COMPARING INDIVIDUAL MUSCLE SIZE AND STRENGTH RESPONSES IN YOUNGER AND OLDER ADULTS AFTER PROLONGED RESISTANCE TRAINING

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Master's Thesis
Science of Sport Coaching and Fitness Testing
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Spring 2021
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ABSTRACT

Vandeweerd, J. 2021. Comparing individual muscle size and strength responses in younger and older adults after prolonged resistance training. Science of Sport Coaching and Fitness Testing, Faculty of Sport and Health Sciences, University of Jyväskylä, Master's thesis, 70 pp. (1 appendix)

Several weeks of systematic resistance exercise, termed resistance training (RT), increases muscle size and strength in both younger and older adults and is recognized as a key measure towards combatting age-related neuromuscular decline. Considerable inter-individual variation exists, however, in the adaptations to RT. Whether this inter-individual variation differs between younger and older adults has not been extensively studied. Further, whether baseline characteristics such as pre-training muscle size and strength can predict individual responses to RT is not definitively known. The purpose of this study was to determine the magnitude of inter-individual variability in responses to prolonged RT, whether it differs between younger and older adults, and whether pre-training characteristics are related to an individual's responses to RT.

Data from three previous studies in untrained younger men and older men and women who performed 6-12 months of supervised, progressive, whole-body RT were pooled for this retrospective analysis. Participants (n = 156) were divided into a younger group (YOUNG, n = 65, 31.6 ± 7.0 years) and an older group (OLD, n = 91, 69.2 ± 2.7 years). Measurements of muscle size – vastus lateralis cross-sectional area (VLCSA) via ultrasound – and strength – quadriceps maximal voluntary contraction (QMVC) by isometric dynamometer – were completed pre- and post-intervention.

Relative changes in VLCSA (ΔVLCSA) were greater in YOUNG (12.8 ± 9.3 %, range: -6.0 to +40.7 %) compared to OLD (5.3 ± 13.0 %, range: -19.5 to +49.9 %) ($p < 0.001$). Ten YOUNG participants (15 %) were classified as muscle size non-responders (post-testing score below the smallest worthwhile change of the measurement) compared to fifty-eight OLD participants (64 %). There was a significant difference in the variability of muscle size changes between YOUNG and OLD ($p = 0.014$). Relative change in QMVC (ΔQMVC) did not differ between YOUNG (6.4 ± 17.3 %, range: -22.8 to +57.2 %) and OLD (9.2 ± 17.2 %, range: -43.0 to +67.8 %) ($p = 0.321$). Twenty-seven YOUNG participants (42 %) were classified as muscle strength non-responders compared to twenty-six OLD participants (29 %). The variability in muscle strength changes did not differ between YOUNG and OLD ($p = 0.802$). Smaller pre-training VLCSA was related to greater ΔVLCSA in YOUNG (r = -0.308, $p = 0.012$) but not OLD (r = -0.044, $p = 0.679$). Lower pre-training QMVC was related to greater ΔQMVC in both YOUNG (r = -0.353, $p = 0.004$) and OLD (r = -0.283, $p = 0.007$).

This investigation shows the considerable heterogeneity that exists in the muscle size and strength adaptations to RT. Older adults appear to exhibit diminished and more variable muscle size but not strength responses to RT compared to younger adults. This indicates that RT prescriptions aimed at maximizing muscle growth may need to be differentiated for older populations. Additionally, pre-training values are only weakly correlated to the RT-induced changes in muscle size and strength indicating that many other factors contribute to the inter-individual variability in muscle size and strength responses to RT.

Keywords: inter-individual variability, hypertrophy, aging, non-responders, cross-sectional area, maximal voluntary contraction

ACKNOWLEDGEMENTS

I would first like to thank all those who participated in the studies used for this thesis. While I did not get to meet any of you, your participation in research is much appreciated. Thank you also to everyone involved in the collection of this data and for permitting its use for my thesis. It certainly would not have been possible without all those involved.

I would also like to thank my brother and Ph.D. candidate at Vrije Universiteit Brussel and Université catholique de Louvain, Nathan Vandeweerd as well as my long-time friend, Dr. Danny Pincivero for their support with statistics and all things research. I'm thankful to have such a supportive network of family and friends who are always there to help when things get tough.

Last but certainly not least, I would like to thank my supervisor, Dr. Juha Ahtiainen, for taking me on as a student and supporting me throughout this process. While it would have been nice to complete our study as originally planned, the events over the last 18 months made that impossible. Thankfully, you helped find a way for me to complete this thesis on time and for that, I am forever grateful. Thank you again, Juha, I look forward to staying in touch in the future.

ABBREVIATIONS

1RM	one-repetition maximum
ALMI	appendicular lean mass index
ANCOVA	analysis of covariance
ARC	androgen receptor content
BMI	body mass index
CSA	cross-sectional area
DXA	dual-energy x-ray absorptiometry
fCSA	fiber cross-sectional area
FFM	fat-free mass
IGF-1	insulin-like growth factor 1
MN	myonuclei
MPB	muscle protein breakdown
MPS	muscle protein synthesis
mRNA	messenger ribonucleic acid
MSTN	myostatin
mTOR	mammalian/mechanistic target of rapamycin
MVC	maximal voluntary contraction
OLD	older adults (60-80 years)
QMVC	quadriceps maximal voluntary contraction
RE	resistance exercise
RT	resistance training
SC	satellite cell
SWC	smallest worthwhile change
TI	type I muscle fiber
TII	type II muscle fiber
VLCSA	vastus lateralis cross-sectional area
YOUNG	younger adults (20-45 years)
η^2p	partial eta squared

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1 INTRODUCTION

Skeletal muscle is a multi-functional organ that plays a key role in both energy metabolism and locomotion as part of the neuromuscular system (Joanisse et al., 2020). The neuromuscular system in general is extremely plastic and thus skeletal muscle mass and function are prone to positive adaptations when exposed to certain stimuli such as chronic exercise (Joanisse et al., 2020; Lavin et al., 2019). Conversely, decrements in neuromuscular function can occur as a consequence of aging, disuse, or pathology which can lead to adverse health outcomes owing to decrements in locomotive and metabolic function (McLeod et al., 2019). Indeed, in those who are sedentary, muscle mass and function progressively decrease beginning around the fifth or sixth decade of life (Lavin et al., 2019). Age-related declines in muscle size – a process known as sarcopenia – and strength are particularly worrisome given the increased risk of injury in the elderly population and the loss of independence that can occur due to frailty (Fragala et al., 2019; Lavin et al., 2019). Fortunately, even in older individuals, skeletal muscle is subject to measurable improvements in its size and function as a result of exercise interventions (Lavin et al., 2019). Resistance training (RT), repeated bouts of resistance exercise (RE), is particularly beneficial in reducing the adverse effects of aging on the neuromuscular system (Fragala et al., 2019). Unsurprisingly, increasing and preserving skeletal muscle mass and function throughout the lifespan with RT has been identified as a crucial measure towards counteracting the deleterious effects of aging and disease on overall health (McLeod et al., 2019). Recognizing this, physical activity guidelines published by exercise authorities such as the American College of Sports Medicine (ACSM) now recommend performing RE at least once per week as part of a regular exercise program for both younger and older adults (Ratamess et al., 2009). It appears, however, that the adaptations to the same RT program are not homogenous between individuals (Hubal et al., 2005). In fact, a small proportion of individuals seem to experience minimal increases or even decreases in muscle size and/or strength despite performing several months of RT (Ahtiainen et al., 2016).

Hubal et al. (2005) were some of the first to quantify the individual variability in responses to RT. They showed that relative changes in elbow flexor size and strength ranged from -2 to 59 % and -32 to 149 %, respectively, in a sample of over 500 young men and women following 12 weeks of identical upper body RT (Figure 1, Hubal et al., 2005). This range of variability has generated interest in identifying the physiological predictors of individual responses to RT.

Indeed, RT intervention studies are increasingly reporting individual response values in an attempt to identify factors that differ between individuals exhibiting varying degrees of response (e.g. Erskine et al., 2010; Mobley et al., 2018). The majority of such research has focused on RT-induced changes in muscle size rather than muscle strength. A particular focus has been placed on the relationships between individual changes in muscle size and the amount of key molecular signalling markers before training, in response to an acute bout of RE, and/or in response to RT (Joanisse et al., 2020; Roberts et al., 2018a). Several other factors, including genetic and epigenetic markers, have also been implicated in mediating the RT-induced muscle size response (Turner et al., 2019). In terms of muscle strength, it has been proposed that a combination of neural and morphological factors, including changes in muscle size, contribute to the inter-individual variability in responses to RT (Balshaw et al., 2017; Folland & Williams, 2007). A factor that has been overlooked as a predictor of muscle size and strength responses to RT, however, is their relative scores before training. Indeed, some researchers posit that lower muscle size and/or strength before initiating RT could be an indicator of enhanced responsiveness due to greater potential for adaptation (Balshaw et al., 2017; Mobley et al., 2018). Interestingly, evidence exists showing significant negative correlations between an individual's pre-training level of muscle size or strength and changes following RT (Balshaw et al., 2017; Haun et al., 2019a; Mobley et al., 2018; Newton et al., 2002). Thus, an individual's pre-training muscle size or strength may be an indirect indicator of the training responsiveness of these traits.

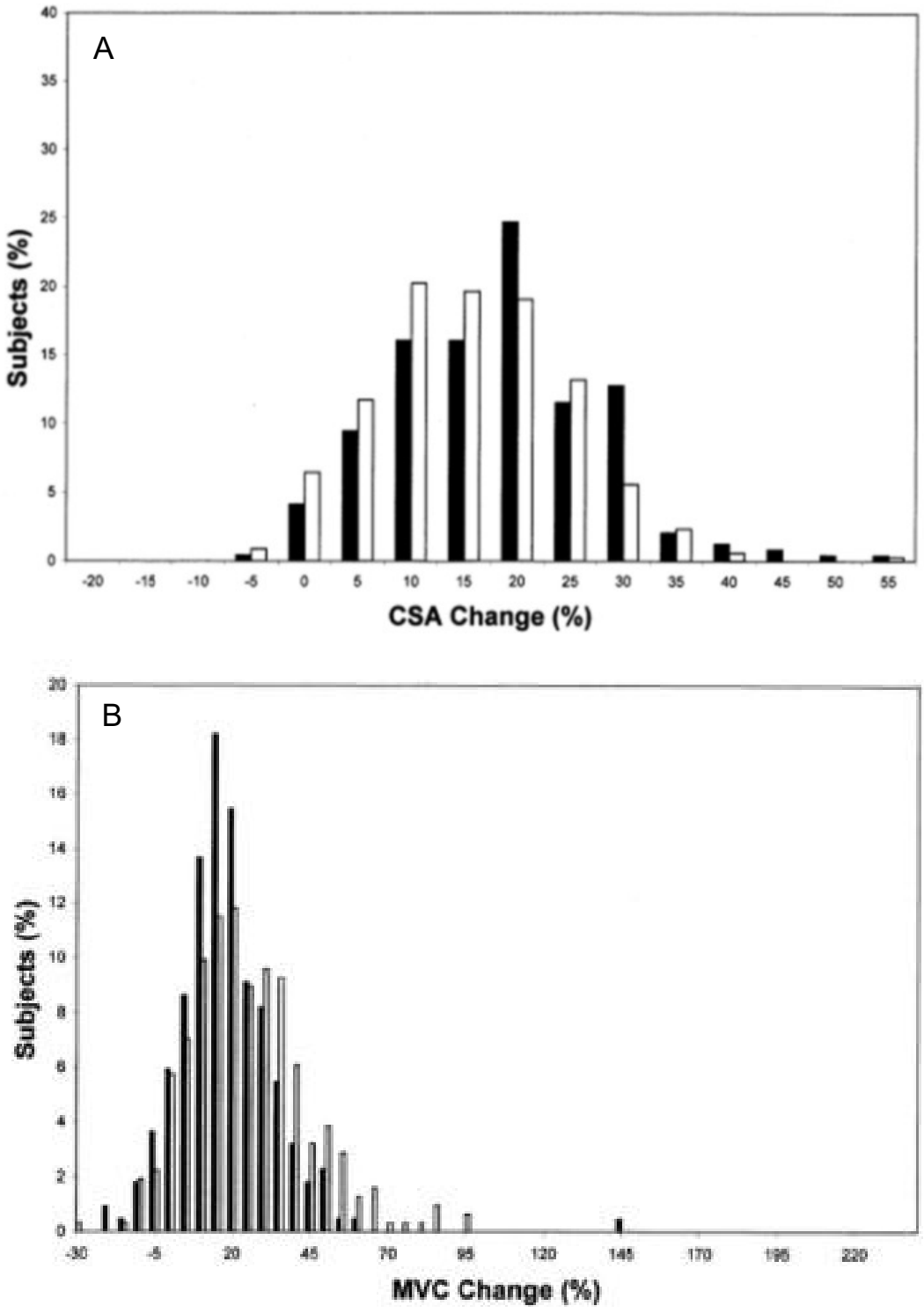

FIGURE 1 Variability in the muscle size (A) and strength (B) responses to 12 weeks of resistance training in young men (black bars) and women (white bars). CSA, cross-sectional area; MVC, maximal voluntary contraction. From Hubal et al., 2005

