

There are no non-responders to resistance-type exercise training in older men and women

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Abstract

Objective: To assess the proposed prevalence of unresponsiveness of older men and women to augment lean body mass, muscle fiber size, muscle strength, and/or physical function following prolonged resistance-type exercise training.

Design/Setting/Participants: A retrospective analysis of the the adaptive response to 12 ($n = 110$) and 24 ($n = 85$) weeks of supervised resistance-type exercise training in older (>65 y) men and women.

Measurements: Lean body mass (DXA), type I and type II muscle fiber size (biopsy), leg strength (1-RM on leg press and leg extension), and physical function (chair rise-time) were assessed at baseline, and after 12 and 24 weeks of resistance-type exercise training.

Results: Lean body mass increased by 0.9 ± 0.1 kg (range: -3.3 to $+5.4$ kg; $P < 0.001$) from 0-12 weeks of training. From 0-24 weeks, lean body mass increased by 1.1 ± 0.2 kg (range: -1.8 to $+9.2$ kg; $P < 0.001$). Type I and II muscle fiber size increased by 324 ± 137 μm^2 (range: -4458 to $+3386$ μm^2 ; $P = 0.021$), and 701 ± 137 μm^2 (range: -4041 to $+3904$ μm^2 ; $P < 0.001$) from 0-12 weeks. From 0-24 weeks, type I and II muscle fiber size increased by 360 ± 157 μm^2 (range: -3531 to $+3426$ μm^2 ; $P = 0.026$) and 779 ± 161 μm^2 (range: -2728 to $+3815$ μm^2 ; $P < 0.001$). 1-RM strength on the leg press and leg extension increased by 33 ± 2 kg (range: -36 to $+87$ kg; $P < 0.001$) and 20 ± 1 kg (range: -22 to $+56$ kg; $P < 0.001$) from 0-12 weeks. From 0-24 weeks, leg press and leg extension 1-RM increased by 50 ± 3 kg (range: -28 to $+145$ kg; $P < 0.001$) and 29 ± 1 kg (range: -19 to $+60$ kg; $P < 0.001$). Chair rise-time decreased by 1.3 ± 0.4 s (range: $+21.6$ to -12.5 s; $P = 0.003$) from 0-12 weeks. From 0-24 weeks, chair rise-time decreased by 2.3 ± 0.4 s (range: $+10.5$ to -23.0 s; $P < 0.001$). Non-responsiveness was not apparent in any subject, as a positive adaptive response on at least one training outcome was apparent in every subject.

Conclusions: A large heterogeneity was apparent in the adaptive response to prolonged resistance-type exercise training when changes in lean body mass, muscle fiber size, strength, and physical function were assessed in older men and women. The level of responsiveness was strongly affected by the duration of the exercise intervention, with more positive responses following more prolonged exercise training. We conclude that there are no non-responders to the benefits of resistance-type exercise training on lean body mass, fiber size, strength, or function in the older population. Consequently, resistance-type exercise should be promoted without restriction to support healthy aging in the older population.

Introduction

Ageing is associated with a progressive decline in skeletal muscle mass, strength, and physical function, a condition termed *sarcopenia*¹. Sarcopenia is an independent risk factor for adverse outcomes including difficulties in carrying out activities of daily living, falls, fractures, hospitalization and readmission, and death². Resistance-type exercise training currently represents the primary therapeutic strategy recommended to prevent and reverse the age-related decline in skeletal muscle mass, strength, and function³. Current public health recommendations for older adults (>65 y) in both Canada and the USA prescribe 150 min of moderate- to vigorous-intensity physical activity to be accumulated per week, with additional muscle strengthening activities performed twice weekly^{4,5}. In further support of the benefits of resistance-type exercise training in the older population, a recent systematic review of the literature confirmed that even the very old (>75 y) retain the capacity for muscle hypertrophy and increased strength in response to exercise training⁶. However, previous work has shown substantial inter-individual variability in resistance-type exercise mediated changes in muscle mass⁷⁻⁹ and strength⁸ following a period of standardized exercise training. In response to both resistance-^{8,9} and endurance-type exercise training^{10,11} some individuals seem to demonstrate exceptionally large responses, whereas others show only a minimal or even an apparent opposite response to prolonged exercise training. Based upon such observations it has been suggested that some people may be non-responsive to the benefits of prolonged exercise training¹²⁻¹⁵. However, while some individuals may show no response or even an opposite response¹⁶ on a single training outcome in response to exercise training, other critically important physiological variables may be improved in those individuals after training. Therefore, a wide range of response outcomes must be examined in order to fully evaluate the efficacy of a resistance training program on participants health¹⁷. If a large proportion of the older population is indeed unresponsive to the effects of resistance-type exercise training on

muscle mass, strength and function, it would be important to identify and possibly even characterize these individuals for alternate treatment strategies. Currently, no studies have examined the prevalence of unresponsiveness to prolonged resistance-type exercise training mediated improvements in lean body mass, muscle fiber size, muscle strength, and physical function in the older population. The aim of the present study was to examine the responsiveness to prolonged resistance-type exercise on multiple training outcomes including lean body mass, muscle fiber size, muscle strength, and physical function following 12 to 24 weeks of training in a large group older men and women¹⁸⁻²⁰. We hypothesized that despite substantial inter-individual variability in the adaptive response to resistance-type exercise training, there are no non-responders to the impact of resistance-type exercise training on increasing lean body mass, muscle fiber size, strength, or physical function.

Methods

Subjects: The subject population included both healthy^{18,20}, pre-frail and frail older¹⁹ men and woman (>65 y). Subjects with cancer, chronic obstructive pulmonary disease, muscle disease, and those unable to perform exercise due to orthopedic limitations were excluded from the study. Subjects with type 2 diabetes (blood glucose >7.0 mmol/L) and renal insufficiency (eGFR < 60 mL/min/1.73 m²) were also excluded. All subjects were living independently. None of the participants had a history of participating in any structured exercise training program designed to improve performance over the past 5 y. All subjects were informed of the nature and associated risks of the experimental procedures of each respective study prior to obtaining their written informed consent.

Study design: Subjects participated in either a 12¹⁸ or 24^{19,20} week program of personally supervised resistance-type exercise training. The primary outcome variables in the current analysis include lean body mass, type I and type II muscle fiber size, muscle strength, and physical function. Lean body mass was assessed by DXA, type I and type II muscle fiber size

was assessed by needle biopsy and subsequent immunohistochemistry, muscle strength was assessed by evaluation of single repetition maximum (1-RM) in both the leg press and leg extension, and physical function was assessed by repeated chair rise-time (sit-to-stand) respectively.

