IMPACT OF EXERCISE WITH BLOOD FLOW RESTRICTION ON MUSCLE HYPERTROPHY AND PERFORMANCE OUTCOMES IN MEN AND WOMEN

by

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ABSTRACT

Blood flow restriction training (BFRT) improves lean mass and strength. In BFRT studies, only 17-29% of participants were female. We compared lean mass and strength following 6-week BFRT between males and females. Thirty-eight adults (age, 25.3 ± 3.1 years; female, n=19) participated. Exercises were performed at 30% of 1-repetition maximum (1-RM) and individual's limb occlusion pressure set at 60%. Lean mass was assessed via dual-energy x-ray absorptiometry, strength was measured using 1-RM. A significant increase in lean mass was observed in males (p= .009) and females (p= .023) without group differences (p= .279). Both males and females increased 1-RM for upper- and lower-body exercises. However, there was a significant interaction effect (time x sex) for knee extension (p= .039), chest press (p= .002), and seated row (p= .033). Lean mass and muscle strength increased following six weeks of BFRT. Males may improve upper-body strength to a greater extent.

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List of Symbols and Abbreviations

Abbreviation	Definition
ANOVA	analysis of variance
BFRT	blood flow restriction training
BMI	body mass index
DXA	dual-energy x-ray absorptiometry
IL-4	interleukin-4
IL-6	interleukin-6
IL-7	interleukin-7
LIF	leukemia inhibitory factor
LOP	limb occlusion pressure
mTOR	mammalian target of rapamycin
ROS	reactive oxygen species
1-RM	one-repetition maximum

Note. Abbreviations are listed alphabetically.

Chapter 1: Introduction

Resistance training has been described as a “medicine,” as it has the ability to prevent several chronic conditions and contribute to maintaining good health [1,2]. Likewise, it is generally understood that resistance training is beneficial for healthy, older, and injured populations. Specifically, it has been shown that resistance training can aid in the development of fitness and maintainence of health, which in turn protects against a number of chronic conditions such as type 2 diabetes mellitus, cardiovascular disease, cancer, and others [2]. One potential reason for the benefits of resistance training is the change in body composition that occurs. Although resistance training may reduce fat mass, generally it leads to an addition of skeletal muscle mass [3–5]. This addition of muscle is known as hypertrophy. It was well established that muscle hypertrophy occurs following moderate to heavy-load resistance training as well as resistance training to volitional failure using a lighter load [6,7]. More recently a novel form of resistance training has emerged as an alternative to heavy-load resistance training. This type of resistance training is known as blood flow restriction training (BFRT) and combines very light loads with the use of a pneumatic cuff placed around the most proximal region of the exercising limb to partially restrict the blood flow [8].

Briefly, BFRT (also known as KAATSU Training for the company that developed it) originated in Japan and has been developed over time since the mid-1900s. Since the 1990s it has undergone rigorous academic research to determine its efficacy as a low-load resistance training alternative. BFRT has been used in a wide range of populations; including elite and high-performance athletes, rehabiliating populations, and elderly adults [9]. In essence, BFRT allows for light loads to be used during resistance training by altering the blood flow into the exercising muscles and occluding the blood flow from leaving the muscles, inducing a high degree of metabolic stress which in turn is believed to stimulate muscle adaptation [8,10]. Although BFRT is an effective low-load alternative to traditional heavy-load resistance training, there are potential risks with exercise of any kind and BFRT must be undertaken with care to ensure the safety of users. A national survery of KAATSU users in Japan found an extremely low incidence rate for any injuries while doing BFRT [11]. Likewise, a number of best-practice guidelines and evidence-based reviews have been published to ensure safe use of BFRT [8,12,13].

It is understood that BFRT is capable of inducing muscle hypertrophy, but there is a lack of a consensus on the actual mechanisms. Within the literature there are several proposed theories on the underlying physiological mechanisms leading to muscle hypertrophy. First, due to the restricted blood flow out of the exercising muscles, there is a build up of metabolites leading to a blood pH shift which signals the expression of anabolic hormones [10]. Second, Type II muscle fibres are recruited at much lower intensities, which is is thought to occur due to an earlier onset of fatigue in Type I fibres because of decreased oxygen delivery and metabolite clearance [10,14]. In addition to these theories there are a combination of others, such as the roles that cell swelling and reactive oxygen species may play in signalling, but in the end it is likely a combination of a variety of these mechanisms that contribute to the hypertrophic effects of BFRT.

Although the exact mechanisms of hypertrophy are not fully understood, there is substantial evidence that BFRT is capable of inducing muscle hypertrophy, increasing strength, and improving functional outcomes. A number of studies have observed significant increases in muscle thickness, muscle cross-sectional area, and limb circumference in both the upper and lower extremeties. Of note, researchers using low-load BFRT performed to failure saw an increase in thigh muscle thickness similar to the traditional resistance training group, however this was achieved with a 33% lower total exercise volume [15]. Likewise, a 2021 study found similar increases in muscle size and muscle strength following short-term BFRT performed to failure and not to failure (four sets: 30-15-15-15 rep scheme) [16]. In a study of females, both the quadriceps and hamstrings cross-sectional areas saw significant increases following a BFRT intervention [17]. Together, along with other research highlighted in this document, it is apparent that low-load BFRT is a sufficient stimulus to induce muscle hypertrophy.

Similarly, low-load BFRT has been shown to not only mediate muscle hypertrophy, but also increase muscle strength. Following a 4-week whole-body BFRT intervention, researchers observed significant improvements in 1-repetition maximums (1-RM) for the knee extension, back squat, calf raise, and seated row [18]. Furthermore, improvements in 3-repetition maximum [19], 3-second maximal voluntary contraction [17], rate of force development [20], and repetitions to failure [19] have been shown to occur follow BFRT interventions, suggesting that BFRT is capable of producing significant strength improvements.

Besides BFRT being shown to improve muscle strength and increase muscle hypertrophy, there is evidence to show that these physiological and morphological changes can be translated to improved physical function and performance. For example, four weeks of BFRT can significantly improve peak, average, and minimum power, as well as isometric muscle strength in collegiate women, although this is one of few studies involving women [21]. Researchers observed significantly greater power output following body-weight lunges in conjuction with blood flow restriction [22]. In a study of semiprofessional male rugby players, vertical jump power and sprint performance were improved compared to the traditional resistance training group following only three weeks of BFRT [23]. Likewise, increases in power have been observed in the upper body [24].

Although, these findings are positive, the vast majority of studies investigating BFRT include only college-aged males (i.e., between the ages of 18-25) [25]. In fact, a call to action in a 2018 review highlights that in studies of chronic and acute (acute meaning one bout of exercise and chronic implying repeated bouts of exercise) BFRT, only 29% and 17%, respectively, of all participants are females [26]. This fact necessitates an urgent response. There is no reason for the exclusion of women in BFRT research. This document will highlight the prominent research regarding muscle hypertrophy, strength, and performance. Likewise, an attempt will be made to equally highlight the very limited research pertaining to young women and propose why further research involving young women is necessary.

Due to the limited evidence for BFRT with respect to women, the current project aims to provide insight as to how males and females may differ in response following six weeks of whole-body low-load resistance training combined with blood flow restriction. Therefore, the objective of this study is to investigate the impact of 6-week, whole-body BFRT on lean body mass, strength, and performance outcomes in males and females with the goal of adding to the growing body of literature, guiding future research on sex differences, and allowing for more specific prescription of this exercise in female populations.

Chapter 2: Literature Review

2.1 Introduction to Blood Flow Restriction Training

Blood flow restriction training, specifically KAATSU Training, was developed in Japan in the 1960s and 1970s, but has since gained notoriety in the Western world for purposes ranging from rehabilitation to high-performance [27]. Primarily, BFRT has been investigated as an intervention for rehabilitation purposes and for those who heavy-load resistance training is contraindicated, but has also been used in healthy populations and high-performance settings [9]. BFRT constitutes undergoing exercise with reduced blood flow to the exercising limb through the use of a pneumatic cuff surrounding the proximal portion of the exercising limb. Blood flow is not fully restricted, but rather arterial blood flow is partially occluded while venous return is fully occluded leading to pooling of blood in the exercising limbs [8,28]

The earliest intentional use of blood flow restriction was by Dr. Yoshiaki Sato (the founder of KAATSU Training) who used rudimentary blood flow restriction to rehabilitate a leg injury [27]. Since then BFRT has been used extensively in rehabilitation settings as a means of improving functional outcomes and muscle mass [29–34]. Alternatively, BFRT has also been researched in the context of healthy and athletic populations, as discussed later in this document. However, the significance of BFRT is that systematic reviews have shown that physiological adaptations have occurred using very low training intensities ranging from 10-50% of 1-RM [35–38]. Training stimuli to induce similar adaptations generally require resistance training with loads from 70-85% 1-RM [39]. The practical application of BFRT is that similar muscular adaptations seen from heavy-load resistance training can be achieved using significantly lesser loads in populations and settings where heavy-load resistance training may otherwise by contraindicated [32–34,36–38,40–45]. However, a number of precautions must be taken to avoid potential injury.

2.2 Safety Considerations for Blood Flow Restriction Training

2.2.1 Adverse Events

In the literature, some potential complications have been highlighted for individuals performing BFRT including venous thromboembolisms and pulmonary embolisms. However, a national survey of over 12,000 KAATSU users in Japan showed incidence rates of 0.055% and 0.008%, respectively [11]. These incidence rates indicate the relatively low risk of BFRT, as the incidence of venous thromboembolisms and pulmonary embolisms in the general population are 0.12% and 0.06-0.07%, respectively [46]. Furthermore, reseachers in Brazil found that practitioners of BFRT reported low rates of adverse events amongst their participants [47]. Therefore, although BFRT must be undertaken with care – preferably administered and supervised by a trained practitioner – the actual occurrences of serious complications are rare. The authors of multiple reviews state that they are confident there are minimal side-effects, especially when performed with the appropriate population and in the presence of a trained practitioner [48,49].

Although BFRT has been demonstrated to be a safe exercise modality in young, healthy adults when administered appropriately, extra precautions should be taken with specific populations to mitigate the chance of serious adverse events. Specifically, BFRT may not be appropriate for pregnant individuals or individuals with uncontrolled hypertension, uncontrolled diabetes, or any individual with a history of thrombotic events or is at greater risk for thrombosis [12,48,50,51].

Furthermore, a study examining the effects of BFRT on thrombin and clot formation factors showed that BFRT does not activate the coagulation system in healthy adults, suggesting that low-load BFRT is a safe method of training [52]. However, low-risk side-effects such as delayed-onset muscle soreness, tingling, and numbness have been reported previously as common side-effects of BFRT [11,13,47,48], hence proper care must be taken to both ease participants into the exercise modality and to ensure proper safety needs are being met.

2.2.2 Cuff Placement, Size, and Material

When applying the KAATSU Training cuffs, they should be tightened snugly around the proximal portion of the exercising limb so that no more than one finger can fit between the cuff and the upper limb or no more than two fingers can fit between the cuff and the lower limb [27].

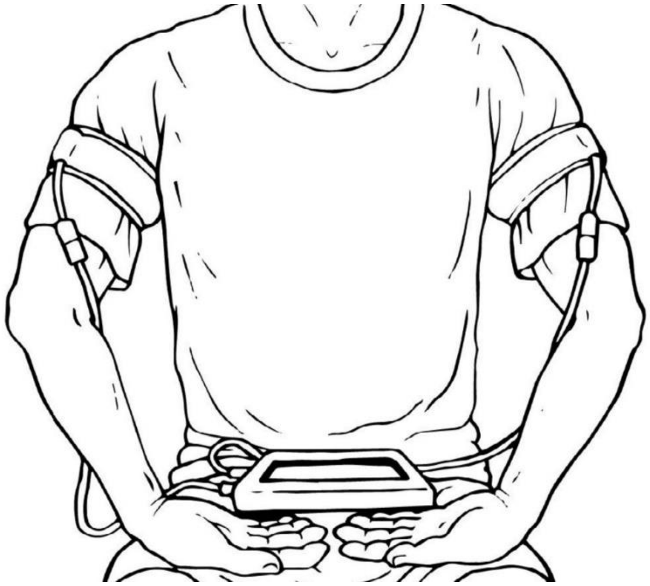


Figure 1. Diagram illustrating approximate arm cuff placement for upper limb BFRT. (Used with permission from KAATSU Global, Inc.).

