Evaluating the Physiological and Perceptual Responses to Inspiratory Muscle Training in Males and Females

By

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Abstract

Background: Although the respiratory system is often considered "overbuilt" for the ventilatory demands of exercise in healthy individuals, respiratory muscle fatigue can limit exercise tolerance by increasing the work of breathing, activating the respiratory muscle metaboreflex, and exacerbating exertional dyspnoea. Inspiratory muscle training (IMT) improves inspiratory muscle strength and reduces respiratory muscle fatigue; however, whether males and females adapt differently remains unclear.

Objective: To determine whether sex influences physiological (inspiratory muscle strength, exercise performance) and perceptual (exertional dyspnoea) responses to IMT in physically active adults.

Methods: Twenty-five healthy, physically active adults (12 males, 13 females; 20–60 years) completed a 5-week IMT program (two daily sessions of 30 breaths, 5 days/week) at 60% of maximal inspiratory pressure (MIP), with weekly workload adjustments. Before and after training, participants completed pulmonary function testing, MIP assessment, incremental and constant-load exercise tests, and ratings of dyspnoea intensity and unpleasantness (modified Borg CR10 scale). Two-way repeated-measures analysis of variance were performed and if significant F ratios were detected, Tukey's or Bonferroni-adjusted post hoc tests were performed. Multiple linear regression analyses examined whether sex and relative change in inspiratory muscle strength (% change in MIP) independently predicted changes in perceptual and physiological exercise outcomes.

Results: Relative MIP increased significantly following IMT in both sexes (43.7 ± 23.9% vs. 40.7 ± 36.4%; $p < 0.0001$), with no sex-by-time interaction, although males exhibited greater absolute increases ($p = 0.01$). Peak oxygen uptake, constant-load exercise endurance time, and dyspnoea during incremental exercise were unchanged after IMT, with no sex differences in training responses. Oxygen uptake at the same submaximal workload decreased following IMT ($p < 0.05$). During constant-load exercise at isotime, dyspnoea intensity and unpleasantness demonstrated significant sex-by-time interactions (both $p = 0.02$). Changes in MIP were not associated with exercise performance or dyspnoea, whereas sex was associated with dyspnoea intensity changes ($p = 0.038$), with greater reductions in females.

Conclusion: In physically active adults, IMT increased inspiratory muscle strength similarly in males and females but did not translate into improved exercise performance. Sex-specific differences were observed only in perceptual responses during constant-load exercise, suggesting limited sex-related effects of IMT.

Keywords: Dyspnoea; Exercise Physiology; Inspiratory Muscle Training; Respiratory System; Sex Differences

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Dedication

This work is dedicated to my lovely sister and my beautiful nieces and nephews.

To my sister, thank you for being my biggest cheerleader. I am deeply grateful for your love, support, and presence in my life.

To my nieces and nephews, being your *massi* (aunty) is my favorite title in the world. Everything I do in my life is to impress you, inspire you, and be someone you can look up to.

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CHAPTER 1: INTRODUCTION

The respiratory system includes the lungs, airways, rib cage, and respiratory muscles. For healthy young individuals of average cardiorespiratory fitness, the functional capacity of the respiratory system far exceeds demand imposed upon it, whereby there are no significant limitations to ventilation, gas exchange, or oxygen transport, even during maximal exercise. At sea level, oxygen transport is not constrained by oxygen diffusion across the alveolar-capillary membrane, and humans seem to have a sufficient breathing reserve even at peak exertion. Indeed, in healthy young adults of average cardiorespiratory fitness, the respiratory system is often considered "overbuilt" for the ventilatory demands of exercise (Dempsey, 1986; Dempsey et al., 2020; Peters at al., 2023). As a result, it was widely assumed that the respiratory system does not limit exercise performance.

Inspiratory muscle fatigue can impair exercise performance by increasing respiratory drive and ventilatory demand, which triggers reflex sympathetic responses that limit blood flow to the working limbs (Dempsey et al., 2006). Electromyography (EMG) studies show that fatigue develops more rapidly in inspiratory muscles than in locomotor muscles, suggesting that respiratory muscle fatigue may precede and constrain overall performance (Harms et al., 1997; Segizbaeva & Isaev, 2013; Spengler & Boutellier, 2000). The diaphragm, the primary muscle of inspiration, is particularly susceptible to fatigue during sustained high-intensity exercise (Harms et al., 1997). When diaphragm fatigue occurs, it activates the respiratory muscle metaboreflex, a sympathetically-mediated response that preserves respiratory muscle oxygenation by diverting blood flow away from locomotor muscles and towards the active respiratory muscles (Sheel et al., 2001; St Croix et al., 2000). This reflex is triggered by metabolically and mechanically

sensitive group III and IV afferent fibers in the phrenic nerve (Hill, 2000; Jammes & Balzamo, 1992; Rodman et al., 2003), leading to increased muscle sympathetic nerve activity (MSNA), vasoconstriction, elevated arterial pressure, and reduced perfusion to active limbs (Sheel et al., 2018). While this mechanism supports pulmonary function and systemic homeostasis under stress, it compromises exercise tolerance by reducing oxygen delivery to active locomotor muscles, thereby accelerating the onset of peripheral fatigue (Harms et al., 1997, 2000; Sheel et al., 2018). These effects are particularly pronounced during maximal effort or under hypoxic conditions (Downey et al., 2007; Witt et al., 2007).

Growing evidence supports respiratory muscle training (RMT) as an effective strategy to mitigate the detrimental effects of respiratory muscle fatigue and the associated metaboreflex (Illi et al., 2012; McConnell & Romer, 2004). RMT enhances respiratory muscle strength and endurance, reduces the severity and rate of respiratory muscle fatigue development, and delays activation of the metaboreflex, thereby preserving blood flow to the locomotor muscles during exercise (Romer et al., 2002b; Witt et al., 2007). These adaptations contribute to lower cardiovascular strain, reduced perceived exertion, and improved ventilatory efficiency. In addition to mechanical benefits, RMT improves acid-base regulation by upregulating monocarboxylate transporters (MCT1 and MCT4), facilitating more efficient lactate and hydrogen ion clearance from respiratory muscles (McConnell & Sharpe, 2005; Shei, 2018). This results in reduced lactate accumulation and attenuated sympathetic responses under both normoxic and hypoxic conditions (Illi et al., 2012; Witt et al., 2007), contributing to improved oxygenation, delayed onset of dyspnoea, and enhanced overall exercise performance. By attenuating the respiratory muscle metaboreflex and enhancing metabolic efficiency, RMT

represents a promising, evidence-based intervention to optimize both respiratory and physical performance (González-Montesinos et al., 2012; Witt et al., 2007).

The respiratory muscles can be broadly categorized into inspiratory and expiratory groups. The diaphragm is the primary muscle of inspiration, assisted by accessory muscles such as the sternocleidomastoid and scalenes (Dempsey et al., 2010). In contrast, expiration at rest is passive, relying on elastic recoil; active expiration during exercise involves muscles like the rectus abdominis, internal/external obliques, and internal intercostals. Because many expiratory muscles serve postural or trunk functions, they are challenging to isolate and study, which may explain the emphasis on inspiratory muscle training (IMT) in the literature. IMT has been shown to improve exercise performance, reduce the perception of breathlessness, and lower resting blood pressure in healthy adults (DeLucia et al., 2018; HajGhanbari et al., 2013; Illi et al., 2012). However, the majority of these studies have involved only male participants. According to the available literature, only two studies have explicitly examined sex differences in response to respiratory muscle training. One reported similar but variable improvements in exercise performance after five weeks of IMT in both sexes (Guenette et al., 2006), while the other found that respiratory muscle endurance training (RMET) yielded greater performance improvements in females than in males (Chambault et al., 2021). Notably, neither study assessed dyspnoea perception or muscle activation patterns.

Despite representing just ~3% of total body mass (i.e., ~960 g), respiratory muscles play a crucial role in the systemic physiological responses to exercise (Brooks & Strohl, 1989; Ofir et al., 2008; Zhang et al., 2020). For example, hypertrophic and histological changes have been observed after IMT, including an 8% increase in transdiaphragmatic pressure at residual volume in young adults (Chambault et al., 2021) and a 21% increase in type II fiber size in the external

intercostals in COPD patients (Ramirez-Sarmiento et al., 2002). Two main lines of evidence suggest that respiratory muscle work limits dynamic exercise performance. First, the respiratory muscle metaboreflex, activated by high inspiratory loads, induces sympathetic vasoconstriction and redistributes blood flow away from locomotor muscles (Harms et al., 1997; Sheel, 2002; Sheel et al., 2001). IMT may raise the threshold for metaboreflex activation, analogous to forearm ischemic thresholds improving with handgrip training (Mostoufi-Moab et al., 1998). Second, altering the work of breathing (WOB) during exercise influences locomotor fatigue and performance, whereby unloading improves endurance and loading impairs it (Harms et al., 2000; Romer et al., 2006).

Increased activation of extradiaphragmatic inspiratory muscles, particularly the scalene and sternocleidomastoid, has been observed during IMT and is linked to reduced dyspnoea (Ramsook et al., 2016, 2017). Sex differences may influence muscle recruitment patterns. During exercise, females rely more on extradiaphragmatic muscles, potentially due to male-female difference in rib cage shape (Bellemare et al., 2003; Mitchell et al., 2018; Molgat-Seon et al., 2018a). Anatomical differences between sexes contribute to observed disparities in respiratory mechanics and fatigue. On average, males are taller than females and therefore have larger lungs (Tan et al., 2011), even when matched for standing or sitting height, a surrogate for chest volume (Schwartz et al., 1988). Modern imaging techniques (e.g., computed tomography) have shown that males not only have larger rib cages and lungs than females, but that these structures also differ in shape; males typically have shorter rib cages and lungs with wider bases compared to females (Garcia-Martinez et al., 2016; Torres-Tamayo et al., 2018). As females generally have smaller lungs, it is unsurprising that they also possess smaller large conducting airways (i.e., from the trachea to the bronchioles) (Dominelli et al., 2018, 2019; Sheel et al., 2009). Although

one might expect lung and airway size to be proportionally related, their growth trajectories are not equal, a mismatch known as “dysanapsis” (Mead, 1980). Even when matched for total lung capacity, females have 14–35% smaller airway luminal areas (Dominelli et al., 2018).

At rest, these structural sex differences in the respiratory system have minimal impact on breathing mechanics. However, when ventilatory demand is increased, such as during exercise, notable functional differences emerge, especially in respiratory muscle use. Airway size strongly influences airflow resistance, and the work needed to overcome this resistance is performed by the respiratory muscles. Consequently, for a given minute ventilation ($\dot{V}E$), the mechanical WOB is higher in females than in males (Molgat-Seon et al., 2018a). To manage this increased level of respiratory muscle work, females tend to distribute inspiratory effort across multiple muscles, including the diaphragm, scalenes, and sternocleidomastoids, rather than relying predominantly on the diaphragm, as is more common in males (Molgat-Seon et al., 2018b). This compensatory recruitment pattern, potentially influenced by sex-specific fatigue resistance (Geary et al., 2019; Welch et al., 2018), may affect both the efficacy of IMT and its impact on the perception of dyspnoea. Surface EMG studies suggest that greater extradiaphragmatic muscle activation in females during IMT correlates with improved dyspnoea ratings, possibly due to neural adaptations or perceptual desensitization (Ramsook et al., 2016, 2017). Overall, there is clear evidence that sex influences the acute mechanical ventilatory response to exercise. Given these differences in respiratory structure and function, it is plausible that IMT elicits distinct adaptations in males and females, with implications for both exercise performance and perceived exertion. However, direct comparative data remain limited, and further research is needed to systematically evaluate these sex-specific responses.

CHAPTER 2: LITERATURE REVIEW

2.1 Overview of the Respiratory System and Ventilation Control

The respiratory system mainly includes the nose, oropharynx, larynx, trachea, airways, and lungs (Haddad & Sharma, 2023). Its primary function is to bring oxygen into the body and remove carbon dioxide (Gransee et al., 2012; Ratnovsky et al., 2008). This process, called ventilation, is an automatic, involuntary process, although it can be voluntarily controlled in certain situations, such as during breath holding, speaking, or singing (Di Pasquasio et al., 2025). $\dot{V}E$ is the product of tidal volume (V_T) and breathing frequency (F_b) (West, 2012), and is modulated by a highly sophisticated negative-feedback system that continuously adjusts breathing to metabolic demand, thereby maintaining arterial blood-gas and acid-base homeostasis (Scano et al., 2006; Welch et al., 2019). Rather than selecting randomly among possible ventilatory patterns, individuals unconsciously adopt the most mechanically efficient breathing strategy that minimises the WOB for a given ventilatory requirement (Benchetrit, 2000). This optimisation persists during exercise, provided the imposed respiratory load does not induce rapid fatigue.

$\dot{V}E$ is produced through the coordinated action of inspiratory and expiratory muscle groups (Welch et al., 2019). During quiet breathing, inspiration is primarily driven by the diaphragm and external intercostal muscles. As ventilatory demand increases, accessory inspiratory muscles, including the scalenes, sternocleidomastoids, and parasternal intercostals, are progressively recruited to augment thoracic expansion (De Troyer et al., 2005; Legrand et al., 2003; McConnell, 2013; Ratnovsky et al., 2008; West, 2012). Expiration is typically passive at rest, resulting from elastic recoil of the lungs and chest wall. During exercise or increased

ventilatory demand, however, expiration becomes active and is driven by the internal intercostal muscles and the abdominal wall musculature, including the rectus abdominis, external and internal obliques, and transversus abdominis (McConnell, 2013; Polkey, 2019; West, 2012).

The mechanical work generated by these muscle groups during breathing can be understood in terms of the forces they must overcome. Elastic force refers to the pressure required to counteract the lung's elastic recoil and expand the respiratory system during inspiration and is determined primarily by lung and chest wall compliance. Resistive force, in contrast, represents the pressure needed to overcome airflow resistance within the airways and tissues and varies with airway calibre, airflow rate, and flow pattern (West, 2012). Together, elastic and resistive forces define the mechanical load against which the respiratory muscles operate across rest, exercise, and respiratory muscle training (McConnell, 2013).

2.1.1 Diaphragm: Muscle Structure and Function

The diaphragm is the primary muscle of inspiration and serves as the main agonist during resting breathing (Janssens et al., 2013; Pickering & Jones, 2002). It is a striated skeletal muscle approximately 2-4 mm thick, composed of two domes (or cupolae) connected by a central tendon (Loukas et al., 2008; McConnell, 2013). Anatomically, the diaphragm separates the thoracic and abdominal cavities and consists of two functionally distinct components: the costal and crural muscles, which contract synchronously during respiration (De Troyer et al., 1981; Sant'ambrogio et al., 1963). The diaphragm is innervated bilaterally by two phrenic nerves (C3-C5), one on each side of the body. Each nerve sends motor signals to the diaphragm muscle on the same side, so each half of the diaphragm is independently controlled by its corresponding phrenic nerve (Kocjan et al., 2017; McConnell, 2013; Sant'ambrogio et al., 1963). The costal diaphragm

accounts for approximately 70% of total diaphragm mass and contributes substantially to lower rib cage expansion. It exhibits a highly oxidative muscle fiber composition, supporting its endurance role in continuous ventilation. In contrast, the crural diaphragm constitutes roughly 30% of the muscle mass, contributes minimally to rib cage motion, and plays a greater role in non-ventilatory functions such as swallowing and vomiting (De Troyer et al., 1981; Hodge et al., 1997; Kocjan et al., 2017; Levine et al., 1997; Powers, 2025).