Resistance-type exercise training program: The resistance-type exercise training was carried out under supervision of a trained investigator either 2¹⁹ or 3^{18,20} times per week and performed for 12¹⁸ and 24^{19,20} weeks, respectively. The 24-week training intervention^{19,20} consisted of evaluation at 12 weeks; this data is included in the present analysis. The details of the exercise training programs including the exercise equipment, exercise selection, number of sets, number of repetitions, interest rest-intervals, and intensity progression (as a percentage of 1-RM maximum) have been described in detail previously¹⁸⁻²⁰.

Lean body mass, muscle fiber size, maximum strength, and physical function: Lean body mass was assessed in the fasted-state via DXA (Lunar Prodigy Advance; GE Health Care, Madison, WI)¹⁹ and (Hologic, Discovery A, QDR Series, Bradford, MA)^{18,20}. All subjects underwent a muscle biopsy from the *vastus lateralis* 3-d prior to initiating the resistance-type exercise training program and 4 d following the 12 and 24 week strength assessments in the overnight fasted state. Maximum strength was assessed via evaluation of 1-RM on a leg press and leg-extension machine (Technogym, Rotterdam, the Netherlands). All 1-RM tests were preceded by a separate familiarization session during which the proper exercise technique was practiced and maximum strength was estimated. In a second session, 1-RM strength was determined as previously described²¹. 1-RM testing is preferred to evaluate changes in muscle strength during resistance-type exercise training²¹. Physical function was assessed via a sit-to-stand test. Briefly, for the sit-to-stand test, participants were instructed to fold their arms across their chest and stand up/sit down five times, as fast as possible, from a seat at 0.42 m from the

floor. Time was recorded from the initial sitting to the final standing position. The fastest out of two attempts was used for analysis²².

Statistics: The mean, minimum, and maximum values were calculated for the entire subject group, and within both men and women, for lean body mass, type I and II muscle fiber size, muscle strength (1-RM on both the leg press and leg extension), and physical function (sit-to-stand test). Differences (absolute changes) from 0-12 weeks and 0-24 weeks for each of the above outcome measures were assessed using a one sample *t* test. Differences (absolute changes) between men and women from 0-12 and 0-24 weeks were examined using unpaired *t* tests. Variability was assessed based on the confidence interval (CI) of the mean. Statistical analyses were performed using IBM SPSS Statistics (version 20). An α -level of 0.05 was used to determine statistical significance.

Results

Subjects' characteristics: Subject characteristics are reported in Table 1. The 12-week analysis of lean body mass, 1-RM leg press, and 1-RM leg extension involved 110 subjects, while the chair-rise time was completed on 85 subjects. Type I and type II fiber cross-sectional area data was available for 92 subjects at 12 weeks. The 24-week analysis of lean body mass, 1-RM leg press, 1-RM leg extension, and chair rise-time consisted of 85 subjects. Type I and type II fiber cross-sectional data was available for 66 subjects at 24 weeks.

Lean body mass: Prior to training, lean body mass averaged 52.3 ± 1.0 kg (CI: 1.9 kg). Women had a lean body mass of 41.8 ± 0.7 kg (CI: 1.5 kg), which was significantly lower ($P < 0.001$) compared to men (59.3 ± 0.7 kg; CI: 1.5 kg). Following 12-weeks of training there was a significant increase ($P < 0.001$) in lean body mass of 0.9 ± 0.1 kg (CI: 0.2 kg). Men showed a 0.8 ± 0.1 kg increase (CI: 0.3 kg) while women showed a 1.0 ± 0.2 kg (CI: 0.4 kg) increase (Table 2 and 3), with no differences between groups ($P = 0.50$). After 24 weeks of resistance-type training, the increase in lean body mass averaged 1.1 ± 0.2 kg ($P < 0.001$; CI: 0.4 kg). Men

demonstrated a 1.0 ± 0.2 kg (CI: 0.4 kg) increase in lean body mass, while women demonstrated a 1.2 ± 0.3 kg (CI: 0.6 kg) increase ($P=0.58$ between groups). A histogram of individual subject changes in lean body mass (absolute changes from baseline) following 12 and 24 weeks of resistance-type exercise training are shown in Figure 1A and B, respectively.

Type I and II fiber size: Prior to training, type I and II fiber CSA (μm^2) was 5741 ± 147 μm^2 (CI: 293 μm^2) and 4540 ± 162 μm^2 (CI: 322 μm^2) respectively. Men had a type I fiber CSA of 6136 ± 174 μm^2 (CI: 348 μm^2) and type II fiber CSA of 5264 ± 166 μm^2 (CI: 332 μm^2), while women had a mean type I fiber CSA of 5063 ± 227 μm^2 (CI: 462 μm^2), and a type II fiber CSA of 3298 ± 209 μm^2 (CI: 424 μm^2). Pre-training muscle fiber size was significantly lower in women in both type I ($P<0.001$) and type II ($P<0.001$) fibers. Following 12-weeks of training, there was an increase in type I ($P=0.021$) and type II ($P<0.001$) fiber CSA of 324 ± 137 μm^2 (CI: 273 μm^2), and 701 ± 137 μm^2 (CI: 273 μm^2) respectively. Men showed an increase of 451 ± 164 μm^2 (CI: 328 μm^2) and 1034 ± 172 μm^2 (CI: 344 μm^2), while women showed an increase of 97 ± 244 μm^2 (CI: 498 μm^2) and 108 ± 191 μm^2 (CI: 389 μm^2) in type I and II fiber size respectively (Table 2 and 3). There was no difference between men and women in the change in type I ($P=0.22$) fiber size from 0-12 weeks, however the change in type II fiber size was significantly greater in men compared to women ($P<0.001$). From 0-24 weeks of training, the increase in type I and II fiber size was 360 ± 157 μm^2 ($P=0.026$; CI: 314 μm^2), and 779 ± 161 μm^2 ($P<0.001$; CI: 322 μm^2). Men showed an increase of 259 ± 213 μm^2 (CI: 432 μm^2) and 946 ± 265 μm^2 (CI: 539 μm^2) in type I and II fiber size, while women showed an increase of 473 ± 236 μm^2 (CI: 481 μm^2) and 589 ± 167 μm^2 (CI: 342 μm^2 ; Table 2 and 3). There were no differences between men and women in the change in type I ($P=0.50$) or type II ($P=0.28$) fiber size from 0-24 weeks. A histogram of individual subject changes in type I and type II fiber size (absolute changes from baseline) following 12 and 24 weeks of resistance-type exercise training are shown in Figure 2A and B, and 3A and B respectively.