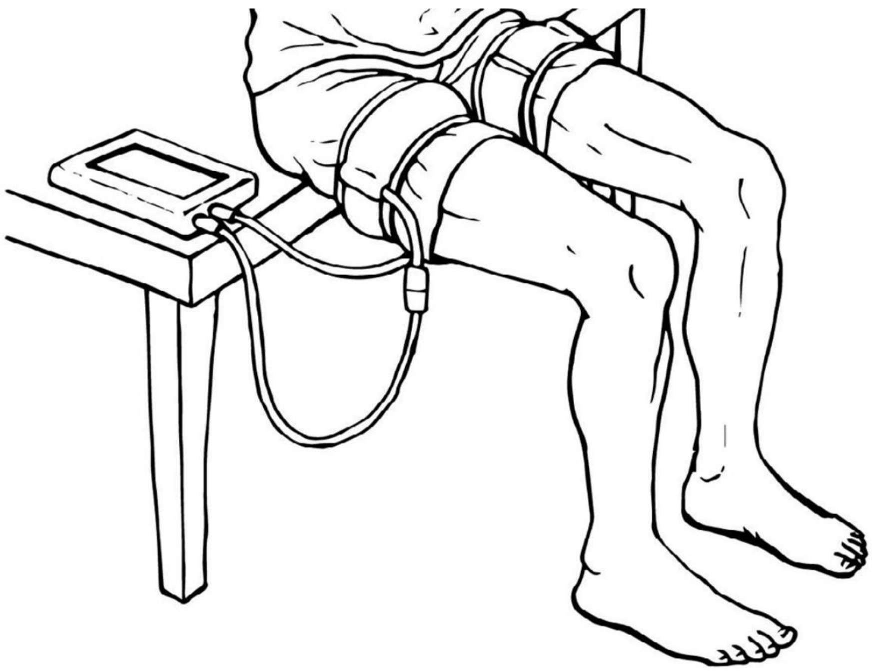


Figure 2. Diagram illustrating approximate leg cuff placement for lower limb BFRT. (Used with permission from KAATSU Global, Inc.).

The pressure necessary to reduce blood flow to the exercising limb is largely determined by the width of the cuff – such that wider cuffs require lower overall pressure and narrow cuffs require higher overall pressures [13,53]. When referenced in the literature, narrow cuffs are typically considered to be 5 cm – the width of KAATSU cuff bands – and wide bands are typically considered to be anything wider than 5 cm [53]. KAATSU offers small, medium, large, and extra-large bands to appropriately meet the demands of a variety of body types. Based on a review of the literature, it is suggested that varied cuff widths can be used, as long as cuff pressure is set appropriately using a relative percentage of limb occlusion pressure [13]. Patterson et al. (2019) suggested that the material of cuff (nylon versus elastic) had a negligible impact on muscular adaptations as a variety of materials have shown muscular adaptations [8,13]. Researchers agree that regardless of cuff material and width, the factor most important to adaptation is the occlusion pressure [8,13,54].

2.2.3 Determining Pressure

Early BFRT research often used an arbitrarily determined absolute restrictive pressure ranging from as low as 50 mmHg to pressures in excess of 200 mmHg [8,55]. The trend over time has shifted away from arbitrary pressures towards using a personalized percentage of limb occlusion pressure (LOP) [54–57]. A 2013 review suggested that by arbitrarily setting the restriction pressure, subjects may undergo blood flow occlusion rather than restriction [55]. Similarly, higher pressures under the cuffs have been associated with an increased risk of nerve-related injury, hence the importance of using an individualized LOP [54]. In fact, Loenneke et al. (2014) hypothesize that BFRT may follow the hormesis theory; such that a low or moderate pressure dose provides beneficial results but too high of a pressure dose may decrease the benefits (i.e., more of a good thing is not necessarily better) [28]. Needless to say, in order for BFRT to remain a viable and safe option, administration should be undertaken with care and the use of personal LOP should be used.

In order to personalize pressures to each exercising individual, the pressure necessary to fully occlude the vasculature must be found. Once the LOP is determined, the chosen percentage for the intervention can be applied. There have been a variety of methods reported in the literature to determine LOP. The primary method to determine LOP, rather than using an arbitrary value, has been to use a Doppler ultrasound probe [32,33,42,58]. Some researchers have attempted to use pulse oximetry to show LOP, but this has only been validated in the upper limbs as there are significant discrepancies between Doppler ultrasound and pulse oximetry results in the lower limbs for determining LOP [59]. In addition, researchers have utilized the technology already used by surgeons by using an automated tourniquet system which provides the LOP via the computer monitor on the device [18,54,60,61]. However, these methods either require the use of costly equipment or well-trained technicians and can be time-consuming. Loenneke et al. (2015) developed regression models to determine LOP using the individual's resting systolic and diastolic blood pressure and their limb circumference – two of the primary factors impacting LOP [62]. These models were developed using 171 participants, both male and female, and have been utilized in blood flow restriction research [21,63].

Although these equations developed by Loenneke et al. (2015) have modest R-squared values of 0.61 and 0.49 for the upper and lower limbs, respectively [62], they have been successfully utilized in a BFRT intervention of trained athletes leading to significant improvements in muscle hypertrophy and functional outcomes with no reported side effects [21]. A study comparing the impact of various cuff pressures showed similar effects on muscle size, torque, strength, and endurance between 40% and 90% pressures [64]. Similarly, following an 8-week BFRT intervention comparing 40% and 80% LOP, muscle size and strength was improved similarly between conditions [65]. These findings imply that as long as the cuffs are set to approximately 60% of LOP based on the equations by Loenneke et al. (2015), participants should undergo a similar stimulus.

Although early blood flow restriction research often utilized an arbitrarily determined pressure [66–70], more recently researchers have consistently advocated for the use of personalized pressures [54–57]. An early review article on enhancing muscular development using BFRT suggests occlusion pressures ranging from 50-80% of LOP [57]. A 2019 review recommends setting blood flow restriction pressure between 40% and 80% of LOP [56]. And most recently, in agreement with Scott et al. (2015) and Patterson et al. (2019), a systematic review by Das and Paton (2022) showcases that using 50-80% of LOP was optimal for BFRT [71].

Several studies are featured below with varying protocols and populations highlighting the efficacy of the use of percentage of LOP in BFRT. A recent study using 60% and 80% of LOP as minimum and maximum thresholds for BFRT, respectively, saw significant strength improvements in patients with chronic atrophic leg musculature following surgery [72]. Noyes and colleagues (2021) saw an increase in lower limb strength of greater than 20% in over 80% of patients following as few as 18 BFRT sessions [72]. A whole-body strength intervention investigating low-load BFRT saw significant increases in 1-RM and muscle mass following 8-weeks of BFRT at 60% of

LOP [18]. Using 70% of LOP, researchers saw significant functional and strength improvements in individuals with knee osteoarthritis following 12-weeks of BFRT, comparable to traditional high-load resistance training [58]. Similar to Ferraz et al. (2018), significant improvements in the functionality of sarcopenic women using 80% of LOP were observed following a 16-week intervention [32]. Furthermore, a low-load BFRT intervention of females with rheumatoid arthritis saw a significant increase in hypertrophy and strength using approximately 70% of LOP [42]. Altogether, these results, as well as the recommendations from countless researchers, suggest that using personal LOP is a safe and effective method of using BFRT, as opposed to alternative methods of determining cuff pressure.

2.3 Resistance Exercise and Blood Flow Restriction

2.3.1 Mechanisms of Muscle Hypertrophy Following Blood Flow Restriction

Some of the primary areas of research regarding BFRT is stimulating muscle hypertrophy; the cause of muscle hypertrophy following resistance training with blood-flow restriction; and the implications blood-flow restriction-induced muscle hypertrophy has for a number of populations. Although blood flow restriction has been shown to induce muscle hypertrophy while using very low loads of resistance [15,17,18,20,32,40,58,73–76], there is not a complete understanding of the underlying physiology that promotes this hypertrophy. However, there have been several hypotheses proposed as to how low-load BFRT induces muscle hypertrophy.

Primarily, the increased metabolic stress that BFRT induces is suggested to mediate a large portion of the hypertrophy observed [10,14,57,61,77]. As blood lactate levels increase and blood pH levels decrease, the muscle cells begin to undergo metabolic stress [10]. This increased metabolic stress in the muscle is thought to promote muscle growth by facilitating the expression of key anabolic hormones such as growth hormone, insulin-like growth factor-1, and mechano-growth factor. Specifically, an acute ninefold increase in serum growth hormone was observed following five sets of knee extensions with a relatively high occlusion pressure and a fourfold increase in serum growth hormone was observed following low-intensity BFRT [78,79]. As well as a heightened endocrine response of anabolic hormones and this increased metabolic stress, the expression of specific proteins has been suggested to initiate other mechanisms of muscle hypertrophy [14,80].

Specific proteins known as myokines play an integral role in muscle hypertrophy [81]. These proteins (myokines) are produced following muscle contraction and have a variety of effects on the physiology of muscle cells. Some key myokines that have been suggested to play a role in hypertrophy following BFRT are interleukin-4 (IL-4), IL-6, IL-7, and leukemia inhibatory factor (LIF) [14,80,81]. A study observed concentrations of IL-4, IL-6, IL-7, and LIF all peaked following an acute bout BFRT suggesting that they may all contribute to muscle hypertrophy as fat free mass was significantly increased following 12-weeks of training in young males [80]. Likewise, the same study showed a relationship between the area under the curve of IL-4, IL-6, and LIF and percent change in strength per kilogram of fat-free mass suggesting these myokines may contribute to mechanistic adaptations [80]. On top of the increased concentrations of these key proteins, BFRT has been shown to activate a key cell growth pathway that can regulate muscle hypertrophy [82]. The mammalian target of rapamycin (mTOR) is a cell growth pathway critical for regulation of muscle hypertrophy [82]. It has been shown that production of nitric oxide, as well as secretion of IL-6 and LIF – all metabolites produced during low-load BFRT – can upregulate the mTOR pathway [14,80]. Together, it appears that a variety of key proteins and pathways contribute to stimulating muscle hypertrophy following BFRT.

BFRT research has demonstrated that fast-twitch (Type II) muscle fibres can be recruited at much lower intensities than typical [14]. This early recruitment of Type II muscle fibres is likely due to the decreased oxygen delivery and increased metabolic stress resulting in premature fatigue of the slow-twitch (Type I) muscle fibres [10]. For example, in a 2000 study by Takarada et al., EMG values were comparable between the low-load BFR and high-intensity groups suggesting a sufficient number of Type II fibres were recruited during low-load BFRT to invoke similar muscle activation as during high-intensity training [83]. Likewise, Yasuda et al., (2009) demonstrated that low-load BFRT leads to significantly greater muscle activation than low-load muscle contractions without BFR, indicating a potentially greater recruitment of Type II muscle fibres [84]. However, it should be noted that BFRT does not necessarily recruit as many Type II muscle fibres as traditional heavy-load resistance training [14]. In fact, it appears as though Type I muscle fibres undergo greater adaptation than Type II muscle fibres. Two studies by Bjørnsen and colleagues showed that Type I muscle fibres underwent greater metabolic stress, and a greater number of satellite cells and myonuclei are generated in Type I muscle fibres when compared to Type II muscle fibres [16,85]. However, taken together it appears as though muscle fibre recruitment plays some role in muscle hypertrophy following low-load BFRT.

There are several other points of view surrounding potential mechanisms of muscle hypertrophy following low-load BFRT. Reactive oxygen species (ROS), which play a key role in cell signalling, have been suggested as a further mechanism for muscle hypertrophy [10,15]. However, mechanical tension, rather than metabolic stress, has been shown to be the dominant factor stimulating ROS development decreasing the likelihood that ROS play a significant role in muscle hypertrophy following low-load BFRT [86]. A novel theory of a potential factor for muscle hypertrophy is cell swelling. As metabolites accumulate during BFRT, this creates a pressure gradient driving blood into the muscle fibres [87]. This is thought to lead to intracellular signalling to reinforce the cells as the structural integrity of the cell membrane is threatened by the swelling, as well as stimulate proliferation of satellite cells [87]. Unfortunately, research on the influence of cell swelling on hypertrophy is very limited denying the ability to draw any conclusive decisions. Although it is agreed that BFRT results in increased metabolic stress for the muscles leading to a cascade of other affects, there is still not a complete understanding of the hypertrophic effects of BFRT.