The diaphragm contains an approximately equal distribution of slow oxidative type I fibers and type II fibers, the latter consisting primarily of fast oxidative–glycolytic type IIA and fast glycolytic type IIX fibers (Chan et al., 2023; Faulkner et al., 1979; Gollnick et al., 1972; Mizuno & Secher, 1989). This mixed fiber composition allows the diaphragm to sustain continuous activity, even at rest (Powers, 2025). Functionally, the diaphragm contributes approximately 65-70% of total ventilatory work (Janssens et al., 2013; Polkey, 2019; Ratnovsky & Elad, 2005; West, 2012). With complete exhalation, the dome of the diaphragm moves up to about the fourth intercostal space anteriorly. Its contraction increases thoracic volume while decreasing intrathoracic pressure, driving airflow into the lungs (De Troyer et al., 2005; McConnell, 2013). Diaphragm activation is regionally heterogeneous and task-dependent, reflecting complex neuromuscular control (Kolar et al., 2009). Beyond its role in respiration, the diaphragm assists the abdominal muscles in maintaining trunk stability and postural control (Griffiths & McConnell, 2007; McConnell, 2013).

Like other skeletal muscles, the respiratory muscles exhibit a force-length relationship in which force generation declines when muscle fibers are excessively shortened or lengthened (McConnell, 2013; Shei et al., 2017). As lung volume increases during inspiration, inspiratory muscles shorten and progressively lose force-generating capacity, with a marked decline

occurring when muscle length falls below approximately 60-70% of optimal length (Brancatisano et al., 1993; McCully & Faulkner, 1983; Sheel & Romer, 2012). This specialization allows the diaphragm to sustain ventilation across a wide range of lung volumes and ventilatory demands. The external and parasternal intercostal muscles also contribute to effective inspiration by elevating the ribs and stabilizing the chest wall, thereby helping to preserve favorable diaphragm length-tension relationships and optimize thoracic compliance (De Troyer et al., 2005; De Troyer & Boriek, 2011; Han et al., 1993).

2.1.2 Extradiphragmatic inspiratory muscles

In healthy individuals, inspiratory work is dominated by the diaphragm and external intercostal muscles, which are rich in oxidative type I and type IIA fibers and together account for approximately 80% of the respiratory workload, making them well suited for sustained ventilatory activity (Gollnick et al., 1972; Kocjan et al., 2017; McConnell, 2013). During quiet breathing, the diaphragm performs the majority of inspiratory work, estimated at 60 to 80% regardless of breathing effort, while extra-diaphragmatic muscles contribute minimally (Ratnovsky and Elad, 2005). Accessory inspiratory muscles, including the scalenes and sternomastoids, elevate the ribs and sternum and typically show little to no activity at rest, becoming progressively recruited only when ventilatory demand increases, such as during exercise or high respiratory loads (Janssens et al., 2013; West, 2012). This recruitment reflects a normal adaptive response to increased mechanical demand, with pressure generation shifting from the diaphragm toward accessory muscles at high workloads (Aliverti et al., 1997).

However, excessive or early activation of accessory muscles is considered a marker of inefficient or labored breathing, as accessory muscle recruitment is associated with increased

ventilatory demand, dyspnoea, respiratory failure, and high-intensity exercise (Johnson et al., 1993; Spengler and Boutellier, 2000). Surface electromyography studies demonstrate that accessory muscles are activated during IMT in healthy individuals, but their engagement intensifies as ventilatory demand rises, whereas persistent activation during low-demand conditions may indicate abnormal breathing patterns (Lee et al., 2021). Structurally, inspiratory muscles exhibit regional specialization: parasternal intercostals consistently act as inspiratory muscles, while external intercostals show topographic variation, with dorsal rostral regions functioning inspiratory and ventral caudal regions potentially acting expiratory, reflecting differences in mechanical advantage and muscle mass (De Troyer et al., 2003, 2005). The scalenes and sternocleidomastoids also demonstrate measurable inspiratory pressure contributions, with inspiratory mechanical advantage distributed preferentially across dorsal rostral intercostals and scalenes (Legrand et al., 2003). As respiratory effort increases, the contribution of extra-diaphragmatic and expiratory muscles rises while diaphragmatic contribution to total respiratory output declines, increasing susceptibility to fatigue in accessory muscles and potentially limiting exercise performance (Johnson et al., 1993; Perlovitch et al., 2007; Spengler and Boutellier, 2000; Verges et al., 2006).

2.2 Sex Differences in Respiratory Structure and Function

2.2.1 Sex-Based Structural Differences in the Respiratory System

Significant sex-based differences in the morphology of the human respiratory system have been well documented in the literature. Compared with males, females generally exhibit smaller absolute lung volumes, narrower conducting airways, reduced thoracic dimensions, and lower maximal expiratory flow rates (Bellemare et al., 2003; Dominelli et al., 2019; Harms &

Rosenkranz, 2008; Mann et al., 2021; Martin et al., 1987; Quanjer et al., 2012; Sheel et al., 2004; Sheel & Guenette, 2008). Importantly, these differences persist even after adjusting for body size (Bellemare et al., 2003; Schwartz et al., 1988). Sex-based differences extend beyond differes in the size of the structures of the respiratory, as lung and rib cage geometry also vary between sexes. Typically, males have a pyramidal lung and rib cage shape, with the lower parts being wider than the upper regions, while females tend to have a more prismatic shape, where the upper and lower lung and rib cage widths are more similar (García-Martínez et al., 2016; Torres-Tamayo et al., 2018). These differences in lung and rib cage shape affect airflow mechanics and the load on respiratory muscles, especially during exercise, with females having smaller lung volumes and at relatively higher F_b (Dominelli & Molgat-Seon, 2022; Sheel et al., 2016).

A central structural consequence of these differences is dysanapsis, defined as a mismatch between airway calibre and lung size (Mead, 1980). Females consistently demonstrate smaller airway-to-lung size ratios than males when indexed to lung volume (Dominelli et al., 2018; Molgat-Seon et al., 2024). Reduced tracheal and bronchial diameters elevate airflow resistance, especially at high ventilatory demands, thereby increasing the mechanical work required to sustain $\dot{V}E$ (Dominelli et al., 2018; Harms et al., 1998; Hesser et al., 1990; Peters et al., 2021). Notably, sex differences in lung and airway elastic properties are minimal (Colebatch et al., 1979), indicating that elevated WOB in females primarily reflects airway geometry rather than differences in tissue viscoelasticity (Guenette et al., 2009; LoMauro & Aliverti, 2018; Marinelli et al., 2025).

2.2.2 Sex Differences in Respiratory Muscle Function and Mechanical Load

Sex-based structural differences directly impact respiratory mechanics during exercise. The $\dot{W}_B$, which reflects the mechanical effort performed by the respiratory muscles to generate a given $\dot{V}E$, is similar between sexes at rest and during low-to-moderate intensity exercise (Abd-Elsayed et al., 2024; Coast et al., 1993; McConnell, 2013). However, when $\dot{V}E$ exceeds approximately 50-60 $L \cdot min^{-1}$, females exhibit a disproportionate rise in $\dot{W}_B$ relative to males (Dominelli & Sheel, 2012; Dominelli et al., 2015b; Grift et al., 2025; Guenette et al., 2007; Peters et al., 2021). This divergence is largely attributable to a greater resistive component of the $\dot{W}_B$ in females, driven by smaller airway diameters and increased airflow resistance (Dominelli et al., 2015a; Guenette et al., 2007; Peters et al., 2021). Consequently, females incur a higher oxygen cost of breathing for a given $\dot{V}E$, particularly during high-intensity or prolonged exercise (Dominelli et al., 2015b; Kipp et al., 2024; LoMauro & Aliverti, 2018).

Underlying morphological differences likely contribute to sex-based disparities in respiratory muscle strength. Females generally have lower absolute diaphragm mass and thickness, as well as lower maximal inspiratory pressure, even after adjusting for body size or thoracic dimensions (Bellemare et al., 2003; Sheel et al., 2004). These differences limit absolute force-generating capacity and require females to work at a higher proportion of their maximal inspiratory muscle capacity during exercise (Dominelli et al., 2015b; Molgat-Seon et al., 2018a). This increased relative load on the respiratory muscles implies that females often experience a greater degree of mechanical ventilatory constraints during exercise than males, particularly during sustained high-intensity exercise (Harms et al., 1998; LoMauro & Aliverti, 2018).

2.2.3 Sex-Based Differences in Inspiratory Muscle Recruitment and Reflex Control

Differences in thoracic morphology further influence sex-specific inspiratory muscle recruitment strategies. During exercise, females rely more heavily on rib cage and accessory inspiratory muscles, including neck and extradiaphragmatic muscles, compared with males (Bellemare et al., 2003; Mitchell et al., 2018). Electromyographic evidence demonstrates greater activation of rib cage musculature during submaximal exercise in females, which may partially unload the diaphragm but increases overall metabolic demand (Mitchell et al., 2018). Increased reliance on accessory muscles has been associated with heightened breathing discomfort and dyspnoea, particularly during prolonged or high-intensity exercise (Dominelli et al., 2019; Romer & Polkey, 2008).

Sex differences also extend to reflex regulation of the respiratory system. Females exhibit a blunted inspiratory muscle metaboreflex during respiratory muscle loading, characterized by attenuated increases in mean arterial pressure and reduced sympathetic vasoconstriction (Benbaruj et al., 2024; Leahy et al., 2024; Smith et al., 2016). This altered reflex response affects blood flow redistribution during exercise and may influence fatigue development in both respiratory and locomotor muscles (Romer & Polkey, 2008; Sheel et al., 2018). Although a diminished metaboreflex could theoretically reduce cardiovascular strain, its functional implications for dyspnoea perception and exercise performance remain uncertain, with existing evidence yielding mixed outcomes (Dominelli et al., 2019; Dominelli & Molgat-Seon,2022).

2.3 Respiratory Muscle Fatigue as a Limiting Factor in Exercise

2.3.1 Role of Respiratory System in Exercise Limitation

Historically, the respiratory system was not considered a limiting factor to exercise performance in healthy individuals (Dempsey, 1986; Dempsey et al., 2020; HajGhanbari et al., 2013; Peters et al., 2023). This assumption has been challenged by evidence showing that, during intense exercise, the respiratory system can meaningfully constrain performance through heightened sensations of breathing effort and reflex reductions in limb blood flow, together establishing it as an important determinant of endurance and high-intensity exercise tolerance. These constraints reflect the substantial metabolic and circulatory demands imposed by the respiratory muscles (Aaron et al., 1992; Harms et al., 1997; Romer & Polkey, 2008). The $\dot{W}_B$ may account for approximately 10-15% of whole-body oxygen uptake and 15-20% of total cardiac output (Aaron et al., 1992; Harms et al., 1998), thereby directly competing with leg muscles for oxygen delivery (Harms et al., 1997; Sheel et al., 2018). As a consequence, fatigue in the exercising limb muscles develops more rapidly, neural drive from the central nervous system is suppressed, and exercise is terminated earlier than would otherwise occur (Gandevia, 2001; McConnell, 2013; Romer et al., 2006; Sheel et al., 2018). Although the diaphragm contributes approximately 60-80% of total inspiratory work under most conditions (Ratnovsky & Elad, 2005), its relative contribution declines at high ventilatory workloads as extra diaphragmatic inspiratory muscles increasingly compensate (Lee et al., 2021; Verges et al., 2006). As a result, fatigue of accessory inspiratory muscles likely contributes meaningfully to exercise limitation, particularly when diaphragmatic efficiency is compromised (McConnell, 2013; Romer et al., 2002b; Verges et al., 2006)

2.3.2 Exercise-Induced Diaphragm Fatigue and Breathing Strategy

Muscle fatigue is defined as a reversible reduction in force-generating capacity that occurs when energy demand exceeds supply and is influenced by substrate availability, oxygen delivery, and metabolite accumulation (Allen et al., 2008; Gandevia, 2001). Within the respiratory system, exercise-induced diaphragm fatigue refers to a reversible decline in diaphragmatic force-generating capacity following sustained or high-intensity exercise (Romer et al., 2002b; Verges et al., 2006). Although exercise-induced diaphragm fatigue rarely compromises alveolar ventilation directly, it can impair exercise performance by reducing diaphragmatic contribution to breathing and increasing reliance on mechanically less efficient accessory inspiratory muscles (Romer et al., 2002b; Romer & McConnell, 2003). Fatigue disrupts optimal relaxation between breaths, impairing diaphragmatic perfusion and increasing both the work and oxygen cost of breathing (Aaron et al., 1992). Notably, sex-related differences have been observed in the development and consequences of exercise-induced diaphragm fatigue, with females demonstrating a lower magnitude of diaphragmatic fatigue than males for a given cumulative diaphragmatic force output (Guenette et al., 2010; Welch et al., 2018). In parallel, females exhibit an attenuated cardiovascular response to inspiratory muscle loading, reflecting a blunted respiratory muscle metaboreflex that may reduce sympathetically mediated blood flow redistribution during exercise and thereby influence exercise tolerance (Geary et al., 2019; Guenette et al., 2010; Leahy et al., 2023; Sheel et al., 2018; Welch et al., 2018). Functionally, exercise-induced diaphragm fatigue is associated with a compensatory shift toward tachypnoeic breathing with reduced V_T, a hallmark of respiratory muscle fatigue that serves to maintain $\dot{V}E$ under fatigued conditions (Gallagher et al., 1985; Lima et al., 2025; McConnell & Lomax, 2006; Romer et al., 2002b; Romer & Polkey, 2008). This altered breathing strategy

further elevates respiratory muscle workload, accelerating fatigue development and increasing dyspnoea (Boyle et al., 2020).

2.3.3 Inspiratory Muscle Metaboreflex and Peripheral Consequences

During heavy or hypoxic exercise, respiratory muscles, particularly the diaphragm, can reach near-maximal force output of approximately 90% (Johnson et al., 1992). The diaphragm's high endurance capacity is supported by dense capillarisation, high mitochondrial content, and an oxidative fiber profile, allowing sustained performance under physiological stress (Dong & Tsai, 2023). During maximal exercise, respiratory muscle oxygen consumption accounts for approximately 10% of whole-body oxygen uptake in untrained individuals and up to 15-16% in highly trained individuals (Aaron et al., 1992; Welch et al., 2019). Correspondingly, respiratory blood flow may reach 14-16% of maximal cardiac output (Harms et al., 1998). Despite these endurance characteristics, respiratory muscles are susceptible to fatigue during high-intensity exercise, particularly at intensities exceeding ~85% of $\dot{V}O_2max$ (Amann, 2012; Johnson et al., 1993, 1996; Mador et al., 1993; Romer et al., 2006). $\dot{V}O_2max$ represents the highest achievable rate of oxygen consumption during maximal exercise, at which point further increases in exercise intensity do not result in additional oxygen uptake (Hawkins et al., 2007). The onset of respiratory muscle fatigue develops progressively and is closely linked to the cumulative WOB (Archiza et al., 2018; Dominelli et al., 2017). During high-intensity exercise, systematic manipulation of the WOB alters the distribution of cardiac output between respiratory and locomotor muscles, such that lower WOB preserves blood flow to the exercising legs, whereas higher WOB increases respiratory muscle perfusion at the expense of leg blood flow (Romer & Dempsey, 2014). This reciprocal redistribution demonstrates a competitive interaction for limited cardiac output, whereby increasing respiratory muscle demand progressively constrains

locomotor muscle perfusion and contributes to the development of peripheral fatigue (Dominelli et al., 2017; Haddad et al., 2023; Katayama et al., 2019; Sheel et al., 2018; Romer & Dempsey, 2014).

