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One year of heavy resistance training modifies muscle fiber characteristics in elderly

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Abstract:
Physical function declines with age, accelerating during the 6th decade of life, primarily due to loss in muscle mass and strength. The present study aimed to investigate the effect of one year of heavy resistance training in older adults (62-70 years) on muscle mass and strength. Further, we investigated muscle characteristics after the intervention by obtaining muscle biopsies from vastus lateralis to compare muscle fiber characteristics between the heavy resistance training (HRT) (n=10) and the sedentary control group (CON) (n=10). We found that one year of resistance training increased isometric muscle strength ($p<0.0001$, ES: 2.43 (Hedges' g)) and lean body mass ($p<0.05$, ES: 0.96), whereas cross-sectional area of vastus lateralis and lean leg mass were unaltered. At year 1, the percentage of type IIX muscle fibers was lower in HRT compared to CON ($p<0.05$, ES: 0.99), whereas the muscle fiber size did not differ between groups for the major fiber types (I and II). In conclusion, one year of resistance training in elderly improved muscle strength and lean body mass but not cross-sectional area and lean leg mass. This indicate that the increase in muscle strength may be caused by neuromuscular adaptations rather than morphological muscle tissue changes per se.

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Abstract

Physical function declines with age, accelerating during the 6th decade of life, primarily due to loss in muscle mass and strength. The present study aimed to investigate the effect of one year of heavy resistance training in older adults (62-70 years) on muscle mass and strength. Further, we investigated muscle characteristics after the intervention by obtaining muscle biopsies from vastus lateralis to compare muscle fiber characteristics between the heavy resistance training (HRT) (n=10) and the sedentary control group (CON) (n=10). We found that one year of resistance training increased isometric muscle strength ($p<0.0001$, ES: 2.43 (Hedges' g)) and lean body mass ($p<0.05$, ES: 0.96), whereas cross-sectional area of vastus lateralis and lean leg mass were unaltered. At year 1, the percentage of type IIX muscle fibers was lower in HRT compared to CON ($p<0.05$, ES: 0.99), whereas the muscle fiber size did not differ between groups for the major fiber types (I and II). In conclusion, one year of resistance training in elderly improved muscle strength and lean body mass but not cross-sectional area and lean leg mass. This indicate that the increase in muscle strength may be caused by neuromuscular adaptations rather than morphological muscle tissue changes per se.

Key Words: Aging, physical function, strength training, hypertrophy

1. INTRODUCTION

Aging is associated with a progressive decline in muscle mass and muscle strength, affecting physical function [1–5]. Low physical function is likely to affect quality of life, independency and increase the risk of falls, morbidity, and mortality in older and frail humans [6,7]. The decline in muscle mass with aging is mainly caused by a reduction in type II muscle fiber size [8–10], with a foreseeable consequence of decreased muscle strength and power and ultimately muscle function. However, also the neural drive is affected in elderly compared with young [11], which could be the result of the loss of spinal motor neurons, that occurs with aging [12,13]. The loss of spinal motor neurons will cause muscle fiber denervation and thereby a decrease in number of active muscle fibers, ultimately causing a decrease in functional capacity during daily living activities [12]. A key target in preventing a decremental decrease in physical function is therefore to preserve fast type II muscle fiber size as well as the neural drive in older adults [14].

Resistance training is often used to either prevent or reverse the age-related loss of muscle mass, muscle strength, and function. More specifically, heavy resistance training leads to an increase in muscle strength and muscle hypertrophy in both moderately old, old, and the oldest old men and women [15–20]. These beneficial effects of resistance training are also observed when analyzing changes at the muscle fiber level, and previous studies in elderly have shown an increase in type II muscle fiber size as a result of the training [9,10,14,16,20–22]. A very well-recognized adaptation to resistance training in both young and elderly individuals is a shift in the relative amount of type IIX and IIA fibers, where a reduction in the relative amount of type IIX fibers and a corresponding increase in the relative amount of type IIA fibers are observed [9,10,23]. This adaptation occurs in the early phase of commencing resistance training and is detectable before myofiber hypertrophy [24], and is considered as favorable for fatigue resistance of the skeletal muscle [10]. Together, these adaptations in muscle fiber characteristics are to some extent the reason why an increase in muscle strength, muscle power, and physical function is observed after a period of intense resistance training [25]. However, previous studies have primarily been of shorter duration, and therefore the current knowledge is sparse when it comes to the responses of human skeletal muscle fibers to a long-term resistance training intervention.