Older individuals, even those > 80 years, are capable of realizing marked improvements in neuromuscular function after RT (Bechshøft et al., 2017; Fragala et al., 2019). The increases in muscle mass in this population, however, tend to be less than those of younger adults following the same RT program despite similar improvements in strength (Mero et al., 2013; Walker & Häkkinen, 2014). This indicates that the neuromuscular adaptations to RT may differ between younger and older adults (Walker & Häkkinen, 2014). Heterogeneity in RT responses has also been observed in older individuals (Ahtiainen et al., 2016; Churchward-Venne et al., 2015; Stec et al., 2017). While some have shown that the variability in muscle size and strength responses is similar between younger and older adults (Ahtiainen et al., 2016), others posit that older participants may be more likely to exhibit negative or "non" responses compared to younger participants, at least in terms of muscle growth (Bamman et al., 2007; Stec et al., 2017). Several mechanisms related to the onset of sarcopenia in aging muscle likely contribute to the diminished capacity for muscle growth in older individuals, and potentially an increased propensity to respond negatively (Fragala et al., 2019; Lavin et al., 2019). Interestingly, these mechanisms may coincide with the molecular signalling markers that have been proposed to mediate the individual muscle growth response to RT (Blocquiaux et al., 2020; Stec et al., 2016, 2017). Hence, the mechanisms responsible for sarcopenia and the blunted RT-induced muscle growth in older individuals may similarly demarcate muscle growth responsiveness in younger individuals (McGlory & Phillips, 2015).

2 RESISTANCE TRAINING ADAPTATIONS

2.1 Changes in muscle size

It is well known that RT increases skeletal muscle size in the majority of individuals regardless of sex, age, and in most cases, health status (Folland & Williams, 2007; McLeod et al., 2019). Muscle growth occurs through a process known as (skeletal muscle) hypertrophy – an increase in whole muscle size and/or the muscle fibers contained within it (Haun et al., 2019b). While some use measures of whole-body muscle or lean tissue mass as a marker of global hypertrophy (determined via dual-energy x-ray absorptiometry [DXA]), measures of individual muscles and/or muscle fibers are more typically used to assess adaptations in the muscle(s) used during training (Haun et al., 2019b). Individual muscle size is usually measured by medical imaging techniques such as magnetic resonance imaging (MRI) or ultrasound to determine a muscle's thickness, cross-sectional area (CSA), or volume. Muscle fiber size, on the other hand, is assessed through direct measurement of single muscle fibers from muscle tissue biopsies (Haun et al., 2019b). It is generally thought that an increase in the size and/or number of contractile muscle proteins (myofibrils) within individual skeletal muscle fibers results in the expansion of the fibers they are contained within and eventually an increase in whole-muscle CSA (Haun et al., 2019b). In general, RT periods of at least 6 weeks are required to induce measurable amounts of skeletal muscle growth in untrained individuals (Figueiredo, 2019), after which gains tend to be linear for at least several months (Folland & Williams, 2007). Thus, interventions aiming to induce skeletal muscle hypertrophy should be several months in duration to maximize this response.

Research into the RT-induced hypertrophic response shows that specific stimuli are responsible for initiating the processes involved in skeletal muscle growth (Wackerhage et al., 2019). These include 1) mechanical stress, whereby modulators within and surrounding the muscle fibers, sensitive to mechanical tension, are stimulated in response to an external load, this activates signalling mechanisms that initiate the growth response; 2) muscle damage, whereby exercise-induced damage to the contractile elements and cytoskeleton, particularly as a result of eccentric (lengthening) contractions, results in an acute inflammatory-like response driving growth factors to the damaged muscle for repair while also serving as stimuli for upstream hypertrophic regulators; and 3) metabolic stress, whereby a series of submaximal contractions

result in the depletion of anaerobic energy stores and the concomitant build-up of metabolites within the muscle, both of which could serve as hypertrophic signals (Schoenfeld, 2010; Wackerhage et al., 2019). While the evidence for mechanical stress in the initiation of hypertrophic mechanisms is abundant, there is little evidence that muscle damage or metabolic stress play any role in hypertrophy independent of mechanical stress (Joanisse et al., 2020; Wackerhage et al., 2019). Despite much research on the topic, there is also little evidence that manipulating RT variables such as load, weekly frequency, or contraction type, alters the hypertrophic response given that adequate levels of weekly volume (total number of repetitions and/or sets per muscle group) and, most importantly, intensities of effort are achieved during each RT session (Morton et al., 2019). Thus, researchers posit that mechanical stress represents the primary hypertrophy stimulus, and the manipulation of RT variables in an attempt to increase the level of muscle damage and/or metabolite accumulation does not support additional increases in skeletal muscle hypertrophy (Morton et al., 2019; Wackerhage et al., 2019).

2.2 **Changes in muscle strength**

Increases in muscle strength are perhaps the most recognizable outcome of RT and are readily observable within the first few weeks of RT in untrained participants, a much faster rate of increase than that seen for muscle size (Figure 2, Moritani & DeVries, 1979). Muscular strength is defined as the amount of force one can exert under a given set of conditions and has been shown to improve following RT interventions regardless of sex, age, and health status (Folland & Williams, 2007; Jaric, 2002; McLeod et al., 2019). While there are several ways to measure muscular strength, typically one-repetition maximum (1RM) testing and/or isometric testing is used (Jaric, 2002). In 1RM testing, an individual performs a dynamic resistance exercise (e.g., the barbell back squat) with a load that only allows the completion of a single repetition. During isometric strength testing, the individual contracts against an immovable resistance (usually a dynamometer), and their maximal force output, termed maximal voluntary contraction (MVC), is measured (Jaric, 2002). Training-induced increases in strength can be attributed to several neurological and morphological factors (Folland & Williams, 2007). It is posited that neurological mechanisms such as increased motor unit activation and firing rate of the agonist muscle(s), increased spinal excitability, and decreased co-activation of the antagonist muscle(s) are the primary drivers of increases in muscle strength with RT, at least early after its initiation (Folland & Williams, 2007; Moritani & DeVries, 1979). While some propose that skeletal muscle hypertrophy also plays a role in RT-induced strength increases due to an increase in the

number and parallel arrangement of contractile fibers (Folland & Williams, 2007), others have questioned this theory, showing that substantial increases in strength can occur with long-term RT despite minimal increases in muscle size (Loenneke et al., 2019). The debate as to whether RT-induced hypertrophy contributes to increases in muscle strength is ongoing. Similar to RT-induced hypertrophy, there is ample research examining the factors that maximize muscular strength adaptations to RT. In untrained individuals, it appears that training specificity and load are the primary mediators of strength improvements (Morton et al., 2019). Indeed, individuals who use loads that are similar or equal to their 1RM and exercises that are similar to those that are tested are more likely to increase strength in a given movement than those who do not (Morton et al., 2019). Thus, if a goal of RT is to increase strength, relatively heavy loads ($\geq$ 85 % 1RM) and exercises similar to the tested movement(s) should be prescribed (Morton et al., 2019; Ratamess et al., 2009).

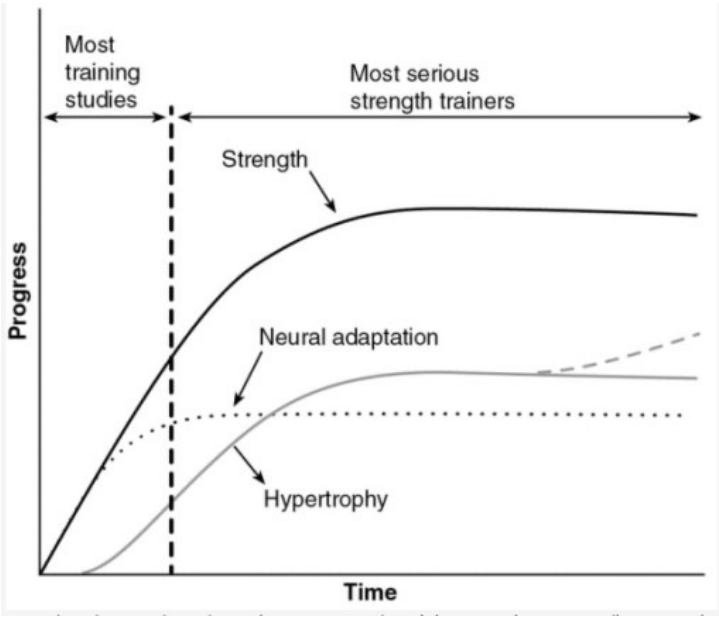

FIGURE 2. Strength and hypertrophy adaptations to resistance training over time. Adapted from Moritani & DeVries (1979)

3 MECHANISMS REGULATING RESISTANCE-TRAINING ADAPTATIONS

The sections below will briefly discuss some of the mechanisms implicated in RT adaptations and how they are affected by age. Since the majority of individual response research has focused on the variability in RT-induced hypertrophy and since muscle size changes may also play a role in individual strength responses to RT (Balshaw et al., 2017; Erskine et al., 2014), the focus will be on the muscle size adaptive responses to RT.

3.1 **The role of protein turnover**

Human skeletal muscle mass is tightly regulated by the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB) (McGlory et al., 2017). Put simply, if the level of MPS exceeds that of MPB for an extended period, muscle growth will occur (Joanisse et al., 2020). In response to anabolic stimuli, such as mechanical load and/or protein consumption, there is a transient increase in MPS and, to a lesser extent, MPB (Joanisse et al., 2020). Since increases in MPB can be attenuated by adequate post-exercise protein consumption, consistent transient increases in MPS and positive net protein balance over several weeks leads to muscle protein expansion and increases in muscle size (Joanisse et al., 2020; McGlory & Phillips, 2015). In older individuals, there is evidence that the RE-induced MPS response is lower compared to younger individuals (Kumar et al., 2009). This indicates that a so-called "anabolic resistance" develops as we age, potentially limiting RT-induced hypertrophy (Hodson et al., 2019). Brook et al. (2016) supported this when they showed that reduced MPS partly explained lower levels of hypertrophy in older, compared to younger, men after 6 weeks of RT.