The effects of respiratory muscle work on skeletal muscle perfusion are primarily mediated by the respiratory muscle metaboreflex. This reflex is initiated when fatigue-induced metabolites accumulate within the inspiratory muscles, activating group III and IV phrenic afferent fibers (Dempsey et al., 2006; Dominelli et al., 2017; Sheel et al., 2018; Shei, 2022; St Croix et al., 2000). Reflex activation of these afferents triggers sympathetic efferent discharge, leading to vasoconstriction in active locomotor muscles and a redistribution of blood flow toward the diaphragm and expiratory muscles (Dempsey et al., 2006; Harms et al., 1997; McConnell & Lomax, 2006; Witt et al., 2007). Studies in human demonstrate that voluntary increases in inspiratory and expiratory muscle work elevate muscle sympathetic nerve activity and reduce blood flow to the working muscles (Derchak et al., 2002; Sheel et al., 2001; St Croix et al., 2000). Accordingly, interventions that unload the respiratory muscles, which prevent exercise-induced diaphragmatic fatigue, are expected to attenuate this sympathetic vasoconstrictor response, whereas increased respiratory muscle loading would intensify it (Babcock et al., 2002; Romer et al., 2006). Functionally, elevated WOB is inversely related to limb perfusion, accelerates peripheral muscle fatigue, reduces exercise tolerance, and increases dyspnoea and perceptual strain (Harms et al., 2000; Volianitis et al., 2001; Romer et al., 2002b, 2006; Lima et al., 2025). Together, these mechanisms establish the respiratory system as a significant limiter of endurance and high-intensity exercise performance (Dempsey et al., 2006; Harms et al., 2000; Lima et al., 2025; Romer et al., 2002b).

2.4 Dyspnoea

2.4.1 Dyspnoea: Definition and its Dimensions

Dyspnoea is defined as a subjective experience of breathing discomfort that "consists of qualitatively distinct sensations that vary in intensity" (American Thoracic Society, 1999). It is a multidimensional symptom encompassing both somatosensory perception of intensity and quality and affective distress or unpleasantness (Parshall et al., 2012). Dyspnoea is inherently subjective and can only be interpreted by the individual experiencing it, as it is shaped by prior experience, expectation, and contextual factors (Chang et al., 2023; Kipp et al., 2022; Scano et al., 2005). It is a cardinal symptom in cardiorespiratory disease (Grønseth et al., 2014) and affects approximately one-quarter of the general population during activities of daily living (Ekström et al., 2018). Perception of dyspnoea is further modulated by afferent feedback from respiratory muscle mechanoreceptors and metaboreceptors, particularly under conditions of respiratory muscle fatigue. Fatigue-induced neuromechanical uncoupling heightens perceptions of both respiratory and limb effort, thereby limiting exercise performance (Harms et al. 2000; McConnell & Romer, 2004; Romer & Polkey 2008).

Dyspnoea is not a single sensation but consists of at least three distinguishable dimensions: air hunger, effort, and chest tightness (Banzett & Moosavi, 2017; McConnell, 2013). The relative contribution of each dimension depends on the underlying physiological and contextual factors, including chemoreceptor stimulation, mechanical constraints, and respiratory muscle effort (Mahler & O'Donnell, 2014; McConnell, 2013). Increased inspiratory effort is directly associated with dyspnoea perception during exercise and may vary by sex. When dyspnoea cannot be alleviated through pacing or conscious control, it may become a primary

factor limiting performance (Laveneziana et al., 2019; McConnell, 2013; Romer & Polkey 2008).

2.4.2 Respiratory Muscle Fatigue and Its Contribution to Dyspnoea

Muscle fatigue is defined as a reversible reduction in force-generating capacity (Fitts, 1994) that occurs when energetic demand exceeds supply, and is influenced by substrate availability, oxygen delivery, and metabolite accumulation (Sundberg & Fitts, 2019; Whipp et al., 2005). In the respiratory system, fatigue is commonly accompanied by a shift toward a tachypnoeic breathing pattern characterized by reduced V_T. This pattern increases the oxygen cost of breathing, reduces ventilatory efficiency, and accelerates the progression of fatigue (Romer et al., 2006; McConnell & Lomax, 2006).

As inspiratory muscle fatigue develops, its consequences extend beyond impaired mechanical performance to include altered sensory feedback and perceptual responses. Metabolite accumulation within fatigued inspiratory muscles activates group III and IV afferent fibres, increasing central respiratory drive and amplifying the perception of breathing effort (Dempsey et al., 2006; St Croix et al., 2000). The resulting compensatory shift toward rapid, shallow breathing further elevates the oxygen cost of breathing and exacerbates fatigue, creating a self-reinforcing cycle (McConnell & Lomax, 2006; Romer et al., 2002a).

Within this framework, dyspnoea represents the perceptual manifestation of an imbalance between ventilatory demand and the mechanical capacity of the respiratory muscles (Banzett & Moosavi, 2017). Despite its structural and functional advantages, the diaphragm becomes susceptible to fatigue when its force-generating or shortening capacity can no longer meet the

increasing neural respiratory drive imposed by exercise or disease. This mismatch between central motor command and mechanical output, commonly described as neuromechanical uncoupling, manifests as dyspnoea and reflects a failure of the respiratory system to satisfy ventilatory requirements (James et al., 2022; Jolley et al., 2015; Schaeffer et al., 2014). As ventilatory demand rises, progressively greater neural drive is required to sustain $\dot{V}E$; when inspiratory muscles cannot generate sufficient pressure or volume change, perceived breathing effort increases disproportionately, even in the absence of impaired gas exchange (Mahler & O'Donnell, 2014; Schaeffer et al., 2014).

Dyspnoea intensity closely tracks the degree of neural drive and mechanical constraint, particularly when V_T plateaus and further increases in $\dot{V}E$ require markedly greater effort (James et al., 2022; Ramsook et al., 2017). These responses are consistent with the length-tension inappropriateness paradigm, which proposes that dyspnoea arises when central motor output fails to produce the expected mechanical response (Gigliotti, 2010).

2.4.3 Sex Differences in Dyspnoea Perception

Females consistently report a higher frequency and intensity of dyspnoea than males across age groups (Ekström et al., 2017; Milne et al., 2025; Molgat-Seon et al., 2018a). These differences are only partially explained by sex-specific variation in respiratory morphology, WOB, oxygen cost, and ventilatory control (Cory et al., 2015; Dominelli et al., 2019). Psychosocial and hormonal influences are also likely contributors, although the precise mechanisms remain incompletely understood. Beyond structural and mechanical factors, females report greater sensations of breathlessness and perceived exertion at matched absolute or relative exercise intensities compared with males (Cory et al., 2015; Dominelli & Molgat-Seon, 2022).

Multiple factors may collectively amplify dyspnoea perception in females, including elevated work and oxygen cost of breathing, heightened neural respiratory drive, structural constraints related to airway size and chest wall mechanics, and other non-physiological factors (Dominelli et al., 2019; Hayen et al., 2013; Mitchell et al., 2018; Welch et al., 2018).

Although dysanapsis increases mechanical respiratory load, it does not consistently predict dyspnoea severity, underscoring the central role of neuromechanical uncoupling and affective processing in shaping perceptual responses to exercise (Dominelli et al., 2019; Molgat-Seon et al., 2024). In many females, respiratory discomfort may develop before peripheral muscle fatigue and become the dominant factor limiting exercise tolerance. Females may also rely more heavily on accessory respiratory muscles and demonstrate greater resistance to diaphragm fatigue, potentially as a protective strategy (Mitchell et al., 2018; Welch et al., 2018). However, increased accessory muscle recruitment has been associated with heightened dyspnoea perception, suggesting a trade-off between mechanical compensation and perceptual burden (Ramsook et al., 2016).

2.5 Overview of Respiratory Muscle Training (RMT)

From a performance perspective, respiratory-related exercise limitation arises primarily through two interrelated mechanisms: an increased perception of breathing effort and reflex-mediated reductions in limb blood flow (Katayama et al., 2019; Romer et al., 2002b; Witt et al., 2007). Together, these mechanical, metabolic, and perceptual responses establish the respiratory system as a meaningful limiter of endurance and high-intensity exercise performance. Reducing respiratory muscle fatigue represents a viable strategy to preserve exercise performance (Illi et al., 2012). Respiratory muscle training (RMT) aims to improve respiratory muscle strength, endurance, and efficiency, thereby reducing the relative intensity of breathing and its

downstream consequences (HajGhanbari et al., 2013; Illi et al., 2012; Sheel, 2002; Shei, 2018). A key mechanism underlying these benefits is attenuation of the inspiratory muscle metaboreflex, which preserves blood flow to locomotor muscles during exercise (Lima et al., 2025; Ramsook et al., 2017; Romer & McConnell, 2003; Turner et al., 2012; Witt et al., 2007).

RMT encompasses both inspiratory and expiratory muscle training and applies targeted overload to the respiratory musculature (Griffiths & McConnell, 2007). Adaptations parallel those observed in limb skeletal muscle, including neural, structural, and metabolic changes that enhance force-generating capacity, fatigue resistance, and oxidative capacity (Downey et al., 2007; Ramírez-Sarmiento et al., 2002; Ren et al., 2025). Training is typically performed using short bouts of moderate-intensity respiratory loading, commonly corresponding to 40-60% of maximal respiratory muscle strength, resulting in improvements in inspiratory muscle strength, power, shortening velocity, and endurance (Katayıfçı et al., 2024; McConnell, 2013; Ramirez-Sarmiento et al., 2002; Romer & McConnell, 2003).

Among RMT modalities, IMT is the most extensively studied and has consistently demonstrated benefits for exercise tolerance across populations (Enright & Unnithan, 2011; Lima et al., 2025; Ren et al., 2025; Xavier et al., 2025). The primary physiological marker of IMT is an increase in maximal inspiratory pressure (MIP), reflecting enhanced inspiratory muscle strength. In parallel, expiratory muscle training (EMT) is characterized by improvements in maximal expiratory pressure (MEP), which serve as the hallmark indicator of effective expiratory muscle adaptation (Shei et al., 2022).

Notably, EMT elicits adaptations that extend beyond the expiratory musculature. In addition to increasing maximal expiratory pressure, EMT has been shown to improve MIP,

suggesting functional involvement and coordination of the inspiratory muscles during active expiration (McConnell, 2013; Shei et al., 2022). This response contrasts with IMT, which improves inspiratory pressures but does not produce corresponding gains in maximal expiratory pressure (McConnell, 2013). Despite these effects, EMT has been less frequently investigated in relation to exercise performance limitation and remains a complementary rather than central intervention compared with IMT. This is likely because expiratory muscles are more difficult to isolate experimentally due to their dual roles in respiration, posture, movement, and trunk stabilization. Consequently, EMT has been most commonly applied in targeted contexts, particularly for enhancing airway clearance and phonatory function, where expiratory muscle strength is of central importance (Shei et al., 2022; Sparks et al., 2025).

2.5.1 Inspiratory Muscle Training: Principles, Prescription, and Measurement

Inspiratory muscles are skeletal muscles and therefore adapt in accordance with established training principles, including overload, specificity, progression, and reversibility (Romer & McConnell, 2003; McConnell, 2013). Overload is achieved when inspiratory work exceeds habitual ventilatory demands, commonly through resistive or pressure-threshold loading that challenges the muscles to near task failure (Leith & Bradley, 1976). The effectiveness of any prescribed inspiratory load therefore depends not only on intensity selection, but also on the device used to deliver that load. IMT is most commonly performed using pressure-threshold or flow-resistive devices, which reliably overload the inspiratory muscles (Clanton et al., 1985; Shei et al., 2016; Van Hollebeke et al., 2020, 2023;).

In threshold loading, inspiratory flow occurs only after the inspiratory muscles generate a predefined threshold pressure (Ptr), resulting in an applied training pressure that is largely flow-independent. Once the threshold is exceeded, inspiratory flow is occurs and the total inspiratory

pressure primarily reflects the sum of lung elastic pressure required to expand the lungs and a smaller resistive component associated with airflow. In contrast, during resistive loading, inspiration occurs against an airway resistor, such that the applied training pressure increases in proportion to inspiratory flow. Consequently, the resistive pressure component becomes a major contributor to the total inspiratory pressure, varying dynamically with flow throughout the breath, while lung elastic pressure reflects the volume-dependent recoil of the lungs. Together, threshold loading provides a fixed, standardized inspiratory load, whereas resistive loading imposes a variable load determined by airflow, with distinct distributions of elastic and resistive pressures shaping the overall mechanical demand on the inspiratory muscles (Vorona et al., 2018).

Targeted threshold-loading devices ensure that the prescribed intensity is consistently achieved, whereas non-targeted resistive modes may fail to maintain sufficient overload (Geddes et al., 2005; Hsiao et al., 2003; McConnell, 2013; Zhang et al., 2024). The magnitude of overload is a critical determinant of training effectiveness, as loads below a minimum threshold may fail to elicit meaningful adaptation (HajGhanbari et al., 2013; Shei & Mickleborough, 2019).

Beyond determining training intensity, the mechanical characteristics of IMT devices also influence breathing pattern and muscle recruitment during training (Walterspacher et al., 2018). Specificity of training dictates that the nature and magnitude of the imposed stimulus determine the resulting adaptations, positioning inspiratory loading as a key training "dose." High-force, low-velocity inspiratory contractions preferentially enhance MIP, whereas lower-force, higher-velocity breathing tasks favor improvements in inspiratory flow and endurance (Romer & McConnell, 2003; Van Hollebeke et al., 2020). Training lung volume further influences specificity, such that training from residual volume enhances low-volume strength,

while training from functional residual capacity improves high-volume inspiratory function (Van Hollebeke et al., 2020). Accordingly, IMT protocols vary substantially in prescribed intensity depending on the targeted outcome, reflecting the graded, dose-dependent nature of adaptations.

Evidence indicates that inspiratory loads exceeding approximately 30% of MIP are required for IMT to be effective, particularly for strength development (Lin et al., 2022; Martin-Sanchez et al., 2021). Moderate-to-high intensities (40–60% MIP) reliably improve inspiratory muscle strength and power (Ando et al., 2020; Chang et al., 2021; Enright & Unnithan, 2011), while higher intensities approaching 80–90% of MIP elicit the greatest gains in maximal strength, albeit with an increased risk of fatigue (Carvajal-Tello et al., 2024; Chang et al., 2021; Enright & Unnithan, 2011; Lin et al., 2022; Ren et al., 2025). These findings collectively support a dose-response relationship in IMT, in which higher training intensity leads to progressively larger improvements in muscle strength and exercise tolerance (Jenkins et al., 2023; Ren et al., 2025).

A distinction is commonly made between acute and chronic IMT applications. Acute IMT, often used as a pre-exercise warm-up, typically involves two sets of 30 breaths at ~40% MIP performed immediately before activity (Cirino et al., 2023; Lorca-Santiago et al., 2020). Chronic IMT consists of repeated daily sessions, often twice per day, designed to induce long-term improvements in inspiratory muscle strength, endurance, and fatigue resistance (Chang et al., 2021; Lorca-Santiago et al., 2020). Acute and chronic approaches differ in cumulative dose, with chronic IMT providing repeated mechanical loading that drives adaptation over time. While some studies have combined both strategies, the optimal integration and sequencing remain poorly defined.

Across the literature, chronic IMT protocols commonly involve ~30 breaths per session performed once or twice daily over 4–12 weeks, with intensities ranging from 30% to 80% of MIP (Edwards et al., 2012; Romer et al., 2002a; McConnell, 2013). Training at ~50% MIP has been shown to improve inspiratory muscle strength, fitness, and power output (Ando et al., 2020; Ohya et al., 2022; Okrzymowska et al., 2024; Rehder-Santos et al., 2021; Romer et al., 2002a), whereas intensities closer to 80% of MIP yield larger strength gains (Edwards et al., 2012; McConnell, 2013; Romer et al., 2002a). Progressive loading is a key feature of effective IMT, allowing the inspiratory muscles to adapt while avoiding premature overload. Progression should be individualized and guided by performance changes and training tolerance rather than absolute starting MIP values, which do not account for anthropometric (i.e., height) or functional differences (i.e., lung size) between individuals (Chan et al., 2023; Shei, 2018; Shei et al., 2022).