We hypothesized that the muscle function would be improved as a response to the resistance training intervention and that the size of type II muscle fibers would be larger in the resistance-trained participants compared to the controls. Secondly, we also hypothesized that there would be more type IIA fibers and fewer type IIX fibers in the resistance training group compared to the controls. Thus, the present study aimed to investigate the effect of one year of heavy resistance training in elderly adults on muscle mass, muscle strength and relate this to specific differences in muscle fiber characteristics of the resistance trained group compared with a non-exercising control group after the intervention.

2. METHODS

2.1 Experimental Approach to the Problem

The present investigation was a sub-study of a larger randomized controlled trial with the primary aim to investigate the effect of one year of resistance training upon muscle mass, strength, and function in 451 participants aged 62-70 years that were randomized to one of three groups; heavy resistance training (HRT), moderate intensity training (MIT) or control (CON) [26]. In the present study, 20 participants (both men and women) were recruited and gave consent to undergo additional muscle-specific tests at the end of the intervention. From the beginning of the original study, the 20 participants included in the present study were allocated to either one year of heavy resistance training or a non-exercising control group.

2.2 Participants

The original study inclusion criteria were an age between 62-70 years and independent living. The participants were not enrolled in the study if they performed more than one hour per week of regular strenuous exercise training, had severe unstable medical diseases (e.g., active cancer or severe heart disease), had musculoskeletal diseases that inhibited training ability, were using medication that may influence the effects of training (e.g., androgens or antiandrogens), and/or drugs that caused safety concerns in relation to training [26]. The participants in the present study were recruited at the end of the one-year intervention and were only included if they have had a high training compliance (HRT) or had not changed their habitual physical activity level (CON) during the intervention.

All participants were informed of the benefits and risks of the investigation prior to signing the informed consent document to participate in the study. The study was approved by the regional ethical committee, complied with the declaration of Helsinki, and approved by the National Data Protection Agency and registered on clinicaltrials.gov.

2.3 Procedures

2.3.1 Interventions

The heavy resistance training intervention has been described elsewhere [17]. In brief, the participants exercised three times/week for one year with at least 48 hours between sessions. Experienced physical trainers supervised all sessions. Initially, the participants were familiarized to the program for 6-8 weeks with low intensity and loads to reduce the risk of musculoskeletal injury and familiarize them with the exercises. For the remaining part of the one-year intervention, the participants performed a progressive whole-body training program with increasing load. The participants performed three sets of 6–12 repetitions corresponding to an estimated intensity between ≈70–85% of 1 repetition maximum (RM) in a linear periodized regime over 9 weeks. Every second week the load was increased and after week 9, which was a restitution week, the participants performed 3 x 12 repetitions with a higher load than the first week of the last periodization, and thus the load increased throughout the entire intervention period. The training program consisted of leg press, knee extension, leg curl, calf raises, hip abduction, chest press, seated row, crunches, and back extensions. The control group was not allowed to perform more than one hour of strenuous physical exercise per week and were encouraged to continue their habitual physical activity level during the one-year intervention.

2.3.2 Measurements

Before and after the intervention all participants went through a comprehensive assessment battery including a medical examination, physical testing, body composition measurements, and determination of muscle size. In the present study, only some of the assessments are included. To determine maximal muscle strength an isometric knee extensor strength test was performed in a Good Strength device (V.3.14 Bluetooth; Metitur, Finland). Body composition was measured by dual-energy X-ray absorptiometry (DEXA) scan, where lean body mass (LBM) and lean leg mass (LLM) were determined. A magnetic resonance imaging (MRI) scan was used to determine cross-sectional area (CSA) of the vastus lateralis muscle. Unfortunately, the MRI scan from two participants (one from each group) could not be used for analysis, and the analysis is therefore based on the remaining 18 participants. A detailed description of all assessments has been described previously [17,26].