While some studies point to a connection between the acute MPS response following a RE session and post-RT hypertrophy (Burd et al., 2010; Mitchell et al., 2012), others, have reported no such relationship (Brook et al., 2016; Mayhew et al., 2009; Mitchell et al., 2014). In untrained participants, both Damas et al. (2016) and Reidy et al. (2017) showed that while the acute post-RE MPS response in the first week of RT did not correlate with individual hypertrophy responses, the response following several weeks of training did. They concluded that at the onset of RT, the initial role of the post-exercise MPS response is to attenuate and repair muscle damage; once individuals are habituated to the RT program and the muscle

damage response is attenuated, however, the role of MPS shifts to one of muscle growth (Figure 3, Damas et al., 2016; Reidy et al., 2017). A more recent study failed to replicate these results in a trained population, however (Damas et al. 2019). Hence, untrained individuals who exhibit an increased post-exercise MPS response, following training habituation, are likely to see greater gains in muscle mass than those who do not. This relationship in trained individuals, however, is unclear.

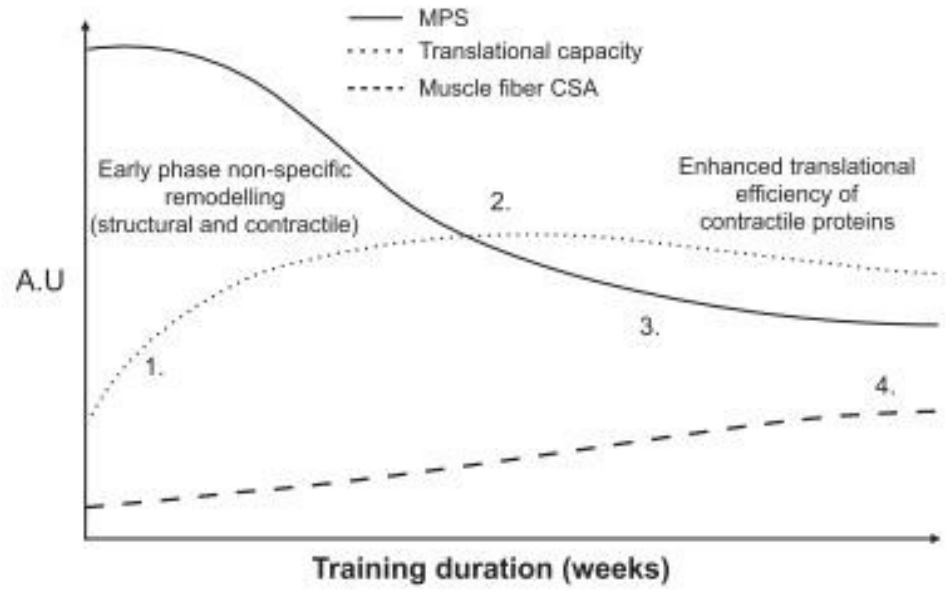

FIGURE 3. Changes in muscle protein synthesis (MPS), translational capacity (ribosome biogenesis) and muscle fiber cross-sectional area (CSA) in response to resistance training. Initial increases in MPS are a biological response to support remodelling of damaged muscle protein and eventually muscle hypertrophy. 1: Early increases in MPS are sustained partly by concomitant elevated translational capacity to support the remodelling of damaged structural and contractile elements of the muscle. 2: After the attenuation of exercise-induced muscle damage, there is a reduction in contribution of MPS to the remodelling of proteins caused by exercise-induced muscle damage. 3-4: After several weeks of resistance training, the rates of MPS are subsequently regulated by the adaptive increase in translational efficiency resulting in a detectable increase in skeletal muscle size and mass. A.U., arbitrary units. From McGlory et al. (2017)

3.2 **Mammalian/mechanistic target of rapamycin complex 1 (mTOR)**

The multi-protein subunit mammalian/mechanistic target of rapamycin complex 1 (mTOR), located within the lysosome of skeletal muscle cells, is recognized as a potent mediator of mechanical loading-induced skeletal muscle hypertrophy due to its essential role in increasing MPS (Ahtiainen, 2019; McGlory & Phillips, 2015). Interestingly, the pharmacological downregulation of mTOR almost completely abrogates the hypertrophic response following several weeks of RT (Schiaffino et al., 2013). The mechanisms by which mTOR is stimulated and subsequently activates MPS leading to muscle hypertrophy have been explored in great detail (Goodman, 2019). Briefly, upon the arrival of an anabolic stimulus such as mechanical loading or the ingestion of protein, several upstream regulators of mTOR are activated, mediated in part by hormones such as insulin-like growth factor-1 (IGF-1). Their activation stimulates the phosphorylation of mTOR which then activates downstream protein kinases; these collectively initiate the processes involved in MPS, mainly messenger ribonucleic acid (mRNA) translation (Goodman, 2019). mTOR activation appears to be blunted in older, compared to younger individuals following an acute bout of RE concomitant with a diminished MPS response (Fry et al., 2011). Interestingly, Greig et al. (2011) observed that reduced post-RE mTOR upregulation in older vs. younger women partly explained the diminished hypertrophy in the older group following 12 weeks of RT. Thus, age-related deficits in mTOR activation likely contribute to the reduced hypertrophic capacities of older individuals.

Downstream targets of mTOR have been implicated in individual response research based on their roles in initiating mRNA translation and the hypothesis that increases in their activity indicates increased mTOR activation (Roberts et al., 2018a). Several studies have shown significant correlations between the amount of hypertrophy following RT and the level of activation of mTOR and/or its downstream targets following an acute bout of RE in both younger and older individuals (Mayhew et al., 2009, 2011; Mitchell et al., 2013, 2014; Terzis et al., 2008). Others, however, have failed to replicate this, showing no differences in the post-RE levels of these markers between different hypertrophic responders (Figueiredo et al., 2015; Haun et al., 2019a; Phillips et al., 2013; Stec et al., 2016). Thus, similar to the acute MPS response, changes in markers of mTOR activation following acute bouts of RE may not be indicative of the long-term hypertrophic response (McGlory & Phillips, 2015).

3.3 **Ribosome biogenesis**

During MPS, the genetic codes of pre-existing proteins are first copied (transcribed) into mRNA within the nucleolus of the muscle cell; this mRNA is then translocated to a ribosome where the genetic code is read and translated into new proteins (Hodson et al., 2019). Increases in the number of ribosomes within the nucleus, termed translational capacity or ribosome biogenesis, increases the myocyte's capacity to synthesize new proteins (i.e., increase MPS). Ribosome biogenesis represents the primary adaptation in mRNA translation during RT (Joanisse et al., 2020; McGlory & Phillips, 2015; Roberts et al., 2018a). Given the contribution of ribosome biogenesis to MPS, it is no surprise that impaired ribosome biogenesis has also been implicated in the diminished hypertrophic capacity of older individuals (Stec et al., 2015). Indeed, ribosome biogenesis appears to be blunted in older compared to younger adults following an acute bout of RE which may affect RT-induced hypertrophy (Stec et al., 2015). This was shown in the aforementioned Brook et al. (2016) study who demonstrated that, along with deficits in MPS, reduced ribosome biogenesis in older vs. younger subjects was concomitant with decreased hypertrophy.

Unsurprisingly, researchers have posited that an individual's translational capacity could be indicative of their hypertrophic capabilities (Joanisse et al., 2020; Roberts et al., 2018a). This is supported by many studies showing that individual variation in the number of ribosomes or ribosomal RNA, either at baseline or in response to RT, correlates well with the individual variation in hypertrophy following RT in both younger (Figueiredo et al., 2015; Mobley et al., 2018; Reidy et al., 2017; Roberts et al., 2018b) and older (Stec et al., 2016), untrained individuals. Data from trained individuals, however, shows no such relation (Fyfe et al., 2018; Haun et al., 2019a), perhaps indicating a ceiling effect for ribosome biogenesis. Interestingly, recent work by Hammarström et al. (2020) showed that increased RT volumes (as is typically required to induce hypertrophy) increased the level of ribosome biogenesis, and this correlated highly with the individual hypertrophic response, albeit in untrained individuals. Given the preponderance of evidence showing a correlation between individual differences in ribosome biogenesis and individual differences in RT-induced hypertrophy, altered ribosome biogenesis likely explains at least some of the individual variability in hypertrophic responses in untrained individuals.

3.4 **Satellite cells and myonuclei**

Satellite cells (SCs) are considered the "stem cells" of muscle for their ability to donate cells for muscle growth (Ahtiainen, 2019; Joanisse et al., 2020). Myonuclei (MN), located within SCs and along the periphery of myofibers, contain the genetic code for muscle proteins (Ahtiainen, 2019). Both SCs and MN have been shown to play key roles in exercise-induced hypertrophy (Blaauw & Reggiani, 2014). In response to mechanical stimuli and/or muscle damage, existing MN within the myofiber are stimulated and begin the processes of MPS eventually leading to muscle fiber hypertrophy (Wackerhage et al., 2019). The myonuclear domain theory, however, posits that MN can only regulate fibers of a specific size. For further hypertrophy, SCs, similarly activated by mechanical stress or muscle damage, proliferate to the myofiber and donate additional MN (Joanisse et al., 2020). Some researchers posit that SC-mediated MN addition is required for hypertrophy based on observations that increases in SCs and/or MN occur in concordance with muscle hypertrophy following RT programs (Blaauw & Reggiani, 2014; Murach et al., 2018b). Others, however, question this hypothesis and have shown hypertrophy in the absence of increases in SCs (Herman-Montemayor et al., 2015; Murach et al., 2018a; Petrella et al., 2006; Verdijk et al., 2009). In agreement with the myonuclear domain theory, some reports show evidence of a hypertrophic threshold whereby myonuclear addition only occurs once a certain amount of muscle growth (~26%) has occurred (Kadi et al., 2004b; Petrella et al., 2006). While this was refuted by Conceição et al. (2018) who showed that myonuclear addition occurs even during lower levels of hypertrophy ($\leq$ 10%), they noted that myonuclear addition was robustly higher when hypertrophy reached levels > 22%. This could indicate a dose-response relationship between MN and hypertrophy. Continuing the trend for older individuals exhibiting lower levels of X compared to younger individuals, older adults tend to have lower SC/MN counts compared to younger adults (Kadi et al., 2004b). Further, SC-mediated myonuclear addition is lower during RT in older, compared to younger adults and this is concomitant with blunted hypertrophy (Petrella et al., 2006, 2008). Thus, age-related deficits in SC and MN activity appear to limit hypertrophy in older individuals.

An overwhelming amount of evidence points to a mediating role of SCs and MN in the individual hypertrophic response (Joanisse et al., 2020; Roberts et al., 2018a). Indeed, several studies have shown strong correlations between the individual hypertrophy response and SC and MN counts at pre-training, following an acute bout of RE, and/or in response to weeks of RT in younger and older adults (Bellamy et al., 2014; Kadi et al., 2004a; Petrella et al., 2008;

Snijders et al., 2016). Similar to the early post-exercise MPS response, Damas et al. (2018a) suggested that early post-exercise SC proliferation could be more indicative of a muscle-damage rather than growth response, given the sensitivity of SCs to muscle damage. Interestingly, when measuring the acute post-exercise satellite cell proliferation after habituating subjects to the RE stimulus and attenuating muscle damage, they found no correlation with the eventual hypertrophic response (Damas et al., 2018a). This indicates that baseline SC levels rather than their response to training may be more indicative of the individual hypertrophy response. That is, individuals with higher amounts of SCs at the onset of RT are likely to exhibit a greater hypertrophic response than those with less (Joanisse et al., 2020).

3.5 **Hormonal regulation**

Given their roles in maturation-related skeletal muscle growth, traditional dogma held that anabolic hormones such as testosterone, growth hormone, and IGF-1 played integral roles during RT-induced hypertrophy by increasing MPS (McGlory & Phillips, 2015). Recent work has shown however that, in the absence of supraphysiological doses of these hormones, like that seen during anabolic steroid use, they may play more of a regulatory role (Ahtiainen, 2019). Indeed, there is little evidence that systemic or post-RE elevations in testosterone, growth hormone, or IGF-1 are correlated with, or potentiate, RT-induced hypertrophy (Joanisse et al., 2020; McGlory & Phillips, 2015; Mitchell et al., 2013). Despite this, IGF-1 has received considerable attention in individual response research given its role in increasing MPS through mTOR stimulation and SC proliferation (Ahtiainen, 2019; Roberts et al., 2018a; Schiaffino et al., 2013). IGF-1 appears to be lower in older vs. younger individuals (Petrella et al., 2006) and some studies show a greater upregulation in IGF-1 mRNA following RT in high versus low hypertrophic responders, regardless of age (Bamman et al., 2007; Davidsen et al., 2011). While this could indicate increased hypertrophic signalling in higher responders, the causal direction between IGF-1 mRNA and mTOR/SC activation is unknown (Roberts et al., 2018a).