Muscle strength: Baseline 1-RM on the leg press and leg extension was 160 ± 4 kg (CI: 8 kg) and 75 ± 2 kg (CI: 4 kg) respectively. Men had a mean 1-RM on the leg press of 183 ± 5 kg (CI: 9 kg), and leg extension of 86 ± 2 (CI: 4 kg) while women had a mean 1-RM on the leg press of 126 ± 4 (CI: 8 kg), and leg extension of 58 ± 2 kg (CI: 4 kg). Men demonstrated significantly greater baseline 1-RM strength than women on both the leg press ($P<0.001$) and leg extension ($P<0.001$). From 0-12-weeks of training, there was an increase in 1-RM strength on the leg press and leg extension of 33 ± 2 kg ($P<0.001$; CI: 4 kg), and 20 ± 1 kg ($P<0.001$; CI: 2 kg) respectively. Men showed an increase of 34 ± 2 kg (CI: 4 kg) and 24 ± 1 kg (CI: 2 kg) while women showed an increase of 31 ± 4 kg (CI: 7 kg) and 14 ± 2 kg (CI: 3 kg) on the leg press and leg extension respectively (Table 2 and 3). There were no differences between men and women on the increase in 1-RM strength on the leg press ($P=0.47$), however the increase in 1-RM strength on the leg extension was significantly greater in men as compared to women ($P<0.001$). From 0-24 weeks, the absolute increase in 1-RM on the leg press and leg extension was 50 ± 3 kg ($P<0.001$; CI: 5 kg), and 29 ± 1 kg ($P<0.001$; CI: 3 kg). Men showed an increase of 53 ± 3 kg (CI: 6 kg) and 36 ± 2 kg (CI: 4 kg), while women showed an increase of 48 ± 4 kg (CI: 9 kg) and 22 ± 2 kg (CI: 3 kg) on 1-RM strength assessed on the leg press and leg extension respectively (Table 2 and 3). There were no differences between men and women on the increase in 1-RM strength on the leg press ($P=0.32$), however the increase in 1-RM strength on the leg extension was significantly greater in men as compared to women ($P<0.001$). A histogram of individual subject changes in leg press and leg extension 1-RM (absolute change from baseline) following 12 and 24 weeks of resistance-type exercise training are shown in Figure 4A and B, and 5A and B respectively.

Physical function: Prior to training, chair rise-time averaged 11.1 ± 0.6 s (CI: 1.3 s), with men having an average of 10.0 ± 0.7 s (CI: 1.4 s) and women having an average of 12.0 ± 1.0 s (CI: 2.1 s), respectively. There were no differences between men and women in baseline chair rise-

time ($P=0.11$). From 0-12-weeks of training, chair rise-time decreased by -1.3 ± 0.4 s ($P=0.003$; CI: 0.8 s), with men and women demonstrating a decrease of -0.6 ± 0.6 s (CI: 1.3 s) and -1.9 ± 0.5 s (CI: 1.0 s) respectively (Table 2 and 3). There were no differences between men and women in the change in chair rise-time after 12 weeks of resistance-type training ($P=0.11$). After 24 weeks of resistance-type training, the absolute change in chair rise-time was -2.3 ± 0.4 seconds ($P<0.001$; CI: 0.8 s), with men and women demonstrating a decrease of -1.2 ± 0.4 s (CI: 0.8) and -3.2 ± 0.7 s (CI: 1.3 s), respectively (Table 2 and 3). The decrease in chair rise-time from 0-24 weeks was significantly greater in women as compared to men ($P=0.01$). A histogram of individual subject changes in chair rise-time (absolute changes from baseline) following 12 and 24 weeks of resistance-type exercise training are shown in Figure 6A and B, respectively.

Discussion

In the present study, we observed that prolonged (12-24 weeks) resistance-type exercise training increased lean body mass, type I and II muscle fiber size, muscle strength, and physical function in a large group older men and women, however large inter-individual variability in the measured changes in these training outcomes was observed (Fig 1-6).

Despite the inter-individual variability in the adaptive response to training, we were unable to identify a single subject who did not positively respond to resistance-type exercise training.

All subjects demonstrated increases in at least one of the training outcomes (lean body mass, muscle fiber size, strength, and/or physical function) examined. Furthermore, we observed that the duration of resistance-type exercise training is an important factor determining an individual's response to exercise training. In other words, there were individuals who demonstrated little to no improvements after 12 weeks of training, but showed a substantial improvement after 24-weeks of training.

Regular resistance-type exercise training has been well-established as an effective interventional strategy to increase skeletal muscle mass and strength in both elderly men and women^{20, 23, 24}, and has been shown to be accompanied by many favorable consequences on a variety of health outcomes²⁵. In the present study we observed increases in lean body mass of 0.9 ± 0.1 kg ($1.8 \pm 0.3\%$) and 1.1 ± 0.2 kg ($2.3 \pm 0.4\%$) after 12 and 24 weeks of training, respectively. The changes in lean body mass were highly variable between subjects, with measured changes ranging from -3.3 (subject #75) to +5.4 kg (subject #63) after 12 weeks, to -1.8 (subject #75) and +9.2 kg (subject #69) following 24 weeks of exercise training (Figure 1A and B). Subject #75, who demonstrated the lowest change in lean body mass in response to training at both 12 and 24 weeks, showed positive increases in both type I and II fiber size and 1-RM strength, and an improvement in chair rise-time. The precision of DXA for whole-body lean soft tissue expressed as CV ranges from 0.4-1.3 % (SEM 0.35-0.54 kg) in sequential measurements²⁶, and it is difficult to assess whether reported changes on an individual level are representative of the actual changes in body mass in the individual. For this reason relatively large groups of subjects are generally included to assess the efficacy of a given exercise intervention to increase lean body mass⁸. However, the present analyses revealed that 23 subjects (~21%) and 16 subjects (~19%) failed to show a measurable increase in lean body mass before and after 12 and 24 weeks of resistance-type exercise training (Figure 1A and B). Despite 23 subjects not demonstrating a measurable increase in lean body mass from 0-12 weeks, 9 of these subjects (subject #: 36, 38, 18, 9, 82, 74, 79, 28, 6) demonstrated a positive increase in lean body mass from 0-24 weeks (Figure 1A and B).