2.3.2 Impact of Blood Flow Restriction on Muscle Hypertrophy

Although the cellular physiology behind muscle hypertrophy following low-load BFRT is not fully understood, there is numerous research indicating that it can induce muscle hypertrophy. A 6-week intervention comparing low-load BFRT performed to failure compared to traditional low-load resistance exercise saw a 7.6% increase in vastus lateralis muscle thickness in the BFRT condition [15]. Although this was not significantly different from the traditional low-load group, this adaptation was achieved with a 33% lower total exercise volume indicating that low-load BFRT is capable of inducing muscle hypertrophy with a reduced workload. However, this was only observed in a sample of 10 young, healthy males reducing its generalizability.

An intervention with collegiate track athletes performing BFRT twice daily for eight days saw significant increases in muscle-bone cross-sectional area and quadricep and hamstring muscle thickness of 4.5%, 5.9%, and 4.5%, respectively [74]. Although promising, training twice daily is not feasible for the general population. Another study involving sprinters saw muscle hypertrophy following six weeks of BFRT performed twice per week in the intervention group versus a control group [20]. Significant hypertrophy occurred in the rectus femoris of the intervention group from pre- to post-intervention, as well as between the intervention and control groups [20]. No significant hypertrophy was observed in the biceps brachii or biceps femoris following sprint training in combination with BFRT [20]. A difference to note between the studies by Abe et al. (2005) and Behringer et al. (2017) is the number of sessions performed and the length of time they are performed over. Abe et al. (2005) performed an 8-day study that included 16 training sessions, whereas the study by Behringer et al. (2017) used 12 training sessions over six weeks suggesting that BFRT is capable of inducing muscle hypertrophy over a variety of intervention durations in well-trained individuals.

In one of the few BFRT studies with a young, female population, Manimmanakorn et al. (2013) observed substantial increases in quadricep and hamstring cross-sectional area in the BFRT group compared to the low-load training group [17]. Specifically, the quadricep cross-sectional area increased by an average of 5.7% and the hamstring cross-sectional area by an average of 7.7%. As well as being a young, female population, this sample were also highly-trained athletes suggesting that BFRT is sufficient to induce muscle hypertrophy in trained, female populations. In a recent study of resistance-trained males and females, following nine weeks of BFRT performed three times per week, significant time effects for quadriceps cross-sectional area and lower body lean mass were observed in both the low-load BFRT and heavy-load resistance training groups [88]. No interaction effects were observed, highlighting that low-load BFRT was as effective as heavy-load resistance training for inducing muscle hypertrophy in resistance trained males and females [88]. Similarly, in a sample of American football athletes, following a 7-week protocol significant increases were observed in thigh and arm circumferences [89]. Conversely, a sample of Australian football players did not increase their muscle thickness or muscle pennation angle [19]. Worth noting regarding the studies in Australian football players: the two interventions had different intervention lengths, different training protocols, and used elastic wraps to induce BFR which could lead to variability in the LOP being used. Needless to say, the 7-week protocol (which included more total exercise volume) was the intervention that observed significant increases in hypertrophy.

A number of other studies have also observed increases in thigh hypertrophy following BFRT interventions [73,83,90,91]. Likewise, several studies have noted increased hypertrophy of the pectoralis major following BFRT [75,90,92], although other studies report no change in pectoralis major hypertrophy following BFRT [18,89]. Of the studies investigating chest adaptation [75,89,90,92], only Brandner et al. (2019) included females in their sample, but failed to account for sex in their statistical analyses. All other studies included samples of young, well-trained males.

Other musculature that has undergone muscle hypertrophy following BFRT include the triceps brachii [18,75,92], biceps brachii [18], forearm [90], calf [18], and less specifically, the upper arm [90]. Furthermore, a 2017 systematic review and meta-analysis supports that low-load BFRT induces similar hypertrophic results as traditional high-load resistance training [93]. Altogether, it is evident that low-load BFRT is capable of inducing muscular hypertrophy similar to that observed using traditional resistance training and following a variety of interventions.

2.3.3 Impact of Blood Flow Restriction on Muscle Strength

A further adaptation to BFRT is an increase in muscle strength. Numerous studies have investigated how low-load BFRT compares to traditional resistance training and whether it is an effective strategy for improving muscle strength. In an exercise intervention examining the effectiveness of BFRT performed to failure rather than a set number of repetitions, researchers observed significant improvements in leg 1-RM despite 33% less work volume (load x repetitions) in the BFRT group [15].

A study of collegiate sprinters using BFRT twice daily for eight days saw a significant 9.6% increase in isotonic leg press strength [74]. Conversely, a six-week BFRT sprint intervention produced no significant improvement in maximal isometric leg press force production [20]. Howevever, a significant improvement in rate of force development was observed in the BFRT group [20]. Together, these results indicate that BFRT, in combination with sprinting, may lead to isotonic, but not isometric strength improvements in well-trained athletes.

Although greater improvements were observed in a heavy-load group, researchers observed significant improvements in upper- and lower-body strength following a four-week low-load BFRT intervention [18]. Specifically, 1-RM improved from baseline to post-testing in the low-load BFRT group for knee extension, back squat, and bicep curl, and for calf raise and seated row at the mid-point testing, but no improvement in bench press was observed [18]. Interestingly, Ozaki et al. (2013) observed significant improvements in bench press 1-RM following only three weeks of BFRT [75]. A key difference between Brandner et al. (2019) and Ozaki et al. (2013) is that the latter did not include females in their sample.

A study examining the effects of supplemental low-load BFRT in team sport athletes observed significant increases in both 3-repetition maximum and repetitions to failure [19]. Following 6-week BFRT, male professional soccer players saw significant improvements in knee extensor and knee flexor strength which were similar to the increases seen in the traditional training group [91]. Interestingly, the dominant limb in the BFRT group saw a greater increase in knee extensor strength compared to the dominant limb in the traditional training group [91]. Similarly, a study investigating the impact of BFRT on muscle strength in netball players observed significant improvements in 3-second maximal voluntary contraction [17]. Furthermore, a seven-week trial using blood-flow restriction in collegiate American football players significantly improved squat 1-RM [89]. Based on these findings, it is apparent that low-load resistance training in combination with blood-flow restriction is able to induce increases in muscle strength in healthy and well-trained adults. However, further investigation is warranted to investigate the generalizability of BFRT to increase strength.

2.3.4 Blood Flow Restriction and Performance Outcomes

Although BFRT has primarily been investigated as a tool to enhance muscle hypertrophy in a variety of populations, there has been some research exploring the impact BFRT has on performance and functional metrics such as power output, dynamic balance, and jump height. Researchers examining the affects of manipulating cuff pressure and exercise intensity observed significant improvements in peak power, average power, minimum power, and isometric muscle strength following four weeks of BFRT in physically active collegiate women [21]. Similarly, in a small sample of healthy young males, average power was significantly improved only in the blood flow restriction group following six weeks of resistance training [15]. This group saw an 18% greater power output from baseline despite a 33% lower overall work volume (repetitions x load) than the control group [15]. In an exercise trial investigating the impact of the body-weight lunge exercise in combination with blood-flow restriction on jump height, researchers observed a significant improvement in power production [22]. Furthermore, researchers have shown that BFRT has the ability to improve peak, minimum, and average power in the upper-body as well [24]. Wilk et al. (2020) saw significant increases in power and maximal velocity during a bench press after using blood-flow restriction [24]. It is evident that BFRT has the ability to induce increases in power output both in the upper- and lower-body.

A currently underresearched area in the BFRT literature is with respect to dynamic balance. Improving balance may reduce risk of injury, and as aging occurs, may reduce the risk of falls. Although young adults may not be immediately at-risk for fall-related incidents, improving power output and dynamic balance may serve to protect against age-related falls or immobilization as they age [94,95]. A study of male and female athletes with chronic ankle instability showed significantly improved Y-Balance Test composite scores following six weeks of BFRT, however results did not differ between the BFRT group and the rehabilitation group [96]. In a study of 46 adults with a history of functional ankle instability, significant improvements in Y-Balance Test composite scores were observed in as little as three weeks for the BFRT group [97]. Over the 6-week intervention, dynamic balance increased similarly between the traditional training group and the BFRT group [97]. Both of these studies investigated the effects of ankle stability training with BFR on dynamic balance, but no study to date, to the best of my knowledge, has investigated whole-body BFRT in a healthy population and its impact on dynamic balance.

Jump height has been used as a practical performance metric in the blood-flow restriction literature. However, there have been conflicting results as to whether or not BFRT improves jump height. Rohde et al. (2021) showed that after 8-weeks of hypertrophy training, jump height significantly improved from baseline to post-intervention for both the high-load (no blood-flow restriction) and the low-load blood-flow restriction groups, with no significant differences between groups, suggesting that BFRT may be a suitable mechanism to improve jump performance [76]. Likewise, it has been shown that just three-weeks of body-weight lunge exercises with blood-flow restriction can significantly improve jump height by approximately 4% [22]. In a study of well-trained male volleyball players, using 70% 1-RM with BFR lead to significant improvements in squat jump and 3-step approach vertical jump height [98]. These results were significantly improved from baseline and significantly greater than the traditional heavy-load resistance training and the low-load (30% 1-RM) BFR group [98]. However, it is worth noting that the BFR device used in this study by Wang et al (2022) has been called into question regarding its ability to achieve sufficient pressures [99]. However, contradictory to Rohde et al. (2021), Doma et al. (2019), and Wang et al. (2022), multiple studies have found no improvement in jump performance following BFRT, but this discrepancy could be due to participants in these studies already being well-trained individuals [73,74,100].

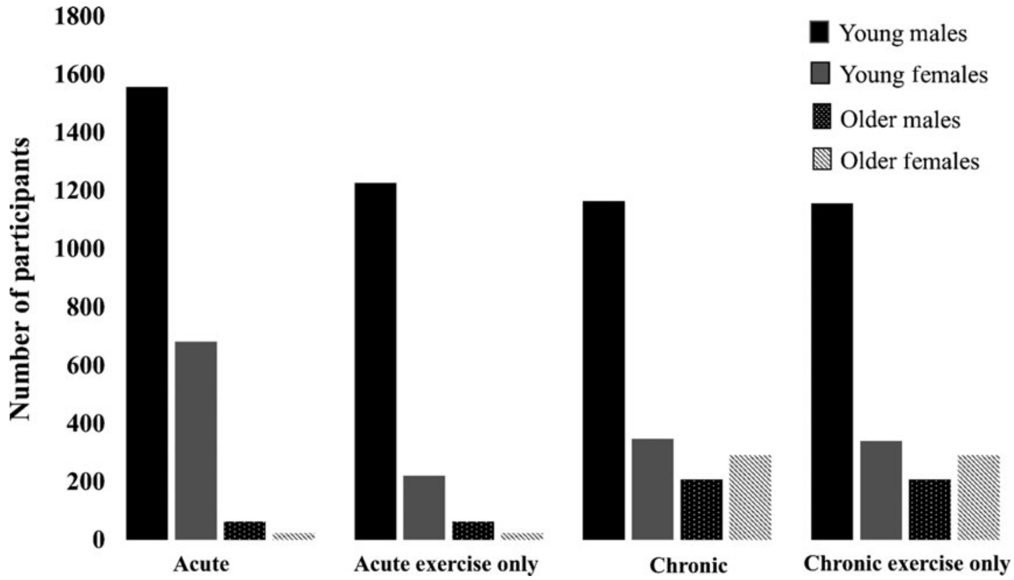
Following four weeks of maximal half-squat jump training with and without blood-flow restriction, only the non-blood-flow restriction group saw significant improvements in jump height [73]. Although both groups significantly increased lean body mass, leg circumference, and knee flexion, only the control group (no BFRT) achieved significant improvements in the squat and countermovement jumps [73]. Likewise, following a five-week resistance training program in Australian football athletes, no improvements in jump height were observed in the blood-flow restriction group [19]. However, contrary to the findings from Horiuchi et al. (2018), there were no significant improvements in jump height in the control group either [19]. In an eight-day study of BFRT performed twice daily, no significant changes were observed in jump distance for either standing jump, standing triple jump, or standing 5-step jump [74]. There is a discrepancy in the current literature surrounding the impact of BFRT on jump performance. This lends itself to further research on the topic to solidify our understanding of the impact BFRT has on performance metrics such as jump height.