IMT is typically performed using pressure-threshold or flow-resistive devices that impose a quantifiable inspiratory load while allowing unimpeded expiration (Tranter et al., 2026; Van Hollebeke et al., 2020, 2023). Inhalation is characterized by a rapid, forceful initial effort followed by a sustained inspiratory phase and prolonged exhalation (Bates et al., 2015; Brinkman et al., 2023). Regardless of loading intensity, IMT engages not only the diaphragm but also the external intercostals and accessory inspiratory muscles, including the sternocleidomastoid, scalene, and pectoral muscles (Ando et al., 2020).

Inspiratory muscle strength is most commonly assessed using MIP or PImax (Laveneziana et al., 2019; López-de-Uralde-Villanueva et al., 2024; Sclauser Pessoa et al., 2014), measured via a mouthpiece connected to a manometer. Standardized testing procedures typically involve seated participants performing repeated maximal inspiratory efforts, with the

highest reproducible value recorded. Reliability criteria commonly require that the best values differ by less than 10% or 10 cmH_2O across attempts (American Thoracic Society/European Respiratory Society, 2002). MIP primarily reflects diaphragm strength but also incorporates contributions from accessory inspiratory muscles, making it a practical and widely accepted index of global inspiratory muscle function (American Thoracic Society/European Respiratory Society, 2002; Ando et al., 2020). These measurement approaches provide the basis for quantifying IMT dose and interpreting the resulting physiological and perceptual adaptations.

2.5.2 Physiological and Perceptual Adaptations to IMT

IMT induces a combination of neural and peripheral adaptations that collectively enhance inspiratory muscle performance. Early increases in MIP, often evident within the first few weeks of training, are largely attributed to neural mechanisms, including improved motor unit recruitment, firing frequency, and synchronization (Enright et al., 2006; McConnell & Romer, 2004; Shei, 2018). With continued training, peripheral and structural adaptations become more prominent. Ultrasound and histological evidence demonstrates increases of approximately 10–12% in diaphragm thickness, along with enlargement of type II fibers in the external intercostals, following 4–8 weeks of IMT (Enright et al., 2006; Ramirez-Sarmiento et al., 2002; Shei, 2018). Longer training durations or higher-intensity protocols appear to further promote muscle hypertrophy and fiber-type remodeling, contributing to sustained strength gains (Chan et al., 2023; Ren et al., 2025).

Consistent with these mechanistic adaptations, reported improvements in MIP vary widely across studies and are strongly influenced by training intensity and duration. Short term, moderate intensity IMT protocols, for example five weeks of training at approximately 50% of MIP, have been shown to increase MIP by 16-18%. Extending a similar protocol to nine weeks

resulted in improvements exceeding 40%, suggesting that strength adaptations had not yet plateaued with shorter training durations (Chan et al., 2023). Likewise, high intensity IMT performed over eight weeks has produced MIP increases of approximately 37%, in some cases accompanied by concurrent improvements in maximal expiratory pressure (Ren et al., 2025). Given the relatively brief intervention periods, these rapid gains are thought to primarily reflect neuromuscular adaptations rather than extensive structural hypertrophy.

Despite substantial interindividual variability in absolute strength gains, improvements in MIP do not appear to depend on baseline inspiratory strength. Percentage increases in MIP show minimal association with initial MIP values, likely because absolute pressure measures fail to account for individual differences in body size, lung volumes, or prior training status (Chan et al., 2023). This highlights the importance of relative loading and individualized progression when prescribing IMT (Witt et al., 2007). Moreover, maintenance strategies should be considered, as gains in MIP are reversible and can diminish with detraining (Romer & McConnell, 2003).

Rather than acting solely on the diaphragm, IMT enhances load sharing among primary and accessory inspiratory muscles, thereby delaying the onset of inspiratory muscle fatigue. IMT further attenuates activation of the respiratory muscle metaboreflex, reducing sympathetic vasoconstriction and preserving blood flow to locomotor muscles during exercise. However, the extent to which these physiological changes translate into systemic cardiovascular effects may depend on training magnitude and study power, as smaller interventions may be insufficient to detect changes in resting hemodynamics (Chan et al., 2023).

Collectively, these adaptations enhance inspiratory muscle efficiency, reduce respiratory muscle fatigue, and translate into measurable improvements in exercise performance. IMT alone

can improve exercise performance by approximately 10-12%, with benefits more consistently observed in constant-load and time-trial protocols than in incremental exercise tests (Illi et al., 2012; McConnell, 2013).

2.5.3 Mechanisms Underlying the Ergogenic Effects of IMT

IMT enhances exercise capacity through multiple structural, functional, perceptual, and reflex-mediated adaptations (Shei et al., 2022). Functionally, IMT reduces the relative intensity and oxygen cost of breathing during exercise by improving force-generating capacity and coordination across the inspiratory muscle ensemble, thereby lowering the muscular tension required to achieve a given $\dot{V}E$ (McConnell, 2013; Ren et al., 2025). These adaptations are supported by hypertrophy of the diaphragm and external intercostals, an increased proportion of type II fibers in the external intercostals, and enhanced efficiency of the respiratory muscle pump (Shei et al., 2016). IMT further improves ventilatory efficiency through favourable alterations in breathing pattern and indices such as $\dot{V}E/VCO_2$, reducing unnecessary ventilatory demand for a given metabolic load.

At the metabolic level, IMT enhances acid–base buffering capacity via upregulation of monocarboxylate transporters, reducing lactate accumulation and sympathetic activation during exercise (McConnell, 2013; Witt et al., 2007). Collectively, these structural and metabolic adaptations delay the onset of inspiratory muscle fatigue, lower the perception of dyspnoea and whole-body exertion per unit work, and improve respiratory muscle endurance (McConnell, 2013; Ren et al., 2025). High-intensity and interval-based IMT protocols have further demonstrated benefits in clinical populations by improving symptom control and reducing respiratory discomfort (Kocak et al., 2025).

A key mechanism underlying these ergogenic effects involves modulation of the respiratory muscle metaboreflex. During high-intensity exercise, the respiratory muscles may demand 14–21% of cardiac output, creating competition with locomotor muscles for blood flow (Harms et al., 1998, 2000; Romer & Dempsey, 2014; Sheel et al., 2018). Fatigue-related metabolite accumulation within the inspiratory muscles, including lactate, hydrogen ions (H^+), inorganic phosphate (Pi), and ATP degradation products, activates group III and IV phrenic afferents, triggering sympathetically mediated vasoconstriction in active limb muscles (Dempsey et al., 2006; Dominelli et al., 2017; Sheel et al., 2018; Shei et al., 2022; St Croix et al., 2000). IMT raises the threshold for activation of this reflex in both healthy individuals and patients with heart failure, thereby attenuating peripheral vasoconstriction, preserving blood flow to locomotor muscles, and improving exercise tolerance (Dempsey et al., 2006; Harms et al., 1998; Witt et al., 2007).

Reductions in respiratory muscle work and afferent feedback to the central nervous system may further preserve central motor drive and delay the development of central and peripheral fatigue (Álvarez-Herms et al., 2019; Dempsey et al., 2006; Illi et al., 2012; Lima et al., 2025; Witt et al., 2007). Collectively, these adaptations reduce the oxygen cost of breathing, improve inspiratory muscle economy, and contribute to consistent improvements in exercise performance (Amann, 2012; Dempsey et al., 1996; Turner et al., 2012).

In parallel, respiratory muscle training (RMT) more broadly shares these mechanisms by reducing inspiratory motor drive while preserving pressure generation, promoting diaphragmatic hypertrophy, modifying fiber-type characteristics of the external intercostals, attenuating the respiratory muscle metaboreflex, reducing perceived breathlessness, decreasing the WOB, and enhancing respiratory muscle endurance (Downey et al., 2007; Enright et al., 2006; Held &

Pendergast, 2014; Huang et al., 2003; Sales et al., 2016; Sheel, 2002; Sheel et al., 2001; St Croix et al., 2000; Turner et al., 2012). These adaptations are interrelated, as improvements in respiratory muscle economy delay fatigue development and reflex-mediated vasoconstriction, although the precise interactions between these mechanisms and whole-body exercise performance remain incompletely understood (Shei, 2018).

2.5.4 Limitations, and Research Gaps

Sex-based differences in respiratory system morphology influence inspiratory muscle function and the development of fatigue. As previously noted, females typically have smaller airways, reduced thoracic and lung volumes, lower absolute MIP, and reduced diaphragm mass, collectively increasing airway resistance and the relative WOB at a given $\dot{V}E$ (Dominelli et al., 2019; McConnell & Romer, 2004; Sheel, 2002; Sheel et al., 2018). Despite these mechanical constraints, females demonstrate greater resistance to respiratory muscle fatigue (Geary et al., 2019; Welch et al., 2018) and comparable relative inspiratory muscle function when normalized to lung size. Furthermore, proportional improvements in MIP, inspiratory muscle endurance, and dyspnoea following IMT suggest similar inspiratory muscle plasticity between sexes (Illi et al., 2012; McConnell, 2013). Notably, this enhanced fatigue resistance does not appear to translate into superior exercise performance under normoxic conditions (Welch et al., 2018).

Interpretation of the IMT literature is complicated by substantial methodological heterogeneity, including variation in training loads, session frequency and duration, and outcome measures. Additional limitations include small sample sizes, inconsistent inspiratory endurance testing, and the underrepresentation of females and athletic populations (HajGhanbari et al., 2013; McConnell, 2013; McConnell & Romer, 2004). Potential learning effects in MIP

assessment, limited use of sham controls, and variability in diaphragm imaging methodologies further constrain interpretation (Brown et al., 2014; Laveneziana et al., 2019). The use of sex- and age-normalized reference values for MIP and maximal expiratory pressure (MEP) is therefore essential for valid between-group comparisons (Evans & Whitelaw, 2009).

Collectively, it is currently unclear whether females require a higher IMT load to achieve optimal adaptation. Although females exhibit greater resistance to respiratory muscle fatigue, this does not consistently translate into improved exercise performance under normoxic conditions. Instead, current evidence supports the potential for sex-specific responsiveness to IMT rather than a simple need for increased training intensity. Notably, females may derive greater ergogenic benefit under conditions of elevated ventilatory stress, such as hypoxia, but further sex-stratified research is needed to define dose–response relationships and elucidate the mechanisms underpinning these responses across different physiological stressors (Chambault et al., 2021; Shei et al., 2022).

CHAPTER 3: THESIS STUDY

3.1 Research question, objective and hypotheses

Research Question: How does sex influence the physiological and perceptual responses to IMT in physically active adults?

Objective: The objective of this study was to investigate the impact of sex on the physiological (e.g., inspiratory muscle strength, exercise performance) and perceptual (e.g., exertional dyspnoea) responses to IMT in physically active adults.

Hypothesis:

1. Following IMT, females would experience a greater reduction in exertional dyspnoea compared to males.

2. Following IMT, males and females would show similar improvements in inspiratory muscle strength and exercise performance.

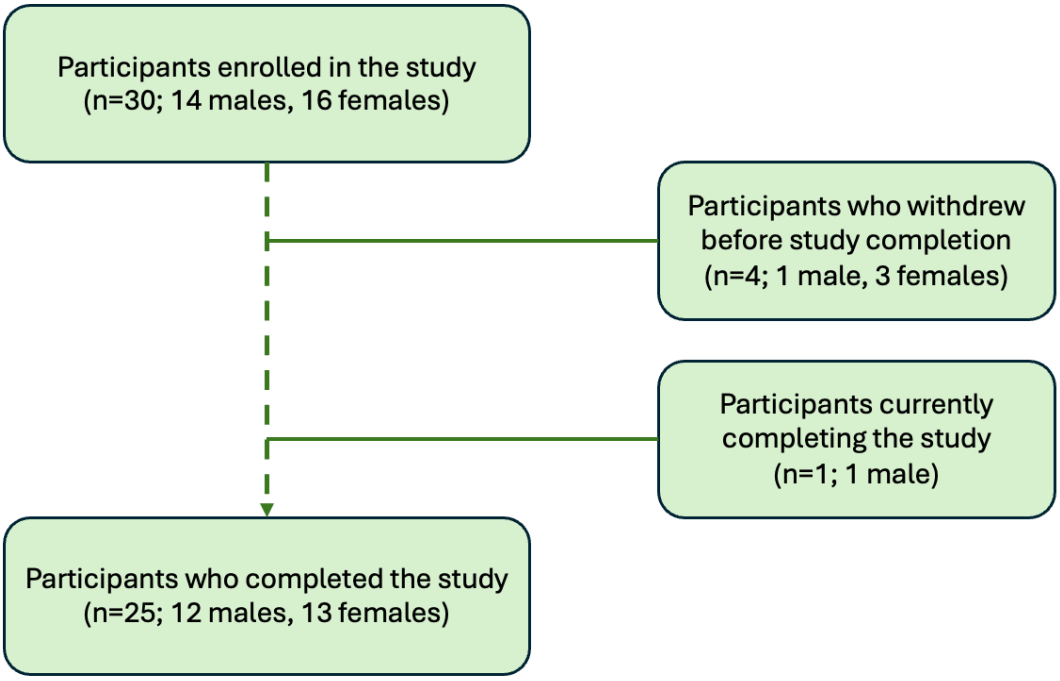
3.2 Methods

3.2.1 Study Participants

A total of 30 participants (14 males and 16 females) were enrolled in the study from the community at large as illustrated in **Figure 1**. Four participants (1 male and 3 females) withdrew before study completion, and one male participant was still completing the protocol. All participants were informed of the experimental procedures, potential risks involved, and provided written informed consent. Participants were included if: i) they were between the ages of 20-60 years (inclusively), ii) could fluently read, speak, and write in English, iii) had normal pulmonary function (i.e., forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio >0.70

and FEV1 >80% predicted) based on population-specific norms (Quanjer et al., 2012), and iv) self-reported physical activity levels as "moderate" or "high" according to the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). Participants were excluded if: i) they had a history of smoking, ii) had a body mass index ≤18 $kg \cdot m^{-2}$ or ≥30 $kg \cdot m^{-2}$, or iii) had a history or current medical condition that interfered with their ability to perform exercise safely.

Figure 1. Flow diagram indicating the total number of participants included in the study

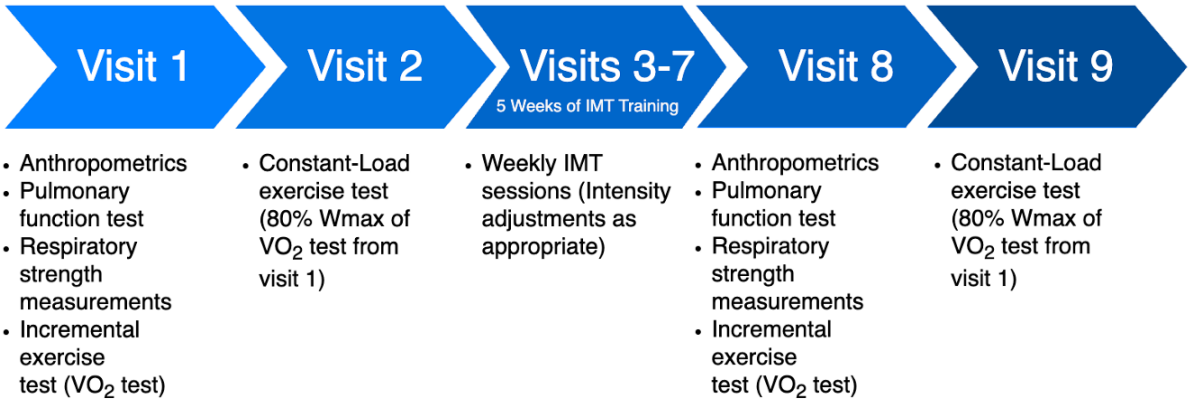


3.2.2 Experimental Overview

As shown in **Figure 2**, participants reported to the exercise laboratory (1D11) on 9 separate occasions over a period of 7-8 weeks. On visit 1, participants' anthropometric data were collected, followed by pulmonary function testing and the measurement of respiratory muscle strength. Next,

participants completed a symptom-limited incremental exercise test on a cycle ergometer (Ergoselect 200K, Ergoline GmbH, Bitz, Germany). Peak work-rate was defined as the highest work-rate sustained for at least 30 s. On visit 2, participants completed a constant-load exercise test at 80% of the peak power achieved during the incremental exercise test performed on visit 1, with the test ending at volitional exhaustion. Participants then began a 5-week IMT program. Throughout the IMT program, participants reported to the laboratory once per week to adjust the intensity of their IMT and perform a supervised IMT session (*i.e.*, visits 3-7). On visits 8 and 9, which took place after the 5-week IMT program, participants repeated the incremental and constant-load exercise tests performed on visits 1 and 2.

