed by a 1W per 2 second increase until volitional exhaustion. Peak power output was recorded as the final stage completed within the target RPM and was used to determine exercise intensity for the subsequent HIIT sessions as follows 90% PPO for 1 minute, 10% PPO for one minute, repeated 10 times. HIIT sessions were completed 3 times per week for 6-weeks.

Exercise Intervention

Participants completed 6 weeks of HIIT; 3 times per week on a cycle ergometer. HIIT protocols were as follows: 5 minute warm-up at 25 Watts, followed by 10% peak power output for 1 minute, 90% peak power output for 1 minute, repeated 10 times.

Lung Function: At the beginning of the first and last HIIT session, participants performed 3 repeatable lung function assessments using a handheld spirometer (EasyOne diagnosotic spirometer, ndd Medizintechnik AG, Switzerland), according to the

American Thoracic Society Guidelines (Miller et al., 2005). At minutes 5, 10, 15, and 20 post-exercise spirometry was re-assessed in duplicate. The decline in FEV_1 was calculated as follows:

% Fall in FEV_1 = 100 [FEV_1 pre-challenge – FEV_1 post-challenge] / FEV_1 pre-challenge

The highest FEV_1 value at each time point post-exercise was used to determine FEV_1 decline. The maximum decline following exercise were used for statistical analysis.

Maximal voluntary ventilation (MVV) was determined using the following equation: [182, 187, 188]

MVV = FEV_1 baseline x 40

Ventilatory measures: Upon arrival to the laboratory, height and weight were assessed using a standardized medical scale (Detecto, USA), and resting heart rate and blood pressure were assessed following a 5-minute rest period. Baseline lung function was assessed using spirometry. Participants in the EIBC group were permitted to take to puffs of their short-acting bronchodilator and lung function was re-assessed 15-minutes post medication to determine reversibility. Reversibility was defined as > 12% and 200mL increase in FEV_1 from baseline[66]. FEV_1 % predicted was calculated using the following formula:

FEV_1% predicted = Race * 1.08 * ((0.043 * height) – (0.029 * age) – 2.49).

Expired gas was collected through a pneumotachograph and analyzed using an automated gas collection system (Parvo Medics 2400, USA). Breath by breath values ventilation

(V_E), tidal volume (V_T), respiratory rate (RR), volume of exhaled carbon dioxide (VCO_2), and maximal oxygen consumption (VO_2max) were analyzed. All ventialtory parameters were calculated by averaged the 5 breaths surrounding each point. The values at these points were used for statistical analysis.

Tissue Oxygen Saturation (TSI):

A two-wavelength (745 and 855nm), continuous wave NIRS system using spatially resolved spectrocscopy was used to measure tissue saturation (TSI) (Oxymon MK III, The Netherlands). TSI was monitored continuously throughout each maximal exercise test and the first and last exercise sessions. The NIRS probe was secured over the muscle belly of the vastus lateralis muscle, 12cm from the knee joint, along the vertical axis of the thigh. Data was sampled at 50 Hx and then down sampled to yield second-by-second data. The distance between the transmitter and received was set at 4.0 cm. The background and additional details of NIRS is described elsewhere [189].

TSI provides an indication of oxygen saturation in the tissue by representing a ratio of oxygenated hemoglobin to total hemoglobin. TSI values were normalized for each participant to the average of the 30 to 60 seconds prior to the start of exercise during warn-up. For statistical purposes, this baseline value represented 100%. Peak desaturation was determined as the lowest 5 second period of TSI at the end of the first high intensity interval was used as 0% so that changes could be observed across intervals and compared. TSI peak desaturation was used for statistical analysis.

Statistical Analysis

Means and standard deviations were used to describe the sample. Independent samples t-test were conducted to determine differences in baseline (T1) characteristics. Paired samples t-test were conducted to determine within group differences from T1 to T2. A one-way analysis of covariance (ANCOVA) was conducted to determine differences between groups and sexes at T2 while controlling for differences at T1 for FEV_1, VO_2max, $V_E$max, RRmax, $V_T$max, V_E/MVV, and peak TSI. An ANCOVA was also used to determine differences during acute exercise during each minute of HIIT session 18, while controlling for each minute of HIIT session 1 (i.e. baseline) measures of each outcome. Effect sizes were reported using partial eta squared (h_p^2) values from the ANCOVA.

All statistics were completed in IBM SPSS statistics 26.0 (Armonk, NY) and statistical significance was declared at $p<0.05$.

Sample Size

GPOWER statistical software indicated that in order to detect a significant improvement in $V_E$max from pre to post-intervention, using a medium effect size (0.5) with an alpha of 0.05 and a power of 0.95, 16 participants would be required for this study.

RESULTS

A total of 20 adults with asthma and 12 healthy adults completed the 6-week HIIT intervention. Groups did not differ on age (asthma: 21.4 ± 2.4, control: 22.5 ± 3.4, p=0.4), height (asthma: 169.5 ± 7.1, control: 165.5 ± 8.0, p=0.1), weight (asthma: 73.8 ± 12.8, control: 69.7 ± 11.9, p=0.3), or VO_2max (asthma: 32.9 ml/kg/min ± 8.0, control: 38.6

ml/kg/min ± 8.2, p=0.6) at T1. Adults with asthma had a higher RRmax (asthma: 49.8 ± 17.5, control: 42.9 ± 8.5, p=0.04) and $V_T$max (asthma: 2.4 ± 0.3 mL, control: 1.8 ± 0.5 mL, p=0.02) when compared to healthy adults at T1. .

Both groups experienced a significant improvement in VO_2max from T1 (Asthma: 32.9 ± 8ml/kg/min; Control: 34.5 ± 11.8ml/kg/min) to T2 (Asthma: 38.6 ± 8.2, p<0.01; Control: 38.9 ± 12.3, p<0.01). Adults with asthma did not experience improvements in $V_E$max, $V_T$max, RRmax, or peak TSI from T1 to T2. Healthy adults experienced significant improvements in $V_E$max, $V_T$max, and RRmax, see Table 1. Additional within and between group differences at T1 and T2 are displayed in Table 1.

TABLE 4.1. Pre-Intervention Baseline Characteristics

Characteristic	ASTHMA T1 (n=20)	ASTHMA T2 (n=20)	CONTROL T1 (n=12)	CONTROL T2 (n=12)	p-value between groups at T1
Age (years)	22.5 ± 3.2	22.5 ± 3.2	21.1 ± 1.9	21.1 ± 1.9	p=0.7
Males/Females	9/11	9/11	4/8	4/8	
Height (cm)	169 ± 7.2	169 ± 7.2	165.5 ± 8.1	165.5 ± 8.1	p=0.4
Weight (kg)	73.8 ± 12.8	74.0 ± 13.1	69.9 ± 11.7	68.9 ± 11.4	p=0.9
Resting Heart Rate (bpm)	79.1 ± 13.6	81 ± 13.4	81 ± 11.9	77.5 ± 12.3	p=0.4
Forced Expiratory Volume in 1 Second	3.6 ± 0.6	3.1 ± 0.7	3.5 ± 0.7	3.3 ± 1.2	p=0.4
Forced Expiratory Volume in 1 Second Percent Predicted (%)	85.5 ± 6.7	85.1 ± 6.1	86.6 ± 7.9	85.6 ± 6.4	p=0.3
Forced Vital Capacity (L)	4.3 ± 0.8	3.8 ± 0.9	4.0 ± 0.8	4.0 ± 0.8	p=0.5
Maximal Voluntary Ventilation (MVV)	147.9 ± 25.7	143.1 ± 31.7	140 ± 29.4	138.8 ± 29.9	p=0.4
Maximal Oxygen Consumption (ml/kg/min)	32.9 ± 8	38.6 ± 8.2†	34.5 ± 11.8	38.9 ± 12.3†	p=0.8
Ventilation Maximum	97.8 ± 22.2	108.7 ± 29.5	82.8 ± 20.1	101.8 ± 18.1†	p=0.7
Respiratory Rate Maximum	49.8 ± 17.5	47.5 ± 10.3	42.9 ± 8.5*	55.3 ± 6.4 †	p=0.04
Tidal Volume Maximum (mL)	2.4 ± 0.3	2.6 ± 1.0	1.8 ± 0.5*	2.5 ± 0.6†	p=0.02

Breathing Reserve (V_E/MVV)	0.67 ± 0.2	0.64 ± 0.1	0.62 ± 0.1	0.74 ± 0.1	p=0.1

*****p<0.05 between EIBC and control

†p<0.05 within group from T1 to T2

Maximal Exercise Response

No between group differences were observed in VO_2max (F(0.5, 1) p=0.8, h_p^2 <0.01)), $V_E$max (F(0.0,1) p=0.9, h_p^2 <0.01)), $V_T$max (F(0.7, 1) p=0.3, h_p^2 = 0.02), RRmax (F(7.4, 1) p=0.07, h_p^2 0.1), or peak TSI (F(1.7, 1) p=0.7, h_p^2 = 0.04) at T2. Figure 1(a-d) depicts the ventilatory patterns between groups and sexes at T1 and T2.

Figure 2.1a-c: Ventilation Maximum Pre and Post-Intervention

Figure 1a. VEmax Asthma vs Non Asthma

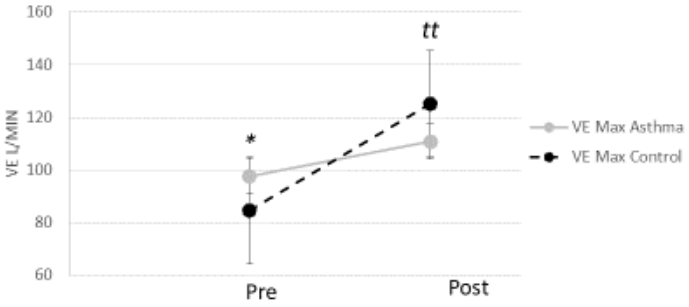


Figure 1b. Vemax Asthma Males vs Control Males

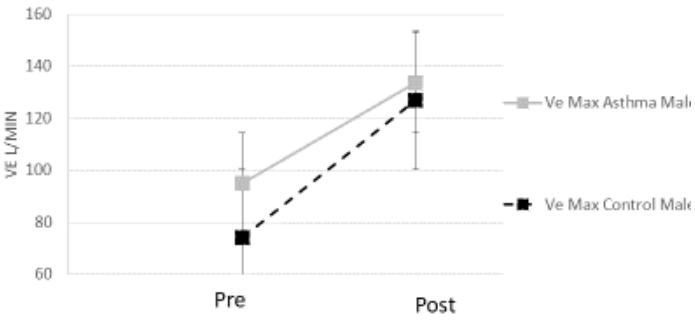
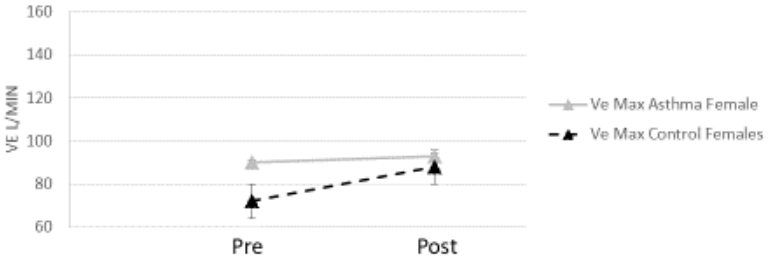


Figure 1c. VEmax Asthma Females vs Control Females



*= p<0.05 b/w groups
tt=p<0.05 within control group
ŧ=p<0.05 within asthma group

Figure 2.2 a-c: Tidal Volume Maximum Pre and Post-Intervention

Figure 2a. VTmax Asthma vs Non Asthma

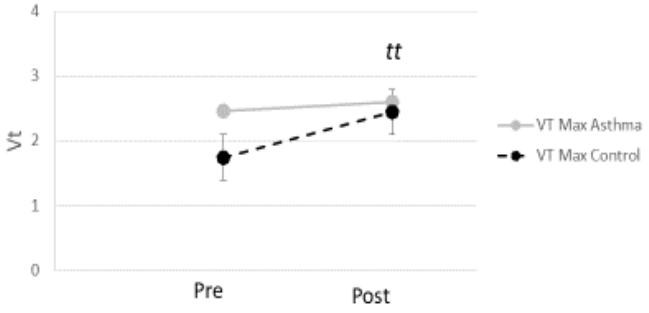


Figure 2b. Vtmax Asthma Males vs Control Males

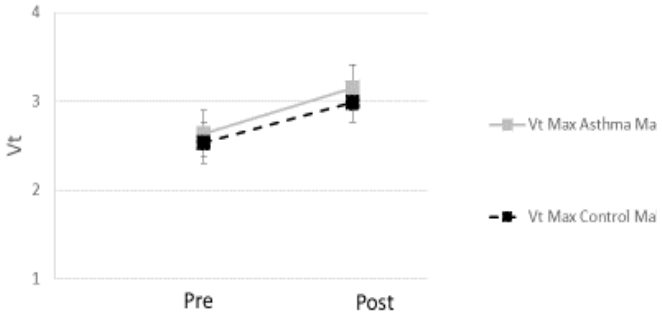
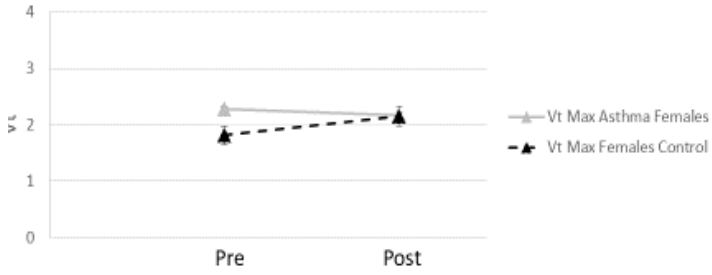
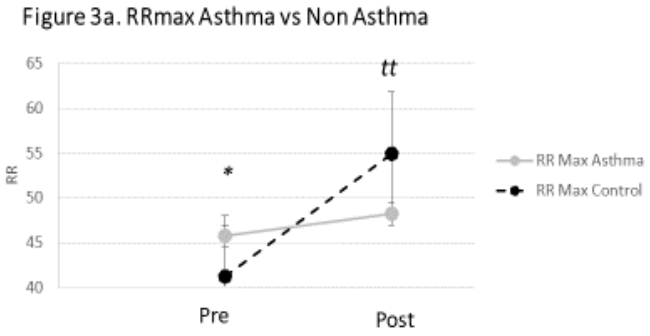


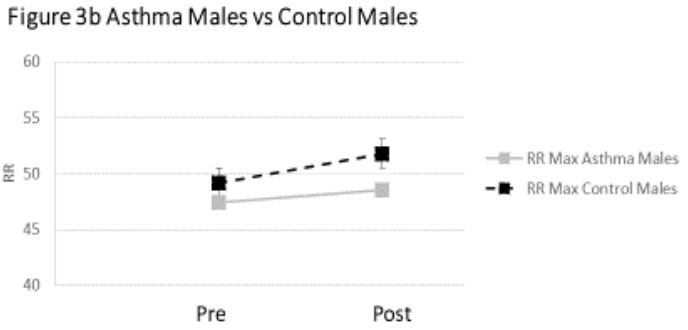
Figure 2c. Vtmax Asthma Females vs Control Females

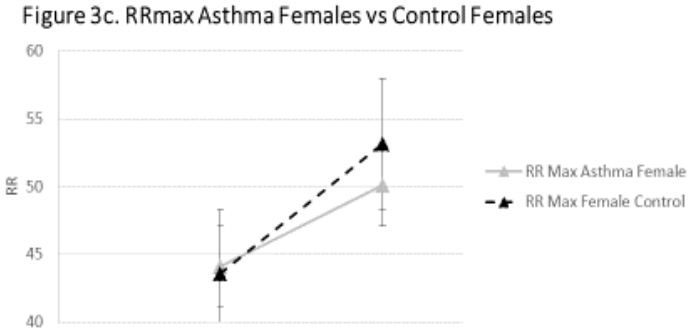


*= p<0.05 b/w groups
tt=p<0.05 within control group
t=p<0.05 within asthma group

Figure 2.3a-c: Respiratory Rate Maximum Pre and Post-Intervention







*= p<0.05 b/w groups
tt=p<0.05 within control group
t=p<0.05 within asthma group

Acute Exercise Response

No differences were observed when comparing $V_E$max (F(0.2,1) p=0.6, h_p^2 = <0.01)), $V_T$max (F(0.4, 1) p=0.7, h_p^2 = 0.02)), RRmax (F(1.4, 1) p=0.09, h_p^2 = 0.04), or peak TSI (F(0.4, 1) p=0.9 h_p^2 = <0.01)) during acute exercise at T1 or T2 when comparing groups. Figures 2(a-c) illustrates the ventilatory pattern during acute HIIT between adults with asthma and healthy controls.

DISCUSSION

The primary finding of this study, in contrast to our hypothesis, was that adults with asthma did not experience significant improvements in $V_E$max, $V_T$max, MVV, V_E/MVV, and RRmax following a 6-week HIIT intervention, whereas control participants did experience improvements. Our secondary finding is that RRmax during maximal exercise was higher among adults with asthma when compared to healthy adults at T1; however, following training, adults with asthma and healthy adults exhibit similar RRmax during maximal exercise.