2.3.3 Experimental protocol

Muscle biopsy: On the day of the muscle biopsy sampling, the participants entered the laboratory facilities in a non-fasted state. A muscle biopsy was obtained from the non-dominant leg using a 6 mm Bergström needle using manual suction. Prior to obtaining the biopsy 1% lidocaine was applied as local anesthesia and an incision of approximately 6 mm was made through a skin incision. The biopsy was extracted from the most central position of m. vastus lateralis in accordance with the procedure by Bergström [27]. After extraction, all visual fat and connective tissue were removed from the biopsy, which was then embedded in Tissue-Tek and transferred into liquid nitrogen-cooled isopentane. Another piece of the biopsy was snap-frozen directly in liquid nitrogen. Both pieces were stored at -80°C until further analysis. Biopsies were obtained after the intervention only.

Immunohistochemistry: The Tissue-Tek embedded piece of the muscle biopsies were cut in 10 µm thick transverse sections at -20°C in a cryostat. The sections from each participant were placed on glass slides and stored in boxes at -80°C until further analysis. The investigator was blinded to the participant's identity and group allocation.

ATPase staining: Four separate slides containing the cut sections from each participant were prepared for staining using the ATPase histochemistry method. The slides were preincubated in solutions with a pH of 4.37, 4.53, 4.57, and 10.30 at room temperature. After preincubation, the slides were rinsed twice in a pH solution of 9.4 for 15 s and 30 s and then incubated for 30 min in a pH 9.4 ATP solution at 37°C. Thereafter, the slides were rinsed in 1% $CaCl_2$ for 1, 2, and 3 min followed by an incubation in a 2% $CoCl_2$ solution for a period of 3 min. Lastly, the slides were then washed 25 times in H_2O, incubated with 1% ammoniumsulfide for 1 min, washed 25 times in H_2O again, and finally, the slides were mounted with polyvinylpyrrolidone [23,28,29].

Capillary staining: A slide from each participant was prepared for immunohistochemical staining of capillaries. The double-staining method combining ulex europaeus lectin 1 (UEA-1) and collagen type IV staining was used [30]. First the sections were dried, then the slides were fixed in acetone for 30 s, incubated in 1% BSA for 20 min followed by an incubation of UEA-1 protein for 30 min at room temperature. Thereafter, the slides were incubated with anti-UEA-I for 15 min and anti-human collagen IV for 30 min. The slides were then incubated with the secondary antibodies, biotinylated goat anti-rabbit antibody, and a biotinylated goat anti-mouse antibody for 30 min before a Vector Elite ABC HRP kit was applied to the slides for an additional 30 min. Lastly, the slides were incubated with a 3,3'-diaminobezidine substrate for 3-4 min before being mounted in aquatex [30].

Analysis of capillary and ATPase staining: To evaluate fiber type, fiber size, and the number of capillaries the ATPase and capillary stainings were analyzed by a blinded assessor. Serial sections were visualized and analyzed using an Olympus BX40 microscope (Olympus Optical Co., Tokyo, Japan), connected to Sanyo Hi-resolution Color CCD camera (Sanyo Electronic Co., Osaka, Japan), and an eight-bit Matrox Meteor Framegrabber (Matrox Electronic Systems, Quebec, Canada), combined with image-analysis software (Tema, Scanbeam, Hadsund, Denmark). Using the capillary staining, a fiber mask was drawn along the cell borders of approximately 200 fibers per biopsy, and capillaries were marked. Afterwards, images from the ATPase staining were fitted into the fiber mask and a number was assigned to each specific fiber. The fibers were then displayed on the screen in multiple images and the individual fibers could be identified. The fibers were then assigned to a specific fiber type group, in order to determine the relative proportion of the various fiber types, fiber type areas, and fiber sizes as well as the number of capillaries associated with each fiber [23,31]. The analysis defined five different fiber types (type I, I/IIA, IIA, IIAX, and IIX) from which the fibers. From this overall classification, the number of fiber types were reduced to three main fiber types (type I, IIA, and IIX) as described previously by Andersen and Aagaard [23], to provide an easier dataset to compare with earlier studies. In extension of this, the number of minor sub-fiber types (I/IIA, IIAX, and IIX) was so small in some individuals, that a reliable statistical comparison of differences in fiber size of these minor fiber types was impossible. Therefore, calculations of fiber type size were done only for the two major fiber types (I and II) [23].