Figure 2. Overview of experimental protocol.



3.2.3 Exercise Protocols

On visits 1 and 8, participants completed an incremental exercise test to volitional exhaustion. The test consisted of rest for 10 min followed by stepwise increases in work rate by 20 Watts every minute until symptom-limitation. A maximal effort will be confirmed based on accepted criteria (American Thoracic Society & American College of Chest Physicians, 2003). On

visits 2 and 9, participants completed a constant-load exercise test at 80% of the peak power they had achieved during the incremental exercise test performed on visit 1. The test consisted of rest for 10 min followed by a 5-min warmup at a self-selected intensity after which the work rate was increased to 80% of the peak power achieved during the incremental exercise test performed on visit 1. Participants were encouraged to exercise until they reached volitional exhaustion.

3.2.4 Inspiratory Muscle Training

Each participant performed IMT using a POWERbreathe IMT device (K4, POWERbreathe International Inc., Southam, Warwickshire, UK). This K4 model was a variable flow-resistive device that employed an electronically-controlled valve to apply a variable resistance throughout an inspiration. Participants were asked to complete 2 training sessions per day (*i.e.*, a session in the morning and a session in the afternoon), 5 days per week for 5 weeks. Each session comprised of 30 sharp inspiratory efforts from residual lung volume up to total lung capacity. The initial training intensity was set at 60% of the participant's MIP, determined during visit 1. MIP was reassessed weekly (*i.e.*, during visits 3–7), and the training workload was adjusted to 60% of the newly measured MIP. Each session of IMT included a respiratory muscle warm-up for breaths 1-5, which were performed at an intensity below the target training intensity, followed by 25 breaths completed at the target intensity of 60 % of MIP. Any repetition that failed to meet the target intensity did not count towards the total completed repetitions for that session. Compliance to IMT was recorded automatically on the IMT device. IMT compliance was defined as the percentage of prescribed training sessions completed during the 5-week training period. IMT compliance (%) was calculated as (number of sessions completed ÷ number of sessions prescribed) × 100.

3.3 Measurements

3.3.1 Pulmonary Function

Spirometry was performed using a commercially available spirometer (Mini-Spir, Roxon, St-Leonard, QC, Canada) and participants were asked to perform 3 repeatable Forced Vital Capacity (FVC) maneuvers according to standard recommendations (Graham et al., 2019). All measures were expressed in absolute units and as a percentage of predicted normal values (Quanjer et al., 2012).

3.3.2 Mouth pressure

At rest, and during supervised sessions of IMT, mouth pressure was measured via a port in the mouthpiece through which participants breathed using a differential pressure transducer (DP15-34, Validyne Engineering, Northridge, USA). MIP was assessed according to standard recommendations (Laveneziana et al., 2019).

3.3.3 Ventilatory Responses to Exercise

At rest and throughout exercise, standard ventilatory, cardiovascular, and metabolic variables were measured using a customized system composed of open-circuit spirometry and expired gas analysis (Dominelli et al., 2014). Participants breathed through a standard mouthpiece and two-way non-rebreathe valve (Series 2700B, Hans Rudolph, Shawnee, KS, USA), connected to large-bore tubing on the inspired and expired limbs. Inspired and expired airflow was measured using independent pneumotachometers (Series 4813, Hans Rudolph, Shawnee, KS, USA). Mixed expired fractions of oxygen and carbon dioxide were sampled from a mixing chamber connected to the expiratory limb of the breathing circuit and measured using a gas analyzer (14-10000, CWE Inc., Ardmore, PA, USA). Arterial oxygen saturation was estimated using finger pulse oximetry

(Model 7500, Nonin Medical Inc., Plymouth, MN, USA). Heart rate was measured using a telemetric sensor (PTK25, AD Instruments, Colorado Springs, CO, USA). Standard cardiorespiratory variables, including oxygen uptake, carbon dioxide production, V_T, F_b, $\dot{V}E$, heart rate, and arterial oxygen saturation were averaged over 30-second epochs at rest and throughout exercise.

3.3.4 Perceptual Responses

Dyspnoea was comprised of multiple, distinct dimensions; thus, dyspnoea response to exercise was assessed using two approaches. During each exercise test, Borg's modified category ratio 10 (CR10) scale was used to quantify perceived dyspnoea intensity (sensory perceptual), unpleasantness (affective) (Borg, 1982). Each minute during exercise, participants were asked "*how intense is your sensation of breathing overall?*" (dyspnoea intensity) and "*how unpleasant or badly does your breathing make you feel?*" (dyspnoea unpleasantness), as previously described (Zhang et al., 2020). The scale was explained in detail to each participant using the following standard script in order to anchor the endpoint such that '0' represented no sensation of dyspnoea intensity or unpleasantness, while '10' represented the most maximal dyspnoea intensity or unpleasantness ever experienced or imagined: "*The distinction between these two aspects of breathing sensation (intensity and unpleasantness) might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. For example, music that you hate can be unpleasant even when the volume is low and will become more unpleasant as the volume increases; music that you like will not be unpleasant, even when the volume increases*" (Zhang et al., 2020).

3.3.5 Data Sampling and Recording

During the exercise tests and the supervised IMT sessions, all raw data were sampled at 2000 Hz and recorded using a PowerLab 8/30 analog-to-digital converter running LabChart Pro software (AD Instruments, Colorado Springs, USA) for subsequent analysis.

3.3.6 Sample Size Calculation

Determining an appropriate sample size for this study was difficult since no previous studies had examined the effect of sex on improvements in dyspnoea perception during exercise following IMT. Based on the literature available prior to study initiation, only one study had compared the effect of IMT on exercise performance between the sexes and there was no significant effect of IMT nor sex (Guenette et al., 2006). Thus, the study was powered to detect a significant difference in dyspnoea between the sexes at baseline. Based on data from previous studies (Molgat-Seon et al., 2018a, 2019), a sample size of n=32 (n=16 males, n=16 females) was calculated to provide 80% power to detect a significant difference in dyspnoea intensity at a standardized oxygen consumption ($\dot{V}O_2$ = 20 $mL \cdot kg^{-1} \cdot min^{-1}$) during incremental exercise. This calculation was based on a relevant difference of ±1 point on the Borg CR10 scale, an SD of ±1, and $\alpha = 0.05$.

3.3.7 Statistical Analysis

Pre-IMT vs. Post-IMT comparisons of anthropometric characteristics, pulmonary function parameters, MIP, and exercise data were made using a two-way repeated measures analysis of variance. If significant *F* ratios were detected, Tukey's or Bonferroni-adjusted *post hoc* test was used to determine the location of group mean differences. Multiple linear regression analyses were performed to examine whether sex and the relative change in inspiratory muscle strength (%

change in MIP) independently predicted changes in physiological and perceptual responses to exercise, including change in maximal oxygen uptake, change in constant-load exercise endurance time, and change in ratings of dyspnoea intensity and unpleasantness during both incremental and constant-load exercise testing. Statistical analyses were performed using the open-access statistical software package Jamovi (Jamovi v1.2, Sydney, Australia), with the level of significance set at $p<0.05$, and all data were presented as means ± SD.

3.4 Results

3.4.1 Participant characteristics

A total of 30 participants (14 males and 16 females) were enrolled in the study. Data from the 25 participants (12 males and 13 females) who completed the intervention were included in the analyses.

Table 1 summarizes participant characteristics and pulmonary function measured before and after IMT Although males and females were similar in age ($p = 0.46$), males were significantly taller, heavier, and had a higher BMI than females (all $p < 0.001$). All participants demonstrated normal spirometry according to predicted reference values (Tan et al., 2011). When expressed as absolute values, males demonstrated greater FVC, FEV_1, and FEF_{25-75} than females (all $p < 0.05$), whereas the FEV_1/FVC ratio did not differ between sexes ($p > 0.05$). When expressed as percentages of predicted values, pulmonary function did not differ between sexes (all $p > 0.05$). No significant main effects of IMT or interaction effects between IMT and sex were observed for any pulmonary function variable (all $p > 0.05$). MIP responses are covered separately in **Section 3.4.4**. On the International Physical Activity Questionnaire (IPAQ), there

were no significant effects of IMT, sex, or interaction effects between IMT and sex (all $p > 0.22$).

Table 1. Participant characteristics and pulmonary function before and after IMT.

	Males (n=12)		Females (n=13)		*p*
Descriptive characteristics	*Pre-IMT*	*Post-IMT*	*Pre-IMT*	*Post-IMT*	
Age, y	36± 14	-	32± 12	-	
Height, cm	182± 6	-	167± 6	-	*
Body mass, kg	91± 9	90 ± 9	64± 9	64 ± 9	*
BMI, $kg \cdot m^{-2}$	27± 2	27 ± 2	23± 3	23 ± 3	*
Spirometry					
FVC, l	5.68± 0.78	5.73 ± 0.84	3.92± 0.66	3.88 ± 0.59	*
FVC, %-predicted	103± 11	103 ± 9	100± 9	100 ± 8	
FEV_1, l	4.45± 0.53	4.45 ± 0.53	3.10± 0.60	3.04 ± 0.56	*
FEV_1, %-predicted	100± 11	101 ± 11	94± 12	93 ± 10	
FEV_1/FVC, %	79± 5	77 ± 6	79± 7	78 ± 7	
FEF_{25-75}, $l \cdot s^{-1}$	4.04± 0.78	4.24 ± 1.67	2.84± 0.94	2.79 ± 0.92	*

MIP, cmH_2O	133± 34	189 ± 43	105± 42	132 ± 34	*†‡
International Physical Activity Questionnaire (IPAQ)					
Total MET-min/week	4327 ± 2960	6153 ± 4510	3696 ± 2451	4185 ± 2753	

*Abbreviations: BMI; body mass index; FVC, forced vital capacity; FEV_1, forced expired volume in 1 s; FEF_{25-75}, forced expired flow between 25 and 75% of forced vital capacity. Values are presented as mean ± SD. *Main effect of sex ($p < 0.05$); †main effect of IMT (pre- vs post-IMT, $p < 0.05$); ‡IMT × sex interaction ($p < 0.05$).*

3.4.2 Cardiorespiratory Responses to Incremental Exercise Test

At peak incremental exercise test, males achieved significantly greater peak work rate, absolute VO_2, VCO_2, tidal volume, $\dot{V}E$, and ventilatory equivalent for oxygen ($\dot{V}E/VO_2$) than females (**Table 2**; all main effects of sex, $p < 0.05$), whereas females demonstrated a lower RER ($p < 0.05$). Peak VO_2 relative to body mass, heart rate, breathing frequency, and ventilatory equivalent for carbon dioxide ($\dot{V}E/VCO_2$) did not differ between sexes (all $p > 0.05$). No significant main effects of IMT or interaction effects between IMT and sex were observed for any physiological variable (all $p > 0.05$).

At the highest equivalent submaximal work rate during the incremental exercise test, absolute and relative VO_2 demonstrated significant main effects of sex and IMT (**Table 2**; both $p < 0.05$), with males exhibiting higher absolute VO_2 but lower body mass-normalized VO_2 than females. Both sexes demonstrated reduced oxygen uptake at the same absolute work rate

following IMT. Males also had significantly lower heart rate, tidal volume and breathing frequency than females (all main effects of sex, $p < 0.05$), whereas VCO_2, RER, $\dot{V}E$, ventilatory equivalents, and leg discomfort did not differ between sexes (all $p > 0.05$). No significant interaction effects between IMT and sex were observed for any physiological or perceptual variable (all $p > 0.05$), indicating similar responses to IMT in males and females.

Table 2. Cardiorespiratory responses at peak exercise and the highest equivalent submaximal work rate during the incremental exercise test before and after IMT.

	Males (n=12)		Females (n=13)		*p*
Cardiorespiratory variables during peak exercise	*Pre-IMT*	*Post-IMT*	*Pre-IMT*	*Post-IMT*	
Work rate (W)	252± 42	257 ± 42	195± 33	197 ± 42	*
VO_2 ($L \cdot min^{-1}$)	3.54± 0.51	3.41 ± 0.46	2.59± 0.43	2.50 ± 0.47	*
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	39.5± 7.2	38.5 ± 7.4	41.2± 8.3	39.2 ± 7.5	
VCO_2 ($L \cdot min^{-1}$)	4.19± 0.67	4.20 ± 0.55	2.95± 0.38	2.82 ± 0.41	*
RER	1.18± 0.07	1.24 ± 0.12	1.15± 0.08	1.14 ± 0.10	*
HR ($beats \cdot min^{-1}$)	174± 13	171 ± 17	197± 74	174 ± 11	
V_T (L)	2.87± 0.58	2.96 ± 0.64	1.82± 0.22	1.85 ± 0.27	*

F_b (breaths·min^{-1})	44± 11	42 ± 9	44± 9	42 ± 9	
$\dot{V}E$ (L·min^{-1})	136± 28	136 ± 23	87± 15	85 ± 16	*
$\dot{V}E/VO_2$	38.4± 5.9	40.1 ± 4.7	34.1± 6.3	34.5 ± 6.6	*
$\dot{V}E/VCO_2$	32.3± 3.8	32.3 ± 2.7	29.5± 3.8	30.2 ± 3.8	
Cardiorespiratory variables at HEWR					
VO_2 (L·min^{-1})	2.06± 0.24	1.86 ± 0.26	1.85± 0.13	1.77 ± 0.12	*†
VO_2 (mL·kg^{-1}·min^{-1})	22.3± 4.01	21.1 ± 4.22	29.5± 5.13	28.0 ± 3.83	*†
VCO_2 (L·min^{-1})	2.01± 0.50	1.83 ± 0.33	1.80± 0.15	1.71 ± 0.22	
RER	0.97± 0.13	0.98 ± 0.09	0.98± 0.09	0.97 ± 0.12	
HR (beats·min^{-1})	121± 18	118 ± 18	146± 19	144 ± 17	*
V_T (L)	2.27± 0.54	2.27 ± 0.81	1.67± 0.23	1.64 ± 0.26	*
F_b (breaths·min^{-1})	22± 6	22 ± 6	28± 7	28 ± 7	*
$\dot{V}E$ (L·min^{-1})	55± 16	50 ± 9	49± 6	49 ± 5	
$\dot{V}E/VO_2$	26.3± 4.7	26.9 ± 3.2	26.8± 3.7	27.8 ± 3.6	
$\dot{V}E/VCO_2$	27.1± 2.1	27.5 ± 2.6	27.6± 2.3	28.9 ± 3.4	

Abbreviations: VO2, oxygen uptake; VCO2, carbon dioxide output; RER, respiratory exchange ratio; HR, heart rate; VT, tidal volume; Fb, breathing frequency; VE, minute ventilation; VE/

*VO2, ventilatory equivalent for oxygen; VE/VCO2, ventilatory equivalent for carbon dioxide. Values are presented as mean ± SD. *Main effect of sex ($p < 0.05$); †main effect of IMT (pre- vs post-IMT, $p < 0.05$); ‡IMT × sex interaction ($p < 0.05$).*

3.4.3 Cardiorespiratory Responses to Constant-Load Exercise Test

At task failure during the constant-load exercise test, endurance time did not differ between males and females and was unchanged following IMT (**Table 3**; all $p > 0.05$). Males demonstrated significantly greater absolute VO_2, VCO_2, tidal volume, and $\dot{V}E$ than females (all main effects of sex, $p < 0.05$). RER and $\dot{V}E$ demonstrated significant main effects of IMT (both $p < 0.05$), with higher values following IMT in both sexes. Relative VO_2, heart rate, breathing frequency, ventilatory equivalents ($\dot{V}E/VO_2$ and $\dot{V}E/VCO_2$), and perceptual responses did not differ between sexes (all $p > 0.05$). No significant interaction effects between IMT and sex were observed for other physiological variables (all $p > 0.05$).