In line with our hypothesis, healthy adults experienced improvements in $V_E$max, $V_T$max, and RRmax following HIIT; however, contrary to our hypothesis, adults with asthma did not experience improvements. Previous research among healthy adults (n=72) reported similar improvements following 3-weeks of high intensity exercise [184]. Among adults with asthma, following 10-weeks of continuous exercise training no changes in $V_E$max, $V_T$max, or RRmax was observed; however significant improvements were observed in V_E/MVV [185], which differs from the present findings. The discrepancies in V_E/MVV

observed between the two studies may be related to the duration of exercise training. It is possible that a longer (i.e. 10-week) HIIT intervention may lead to improvements in V_E/MVV by increasing the volume of exercise training. Despite the improvements observed in $V_E$max, $V_T$max, and RRmax within the healthy control group in the present study, the ventilatory responses to exercise following HIIT did not differ between groups. This aligns with previous research examining the impact of continuous exercise training between adults with asthma and healthy adults. Specifically, in a study of eight adults with mild asthma and nine healthy controls, the ventilation response to constant work rate cycling (70%) was remarkably similar between groups, despite differences in baseline lung function [190]. Therefore, it appears that adults with asthma are able to meet the acute exercise requirements in increased ventilation during acute maximal exercise; however, that exercise training may not be able to improve indices of ventilation.

In line with our hypothesis, we observed that adults with asthma had a higher RRmax at baseline when compared to healthy adults. This finding adds to the evidence that adults with asthma experience hyperventilation [135]; however, differs from previous research examining the impact of exercise training among adults with asthma. Specifically, in a study consisting of 5 adults with mild asthma and 5 controls participants completed a 10-week aerobic conditioning program [185]. No differences in RR at baseline were observed between the two groups; however, although not significantly different, the asthma group did have a higher RR at VO_2max (asthma RR: 34.6 ± 6.6; control RR: 32.4 ± 8.8) [185]. One possible explanation for the differences observed between the current study and the study described above may be in relation to sample size. The current study had a larger sample size and thus, it is possible that the study by Hallstrand and

colleagues was not sufficiently powered to determine differences in RRmax between groups [185]. Furthermore, participants in the present study were screened for exercise induced bronchoconstriction whereas, participants (4/5) in the study by Hallstrand and colleagues self-reported a history of exercise induced bronchoconstriction. As such, it is possible that not all participants in the study by Hallstrand and collegaues had exercise induced bronchoconstriction and thus, perhaps differences in RR exist between those with asthma versus those with asthma and confirmed exercise induced bronchoconstriction. Future research should be conducted to determine if such differences exist.

Contrary to our hypothesis, no differences in TSI desaturation were observed between groups; however, given the lack of differences observed in ventilation during exercise between groups this finding is not surprising. These findings are in line with previous research examining the TSI desaturation among adults with asthma and healthy controls during sprint interval exercise [191]. No differences in TSI desaturation were observed between adults with EIBC (n=8) and healthy controls (n=8) during 4x30 second bouts of sprint interval exercise interspersed with 4.5 minutes of active recovery [191]. In contrast, differences in TSI desaturation have been observed in a study among male cyclists (n=10) who completed six 30 second sprint interval bouts interspersed with 2 minutes of recovery [192]. The lack of differences in TSI desaturation observed in the current study and the study by Good et al. (2019) may be explained by differences in intensity and recovery periods. For example, the present study had participants complete 1-minute bouts of 90% PPO versus sprint intervals. The short recovery period in the

study by Buchheit et al., (2012) following such intense exercise may suggest that oxygen delivery limitations may be related to intensity and recovery time.

Our findings of a significant improvement in VO_2max among adults with EIBC is similar to what has been reported in previous literature surrounding exercise interventions among adults with asthma. Specifically, in a study examining the impact of a 3-month exercise intervention at an intensity between 60-80%, twice weekly, an improvement in VO_2max of 3.5% was observed [109]. Similarly, in a 12-week supervised aerobic exercise intervention among adults with asthma a 9.5% improvement in VO_2max was reported [10]. Limited research has sought to determine the impact of HIIT among adults with asthma; however, of the literature that is available in an 8-week HIIT intervention among 29 adults with asthma an 8.5% improvement in VO_2max was observed. As such, our findings add to the literature that HIIT is an effective form of training to improve fitness among adults with EIBC, and these improvements are similar as to what is observed among healthy adults.

Results from the current study should be interpreted in light of the following limitations. First, adults with asthma in the current study had mild and well-controlled asthma, according to the asthma control questionnaire [193]. As such, future research should aim to determine the pulmonary responses to HIIT among adults with severe and less controlled asthma, in order to better understand its' impact among this population. Second, all participants in the current study were young adults and as such, it remains unclear as to whether middle-aged or older adults with and without asthma would experience similar improvements in the pulmonary responses to HIIT.

In conclusion, it appears that a 6-week HIIT intervention does not lead to improvements in $V_E$max, MVV, $V_T$max, V_E/MVV, and RRmax among adults with asthma; however, the pulmonary response to maximal exercise remains similar between adults with asthma and healthy controls following HIIT training. Future research should aim to determine the optimal mode of exercise and exercise intensity for improving pulmonary responses among adults with asthma.

Connecting Statement II

As described by previous research, high ventilation during exercise has been suggested as the root cause for acute bronchoconstriction (i.e. acute inflammatory response) due to evaporative water and heat loss from the airways [4]. Our findings suggest that adults with EIBC are able to meet the acute demands of exercise, similar to healthy adults; however, adults with EIBC do not experience improvements in ventilatory outcomes following exercise training in contrast to their healthy counterparts. Despite this, at the same absolute workload, following exercise training, adults with EIBC experience a reduction in RR and thus, ventilation. As such, it is possible that a reduction in RR may reduce the perceptions of dyspnea experienced as well as reduce the EIBC related symptoms (due to a reduction in evaporative water and heat loss) thus, reducing asthma and exercise related anxiety. Repeated exposure to high ventilations during exercise may serve to reduce anxiety and thus, reduce hyperventilation. The following chapter examines the impact of the 6-week HIIT intervention on anxiety and anxiety sensitivity among adults with and without asthma.

Chapter 5: Reducing anxiety and anxiety sensitivity with high intensity interval training in adults with asthma

TITLE: Reducing Anxiety and Anxiety Sensitivity with High Intensity Interval Training in Adults with Asthma

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Abstract

Low and moderate intensity exercise training has been shown to be effective for reducing general anxiety and anxiety sensitivity among adults with asthma. Exercise frequency and intensity have been shown to play an integral role in reducing anxiety sensitivity, however less is known about the impact of high intensity interval training (HIIT) on anxiety in adults with asthma. METHODS: A six week HIIT intervention was conducted with adults with asthma. Participants completed 6 weeks of HIIT (10% peak power output (PPO) for 1 minute, 90% PPO for 1 minute, repeated 10 times); 3 times per week on a cycle ergometer. Pre and post-intervention assessments included the Anxiety Sensitivity Index-3 (ASI) and the Body Sensations Questionnaire (BSQ). RESULTS: Participants (n=20) were 22.5 ± 3.2 years and 11 of 20 were female. Total ASI improved from pre to post-intervention (PRE: 17.9 ± 11.8; POST 12.4 ± 13, p = 0.002, Cohens d = 0.4). BSQ improved from pre to post intervention (PRE: 2.4 ± 1.0; POST: 2.0 ± 0.8, p=0.007, Cohens d = 0.3). CONCLUSION: A 6-week HIIT intervention leads to improved anxiety among adults with asthma. Future research should determine the impact of HIIT among adults with asthma with clinical anxiety.

INTRODUCTION

General anxiety refers to a feeling of worry, nervousness, or unease about an event or something with an unknown outcome. Among adults with asthma, exercise participation may elicit feelings of anxiety for fear of an unknown outcome such as experiencing shortness of breath or wheezing. Anxiety sensitivity on the other hand refers to the fearful belief that bodily sensations such as breathlessness, wheezing, and an increased heart rate will lead to a negative social, physical, or cognitive consequence [146]. Adults with asthma experience these same symptoms during an acute asthma attack, or to a lesser extent, following an exercise session [3]. Furthermore, many of the feared bodily sensations associated with anxiety sensitivity are normal physiological responses to exercise [194]. Thus adults with asthma may misinterpret normal physiological responses to exercise as an imminent threat of an asthma attack and may experience heighted anxiety at the thought of exercise.

Low and moderate intensity exercise training has been shown to be effective in reducing general anxiety among adults with asthma [195, 196]. Limited research exists on the impact of high intensity interval training (HIIT) on reducing general anxiety, anxiety sensitivity (i.e. worry about experiencing anxiety related sensations) and asthma specific exercise anxiety among adults with asthma. This is important because HIIT is composed of brief bouts of high intensity activity followed by intermittent recovery periods, as such, high intensity intervals require high ventilation rates whereas the low intervals allow for ventilation to recover intermittently. This pattern of exercise and ventilation may allow for asthma and anxiety symptoms to recover intermittently. A 10-week HIIT intervention in an indoor swimming pool (exercise training twice per week at 80-90%

heart rate max for 2 minutes, followed by 1.5 minutes recovery of "mild" exercise) revealed that adults with exercise induced asthma were less afraid of experiencing breathlessness during exercise and less anxious about exercise following training [197]. Of note, the recovery intervals were only described as "mild" and swimming is unique in the heart rate and ventilation response to exercise [197]. There exists a gap therefore in the literature pertaining to HIIT and anxiety in adults with asthma that needs to be addressed to better prescribe exercise in this population.

With regards to anxiety sensitivity, exercise frequency is positively correlated with anxiety sensitivity such that greater exercise frequency is associated with lower anxiety sensitivity among healthy adults (n=955) [198]. As well, exercise intensity has been shown to play an integral role in reducing anxiety sensitivity. In a study assessing the impact of exercise training on anxiety, participants with high anxiety sensitivity (>25 total ASI) (n=77) completed five sessions of either moderate or low intensity exercise (70% and 30% of maximal oxygen uptake, respectively). Significant improvements were observed in anxiety pertaining to the fear of bodily sensations assessed using the Body Sensations Questionnaire (BSQ); greater improvements were observed among those in the moderate intensity group [199]. High intensity *continuous* aerobic activity has been shown to improve anxiety sensitivity and fear of anxiety-related physiological sensations to a greater extent than traditional low intensity exercise, in a short period of time among those with elevated anxiety sensitivity [200]. Less is known about the effect of HIIT on anxiety sensitivity. Among adults with asthma who are physically active (i.e. meeting the current physical activity guidelines) increasing the frequency and intensity of exercise through a HIIT intervention may result in improvements in anxiety sensitivity by

repeatedly exposing adults with asthma to anxiety-related physiological sensations, but providing intermittent recovery.

It is important to note that there may be gender differences in the types of anxiety [201]; however, conflicting research exists [202]. For example, some studies have reported that women generally experience greater anxiety related to physical concerns when compared to men. These differences have been observed by assessing the physical concern sub-component of the widely used Anxiety Sensitivity Index (PC-ASI) [201]. Gender differences observed in the improvements in anxiety sensitivity are thought to be due to differences in the physiological adaptations that contribute to physical discomfort during and after exercise in response to exercise training [203]. Therefore, women with asthma may experience greater discomfort during exercise when compared to men and thus, have greater anxiety sensitivity to those symptoms during exercise. Interestingly, other studies have reported no gender differences following a 2-week moderate to high exercise intervention [202]. Improvements in anxiety sensitivity following exercise training among both men and women have largely been attributed to the exposure theory (i.e. repeated exposure to a feared stimuli reduces the fear of that stimulus) [204] therefore, repeated exposure to HIIT, and the accompanying normal physiological responses may reduce anxiety sensitivity surrounding exercise participation among adults with asthma.

Although exercise has been shown to improve anxiety among those with a clinical diagnosis [199], less research has focused on its' impact in non-clinical populations. A 2015 meta-analysis of 306 studies examining the role of regular exercise on reducing anxiety symptoms, revealed that regular exercise elicits a small effect on reducing anxiety symptoms among non-clinical populations [205]. Improving anxiety symptoms

among those with non-clinical levels of anxiety adds to the therapeutic evidence of regular exercise among the general population. Among those with non-clinical anxiety and an asthma diagnosis, the relationship between anxiety and exercise is further convoluted. Given that HIIT allows for intermittent recovery, it may be a promising intervention for those with asthma. The primary purpose of this study was to determine whether a 6-week HIIT intervention would lead to improvements in general anxiety, anxiety sensitivity, and asthma-specific exercise anxiety among adults with asthma. The secondary purpose of this study was to determine whether gender impacts improvement in general, anxiety sensitivity, and asthma specific exercise anxiety following a 6-week HIIT intervention among adults with asthma. Based on the literature available, we hypothesized that participating in HIIT would lead to reductions in general anxiety, anxiety sensitivity and asthma-specific anxiety as a result of chronic exposure to HIIT [200]. Furthermore, it was hypothesized that women would experience greater reductions in anxiety surrounding physical concerns when compared to men [201].

METHODS

Study Design & Protocol

A one-group pretest – posttest study design was used. Participants completed 6 weeks of HIIT; 3 times per week on a cycle ergometer (LODE Excaliber, Lode B.V., Netherlands or Monark Ergomedic 894E, Monark Exercise AB, Poland). HIIT protocols were as follows: 5 minute warm-up at 25 Watts, followed by 10% peak power output for 1 minute, 90% peak power output for 1 minute, repeated 10 times. Participants completed a maximal exercise test at the beginning of the intervention to determine intensity for the exercise sessions.

Participants

Participants were eligible for the study if they were between the ages of 18-44 years, self-reported currently meeting the physical activity recommendations of 150 minutes of moderate-vigorous intensity physical activity per week, had a self-reported physician diagnosis of asthma, a current prescription for a short-acting bronchodilator, a positive response (>12% decline in forced expiratory volume in 1 second from pre to post-challenge) to the eucapnic voluntary hyperpnea challenge, described elsewhere [69], and to those without a self-reported diagnosis of any mental health condition.

Methodology

Participants completed a series of questionnaires (described below) pertaining to general and asthma-specific anxiety at the beginning and end of the 6 week exercise intervention.

Anxiety

The ASI is a 16-item questionnaire used to determine the degree of worry surrounding anxiety-related sensations would lead to a negative social, physical, or cognitive consequence. Worry has been described as a cognitive process that serves an avoidant function used as a strategy to avoid or reduce internal distress [206]. Items on the ASI are scored on a 5-point likert scale ranging from 0 = very little to 4 = very distressing. The ASI assesses feelings of distress in three components 1) Physical Concerns (ASI-PC) (i.e. "It scares me when my heart beats rapidly"), 2) Cognitive Concerns (ASI-CC) (i.e. "When I can't keep my mind on task, I worry I might be going crazy"), and 3) Social Concerns (ASI-SC) (i.e "It is important for me not to appear nervous"). Based on previous work, ASI scores can be classified as low (<17), moderate-high (17-23), and

high AS (>23) [207]. The ASI has been shown to have high internal consistency [*a* ranging from 0.8 to 0.9][208], good retest reliability (*r* ranging from 0.75 for 2-week periods to 0.71 for periods over 3 years), and has been shown to have good construct validity in clinical and non-clinical populations [209]. Previous research around ASI and exercise training has reported clinically meaningful improvements defined as a reduction in total ASI of one or more standard deviations (9 points) from pre to post-exercise intervention [200].

The BSQ was administered to determine participants' fear of anxiety-related physiological sensations. Fear is described as a feeling of perceived danger or threat and research has shown that a fear of anxiety is highly associated with worry [210]. The BSQ is a 16-item questionnaire comprised of sensations related to autonomic nervous system arousal, scored on a 5-point likert scale (0=very little to 5=very much) used to determine the magnitude of which the sensations elicit nervousness or feelings of fright. The BSQ has been shown to have good test re-test reliability (r = 0.67) and high internal consistency (Cronbach alpha = 0.87) [211]. To date, there are no established minimally important clinical differences for this tool. In the study by Bromon et al (2004), described above, significant improvements in BSQ from pre to post-intervention were observed among those in the high intensity group (pre: 2.52 ± 0.53; post: 1.96 ± 0.53) but not in the low intensity group (pre: 2.69 ± 0.57; post: 2.5 ± 0.65) [200]. We thus expect that as a result of repeated exposure to bodily sensations during exercise, adults with asthma will experience reductions of approximately 0.5 in their BSQ score.

The GAD-7 is a 7-item tool used to determine symptoms of generalized anxiety disorder. Adults with asthma have a greater prevalence of anxiety related disorders [144] and thus,

it is possible that adults with asthma have undiagnosed GAD, due to their asthma. Participants are required to think back over the past 2-weeks and report how often they were bothered by 7 core generalized anxiety disorder symptoms (i.e. feeling nervous, anxious or on edge). Response options are "not at all", "several days", "more than half the days", and "nearly every day", scored as 0, 1, 2, and 3, respectively. Scores of >5, >10, >15 represent mild, moderate, and severe level anxiety symptoms [212]. Clinically meaningful reductions in the GAD-7 are determined by a change in classification (i.e. reduction from severe (>15) to moderate anxiety (>10)).