Interestingly, there is evidence that possessing a higher proportion of anabolic hormone receptors (androgen receptors), regardless of circulating hormone levels, could predispose an individual to higher levels of hypertrophy (Joanisse et al., 2020). This theory postulates that increased uptake of androgen hormones into the muscle indicates a higher anabolic state and greater potential for growth (Roberts et al., 2018a). Both Ahtiainen et al. (2011) and Mitchell et al. (2013) showed that increases in androgen receptor content (ARC) correlated with

increases in muscle fiber cross-sectional area (fCSA) following RT. Importantly, Ahtiainen et al. (2011) also showed that ARC did not differ between younger and older participants before training indicating that age may not affect ARC. Recent work from Michael Roberts' lab, showed no differences in the changes in ARC between high versus low hypertrophic responders (Haun et al., 2019a; Mobley et al., 2018). In contrast, Morton et al. (2018b) showed that changes in ARC correlated with muscle mass increases during 12 weeks of RT in a highly trained population. Importantly, they also showed strong correlations between pre-training ARC and eventual hypertrophy, indicating that baseline ARC could be the more important mediator of hypertrophy rather than change with training (Morton et al., 2018b).

Another hormone that has been studied extensively in hypertrophy and aging research is myostatin (MSTN) due to its inhibitory role in mTOR activation (Roberts et al., 2018a; Schiaffino et al., 2013). Lower levels of MSTN mean less mTOR inhibition (i.e. more activation) and, subsequently, increased muscle growth (Ahtiainen, 2019). MSTN levels have been shown to downregulate both acutely following a RE bout as well as chronically following RT (Roberts et al., 2018a). However, the majority of individual-response studies have reported that MSTN and/or its mRNA before and after RT do not correlate with post-training hypertrophy (Bellamy et al., 2014; Brook et al., 2016; Kim et al., 2007; Mobley et al., 2018; Phillips et al., 2013; Thalacker-Mercer et al., 2013). Thus, individual variation in MSTN likely does not contribute to hypertrophic variation. The role of MSTN in aging has yet to be fully elucidated (White & Lebrasseur, 2014).

Lastly, there is evidence that certain pro-inflammatory hormones or cytokines such as interleukin-6 (IL-6) or tumour necrosis factor-alpha (TNF-α) could mediate hypertrophic responses via their roles in MPB (Roberts et al., 2018a; Schiaffino et al., 2013). While high-volume RE induces low levels of local muscular inflammation which is likely required to repair damaged muscle tissue post-RE (Wackerhage et al., 2019), the majority of evidence points to an increased downregulation of inflammatory markers post-RE correlating with greater muscle growth (Mobley et al., 2018; Raue et al., 2012; Thalacker-Mercer et al., 2013). This indicates that those who can more adequately blunt the post-RE inflammatory response, are primed for greater muscle growth during RT. Interestingly, the muscles of older individuals may exhibit heightened inflammatory markers both at rest and in response to RE (Merritt et al., 2013). Increased inflammation in older individuals could limit their hypertrophic capacity (Stec et al., 2017), though further research is required to confirm this. Nonetheless, Mitchell et al. (2013),

showed that individuals who exhibited the largest post-RE increases in IL-6 also showed the highest levels of muscle fiber growth following 12 weeks of RT. Others have shown no differences in inflammatory cytokines or their mRNA between high and low hypertrophic responders to RT (McMahon et al., 2019; Mobley et al., 2018; Riechman et al., 2004). Thus, the role of inflammatory hormones in individual hypertrophic responses requires further investigation.

4 OTHER FACTORS IMPLICATED IN INDIVIDUAL RESPONSES

4.1 Fiber-type distribution

Human skeletal muscles are classified into two main fiber types based on their relative proportions of myosin heavy chain polymorphisms which determine their phenotypic characteristics (Ahtiainen, 2019). Type I (slow-twitch) fibers, characterized by high mitochondrial density and capillarization, are associated with an endurance phenotype while type II (fast-twitch) fibers, characterized by their larger CSAs and faster shortening velocities, are associated with a strength/speed phenotype (Ogborn & Schoenfeld, 2014). An individual's predominant fiber type has been shown to differ between those competing in different sports (Ogborn & Schoenfeld, 2014). Indeed, endurance athletes tend to have higher proportions of type I (TI) fibers while strength and speed athletes tend to have higher proportions of type II (TII) fibers (Roberts et al., 2018a). In terms of aged muscle, while there is a gradual decrease in overall fiber number, reductions are similar between fiber types (Deschenes, 2004; Lexell et al., 1988). Thus, while older individuals generally possess lower numbers of muscle fibers, explaining their smaller muscle sizes compared to younger individuals, their proportions of TI to TII fibers are similar (Deschenes, 2004; Lexell et al., 1988).

While some researchers posit that TII fibers respond better to RT (i.e. grow more) than TI fibers (Folland & Williams, 2007), a more recent review refutes this, showing equivalent hypertrophy between TI and TII fibers following RT (Ogborn & Schoenfeld, 2014). This may differ in older individuals, however, as some have shown hypertrophy in TII but not TI muscle fibers following RT (Verdijk et al., 2009). Nonetheless, given the association between TII phenotypes and strength sports, it has been hypothesized that individuals with a higher proportion of TII fibers experience greater muscle growth during RT (Roberts et al., 2018a). Studies in untrained individuals, however, challenge this theory, showing that pre-training fiber-type distribution did not differ between high versus low hypertrophic responders in younger, or older individuals (Bamman et al., 2007; Mobley et al., 2018; Stec et al., 2016). On the other hand, Haun et al. (2019a) recently showed that TII fiber proportion was one of the best predictors of hypertrophy following 6 weeks of RT in a group of well-trained young men. The effect of training status could indicate that a high proportion of TII fibers potentiates RT-induced hypertrophy only

once a certain level of muscle growth has occurred. More research is required, however, to substantiate this.

4.2 **Genetic and epigenetic markers**

Ten years ago, Bouchard et al. (2011) used genome-wide association techniques to determine that genetics account for almost 50% of the variance in the maximal oxygen uptake (VO_2max) response to endurance training. Until recently, a similar genome-wide study on RT-induced hypertrophy had yet to be published. However, a pair of recent studies using transcriptome-wide DNA methylation techniques identified a multitude of genetic and epigenetic markers associated with skeletal muscle mass adaptations to RT (Seaborne et al., 2018; Turner et al., 2019). Preceding these investigations, several studies in both younger and older populations had identified specific genes or epigenetic markers that differentiated between those with divergent muscular phenotypes and/or those with differing responses to RT (Bellamy et al., 2014; Damas et al., 2018b; Kostek et al., 2005; Li et al., 2014; Norman et al., 2014; Phillips et al., 2013; Popadic Gacesa et al., 2012; Raue et al., 2012; Riechman et al., 2004; Roberts et al., 2018b; Thalacker-Mercer et al., 2013). While an in-depth discussion of all genes associated with RT-induced hypertrophy is beyond the scope of this text (see Seaborne et al., 2018 and Turner et al., 2019), these studies indicate that, similar to the VO_2max response, genetics likely account for a significant proportion of the variance in hypertrophic adaptations to RT (Roberts et al., 2018a). It should be noted, however, that the genetic and epigenetic interactions during muscle size adaptations are still poorly understood and individuals are likely to display a range of genes coding for a range of responses that have yet to be elucidated (Roberts et al., 2018a). Interestingly, some have proposed that the processes underlying RT-induced hypertrophy and sarcopenic muscle loss are similar (McGlory & Phillips, 2015). Phillips et al. (2013) investigated this theory and found that, while some overlap existed, the genetic biomarkers activated in response to RE coding for muscle growth were mostly distinct from those involved in muscle aging. This indicates that RT-induced hypertrophy and age-related muscle loss are two distinct processes (Phillips et al., 2013).

4.3 **Vascular and mitochondrial characteristics**

Given that repeated high-intensity contractions result in the rapid depletion of muscle glycogen due to anaerobic glycolysis, skeletal muscle plays a key role in metabolism and has been shown

to account for up to 80% of insulin-mediated blood glucose uptake (Ahtiainen, 2019; Joanisse et al., 2020). As a result, chronic RT leads to increases in muscle glycogen and other anaerobic substrate stores with concomitant increases in the activity of mitochondrial enzymes involved in anaerobic glycolysis. Chronic RT is also associated with increased capillarization of the involved muscle(s) as well as increased activity (but not density) of mitochondrial enzymes involved in aerobic metabolism. These adaptations indicate that chronic RT improves muscular metabolic function by increasing nutrient delivery, uptake, and handling (Ahtiainen, 2019; Roberts et al., 2018a). Further, since MPS is an energy-depleting process, some researchers have proposed that increases in muscle mitochondrial number, activity, or capillarization could be responsible for enhanced RT-induced hypertrophy by increasing the amount of energy available for this process (Roberts et al., 2018a). This is perhaps more important in older individuals as they have been shown to exhibit lower muscle capillarization compared to their younger counterparts (Ryan et al., 2006). Interestingly, the above-mentioned study by Phillips et al. (2013) showed a greater upregulation of genes coding for angiogenesis in higher compared to lower hypertrophic responders in a combined cohort of younger and older individuals. More recently, a trio of studies in older individuals showed a correlation between RT-induced hypertrophy and muscle capillary density at baseline (Snijders et al., 2017) and in response to training (Nederveen et al., 2017; Verdijk et al., 2016). This has yet to be confirmed in younger individuals, however. In terms of mitochondrial adaptations, Roberts et al. (2018b) showed that high hypertrophic responders may exhibit greater pre-training mitochondrial volumes than low responders as demonstrated by higher citrate synthase activity levels. Haun et al. (2019a) failed to replicate this finding. Thus, muscle capillarization may play an important role in the hypertrophic response to RT, at least in older subjects. More research is required, however, to determine the hypertrophic role of capillarization in younger cohorts and whether mitochondrial density and/or activity also contributes.

5 PREDICTABILITY OF PRE-TRAINING CHARACTERISTICS

5.1 **Pre-training muscle size**

Table 1 presents a summary of the evidence for the factors implicated in underpinning the variability in muscle size responses to RT and their effects due to aging so far. Evidence for the majority of these factors is conflicting or is still yet to be investigated. Nonetheless, several factors that show promise as predictors of the individual response are those that are already present at the onset of training (i.e. SC/MN counts, ARC, genetic markers, and/or muscle capillarization) rather than those associated with the physiological changes in response to one or several bouts of RE. Likely, an individual expressing a higher amount of one or more of these markers will respond favourably to RT (Roberts et al., 2018a). Currently, the measurement of several of these factors requires invasive muscle biopsies (SC/MN counts, ARC, muscle capillarization) or expensive and time-consuming genetic testing. Alternatively, a muscle's initial size – assessed via less-invasive medical imaging techniques – could be an indirect marker of an individual's hypertrophic responsiveness.

TABLE 1 Summary of factors proposed as responsible for the variability in individual hypertrophy responses.