At isotime, males also exhibited significantly greater absolute VO_2, VCO_2, tidal volume, and $\dot{V}E$, whereas females demonstrated a higher heart rate (**Table 3**; all main effects of sex, $p < 0.05$). RER demonstrated a significant main effect of IMT ($p < 0.05$), with higher values following IMT in both sexes. No significant interaction effects between IMT and sex were observed for other physiological variables (all $p > 0.05$).

Table 3. Cardiorespiratory responses at peak exercise and at isotime during the constant-load exercise test before and after IMT.

	Males (n=12)		Females (n=13)		*p*
Cardiorespiratory variables during peak exercise	*Pre-IMT*	*Post-IMT*	*Pre-IMT*	*Post-IMT*	
Endurance time (sec)	763± 511	719 ± 411	596± 338	614 ± 349	
VO_2 ($L \cdot min^{-1}$)	3.52± 0.45	3.41 ± 0.44	2.50± 0.34	2.52 ± 0.44	*
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	48.9± 44.7	38.3 ± 6.4	40.6± 4.8	40.9 ± 7.3	
VCO_2 ($L \cdot min^{-1}$)	3.87± 0.58	3.89 ± 0.59	2.65± 0.34	2.74 ± 0.37	*
RER	1.04± 0.21	1.15 ± 0.14	1.07± 0.08	1.10 ± 0.08	†
HR ($beats \cdot min^{-1}$)	169± 17	166 ± 19	161± 32	176 ± 12	
V_T (L)	2.88± 0.69	2.90 ± 0.66	1.76± 0.22	1.84 ± 0.31	*
F_b ($breaths \cdot min^{-1}$)	42± 11	45 ± 8	44± 6	44 ± 9	
$\dot{V}E$ ($L \cdot min^{-1}$)	130± 27	140 ± 22	86± 16	89 ± 15	*†
$\dot{V}E/VO_2$	38.0± 5.8	41.3 ± 6.7	34.8± 6.7	35.8 ± 7.4	
$\dot{V}E/VCO_2$	34.5± 4.4	36.0 ± 4.3	32.4± 4.1	32.6 ± 5.6	
Cardiorespiratory variables at iso-time					
VO_2 ($L \cdot min^{-1}$)	3.08± 0.31	2.88 ± 0.33	2.33± 0.33	2.37 ± 0.52	*
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	34.6± 3.74	32.3 ± 4.77	37.9± 4.64	38.4 ± 7.90	

VCO_2 ($L \cdot min^{-1}$)	3.55± 0.39	3.44 ± 0.49	2.57± 0.27	2.63 ± 0.39	*
RER	1.16± 0.08	1.20 ± 0.12	1.11± 0.09	1.13 ± 0.11	†
HR ($beats \cdot min^{-1}$)	148± 17	146 ± 15	164± 14	166 ± 13	*
V_T (L)	2.93± 0.81	2.99 ± 0.82	1.87± 0.27	1.93 ± 0.37	*
F_b ($breaths \cdot min^{-1}$)	31± 10	31 ± 8	36± 5	36 ± 6	
$\dot{V}E$ ($L \cdot min^{-1}$)	97± 15	95 ± 13	73± 8	76 ± 12	*
$\dot{V}E/VO_2$	32.1± 4.5	33.3 ± 4.3	31.9± 5.5	32.6 ± 5.7	
$\dot{V}E/VCO_2$	27.8± 2.7	27.8 ± 2.9	28.5± 3.0	28.8 ± 3.2	

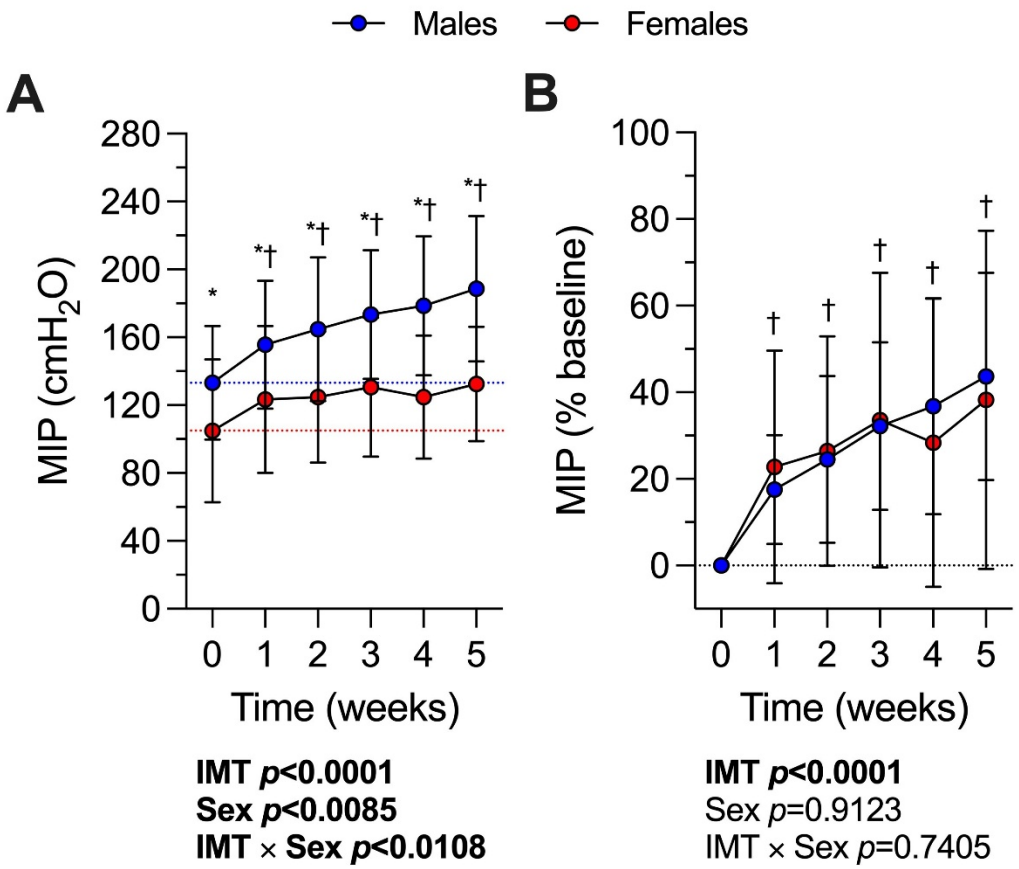
*Abbreviations: VO2, oxygen uptake; VCO2, carbon dioxide output; RER, respiratory exchange ratio; HR, heart rate; VT, tidal volume; Fb, breathing frequency; VE, minute ventilation; VE/ VO2, ventilatory equivalent for oxygen; VE/VCO2, ventilatory equivalent for carbon dioxide. Values are presented as mean ± SD. *Main effect of sex ($p < 0.05$); †main effect of IMT (pre- vs post-IMT, $p < 0.05$); ‡IMT × sex interaction ($p < 0.05$).*

3.4.4 Maximal Inspiratory Pressure Responses

MIP increased over the 5-week IMT intervention in both males and females (Figure 11). For absolute MIP (**Figure 3A**), there were significant main effects of IMT ($p < 0.0001$) and sex ($p = 0.0085$), with MIP increasing over the intervention and remaining higher in males than females. A significant interaction effect between IMT and sex ($p = 0.0108$) indicated greater absolute increases in MIP in males than females. When expressed relative to baseline (**Figure 3B**), MIP

also increased over time (main effect of IMT, $p < 0.0001$), with no main effect of sex ($p = 0.9123$) or interaction effects between IMT and sex ($p = 0.7405$), indicating similar relative improvements in MIP between males and females. Compliance with the IMT intervention was high in both males (96.8 ± 3.8%) and females (95.0 ± 11.9%). Relative MIP improvements were 43.7 ± 23.9% in males and 40.7 ± 36.4% in females.

Figure 3. Absolute (panel A) and relative (panel B) changes in MIP during IMT in males and females.

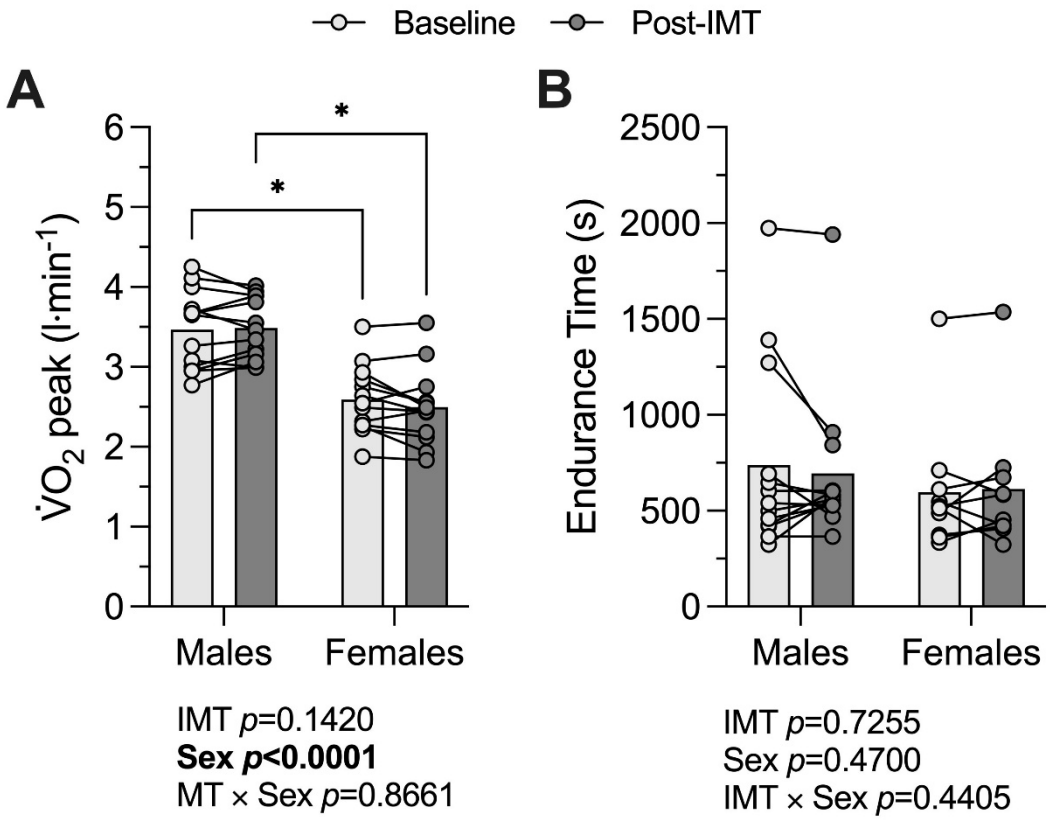


**Main effect of sex ($p < 0.05$); †main effect of IMT (pre- vs post-IMT, $p < 0.05$); ‡IMT × sex interaction ($p < 0.05$).*

3.4.5 Exercise Performance Responses Following IMT

Peak oxygen uptake ($\dot{V}O_2peak$) did not change following the 5-week IMT intervention (**Figure 4A**; main effect of IMT, $p = 0.1420$). Males demonstrated higher $\dot{V}O_2peak$ than females (main effect of sex, $p < 0.0001$), with no interaction effect between IMT and sex ($p = 0.8661$), indicating similar responses to IMT between sexes. Similarly, endurance time during the constant-load exercise test was unchanged following IMT (**Figure 4B**; main effect of IMT, $p = 0.7255$), with no main effect of sex ($p = 0.4700$) or interaction effect between IMT and sex ($p = 0.4405$).

Figure 4. VO2peak during the incremental exercise test (panel A) and endurance time during the constant-load test (panel B) at baseline and post-IMT in males and females.



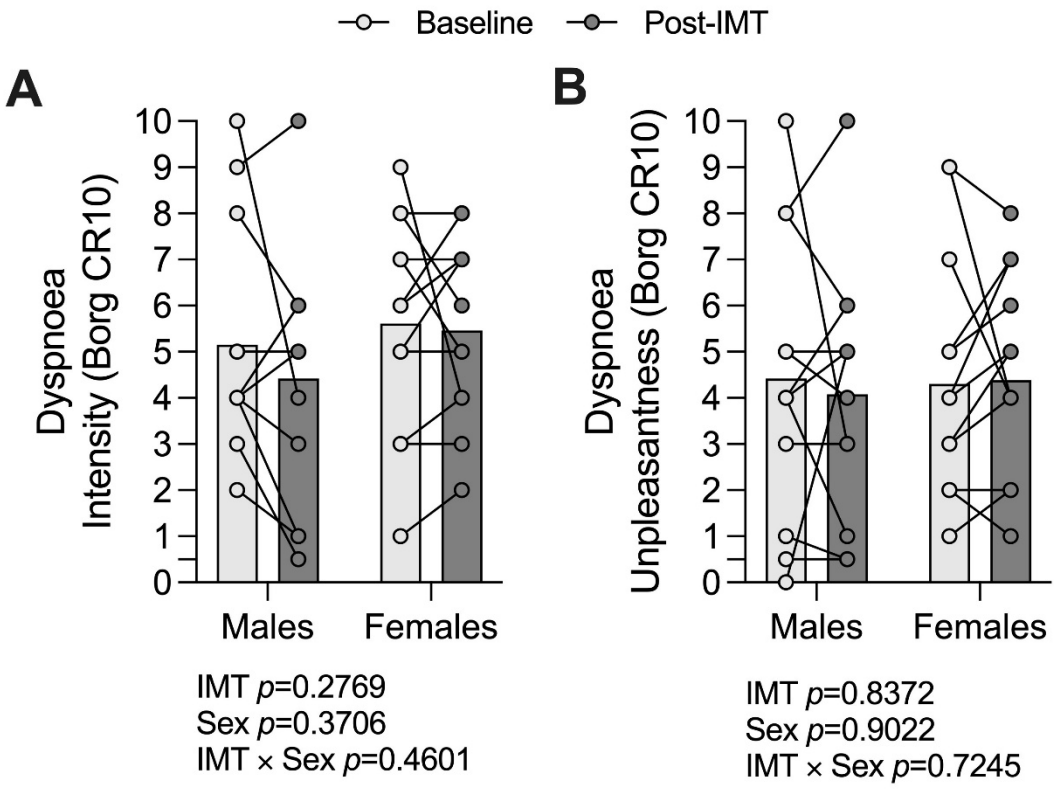
**Main effect of sex ($p < 0.05$); †main effect of IMT (pre- vs post-IMT, $p < 0.05$); ‡IMT × sex interaction ($p < 0.05$).*

3.4.6 Dyspnoea Responses Following IMT

Dyspnoea intensity at the highest equivalent submaximal work rate during the incremental exercise test was unchanged following IMT (**Figure 5A**), with no main effects of

IMT (p = 0.2769) or sex (p = 0.3706), and no interaction effect between IMT and sex (p = 0.4601). Similarly, dyspnoea unpleasantness did not change following IMT (**Figure 5B**), with no main effects of IMT (p = 0.8372) or sex (p = 0.9022), and no interaction effect between IMT and sex (p = 0.7245).