As evidenced by a review of the current literature exploring functional and performance outcomes following BFRT interventions; although there exists research on the impact of BFRT on power and jump height, there is limited research investigating dynamic balance and there exists discrepancies in the findings related to jump performance. Furthermore, other than the studies by Amani-Shalamzari et al. (2019), Werasirirat & Yimlamai (2022), and Rohde et al. (2021), no other study included women in their sample and Rohde et al. (2021) did not account for sex in their analysis. This warrants further research to better understand the impacts BFRT has on functional and performance outcomes in men and women alike.

2.4 Blood Flow Restriction and Sex Differences

Although it has been established that BFRT is an effective means of producing muscle hypertrophy, increasing strength, and improving functional and performance outcomes, there is little research with regard to how young, healthy women may respond to BFRT. Counts et al. (2018) stress that only 17% of all participants in chronic BFRT studies were young females [26]. The authors present a graphical figure to illustrate this skewed representation in the literature (Figure 1) where it is evident that there is nearly three males to ever one female in chronic exercise BFRT studies.

Figure 3. Distribution of Participants in Blood Flow Restriction Studies



Note. The total number of participants included in all blood flow restriction studies categorized by study durations, then separated by sex and age. From “Let’s talk about sex: where are the young females in blood flow restriction research?,” by B. R. Counts, L. M. Rossow, K. T. Mattocks, J. G. Mouser, M. B. Jessee, S. L. Buckner, S. J. Dankel, & J. P. Loenneke, 2018, *Clinical Physiology and Functional Imaging, 38,* pp. 1-3. Reprinted with permission.

The authors suggest that rather than excluding young females from BFRT research, both sexes should be included and results plotted separately to investigate whether any sex differences exist [26]. Although young females have historically been excluded from BFRT research, there are some exceptions.

In a study of 17 young females examing the effects of eccentric resistance training and blood flow restriction, a significant increase in arm circumference, muscle thickness, cross-sectional area, and 1-RM was observed [101]. No group differences were observed, suggesting that low-load eccentric BFRT is as effective as traditional eccentric training in females [101]. Likewise, similar levels of muscle hypertrophy were observed in their sample of females compared to previous results in males, but no direct comparisons could be performed [101]. In a 12-week intervention comparing heavy-load resistance training to low-load BFRT in young women, researchers reported similar functional and physiological adaptations [102]. However, in a study of 40 untrained women (18-40 years) no significant improvements in muscle power were observed following eight sessions of low-intensity BFRT [103]. The authors did observe an improvement in submaximal knee extension strength [103]. Together these studies suggest that BFRT may induce muscular adaptations across four- and 12-week interventions in young women. However, the limited and conflicting literature implies a need for further research to better understand whether BFRT training influences performance outcomes in men and women.

Additionally, there have been a few studies specifically investigating sex differences following BFRT, however these have not investigated muscle hypertrophy response to BFRT. Freitas et al. (2020) investigated acute physiological responses to traditional and practical BFRT in untrained men and women, such as muscle swelling, whole blood lactate, hematocrit, and surface electromyography [104]. It was observed that males displayed greater surface electromyography amplitude during leg press and whole blood lactate levels 15 minutes post-exercise compared to females [104]. Dankel et al. (2016) explored whether post-exercise blood flow restriction would augment muscle hypertrophy [105]. Applying blood flow restriction immediately following traditional high-load resistance training did not augment muscle hypertrophy, and appeared to attenuate muscle growth in the female sample [105]. In an investigation of muscle fatigue response following low-load BFRT, reseachers observed a similar relative torque decrement between both sexes suggesting that the fatigue induced by low-load BFRT occurs similarly in both males and females [106]. A study comparing 10 males and 10 females performing low-load knee extension to failure showed that females performed significantly more repetitions, but had similar torque decrements and electromyography activity to the males [107]. This suggests that females have greater muscular endurance even under blood flow restricted conditions [107]. Altogether, there are several studies examining sex differences following BFRT; each investigating a variety of outcomes.

Although a study of solely young females showed that low-load BFRT was capable of inducing muscular hypertrophy, no further studies have confirmed these findings nor compared the results to males undergoing the same exercise intervention [101]. Specifically, there have been no studies investigating sex differences in muscle hypertrophy following BFRT and a 2021 review article highlights the continued absence of young females in BFRT research [25]. Together with the varied results in female-only studies, this indicates a need for further research to examine any potential differences in how males and females respond to a BFRT resistance exercise intervention.

2.5 Knowledge Gap

As previously outlined, there is a substantial gap in the literature surrounding how males and females may be impacted differently following BFRT. Although some studies exist examining sex differences following a BFRT intervention, these studies have investigated outcomes such as electromyography signal [104,107], muscle fatigue based on torque and maximal voluntary contraction [106,107], metabolic responses [104], and post-exercise application of blood flow restriction [105]. However, there is some understanding in the literature regarding physiological sex-differences following exercise without blood flow restriction. It is understood that typically, males have a greater proportion of Type II muscle fibers and females have greater proportions of Type I muscle fibers [108,109]. Due to this difference in muscle fiber type areas, females have greater oxidative capacity and tend to undergo less metabolic stress during high-intensity exercise, which could translate to less adaptative stimulus than males at the same work intensity [110].

No study thus far has investigated whether whole-body muscle hypertrophy response following a chronic BFRT intervention differs between the sexes. However, Wells et al. (2019) did observe muscle hypertrophy following a four-week BFRT intervention in a female-only sample and reported that their findings were similar to previous results observed in males [101]. However, no further study has supported or refuted this finding.

The relevance of increased lean body mass in a young population is that increased predicted lean body mass has been shown to be protective against development of cardiovascular disease [111]. This population-based cohort study of 3.7 million young Korean adults (64.5% males) showed that increasing lean body mass and appendicular skeletal muscle mass was protective against cardiovascular disease, but that decreases in these muscle masses were associated with greater risk of cardiovascular disease [111]. Likewise, a prospective cohort study of 38,006 American adult males showed that too low of lean body mass increases risk of all-cause mortality, cardiovascular disease, and cancer [112]. Furthermore, a 2018 review of epidemiological studies linking body composition of the general population and mortality showed that adults with low lean body mass had an increased risk of mortality [113]. In another population-based cohort study of 11,687 American adults (≥ 20 years old, no indication of proportion of sexes), researchers indicated that for any BMI ≥ 22 (i.e., "normal"), low muscle mass indicated a greater risk of diabetes and mortality [114].

Altogether, these findings suggest that increasing lean body mass is not only relevant, but imperative for the sustained health of young adults. Increasing muscle mass might have previously been viewed as an athletic endeavour and weight loss viewed as a health endeavour, but it is now understood that fat mass and muscle mass play independent roles in long-term health and each serve their own purpose. By better understanding the effects of BFRT on lean body mass of males and females, better prescription of exercise can be utilized to maximise lean body mass increases.

2.6 Objectives and Hypotheses

Objective 1: Determine whether any differences in lean body mass or strength are observed between males and females following a six-week whole-body resistance training program with blood flow restriction.

Hypothesis 1: We hypothesize that following a six-week whole-body resistance training program with blood flow restriction, we will see sex-specific adaptations in lean body mass, strength, and performance outcomes.

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Chapter 3: Article

IMPACT OF EXERCISE WITH BLOOD FLOW RESTRICTION ON MUSCLE HYPERTROPHY AND PERFORMANCE OUTCOMES IN MEN AND WOMEN

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3.1 Abstract

Blood flow restriction training (BFRT) improves lean mass and strength. In BFRT studies, only 17-29% of participants were female. We compared lean mass and strength following 6-week BFRT between males and females. Thirty-eight adults (age, 25.3 ± 3.1 years; female, n=19) participated. Exercises were performed at 30% of 1-repetition maximum (1-RM) and individual's limb occlusion pressure set at 60%. Lean mass was assessed via dual-energy x-ray absorptiometry, strength was measured using 1-RM. A significant increase in lean mass was observed in males (p= .009) and females (p= .023) without group differences (p= .279). Both males and females increased 1-RM for upper- and lower-body exercises. However, there was a significant interaction effect (time x sex) for knee extension (p= .039), chest press (p= .002), and seated row (p= .033). Lean mass and muscle strength increased following six weeks of BFRT. Males may improve upper-body strength to a greater extent.

3.2 Introduction

Exercise, including resistance training, has been called a “medicine” as it prevents and reduces the risk for chronic conditions such as type 2 diabetes mellitus, cardiovascular disease, and cancer [1,2]. One possible explanation for this risk reduction is the alteration in body composition, characterized by increased skeletal muscle mass and decreased fat mass [3–5]. This increase in muscle mass, known as hypertrophy, occurs with moderate to heavy-load resistance training and resistance training to volitional failure [6,7]. However, blood flow restriction training (BFRT) has emerged as an alternative to heavy-load resistance training. BFRT involves the utilization of a pneumatic cuff placed around the proximal region of the exercising limb to partially reduce blood flow combined with very light loads [8].

Although the exact physiological mechanisms of hypertrophy following BFRT are not fully understood, there is substantial evidence that BFRT can induce muscle hypertrophy [9–12]. A BFRT study using low-load BFRT performed to failure saw an increase in thigh muscle thickness similar to the traditional resistance training group despite a 33% lower total exercise volume [13]. Similarly, several BFRT meta-analyses indicated that BFRT can increase shoulder lean mass, pectoralis major thickness, and that muscle hypertrophy was comparable to high-load resistance training [9,14]. Interestingly, these increases in muscle mass translate into improvement in performance outcomes. Following a 4-week whole-body BFRT intervention, significant 1-repetition maximum (1-RM) improvements were observed in healthy adults for the knee extension, back squat, calf raise, and seated row [15]. Furthermore, several systematic reviews and meta-analyses support the impact of BFRT on muscle strength [9,11,14,16,17].

Although these findings are interesting, there is a growing interest in physiological sex differences in exercise training, of which there are many [18,19]. For instance, females tend to have greater resistance to fatigue during exercise, but males tend to exhibit greater strength, especially in the upper body [18,20]. Also, females have been shown to undergo less contractile dysfunction during high-intensity exercise compared to males [18]. In addition, females have higher relative proportions of Type I versus Type II muscle fibers than males. Finally, females have greater oxidative capacity and tend to undergo less metabolic stress during high-intensity exercise, which could translate to less adaptative stimulus than males at the same work intensity [18]. These already-established sex differences laid the foundation for this study and our hypothesis of sex differences in lean body mass, strength, and performance outcomes.

Furthermore, even if clear physiological sex differences exist for typical exercise training, the vast majority of studies investigating BFRT include only college-aged males (i.e., between the ages of 18-25) [21]. In fact, a call to action highlights that in studies of chronic and acute BFRT, only 29% and 17%, of all participants were females [22]. This call is echoed in a more recent review highlighting the continued absence of young females in the literature [21]. This fact strengthens an urgent need to study the impact of BFRT in young females to understand muscle mass adaptation better and investigate if these changes translate into increased performance. Therefore, the primary objective of this study was to study sex-based differences and to compare the impact of

6-week whole-body BFRT on lean body mass, muscle strength, and performance outcomes in males and females.

3.3 Methodology

3.3.1 Study Design

The current project is a parallel control experimental study comparing men and women following a 6-week resistance training intervention in conjunction with partial blood-flow restriction. (Clinical Trial #: NCT05615831). A study overview is presented in Figure 1. Briefly, participants underwent baseline testing separated into two visits within a one-week span and presented at the Cardiometabolic Exercise and Lifestyle Laboratory at the University of New Brunswick for each visit. Participants began six weeks of BFRT within one week of the last baseline testing visit. Following the intervention, participants underwent follow-up testing at least two days [23], but no more than one week [10], following the last exercise session. All participants provided written and informed consent prior to participation. The project was reviewed and approved by the University of New Brunswick Research Ethics Board (REB 2021-124).