Asthma specific anxiety was assessed using a researcher developed visual analog scale (VAS). The VAS is a common tool used to overcome issues with Likert-type scales such as the ambiguous number of response categories [213]. The VAS overcomes this issue by providing respondents with a visual field rather than numerical and greatly reduces the risk of memory or expectation bias over time. As such, it has been argued that the VAS provides a more accurate representation of the respondents experience versus likert scales [214]. The VAS consisted of a 10cm straight line with the endpoints defining extreme limits. Participants were asked to mark on the line between the endpoints to determine each of the following "Please place an "x" along the line below at a point that you feel best represents 1) how much of a barrier is your asthma to exercise participation 2) how much anxiety do you experience due to your asthma when thinking about exercise participation, 3) how confident do you feel in your ability to exercise without experiencing asthma symptoms (without taking medication)." The distance between the mark and the endpoints determined the VAS scores for each scale. In previous studies using a VAS to determine anxiety pertaining to breathlessness during exercise, a change

of 2cm was considered significant from pre to post-10 week intervention [197] . Due to the shorter intervention period and the younger and less anxious participants in the current study, we considered a 1.5cm change to be clinically meaningful.

Statistical Analyses

Means and standard deviations were used to describe the sample. Paired samples t-tests were conducted to determine differences from pre to post-intervention for all anxiety outcomes. Statistical significance was declared at $p<0.01$ (Bonferroni correction applied to adjust for multiple comparisons (n=5)). A repeated-measures ANOVA using mixed-effects models was conducted to determine the interactions between men and women and ASI outcomes, BSQ, and the GAD-7. The independent variables in the $2 \times 2 \times 2$ mixed-effects ANOVA were gender, anxiety measure, and Time (pre-treatment and post-treatment). Effect sizes were calculated by determining the standardized difference between the two means (mean pre-intervention)-(mean post-intervention)/standard deviation. Cohens d effect sizes were categorized as small (0.2), moderate (0.5), or large (0.8). All statistics were completed in IBM SPSS statistics 25.0 (Armonk, NY) and statistical significance was declared at $p<0.05$.

RESULTS

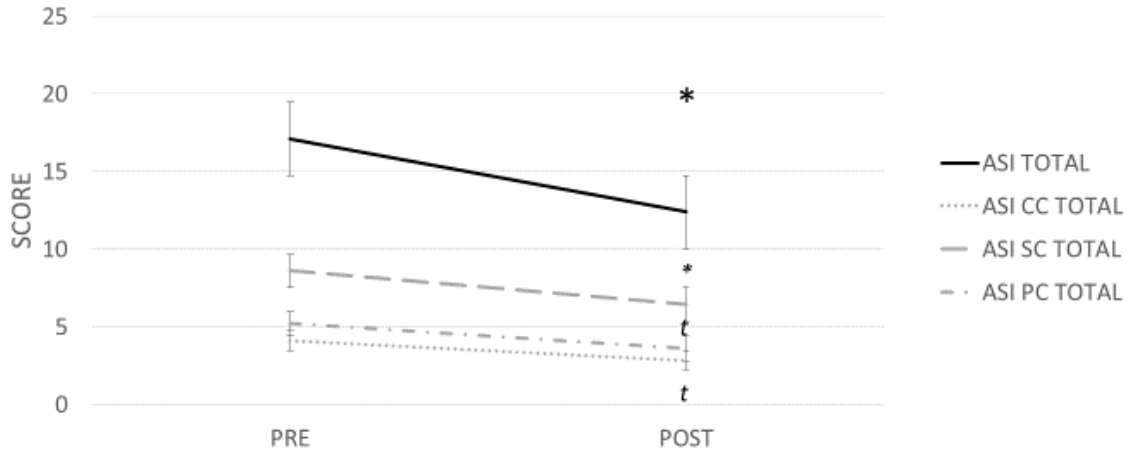
Participants (n=20) were 22.5 ± 3.2 years and 11 of 20 were female. Additional participant characteristics can be found in Table 1.

Table 5.1. Baseline Participant Characteristics

Characteristic	
Sex (M/F)	9/11
Age (years)	22.5 ± 3.2
Height (cm)	169.5 ± 7.2
Weight (kg)	73.8 ± 12.8
Forced Expiratory Volume in 1 Second at Baseline	3.3 ± 0.8
Forced Expiratory Volume Post-Intervention	3.5 ± 0.8
Peak Power Output at Baseline	217.8 ± 49
Peak Power Output Post-Intervention	252.1 ± 56.8 *

Results from total ASI and each component are displayed in Figure 1. Total ASI improved from pre to post-intervention (PRE: 17.9 ± 11.8; POST 12.4 ± 13, p = 0.002, Cohens d = 0.4). A total of 3/20 (15%) of participants experienced a clinically meaningful improvement from pre to post intervention. At pre-intervention 7/20 participants were classified as low anxiety sensitivity whereas, at post-intervention 16/20 were classified as low anxiety sensitivity. No differences were observed in the ASI-SC (PRE: 8.6 ± 5.4; POST 6.4 ± 5.9, p = 0.04, Cohens d = 0.3), the ASI-PC (PRE: 5.2 ± 4.4; POST 3.2 ± 4.2, p = 0.051, Cohens d = 0.6) or the ASI-CC (PRE: 4.1 ± 4; POST: 2.8 ± 4.4, p=0.08, Cohens d = 0.4) from pre to post-intervention.

Figure 3.1. ASI Total & ASI Components Pre and Post-Intervention



*= p<0.05 from pre to post-intervention
t= p<0.01 from pre to post-intervention

BSQ improved from pre to post intervention (PRE: 2.4 ± 1.0; POST: 2.0 ± 0.8, p=0.007, Cohens d = 0.3). No differences were observed for the GAD-7 (PRE: 14/20 low, 6/20 high; POST: 15/20 low, 5/20 high).

Improvements in the VAS "how much of a barrier is your asthma to exercise participation" (mean pre = 3.7 ± 2.7, mean post = 2.0 ± 1.2; p=0.002, Cohens d = 0.8) and VAS "how much anxiety you experience due to your asthma when thinking about exercise participation" were observed (mean pre = 2.8 ± 2.5, mean post = 1.3 ± 1.1; p=0.005, Cohens d = 0.5). No difference was observed in VAS "how confident you feel in your ability to exercise without experiencing asthma symptoms (without taking medication)" was observed (p=0.053, Cohens d = 0.4).

Results from the mixed-effects ANOVA revealed no significant interactions between gender and any of the anxiety outcomes; however, a trend towards a significant difference was observed between men and women for the cognitive concerns component of the ASI ($F(1,1) = 3.025$, $p=0.072$).

DISCUSSION

The purpose of the present study was to determine whether a 6-week HIIT intervention would lead to improvements in general anxiety, anxiety sensitivity, and asthma related exercise anxiety among adults with asthma. Our primary finding is that a 6-week HIIT intervention leads to improvements in anxiety sensitivity and asthma specific exercise anxiety in adults with asthma with non-clinical anxiety. These results are in line with previous research examining the impact of aerobic exercise training on reducing anxiety among clinical and non-clinical populations [201], and indicate that HIIT may be a useful tool when working with adults with asthma.

Our hypothesis that a 6-week HIIT intervention would lead to improvements in anxiety sensitivity was confirmed using a sample of 20 adults who had low levels of anxiety sensitivity and well-controlled asthma at baseline. The strength of the effect size observed in the ASI-PC subcomponent, suggest that a 6-week HIIT intervention may play an important role in reducing physical sensations that are commonly experienced during exercise as well as during an asthma exacerbation (i.e. shortness of breath). These findings are in line with previous research that has reported that exercise frequency and exercise intensity play an important role in reducing anxiety sensitivity [198, 199]. It is likely, that the frequency (i.e. 3 times per week) paired with the high intensity nature of the present protocol (i.e. 90% PPO for 1 minute, 10% PPO for 1 minute) offered repeated

exposure to the potentially feared stimuli (i.e. asthma related symptoms during exercise) and thus led to the reductions in anxiety sensitivity among adults with asthma. Despite the low baseline levels of anxiety sensitivity, and the health of the sample, 15% of participants experienced clinically meaningful improvements. Previous research has shown clinically meaningful changes in over 50% of participants [200]. The differences in the proportion of those experiencing these clinically meaningful improvements is likely explained by the differences in anxiety sensitivity scores at baseline between studies. Specifically, the present studied included individuals with asthma without a self-reported diagnosis of a mental health condition; whereas, in the study by Bromon and colleagues participants had to have a minimum score of >25 on the ASI at pre-intervention. The average ASI score at baseline in the present study was 17.9 ± 11.8 compared to 34.17 ± 6.3 in the Bromon study [200]. Of note, despite the lower ASI scores in the present study at baseline, 9/20 (45%) of participants moved down into the low ASI classification from pre to post-intervention. These findings therefore have important implications for exercise prescription among adults with asthma, regardless of whether they have an existing diagnosis of anxiety.

The inclusion criteria of adults with asthma without a diagnosis of a mental health condition may also explain why no differences were observed in GAD-7 from pre to post-intervention and why few clinically meaningful differences were reported. Future research should assess the impact of varying HIIT protocols (i.e. frequency and intensity) in order to better determine and prescribe the optimal exercise for reducing anxiety sensitivity among adults with asthma. As well, research should aim to assess the impact of chronic HIIT training among adults with asthma and with high anxiety sensitivity

(>25) in order to better determine the impact of HIIT on anxiety sensitivity among adults with asthma.

Our observation that the fear of experiencing anxiety related sensations improved following 6-weeks of HIIT is in line with previous research. Specifically, previous studies have reported improvements in the level of fear surrounding anxiety related sensations, using the BSQ, following 5 sessions of moderate intensity exercise [199]. In a study among adults with agoraphobia (n=77) participants were randomized into either a low intensity exercise or moderate intensity exercise group with a combination of cognitive behavior therapy. Results showed that greater improvements in BSQ were reported among those in the moderate intensity group [202] thus, suggesting that exercise intensity plays an important role in reducing anxiety. To date, no study has examined the impact of HIIT on reducing fear of anxiety related sensations among adults with asthma; however, it appears that among adults with asthma and without a diagnosis of a mental health condition, HIIT can lead to improvements in levels of fear of anxiety related sensations. Reducing fear of these sensations may lead to a reduction in barriers related to regular exercise among this population.

Our hypothesis that a 6-week HIIT intervention would lead to improvements in asthma specific exercise anxiety was also confirmed. Participants in the present study reported a significant reduction in asthma-related barriers to exercise participation and reported significantly reduced anxiety at the thought of exercise using the VAS. These findings are in line with previous research that has implemented VAS to assess anxiety among adults with asthma, which found significant improvements in feelings of fear surrounding breathlessness during exercise following a 10-week HIIT swimming intervention [197].

Reductions in asthma related barriers to exercise and improved perceptions of anxiety have important implications for exercise prescription among adults with asthma. Of note, an important limitation to consider in the present study is the lack of validity and reliability of the VAS used. Unfortunately, no validated or reliable VAS scales exist for assessing exercise-specific anxiety among adults with asthma. Importantly, the two VAS scales used in the present study that revealed significant improvements also yielded large and moderate effect sizes. The strength of these effect sizes suggest that a 6-week HIIT intervention may have important implications in improving asthma-specific anxiety surrounding exercise participation. Future research should aim to create valid and reliable tools to assess asthma specific anxiety among adults with asthma in order to better understand the impact of exercise training on these outcomes.

The lack of gender differences observed in the present study add to the evidence that gender may not impact improvements in anxiety following exercise training [202]. A study implementing a 2-week moderate to high intensity (60-80% heart rate) exercise intervention reported that men experienced greater reductions in anxiety in response to exercise training compared to women, these reported differences were only evident mid-treatment [202]. Similar findings were reported in the study described above by Bromon and colleagues (2004), in that following the first week of exercise training, men had a greater reduction in anxiety when compared to women; however, following the 2-weeks of exercise training men and women had similar improvements [200]. Therefore, one important limitation of the present study is the lack of mid-treatment anxiety assessment. It is possible that there may be gender differences in the rate at which anxiety improves in response to exercise. Interestingly, the present study reported a trend towards significance

in the cognitive component of the ASI wherein, men had higher anxiety scores within this sub-component. This is in line with previous research that has reported men typically score higher than women on this sub-component while females typically score higher on the PC component [201]; however, the present study did not find a higher score for women on the PC component. Thus, it is possible that at non-clinical levels of anxiety, gender differences do not occur. Of note, it is possible that the present study was underpowered and thus, definitive gender differences in anxiety cannot be determined.

In conclusion, it appears that a 6-week HIIT intervention is able to reduce anxiety sensitivity and asthma-specific anxiety among adults with asthma who have non-clinical levels of anxiety. Furthermore, it appears that reductions in anxiety sensitivity and asthma specific anxiety occur following a 6-week HIIT intervention, regardless of gender. Future large scale randomized control studies should aim to evaluate the differences in different intensities of exercise training and their impact on reducing anxiety sensitivity and asthma specific exercise anxiety among adults with asthma.

Connecting Statement III

In the previous three chapters, we've reported a reduction in inflammation, an improvement in aerobic fitness, a lack of improvement in indices of ventilation among adults with EIBC, and a reduction in anxiety levels. As stated previously, improvements in aerobic fitness have been linked to improvements in asthma control[10]. As well, the reduction in anxiety observed following HIIT may have led to a de-sensitization to asthma related symptoms (i.e. dyspnea) as a result of repeated exposure and thus, may have reduced perceptions of the frequency and severity of asthma symptoms; therefore, leading to an improvement in asthma control. As such, the following chapter will examine the impact of a 6-week HIIT intervention on clinical outcomes of asthma.

Chapter 6: Low volume high intensity interval training leads to improved asthma control in adults

TITLE: Low volume high intensity interval training leads to improved asthma control in adults

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Abstract

Regularly engaging in aerobic exercise is associated with improved asthma control and quality of life. Previous research has focused on continuous aerobic exercise; the impact of high intensity interval training (HIIT) on asthma control is poorly described. METHODS: A six-week, low volume HIIT intervention (3 times/week, 20 minute bouts) was conducted in adults with asthma (n=20). Asthma control was assessed using the Asthma Control Questionnaire (ACQ). RESULTS: ACQ improved from pre to post intervention (pre: 0.8 ± 0.6; post: 0.5 ± 0.4, p = 0.02, Cohens d = 0.5). In total, 7/20 (35%) participants experienced clinically meaningful improvements in ACQ. CONCLUSION: A low-volume HIIT intervention leads to statistically and clinically significant improvements in asthma control as well as improved exertional dyspnea and exercise enjoyment.

Exercise acts a trigger for bronchoconstriction in approximately 90% of adults with asthma [3]. Exertional dyspnea, that is, shortness of breath during exercise [216], is commonly experienced among those with asthma and may be a barrier to regular exercise. Nevertheless, asthma control and exertional dyspnea can be improved by engaging in regular exercise training, particularly aerobic exercise [10, 217, 218].

Adherence to aerobic exercise among adults with asthma is suboptimal [164]. Interestingly, while research suggests that adults with asthma are less likely to engage in higher intensity activities [219], recent work from our laboratory showed that adults with asthma enjoy high intensity interval exercise more than moderate intensity continuous exercise (MICE) [220]. This may be particularly relevant in adults with asthma, as continuous exercise requires sustained ventilations, which results in evaporative water and heat loss from the airways [4] thus, triggering bronchoconstriction. In fact, work from our laboratory also found that an acute bout of high intensity interval exercise led to a smaller decline in FEV_1 post-exercise than MICE [162]. The high intensity interval exercise was also associated with lower exertional dyspnea during exercise, and greater exercise enjoyment.

High intensity interval training (HIIT) is composed of brief bouts of high intensity activity followed by intermittent recovery periods. Based on our work, HIIT appears to be a safe option for exercise prescription; however, limited research exists on the impact of regularly engaging in HIIT on asthma control, exertional dyspnea, and exercise enjoyment. The purpose of this study was to determine the impact of a 6-week, low volume HIIT intervention on asthma control among adults with asthma. We also wanted to determine the impact of HIIT on exertional dyspnea during exercise and exercise

enjoyment following the 6-week HIIT intervention. We hypothesized that despite the low volume, regular participation in HIIT would lead to improvements in asthma control and exertional dyspnea based on previous research indicating such responses to MICE [10], and that exercise enjoyment would improve due to desensitization to exertional dyspnea symptoms [218, 221], and improvements in asthma control.

METHODS

Study Protocol

A one group pre-test (first HIIT session), post-test (last HIIT session) study design was conducted in which eligible participants (non-smoking, moderately active adults with a self-reported physician diagnosis asthma, with a current prescription for a short-acting bronchodilator, aged 18-44 years) completed 6 weeks of HIIT, 3 times per week on a cycle ergometer (5 minute warm-up at 25 Watts, followed by 10% peak power output for 1 minute, 90% peak power output for 1 minute, repeated 10 times).