Proposed Predictor of Individual Hypertrophic Responsiveness	Evidence for Improved Responsiveness based on:		Effect of Age	Section of Text	Notes
	Post-RE/RT Response?	Pre-Training Values?			
↑ MPS Response	Yes*†	N/A	↓	3.1	*only after muscle damage is attenuated † not in trained individuals
↑ mTOR Activation	??	N/A	↓	3.2	
↑ Ribosome Biogenesis	Yes*	Yes*	↓	3.3	*not in trained individuals
↑ Satellite Cell Proliferation and/or Myonuclei Content	??	Yes*	↓	3.4	
↑ Anabolic Hormones / ↓ Catabolic Hormones	IGF-1: ?? ARC: ?? MSTN: No IL-6: ?? TNF-α: No	IGF-1: ?? ARC: Yes MSTN: No IL-6: ?? TNF-α: No	IGF-1: ↓ ARC: N/C MSTN: N/A IL-6: ↑ TNF-α: ↑	3.5	
↑ TII Muscle Fibers	N/A	??*	??	4.1	* Could be a predictor in trained individuals
↑ Genetic Markers	Yes	Yes	N/A	4.2	
↑ Mitochondrial Activity/Number	N/A	??	N/A	4.3	
↑ Muscle Capillarization	Yes*	Yes*	↓	4.3	* Evidence only in elderly individuals

ARC, androgen receptor content; IGF1, insulin-like growth factor-1; IL-6, interleukin-6; MN, myonuclei; MPS, muscle protein synthesis; MSTN, myostatin; mTOR, mammalian/mechanistic target of rapamycin; SCs, satellite cells; TNF-α, tumour necrosis factor alpha; N/A, no evidence available, N/C, no change; ??, conflicting evidence

Work from Roberts' lab shows that those with relatively smaller muscle sizes at baseline have greater potential for muscle growth and plasticity (Haun et al., 2019a; Mobley et al., 2018). Indeed, their studies have shown significant relationships between higher hypertrophic responsiveness following multi-week RT and smaller pre-training muscle size in younger subjects at both the whole-muscle level (Mobley et al., 2018) and at the muscle fiber level (Figure 4, Haun et al., 2019a). Their lab has also shown that high hypertrophic responders tend to have lower pre-training myofibrillar protein concentrations compared to low responders (Roberts et al., 2018b). Lower pre-training levels of these proteins could mean greater potential for them to proliferate and, hence, an augmented hypertrophy response (Roberts et al., 2018b). In older individuals, Bechshøft et al. (2017) showed that relative increases in quadriceps CSA following 12 weeks of RT were negatively correlated to pre-training CSA in a group of very old (86.9 ± 3.2 years) men and women. The authors concluded that, in older individuals, relative improvements in muscle size are greater when initial size is low (Bechshøft et al., 2017).

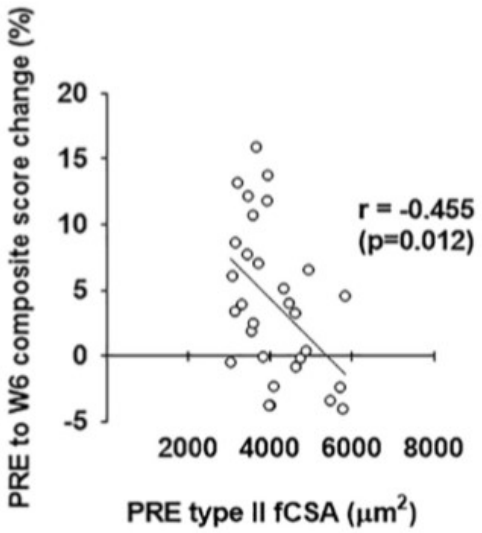

FIGURE 4. Relationship between pre-training type II muscle fiber cross-sectional area (PRE type II fCSA) and a composite score of the change in muscle size after 6 weeks of resistance training (PRE to W6 composite score change). Composite hypertrophy score included right leg: vastus lateralis (VL) muscle thickness assessed via ultrasound, lean soft tissue assessed via DXA, mid-thigh circumference, and VL mean (type I and type II) muscle fCSA. from Haun et al., 2019a

While this data is compelling, like several of the factors discussed above, conflicting evidence exists for the hypertrophic predictability of pre-training muscle size. Indeed, several of the individual response studies discussed in the previous sections have reported no differences in pre-training muscle size between high or low hypertrophic responders in younger (Davidsen et al., 2011), older (Stec et al., 2016), or combined cohorts (Bamman et al., 2007; Petrella et al., 2008; Phillips et al., 2013). However, a closer look at the data from some of the aforementioned studies suggests a trend for high responders exhibiting smaller pre-training muscle sizes (Table 2). While differences are not significant, it does hint that larger sample sizes may reveal a significant difference (Bamman et al., 2007; Phillips et al., 2013; Stec et al., 2016). This conclusion is speculative, however, and indicates a need for further research with larger sample sizes into the ability of pre-training muscle size to hypertrophy.

TABLE 2 Studies showing trends for low responders exhibiting larger pre-training muscle sizes than high responders (data are mean ± SE). *Note: differences are insignificant ($p > 0.05$)*

Reference	*n* (Low, High)	Measure of Muscle Size	Low Pre-Training Muscle Size	High Pre-Training Muscle Size
Bamman et al., 2007	34 (17, 17)	TI fCSA (cm^2) TII fCSA (cm^2)	4,905 ± 267 4,296 ± 367	4,131±263 4,273±342
Phillips et al., 2013	22 (11, 11)	Upper Leg Lean Mass (g)	5550 ± 442	4689 ± 239
Stec et al., 2016	23 (17, 6)	TI fCSA (cm^2) TII fCSA (cm^2)	4,836 ± 512 4,344 ± 595	4,132 ± 300 4,015 ± 720

low, low-responder; high, high-responder; TI, type I muscle fiber; TII, type II muscle fiber, fCSA, fiber cross-sectional area

Recent work from Damas et al. (2019a) suggests that the effect of pre-training muscle size on hypertrophic responsiveness in highly trained individuals may show the opposite response. That is, individuals who demonstrated the largest increases in vastus lateralis CSA following 8 weeks of RT also exhibited greater CSAs at pre-training. The authors concluded that, since all participants were highly trained at the beginning of the study, those with larger muscle sizes at baseline had already demonstrated a greater propensity to gain muscle and the RT intervention was simply a continued reflection of this (Damas et al., 2019a). These results contradict one of

the above-mentioned studies from Roberts' lab, however, which showed that smaller pre-training fCSA correlated with greater muscle growth following 6 weeks of high-volume RT in well-trained young men (Haun et al., 2019a). Thus, the relationship between pre-training muscle size and hypertrophic responsiveness in trained individuals requires further research.

5.2 **Pre-training muscle strength**

As in muscle size, the predictability of strength increases from pre-training strength is similarly convoluted. Indeed, while some studies have shown larger relative strength improvements in those with smaller pre-training strength in younger (Balshaw et al., 2017; Erskine et al., 2014; Hubal et al., 2005), older (Lexell et al., 1995), and combined cohorts (Newton et al., 2002), others have shown no such relationship (Chmelo et al., 2015; Erskine et al., 2010; Karavirta et al., 2011). Interestingly, Peltonen et al. (2018) showed that younger men with lower pre-training strength were more likely to be low-responders in terms of rate of force development, a measure that may be more indicative of neuromuscular adaptations, following 10 weeks of RT. Thus, whether lower pre-training strength predicts increased strength responsiveness may depend on the definition of strength. This argument is furthered by observations of dynamic strength (1RM) improvements being much greater than those of isometric strength (MVC) following the same RT program (Blocquiaux et al., 2020; Hubal et al., 2005; Lexell et al., 1995). This is likely a reflection of increases in 1RM strength being influenced more by learning and intermuscular coordination than improvements in force-generating capacity (Erskine et al., 2010; Rutherford & Jones, 1986). Thus, MVC may be the better indicator of physiological muscle strength compared to 1RM. Since studies have used a variety of different methods to determine muscular strength, including 1RM and MVC, it is difficult to determine the level at which pre-training strength predicts RT-induced change.

6 CHALLENGES WITH INDIVIDUAL RESPONSE RESEARCH

While this work aimed to provide a comprehensive overview of the physiological predictors of inter-individual differences in muscle size responsiveness, several factors were not discussed but should be mentioned. First, many exogenous variables can affect the muscle size response and the variability within it (Joanisse et al., 2020; Roberts et al., 2018a). Some of these include training status – as discussed, the physiological adaptations to RT in trained individuals may not mirror those in untrained individuals; nutrition – protein supplementation may enhance the hypertrophic response to RT, especially in older individuals (Morton et al., 2018a); and other lifestyle-related factors such as sleep and daily activity. It is difficult, if not impossible, to control all of these exogenous variables during a training intervention study. This makes the delineation between the effects of exogenous versus endogenous variables on strength, hypertrophy, and individual response variability extremely difficult.

Methodological differences in the measurement of muscle size and strength as well as the stratification of responders versus non-responders likely also affect the magnitude of individual responses between studies. Indeed, many of the individual response studies discussed herein used different measures of muscle size and/or strength to determine adaptations. Research shows, however, that different measures of muscle size and strength do not necessarily correlate within the same individual (Haun et al., 2019b; Rutherford & Jones, 1986). This is especially true when comparing changes over time. Indeed, Haun et al. (2019b) have shown a significant level of disagreement both within and between studies when comparing changes in DXA measures of whole muscle mass, MRI or ultrasound measures of individual muscles, and biopsy measurements of muscle fibers. Importantly, increases in whole-muscle size may not accurately reflect increases in muscle fCSA due to the influence of non-contractile tissue on whole muscle size, and the large variability in the number of muscle fibers between individuals (Lexell et al., 1983), especially in sarcopenic individuals who experience motor unit loss (Hunter et al., 2004; Lavin et al., 2019; Mobley et al., 2018). Similarly, as explained above, changes in dynamic (1RM) and isometric (MVC) measures of muscle strength do not agree due to the effects of practice and coordination on 1RM strength (Rutherford & Jones, 1986). Additionally, different muscles and muscle groups have been used to assess changes in size and strength (e.g., upper versus lower body). This further complicates comparisons between individual response studies given that upper body size and strength tend to improve at a greater rate than that of the lower

body (Abe et al., 2000). Finally, different studies have used different methods to define individuals as “responders” and “non-responders” and the viability of some of these methods has been questioned based on the inability to distinguish true change scores from random error (Swinton et al., 2018). Thus, standardized techniques are needed for a) the assessment of muscle size and strength and b) individual response stratification to allow for better comparison across studies.

Notwithstanding these methodological challenges, current evidence suggests that the pre-training value of several key mediators such as ribosomes, SCs/MN, androgen receptors, genetic markers, and muscle capillarization likely determine an individual’s hypertrophic responsiveness to RT. Interestingly, the majority of these biomarkers also experience decrements as a result of aging which may explain the blunted hypertrophy commonly observed in older individuals. Measuring these aforementioned biomarkers, however, can be expensive, invasive, and time-consuming. Pre-training muscle size, on the other hand, which can be measured less invasively, may also determine an individual’s responsiveness to RT. Indeed, untrained individuals with smaller muscles at the onset of RT may demonstrate an increased capacity for muscle growth. Further research is required, however, to substantiate this.

7 PURPOSE, RESEARCH QUESTIONS, AND HYPOTHESES

While prolonged resistance training tends to induce increases in muscle size and strength in the majority of individuals, the variation in these responses between individuals is large and may depend on age. Interestingly, the incidence of non-response may be higher among older participants compared to younger. Comparisons of individual responses between younger and older individuals within the same study, however, are rare. Further, while some research points to smaller muscle sizes at pre-training being an indicator of increased hypertrophic responsiveness, others have shown no such relationship. Thus, the purposes of this investigation were to 1) compare the variability in individual responses between younger and older individuals following prolonged resistance training to determine whether older individuals are at an increased risk of non-response and 2) examine whether pre-training muscle size or strength can predict the level of responsiveness to resistance training.

Research Question 1: Do older individuals exhibit higher variability in muscle responses compared to younger individuals following prolonged resistance training?

Hypothesis 1: Older individuals will demonstrate higher levels of variability, specifically non-responses, compared to younger individuals following prolonged resistance training.