In agreement with previous studies demonstrating that even the very old maintain the capacity to augment muscle fiber size in response to resistance-type exercise training^{27, 28}, type I fiber CSA increased by $8 \pm 3\%$ and $9 \pm 3\%$ following 12 and 24 weeks of resistance-type training, respectively. Similarly, type II fiber CSA increased by $17 \pm 3\%$ and $23 \pm 4\%$ following

12 and 24 weeks of training. Despite such large average increases in type I and II fiber size, there was substantial heterogeneity in the individual changes. For example, changes in type I and II muscle fiber size ranged from -4458 (subject #53) and -4041 (subject #55) μm^2 to +3386 (subject #55) and +3904 (subject #88) μm^2 from 0-12 weeks of training (Figure 2A and 3A; Table 2 and 3). Similar observations of inter-individual variability were observed from 0-24 weeks of training (Figure 2B and 3B; Table 2 and 3). The present analyses revealed that 36 subjects (~39%) and 22 subjects (~33%) did not show an increase in type I muscle fiber size, while we failed to detect a measurable increase in type II muscle fiber size in 25 subjects (~27%) and 17 subjects (~26%) following 12 and 24 weeks of training (Figures 2-3). Despite the relatively large number of subjects who did not show measurable increases in muscle fiber size, every one of these subjects demonstrated substantial increases in 1-RM leg strength, possibly implying improved neurological function in response to training²⁹.

Consistent with previous work¹⁸⁻²⁰, resistance-type exercise training resulted in substantial increases in muscle strength (Figure 4 and 5). Leg press 1-RM increased by 23 ± 2 and $35\pm 2\%$ following 12 and 24 weeks of training. Similar observations were observed for the leg extension (28 ± 2 and $42\pm 2\%$, respectively). Although there was substantial inter-individual variability in the changes in 1-RM leg strength, only 2 subjects failed to demonstrate measurable increases in 1-RM leg press (subject #85 and #26) and leg extension (subject #85 and #79) strength after 12 weeks of training. Similarly, only a single subject (subject #85) did not show an increase in leg strength after 24 weeks of training. Of interest, this subject (#85) demonstrated the greatest improvements in chair rise-time ability at both 12 and 24 weeks post-training. Substantial improvements in physical function were also observed, with a large 8.2 ± 2.5 and $17.8\pm 2.0\%$ reduction in the time required for the chair rise test following 12 and 24 weeks of training. Twenty subjects (20%) failed to show improvement on the chair rise-time test after 12 weeks of training. After 24 weeks, only 5 subjects (6%) showed no

improvement compared to baseline values (Figure 6). This observation demonstrates that being non-responsive after 12 weeks of training certainly is not predictive on the outcome after a more prolonged training intervention.

In the present study, we present the individual changes in lean body mass, type I and II muscle fiber size, leg strength, and functional capacity in a large group of older men and women. There was quite some variance in the changes in lean body mass, muscle fiber size, strength, and function between individuals. This is in line with the established heterogeneity in the adaptive response to training⁷⁻⁹ and this may be further augmented by the differences between subjects regarding the level of frailty, nutritional status, protein supplementation, and training regimen within the included cohorts^{18-20, 30}. Some individuals seemed to show no or even an apparent negative response on one of the outcome parameter (Figures 1-6) and could, therefore, be referred to as “non-responders”⁹ or “adverse responders”¹⁶. However, a critical evaluation of the individual data demonstrates that subjects who seemed unresponsive in regard to, for example, an increase in lean body mass after 12 (subject #74, 94, 5, 61, 85, 2, 36, 88, 3, 56, 70, 109, 38, 18, 108, 9, 53, 82, 74, 55, 79, 28, 6) or 24 (subject #75, 5, 53, 2, 57, 61, 11, 55, 70, 3, 81, 85, 56, 17, 77, 66) weeks of exercise training, were all highly responsive to one or more of the other training outcomes. In fact, only 2 out of 110 subjects (<1%) failed to show improvements in 1-RM leg strength after 12 weeks of training. Our findings appear to agree with the suggestion that the inter-correlation between being unresponsive to training on one physiological trait and another is very low ($\sim r = 0.1-0.05$)¹⁵. Thus, lack of improvement on one specific phenotype (i.e. lean body mass or muscle fiber size) is not a reason not to recommend or prescribe resistance-type exercise training because substantial improvements in another phenotype (strength and/or physical function) can still be obtained. Furthermore, there was a decline in the number of people deemed unresponsive when comparing responses following 12 and 24 weeks of training. In other words, being non-responsive to the impact of

12 weeks of exercise training on a certain parameter does not preclude a normal adaptive response observed after more prolonged intervention. Consequently, our data do not provide any sign of the existence of non-responsiveness to the benefits of resistance-type exercise training. Moreover, we feel it is a misconception to assume that a few single measurements in time provide realistic insight in the absolute changes in a certain physiological trait within a single individual. There is a reason why groups of subjects are included in clinical studies and why statistical tests are used to test research hypotheses. The present data set shows that conclusions based on an $n=1$ can be quite deceiving. The important work of many of our colleagues addressing the basis of the observed heterogeneity in the adaptive response to exercise interventions^{7-10, 12, 31-33} is often misinterpreted by the popular media suggesting that a substantial part of the population does not benefit from an exercise intervention.

Conclusions

The present data show that there is no rationale to assume that there is such a thing as unresponsiveness to the benefits of exercise training and, as such, we should not be restrictive in the prescription of resistance-type exercise training to augment lean body mass, muscle fiber size, muscle strength, and physical function in the older population. Even in situations where an individual demonstrates what might be classified as an adverse response to exercise¹⁶ on a single outcome measure, that response needs to be carefully weighed against the myriad of health benefits derived from regular exercise training. Of course, we can only speculate on the relative contribution of musculo-skeletal, neurological or behavioral adaptation on the reported increases in muscle mass, strength and function in the older population. In conclusion, there are no non-responders to the benefits of resistance-type exercise training on lean body mass, muscle fiber size, muscle strength, or function in the older population. Resistance-type exercise should be promoted to support healthy aging in the older population.

References

1. Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr.* 1997;127(5 Suppl):990S-1S.
2. Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing.* 2014.
3. Morley JE, Anker SD, von Haehling S. Prevalence, incidence, and clinical impact of sarcopenia: facts, numbers, and epidemiology—update 2014. *Journal of Cachexia, Sarcopenia and Muscle.* 2014:1-7.
4. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc.* 2007;39(8):1435-45.
5. Tremblay MS, Warburton DE, Janssen I, et al. New Canadian physical activity guidelines. *Appl Physiol Nutr Metab.* 2011;36(1):36-46; 7-58.
6. Stewart VH, Saunders DH, Greig CA. Responsiveness of muscle size and strength to physical training in very elderly people: a systematic review. *Scand J Med Sci Sports.* 2014;24(1):e1-10.
7. Davidsen PK, Gallagher IJ, Hartman JW, et al. High responders to resistance exercise training demonstrate differential regulation of skeletal muscle microRNA expression. *J Appl Physiol (1985).* 2011;110(2):309-17.
8. Hubal MJ, Gordish-Dressman H, Thompson PD, et al. Variability in muscle size and strength gain after unilateral resistance training. *Med Sci Sports Exerc.* 2005;37(6):964-72.
9. Bamman MM, Petrella JK, Kim JS, et al. Cluster analysis tests the importance of myogenic gene expression during myofiber hypertrophy in humans. *J Appl Physiol (1985).* 2007;102(6):2232-9.
10. Bouchard C, An P, Rice T, et al. Familial aggregation of VO₂max response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol (1985).* 1999;87(3):1003-8.
11. Kohrt WM, Malley MT, Coggan AR, et al. Effects of gender, age, and fitness level on response of VO₂max to training in 60-71 yr olds. *J Appl Physiol (1985).* 1991;71(5):2004-11.
12. Stephens NA, Sparks LM. Resistance to the Beneficial Effects of Exercise in Type 2 Diabetes: Are Some Individuals Programmed to Fail? *J Clin Endocrinol Metab.* 2014;jc20142545.
13. Booth FW, Laye MJ. The future: genes, physical activity and health. *Acta Physiol (Oxf).* 2010;199(4):549-56.