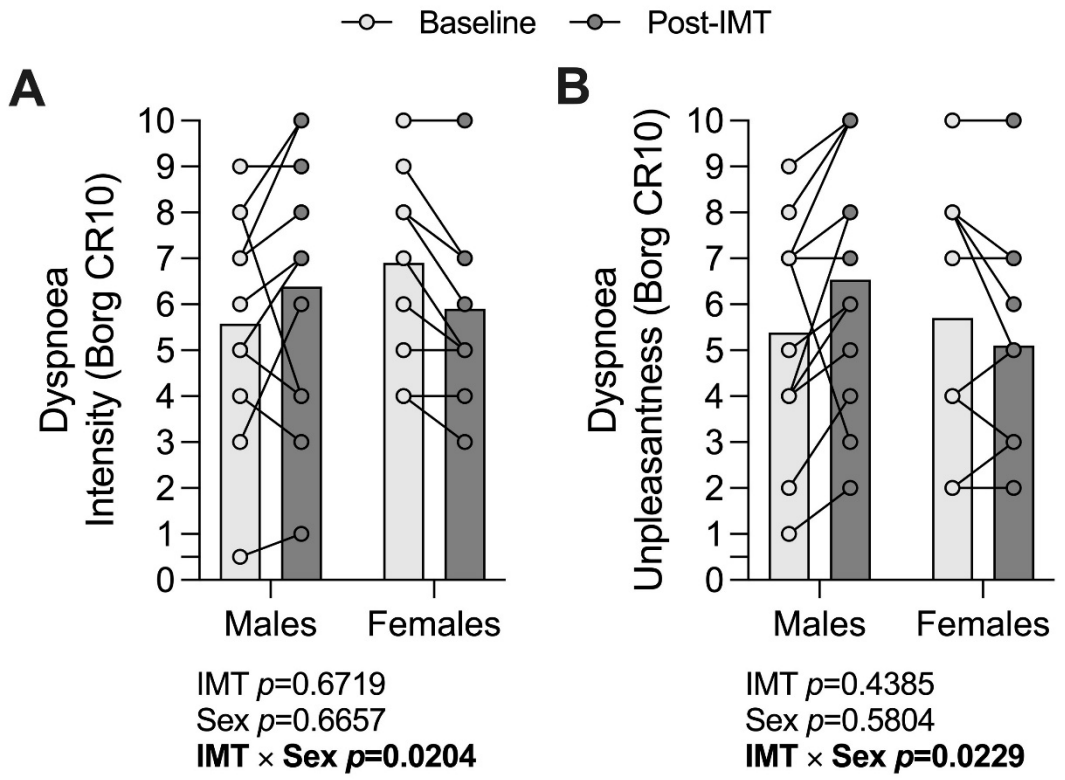
Figure 5. The perception of dyspnoea intensity (panel A) and unpleasantness (panel B) at the highest-equivalent submaximal work rate during the incremental exercise test at baseline and post-IMT in males and females.



**Main effect of sex ($p < 0.05$); †main effect of IMT (pre- vs post-IMT, $p < 0.05$); ‡IMT × sex interaction ($p < 0.05$).*

At isotime during the constant-load exercise test, both dyspnoea intensity (**Figure 6A**) demonstrated no main effects of IMT (p = 0.6719) or sex (p = 0.6657), but a significant interaction effect between IMT and sex was observed (p = 0.0204). Similarly, dyspnoea unpleasantness (**Figure 6B**) showed no main effects of IMT (p = 0.4385) or sex (p = 0.5804), but a significant interaction effect between IMT and sex was observed (p = 0.0229).

Figure 6. The perception of dyspnoea intensity (panel A) and unpleasantness (panel B) at iso-time during the constant-load exercise test at baseline and post-IMT in males and females.



**Main effect of sex ($p < 0.05$); †main effect of IMT (pre- vs post-IMT, $p < 0.05$); ‡IMT × sex interaction ($p < 0.05$).*

3.4.7 Correlates of IMT Responses

Table 4 illustrates the regression models examining sex and relative changes in MIP following IMT as predictors of physiological and perceptual responses during exercise. No significant associations were observed between change in MIP and change in VO_2max during CPET, endurance time during CLT, or measures of dyspnoea intensity and unpleasantness during CPET or CLT (all $p > 0.05$). Similarly, sex was not a significant predictor of changes in VO_2max, endurance time, or dyspnoea responses during CPET or dyspnoea unpleasantness

during CLT (all $p > 0.05$). However, sex was significantly associated with change in dyspnoea intensity during CLT ($p = .038$), with females demonstrating a lower change in dyspnoea intensity than males after controlling for change in MIP (b = −1.47, SE = 0.66).

Table 4. Regression models examining sex and change in MIP (%) as predictors of exercise and dyspnoea outcomes.

Dependent variable	R	R^2	Female vs. male, *b* (SE)	*p*	Change in MIP, *b* (SE)	*p*
Change in VO_2max during CPET ($L \cdot min^{-1}$)	.080	.006	0.014 (0.160)	.932	−0.001 (0.004)	.752
Change in Endurance time during CLT (s)	.428	.183	90.52 (82.37)	.286	3.60 (1.85)	.067
Change in Dyspnoea intensity during CPET	.396	.157	1.50 (0.87)	.101	0.028 (0.020)	.174
Change in Dyspnoea unpleasantness during CPET	.216	.047	0.365 (0.888)	.685	0.021 (0.021)	.327
Change in Dyspnoea intensity during CLT	.457	.209	−1.47 (0.66)	.038*	−0.005 (0.015)	.722
Change in Dyspnoea unpleasantness during CLT	.307	.094	−0.947 (0.697)	.190	0.0003 (0.016)	.985

Note. R = multiple correlation coefficient; R^2 = coefficient of determination; b = unstandardized regression coefficient; SE = standard error; p = probability value; MIP = maximal inspiratory

*pressure; VO_2max = maximal oxygen uptake; CPET = cardiopulmonary exercise testing; CLT = constant-load exercise test; IMT = inspiratory muscle training. The female-versus-male coefficient represents the adjusted difference in the dependent variable between females and males, controlling for change in MIP (%). *Statistical significance was set at $p < .05$.*

3.5 Discussion

3.5.1 Main Findings

This study investigated whether sex influences the physiological and perceptual responses to a 5-week IMT intervention in ostensibly healthy, physically active adults. The main findings were threefold: (1) IMT significantly improved inspiratory muscle strength in both males and females, with comparable relative adaptations between sexes; (2) these improvements did not translate into changes in maximal exercise capacity or endurance performance, although both sexes demonstrated reduced oxygen uptake during standardized submaximal exercise, suggesting improved exercise economy; and (3) perceptual responses to exercise were largely unchanged following IMT, with limited evidence of a sex-specific effect on dyspnoea unpleasantness during constant-load exercise, where females reported lower unpleasantness following training.

3.5.2 Inspiratory Muscle Strength Responses

IMT resulted in improved inspiratory muscle strength in both males and females (**Figure 3**). Compliance with the intervention was high in both sexes, supporting the feasibility of the 5-week protocol. Although males demonstrated greater absolute MIP values before and after

training, relative improvements were similar between sexes after normalization to baseline values, indicating comparable responsiveness to IMT. These findings support the hypothesis that males and females would exhibit similar physiological adaptations to IMT and are consistent with the ability of respiratory muscles to adapt to an appropriate overload stimulus, similar to other skeletal muscles (McConnell, 2013; McConnell & Romer, 2004).

The present findings contribute to the limited literature examining potential sex differences in inspiratory muscle trainability. While sex differences in absolute MIP are well established and are attributed to differences in thoracic dimensions, respiratory muscle mass, and lung size (Evans & Whitelaw, 2009), fewer studies have directly compared IMT-induced adaptations between males and females. Previous investigations have frequently combined sexes or included predominantly male samples (Illi et al., 2012; Shei et al., 2022). In the current study, similar relative improvements observed between sexes suggest that IMT may produce comparable adaptations in ostensibly healthy, physically active males and females.

These findings suggest that 5 weeks of IMT was sufficient to produce a substantial improvement in inspiratory muscle strength. This is consistent with the systematic review by HajGhanbari et al. (2013), which demonstrated that meaningful improvements in inspiratory muscle strength typically occur within 4–11 weeks of IMT. The approximately 42% increase in MIP observed in the present study is therefore consistent with the expected time course of adaptation and places the magnitude of improvement toward the upper end of that reported following short-term IMT interventions. Across previous short-term IMT interventions lasting 4–6 weeks, improvements in MIP have generally ranged from 16% to 41%, with the magnitude of improvement varying considerably across studies (Ando et al., 2020; Bostanci et al., 2019; Ramsook et al., 2017; Romer et al., 2002c; Volianitis et al., 2001).

Importantly, the relative improvement in MIP was similar between males (43.7 ± 23.9%) and females (40.7 ± 36.4%) in the present study, suggesting comparable inspiratory muscle trainability between sexes. This finding is consistent with previous evidence demonstrating similar relative adaptations to IMT in males and females despite greater absolute inspiratory muscle strength in males (Guenette et al., 2006). The variability in MIP improvements reported across studies may therefore reflect differences in training methodology and participant characteristics rather than intervention duration alone. Although several studies have employed similar protocols involving 30 inspiratory efforts performed twice daily (Ramsook et al., 2017; Bostanci et al., 2019; Romer et al., 2002; Ando et al., 2020), differences in training intensity, frequency, supervision, and participant characteristics may influence the magnitude of adaptation. Furthermore, differences in whether outcomes are reported for combined samples or separately by sex may contribute to variation between studies. Taken together, the present findings indicate that 5 weeks of IMT is sufficient to elicit a robust improvement in inspiratory muscle strength, with the magnitude of the response being relatively large while remaining consistent with the range of adaptations previously reported following short-term IMT.

3.5.3 Physiological Exercise Responses

Despite improvements in inspiratory muscle strength, IMT did not alter maximal or endurance exercise performance in either sex (**Figure 4**). This finding is consistent with previous studies and systematic reviews showing that, although IMT reliably improves inspiratory muscle strength, its effects on $\dot{V}O_2$peak and exercise performance are variable in healthy individuals (HajGhanbari et al., 2013; Illi et al., 2012; Ren et al., 2025). In healthy, physically active adults, inspiratory muscle function is unlikely to be a primary limitation during maximal exercise, which

may explain why improvements in inspiratory muscle strength did not translate into changes in $\dot{V}O_2$peak or exercise capacity.

A reduction in oxygen uptake at the standardized submaximal work rate during the incremental exercise test was observed following IMT, without corresponding changes in ventilation or heart rate (**Table 2**). This finding is consistent with improved exercise economy, whereby a lower oxygen requirement is observed for the same external workload. Similar reductions in submaximal oxygen uptake following IMT have been reported and attributed to improved inspiratory muscle efficiency and reduced metabolic demands associated with breathing (Downey et al., 2007; McConnell & Romer, 2004; Ren et al., 2025). Potential contributing mechanisms include reduced respiratory muscle oxygen requirements and altered respiratory muscle metaboreflex responses (Chan et al., 2023; McConnell & Romer, 2004). However, given that these changes were not accompanied by improvements in endurance time or maximal exercise performance, their functional relevance remains uncertain.

Baseline physiological characteristics differed between males and females in the present study (**Table 1**), consistent with established sex-related differences in body size, lung volumes, and cardiovascular capacity (Evans & Whitelaw, 2009). Across both exercise protocols, males exhibited greater absolute cardiorespiratory responses, whereas body mass-normalized $\dot{V}O_2$peak during maximal incremental exercise was similar between sexes, indicating comparable aerobic fitness despite differences in absolute exercise capacity (**Tables 2 and 3**). Following IMT, males and females demonstrated similar physiological responses, suggesting that sex did not substantially influence adaptation to the intervention. These findings align with previous work showing that, although males generally have greater absolute inspiratory muscle strength and aerobic capacity, relative adaptations to IMT are comparable between sexes (Guenette et al., 2006).

3.5.4 Perceptual Exercise Responses

Contrary to expectations, IMT resulted in minimal changes in perceptual responses to exercise. Ratings of dyspnoea intensity and unpleasantness during the standardized submaximal stage of the incremental exercise test were unchanged following IMT in both sexes despite improvements in inspiratory muscle strength (**Figure 5**). These findings are consistent with previous work showing that improvements in inspiratory muscle function do not consistently translate into reductions in exertional dyspnoea in healthy individuals (HajGhanbari et al., 2013; Illi et al., 2012), although reductions in dyspnoea following IMT have also been reported (Downey et al., 2007; Ramsook et al., 2017). Collectively, these findings suggest that perceptual responses to IMT in healthy individuals may vary depending on the exercise task, training protocol, and characteristics of the study population.

During the constant-load exercise test at iso-time, leg discomfort was unchanged following IMT. However, dyspnoea intensity and unpleasantness demonstrated a sex-dependent response, with females reporting lower ratings and males showing a slight increase following training (Figure 6). This finding should be interpreted cautiously because the interaction was limited to perceptual outcomes and was not accompanied by changes in physiological responses or endurance performance. Overall, these findings provide limited evidence of a sex-specific perceptual response to IMT, with differences between males and females observed for dyspnoea intensity and unpleasantness during constant-load exercise.

3.5.5 Correlates of IMT Responses

The present regression analyses examined whether sex and relative change in MIP following IMT were associated with changes in exercise performance and dyspnoea responses (**Table 4**). Change in MIP was not significantly associated with changes in VO_2max, endurance

time, or dyspnoea intensity or unpleasantness during incremental or constant-load exercise. Although the association between change in MIP and endurance time approached significance (b = 3.60, p = .067), these findings suggest that the magnitude of improvement in inspiratory muscle strength alone does not explain individual differences in exercise or perceptual responses following IMT. This is consistent with Guenette et al. (2006), who reported that improvements in inspiratory muscle strength were not directly associated with changes in exercise performance following IMT. Other adaptations, including changes in respiratory muscle efficiency, inspiratory muscle recruitment, and the perception of respiratory effort, may contribute to functional responses to IMT (Chan et al., 2023; McConnell & Romer, 2004).

Sex was independently associated with change in dyspnoea intensity during the constant-load exercise test, with females demonstrating a lower change than males after controlling for change in MIP (b = −1.47, p = .038). However, sex was not associated with dyspnoea intensity during incremental exercise or dyspnoea unpleasantness during either exercise condition, suggesting that this finding may be specific to dyspnoea intensity during sustained exercise. Overall, the relatively low variance explained by the models (R^2 = .006–.209) indicates substantial individual variability in responses to IMT, consistent with evidence that adaptations to IMT can differ considerably between individuals, even within healthy populations (Shei et al., 2022).

3.5.6 Strengths and Limitations

This study possesses several important strengths. First, both incremental exercise test (*i.e.,* cardiopulmonary exercise testing or CPET) and constant-load exercise testing were used to provide a comprehensive assessment of physiological and perceptual responses. CPET is the reference method for evaluating cardiorespiratory fitness and peak oxygen uptake ($\dot{V}O_2peak$), while constant-load testing provides a sensitive measure of exercise tolerance (Puente-Maestu et

al., 2009). Second, males and females were recruited in an approximately 1:1 ratio (12 males, 13 females), allowing direct comparison of sex-specific responses to IMT. Third, habitual physical activity was assessed before and after the 5-week intervention using the International Physical Activity Questionnaire (IPAQ). Activity levels remained stable throughout the study and did not differ between sexes, reducing the likelihood that changes in physical activity influenced the observed responses to IMT.