2.4 Statistical Analyses

A two-way mixed model with repeated measures was used to evaluate the overall effects of group and time for all parameters, except data from the muscle biopsies, including data from pre and post-intervention. In case of a significant group × time interaction, Tukey post hoc analysis was used to evaluate within-group comparisons as well as a one-way ANOVA (a generalized linear model) to detect any group differences from baseline to 1-year. If no significant group × time interaction was observed, the same model but without interaction was used to evaluate the effect of time. As we only have post-intervention muscle biopsies, a one-way ANOVA was used to evaluate whether there were any differences between HRT and CON. In addition, to evaluate the magnitude of the mean differences, Hedges' g effect sizes (ES) were calculated for comparison groups (HRT vs. CON). The interpretation of the effect sizes is similar to the scale proposed by Rhea 2004 for untrained participants [32]: trivial <0.50, small=0.50-1.25, moderate=1.25-1.9, and large >2.0. Further, a two-way mixed model was used to evaluate any potential group and sex differences in fiber size. If no significant group × sex interaction was observed, a one-way ANOVA was used to evaluate sex differences. All data are presented as mean ± SE unless otherwise stated. All missing data were removed for the same participant at all time points (e.g. if a participant had one missing data from baseline, data from 1-year were removed). We chose a significance level of 0.05 for the mixed model and ANOVA. All statistical analysis was performed using SAS Enterprise Guide 8.3 (SAS Institute Inc., Cary, NC, USA).

3. RESULTS

3.1 Participants

Twenty participants (10 men/10 women) with an average age of 67 ± 2.2 years were enrolled in the study, all participants, from a larger cohort that had concluded the one-year intervention [17]. Table 1 provides baseline characteristics of the participants. Only age differed between the two groups, where participants in HRT were younger than CON (p<0.05). For all other parameters, there was no difference between groups. In the present study, the participants randomized to the heavy resistance training had a training compliance of 88 % ± 5 % (mean ± SD) during the intervention.

3.2 Fiber type composition, size, and capillarization

On average, the muscle biopsy sample was obtained 6.9 ± 0.3 days after the last exercise session. The number of fibers analyzed for each group was 207 ± 4 and 207 ± 2 (mean ± SE) for HRT and CON, respectively. There was no difference in the percentage of type I and IIA fibers between groups. However, the percentage of type IIX fibers was significantly lower in HRT than in CON (4.7 % ± 1.4 % and 12.3 % ± 3.0 %, respectively) ($p<0.05$, ES: 0.99) (fig. 1A). This was also the case when the type IIX fibers were expressed in percentage of the fiber size ($p<0.05$).

The size of the fibers did not differ between groups in either muscle fiber type I (4725 μm^2 ± 245 μm^2 and 4795 μm^2 ± 267 μm^2 for HRT and CON, respectively) or II (3660 μm^2 ± 389 μm^2 and 3821 μm^2 ± 584 μm^2 for HRT and CON, respectively) (fig. 1B). When the fiber size was analyzed to evaluate any sex differences, we observed that men in general had a significantly higher fiber size in the type II fibers compared with women ($p<0.01$) (data not shown). This was independent of which group the participants were allocated to as there was no significant group × sex interaction.

We did not observe any difference between groups in capillarization. The number of capillaries per fiber was 2.2 ± 0.1 capillaries for both groups and the amount of capillaries per mm^2 was 470.4 ± 27.3 and 486.7 ± 21.1 capillaries for HRT and CON, respectively.

3.3 Muscle strength

Similar to the original study with a much larger number of participants [17], participants in the heavy resistance training group experienced an increase in isometric muscle strength as a response to the training intervention, resulting in a significant group × time interaction ($p<0.0001$). The change from baseline to 1-year in isometric muscle strength in HRT was significantly higher than in CON (33.7 Nm ± 4.3 Nm and -4.7 Nm ± 5.2 Nm, respectively) ($p<0.0001$, ES: 2.43) (fig. 2A). Additionally, compared with baseline the isometric muscle strength at 1-year was higher in HRT ($p<0.0001$) and unchanged in CON.