14. Sisson SB, Katzmarzyk PT, Earnest CP, et al. Volume of exercise and fitness nonresponse in sedentary, postmenopausal women. *Med Sci Sports Exerc.* 2009;41(3):539-45.
15. Timmons JA. Variability in training-induced skeletal muscle adaptation. *J Appl Physiol (1985).* 2011;110(3):846-53.
16. Bouchard C, Blair SN, Church TS, et al. Adverse metabolic response to regular exercise: is it a rare or common occurrence? *PLoS One.* 2012;7(5):e37887.
17. Buford TW, Roberts MD, Church TS. Toward exercise as personalized medicine. *Sports Med.* 2013;43(3):157-65.
18. Verdijk LB, Jonkers RA, Gleeson BG, et al. Protein supplementation before and after exercise does not further augment skeletal muscle hypertrophy after resistance training in elderly men. *Am J Clin Nutr.* 2009;89(2):608-16.
19. Tieland M, Dirks ML, van der Zwaluw N, et al. Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: a randomized, double-blind, placebo-controlled trial. *J Am Med Dir Assoc.* 2012;13(8):713-9.
20. Leenders M, Verdijk LB, Van der Hoeven L, et al. Protein supplementation during resistance-type exercise training in the elderly. *Med Sci Sports Exerc.* 2013;45(3):542-52.
21. Verdijk LB, van Loon L, Meijer K, et al. One-repetition maximum strength test represents a valid means to assess leg strength in vivo in humans. *J Sports Sci.* 2009;27(1):59-68.
22. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol.* 1994;49(2):M85-94.
23. Leenders M, Verdijk LB, van der Hoeven L, et al. Elderly men and women benefit equally from prolonged resistance-type exercise training. *J Gerontol A Biol Sci Med Sci.* 2013;68(7):769-79.
24. Tieland M, Dirks ML, van der Zwaluw N, et al. Protein Supplementation Increases Muscle Mass Gain During Prolonged Resistance-Type Exercise Training in Frail Elderly People: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Am Med Dir Assoc.* 2012.
25. Phillips SM. Resistance exercise: good for more than just Grandma and Grandpa's muscles. *Appl Physiol Nutr Metab.* 2007;32(6):1198-205.
26. Fosbol MO, Zerahn B. Contemporary methods of body composition measurement. *Clin Physiol Funct Imaging.* 2014.
27. Trappe S, Williamson D, Godard M, et al. Effect of resistance training on single muscle fiber contractile function in older men. *J Appl Physiol (1985).* 2000;89(1):143-52.
28. Trappe S, Godard M, Gallagher P, et al. Resistance training improves single muscle fiber contractile function in older women. *Am J Physiol Cell Physiol.* 2001;281(2):C398-406.

29. Sale DG. Neural adaptation to resistance training. *Med Sci Sports Exerc.* 1988;20(5 Suppl):S135-45.
30. Verdijk LB, Koopman R, Schaart G, et al. Satellite cell content is specifically reduced in type II skeletal muscle fibers in the elderly. *Am J Physiol Endocrinol Metab.* 2007;292(1):E151-7.
31. Phillips BE, Williams JP, Gustafsson T, et al. Molecular networks of human muscle adaptation to exercise and age. *PLoS Genet.* 2013;9(3):e1003389.
32. Petrella JK, Kim JS, Mayhew DL, et al. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. *J Appl Physiol (1985).* 2008;104(6):1736-42.
33. Kosek DJ, Kim JS, Petrella JK, et al. Efficacy of 3 days/wk resistance training on myofiber hypertrophy and myogenic mechanisms in young vs. older adults. *J Appl Physiol.* 2006;101(2):531-44.

Figure legends

Figure 1. Histogram of the absolute changes in lean body mass (kg) for each individual subject following 12 (A) and 24 (B) weeks of resistance-type exercise training in elderly men and women. Numbers next to the bars represent the individual subjects and match with the same subject number presented in Figures 1-6.

Figure 2. Histogram of the absolute changes in type I muscle fiber cross-sectional area (μm^2) for each individual subject following 12 (A) and 24 (B) weeks of resistance-type exercise training in elderly men and women. Numbers next to the bars represent the individual subjects and match with the same subject number presented in Figures 1-6.

Figure 3. Histogram of the absolute changes in type II muscle fiber cross-sectional area (μm^2) for each individual subject following 12 (A) and 24 (B) weeks of resistance-type exercise training in elderly men and women. Numbers next to the bars represent the individual subjects and match with the same subject number presented in Figures 1-6.

Figure 4. Histogram of the absolute changes in 1-RM on the leg press (kg) for each individual subject following 12 (A) and 24 (B) weeks of resistance-type exercise training in elderly men and women. Numbers next to the bars represent the individual subjects and match with the same subject number presented in Figures 1-6.

Figure 5. Histogram of the absolute changes in 1-RM on the leg extension (kg) for each individual subject following 12 (A) and 24 (B) weeks of resistance-type exercise training in elderly men and women. Numbers next to the bars represent the individual subjects and match with the same subject number presented in Figures 1-6.

Figure 6. Histogram of the absolute changes in chair rise-time (seconds) for each individual subject following 12 (A) and 24 (B) weeks of resistance-type exercise training in elderly men and women. Numbers next to the bars represent the individual subjects and match with the same subject number presented in Figures 1-6.