Several limitations should also be acknowledged. Recruitment did not reach the a priori target sample size of 32 participants, increasing the risk of a type II error and reducing the ability to detect small sex-related differences. Although the overall findings consistently demonstrated minimal sex differences, subtle effects cannot be excluded. Participant attrition related to illness, travel, scheduling conflicts, and other lifestyle factors further reduced statistical power. A constant-load exercise test was performed before and after IMT at 80% of the peak power achieved during the incremental exercise test. A familiarization session before the baseline high-intensity endurance test was not feasible because it would have required additional laboratory visits and increased participant burden. Therefore, potential learning effects between the pre- and post-IMT assessments cannot be entirely excluded. Although standardized instructions were provided during IMT, the contribution of specific inspiratory muscles (e.g., diaphragm versus accessory muscles) during training was not controlled or assessed. It is possible that differences in muscle recruitment patterns between participants may have influenced the extent of adaptation in specific respiratory muscles (Ramsook et al., 2016). Additionally, diaphragmatic activation and transdiaphragmatic pressures were not measured, limiting mechanistic interpretation of the training response. Finally, menstrual cycle phase was not controlled because the objective was to evaluate responses under ecologically valid conditions representative of recreationally active women. Although hormonal

fluctuations may have contributed to inter-individual variability, previous evidence suggests that menstrual and oral contraceptive cycle phases do not meaningfully influence submaximal or maximal exercise performance, despite potential differences in perceived exertion (Mattu et al., 2020; Wilkie et al., 2015).

CHAPTER 4: CONCLUSION

Based on the available literature, this is the first study to systematically examine sex differences in both physiological and perceptual responses to IMT in ostensibly healthy, physically active adults. By directly comparing males and females using an identical IMT protocol and comprehensive physiological and perceptual assessments, this thesis addresses an important gap in the current literature, where previous research has frequently combined sexes or focused predominantly on male populations. The findings demonstrate that males and females exhibit comparable improvements in inspiratory muscle strength following IMT, with limited evidence of sex-specific differences in exercise performance or perceptual responses. These results suggest that biological sex alone may not be a major determinant of IMT responsiveness in ostensibly healthy, physically active adults and that factors contributing to variability between individuals may be more important considerations when evaluating responses to training.

Consistent with the hypothesis, males and females demonstrated similar improvements in inspiratory muscle strength following IMT. However, improvements in inspiratory muscle strength did not consistently translate into enhanced maximal exercise capacity, endurance performance, or reductions in exertional dyspnoea. Although females demonstrated a reduction in dyspnoea unpleasantness during constant-load exercise, this finding was limited to a single perceptual outcome and was not accompanied by corresponding changes in physiological responses or exercise performance. Therefore, the mechanisms underlying this observation remain uncertain and require further investigation. Future studies should examine whether differences in respiratory muscle function, exercise-related perceptual processing, or other individual characteristics contribute to variability in perceptual responses following IMT.

Although the 5-week intervention was sufficient to improve inspiratory muscle strength, longer interventions may be required to determine whether additional physiological adaptations translate into meaningful functional outcomes. Future research should investigate the time course of adaptations following IMT, factors underlying inter-individual variability in responsiveness, and whether sex influences IMT adaptations in populations where respiratory muscle limitations may represent a greater physiological constraint, including older adults and individuals with chronic respiratory or cardiovascular disease.

In conclusion, this thesis advances understanding of IMT responses by demonstrating that healthy males and females exhibit largely comparable physiological adaptations following a standardized training intervention. The primary contribution of this work is the identification that sex does not appear to be a major determinant of IMT responsiveness in ostensibly healthy, physically active adults, while highlighting the importance of considering individual variability in training adaptations. These findings provide a foundation for future research aimed at optimizing IMT prescription and determining whether sex-specific responses emerge in populations with greater respiratory muscle impairment.

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Appendix

PARTICIPANT CONSENT FORM

Version 1 (23/01/2024)

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Evaluating the physiological and perceptual responses to inspiratory muscle training in healthy males and females

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Invitation:

You are being invited to take part in this research study because you are between the ages of 20-60 years (inclusively), are physically active, do not smoke, have a body mass index greater than 18 and lower than 30 $kg \cdot m^{-2}$, have normal pulmonary function, do not have a history of lung or heart disease, and are able to safely perform exercise.

Your participation is voluntary. You have the right to refuse to participate in this study. If you decide to participate, you may still choose to withdraw from the study at any time without any negative consequences.

Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study, and the possible benefits, risks and discomforts.

The principal investigator and supervisors do not have any conflicts of interest in this study. This research has been approved by the University Human Research Ethics Board at The University of Winnipeg and the University of Manitoba. If you wish to participate in this study, you will be asked to sign this form.

Funding:

This study is funded by grants from the Natural Sciences and Engineering Research Council of Canada (NSERC), Research Manitoba, and the University of Winnipeg.

Background information:

During intense exercise the muscles you use to breathe in (*i.e.*, the inspiratory muscles) must work much harder than at rest. Due to this, some people believe that training your inspiratory muscles in a similar way to training your leg or arm muscles, can make exercise easier and reduce sensations of breathlessness during exercise. However, the effects of training your inspiratory muscles have mostly been investigated in males, and it is unclear if males and females respond to training their inspiratory muscles in the same way. Examining how males and females respond to inspiratory muscle training will help us understand how to best improve exercise capacity and minimize sensations of breathlessness during exercise in both males and females.

What is the purpose of this study?

The purpose of the proposed project is to evaluate how inspiratory muscle training affects exercise performance and the perception of breathlessness during exercise in males and females.

Who can participate in this study?

You may be able to participate in this study if you:

- are between the ages of 20-60 years (inclusively)
- can fluently read, speak, and write in English
- are considered physically active
- have a body mass index greater than 18 and lower than 30 $kg \cdot m^{-2}$
- have normal lung function based on your age and sex

* *Please note that your lung function and body mass index will be measured during the visit after written informed consent is obtained. If you do not meet the respective criteria, you will not be able to participate in the remainder of the study.*

Who should *NOT* participate in this study?

You cannot participate in this study if you:

- are current smoker or previously smoked more than 10 pack-years
    - *"pack-years" is a way to measure the amount a person has smoked over a long period of time. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, smoking 1 pack of cigarettes per day for 10 years is equivalent to 10 pack-years.*
- have a history of or current symptoms of heart and/or lung disease
- have any medical condition that prevents you from exercising safely, such as: a problem with your heart; a serious infection within your body; a disorder the affects your nerves, bones and/or muscles; or other health problem that will be made worse with exercise testing.

What does the study involve?

Overview of the Study: You will be asked report to the Duckworth Centre at the University of Winnipeg on 9 occasions. Prior to each visit, all procedures will be explained to you in detail. During the first visit you will perform breathing tests and an exercise test on a stationary bicycle. During the second visit you will complete a second exercise test on a stationary bicycle. Next, you will be asked to perform inspiratory muscle training for 5 weeks. Each week, you will come to the

laboratory to complete a supervised inspiratory muscle training session and your progress will be monitored. Once you've completed your training, your will perform the same breathing and exercise tests as you completed before the start of your training. If you complete all testing visits and the inspiratory muscle training, approximately 8 hours of your time over 7-8 weeks will have been spent as a participant in this study.

Specific Procedures:

Visit 1: After signing the consent form, measurements of your height and weight will be taken. This will be followed by breathing tests to measure how your lungs are functioning and the strength of your inspiratory muscles. This requires that you to breathe quickly and deeply through a mouthpiece while wearing a nose clip (so that you are only breathing out of your mouth).

Next, two small sensors will be placed on the right side of you neck to measures the activity of your respiratory muscles. You will then perform an exercise test on an upright stationary bicycle while breathing through a mouthpiece and wearing a nose clip. The test will begin with a 1-minute warm-up and become more difficult until you feel that you cannot cycle any more. The exercise test should last approximately 10-20 minutes, depending on your fitness level. During the test, you will breathe through a mouthpiece while wearing a nose clip so that your breathing can be monitored. A small clip will also be placed on your finger to non-invasively monitor the amount of oxygen in your blood.

Visit 2: You will perform an exercise test on an upright stationary bicycle while breathing through a mouthpiece and wearing a nose clip. The test will begin with a 1-minute warm-up and the intensity will increase to 80% of the intensity you achieved during the exercise test on visit 1. You will be asked to exercise at this intensity until you feel that you cannot cycle any more. The

exercise test should last approximately 10-20 minutes, depending on your fitness level. During the test, you will breathe through a mouthpiece while wearing a nose clip so that your breathing can be monitored. A small clip will also be placed on your finger to non-invasively monitor the amount of oxygen in your blood.

Inspiratory Muscle Training: After completing visits 1 and 2, you will begin 5 weeks of inspiratory muscle training. A portable breathing trainer will be given to you for the 5 weeks training period, and you will use it to complete your training at home. The training will be explained to you in detail, but each session will involve 30 breaths at a load equivalent to 60% of your maximal inspiratory muscle strength (assessed during visit 1) and will take approximately 5 minutes to complete. You will be asked to complete 2 training session per day, 5 days per week for 5 weeks (*i.e.*, 50 training session in total). This training will not interfere with any regular activities, and you will be able to continue any other regular activities during this time.

Visits 3, 4, 5, 6, and 7: Each week during your training, you will be asked to report to the laboratory so that we can monitor the progress of your training. Each of these visits will take approximately 10-15 minutes. We will reassess your inspiratory muscle strength and you will complete one of your training sessions in the laboratory.

Visit 8: After you complete the 5 weeks of inspiratory muscle training, measurements of your height and weight will be taken. This will be followed by breathing tests to measure how your lungs are functioning and the strength of your inspiratory muscles. This requires that you to breathe

quickly and deeply through a mouthpiece while wearing a nose clip (so that you are only breathing out of your mouth).

Next, two small sensors will be placed on the right side of you neck to measures the activity of your respiratory muscles. You will then perform an exercise test on an upright stationary bicycle while breathing through a mouthpiece and wearing a nose clip. The test will begin with a 1-minute warm-up and become more difficult until you feel that you cannot cycle any more. The exercise test should last approximately 10-20 minutes, depending on your fitness level. During the test, it is necessary that you breathe through a mouthpiece while wearing a nose clip so that your breathing can be monitored. A small clip will also be placed on your finger to non-invasively monitor the amount of oxygen in your blood.

Visit 9: You will perform an exercise test on an upright stationary bicycle while breathing through a mouthpiece and wearing a nose clip. The test will begin with a 1-minute warm-up and the intensity will increase to 80% of the intensity you achieved during the exercise test on visit 1. You will be asked to exercise at this intensity until you feel that you cannot cycle any more. The exercise test should last approximately 10-20 minutes, depending on your fitness level. During the test, it is necessary that you breathe through a mouthpiece while wearing a nose clip so that your breathing can be monitored. A small clip will also be placed on your finger to non-invasively monitor the amount of oxygen in your blood.

What are my responsibilities?

The day before each visit to the laboratory, you will be asked to avoid strenuous exercise. You will also be asked to complete inspiratory muscle training for 5 weeks.

What are the possible harms and discomforts?

Risks and discomforts of the study are related to the measurements being performed. In the unlikely event of a medical emergency during the study, immediate care will be provided by the researchers, who all have current first-aid certificates. It is also possible that you experience psychological discomfort (*e.g.*, stress or anxiety) while participating.

Lung Function Testing: You may experience mild light-headedness or breathlessness, or you may cough or wheeze at the end of some of the breathing tests, but these sensations are temporary and subside once the test has stopped for a few moments. There are no harms or discomforts associated with the breathing apparatus.

Cycle Exercise Tests: How people respond to exercise is not always predictable, and sometimes unexpected problems happen that might require medical attention. You are asked to report immediately any unusual symptoms during the test. You may stop the test when you wish to if you feel tired or uncomfortable. Every effort will be made so that the tests are comfortable and as safe as possible. Potential risks from maximal exercise include:

- vomiting (5%)
- abnormal blood pressure (pressure of your blood) (less than 1%)
- fainting (less than 1%)
- disorders of heartbeat (less than 0.1%)
- very rare instances of heart attack (less than 0.001%)
- anxiety (less than 1%)

If you feel that you are experiencing any side effects as a result of the study you should immediately report this to the researchers conducting the test.

Inspiratory Muscle Training: You may experience mild light-headedness or breathlessness during your training session, similar to moderate-to-high intensity exercise. You may also feel some mild soreness in your neck muscles following each training session.

Incidental Findings: None of the tests performed as part of this study are considered diagnostic. However, if abnormal responses are detected, you will be advised to consult a family physician in order to further investigate these potential health issues. To facilitate this process, Jasvir Dhaliwal will provide any and all relevant information to you and your physician, if required.

What are the potential benefits of participating?

There may or may not be direct benefits to you from taking part in this study. We hope that the information learned from this study can be used in the future to help us understand more about how our respiratory muscles respond to exercise. You will receive a summary of your personal results. If you are interested in hearing about the results of the study, please notify the investigators and they will share the study results once they become available.

What happens if I decide to withdraw my consent to participate?

You may withdraw from the study at any time without giving reasons. If you choose to enter the study and then decide to withdraw at a later time, all data collected about you during your enrolment in the study will not be retained for analysis.

Can I be asked to leave the study?

If you are not able to follow the requirements of the study or for any other reason, the study investigator may withdraw you from the study. If this is the case, you will be notified by telephone.

Will my taking part in this study be kept confidential?

Your confidentiality will be respected. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless required by law. All research-related information collected as part of this study will be anonymized. You will be assigned a unique study number as a participant in this study, and only this number will be used on any research-related information collected about you during the course of this study, so that your identity (*i.e.*, your name or any other information that could identify you) as a participant in this study will be kept confidential. Information that contains your identity will remain only with the Principal Investigator. Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected and also give you the right of access to the information about you that has been provided to the research team and, if need be, an opportunity to correct any errors in this information. Further details about these laws are available on request to the Principal Investigator.

Digital data files will be kept on an encrypted, password-protected computer in Yannick Molgat-Seon's laboratory and hard copy data will be stored in Yannick Molgat-Seon's office in a filing cabinet under lock and key. Only authorized members of the research team and Yannick Molgat-

Seon will have access to the data. All data will be kept for a minimum of 7 years and will be disposed of by permanently erasing digital files and securely shredding hard copy files.

Your deidentified data may be shared with an academic publisher or posted publicly as part of a publication; however, any information that could potential be used to identify you will not be included.

Who do I contact if I have questions about the study during my participation?

If you have any questions or desire further information about this study before or during participation, or if you experience any adverse effects, you can contact Jasvir Dhaliwal by email at dhaliw15@myumanitoba.ca

If you have any questions or concerns about this study or how it is being conducted, please contact the researcher directly. If you have any remaining concerns that the researcher has not been able to address, you may contact the Ethics Program Officer at the University of Winnipeg by phone at 204-786-9058 or by email at ethics@uwinnipeg.ca. Alternatively, you may contact the University of Manitoba's Office of Human Research Ethics by phone at 204-474-7122 or by email at humanethics@umanitoba.ca.

Please note that your participation is voluntary and you may refuse to answer any question(s) and are free to stop participating in the study any time prior to publication and/or presentation of the findings without consequence. By consenting to participate, you do not waive any rights to legal

recourse in the event of research-related harm. If you wish to receive a summary of the study's results please contact Jasvir Dhaliwal by email at dhaliw15@myumanitoba.ca

Notice Regarding Collection, Use, and Disclosure of Personal Information

Your personal information is being collected under the authority of *The University of Manitoba Act*. The University of Manitoba is committed to preserving your right to privacy. The information you provide will be used by the University to support our research. Your personal information will not be used or disclosed for other purposes, unless permitted by The Freedom of Information and Protection of Privacy Act or The Personal Health Information Act. If you have any questions about the collection of personal information: Ph: 204-474-9462 or Email: fippa@umanitoba.ca

My signature on this consent form means:

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific objectives.

- I understand that my participation in this study is voluntary and that I am completely free to refuse to participate or to withdraw from this study at any time
- I understand that there are certain risks associated with this study as described this form
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this study will provide any benefits to me.

Name (please print): _____

Signature: _____ Date: _____

Principal Investigator's Signature: _____ Date: _____

A copy of this consent form will be provided to you. Thank you for your consideration.