Older individuals tend to exhibit diminished resistance training responses compared to their younger peers, at least in terms of muscle growth (Lavin et al., 2019). Interestingly, several of the mechanisms implicated in the individual muscle size response have also been associated with the decreases in muscle size and the blunted hypertrophic response in older individuals due to aging (Lavin et al., 2019; Stec et al., 2017). Because of this, older RT participants may be more prone to exhibit hypertrophic non-response compared to younger participants.

Research Question 2: Do smaller or weaker muscles before training predict an increased propensity for muscle growth or strength responses to prolonged resistance training?

Hypothesis 2: Those with smaller or weaker muscles at pre-training will demonstrate an increased capacity for muscle growth or strength increases and vice versa.

While the research from Michael Roberts' lab demonstrating increased hypertrophic responsiveness in those with smaller pre-training muscles due to increased muscle plasticity is compelling (Haun et al., 2019a; Mobley et al., 2018; Roberts et al., 2018b), other researchers have failed to replicate this (Bamman et al., 2007; Davidsen et al., 2011; Petrella et al., 2008; Phillips et al., 2013; Stec et al., 2016). The relatively small sample sizes in most individual response studies, however, make it difficult to draw definitive conclusions regarding the hypertrophic predictability of pre-training muscle size. Interestingly, an analysis of several of these studies revealed trends for lower responders demonstrating smaller muscle sizes at pre-training compared to higher responders although statistical significance was not reached (Bamman et al., 2007; Phillips et al., 2013; Stec et al., 2016). Thus, it is hypothesized that a larger sample size will show that smaller pre-training muscle size predicts increased hypertrophic responsiveness.

8 METHODS

8.1 Experimental design

A retrospective analysis was carried out on a subset of participants (n = 156) from the datasets of three separate resistance training intervention studies on apparently healthy, Caucasian Finnish adults. The studies were conducted during the years 2007-2016 at the University of Jyväskylä using the same laboratory facilities (Ahtiainen et al., 2015; H. Peltonen et al., partly unpublished data, partly published in Hulmi et al., 2015; S. Walker et al., unpublished data). All three studies were conducted in accordance with the Declaration of Helsinki and were approved by the institutional ethical committees (University of Jyväskylä and the Central Finland Health Care District, Jyväskylä, Finland). All subjects gave written informed consent after receiving comprehensive verbal and written explanations of the procedures as well as the possible risks and benefits of the study.

8.2 Subjects

Table 3 lists the demographic characteristics of the participants in each study. Study 1 involved a cohort of older men and women (S. Walker et al., unpublished data), study 2 was comprised of younger men (H. Peltonen et al., partly unpublished data, partly published in Hulmi et al., 2015), and study 3 included younger and older men (Ahtiainen et al., 2015). Participants were included in the analysis based upon having completed both pre- and post-intervention muscle size and strength testing. Participants from each study were grouped based on age. Participants in the younger group (YOUNG) were between the ages of 20 and 45 years (n = 65). Participants in the older group (OLD) were between the ages of 60 and 80 years (n = 91). Although OLD was made up of both men (n = 47) and women (n = 44), both groups behaved statistically similarly in all variables of interest ($p > 0.05$) and were thus treated as one group. Each prospective subject underwent a health screening and a resting electrocardiogram (ECG) before being granted permission to participate. Subjects with abnormal resting ECGs were excluded. The subjects were required not to have previous strength training experience or to have not participated in systematic resistance training for at least one year prior to the study. Habitual endurance exercisers (≥ 2 training sessions or ≥ 180 minutes/week) were also excluded as were those with serious cardiovascular disease or lower-limb injuries/disease that could lead to

complications during exercise or affect the ability to perform testing and training. Additionally, smokers, those using medications known to affect the neuromuscular or endocrine systems, those with previous testosterone-altering treatment, or those with a body mass index above 37 kg/m^2 were excluded.

TABLE 3. Descriptive characteristics of the participants from the three studies used for the analysis (mean ± SD)

Study #	**1**		**2**	**3**	
(n)	(75)		(55)	(26)	
Sex	Male (n = 31)	Female (n = 44)	Male	Male	
Age (years)	70.0 ± 2.9	68.9 ± 2.7	32.9 ± 6.7	Young (n = 10)	Old (n = 16)
				24.2 ± 3.2	68.6 ± 2.1

8.3 **Resistance training interventions**

Subjects performed 6-12 months (depending on the intervention they participated in) of resistance training 2-3 days per week on non-consecutive days, periodized into mesocycles focusing on either muscle hypertrophy, maximal strength, and/or power. The training interventions were designed according to the ACSM guidelines for healthy adults to increase muscle size and strength (Garber et al., 2011; Ratamess et al., 2009). All training sessions were performed at the laboratory facilities and supervised by a member of staff. Exercises were performed mainly on weight-stack equipment and consisted of both whole-body and split-routine sessions. The main focus of the training programs was on lower body strength but also included exercises for the upper body and trunk. Multiple (2-5) sets with a repetition range of 4-15 were utilized for both upper and lower body exercises. Intensity ranged between 50 and 90% of 1RM (30-80% 1RM for power training) with inter-set rests of 1-3 minutes depending on the training focus of the mesocycle. An example of one of the resistance training protocols that was used can be found in appendix 1.

8.4 **Body composition**

Body composition (body mass, fat mass, fat-free mass) was assessed by dual-energy x-ray absorptiometry (DXA, Lunar Prodigy Advance, GE Medical Systems, Madison, Wisconsin, USA). Quality assurance testing and calibration were performed on each data collection day to ensure that the device was operating properly. Leg position was fixed with Velcro straps at the knees and ankles. Automated soft tissue analyses with the manufacturer's pre-defined regions of interest (ROI) were conducted for total and upper body fat-free mass and total body fat and fat-free mass (Encore-software).

8.5 **Assessment of sarcopenia**

The sarcopenic state of participants was assessed based on appendicular lean mass index (ALMI), by dividing DXA-measured appendicular lean mass by body height (kg/m^2) at baseline (Baumgartner et al., 1998). Sarcopenia was determined separately for men and women according to cutoffs defined in earlier investigations (men: <7.59 kg/m^2, women: <5.47 kg/m^2) (Coin et al., 2013).

8.6 **Muscle size**

The cross-sectional area of the vastus lateralis muscle (VLCSA) of the right leg was measured using a B-mode axial plane ultrasound machine (model SSD-2000, Aloka, Tokyo, Japan) in the extended field of view mode with a 10-MHz linear-array probe before and after the training interventions. This method has previously shown a high level of repeatability and agreement with magnetic resonance images in participants undergoing RT (Ahtiainen et al., 2010). To assure a perpendicular measurement and to evenly distribute pressure on the tissue, a customized convex-shaped probe support coated with water-soluble transmission gel was used. Participants lied supine and the transducer was moved manually from lateral to medial along a marked line on the skin (Figure 5). Panoramic cross-sectional images were conducted at 50 % of the femur length from the lateral aspect of the knee joint to the greater trochanter and CSA was determined manually using ImageJ software (National Institutes of Health, Bethesda, MD). Three to four panoramic cross-sectional images were taken and the average of the two closest values was used as VLCSA.

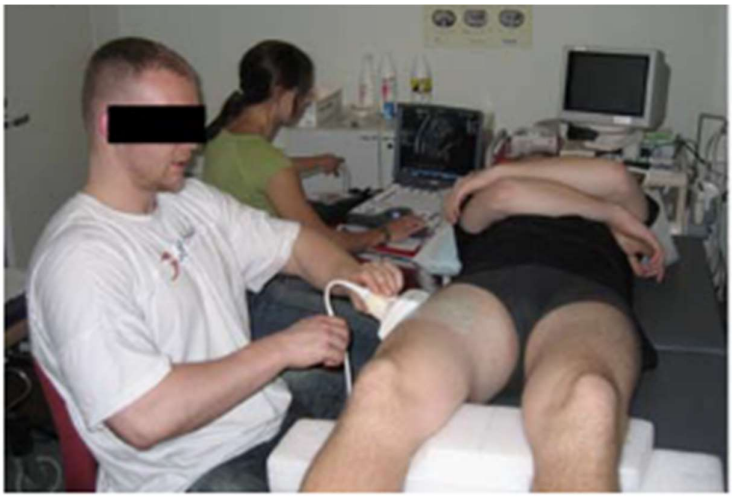

FIGURE 5. Set up for the ultrasound measurements of vastus lateralis cross-sectional area. From Ahtiainen et al. (2010)

8.7 **Muscle strength**

A horizontal leg press extension dynamometer (Department of Biology of Physical Activity, University of Jyväskylä, Jyväskylä, Finland) was used to determine maximal isometric quadriceps bilateral leg press force (quadriceps maximal voluntary contraction, [QMVC]) before and after the training interventions (Figure 6). Subjects were seated with hip and knee angles of 110° and 107°, respectively, and were secured by a seatbelt at the hip and a pad strapped over the right knee. Subjects were instructed to exert maximal force against the dynamometer upon verbal command and to maintain this force for 3–4 s. Three trials separated by a rest period of 1 minute or more when needed were conducted. If the maximum force during the third trial was greater than the previous attempt by 5 % or more, up to two additional trials were performed. The trial with the highest maximal force measured was used as QMVC.

FIGURE 6. Set up for isometric strength measurements of quadriceps maximal voluntary contraction. From Peltonen at al. (2018)

8.8 **Normalization to fat-free mass**

Since absolute muscle size and strength are proportional to body size (Folland et al., 2008; Handsfield et al., 2014), VLCSA and QMVC were allometrically scaled to fat-free mass (FFM) by dividing by FFM^0.76 (Folland et al., 2008). Statistical analyses of VLCSA and QMVC were repeated using scaled values to ensure that body size did not account for any observed relationship.

8.9 **Determination of responders and non-responders**

Participants were classified as responders or non-responders based on the smallest worthwhile change (SWC) framework proposed by Swinton et al. (2018). Briefly, those with a post-training score above the SWC of each measurement were classified as responders while those with a post-training score below the SWC were classified as non-responders. For muscle size, SWC was defined as an absolute change in VLCSA of 1.10 cm^2 based on the methodological analysis of the aforementioned ultrasound technique by Ahtiainen et al. (2010). Thus, those with absolute changes in VLCSA > 1.10 cm^2 were classified as muscle size responders while those with changes $\leq$ 1.10 cm^2 were classified as non-responders. For muscle strength, since no measure of SWC for this protocol could be found in the literature, responders and non-

responders were classified based on relative changes from baseline above 0 %. Those with relative changes in strength > 0 % were classified as strength responders while those with scores $\leq$ 0 % were classified as strength non-responders.

8.10 **Statistical analysis**

All data are presented as mean ± standard deviation (SD). Statistical analyses were carried out using SPSS 26.0 software (SPSS, Inc., Chicago, IL). Differences between age groups at baseline and relative changes with RT and differences between responder groups were tested using independent samples *t*-tests. Training-induced absolute and relative changes in body composition and muscle size and strength were analyzed using 2-factor repeated-measures analysis of covariance (ANCOVA) with age as the grouping factor, pre-training value as the covariate, and repeated measures over time. Bonferroni post hoc testing was used to confirm any main effects. Effect size (partial eta squared, η^2_p) is reported for any difference in relative change between age groups where 0.01, 0.06, and 0.14 represent small, medium, and large effects, respectively (Cohen, 1988). To examine the variability in muscle size responses between age groups, Levene's test for equality of variances was used. To determine the relationship between pre-training muscle size and strength and their relative changes with training, Pearson product-moment correlations were conducted. If a significant correlation was identified, linear regression analyses were conducted to determine the amount of variance in relative change explained by pre-training score. The alpha level for statistical significance was set at $p < 0.05$.

9 RESULTS

9.1 **Descriptive characteristics**

At baseline, there were significant differences between YOUNG and OLD for height, body mass, body mass index (BMI), body fat, and appendicular lean mass index (ALMI) ($p < 0.05$, Table 4). A total of 15 subjects were considered sarcopenic prior to the intervention according to the ALMI cut-offs listed above; all of which were in the OLD group.