Spirometry

Participants performed three repeatable lung function maneuvers using a handheld spirometer (EasyOne, Medizintechnik AG, Zurich, Switzerland) in accordance with the American Thoracic Society Guidelines before exercise at pre and post HIIT sessions [222]. At minutes 5, 10, 15, and 20 post-exercise during the pre and post HIIT sessions, FEV_1 was re-assessed in duplicate. The highest FEV_1 value at each of the post-exercise time points was used to determine FEV_1 decline. The decline in FEV_1 was calculated as follows:

% Fall in FEV_1 = 100 [FEV_1 pre-challenge – FEV_1 post-challenge] / FEV_1 pre-challenge.

The maximum FEV_1 decline following exercise were used for statistical analysis. Participants were not permitted to take their short-acting bronchodilator prior to any of the HIIT sessions; however, participants were permitted to maintain their regular usage of inhaled glucocorticoids throughout the duration of the intervention.

Asthma Control

Asthma control was assessed using the Asthma Control Questionnaire (ACQ) -7 at pre and post HIIT sessions. The ACQ has been shown to have strong evaluative and discriminative properties and can be used to measure asthma control with confidence [193]. A score on the ACQ of <0.75-1.5 is indicative of relatively well-controlled asthma and a score >1.5 indicates poorly controlled asthma. A change on the ACQ >0.5 is considered clinically significant.

Exercise Enjoyment

Exercise enjoyment was assessed 5-minutes following pre and post HIIT sessions using the Physical Activity Enjoyment Scale. Given that the questionnaire was used post-exercise, the questionnaire was modified by removing the following question "I am very absorbed in this activity-I am not very absorbed in this activity." Each question is scored on a 7-point bipolar scale with a maximum score of 119. This modified version has been used previously for the assessment of HIIT [162, 223].

Exertional Dyspnea

Exertional dyspnea was assessed each minute during the second and 17^{th} session using the Ratings of Perceived Dyspnea (RPD) scale. RPD was not measured during the first

and last session due to timing of various measurements. The peak RPD and the average RPD for each minute during exercise was used for analysis. The RPD scale has been shown to be valid and reliable for use during exercise [224].

Statistical Analysis

Means and standards deviations were used to describe the sample. Paired samples t-tests were used to determine differences between pre and post HIIT sessions. A repeated measures ANOVA was used to determine differences in FEV_1 (L/min) from before and after the exercise session at pre and post HIIT sessions. A repeated measures ANOVA was used to determine differences in RPD at pre and post HIIT sessions. Effect sizes were calculated by determining the standardized difference between the two means (mean pre-intervention)-(mean post-intervention)/standard deviation. Cohens d effect sizes were categorized as small (0.2), moderate (0.5), or large (0.8). As well, estimated effect sizes were reported using partial eta squared (h_p^2) values from the ANOVA. Partial eta squared effect sizes were categorized as small ($h_p^2 = 0.01$), medium ($h_p^2 = 0.06$), and large ($h_p^2 = 0.14$) All statistics were completed in IBM SPSS statistics 26.0 (Armonk, NY) and statistical significance was declared at $p<0.05$.

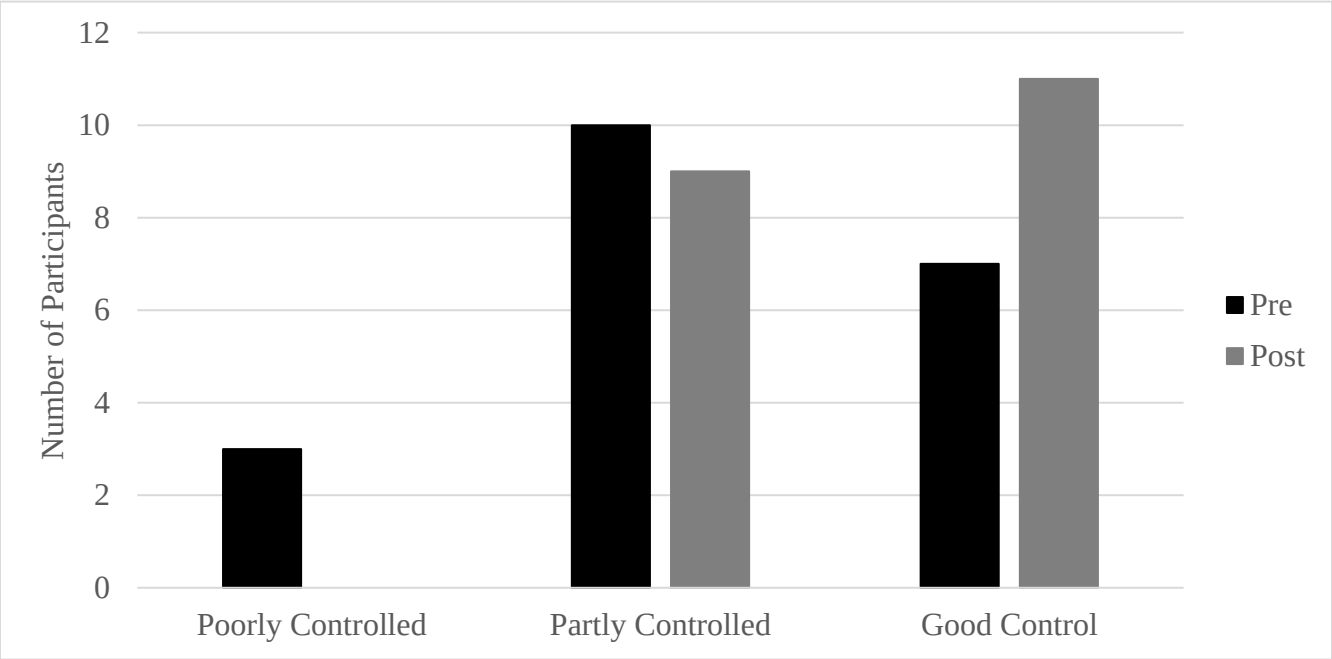
All participants provided written informed consent prior to participation in the study. This study was approved by the Research Ethics Board at the University of Ontario Institute of Technology.

RESULTS

Participants (n=20) were 22.5 ± 3.2 years and 11 of 20 were female. Nine participants had good asthma control (ACQ>0.5) and three had poor asthma control (ACQ >1.5) at baseline. FEV_1 did not change from pre to post-exercise ($F(1,19) = 0.3$, $p=0.5$, $h_p^2 = 0.01$).

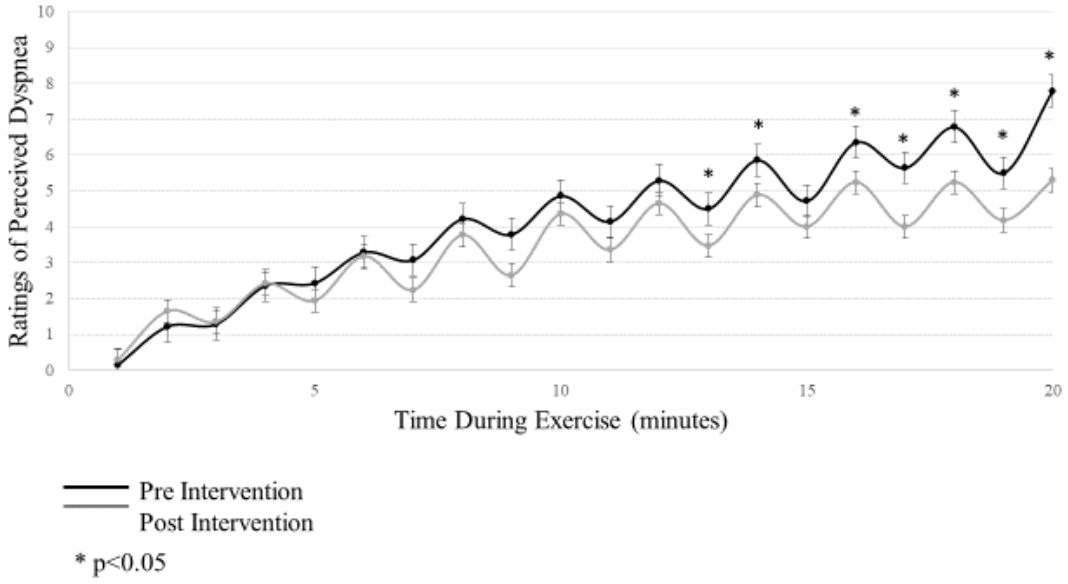
Improvements in ACQ were observed when comparing pre and post HIIT sessions (pre: 0.8 ± 0.6; post: 0.5 ± 0.4, p = 0.02, Cohens d = 0.5). A total of 7/20 (35%) participants experienced clinically meaningful improvements in ACQ. Those who experienced a clinically meaningful improvement in asthma control had the highest ACQ at pre-intervention (1.5 ± 0.5, n=7); no differences were observed between these groups (high vs. low ACQ at pre-intervention) in baseline characteristics. Figure 1 illustrates the number of participants with poor, partly, and good asthma control at pre and post-intervention.

Figure 4.1. Changes in Asthma Control from Pre to Post Intervention (n=20)



During the first HIIT session, four participants were unable to complete the session due to volitional fatigue. Thus, only participants who completed the full 20 minute session were included for RPE analysis (n=16). No differences were observed in peak RPD; however, significant improvements were observed in average RPD when comparing pre and post HIIT sessions (pre: 4.3 ± 1.8; post: 3.1, $p = 0.03$, Cohens $d = 0.8$). Figure 2 illustrates the changes observed in average exertional dyspnea during each minute of exercise during the pre and post-HIIT sessions.

Figure 4.2. Perceived dyspnea during exercise at pre-intervention and post-intervention (n=16)



Improvements in exercise enjoyment were observed when comparing pre and post HIIT sessions (pre: 69.5 ± 7.3; post: 73.25 ± 6.3, p=0.03, Cohens d = 0.8).

DISCUSSION

The purpose of this study was to determine the impact of a HIIT intervention on asthma control, exertional dyspnea, and exercise enjoyment. Our primary finding is that a 6-week, low volume HIIT intervention led to statistically and clinically significant changes in asthma control. We also found that exertional dyspnea was reduced and exercise enjoyment was improved following the intervention. Together, these findings suggest that HIIT can be prescribed to adults with asthma, and may even be a preferred exercise option.

As hypothesized, HIIT led to improvements in asthma control. This is in line with previous research on changes in asthma control following exercise training. Specifically, following a 12-week moderate intensity exercise training program among adults with asthma (n=18), ACQ scores improved from 1.3 (±0.19) to 0.72 (±0.17), while a study of overweight adults with asthma (n=55) found that 69% of participants experienced improvements in asthma control over 12 weeks of moderate intensity exercise training [225]. In our study, ACQ improved from 0.8 ± 0.6 to 0.5 ± 0.4, and 35% of the sample has clinically meaningful improvements. This is important as the majority of previous research has examined the impact of larger volume interventions, that is, exercise sessions are typically longer (e.g. ≥30 minutes) and the length of the intervention is greater (>12 weeks) [10, 225, 226]. The improvements observed in our study occurred following only 6-weeks of exercise training that consisted of one hour per week of exercise. Thus, adults with asthma who wish to improve asthma control but indicate that time is a barrier to adopting exercise, could be advised to perform HIIT instead of MICE.

We also hypothesized that RPD during exercise would be reduced due to desensitization to exertional dyspnea symptoms due to repeated exposure to HIIT. It should be noted that improved cardiorespiratory fitness is likely the primary reason for the observed improvements in RPD; however, repeated exposure to a feared stimuli (i.e. dyspnea among adults with asthma) may result in a desensitization to that stimuli [204, 221] and thus, may explain the improvements observed in exertional dyspnea during exercise. Our data suggest that average RPD did improve; this is in line with previous literature reporting an improvement in exertional dyspnea (using the Medical Research Council dyspnea scale) from 2.58 (±0.69) to 1.37 (±1) over an 8 week moderate continuous exercise intervention [227]. In other words, HIIT would allow adults with asthma to perform daily activities that require higher intensities at a lower level of perceived dyspnea. This is important for asthma related quality of life and overall perceptions of asthma control [228].

Finally, our hypothesis that the intervention would improve exercise enjoyment was also confirmed [227]. These improvements may have important implications for increasing exercise adherence among this population, given the strong association between exercise enjoyment and future exercise participation [229]. Improving exercise adherence would have an important impact on health, asthma control, and asthma related symptoms among adults with asthma.

The results of the present study should be interpreted in light of the following limitations. First, the majority of participants in the present study had good asthma control and thus, the generalizability of these findings among adults with less controlled asthma is limited. As well, our sample was composed of younger adults and thus, caution should be aired when generalizing these findings to older adults with asthma. Despite these limitations, these findings offer promise

for the implementation of HIIT among young adults to help improve asthma control and asthma symptoms.

In conclusion it appears that a 6-week, low volume HIIT intervention is able to improve asthma control, exertional dyspnea, and exercise enjoyment among adults with asthma. These findings suggest that clinicians and allied healthcare professionals working with adults with asthma can counsel patients on incorporating HIIT. Further work is needed to better understand differences in adherence to HIIT versus MICE programs in adults with asthma.

CHAPTER 7: EXTENDED METHODS

Study Design: A 6-week high intensity interval training (HIIT) intervention among adults with and without exercise induced bronchoconstriction (EIBC) was conducted, using a quasi-experimental study design. Exercise training occurred 3 times per week for 6 weeks. All exercise training was conducted on a cycle ergometer, and all exercise sessions were supervised by researcher or a trained research assistant.

Participants:

Inclusion Criteria EIBC Group: Inclusion in the EIBC group was limited to adults between the ages of 18-44 years, with a current prescription for a short-acting bronchodilator, who were participating in ≤ 150 minutes of moderate to vigorous intensity physical activity per week, who were not taking medications that could alter the outcomes of interest (with the exception of asthma medications), and who were non-smokers. Further eligibility criteria included a positive response to either the eucapnic voluntary hyperpnea (EVH) challenge or the bronchodilator reversibility assessment to confirm EIBC (described below).

Inclusion Criteria Control Group: Inclusion in the control group was limited to adults between the ages of 18-44 years, who were participating in ≤ 150 minutes of moderate to vigorous intensity physical activity per week, who were not taking medications that could alter the response of the outcomes of interest, and who were non-smokers.

Exclusion Criteria: The upper age limit of 44 years was to minimize inclusion of participants who may have had undiagnosed chronic obstructive pulmonary disorder (COPD), or compromised lung function.[230] Participants who were current smokers were excluded from this study, due to the likelihood that smokers would present with more impaired lung function and an increase in inflammation.[231] Participants with musculoskeletal injuries that would

impact performance or exacerbate their injury on the cycle ergometer were excluded from this study. Certain types of medications, for example beta blockers, alter cardiovascular responses;[232] therefore, participants using those medications were excluded from this study. Participants with a diagnosis of a mental health problem (i.e. depression, generalized anxiety disorder) were excluded from this study, in order to obtain a more homogenous and accurate representation of the impact of a HIIT intervention among adults with non-clinical mental health issues. Pregnant women were excluded from the study.

Recruitment: Participants were primarily recruited from the UOIT North and Downtown campuses using posters displayed on the campuses, announcements made in undergraduate lectures and laboratories, posts made on Dr. Dogras' laboratory website, and through word of mouth. Permission was sought from course instructors to make classroom announcements in undergraduate courses. Recruitment was also conducted at local community and fitness centers in Whitby and Oshawa, with the use of recruitment posters. Efforts were made to ensure participants in each group were age and sex matched.

Sample Size: GPOWER statistical software indicated that for a medium effect size (0.5) with an alpha of 0.05 and a power of 0.95, 16 participants for each group were required for this study.