TABLE 1. Subjects' characteristics

Group	Age (y)	Height (m)	Bodyweight (kg)	BMI
<u>12 week analysis</u>				
All (<i>n</i> =110)	72.6 ± 0.6	1.70 ± 0.01	78.1 ± 1.1	27.1 ± 0.4
Men (<i>n</i> =66)	72.6 ± 0.9	1.74 ± 0.01	82.9 ± 1.4	27.2 ± 0.4
Women (<i>n</i> = 44)	72.6 ± 0.9	1.62 ± 0.01	71.0 ± 1.8	26.9 ± 0.7
<u>24 week analysis</u>				
All (<i>n</i> = 85)	72.8 ± 0.8	1.69 ± 0.01	77.7 ± 1.5	27.2 ± 0.4
Men (<i>n</i> = 41)	73.0 ± 1.2	1.76 ± 0.01	84.8 ± 1.7	27.4 ± 0.5
Women (<i>n</i> = 44)	72.6 ± 0.9	1.62 ± 0.01	71.0 ± 1.8	26.9 ± 0.7

Data represent means±SEM.

TABLE 2. Absolute changes in lean body mass, type I and II muscle fiber size, leg strength, and functional function.

Variable	Absolute change from baseline					
	12-weeks	Min 12-weeks	Max 12-weeks	24-weeks	Min 24-weeks	Max 24-weeks
Lean body mass (kg)						
All	0.9 ± 0.1			1.1 ± 0.2		
Men	0.8 ± 0.1	-3.3	+3.4	1.0 ± 0.2	-1.8	+3.8
Women	1.0 ± 0.2	-1.2	+5.4	1.2 ± 0.3	-1.5	+9.2
Type I fiber size (μm ²)						
All	324 ± 137			360 ± 157		
Men	451 ± 164	-1694	+3170	259 ± 213	-3509	+2249
Women	97 ± 244	-4458	+3386	473 ± 236	-3531	+3426
Type II fiber size (μm ²)						
All	701 ± 137			779 ± 161		
Men	1034 ± 172	-3212	+3904	946 ± 265	-2728	+3815
Women	108 ± 191	-4041	+2010	589 ± 167	-1737	+1896
1-RM leg press (kg)						
All	33 ± 2			50 ± 3		
Men	34 ± 2	+10	+75	53 ± 3	+24	+115
Women	31 ± 4	-36	+87	48 ± 5	-28	+145
1-RM leg ext (kg)						
All	20 ± 1			29 ± 2		
Men	24 ± 1	0	+56	26 ± 2	+2	+57
Women	14 ± 2	-22	+45	22 ± 2	-19	+60
Chair rise-time (s)						
All	-1.3 ± 0.4			-2.3 ± 0.4		
Men	-0.6 ± 0.6	+21.6	-6.0	-1.2 ± 0.4	+10.5	-6.3
Women	-1.9 ± 0.5	+3.1	-12.5	-3.2 ± 0.7	+2.3	-23.0

TABLE 3. Percent changes in lean body mass, type I and II muscle fiber size, leg strength, and functional function.

Variable	Percent (%) change from baseline					
	12-weeks	Min 12-weeks	Max 12-weeks	24-weeks	Min 24-weeks	Max 24-weeks
Lean body mass (%)						
All	1.8 ± 0.3			2.3 ± 0.4		
Men	1.4 ± 0.3	-5.7	+6.7	1.6 ± 0.3	-3.1	+5.7
Women	2.4 ± 0.5	-3.3	+13.2	2.8 ± 0.6	-3.5	+19.0
Type I fiber size (%)						
All	8 ± 3			9 ± 3		
Men	9 ± 3	-28	+74	7 ± 4	-43	+51
Women	6 ± 5	-54	+92	11 ± 5	-56	+69
Type II fiber size (%)						
All	17 ± 3			23 ± 4		
Men	20 ± 3	-39	+74	21 ± 6	-51	+104
Women	12 ± 5	-50	+74	24 ± 6	-37	+78
1-RM leg press (%)						
All	23 ± 2			35 ± 2		
Men	20 ± 1	+3	+50	29 ± 2	+13	+85
Women	27 ± 4	-37	+106	40 ± 4	-29	+126
1-RM leg ext (%)						
All	28 ± 2			42 ± 2		
Men	29 ± 2	0	+75	44 ± 3	+3	+91
Women	26 ± 4	-45	+108	41 ± 4	-39	+113
Chair rise-time (%)						
All	-8.2 ± 2.5			-17.8 ± 1.9		
Men	-5.3 ± 4.3	+140.8	-30.4	-13.8 ± 3.0	+52.6	-42.9
Women	-10.9 ± 2.7	+40.3	-53.9	-21.5 ± 2.4	+18.0	-54.0