TABLE 4. Descriptive characteristics of participants at baseline (mean ± SD)

	All Subjects (n = 156)	YOUNG (n = 65)	OLD (n = 91)	Between Age Group Difference
Age (years)	53.5 ± 19.3	31.6 ± 7.0	69.2 ± 2.7	$p < 0.001$
Height (cm)	173.2 ± 9.7	179.8 ± 7.0	168.6 ± 8.6	$p < 0.001$
Body Mass (kg)	80.4 ± 12.2	82.8 ± 10.0	78.7 ± 13.3	$p = 0.036$
BMI (kg/m^2)	26.8 ± 3.6	25.7 ± 3.1	27.6 ± 3.8	$p = 0.001$
Body Fat (%)	29.4 ± 9.8	23.2 ± 8.1	33.8 ± 8.5	$p <0.001$
ALMI (kg/m^2)	8.3 ± 1.6	9.7 ± 0.9	7.4 ± 1.3	$p <0.001$
Sarcopenic (n)	15	0	15	

BMI, body mass index; ALMI, appendicular lean mass index

9.2 **Age differences in resistance training responses**

Absolute pre- and post-training values and relative changes in body composition, muscle size, and muscle strength with resistance training are presented in Table 5. At pre-training, body mass, FFM, VLCSA, and QMVC were greater in YOUNG compared to OLD whereas fat mass was less ($p < 0.05$). From pre- to post-training, body mass increased in YOUNG ($p = 0.002$) but decreased in OLD ($p < 0.001$). There was a significant age × time interaction for body mass such that adjusted post-training body mass and relative change from pre-training were greater in YOUNG compared to OLD ($p < 0.001$, $\eta^2_p = 0.134$). In both age groups, FFM, VLCSA, and QMVC increased whereas fat mass decreased from pre- to post-training ($p < 0.05$). There was a significant age × time interaction for FFM such that adjusted post-training FFM was greater in YOUNG vs. OLD ($p = 0.028$). Relative change in FFM from pre-training, however, was not significantly different between ages ($p = 0.097$).

TABLE 5. Absolute and relative changes in body composition and strength after 6-12 months of resistance training (mean ± SD)

	Absolute Change			Relative Change from Pre-Training				
	Pre	Post	Δ	%Δ	95% CI	η^2_p	Min	Max
Body Mass (kg)								
All Subjects (n = 156)	80.4 ± 12.2	80.2 ± 12.3	-0.2 ± 2.7	-0.2 ± 3.2	-0.7 – +0.3			
YOUNG (n = 65)	82.8 ± 10.0#	83.8 ± 10.3*#	+0.9 ± 2.3†	+1.1 ± 2.7†	+0.5 – +1.8	0.134	-4.5	+12.0
OLD (n = 91)	78.7 ± 13.3	77.7 ± 13.0*	-1.0 ± 2.7	-1.2 ± 3.2	-1.9 – -0.6		-17.8	+7.3
Fat Mass (kg)								
All Subjects	23.7 ± 8.9	22.4 ± 8.7*	-1.3 ± 2.4	-5.2 ± 12.5	-7.1 – -3.2			
YOUNG	19.7 ± 8.6#	18.7 ± 8.7*#	-1.0 ± 2.7	-4.4 ± 14.8	-8.1 – -0.8		-33.4	+54.3
OLD	26.5 ± 7.9	25.0 ± 7.9*	-1.5 ± 2.2	-5.7 ± 10.5	-3.5 – -7.9		-31.9	+53.2
FFM (kg)								
All Subjects	53.6 ± 10.2	54.4 ± 10.5*	+0.8 ± 1.5	+1.5 ± 2.8	+1.0 – +1.9			
YOUNG	59.7 ± 5.4#	60.9 ± 5.8*#	+1.1 ± 1.4†	+1.9 ± 2.2	+1.4 – +2.5		-2.1	+9.5
OLD	49.2 ± 10.6	49.8 ± 10.7*	+0.5 ± 1.6	+1.2 ± 3.1	+0.5 – +1.8		-12.1	+7.5
VLCSA (cm^2)								
All Subjects	19.1 ± 6.3	20.8 ± 7.5*	+1.7 ± 2.4	+8.4 ± 12.2	+6.5 – +10.3			
YOUNG	24.8 ± 4.6#	27.8 ± 5.0*#	+3.0 ± 2.3†	+12.8 ± 9.3†	+10.5 – +15.1	0.094	-6.0	+40.7
OLD	15.0 ± 3.5	15.7 ± 4.2*	+0.8 ± 1.9	+5.3 ± 13.0	+2.5 – +8.0		-19.5	+49.9
QMVC (N)								
All Subjects	579.9 ± 174.1	617.8 ± 179.6*	+37.9 ± 93.0	+8.1 ± 17.3	+5.3 – +10.8			
YOUNG	705.8 ± 151.9#	742.1 ± 157.9*#	+36.3 ± 113.3	+6.4 ± 17.3	+2.1 – +10.7		-22.8	+57.2
OLD	489.9 ± 127.0	529.0 ± 136.7*	+39.1 ± 75.9	+9.2 ± 17.2	+5.6 – +12.8		-43.0	+67.8

CI, confidence interval; FFM, fat-free mass; VLCSA, vastus lateralis cross-sectional area; QMVC, quadriceps maximal voluntary contraction

* significantly different from within group pre-training value ($p < 0.05$)

significantly different from OLD at same time point ($p < 0.05$)

† significant age × time interaction ($p < 0.001$)

There was a significant age × time interaction for VLCSA such that adjusted post-training VLCSA was significantly greater in YOUNG compared to OLD ($p < 0.001$). Similarly, ΔVLCSA was significantly greater in YOUNG vs. OLD ($p < 0.001$, $\eta^2_p = 0.094$, Figure 7). There was no significant age × time interaction for QMVC ($p = 0.073$) and there was no difference in ΔQMVC between YOUNG and OLD ($p = 0.321$). Between group differences in VLCSA, QMVC, and their relative changes were similar after normalizing for FFM.

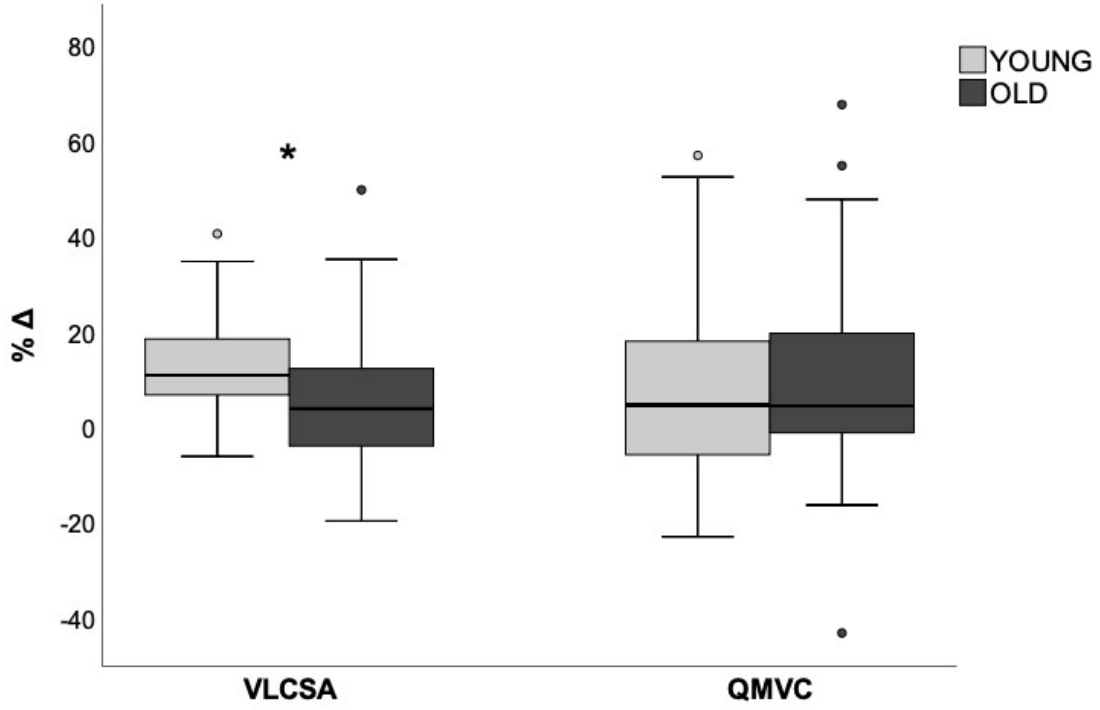

FIGURE 7. Changes in muscle size and strength relative to baseline after 6-12 months of resistance training in younger (YOUNG, 20-45 years, *light grey boxes*) and older (OLD, 60-80 years, *dark grey boxes*) adults. Data are presented as box and whisker plots (including the median [line], interquartile range [box], 1.5x the interquartile range [whiskers], and outliers [dots]). VLCSA, vastus lateralis cross-sectional area; QMVC, quadriceps maximum voluntary contraction

* significant difference between age groups ($p < 0.001$)

9.3 **Individual variability in resistance training responses**

9.3.1 **Muscle size**

Figure 8 illustrates the individual responses in relative VLCSA change (ΔVLCSA) from pre- to post-training. Relative changes ranged from –6.0 to 40.7 % in YOUNG and -19.5 to 49.9 % in OLD. Levene's test revealed significant differences in variance between the age groups (p = 0.014). A large proportion of participants (n = 68, 44 %) did not meet the SWC threshold for absolute change in VLCSA of 1.10 cm^2 and were classified as muscle size non-responders. Of the muscle size non-responders, 10 (15 %) were YOUNG and 58 (85 %) were OLD. Of the 15 OLD participants who were classified as sarcopenic prior to the study, 10 were classified as muscle size non-responders.

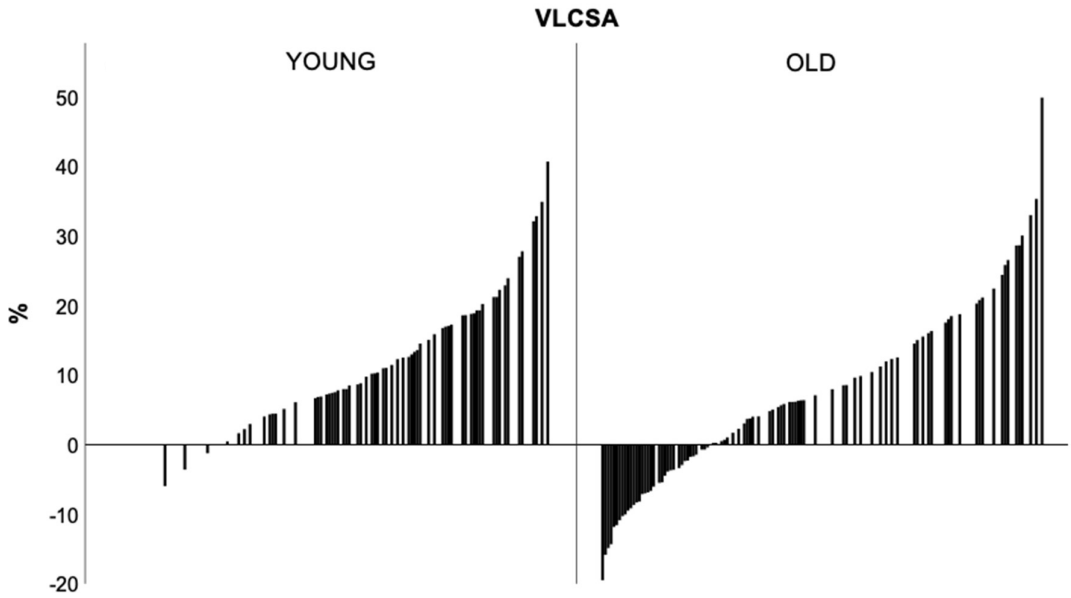

FIGURE 8. Individual responses in relative muscle size change after 6-12 months of resistance training in younger (YOUNG, n = 65) and older (OLD, n = 91) adults. VLCSA, vastus lateralis cross-sectional area

9.3.2 **Muscle strength**

Figure 9 illustrates the individual responses in relative muscle strength change (ΔQMVC) from pre- to post-training. Relative changes ranged from -22.8 to 57.2 % in YOUNG and -43.0 to 67.8 % in OLD. Levene's test did not indicate significant differences in variance between age groups (p = 0.802). Fifty-three (53) participants (34 %) demonstrated change scores $\leq$ 0 % and were classified as muscle strength non-responders. Of the muscle strength non-responders, 27 (51 %) were YOUNG and 26 (49 %) were OLD. Of the 15 sarcopenic participants, 6 were classified as muscle strength non-responders.