Overview of Sessions

Pre-Screening and Familiarization, Pre-Intervention, and Post-Intervention Testing Sessions:

Individuals that met the inclusion criteria (described above) were asked to provide written informed consent prior to participation. Eligible participants were asked to attend a pre-screening and familiarization session, used to confirm EIBC. Participants were also asked to attend a pre-intervention session to determine peak power output (PPO) prior to the HIIT intervention. Details on each of these sessions are described below. Following the 6-week HIIT intervention, participants attended a post-intervention session to determine training improvements in the outcomes described below. Prior to each of these sessions, participants were emailed the following instructions:

- refrain from taking any long acting medication 48 hours prior to testing
- refrain from taking short acting medication 8 hours prior to testing
- refrain from consuming caffeinated beverages at least 4 hours prior to testing
- refrain from consuming a heavy meal at least 2 hours prior to testing
- bring shorts and sneakers to testing session
- bring current rescue medication to testing session

Additionally, in order to accurately assess salivary markers of inflammation participants were asked to document the following prior to pre-intervention and post-intervention testing sessions:

- consumption of alcohol, caffeine, nicotine, and prescription/over-the-counter medications within the 12 hours prior to sample collection
- consumption of meals within the previous 60 minutes
- consumption of foods with high sugar, acidity, or caffeine content, immediately before sample collection

- physical activity levels 24 hours prior to sample collection
- the presence of any oral disease or injury

Exercise Sessions 1 & 18: Following the pre-screening and familiarization and the pre-intervention testing sessions, participants were asked to complete a total of 18 exercise sessions (3 sessions per week for 6 weeks). During exercise sessions 1 and 18 inflammatory, pulmonary, cardiovascular, and psychological variables were assessed. Details on each of these parameters and assessment methods are described below. Prior to exercise sessions 1 and 18 participants were emailed the following instructions:

- refrain from heavy exercise at least 24 hours prior
- refrain from consuming a heavy meal at least 2 hours prior
- refrain from consuming caffeinated beverages at least 4 hours prior
- refrain from taking any short acting asthma medication at least 8 hours prior
- bring shorts and sneakers to the testing session
- bring current rescue medication to testing session

Additionally, in order to accurately assess salivary inflammation participants were asked to document the following prior to exercise sessions 1 and 18:

- consumption of alcohol, caffeine, nicotine, and prescription/over-the-counter medications within the 12 hours prior to sample collection
- consumption of meals within the previous 60 minutes
- consumption of foods with high sugar, acidity, or caffeine content, immediately before sample collection
- physical activity levels 24 hours prior to sample collection

- the presence of any oral disease or injury

Exercise Sessions 2 & 17: During exercise sessions 2 and 17 participants completed the exercise protocol. Perceptions of effort and dyspnea and in-task affect were assessed each minute during exercise. Physical activity enjoyment was assessed following the exercise protocol. Participants were emailed the following instructions prior to exercise sessions 2 and 17:

- Refrain from consuming caffeinated beverages at least 4 hours prior to testing
- Refrain from consuming a heavy meal at least 2 hours prior to testing
- Withhold any short acting asthma medication 8 hours prior to testing
- Bring your current rescue medication to the testing session

Exercise Sessions 3-16: During sessions 3-16 participants completed the HIIT sessions under the supervision of the researcher or a trained research assistant. Research assistants were instructed to limit interaction with the participants, in order to help prevent influencing enjoyment variables (described below) during the session. In order to ensure participant safety, for each HIIT session participants were instructed to bring their short acting bronchodilator. HIIT sessions were cancelled if the participant forgot their medication.

Variables of Interest

Inflammation

Salivary Cytokines:

Measurement: Concentrations of salivary cytokines were assessed (Salimetrics, USA). Upon arrival to the laboratory, participants were provided with water to rinse their mouths, in order to remove any food residue. The sample was collected a minimum of 10 minutes following rinsing. Participants were instructed to pool saliva in their mouth and provide a sample in a high quality polypropylene 2mL cryovial (Salimetrics Item No. 5002.01, USA). In order to assist participants in obtaining the required sample volume, participants were prompted to think of eating salty foods (i.e. pickles, potato chips). Samples were immediately placed on ice, securely sealed and packaged prior to transport to a Level 2 Biohazard laboratory. Samples were transported in accordance with the Transportation of Dangerous Goods Act and regulations. Samples were then aliquoted into 0.5ml vials, samples were sealed tightly and coded, using labels recommended for freezing (i.e. cryolabels), and placed in a -80 degree freezer until analysis. For additional information on saliva sample procedures refer to Appendix C2. Enzyme immunoassay kits for pro-inflammatory cytokines Tumor necrosis factor (TNF) *a,* interleukin (IL)-1β, IL-8, and Interferon-gamma inducible protein, CXCL10/ (IP-10) CXCL10/IP-10 and anti-inflammatory cytokines interleukin-1 Receptor antagonist (IL-1Ra) and transforming growth factor beta (TGF-β) were used to analyze saliva samples. Saliva samples were thawed and centrifuged for 15 minutes at 1500 x *g* to pellet mucins and other debris. Prior to cytokine analysis, total protein content within each saliva sample was determined using the Coomassie PLUS Protein Assay Reagent (Thermo Fisher Scientific, MA, USA). Levels of IL-8 (R&D Systems, Catalog# DY208), IL-1Ra (R&D Systems, Catalog#DY280), and TNF α (R&D Systems, Catalog# DY210) were determined in both EIBC

and non-EIBC groups using enzyme-linked immunosorbent assays (ELISA) following manufacturer's protocols (R&D Systems, MN, USA). Levels of IL-1β (R&D Systems, Catalog# DY201) and CXCL10/IP-10 (R&D Systems, Catalog#DY266) were determined in the EIBC group only, using enzyme-linked immunosorbent assays (ELISA) following manufacturer's protocols (R&D Systems, MN, USA). Samples were analyzed using 96-well high-binding microplates (Greiner Bio-One, Frickenausen, Germany) and plates were read at a wavelength of 450 nm using a Synergy HTTR microplate reader (Bio-Tek Instrumentation, VT, USA). Cytokine data was standardized with the amount of total protein found within each saliva sample and expressed as pg/µg of protein.

Time of Measurement*:* Concentrations of salivary levels of cytokines were assessed before and 15-30 minutes after exercise during the pre-intervention and post-intervention testing sessions. As well, saliva samples were collected before and 15-30 minutes after exercise during exercise sessions 1 and 18. Among the EIBC group, samples were collected in duplicate during the pre-intervention testing session and exercise session 1.

Pulmonary

Maximal Oxygen Consumption (VO_{2max}) and Ventilation

Measurement: A metabolic cart (Parvo Medics, TrueOne 2400, Murray, Utah USA) was used during maximal exercise testing on the cycle ergometer (Lode Excalibur, Gronigen, The Netherlands). Expired CO_2 and O_2 was collected through a pneumotachograph and analyzed using an automated gas collection system. Participants' with EIBC were instructed to take their medication 15 minutes prior to maximal exercise testing to ensure safety and to determine

bronchodilator reversibility (described below). The cycle ergometer was adjusted to the appropriate height for each participant by adjusting the seat to hip level. Participants were fitted with the headset and mouthpiece required for direct gas analysis. Participants were then instructed to mount the cycle ergometer. A nose clip was placed on the participants' nose to ensure all expired air is expelled via the mouth. Participants were instructed to maintain a closed seal around the mouthpiece at all times. Participants were then instructed to begin cycling at 70-80rpm at 25Watts for a 5 minute warm-up. Exercise testing began at 25Watts, and increased by 1Watt every 2 seconds until volitional exhaustion. Upon exhaustion, participants entered an active cool down and the mouthpiece was removed by the researcher 30 seconds post-exhaustion. Outliers were visually determined and removed. VO_2max was determined by taking a 5-breath average of the highest VO_2 throughout the test. Ventilatory threshold was visually determined at the point where ventilation increased non-linearly to the increase in oxygen uptake, and by identifying the point at which carbon dioxide production increased at a faster rate than VO_2.

Time of Measurement: VO_2max was assessed during pre-intervention and post-intervention testing sessions. Ventilatory variables were assessed during pre and post-intervention testing sessions and during exercise sessions 1 and 18.

Cardiovascular

Tissue Saturation Index (TSI)

Measurement: A two-wavelength (765 and 855nm) continuous wave near infrared spectroscopy system (NIRS) was used to monitor TSI (Artinis Medical Systems, The Netherlands). The background and additional details of NIRS are described elsewhere.[189] Briefly, light in the

near infrared range is used to determine relative concentrations of oxygenated and deoxygenated hemoglobin, due to their different absorption patterns. TSI represents a ratio of oxygenated hemoglobin to total hemoglobin, which indicates oxygen saturation in the tissue. For additional information on NIRS procedures as it pertains to the proposed study, refer to Appendix C3. Upon arrival to the lab, a thigh skin fold was taken at the midway point of the iliac crest and patella. Participants were then seated and fitted with a non-invasive probe that was attached to the belly of the quadriceps vastus lateralis muscle, 12 cm from the knee joint, along the vertical axis of the thigh. The probe was secured in place with an elastic strap, which was tightened to prevent movement, and covered with an optically dense, black vinyl sheet to minimize the intrusion of extraneous light and probe movement. A tensor bandage was applied over the black vinyl sheet to minimize movement of the probe. TSI during exercise was normalized and expressed as a percentage of TSI at rest.

Time of Measurement: TSI was assessed during pre-intervention and post-intervention testing sessions and during exercise sessions 1 and 18.

Heart Rate and Blood Pressure

Measurement: Resting and exercise heart rates were monitored using a heart rate monitor (Polar V800). Resting blood pressure was assessed using a blood pressure cuff (Welch Allen, Germany). Upon arrival to the laboratory, participants were instructed to sit quietly in the laboratory for 5 minutes. Blood pressure was then manually assessed and recorded twice at the antecubital space using a stethoscope and sphygmomanometer (Welch Allen, Germany). Participants were then instructed to lift their shirt slightly above the Xiphoid process and were fit with a heart rate monitor (Polar, V800). The heart rate monitor was attached around the chest with a wearable strap, and a heart rate monitor watch was attached to the participants left wrist.

Time of Measurement: Resting heart rate and resting blood pressure was assessed at the beginning of the pre-screening and familiarization, pre-intervention, and post-intervention testing sessions. As well, resting heart rate and blood pressure was assessed at the beginning of exercise sessions 1 and 18. Resting heart rate and blood pressure assessments taken during the pre-screening and familiarization, pre-intervention testing, and post-intervention testing were used for safety purposes, while measurements taken at the beginning of exercise sessions 1 and 18 were used for analysis. Exercise heart rate was assessed each minute of exercise during pre-intervention and post-intervention testing and during exercise sessions 1 and 18.

Psychological

Anxiety & Anxiety Sensitivity

Measurement: Anxiety levels were assessed using the Generalized Anxiety Questionnaire, the Anxiety Sensitivity Scale III, and Visual analog scales. The Anxiety Sensitivity Scale III has been shown to have higher construct validity and reliability than earlier versions [233]. Additional assessments of anxiety levels and exercise participation, specific to adults with EIBC, were assessed using 3 researcher developed Visual Analog scales evaluated on a 100mm scale (Appendix C1). Participants were provided with the Anxiety Sensitivity Scale III and the Visual Analog scales upon arrival to the laboratory during the pre-intervention and post-intervention testing sessions. Instructions for each scale was read by the researcher to the participant. Participants were then instructed to complete the scales. The following instructions were given to the participant in regards to the visual analog scales:

- "A visual analog scale is a tool that aims to measure a characteristic or attitude that is believed to range across a continuum, for example anxiety. These visual analog scales will be used to measure your anxiety levels as it pertains to exercise participation and asthma. Please indicate on the scale your level of anxiety as it pertains to each question by marking an "x" on the scale."

Time of Measurement: Anxiety scales were completed during pre-intervention and post-intervention testing sessions.

Perceptual Feedback

Perceived Dyspnea, Effort, and Exercise Enjoyment

Measurement: Perceptions of effort were assessed in relation to leg fatigue using the Borg Ratings of Perceived Exertion Scale (6-20). The Ratings of Perceived Exertion Scale has been shown to be a reliable measure of exercise intensity ($r = 0.83$).[234] Perceptions of dyspnea were assessed using the modified Ratings of Perceived Dyspnea Scale (1-10). Affect was assessed using the 1-Item Feelings Scale. Exercise enjoyment was assessed using the Physical Activity Enjoyment Scale. The Physical Activity Enjoyment Scale has been shown to have a very high internal consistency (Cronbach's alpha = 0.906) and good test-retest reliability (rho = 0.868, $p<0.001$).[235] Participants were familiarized with each scale, and were instructed to point to the number on the scale corresponding with how they feel at the end of each minute of exercise in relation to leg fatigue, breathlessness, and affect.

Time of Measurement: Ratings of perceived exertion, ratings of perceived dyspnea, and the 1-item feelings scale were assessed at the end of each minute of exercise during the pre-

intervention and post-intervention testing sessions, and during exercise sessions 2 and 17. The physical activity enjoyment scale was completed following exercise during exercise sessions 2 and 17.

EIBC Specific

EIBC Confirmation

Measurement: Participants had their height and weight assessed (described below) and the handheld spirometer was updated accordingly. Participants completed 3 repeatable lung function assessments using handheld spirometry (described below) to determine their forced expiratory volume in 1 second (FEV_1) in accordance with the American Thoracic Society guidelines.[236] EIBC was confirmed using the EVH challenge. Participants were instructed to sit in front of the metabolic cart and were fitted with the mouthpiece, which was connected to the dry air used for the EVH challenge. Participants were fitted with a nose clip and were provided with a 30-second practice ventilation period, in order for participants to become familiarized with the required ventilation rate. Participants were given a 1 minute rest period breathing room air prior to the challenge. Participants were instructed to maintain a ventilation rate of 25-30 times their FEV_1 at baseline (determined by the researcher) for 6 minutes. Spirometry was performed post EVH at minutes 5, 10, 15, and 20 to determine the decline in FEV_1. If the participants FEV_1 was not beginning to recover at 20 minutes post-EVH, participants were instructed to take their short acting bronchodilator. The percentage decline in FEV_1 was calculated as follows:

- 100 x (FEV_1 (before test) – lowest value for FEV_1 (20 minutes after the test)) / FEV_1 (before test).

A decline in FEV_1 from pre to post-EVH challenge of 12% or greater was considered a positive EIBC response. For additional details on the EVH protocol in the proposed study refer to Appendix C1.

EIBC was also confirmed using a bronchodilator reversibility assessment. Upon arrival to the pre-intervention testing session, baseline spirometry was assessed. Participants were instructed to take their short acting bronchodilator. Fifteen minutes following bronchodilator administration, spirometry was re-assessed to determine improvements in lung function. A positive reversibility assessment was defined as $\geq$ 12% increase and $\geq$ 200mL as an absolute value compared to baseline FEV_1 or forced vital capacity.

Time of Measurement: The EVH challenge was conducted during the pre-screening and familiarization session and the bronchodilator reversibility was assessed during the pre-intervention testing session.

Lung Function

Measurement: Lung function was assessed using a handheld spirometer (EasyOne, Medizintechnik AG, Zurich, Switzerland). Spirometry was conducted in accordance with the American Thoracic Society standardized protocols.[236] Participants were emailed a video on proper spirometry technique prior to the pre-screening and familiarization session. Upon arrival to the laboratory, participants were given the following verbal instructions:

- "Please take a maximal inhale and at the top of the inhale, place your mouth over the mouthpiece and forcefully exhale as fast as you can and continue exhaling for 6 seconds, then take a maximal inhale."

Following the verbal instructions, participants were given a demonstration by the researcher or research assistant on proper spirometry technique. Participants were then fitted with a nose clip and were asked to perform spirometry according to standardized guidelines.

Time of Measurement: During the pre-screening and familiarization session, spirometry was conducted pre-EVH challenge and at minutes 5, 10, 15 and 20 minutes post-EVH. During the pre-intervention and post-intervention testing sessions, spirometry was taken upon arrival to the laboratory, 15 minutes following medication administration, and 10 minutes post-maximal exercise test. Spirometry was conducted upon arrival to the laboratory and following exercise at 5, 10, 15, and 20 minutes post exercise sessions 1 and 18.

Asthma Control and Quality of Life

Measurement: Asthma control was assessed using the Asthma Control Questionnaire. The Asthma Control Questionnaire was developed and validated to measure asthma control in adults.[193] Asthma related quality of life was assessed using the Mini-Asthma Quality of Life Questionnaire. The Mini-Asthma Quality of Life Questionnaire has been shown to have good reliability (Intra-class correlation coefficient=0.83) as well as validity, measured by responsiveness (p=0.0007).[237] Participants were read the instructions from the Asthma Control Questionnaire and the Mini-Asthma Quality of Life Questionnaire and were provided with a pen to complete the questionnaires.

Time of Measurement: Asthma specific outcomes were assessed at the beginning of exercise sessions 1 and 18.

Covariates

Height, Weight, and Waist Circumference

Measurement: Height and weight were assessed using a standardized medical scale (Detecto, USA). Participants were instructed to remove their shoes, jacket, sweater, hat, and all extraneous materials from their pockets. Participants were then asked to step onto the scale and weight was measured to the nearest 0.1 kg and height was measured to the nearest 0.1 cm. Waist circumference was assessed using a measuring tape. Measurements were taken at the top of the border of the iliac crest on the right hand side of the body using the cross handed technique.

Time of Measurement: Height was assessed during the pre-screening and familiarization session. Weight was assessed during the pre-screening and familiarization session, pre-intervention and post-intervention testing sessions, and during exercise sessions 1 and 18. Waist circumference was assessed during exercise sessions 1 and 18.