Figure 1

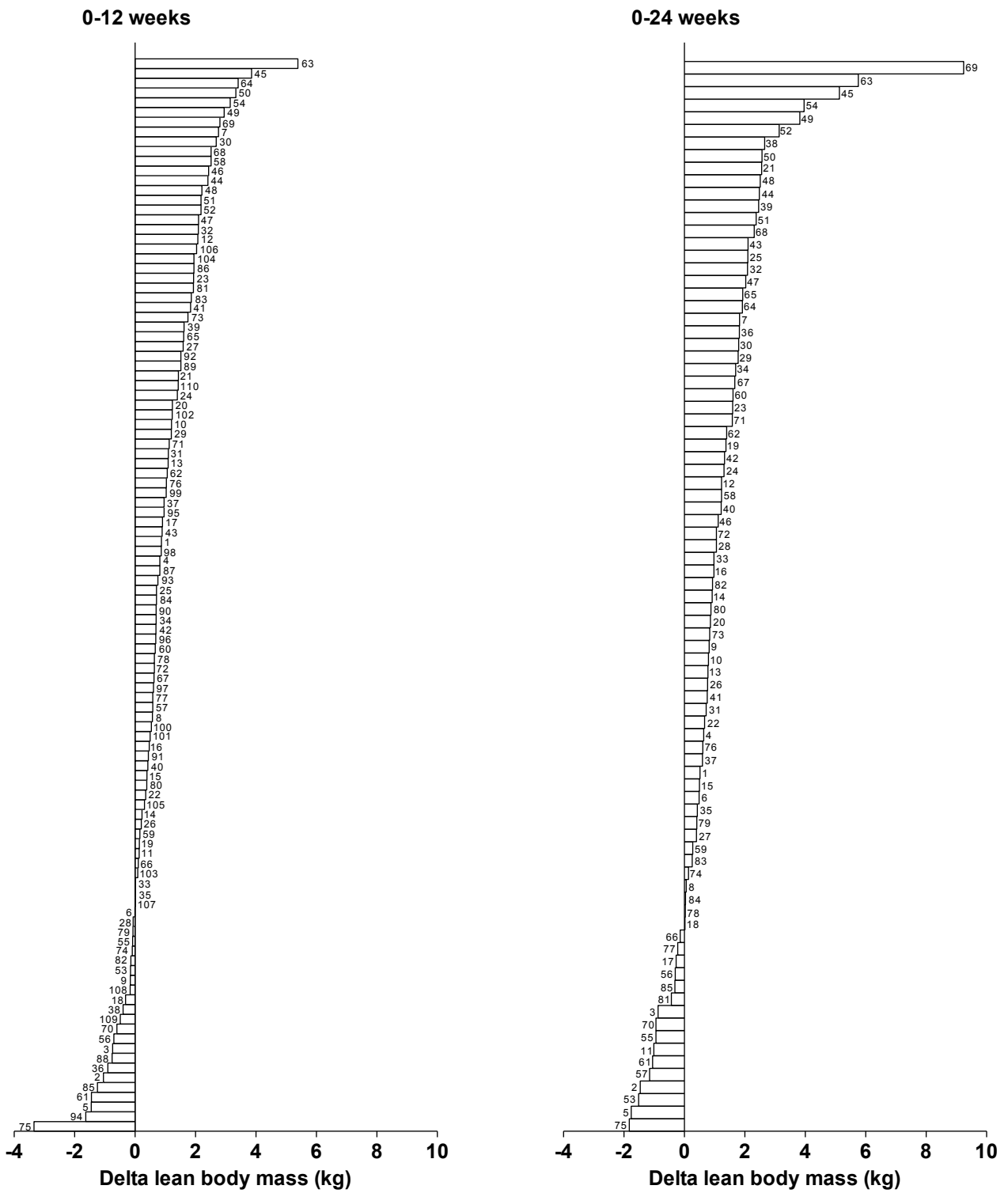


Figure 2

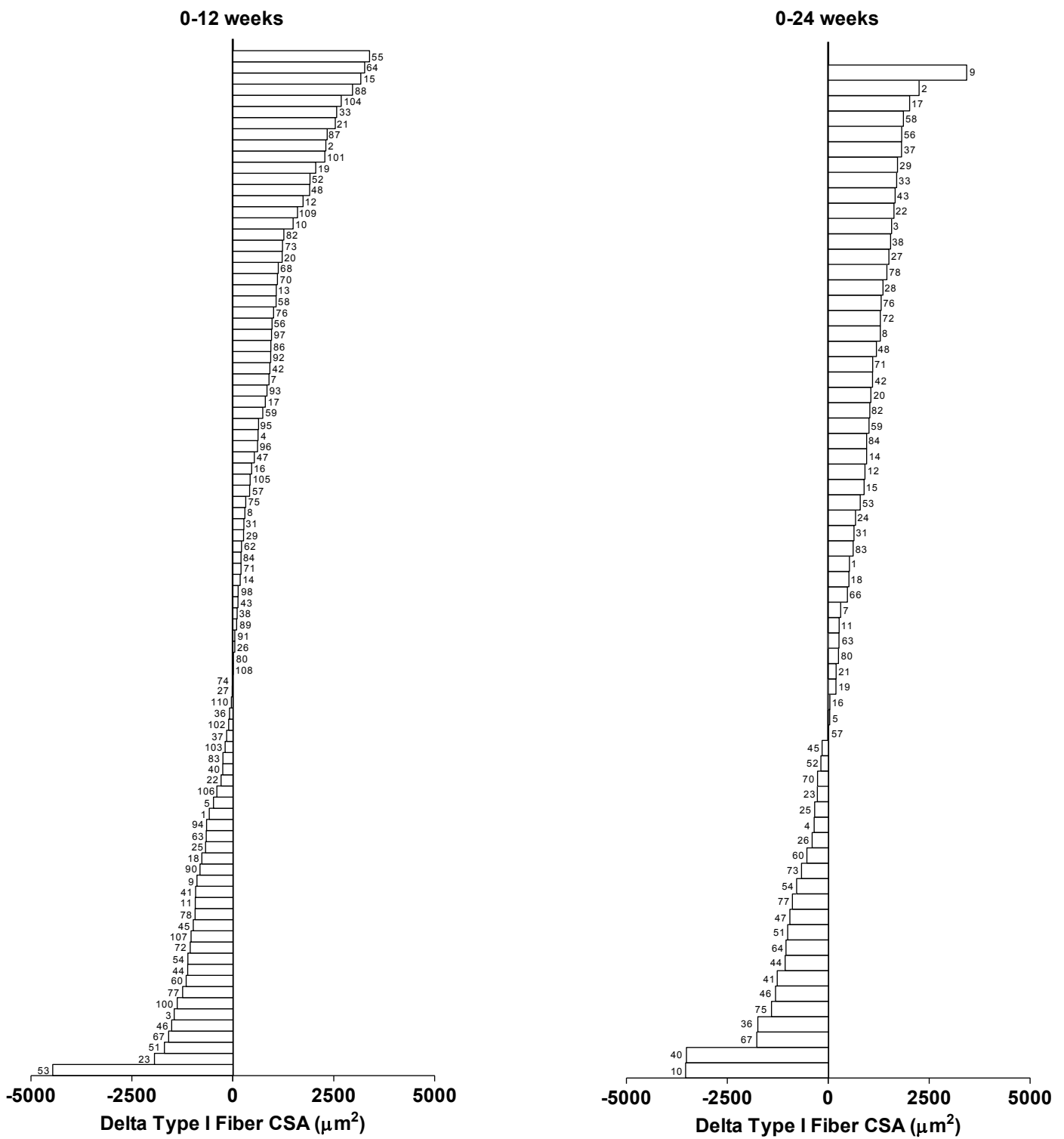


Figure 3