3.4 Body composition and muscle size

In line with isometric muscle strength, we observed an overall interaction in LBM ($p<0.05$), which was similar to what we found in the original study [17]. The change from baseline to 1-year in LBM was significantly higher in HRT compared with CON (1086 g ± 302 g and 177 g ± 169 g, respectively) ($p<0.05$, ES:

0.96) (fig. 2B). In addition, LBM was higher after the 1-year intervention in HRT compared with baseline ($p<0.01$), whereas it was unchanged in CON.

For either the CSA of the vastus lateralis muscle or LLM, we could not detect any difference between groups as a response to the intervention in this study (table 2).

4. DISCUSSION

The main finding of the study was that one year of organized systematic heavy-load resistance training improved muscle strength and muscle mass in older adults and that these adaptations were accompanied by the observation of a significantly lower relative number of muscle fiber type IIX in the trained group compared to the control group after the intervention. A decrease in the relative amount of type IIX fibers is a well-known adaptation to heavy resistance training when carried over a shorter period [23], and we here demonstrate that this seems also to be the case when training is continued up till one year in elderly individuals.

Somewhat unexpected, we could not detect any differences in muscle fiber size between the two groups after the intervention. This lack of difference in muscle fiber size is in contrast to the general hypothesis of resistance training stimulating an increase in muscle fiber size, especially in type II fibers [9,10,14,21,22,31,33]. However, in a study by Ziegler et al, also using a sub-population (n=25) from the same original study as the present study, no significant increase in fiber size between the HRT and the control group was observed [34]. In that study muscle biopsies from both pre-training and post-training were directly compared.

As we did not have biopsies before the training, it cannot be ruled out that the HRT group could have had a somewhat lower fiber size at baseline than the CON group and that we could have missed any true increase in fiber size. Another explanation could be the relatively small number of participants in the present study, and in fact in the much larger study from which these participants in this study were recruited from, does in fact demonstrate that training increased both strength and cross-sectional area of skeletal muscle with training [17]. Further, the determination of fiber size from muscle biopsy sections is widely used as a reliable assessment of muscle hypertrophy, but it has also been demonstrated that there is an increasing variation in fiber size with age [35], which potentially could have contributed to our lack of findings in hypertrophy in muscle fiber size. In addition, it is worth mentioning that it is not unusual to find a discrepancy between adaptation at fiber level and whole muscle [36] or whole-body level [37].

Our finding of an increase in muscle strength and lean body mass in response to a resistance training intervention has been observed previously in all age groups including the oldest old [9,10,20,38,39]. The gains in isometric muscle strength and lean body mass were ~22 % and ~2 %, respectively, and are similar to what has been reported with resistance training interventions in older adults [15,18,20,31,40]. Therefore, it is likely that our training program has provided an appropriate stimulus to the skeletal muscle. Likewise, the apparent decrease in the percentage of type IIX fibers and corresponding increase in type IIA fibers found in the resistance-trained participants compared with the controls is a response that has been observed in earlier resistance training studies [9,10,21,23,25]. It should be noted that we did not see a difference in the percentage of type IIA fibers between the two groups.

Even though we could not detect any difference in muscle fiber size, there was a relatively high increase in muscle strength, which could indicate that the increased strength could be primarily a consequence of neuromuscular changes in response to the resistance training intervention rather than changes at the muscle level, in line with earlier resistance training studies that have found increased neural drive [11,41] and increased motoneuron firing frequency [41]. A combination of these changes would increase the amount of recruited muscle fibers and thereby the potential to increase muscle strength.

In conclusion, one year of heavy resistance training increased muscle strength and lean body mass in elderly individuals, and we observed a lower percentage of type IIX muscle fibers in the heavy resistance training participants compared with the non-training controls. The lack of any difference in muscle fiber size in muscle biopsies between groups obtained after the training intervention indicates that long-term resistance training in elderly individuals predominantly improves muscle strength through neuromuscular adaptation rather than to morphological changes per se.