3.3.2 Sample Size

A power calculation was performed using G-power software (version 3.1.9.4, Germany) to determine the appropriate sample size for statistical significance. Based on an alpha of 0.05, a power of 0.8, and an effect size of 0.4, we determined the required total sample size to be eight participants for a repeated measures analysis of variance (ANOVA). However, we anticipate a dropout percentage of 13% as reported by

Høgsholt et al. (2022) [24]. Furthermore, it has been suggested that in order to detect interaction effects between sexes, as well as main effects, the sample size needs to be four-times the size [25]. To account for dropout rate, and to ensure adequate ability to detect interaction and main effects, we attempted to recruit approximately 20 per group for a total of 40 participants.

3.3.3 Participation

Inclusion Criteria

Participants were eligible for inclusion if they were between the ages of 19 and 30 years. In addition, participants had to be physically inactive, but otherwise healthy. Physical inactivity was defined as not meeting the World Health Organization's 2020 physical activity guidelines: 150 minutes of moderate-vigorous physical activity and two muscle-strengthening activities per week [26]. Physical activity levels were estimated through questionnaires and using Fitbit Charge 3 activity trackers. It was shown in a 2018 systematic review that Fitbit activity trackers provide accurate measures of steps in adults with no mobility limitations [27]. Using a pre-determined threshold (10,000 steps/day) as the minimum number of steps required to reach moderate intensity physical activity, anybody who averaged under 10,000 steps/day over a 4-7 day window <u>and</u> did not perform muscle strengthening activities twice per week was considered physically inactive [28].

Exclusion Criteria

Exclusion criteria included: 1) aged outside prearranged threshold (19 – 30 years), 2) the presence of cardiovascular disease such as coronary heart disease, uncontrolled hypertension, peripheral vascular disease, venous thromboembolism, other blood clotting disorders, or hemophilia, 3) surgery, bone fracture, or a skin graft within the last three months, 4) pregnancy, and 5) meeting or exceeding physical activity guidelines.

Recruitment

Recruitment was performed between May 2022 and July 2023 through the distribution of promotional flyers, University of New Brunswick's newsletter, and social media advertisements through Facebook and Instagram. An overview of recruitment can be seen in Figure 2. Of note for future research, recruitment of young females occurred much more rapidly than young males.

3.3.4 Exposure Variable – Blood Flow Restriction Training

Participants undertook 6 weeks of whole-body resistance training in conjunction with blood flow restriction to their exercising limbs. The intervention consisted of three supervised exercise sessions per week consisting of five different exercises: knee flexion (hamstring curl), knee extension, leg press, chest press, and seated row. The exercise load was individualized to 30% of each participant's 1-RM for each exercise. Participants were required to complete 75 total repetitions broken into four sets for each exercise. The sets were broken up in the following manner: set 1: 30 repetitions; set 2: 15 repetitions; set 3: 15 repetitions; set 4: 15 repetitions, as this protocol has previously been used in blood flow restriction research to induce muscle hypertrophy in a variety of populations[29,30] and has been suggested by multiple reviews [31,32]. At week 4, participants had their 1-RM reassessed to adjust the 30% 1-RM exercising loads. This occurred during the first exercise session of Week 4. As such, following the 1-RM reassessment, participants performed two sets per exercise (30 reps and 15 reps) using the newly adjusted 30% 1-RM weight, before returning to the original rep scheme for their remaining exercise sessions.

Blood flow restriction cuffs were placed at the most proximal portion of the exercising limb (just above biceps brachii on the arm and near the inguinal crease on the thigh), which is what has previously been used in BFRT research [8,29–31,33–36]. Blood flow restriction was achieved using the KAATSU C3 device (KAATSU Global, Inc., Huntington Beach, CA, USA). The KAATSU arm and leg cuffs are 5 cm wide, respectively, and are single-bladder cuffs. Cuffs were inflated to 60% of each individual's total limb occlusion pressure as this has been shown to be a safe and effective pressure to induce muscular adaptations [15], and is within the recommended pressure range for BFRT [8,31]. Each participant's total limb occlusion pressure (LOP) was estimated using equations developed by Loenneke et al. (2015) listed here [33]:

(1) $Leg\ arterial\ occlusion\ (mmHg) = 5.893(thigh\ circumference) + 0.734(diastolic\ blood\ pressure) + 0.912(systolic\ blood\ pressure) - 220.046$

$$(2)\ Arm\ arterial\ occlusion\ (mmHg) = 0.514(systolic\ blood\ pressure) + 0.339(diastolic\ blood\ pressure) + 1.461(arm\ circumference) + 17.236$$

Although these equations have modest R-squared values of 0.61 and 0.49, respectively [33], they have been successfully utilized in a BFRT intervention of trained athletes leading to significant improvements in muscle hypertrophy and functional outcomes with no reported side effects [37]. Furthermore, although LOP was estimated, a study comparing the impact of various cuff pressures showed similar effects on muscle size, torque, strength, and endurance between 40% and 90% pressures [38]. These findings suggest that greater pressures are not necessarily more effective at inducing adaptations and that small pressure fluctuations will not necessarily serve as greater or lesser stimuli during training. Cuffs remained inflated during the rest in between sets of each exercise but were deflated for the rest period between exercises [29,39–42]. The set rest was 60 seconds, and the rest between exercises was four minutes.

3.3.5 Primary Outcome Measure – Lean Body Mass Differences Between Sexes

Lean body mass was estimated using duel-energy x-ray absorptiometry (DXA) prior to the 6-week BFRT intervention, and again following the intervention. Body composition was estimated using a Hologic Horizon® DXA System (Hologic Canada ULC, Mississauga, ON, Canada). Lean body mass constitutes that which is not fat mass nor bone mineral mass [43]. Participants presented to the laboratory following a 12-hr fast and were asked to refrain from exercise for a 24-hr period prior to testing. Participants were instructed to wear loose-fitting clothing with no metal (buckles, zippers, buttons, etc.) and then instructed to lie supine on the scanner's table and remain still for the duration of the scan. Arms were placed at the participants' sides with palms facing medially and thumbs pointed upwards. For individuals too large for the width of the table, they were positioned with their left arm outside of the scan area and results of the scanned arm were duplicated. The coefficient of variation in our lab for lean mass is 0.6% and for body fat percentage is 0.7%. This was performed on 33 people (males, n=10) with a mean age of 23.4 years and a mean body mass index (BMI) of 25.6.

3.3.6 Exploratory Variables

Anthropometric measurements, muscular power and endurance, and strength were measured for exploratory purposes and sample description. Participants' height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively, according to the CSEP protocol [44]. Weight was measured using a calibrated column scale (SECA® model #213). Height was measured using a standardized stadiometer. With no shoes, feet together, and arms at their side, height was taken following an inhalation. Hip and waist circumference were measured using an anthropometric tape measure and recorded to the nearest 0.5 cm. For hip and waist measurements, participants stood with their feet shoulder-width apart and their arms folded across their chest. Waist circumference was measured at the upper lateral border of the iliac crest following a normal exhalation, hip circumference was measured around the widest portion of the buttocks after a normal exhalation [45].

Strength was assessed by 1-RM for the five exercises used during the intervention. 1-RM was measured during the second baseline testing visit, at the midpoint of the study during the first exercise session of week four, and again during the second testing visit in the follow-up testing. Each participant's 1-RM was determined using the following protocol: one set of 6-10 repetitions, followed by one set of 3-5 repetitions, followed by small incremental increases for one repetition until a failure is achieved within seven attempts. If no failure was achieved within seven attempts, the 1-RM for that exercise was redone prior to their first exercise session.

Muscular power was estimated using the squat jump equation derived by Sayers et al. (1999) and is as follows [46]:

(3) $Peak\ Power\ (W) = 60.7\ x\ (jump\ height\ [cm]) + 45.3\ x\ (body\ mass\ [kg]) - 2055$

This equation was chosen as it has been shown to be more accurate than previously used power estimation equations and was developed from a large and diverse population which enhances our external validity [46]. Jump height was recorded using the Perform Better® Just Jump System. The Just Jump System has been validated against a 3-camera motion analysis system for estimating vertical jump height in a sample of males and females between the ages of 18-25 [47]. Participants were instructed to stand on the mat with their feet shoulder-width apart, place their hands on their hips, lower into the jump position (knees at approximately a 90° angle), hold for 2 seconds, explode upwards as high as possible, and land back on the mat. Participants performed three squat jumps separated by a 60 second recovery period. The highest jump was used to estimate muscle power.

Dynamic balance was measured using the Y-Balance Test. Briefly, after no more than four practice attempts, participants started by balancing on their left leg and then reached forward as far as they could and touched down. The distance was recorded, and the process was repeated two more times. The same process was then followed when balancing on the right leg. This was performed three times in each direction, alternating between balancing on the left and right feet. All six reaches per direction (left then right) were performed before moving to another direction.

Muscular endurance of the dominant knee extensors and flexors was assessed using a Humac® NORM isokinetic dynamometer system (Computer Sports Medicine, Inc., Stoughton, MA, USA). Prior to testing, participants performed a 5-minute walking warmup. The participants were seated and secured to the device using straps across the trunk and thighs. The positioning of the seat was adjusted to the comfort level of the participant, so long as the approximate axis of the knee (through the lateral femoral epicondyle) was aligned with the dynamometer's mechanical axis, and recorded so the same settings were used following the intervention. Range of motion was then prescribed on an individual basis (0° corresponds to full knee extension). Prior to testing, participants performed five repetitions at 120°/s as a familiarization. Upon completion of the familiarization, participants were given a two-minute recovery period before testing commenced. The testing protocol consisted of 30 reciprocal maximal contractions of the knee extensors and flexors performed at 180°/s, as previously described [48]. Total work, average power per repetition, and peak torque were recorded.

3.3.7 Statistical Analysis

To test for normality within the sample, Shapiro-Wilk test was performed and confirmed with a visual examination of the data. General characteristics of the sample are presented as mean ± SD for continuous variables and n (%) for categorical variables, along with their effect sizes. Effect sizes were calculated using Hedges *g* formula, which is calculated by dividing the difference between the means by the pooled weighted standard deviation. Differences in baseline and post-intervention values, stratified by sex, were analyzed using paired sample t-tests. Independent sample t-tests were used to identify differences between groups. A repeated measures ANOVA was performed to determine whether there was a significant interaction effect between time and sex with changes in primary and exploratory outcomes. Data management and statistical analyses were performed using SPSS version 29. A $p \leq 0.05$ was considered significant.

3.4 Results

3.4.1 Descriptive Characteristics

The total number of participants that completed the study was 38: 19 males and 19 females. An overview of the baseline descriptive characteristics is outlined in Table 1. Briefly, the average age of males was 24.2 ± 2.76 years, and was 22.7 ± 3.37 years (p= .135) for females. 63.2% of the total sample were White, with equal number males and females. There were no statistically significant differences in weight, BMI, waist circumference, or steps per day (all p-values > .05). High-density lipoprotein levels were significantly higher in females compared to males (p= .002).

3.4.2 Changes in Body Composition

Table 2 describes the impact of six-week BFRT on body composition in males and females. Baseline fat mass was not significantly different between males and females (p= .303), but baseline lean mass was significantly greater in the male group (p< .001). Males significantly increased weight, BMI, and waist circumference (p= .006, .046, .025; g= 0.07, 0.04, 0.12), whereas females saw no significant changes in these anthropometric measures. No significant changes were observed in males or females' body fat percentage or fat mass. Males (p= .009, g= 0.11) and females (p= .023, g= 0.08) significantly increased lean mass following six-week BFRT (Figures 3A and 3B). However, the change in lean mass was not significantly different between males and females (p= .279; Figure 3C). Similar results were observed for the impact of BFRT on relative lean mass in males (p= .020, g= 0.09) and females (p= .011, g= 0.08; Figures 4A and 4B) and the change in relative lean mass (p= .472; Figure 4C). Repeated measures ANOVA revealed a time effect for lean body mass (p< .001) but no interaction between time and sex (p= .279). Similar results were observed for relative lean mass, with a time effect (p= .004) and no interaction between time and sex (p= .693).