Thigh Skinfold

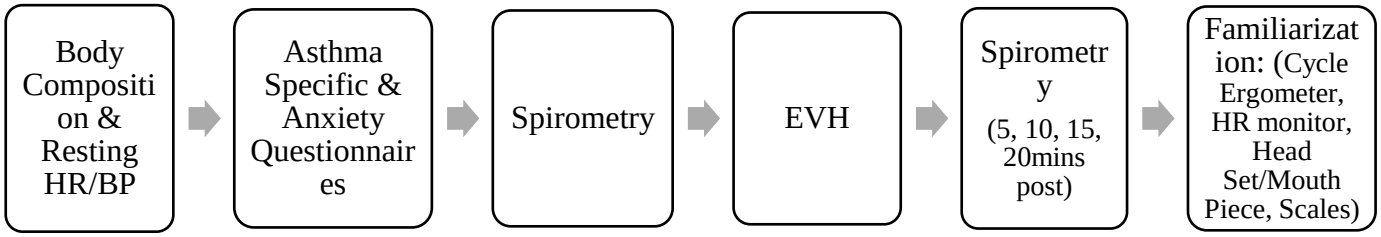
Measurement: Skinfold thickness of the thigh was measured midway between the proximal border of the patella and the inguinal crease, on the anterior midline of the thigh using calipers (Harpenden Skinfold Calipers, Baty International, United Kingdom). Participants were instructed to put their right foot forward balancing on their toe with all their weight on their back left leg. The anatomical location described above was landmarked using a common eyebrow pencil. The skin was grasped firmly with the thumb and index finger and the calipers were held perpendicular to the landmarked site. Calipers were placed one-quarter inch below the thumb and forefinger. The measurement was taken approximately 1 to 2 seconds after the trigger had been

released and recorded to the nearest 0.5 millimeter. A minimum of two measurements were taken, with at least 15 seconds between measurements to allow the fat to return to normal thickness.

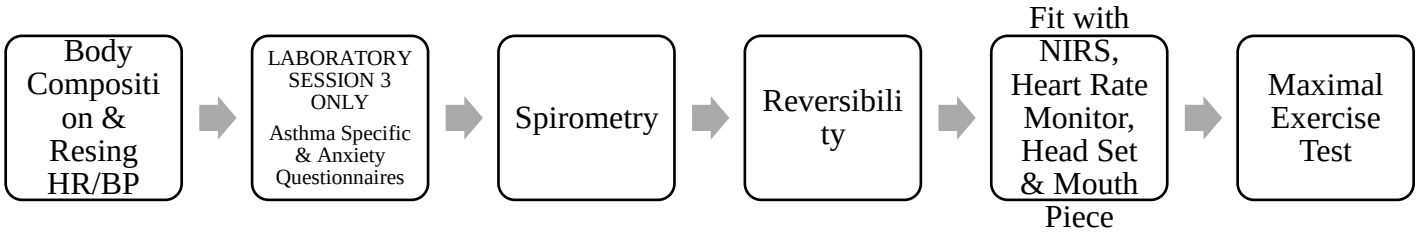
Time of Measurement: Thigh skinfolds were assessed during pre-intervention and post-intervention testing sessions and during exercise sessions 1 and 18.

Session Overviews:

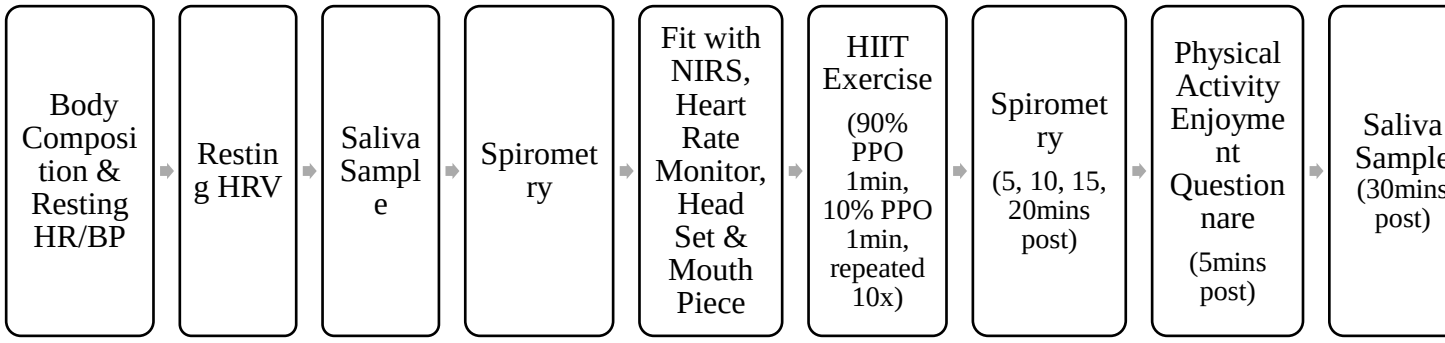
Pre-Screening and Familiarization Session: Overview



Pre-Intervention and Post-Intervention Testing Sessions: Overview



Exercise Sessions 1 and 18: Overview



Chapter 8: General Discussion

Primary Overarching Goal

The primary overarching goal of this dissertation was to examine the impact of HIIT on the physical,psychological, and clinical domains of health among adults with EIBC and healthy adults. In contrast to the primary hypothesis that similar improvements in the inflammation and ventilation outcomes would be observed between healthy adults and adults with asthma, our findings showed an improvement in salivary levels of inflammation among the asthma group only, and improvements in ventilation among the healthy control group only. These findings offer novel insight into the benefits of HIIT for reducing salivary levels of inflammation among adults with asthma and also points to potential limitations of improving ventilation outcomes as a result of EIBC.

Physiological Outcomes

In contrast to the primary hypothesis that a 6-week HIIT intervention would lead to improvements in IL-8 and IL-1Ra among adults with asthma and healthy controls, our findings showed no changes in IL-8 in either group and a reduction in IL-1Ra among the asthma group only.

Our findings of a reduction in salivary IL-1Ra levels following exercise training may be related to the reduction observed in salivary IL-1β levels among adults with asthma. IL-1β is elevated in the sputum of individuals with stable and exacerbating asthma [100] and the dysregulation between the IL-1β /IL-Ra ratio is important for the inflammation observed among adults with asthma [117]. Therefore, our findings suggest that HIIT may serve to improve the IL-1β /IL-Ra

ratio and these changes can be observed via salivary levels of each cytokine. Salivary assessment of cytokines is a non-invasive and efficient method, which may be preferable over a serum sample and thus, have important clinical implications among this population.

Secondly, in contrast to our hypothesis that adults with asthma and healthy controls would experience similar improvements in ventilation, we found that healthy controls were able to improve maximal ventilation, maximal respiratory rate, and tidal volume; however, adults with asthma were not. Previous research among healthy adults (n=72) reported similar improvements following 3-weeks of high intensity exercise [184]. Among adults with asthma, following 10-weeks of continuous exercise training no changes in $V_E$max, $V_T$max, or RRmax was observed [185]. Despite no changes in ventilatory outcomes among adults with asthma in response to exercise training, cardiorespiratory fitness is improved. Significant improvements among adults with asthma and healthy controls and these improvements did not differ between groups. This finding suggests that a 6-week HIIT intervention is effective in improving fitness regardless of an asthma diagnosis.

Psychological Outcomes

We predicted that a 6-week HIIT intervention would lead to a reduction in anxiety sensitivity and exercise specific anxiety among adults with asthma. In support of our hypothesis, we observed a significant reduction in both measures of anxiety. The strength of the effect size observed in the ASI-PC subcomponent (Cohens d = 0.6), suggests that a 6-week HIIT intervention may play an important role in reducing the anxiety surrounding physical sensations commonly experienced during exercise as well as during an asthma exacerbation (i.e. shortness

of breath). These findings are in line with previous research that has reported that exercise frequency and exercise intensity play an important role in reducing anxiety sensitivity [198, 199]

We also observed a significant reduction in asthma-related barriers to exercise participation and reported significantly reduced anxiety at the thought of exercise using the VAS. These findings are in line with previous research implemented a VAS to assess anxiety among adults with asthma, which noted significant improvements in feelings of fear surrounding breathlessness during exercise following a 10-week HIIT swimming intervention [197]. The use of VAS in this dissertation is a considerable strength as it allows for a greater understanding of subjective perceptions of each participants EIBC. VAS have high internal consistency and are sensitive to change [238]. Although statistically significant changes were not observed in the "how confident you feel in your ability to exercise without experiencing asthma symptoms (without taking medication)" VAS, a trend towards significance to medium was observed ($p=0.053$, Cohens $d = 0.4$). This finding, paired with the significant improvements and medium to large effect sizes in the VAS ""how much of a barrier is your asthma to exercise participation" (mean pre = 3.7 ± 2.7, mean post = 2.0 ± 1.2; $p=0.002$, Cohens $d = 0.8$) and "how much anxiety you experience due to your asthma when thinking about exercise participation" (mean pre = 2.8 ± 2.5, mean post = 1.3 ± 1.1; $p=0.005$, Cohens $d = 0.5$) suggesting that not only is HIIT able to elicit statistical changes but large differences in perceived asthma and exercise related anxiety.

Clinical Outcome

Our findings of an improvement in asthma control following a 6-week HIIT intervention, is in line with our hypothesis. Although previous research has observed similar findings following

continuous exercise training, [10] our findings are the first to demonstrate improvements in asthma control following HIIT. This novel finding, allows for greater diversity in exercise prescription among health care professionals working closely with the asthma population. Research has shown greater adherence to exercise when personal preference and exercise enjoyment are incorporated [160]. HIIT may allow for greater exercise adherence among those adults with asthma who may prefer HIIT over continuous exercise training, while still reaping the benefits of improved asthma control.

The improvements in the physiological, psychological, and clinical outcomes that were reported throughout this dissertation offer further evidence in support of exercise, and in particular HIIT, as a viable adjunct method of disease management among adults with EIBC..

Secondary Overarching Goal

The secondary overarching goal of this dissertation was to examine the interconnectedness between the physiological and psychological domains of health. There exists a close relationship between these domains, which has been noted in regards to anxiety and inflammation, in that high anxiety is positively associated with elevated inflammation [239]. To determine whether the data within this dissertation offered further support to this link, we tested our sample by running Pearson's Correlation coefficient. Our results revealed that IL-8 was the only cytokine we assessed that was moderately correlated anxiety. A moderate correlation (r=0.4) between salivary levels of IL-8 and anxiety among adults with asthma, while a small relationship was observed among healthy controls (r=0.2) was observed. Our findings further the evidence that those with higher levels of anxiety exhibit higher salivary levels of IL-8. Taking this one step further, we also analyzed our data to examine the relationship between asthma control and inflammation. Our findings did not show a strong correlation between the two (r=0.3); however,

previous research has suggested that asthma control is linked with levels of inflammation, in that those with worse asthma control have higher levels of inflammation [240]. It is likely that the homogeneity of our sample in terms of asthma control limited our ability to see a relationship between varying levels of asthma control and inflammation. An important avenue for future research will be to further examine the relationship between salivary levels of inflammation and asthma control following HIIT, among adults with varying levels of asthma control. The additional analyses of our data, further illustrate the importance of taking a broader approach to research in order to better understand the link between the physiological and psychological components of health and how this contributes to clinical outcomes.

Limitations

The results shared within this dissertation should be interpreted in light of the limitations addressed in Chapters 3-7, as well as the following. The lack of a control group of adults with EIBC limits the generalizability of our findings within the EIBC population. As well, in order to better determine the benefits of HIIT among adults with asthma, including a second treatment group composed of moderate intensity continuous exercise among adults with EIBC would have shone light on the ideal intensity of exercise for improving various components of health among this population. Finally, the assessment of cytokines via the saliva is a substantial limitation; however, incorporating an additional method of cytokine analysis (i.e. via the blood) would have given strength to our findings as well as provided valuable insight into the validity and reliability of using saliva samples to assess inflammation pre and post-exercise training among adults with and without EIBC. Despite these limitations, the results shared within this dissertation offer novel insight into the physical, psychological, and clinical impact of HIIT among adults with EIBC.

Future Directions

This dissertation provides foundational insight into the physiological, psychological, and clinical benefits of HIIT among adults with asthma and healthy controls. Future research should conduct large scale randomized controlled trials to determine the optimal and preferred mode of exercise training (e.g. HIIT vs continuous exercise) among adults with asthma. Determining an optimal and most preferred mode would aid in exercise prescription and could have an important impact on exercise adherence among this population. As well, future research should expand on the sex differences analyses within this dissertation in a larger sample to better understand the role of sex and the benefits of HIIT among adults with asthma. Finally, future research examining the impact of HIIT among adults with asthma should implement mid-intervention assessments in order to better understand the rate of improvements within all domains of health. A better understanding of the rate of change associated with HIIT would inform timelines for exercise interventions and training programs.

Conclusions

In conclusion, this dissertation sought to determine the impact of a 6-week HIIT intervention on physical fitness, inflammation, ventilation, and anxiety among adults with and without asthma. Furthermore, we sought to determine the effectiveness of a HIIT intervention on improving asthma control. This body of work demonstrates that a 6-week HIIT intervention leads to statistical and clinically meaningful improvements in salivary levels of inflammation, cardiorespiratory fitness, anxiety, and asthma control among adults with EIBC. These findings offer novel insight into the importance of assessing the impact of exercise interventions on the various components of health in order to improve the health of adults with and without asthma.

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APPENDICES

Appendix A: Questionnaires

A1) Eligibility and Demographic Questionnaire

A2) Physical Activity Readiness Questionnaire Plus

A3) Asthma Control Questionnaire – 7

A4) Mini Asthma Quality of Life Questionnaire

A5) Body Sensations Questionnaire

A6) Generalized Anxiety Disorder – 7

A1. Eligibility and Demographic Questionnaire

1. Age: _____

2. Sex:

   ❑ Female ❑ Male

   If you are a female, how many days has it been since the start of your last period? _____ _____

3. Has a doctor ever told you that you have asthma or exercise-induced asthma?
   a. Yes
   b. No

4. Do you currently have a rescue/reliever inhaler? (example: Ventolin or Bricanyl, blue puffer)
   a. Yes
   b. No

   If yes, please write the name of the medication here: _____
   _____

5. Are you currently taking any prescription or over the counter medications regularly (not previously listed in question 5)?
   a. Yes
   b. No

   If yes, please list the medications here: _____
   _____
   _____

6. When you are exercising at a moderate to vigorous intensity (i.e. your heart is beating faster and you begin to sweat) do you experience any of the following symptoms? Choose all that apply:
   a. Coughing
   b. Wheezing
   c. Chest Tightness
   d. Increased Mucus Production
   e. Difficulty Breathing

7. Do you have any injuries that would limit your ability to cycle on a stationary bicycle? (i.e. knee injury)
   a. Yes
   b. No

   If yes, please describe the injury here: _____
   _____
   _____

8. If you are a female, are you currently pregnant?
   a. Yes

b. No

9. Have you ever been a regular smoker?
    a. Yes
    b. No
    If yes, please indicate for how long: _____
    _____

10. At any point in the past six months, were you a regular smoker?
    a. Yes
    b. No

11. In a typical week, how much time to you spend participating in moderate to vigorous physical activity?
    a. Yes
    b. No
    Please describe the type of physical activity you engage in (i.e. walking, jogging, cycling): _____
    _____
    _____

12. Please list an emergency contact
    Name:_____
    Relationship: _____
    Phone Number:_____

A2. Physical Activity Readiness Questionnaire Plus

CSEP approved Sept 12 2011 version

PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

Regular physical activity is fun and healthy, and more people should become more physically active every day of the week. Being more physically active is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

SECTION 1 - GENERAL HEALTH

	Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1.	Has your doctor ever said that you have a heart condition OR high blood pressure?	☐	☐
2.	Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?	☐	☐
3.	Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4.	Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?	☐	☐
5.	Are you currently taking prescribed medications for a chronic medical condition?	☐	☐
6.	Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer NO if you had a joint problem in the past, but it does not limit your current ability to be physically active. For example, knee, ankle, shoulder or other.	☐	☐
7.	Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.

Go to Section 3 to sign the form. You do not need to complete Section 2.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow the Canadian Physical Activity Guidelines for your age (www.csep.ca/guidelines).
- You may take part in a health and fitness appraisal.
- If you have any further questions, contact a qualified exercise professional such as a CSEP Certified Exercise Physiologist® (CSEP-CEP) or CSEP Certified Personal Trainer® (CSEP-CPT).
- If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the questions above, please GO TO SECTION 2.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- You are pregnant – talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes – please answer the questions on Section 2 of this document and/or talk to your doctor or qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity programme.