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Figure legends

Fig. 1: Fiber type composition (%) (A) and fiber size (μm^2) (B) of muscle fibers from the vastus lateralis muscle after 1-year of heavy resistance training (HRT, black bars) or habitual physical activity (CON, grey bars) (mean ± SE). *significant difference between groups ($p<0.05$, ES: 0.99).

Fig. 2: Changes in muscle strength (Nm) (A) and lean body mass (g) (B) after either 1-year of heavy resistance training (HRT, black bars) or habitual physical activity (CON, grey bars) (mean ± SE). *significant difference between groups (A: $p<0.0001$, ES: 2.43, B: $p<0.05$, ES: 0.96).

Table legends

Table 1: Participant characteristics at baseline (mean ± SD). The isometric muscle strength test was performed in a Good Strength device.

Table 2: Lean leg mass and muscle size before (baseline) and after either 1-year of heavy resistance training (HRT) or habitual physical activity (CON) (mean ± SE).

Table 1: Participant characteristics at baseline (mean ± SD). The isometric muscle strength test was performed in a Good Strength device.

	Total (n=20)	HRT (n=10)	CON (n=10)	Sample size
Age (years)	67 ± 2	66 ± 2*	68 ± 2	20
Sex (women %)	50	50	50	20
BMI (kg/m^2)	23.5 ± 2.4	23.8 ± 2.8	23.2 ± 2.2	20
Lean body mass (kg)	47.7 ± 7.8	48.5 ± 7.9	46.8 ± 8.0	20
Isometric muscle strength (Nm)	151.7 ± 36.7	151.5 ± 38.2	151.9 ± 37.2	20
30 s chair-stand (reps)	17 ± 4	18 ± 4	17 ± 3	20
Total step count (steps/day)	9992 ± 4462	11254 ± 5398	8729 ± 3058	20

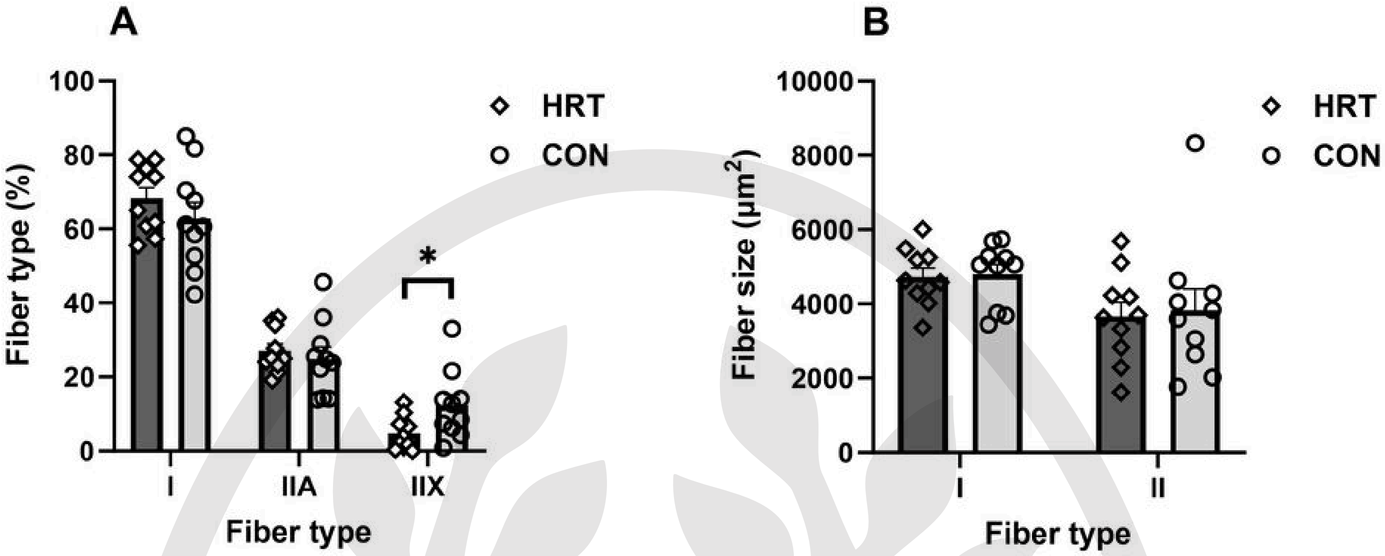
*Significant difference between HRT and CON ($p<0.05$).