3.4.3 Changes in Strength and Performance Outcomes

Table 3 shows changes in performance outcomes, while Figures 5A-C and 6A-C show changes in 1-RM from baseline to post-testing for chest press and knee extension, respectively, for males and females. Exception for females' leg press (p= .110), males and females significantly improved knee extension (male: p< .001.; female: p< .001), knee flexion (p< .001; p< .001), chest press (p< .001; p= .004), and seated row (p= .003; p= .004) following 6-week BFRT. Changes in knee extension (p= .035), chest press (p= .003) and seated row (p= .042) were significantly different between males and females. Repeated measures ANOVA revealed time and group effects for leg press (time: p=

.002; group: $p < .001$, knee extension ($p < .001$; $p = .002$), knee flexion ($p < .001$; $p < .001$), chest press ($p < .001$; $p < .001$), and seated row ($p < .001$; $p < .001$),while an interaction effect was only observed for knee extension ($p = .039$), chest press ($p = .002$), and seated row ($p = .033$).

Both males and females increased peak power produced during the vertical jump (male: $p < .001$, $g = 0.46$; female: $p = .002$, $g = 0.15$), and males increased jump peak power significantly more than females ($p = .040$). An interaction between time and sex was observed for jump peak power ($p = .038$). Males also improved their Y-Balance Test scores significantly for the left ($p = .002$, $g = 0.56$) and right ($p = .002$, $g = 0.55$) legs, whereas females did not. The change was not significant between groups for either the left ($p = .218$) or right ($p = .328$) legs. Both males and females significantly improved their average power, peak torque, and total work for their dominant knee flexors (all *p*-values $< .05$), but none were significantly different from each other (all *p*-values $> .05$). Females improved average power, peak torque, and total work for their dominant knee extensors (all *p*-values $< .05$). Males improved average power ($p = .031$) and total work ($p = .016$), but not peak torque ($p = .055$) for their dominant knee extensors. There were no significant differences in the improvements between males and females or interaction between time and sex (all *p*-values $> .05$).

3.5 Discussion

The main objective of this study was to investigate sex-based differences and to compare the impact of 6-week BFRT on lean body mass, muscle strength, and performance outcomes between males and females. The principal findings of our study suggested a lack of sex differences for change in lean body mass following BFRT and showed a sex difference for muscle strength and performance outcomes (peak power). These results are pertinent as they fill the gap in the literature about the impact of BFRT and sex-based differences in adaptation for lean body mass, muscle strength, and performance outcomes. This is of great interest as it might help guide future research on sex differences in specific populations, such as in sport-specific athletes and injury rehabilitation.

Six weeks of BFRT resulted in a significant increase in lean body mass and relative lean body mass in both males and females. Furthermore, there was no difference between males and females for this change in absolute or relative lean body mass. Our findings corroborate previous findings of studies showing that BFRT induces muscle hypertrophy [10,12,15,37,49–52]. However, our results are surprising considering physiological sex differences have been documented in the literature with respect to muscle fiber types [18,20]. For example, it was reported that males have a lower proportion of Type I muscle fibers and a greater proportion of Type II muscle fibers [18,20]. Secondly, it has been shown that females undergo less metabolic stress during high-intensity exercise than males, which could translate to less of an adaptative stimulus [18]. Furthermore, following six weeks of BFRT, males demonstrated greater effect sizes for Type II muscle fiber hypertrophy than females, although not statistically significant [12]. Nevertheless, the lack of sex differences in absolute and relative lean body mass from our study aligns with other studies that reported that both sexes appear to adapt to resistance training to a similar extent [12,54]. Therefore, the findings of this present study are novel as they add to the body of literature by directly comparing males and females and show an absence of any hypertrophic sex-based differences as males and females underwent similar whole-body muscle hypertrophy following only six weeks BFRT.

Our results showed a significant increase in muscle strength, and this is supported by previous systematic reviews [16,17]. However, we showed a sex-specific difference for muscle strength with males increasing knee extension, chest press, and seated row 1-RM to a greater extent than females. In a systematic review of the impact of BFRT on strength, Gear et al. (2022) showed that the female-only studies had a larger effect size for muscle strength than the mixed or the male-only studies [17]. This difference could be explained by the very few female-only studies included (only two), which could impact the effect size. In support of our findings, sex differences in upper-body muscle strength have been shown following traditional resistance training, even when accounting for differences in lean body mass [53]. This sex-difference in upper-body strength could be due to differences in lean mass distribution between males and females, where males have been shown to have greater lean mass in the upper limbs and upper trunk [20,55,56]. Altogether, our findings continue to add to the current body of literature by directly comparing males and females and showing that only six weeks of BFRT is sufficient for increasing muscular strength in both sexes, but males may increase strength to a greater extent in the upper-body.

While some studies have found BFRT to improve jump performance [57–59], others have not [60,61]. Our findings compared males and females and showed that jump power is significantly increased after six weeks of whole-body BFRT in physically inactive young adults, and that males improved to a greater extent. Males may have increased their jump performance to a greater extent than the females due to them seeing a greater increase in lower-limb lean mass. Furthermore, as previously demonstrated, males tend to have a greater area of muscle occupied by Type II muscle fibers than females, which would contribute more to an explosive movement such as a vertical jump [20]. In fact, it has been shown that following six weeks of low-load BFRT in untrained men and women, males increased the cross-sectional area of their Type II muscle fibers to a greater extent than females [12]. Therefore, we demonstrated sex-based differences in power produced during a vertical jump following six weeks of BFRT that could be explained by a greater development of Type II muscle fibers following BFRT in men than in women.

Following 6-week BFRT, we demonstrated that males and females similarly improved their muscular endurance performance. A meta-analysis suggests that low-load BFRT is effective at increasing knee extensor and knee flexor peak torque, which is in line with our findings [16]. Previous findings have also shown that BFRT performed to failure is capable of improving muscle power during a similar high-intensity isokinetic fatigue test in healthy males, which our findings corroborate [13]. Interestingly, Korkmaz et al. (2020) observed significant improvements in the dominant knee extensors concentric isokinetic peak torque in the BFRT group over the traditional resistance exercise group (study only included males), whereas that is the only metric that was not improved in our male sample [50]. This discrepancy could be due differences in samples, where the sample in the study by Korkmaz et al. (2020) were trained male soccer athletes and ours were young adults who did not meet the physical activity guidelines [50]. Interestingly, other lower-body performances in our study were either improved in males and not in females, or improved to a greater extent in males, but not muscular endurance. The difference in lower-limb lean mass seen in the males may have been offset by females potentially having greater fatigue-resistance to repeated knee extensions, as highlighted by Labarbera et al. (2013) [62]. The greater resistance to fatigue in females could be explained by the greater proportional area of Type I muscle fibers which translates to a greater oxidative capacity than in males, and, in turn, less contractile dysfunction during high-intensity exercise [18]. Our results continue to build on previous findings by highlighting how BFRT impacts muscle strength and muscle endurance, and by documenting sex-specific differences in performance outcomes in young adults not meeting the physical activity guidelines.

3.5.1 Strengths and Limitations

Our work has some limitations that need to be highlighted. First, our intervention had a short duration of only six weeks, and it is possible that some sex-specific differences in outcomes could have occurred over longer durations of BFRT. Second, we did not include a control condition in our study which limited the conclusion drawn from this study. Finally, although we asked participants to maintain their current lifestyle, including diet, we did not control diet every week for the duration of the study. However, our work is strengthened by the compliance of participants to the study – every participant completed 100% of the exercise sessions. Also, exercise sessions were supervised in very small groups by research staff, allowing for a tightly controlled environment. Furthermore, our work is strengthened by our sufficiently powered sample to directly compare males and females, allowing us to draw insights on potential sex differences in lean mass, muscle strength and performance outcomes following BFRT.

3.5.2 Conclusion

In summary, our findings suggest that following 6-week whole-body BFRT, males and females significantly increase lean body mass without sex differences. Moreover, BFRT significantly increased muscle strength for males and females. However, males increase muscle strength to a greater extent than females. We also demonstrated that males produced more power during a vertical jump than females, however males and females improved muscular endurance to a similar degree. Altogether, our research adds novelty to the current body of literature by documenting sex differences following BFRT and enhancing our knowledge of BFRT effects on females. Future studies should continue to investigate sex differences following BFRT, but over longer durations, with different populations, and with a focus on the underlying physiological mechanisms underpinning these adaptations.

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Table 1. General characteristics of the study sample.

	Total (*N*=38)	Male (*n*=19)	Female (*n*=19)
Age (years)	23.5 ± 3.13	24.2 ± 2.76	22.7 ± 3.37
Ethnicity			
White n (%)	25 (65.8)	13 (68.4)	12 (60.0)
Activity Levels			
Physical Activity (steps/day)	6496 ± 2198	6374 ± 2179	6619 ± 2269
Anthropometrics			
Weight (kg)	79.5 ± 22.0	86.4 ± 21.5	72.6 ± 20.9
Body Mass Index (kg/m^2)	27.0 ± 6.53	27.2 ± 6.83	26.8 ± 6.4
Waist Circumference (cm)	91.3 ± 14.7	94.5 ± 16.0	88.0 ± 12.9
Metabolic Profile			
Cholesterol (mmol/L)	4.33 ± 0.87	4.05 ± 0.82	4.54 ± 0.86
HDL (mmol/L)	1.44 ± 0.39	1.27 ± 0.33	1.61 ± 0.37*
LDL (mmol/L)	2.28 ± 0.74	2.11 ± 0.75	2.41 ± 0.73
Triglycerides (mmol/L)	1.36 ± 0.98	1.60 ± 1.32	1.15 ± 0.46
Glucose (mmol/L)	5.24 ± 1.68	5.60 ± 2.36	4.89 ± 0.41

Variables are presented as means ± standard deviation. HDL: high-density lipoproteins, LDL: low-density lipoproteins. * represents significant difference between groups using an independent sample t-test. Alpha level at 0.05.