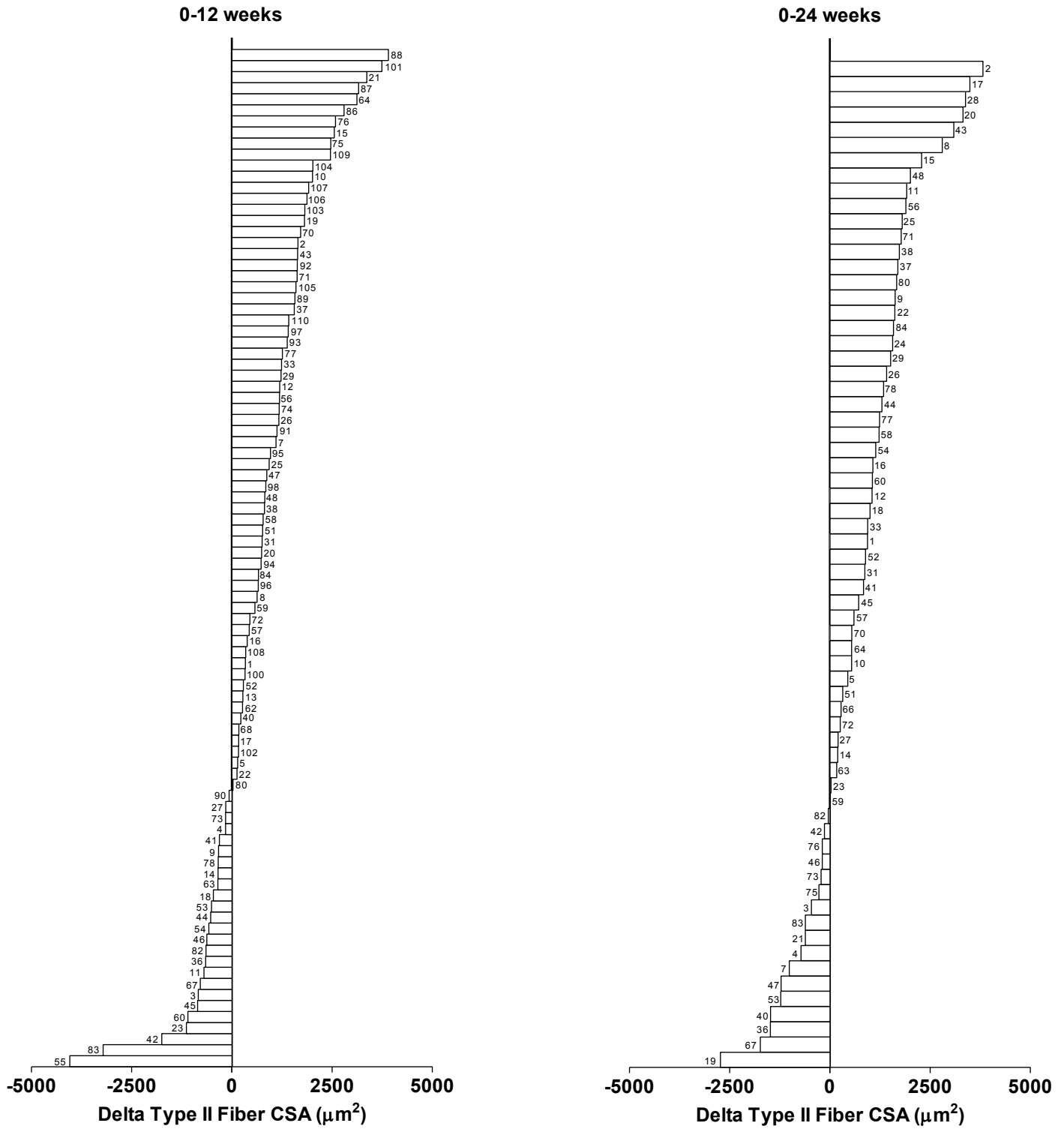


Figure 4

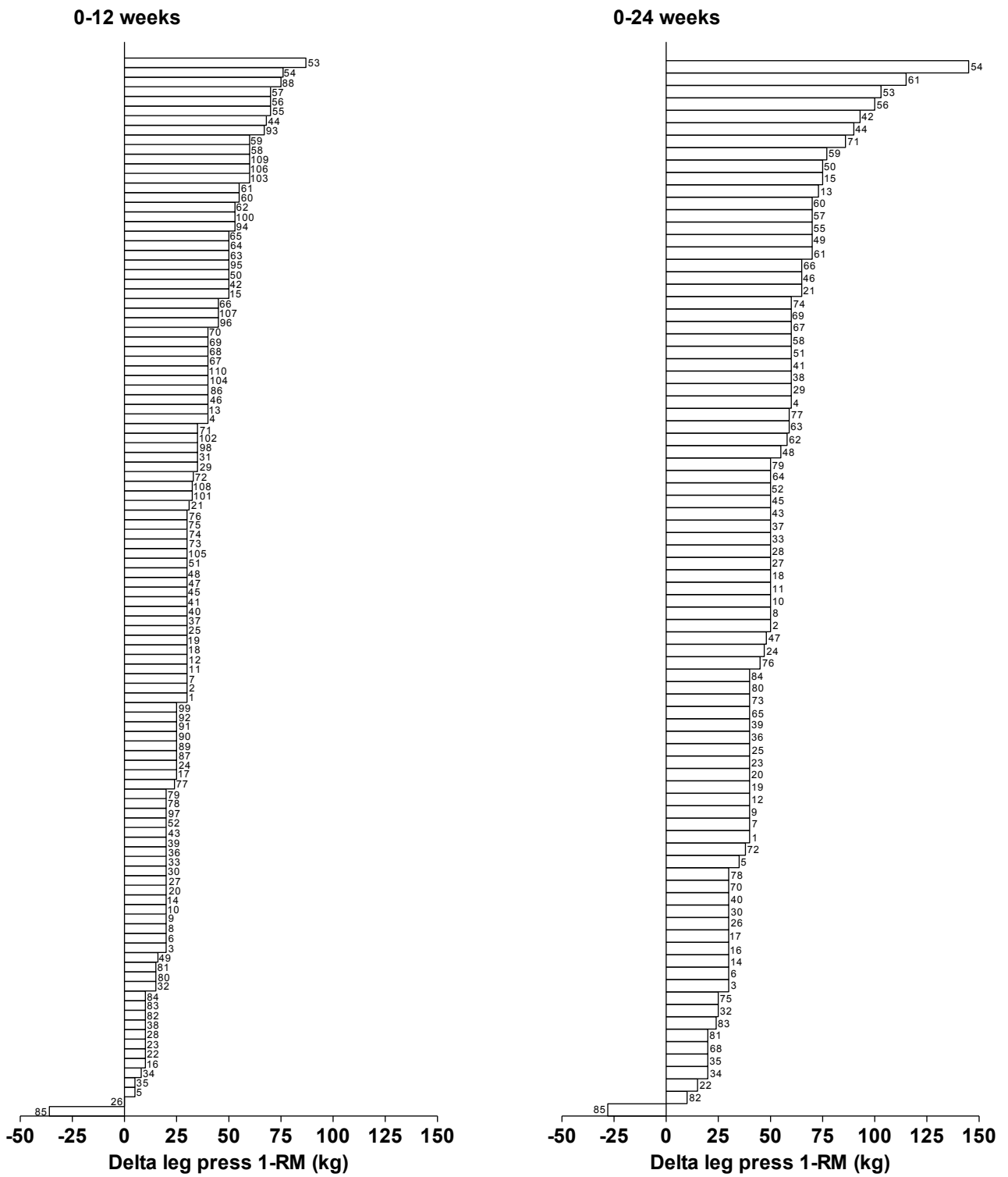


Figure 5



Figure 6