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SECTION 2 - CHRONIC MEDICAL CONDITIONS

Please read the questions below carefully and answer each one honestly: check YES or NO.			YES	NO
1.	Do you have Arthritis, Osteoporosis, or Back Problems?		☐ If yes, answer questions 1a-1c	☐ If no, go to question 2
	1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/ or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	☐	☐
	1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	☐	☐
2.	Do you have Cancer of any kind?		☐ If yes, answer questions 2a-2b	☐ If no, go to question 3
	2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?	☐	☐
	2b.	Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?	☐	☐
3.	Do you have Heart Disease or Cardiovascular Disease? This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm		☐ If yes, answer questions 3a-3e	☐ If no, go to question 4
	3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	3b.	Do you have an irregular heart beat that requires medical management? (e.g. atrial fibrillation, premature ventricular contraction)	☐	☐
	3c.	Do you have chronic heart failure?	☐	☐
	3d.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer YES if you do not know your resting blood pressure)	☐	☐
	3e.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	☐	☐
4.	Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes		☐ If yes, answer questions 4a-4c	☐ If no, go to question 5
	4a.	Is your blood sugar often above 13.0 mmol/L? (Answer YES if you are not sure)	☐	☐
	4b.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the sensation in your toes and feet?	☐	☐
	4c.	Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?	☐	☐
5.	Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome)		☐ If yes, answer questions 5a-5b	☐ If no, go to question 6
	5a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	5b.	Do you also have back problems affecting nerves or muscles?	☐	☐

Please read the questions below carefully and answer each one honestly: check YES or NO.			YES	NO
6.	Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure		☐ If yes, answer questions 6a-6d	☐ If no, go to question 7
	6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	6b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	☐	☐
	6c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	☐	☐
	6d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	☐	☐
7.	Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia		☐ If yes, answer questions 7a-7c	☐ If no, go to question 8
	7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	7b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	☐	☐
	7c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	☐	☐
8.	Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event		☐ If yes, answer questions 8a-c	☐ If no, go to question 9
	8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	8b.	Do you have any impairment in walking or mobility?	☐	☐
	8c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	☐	☐
9.	Do you have any other medical condition not listed above or do you live with two chronic conditions?		☐ If yes, answer questions 9a-c	☐ If no, read the advice on page 4
	9a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months OR have you had a diagnosed concussion within the last 12 months?	☐	☐
	9b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	☐	☐
	9c.	Do you currently live with two chronic conditions?	☐	☐

Please proceed to Page 4 for recommendations for your current medical condition and sign this document.

PAR-Q+

If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active:

- It is advised that you consult a qualified exercise professional (e.g., a CSEP-CEP or CSEP-CPT) to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually – 20-60 min. of low- to moderate-intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate-intensity physical activity per week.
- If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the follow-up questions about your medical condition:

- You should seek further information from a licensed health care professional before becoming more physically active or engaging in a fitness appraisal and/or visit a or qualified exercise professional (CSEP-CEP) for further information.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise profesional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes - please talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity programme.

SECTION 3 - DECLARATION

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The Canadian Society for Exercise Physiology, the PAR-Q+ Collaboration, and their agents assume no liability for persons who undertake physical activity. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.
- Please read and sign the declaration below:

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that they maintain the privacy of the information and do not misuse or wrongfully disclose such information.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact:
Canadian Society for Exercise Physiology
www.csep.ca

KEY REFERENCES
1. Jamnik VJ, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, and Gledhill N. Enhancing the eectiveness of clearance for physical activity participation; background and overall process. APNM 36(S1):S3-S13, 2011.
2. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, Charlesworth S, and Shephard RJ. Evidence-based risk assessment and recommendations for physical activity clearance; Consensus Document. APNM 36(S1):S266-s298, 2011.

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or BC Ministry of Health Services.

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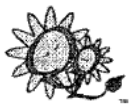
CSEP approved Sept 12 2011 version

A3. Asthma Control Questionnaire

ASTHMA CONTROL QUESTIONNAIRE



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ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID: _____

DATE: _____

Please answer questions 1 - 6.

Circle the number of the response that best describes how you have been during the past week.

1. On average, during the past week, how often were you **woken by your asthma** during the night?
   - 0 Never
   - 1 Hardly ever
   - 2 A few times
   - 3 Several times
   - 4 Many times
   - 5 A great many times
   - 6 Unable to sleep because of asthma

2. On average, during the past week, how **bad were your asthma symptoms when you woke up** in the morning?
   - 0 No symptoms
   - 1 Very mild symptoms
   - 2 Mild symptoms
   - 3 Moderate symptoms
   - 4 Quite severe symptoms
   - 5 Severe symptoms
   - 6 Very severe symptoms

3. In general, during the past week, how **limited were you in your activities** because of your asthma?
   - 0 Not limited at all
   - 1 Very slightly limited
   - 2 Slightly limited
   - 3 Moderately limited
   - 4 Very limited
   - 5 Extremely limited
   - 6 Totally limited

4. In general, during the past week, how much **shortness of breath** did you experience because of your asthma?
   - 0 None
   - 1 A very little
   - 2 A little
   - 3 A moderate amount
   - 4 Quite a lot
   - 5 A great deal
   - 6 A very great deal

Revised September 2010
ACQ-SA North American English Version

ASTHMA CONTROL QUESTIONNAIRE© PATIENT ID: _____

DATE: _____

5. In general, during the past week, how much of the time did you **wheeze?**	0	Not at all
	1	Hardly any of the time
	2	A little of the time
	3	A moderate amount of the time
	4	A lot of the time
	5	Most of the time
	6	All the time
6. On average, during the past week, how many **puffs/inhalations of short-acting bronchodilator** (eg. Ventolin/Bricanyl) have you used each day? *(If you are not sure how to answer this question, please ask for help)*	0	None
	1	1 - 2 puffs/inhalations most days
	2	3 - 4 puffs/inhalations most days
	3	5 - 8 puffs/inhalations most days
	4	9 - 12 puffs/inhalations most days
	5	13 - 16 puffs/inhalations most days
	6	More than 16 puffs/inhalations most days

To be completed by a member of the clinic staff

7. FEV_1pre-bronchodilator:	0	> 95% predicted
	1	95 - 90%
FEV_1predicted:	2	89 - 80%
	3	79 - 70%
FEV_1%predicted:	4	69 - 60%
(Record actual values on the dotted lines and score the FEV_1 % predicted in the next column)	5	59 - 50%
	6	< 50% predicted

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A4. Mini Asthma Quality of Life Questionnaire

MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE (MiniAQLQ)

SELF-ADMINISTERED

For further information:

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Developement and validation supported by GLAXO WELLCOME, INC.

OCTOBER 2000

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MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE PATIENT ID_____

SELF-ADMINISTERED DATE_____

Please complete **all** questions by circling the number that best describes how you have been during the **last 2 weeks as a result of your asthma.**

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

		All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
1.	Feel SHORT OF BREATH as a result of your asthma?	1	2	3	4	5	6	7
2.	Feel bothered by or have to avoid DUST in the environment?	1	2	3	4	5	6	7
3.	Feel FRUSTRATED as a result of your asthma?	1	2	3	4	5	6	7
4.	Feel bothered by COUGHING?	1	2	3	4	5	6	7
5.	Feel AFRAID OF NOT HAVING YOUR ASTHMA MEDICATION AVAILABLE?	1	2	3	4	5	6	7
6.	Experience a feeling of CHEST TIGHTNESS or CHEST HEAVINESS?	1	2	3	4	5	6	7
7.	Feel bothered by or have to avoid CIGARETTE SMOKE in the environment?	1	2	3	4	5	6	7
8.	Have DIFFICULTY GETTING A GOOD NIGHT'S SLEEP as a result of your asthma?	1	2	3	4	5	6	7
9.	Feel CONCERNED ABOUT HAVING ASTHMA?	1	2	3	4	5	6	7

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MINI ASTHMA QUALITY OF LIFE QUESTIONNAIRE PATIENT ID_____

SELF-ADMINISTERED DATE_____

IN GENERAL, HOW MUCH OF THE TIME **DURING THE LAST 2 WEEKS** DID YOU:

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	Hardly Any of the Time	None of the Time
10. Experience a WHEEZE in your chest?	1	2	3	4	5	6	7
11. Feel bothered by or have to avoid going outside because of WEATHER OR AIR POLLUTION?	1	2	3	4	5	6	7

HOW LIMITED HAVE YOU BEEN DURING **THE LAST 2 WEEKS** DOING THESE ACTIVITIES **AS A RESULT OF YOUR ASTHMA?**

	Totally Limited	Extremely Limited	Very Limited	Moderate Limitation	Some Limitation	A Little Limitation	Not at all Limited
12. STRENUOUS ACTIVITIES (such as hurrying, exercising, running up stairs, sports)	1	2	3	4	5	6	7
13. MODERATE ACTIVITIES (such as walking, housework, gardening, shopping, climbing stairs)	1	2	3	4	5	6	7
14. SOCIAL ACTIVITIES (such as talking, playing with pets/children, visiting friends/relatives)	1	2	3	4	5	6	7
15. WORK-RELATED ACTIVITIES (tasks you have to do at work*)	1	2	3	4	5	6	7

** If you are not employed or self-employed, these should be tasks you have to do most days.*

DOMAIN CODE:

Symptoms: 1, 4, 6, 8, 10
Activity Limitation: 12, 13, 14, 15
Emotional Function: 3, 5, 9
Environmental Stimuli: 2, 7, 11

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A5. Body Sensations Questionnaire

BSQ

Below is a list of body sensations that may occur when you are nervous or frightened. Please circle how afraid you are by circling any of the numbers from 1 to 5 on the scales below.
Please rate all items in that matter.

	very little	a little	some	much	very much
1. Heart palpations.....	1	2	3	4	5
2. Pressure, pain, or heavy feeling in chest.....	1	2	3	4	5
3. Numbness in legs or arms.....	1	2	3	4	5
4. Tingling in fingertips.....	1	2	3	4	5
5. Numbness in another part of body.....	1	2	3	4	5
6. Feeling short of breath.....	1	2	3	4	5
7. Dizziness.....	1	2	3	4	5
8. Blurred or distorted vision.....	1	2	3	4	5
9. Nausea.....	1	2	3	4	5
10. It scares me when I become short of breath.....	1	2	3	4	5
11. Having "butterflies" in my stomach.....	1	2	3	4	5
12. Feeling a "knot" in my stomach.....	1	2	3	4	5
13. Having a lump in my throat.....	1	2	3	4	5
14. Sweating.....	1	2	3	4	5
15. A dry throat.....	1	2	3	4	5
16. Feeling disoriented and confused.....	1	2	3	4	5

A6. Generalized Anxiety Disorder – 7

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

Appendix B: Scales

B1) Ratings of Perceived Exertion
B2) Ratings of Perceived Dyspnea
B3) One-Item Feelings Scale
B4) Physical Activity Enjoyment Scale
B5) Anxiety Sensitivity Index – 3
B6) Visual Analog Scales

B1. Borg Scale of Perceived Exertion

6 – No Exertion at all

7 – Extremely Light

8

9 – Very Light

10

11 – Light

12

13 – Somewhat Hard

14

15 – Hard (heavy)

16

17 – Very Hard

18

19 – Extremely Hard

20 – Maximal Exertion

B2. Revised Borg Scale for Grading Severity of Dyspnea

0 – Nothing at all

1 – Just Noticeable

2 – Very Slight

3 – Slight

4 – Slight/Moderate

5 – Moderate

6 – Some Difficulty

7 – Moderately Severe

8 - Severe

9 – Very Severe

10 – Panic Level, Maximal Shortness of Breath

B3. One-Item Feelings Questionnaire Feeling Scale (FS)

(Hardy & Rejeski, 1989)

+ 5 – Very Good

4

3 – Good

2

1

0 – Neutral

-1 – Fairly Bad

-2

-3 - Bad

-4

-5 – Very Bad

B4. Physical Activity Enjoyment Scale

Please rate how you feel at the moment about the physical activity you have been doing. •

	1	2	3	4	5	6	7	
I enjoy it								I hate it
	1	2	3	4	5	6	7	
I feel bored								I feel interested
	1	2	3	4	5	6	7	
I dislike it								I like it
	1	2	3	4	5	6	7	
I find it pleasurable								I find it unpleasurable
	1	2	3	4	5	6	7	
I am very absorbed in this activity								I am not at all this activity absorbed in this activity
	1	2	3	4	5	6	7	
It's no fun at all								It's a lot of fun
	1	2	3	4	5	6	7	
I find it energizing								I find it tiring
	1	2	3	4	5	6	7	
It makes me depressed								It makes me happy
	1	2	3	4	5	6	7	
It's very pleasant								It's very unpleasant
	1	2	3	4	5	6	7	

I feel good physically while doing it I feel bad physically while doing it

1 2 3 4 5 6 7

It's very invigorating It's not at all invigorating

1 2 3 4 5 6 7

I am very frustrated by it I am not at all frustrated by it

1 2 3 4 5 6 7

It's very gratifying It's not at all gratifying

1 2 3 4 5 6 7

It's very exhilarating It's not at all exhilarating

1 2 3 4 5 6 7

It's not at all stimulation It's very stimulating

1 2 3 4 5 6 7

It gives me a strong sense It does not give me any sense

of accomplishment accomplishment at all

1 2 3 4 5 6 7

It's very refreshing It's not at all refreshing

1 2 3 4 5 6 7

I felt as though I would rather be I felt as though there was

doing something else nothing would rather be doing

1 2 3 4 5 6 7

Item is reversed scored(i.e..1=7,2=6,. .. 6=2,7=1).

B5. Anxiety Sensitivity Index - 3

ASI-3

Please circle the number that best corresponds to how much you agree with each item. If any items concern something that you have never experiences (e.g. fainting in public) answer on the basis of how you think you might feel *if you had* such an experience. Otherwise, answer all items on the basis of your own experience. Be careful to circle only one number for each item and please answer all items.

		Very little	**A little**	**Some**	**Much**	**Very much**
1.	It is important for me not to appear nervous.	0	1	2	3	4
2.	When I cannot keep my mind on a task, I worry that I might be going crazy.	0	1	2	3	4
3.	It scares me when my heart beats rapidly.	0	1	2	3	4
4.	When my stomach is upset, I worry that I might be seriously ill.	0	1	2	3	4
5.	It scares me when I am unable to keep my mind on a task.	0	1	2	3	4
6.	When I tremble in the presence of others, I fear what people might think of me.	0	1	2	3	4
7.	When my chest feels tight, I get scared that I won't be able to breathe properly.	0	1	2	3	4
8.	When I feel pain in my chest, I worry that I'm going to have a heart attack.	0	1	2	3	4
9.	I worry that other people will notice my anxiety.	0	1	2	3	4
10.	When I feel "spacey" or spaced out I worry that I may be mentally ill.	0	1	2	3	4
11.	It scares me when I blush in front of people.	0	1	2	3	4

12. When I notice my heart skipping a beat, I worry that there is something seriously wrong with me.	0	1	2	3	4
13. When I begin to sweat in a social situation, I fear people will think negatively of me.	0	1	2	3	4
14. When my thoughts seem to speed up, I worry that I might be going crazy.	0	1	2	3	4
15. When my throat feels tight, I worry that I could choke to death.	0	1	2	3	4
16. When I have trouble thinking clearly, I worry that there is something wrong with me.	0	1	2	3	4
17. I think it would be horrible for me to faint in public.	0	1	2	3	4
18. When my mind goes blank, I worry there is something terribly wrong with me.	0	1	2	3	4

Note. Scoring: Physical concerns = sum of Items 3, 4, 7, 8, 12, 15. Cognitive concerns = sum of Items 2, 5, 10, 14, 16, 18. Social concerns = sum of Items 1, 6, 9, 11, 13, 17.