Table 2. Body Composition of Male and Female Groups

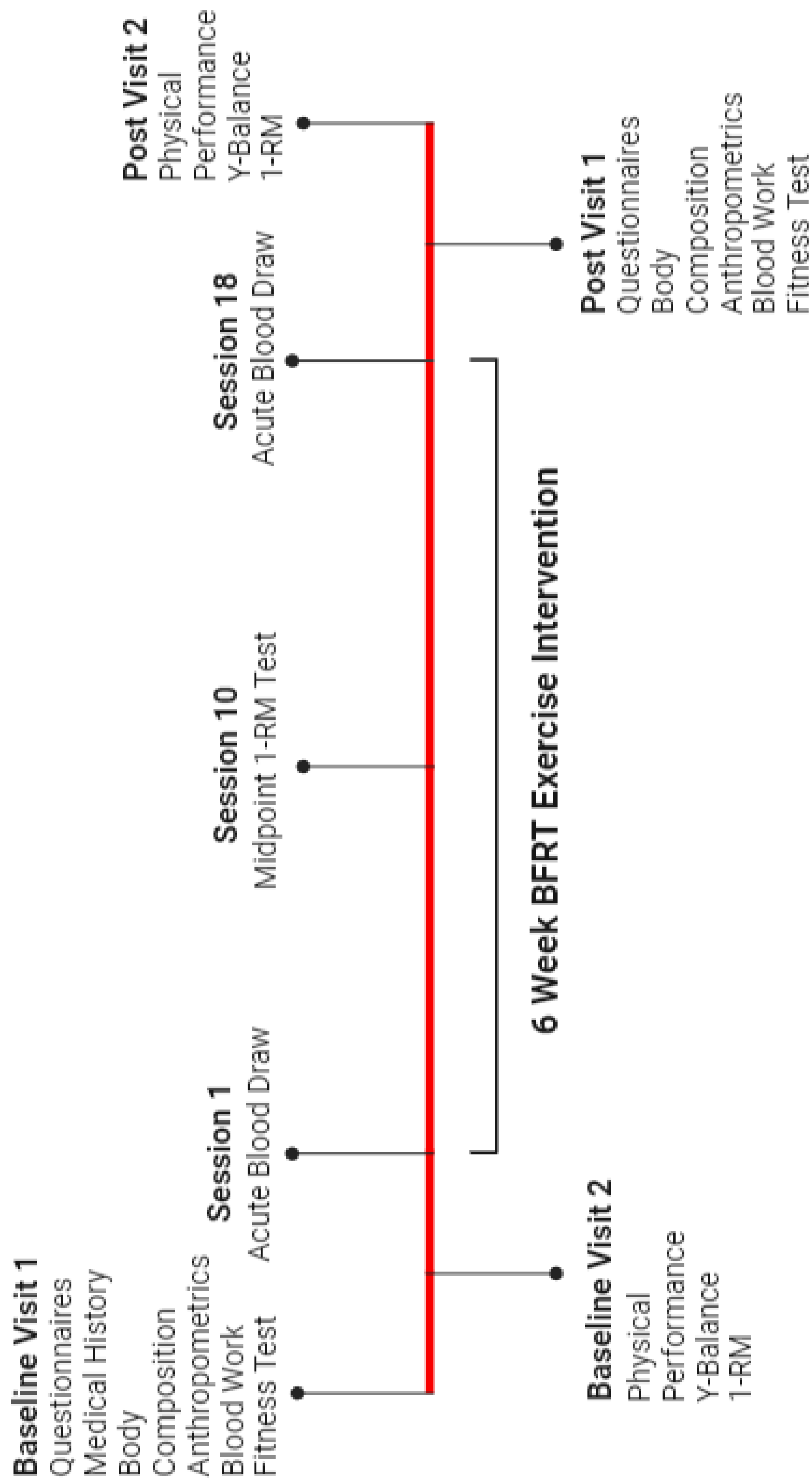
	Males (n=19)				Females (n=19)			
	Pre	Post	Effect Size (g)	p	Pre	Post	Effect Size (g)	p
Anthropometrics								
Weight (kg)	86.4 ± 21.5	87.9 ± 22.5	0.07	**.006**	72.6 ± 20.9	73.2 ± 20.2	0.03	.161
Body Mass Index (kg/m^2)	27.2 ± 6.83	27.7 ± 7.18	0.07	**.006**	26.8 ± 6.40	27.0 ± 6.15	0.03	.138
Waist Circumference (cm)	94.5 ± 16.0	96.4 ± 16.1	0.12	**.025**	88.0 ± 12.9	87.9 ± 11.0	-0.01	.304*
Body Composition								
Body Fat (%)	26.8 ± 8.06	26.7 ± 8.04	-0.01	.521	38.0 ± 5.86	37.5 ± 5.80	-0.08	.055
Fat Mass (kg)	23.8 ± 12.2	24.1 ± 12.4	0.02	.200	27.8 ± 11.6	27.7 ± 11.4	-0.01	.426
Upper Limb Fat Mass (kg)	2.36 ± 1.30	2.33 ± 1.33	-0.02	.320	3.00 ± 1.25	2.97 ± 1.28	-0.02	.420
Lower Limb Fat Mass (kg)	8.13 ± 3.76	8.21 ± 4.00	0.02	.525	10.9 ± 4.07	10.6 ± 4.12	-0.07	.084
Trunk Fat Mass (kg)	12.2 ± 7.43	12.4 ± 7.37	0.03	.123	13.0 ± 6.44	13.1 ± 6.15	0.02	.501
VAT Area (cm^2)	101.6 ± 41.1	104.1 ± 43.1	0.06	.361	90.6 ± 50.6	90.0 ± 50.6	-0.01	.749
Android Fat Mass (kg)	2.22 ± 1.44	2.29 ± 1.48	0.05	.064	2.01 ± 1.00	2.02 ± 1.02	0.01	.759
Gynoid Fat Mass (kg)	4.02 ± 1.93	4.04 ± 2.00	0.01	.667	5.29 ± 1.93	5.19 ± 1.87	-0.05	.082
Upper Limb Lean Mass (kg)	6.46 ± 1.07	6.59 ± 1.10	0.12	.051	3.61 ± 0.83	3.66 ± 0.82	0.06	.056
Lower Limb Lean Mass (kg)	19.8 ± 2.73	20.4 ± 3.20	0.20	**.004**	13.6 ± 3.13	13.7 ± 3.09	0.03	.153*
Trunk Lean Mass (kg)	28.1 ± 6.15	28.4 ± 6.24	0.05	.146	20.6 ± 4.94	21.1 ± 4.55	0.10	**.050**

Variables are presented as means ± standard deviation. VAT: visceral adipose tissue. * represents significant difference in the change between groups using independent sample t-tests. Alpha level at 0.05.

Table 3. Performance Outcomes of Male and Female Groups.

	Males (n=19)				Females (n=19)			
	Pre	Post	Effect Size (g)	p	Pre	Post	Effect Size (g)	p
Vertical Jump								
Jump Peak Power (Nm)	4296.7 ± 674.0	4545.7 ± 749.4	0.46	**<.001**	2897.2 ± 815.6	3012.7 ± 742.6	0.15	**.002***
Dynamic Balance								
Y-Balance Right Score	84.9 ± 7.64	89.6 ± 9.06	0.55	**.002**	83.5 ± 8.17	86.0 ± 6.34	0.33	.159
Y-balance Left Score	84.8 ± 8.10	89.5 ± 8.46	0.56	**.002**	84.0 ± 7.33	86.2 ± 7.48	0.29	.180
Isokinetic Dynamometry								
KF Peak Torque (Nm)	61.1 ± 21.0	71.6 ± 27.2	0.42	**.005**	41.2 ± 12.0	47.2 ± 14.6	0.44	**.010**
KE Peak Torque (Nm)	150.5 ± 29.2	159.5 ± 34.0	0.28	.055	90.1 ± 21.2	96.5 ± 18.9	0.31	**.033**
KF Total Work (Nm)	1342.8 ± 546.6	1649.3 ± 645.0	0.50	**.008**	1005.9 ± 417.4	1166.2 ± 391.0	0.39	**.032**
KE Total Work (Nm)	3695.3 ± 798.0	4174.8 ± 697.0	0.63	**.016**	2281.3 ± 642.0	2541 ± 539.8	0.43	**< .001**
KF Average Power (W)	99.9 ± 37.1	116.6 ± 40.1	0.42	**.010**	64.1 ± 23.4	77.6 ± 23.0	0.57	**.002**
KE Average Power (W)	232.4 ± 53.4	254.8 ± 62.2	0.38	**.031**	135.2 ± 41.7	153.2 ± 31.3	0.48	**.003**
Total Work Combined (W)	5038.1 ± 1139.6	5824.1 ± 1183.6	0.66	**.006**	3287.3 ± 969.0	3707.7 ± 837.5	0.45	**.002**

Variables are presented as means ± standard deviation. KF: knee flexors, KE: knee extensors. * represents significant difference in change between groups using independent sample t-tests. Alpha level at 0.05.



Baseline Visit 1
Questionnaires
Medical History
Body
Composition
Anthropometrics
Blood Work
Fitness Test
Baseline Visit 2
Physical
Performance
Y-Balance
1-RM
Session 1
Acute Blood Draw
Session 10
Midpoint 1-RM Test
6 Week BFRT Exercise Intervention
Session 18
Acute Blood Draw
Post Visit 1
Questionnaires
Body
Composition
Anthropometrics
Blood Work
Fitness Test
Post Visit 2
Physical
Performance
Y-Balance
1-RM

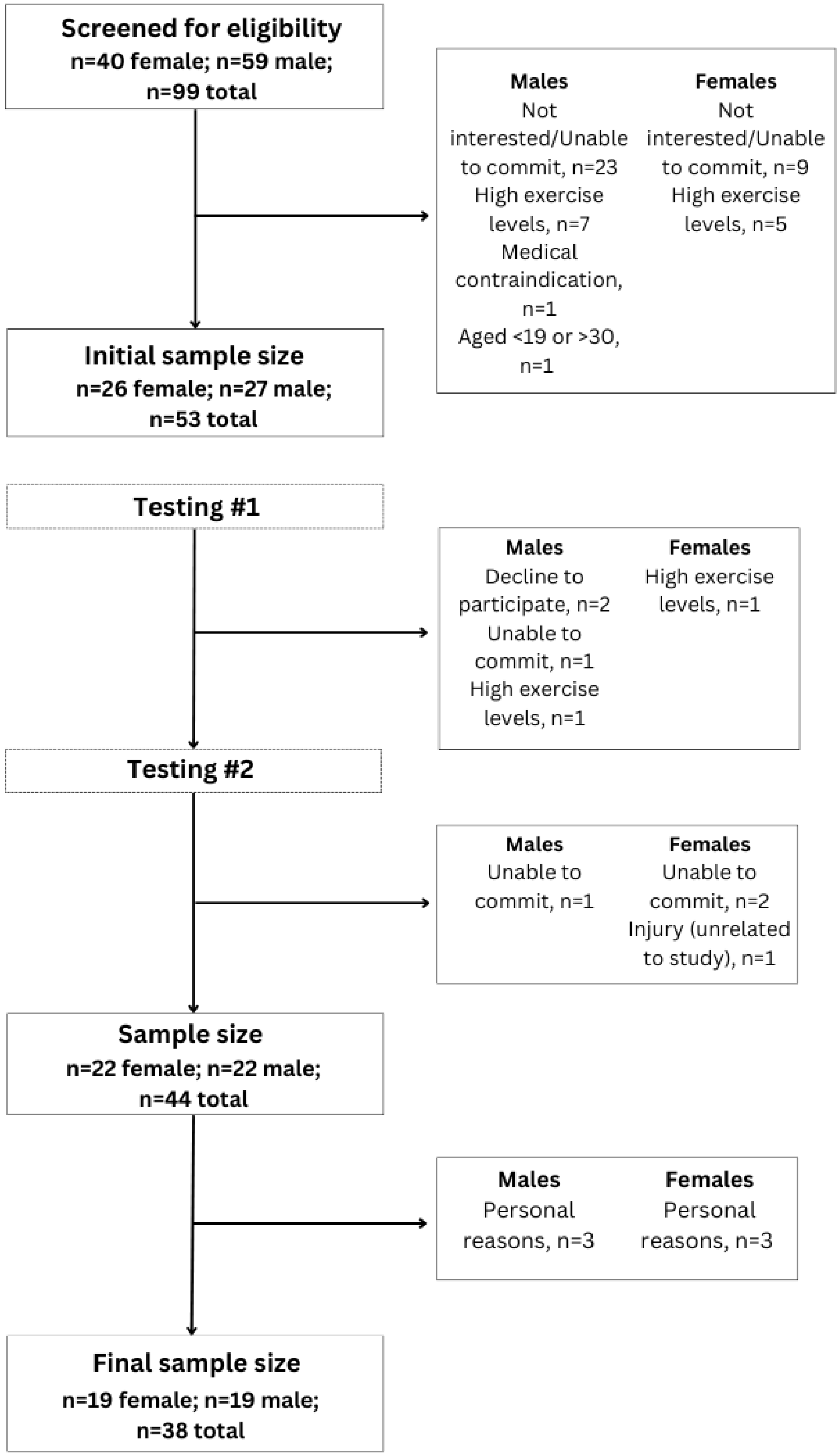


Figure 2. Participant Flowchart.

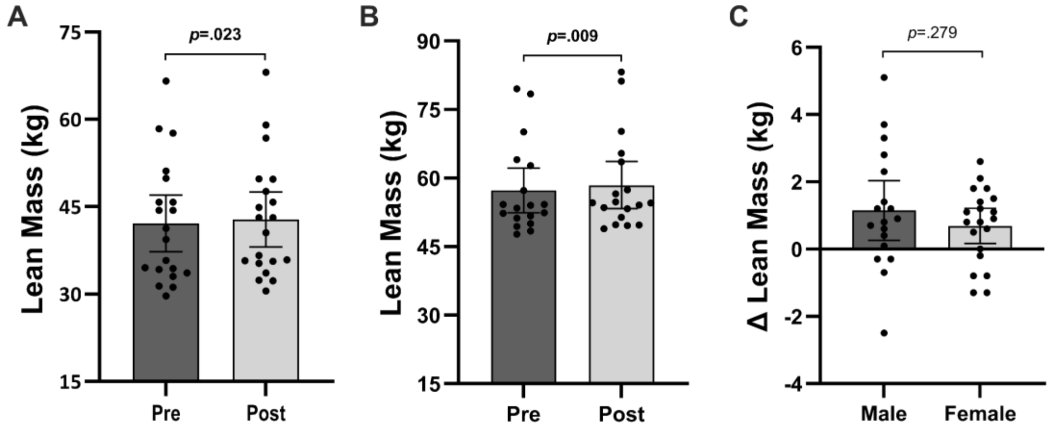


Figure 3A. Lean mass of females at baseline and post-testing. **3B.** Lean mass of males at baseline and post-testing. **3C.** Absolute change of lean mass for males and females. Data are presented as mean and 95% confidence intervals with *p*-values.