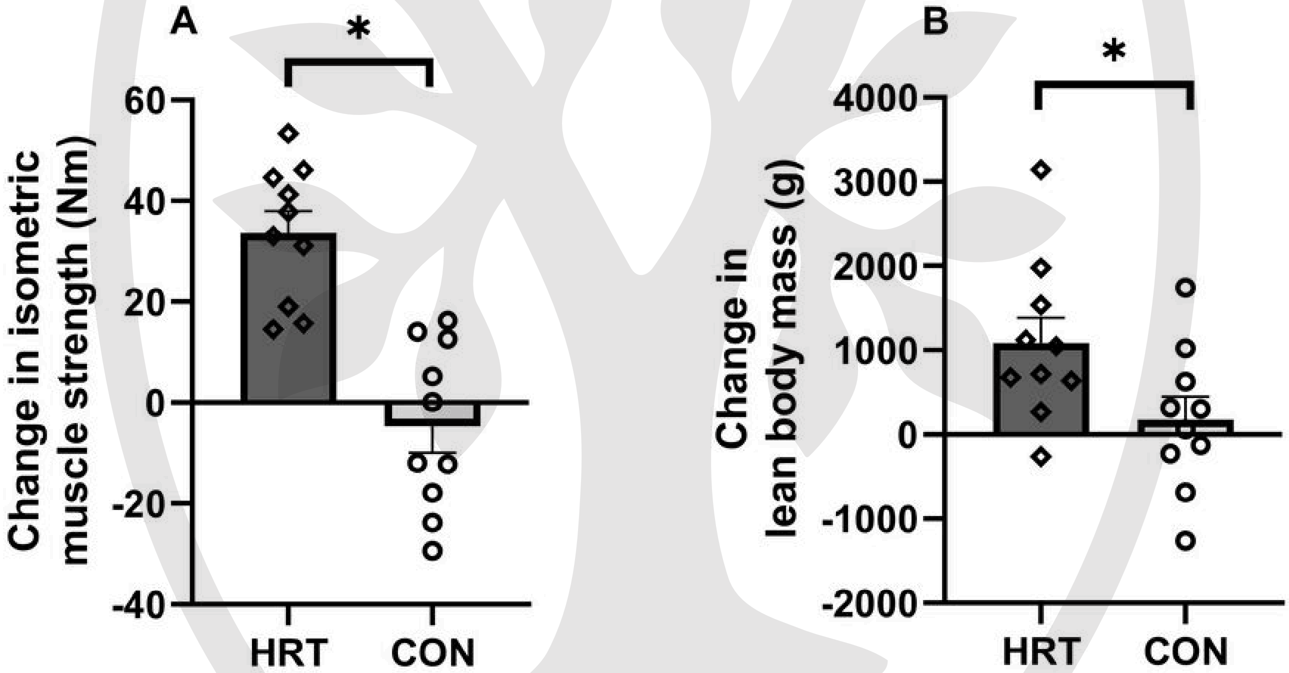
BMI: body mass index

Table 2: Lean leg mass and muscle size before (baseline) and after either 1-year of heavy resistance training (HRT) or habitual physical activity (CON) (mean ± SE).

	HRT		CON		Sample
	Baseline	1 yr	Baseline	1 yr	size
Lean leg mass (kg)	17.2 ± 1.1	17.6 ± 1.2	16.5 ± 1.1	16.6 ± 1.0	20
CSA m. vastus laterlis (mm^2)	1494 ± 139	1502 ± 136	1476 ± 85	1493 ± 88	18

CSA: cross-sectional area


A
B
HRT
CON
Fiber type (%)
100
80
60
40
20
0
*
I
IIA
IIX
Fiber type
Fiber size (μm2)
10000
8000
6000
4000
2000
0
I
II
Fiber type


A
B
*
Change in isometric muscle strength (Nm)
60
40
20
0
-20
-40
HRT
CON
Change in lean body mass (g)
4000
3000
2000
1000
0
-1000
-2000
HRT
CON