B5. Visual Analog Scale Questions (100mm)

1) Please indicate how much your asthma impacts your willingness to exercise by placing an x along the line below:

No Impact Extreme Impact

2) Note how much anxiety you experience due to your asthma when thinking about exercise participation:

No Anxiety Extreme Anxiety

3) Note how confident you feel in your ability to exercise without experiencing asthma symptoms (without taking medication):

Not Confident Extremely Confident

Appendix C: Standard Operating Procedures

C1) Eucapnic Voluntary Hyperpnea Challenge

C2) Saliva

C3) Near Infrared Spectroscopy

C1. Eucapnic Voluntary Hyperpnea Challenge

Preparation and Instructions

Materials:

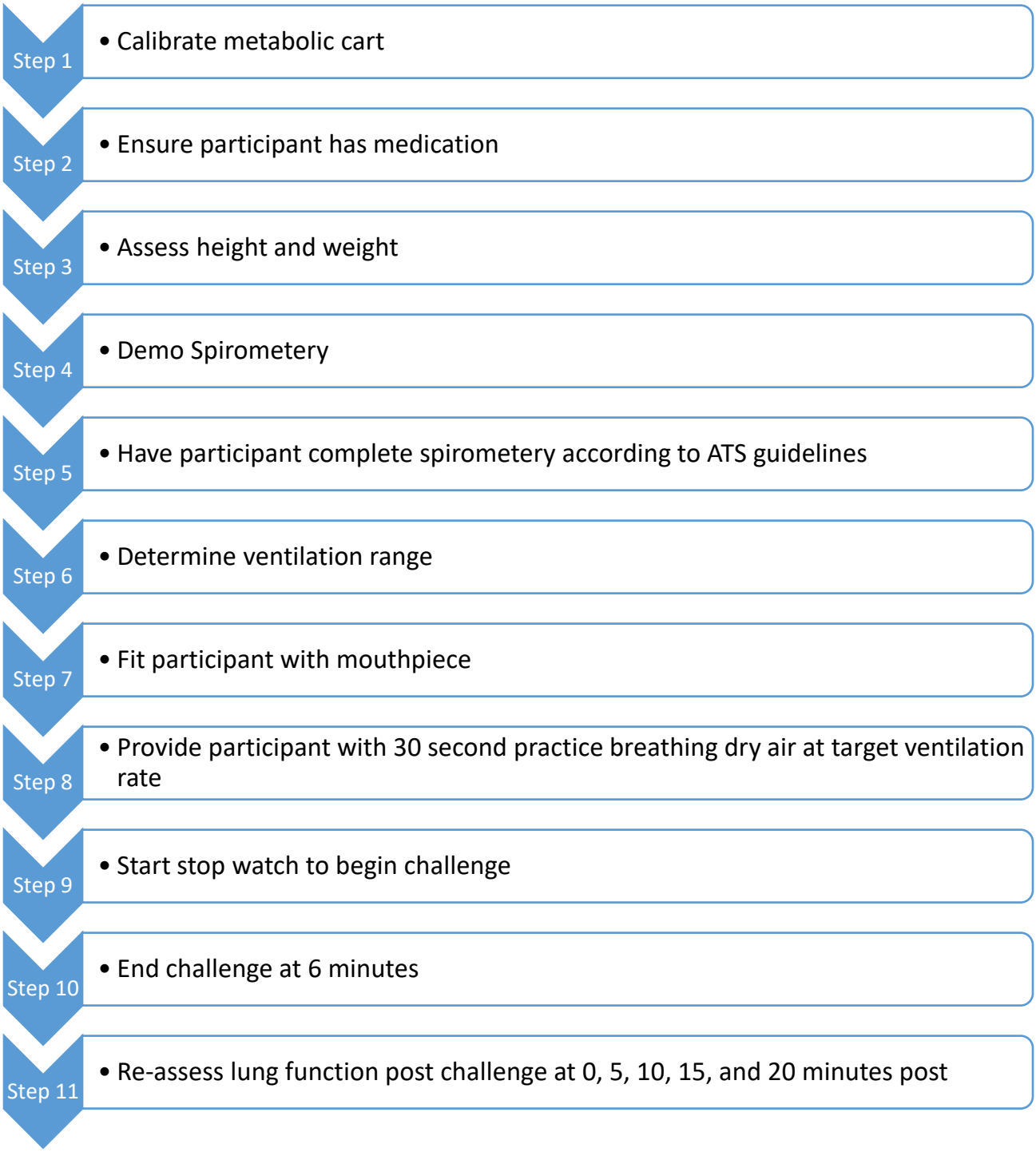
- Medical Scale
- Handheld Spirometer
- Metabolic Cart
- Mouth Piece
- Dry Air
- Nose Clip

Participant Instructions:

- With-hold long acting medication 48 hours prior to testing
- With-hold short acting medication 8 hours prior to testing
- Refrain from consuming caffeinated beverages at least 2 hours prior to testing
- Refrain from consuming a heavy meal at least 2 hours prior to testing
- Bring shorts and sneakers to testing session
- Bring current rescue medication to testing session

EVH Challenge Procedures

Sample Collection Instructions:



Sample Handling Procedures

Storage: Data will be immediately coded and stored on the password protected laptop of the student researcher and backed up onto a password protected USB.

Data Analysis: Lung function will be assessed pre and post challenge at minutes 0, 5, 10, 15, and 20. The decline in lung function will be determined using the following equation:

$$\% \text{ fall in } FEV_1 = 100 \times [FEV_1 \text{ (pre-challenge)} - (\text{lowest value for } FEV_1 \text{ post-challenge})] \; FEV_1 \text{ pre-challenge}$$

Confirmation of EIBC will be determined by a decline in $FEV_1 \geq 12\%$.

C2. Saliva

Preparation and Instructions

Materials:

- Cryovials
- Saliva Collection Aid
- Bar-Coded Labels
- Cryostorage Box
- Medical Gloves
- Water

Instructions:

- To ensure participants have followed instructions, document:
  - consumption of alcohol, caffeine, nicotine, and prescription/over-the-counter medications within the previous 12 hours,
  - consumption of meal within the previous 60 minutes, AND
  - consumption of foods with high sugar, acidity, or caffeine content, immediately before sample collection.
- Document the participant's physical activity levels and the presence of oral diseases or injury.
- Have participant rinse mouth with water (provided by researchers) to remove food residue and wait at least 10 minutes after rinsing to collect sample.

Saliva Collection Procedures

Sample Collection Instructions:

Step 1
- Provide participant with water to rinse their mouth and wait 10 minutes before sample collection

Step 2
- Put on medical gloves

Step 3
- Remove cap from cryovial

Step 4
- Remove saliva collection aid from packaging and place securely into cryovial

Step 5
- Instruct participant to allow saliva to pool in mouth

Step 6
- With head tilted forward, participants should drool through the saliva collection aid to collect saliva in the cryovial

Step 7
- Repeat until sufficient sample (2mL) is collected

Step 8
- *Special Consideration*
- If sample contains visible blood re-collect sample

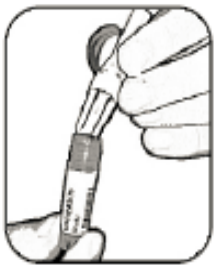
Step 9
- Reserve air space in the vial to accommodate the expansion of saliva during freezing

Step 10
- Replace cap onto cryovial

Step 11
- Code sample, record date and time and place immediately into -80 freezer

Visual Aid for Saliva Collection:

Step 1:
Open foil pouch and remove the Saliva Collection Aid (SCA).



Step 2:
Place ribbed-end of the SCA securely into a pre-labeled collection vial *(see Caution 3 above)*.

Step 3:
Allow saliva to pool in mouth. Then, with head tilted forward, **gently** force saliva through the SCA into the vial. Fill to the required volume.*

Step 4:
Remove and discard SCA. Attach cap to collection vial and tighten.

Sample Handling Procedures

Storage: Samples will be collected using Salimetrics high quality polypropylene 2ml cryovials (Salimetrics Item No. 5002.01). Samples will be transported in accordance with the Transportation of Dangerous Goods Act and regulations. Briefly, all samples will be securely sealed and packaged prior to transport. To allow for multi-analyte testing, samples will be aliquoted to smaller vials within a biosafety cabinet using aseptic technique and guidelines as outlined in the UOIT Biosafety manual. Samples will be sealed tightly and immediately coded using labels recommended for freezing (i.e. cryolabels) and placed into a -80 degree freezer in Dr. Dogra's laboratory and stored until analysis.

Analysis: All samples will be handled in a level 2 Bio-Safety Cabinet in Dr. Jones Taggart laboratory. The student researcher has completed the Laboratory Bio-Safety training program and has been included on Dr. Jones Taggart's biosafety certificate. During analysis, one saliva sample from each participant collected at baseline will be combined to run a pooled sample cytokine array. As well, one saliva sample from each participant collected following the first HIIT session will be combined to run a pooled sample cytokine array. Results from the pooled analysis will determine the specific cytokine arrays that will be used for subsequent salivary analyses. Multi-analyte testing will occur and each analyte sample will be analyzed at the same time to avoid multiple freeze thaw cycles.

Sample Disposal: Saliva samples will be disposed using the UOIT pre-approved protocol as outlined in the Biosafety Manual, which involves autoclaving for at least 30 minutes at 121 C prior to disposal in a regular garbage

C3. Near Infrared Spectroscopy SOP

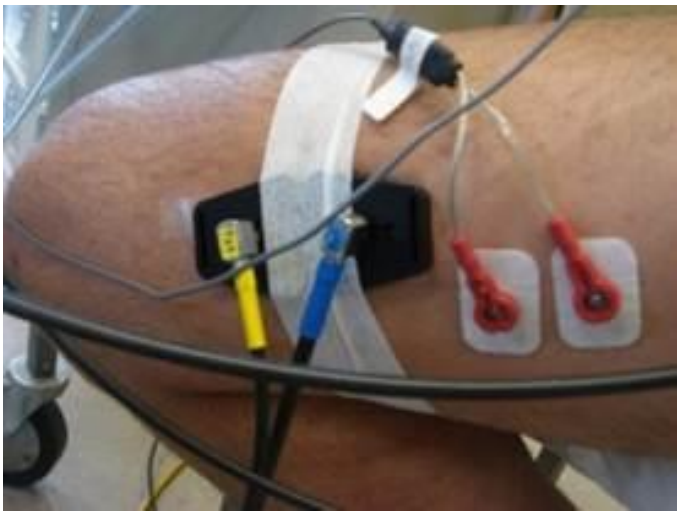
Preparation and Instructions

Materials:

- Near Infrared Spectroscopy (NIRS) Probe
- Black Cloth
- Double Sided Tape
- Tensor Bandage

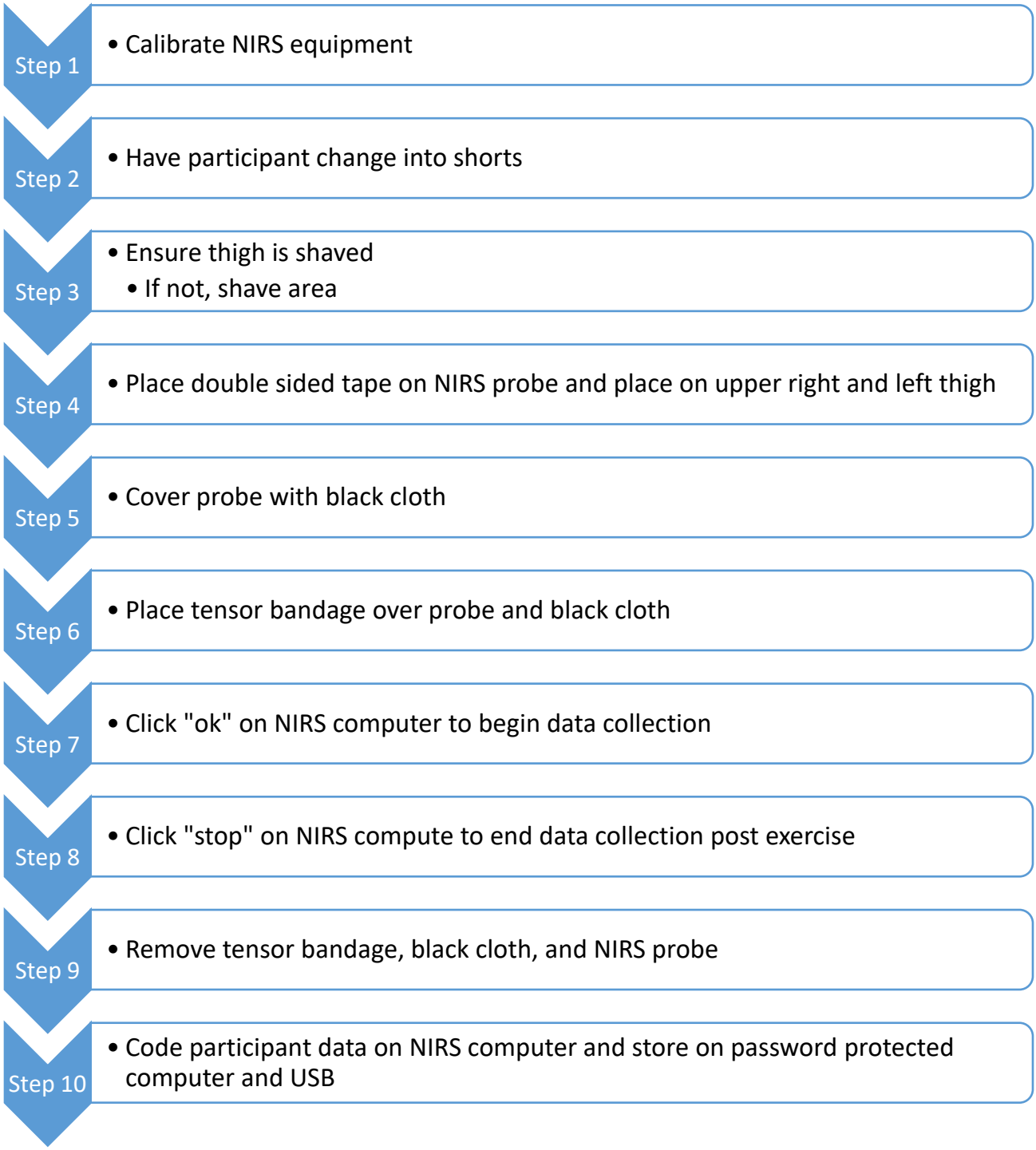
Participant Instructions:

- Shave upper thigh
- Wear shorts such that upper thigh can be accessed as shown below:



NIRS Collection Procedures

Sample Collection Instructions:



Sample Handling Procedures

Storage: Data will be immediately coded and stored on the password protected laptop of the student researcher and backed up onto a password protected USB.

Analysis: All data will be cleaned in Microsoft Excel. Any down sampling will occur in the NIRS software (Artinis Oxymon III, Netherlands).

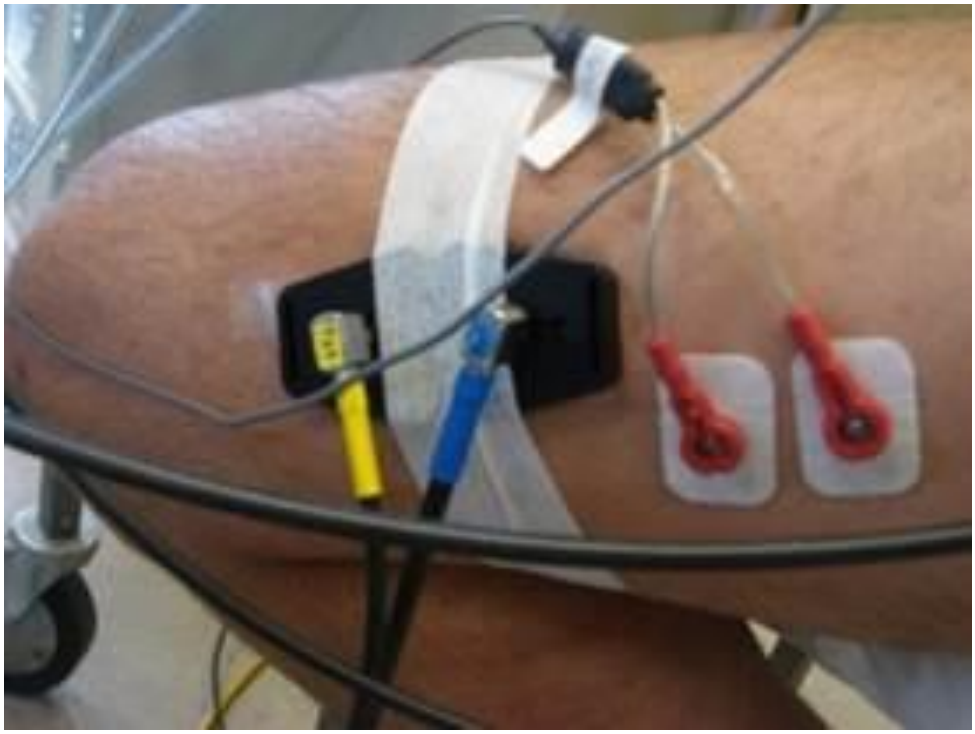
Appendix D: Figures

1) Handheld Spirometry
2) Eucapnic Voluntary Hyperpnea Challenge
3) Near Infrared Spectroscopy Probe
4) Near Infrared Spectroscopy System
5) PhysioFlow Enduro
6) Direct Maximal Exercise Test on Cycle Ergometer

H1. Handheld Spirometry

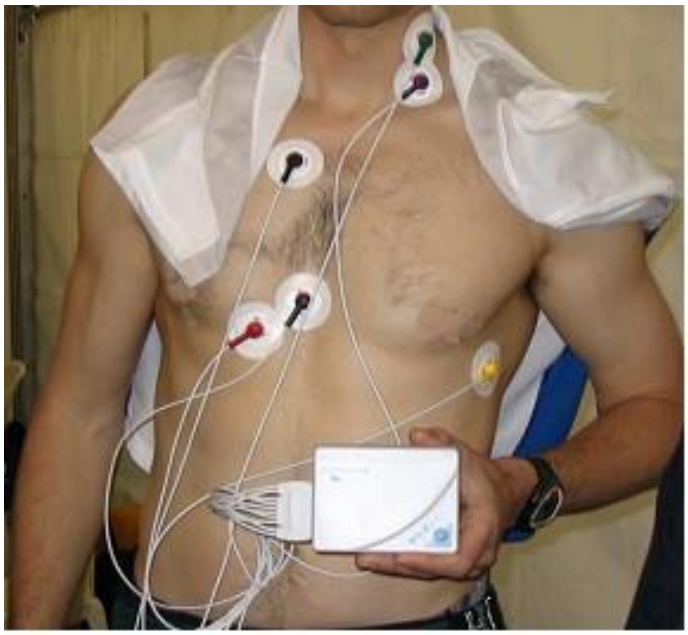
H2. Eucapnic Voluntary Hyperpnea Challenge

H3. Probe used for Near Infrared Spectroscopy



H4. Near Infrared Spectroscopy System

H5. Physioflow Enduro



H6. Direct Maximal Exercise Test