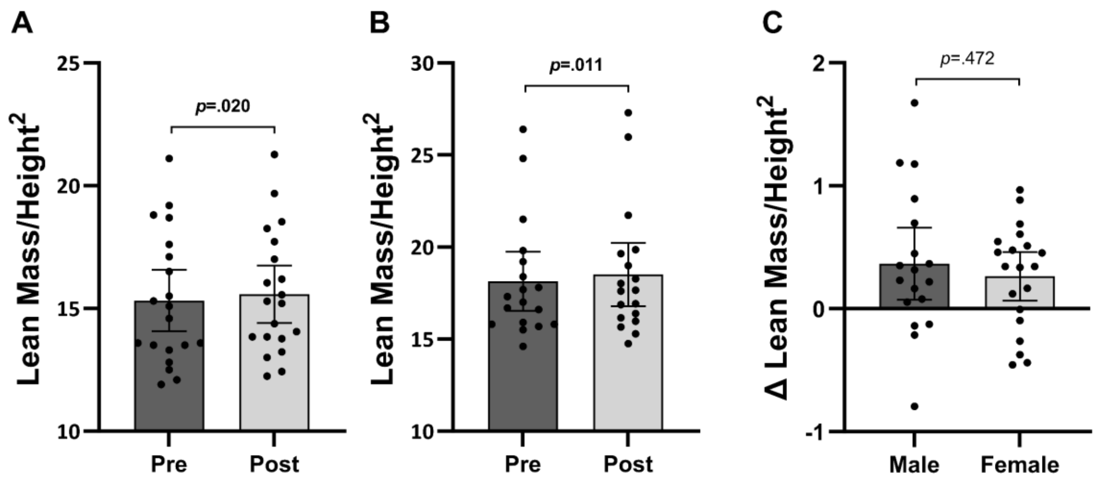


Figure 4A. Relative lean mass of females at baselines and post-testing. **4B.** Relative lean mass of males at baseline and post-testing. **4C.** Absolute change of relative lean mass for males and females. Data are presented as mean and 95% confidence intervals with *p*-values.

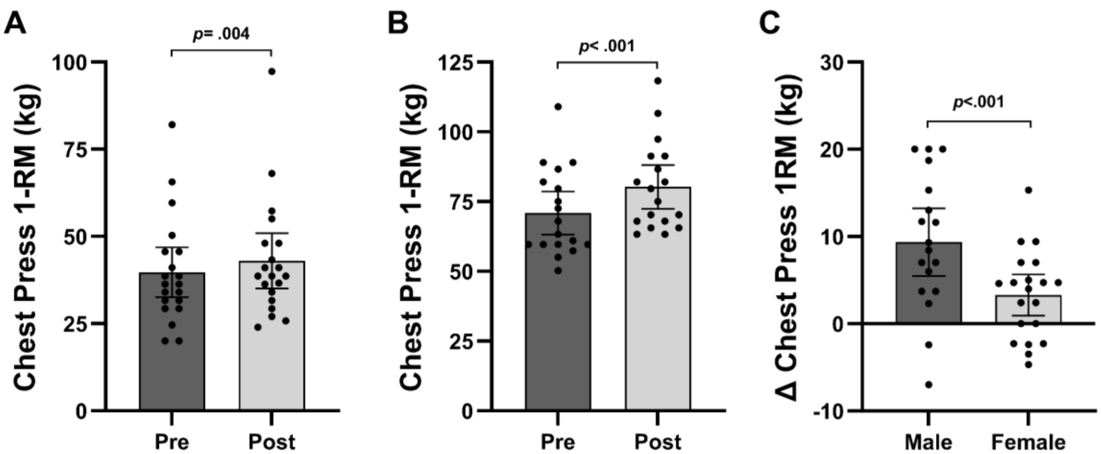


Figure 5A. 1-RM for chest press of females at baseline and post-testing. **5B.** 1-RM for chest press of males at baseline and post-testing. **5C.** Absolute change of 1-RM for chest press from baseline to post-testing of males and females. Data are presented as mean and 95% confidence intervals with *p*-values.

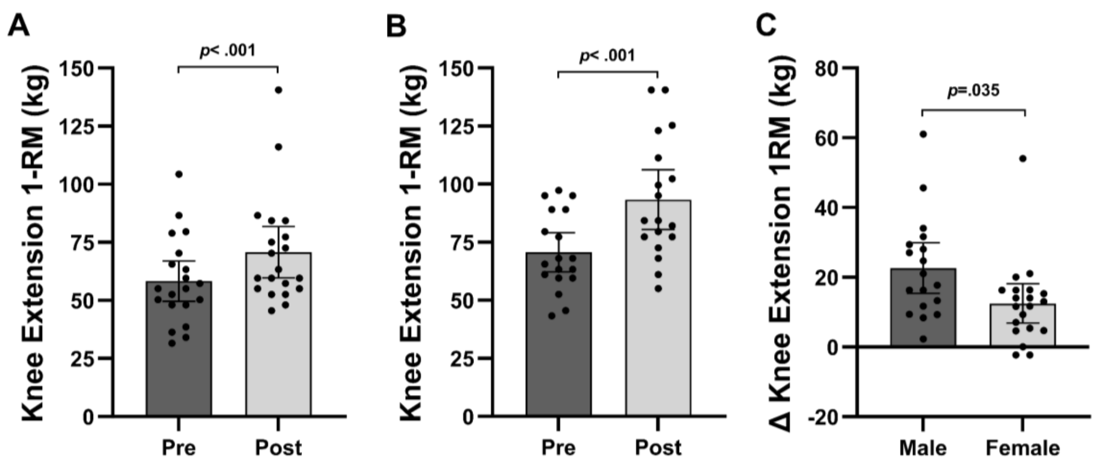
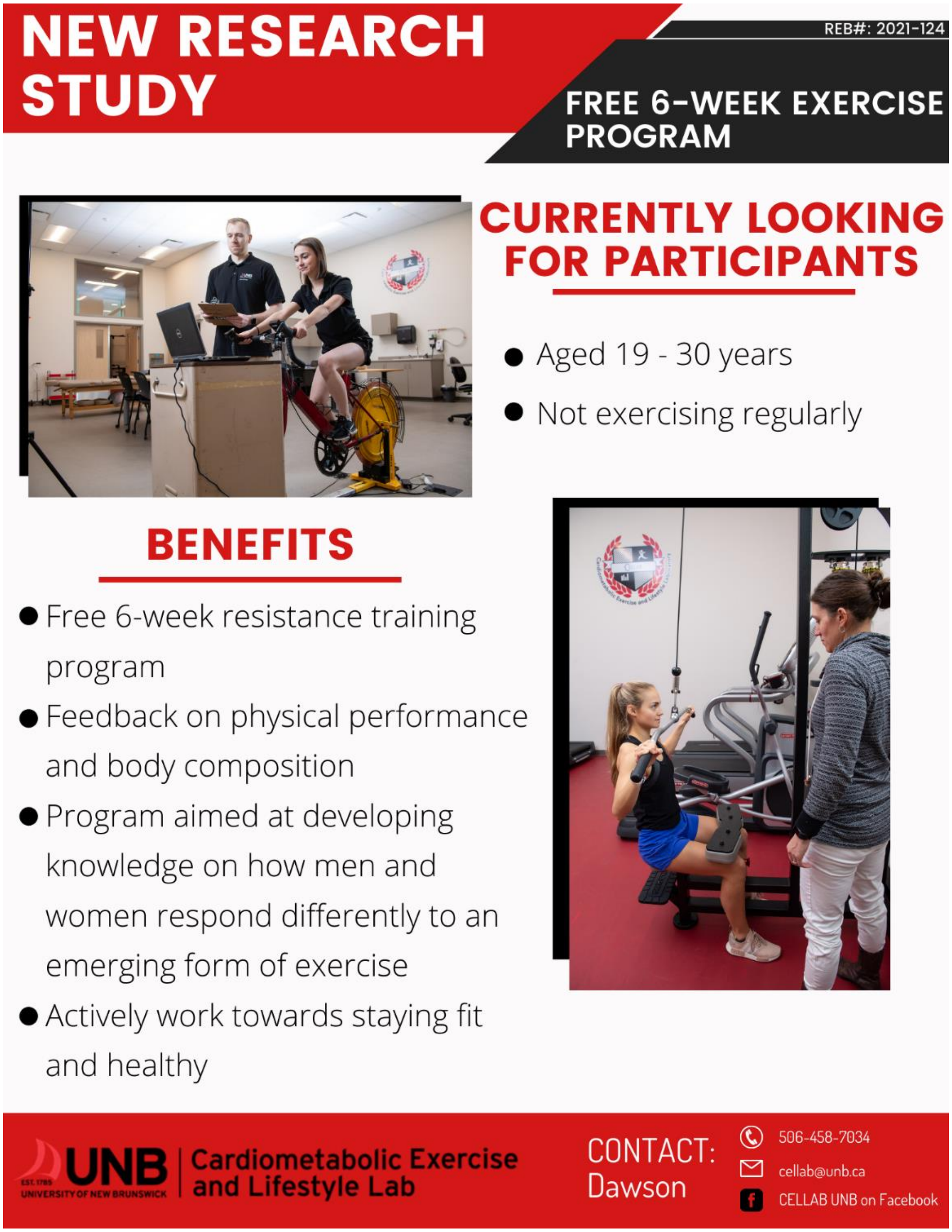


Figure 6A. 1-RM for knee extension of females at baseline and post-testing. **6B.** 1-RM for knee extension of males at baseline and post-testing. **6C.** Absolute change of 1-RM for knee extension from baseline to post-testing of males and females. Data are presented as mean and 95% confidence intervals with *p*-values.

Appendices

Appendix A: Promotional flyer used to advertise



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University of New Brunswick, Master of Science in Kinesiology, 2021-Present

Publications:

Nancekievill, D., Colpitts, B. H., Seaman, K., Girard, M., & Sénéchal, M. (2023). **The impact of sprint interval training with or without weight loss on substrate oxidation in adults: A secondary analysis of the i-FLEX study**. *Physiological Reports, 11,* e15684. https://doi.org/10.14814/phy2.15684

Conference Presentations and Publications:

Peskett, L., Nancekievill, D., Thomson, A.M., Arnason, J., Paudel, Y., & Sénéchal M. (2023) **Impact of blood flow restriction training performed at different times of day on performance and irisin response**. *Poster Presentation.* New Brunswick Health Research Conference, Saint John, NB, Canada

Nancekievill, D., Meister, D. J., Cull, C. C. I., Bouchard, D. R., Sénéchal, M. (2022). **The impact of 16-week resistance training performed with elastic bands along with diabetes education on quality of life in frail older adults living with type 2 diabetes: A sub analysis of the Band-Frail study**. Applied Physiology, Nutrition, and Metabolism. Canadian Society for Exercise Physiology Annual General Meeting, Fredericton, (86). Canadian Science Publishing, http://dx.doi.org/https://doi.org/10.1139/apnm-2022-0269

Nancekievill, D., Colpitts, B., Bouchard, D., Sénéchal, M. (2021). **The Impact of Weight Loss following Sprint Interval Training on Substrate Oxidation in Adults**. Journal of Physical Activity and Health. International Society for Physical Activity and Health: 8th Congress, Vancouver, Canada. Human Kinetics, Canada http://dx.doi.org/https://doi.org/10.14288/hfjc.v14i3.767

Nancekievill, D., Colpitts, B., Bouchard, D., Sénéchal, M. (2021). **The Impact of Sprint Interval Training with or Without Weight Loss on Substrate Oxidation in Adults**.
Poster Presentation. Atlantic Health Exploration and Discovery: Collaborative Health Research Conference, Saint John, NB, Canada

Nancekievill, D., Colpitts, B., Seaman, K., Sénéchal, M. (2021). **The Impact of Sprint Interval Training with or Without Weight Loss on Substrate Oxidation in Adults**. *Poster Presentation.* New Brunswick Healthy Research Foundation: Health Research Week, Fredericton, NB, Canada