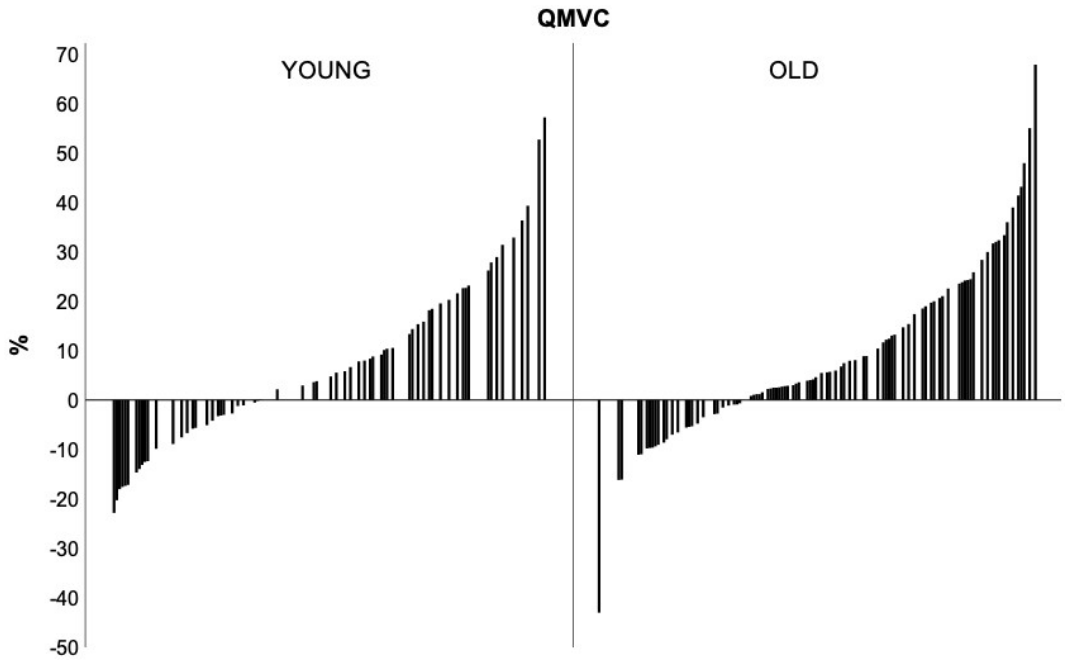

FIGURE 9. Individual responses in relative muscle strength change after 6-12 months of resistance training in younger (YOUNG, n = 65) and older (OLD, n = 91) adults. QMVC, quadriceps maximal voluntary contraction

9.3.3 **Muscle size and strength**

Figure 10 displays the change scores for muscle size and strength following RT for each participant. A total of 59 participants (38 %) showed responses above the SWC for both muscle size and strength following RT and were classified as Multi-Responders; 74 participants (47 %) demonstrated responses above the SWC for either muscle size or strength following RT and

were classified as Single-Responders, and 24 participants (15 %) showed responses below the SWC for both muscle size and strength following RT and were classified as Non-Responders. Of the Multi-Responders, 34 (58%) were YOUNG while 25 (42 %) were OLD. Of the Non-Responders, 8 (33 %) were YOUNG and 16 (67 %) were OLD. Of the 15 sarcopenic participants, 4 were Multi-Responders, 6 were Single-Responders, and 5 were Non-Responders.

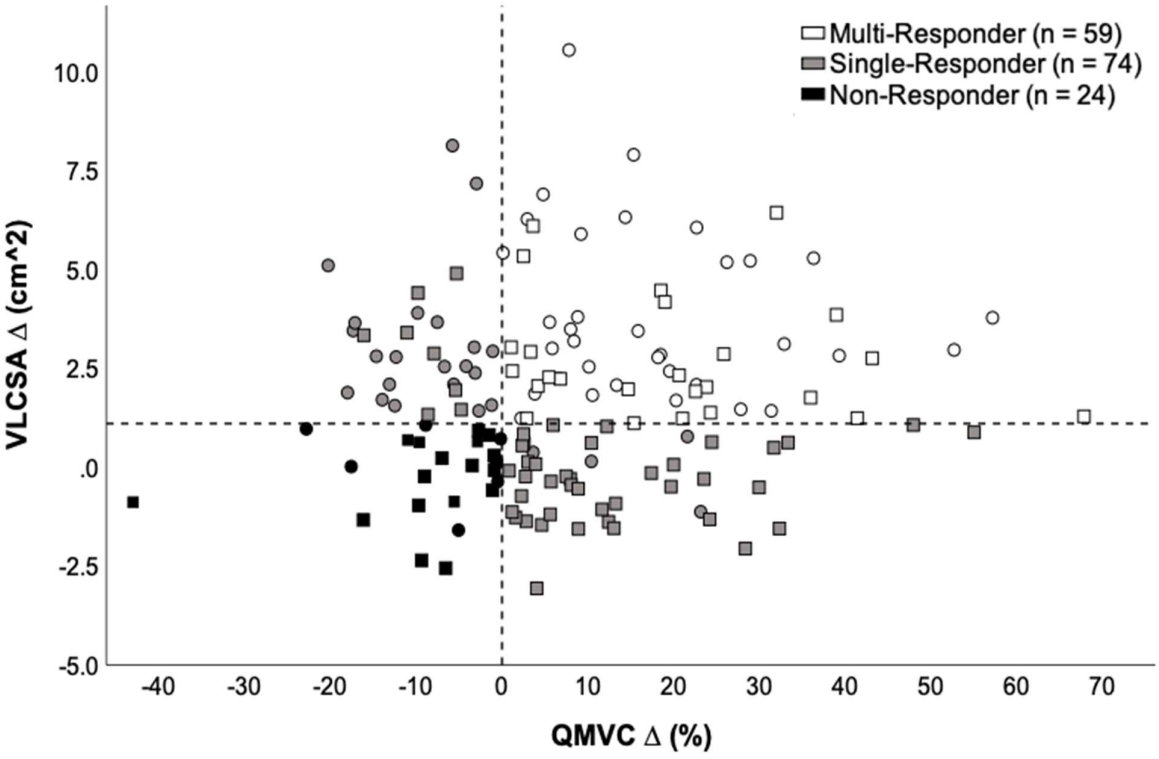

FIGURE 10. Individual changes in muscle size and strength after 6-12 months of resistance training in younger (YOUNG, *n* = 65, *circles*) and older (OLD, *n* = 91, *boxes*) adults. *Dashed lines* represent responder thresholds based on smallest worthwhile change (SWC). Muscle size responders were defined as those with absolute changes in vastus lateralis cross-sectional area (VLCSA) > 1.10 cm^2; muscle strength responders were defined as those with relative changes in quadriceps maximal voluntary contraction (QMVC) > 0 %. Multi-Responder refers to an individual who exhibited changes in both muscle size and strength that were above the SWC; Single-Responder refers to an individual who exhibited a change in either muscle size or strength that was above the SWC; Non-Responder refers to an individual who exhibited changes in both muscle size and strength that were below the SWC.

9.4 **Relationship between pre-training characteristics and training responses**

Table 6 shows pre-training muscle size and strength and their relative changes with RT for responders and non-responders in each age group. There were significant differences between muscle size responders and non-responders in ΔVLCSA and between muscle strength responders and non-responders in ΔQMVC in both age groups ($p < 0.001$). Pre-training VLCSA did not differ between muscle size response groups in either age group ($p > 0.05$). Pre-training QMVC was significantly lower in muscle strength responders compared to non-responders in YOUNG ($p = 0.030$) but not OLD ($p = 0.275$).

TABLE 6. Pre-training muscle size and strength in young (YOUNG, $n = 65$) and old (OLD, $n = 91$) responders and non-responders to 6-12 months of resistance training (mean ± SD)

	Muscle Size (VLCSA)					
	YOUNG			OLD		
	R ($n = 55$)	NR ($n = 10$)	*p*	R ($n = 33$)	NR ($n = 58$)	*p*
Pre (cm^2)	24.5 ± 4.6	26.5 ± 4.4	0.208	15.2 ± 3.9	14.8 ± 3.3	0.599
Δ (%)	15.0 ± 8.2	0.6 ± 3.4	<0.001	18.9 ± 9.6	-2.5 ± 6.7	<0.001
	Muscle Strength (QMVC)					
	YOUNG			OLD		
	R ($n = 38$)	NR ($n = 27$)	*p*	R ($n = 65$)	NR ($n = 26$)	*p*
Pre (N)	671.7 ± 139.7	753.9 ± 158.0	0.030	480.7 ± 128.4	513.0 ± 122.8	0.275
Δ (%)	17.6 ± 13.5	-9.2 ± 6.8	<0.001	16.2 ± 14.8	-8.1 ± 8.3	<0.001

Muscle size responders (R) and non-responders (NR) were defined as those with absolute changes in vastus lateralis cross-sectional area (VLCSA) > 1.10 cm^2 and ≤ 1.10 cm^2, respectively; muscle strength responders and non-responders were defined as those with relative changes in quadriceps maximal voluntary contraction (QMVC) > 0 % and ≤ 0 %, respectively. YOUNG consisted of men between the ages of 20-45 years, OLD consisted of men and women between the ages of 60-80 years.

9.4.1 **Muscle size**

Figure 11 shows the relationship between pre-training muscle size and relative change in muscle size from pre- to post-training at the whole-group level (A) and when separated by age (B). Correlations between pre-training VLCSA and ΔVLCSA at the whole-group level were not significant (r = 0.151, p = 0.060). Separate age group analyses revealed a moderate but significant negative correlation between pre-training VLCSA and ΔVLCSA in YOUNG (r = -0.308, p = 0.012) but no significant correlation in OLD (r = -0.044, p = 0.679). Linear regression analysis showed that pre-training VLCSA explained 9.5 % of the variance in ΔVLCSA in YOUNG (R^2 = 0.095, p = 0.12).

9.4.2 **Muscle strength**

Figure 12 shows the relationship between pre-training muscle strength and relative change in muscle strength from pre- to post-training at the whole-group level (A) and when separated by age (B). Pre-training QMVC and ΔQMVC demonstrated a weak but significant negative correlation in all participants (r = -0.296, p < 0.001). Weak to moderate significant correlations were also observed in YOUNG (r = -0.353, p = 0.004) and OLD (r = -0.283, p = 0.007) when analyzed separately. Linear regression analyses showed that pre-training QMVC explained 8.8 % (R^2 = 0.088, p < 0.001), 12.5 % (R^2 = 0.125, p = 0.004), and 8.0 % (R^2 = 0.080, p = 0.007) of the variance in ΔQMVC in all subjects, YOUNG, and OLD, respectively.

9.4.3 **Muscle size and strength**

Figure 13 shows the relationships between pre-training muscle size and strength (A) and relative changes in muscle size and strength from pre- to post-training (B). There were moderate to strong positive correlations between pre-training VLCSA and QMVC at the whole-group level (r = 0.755, p < 0.001) and in YOUNG (r = 0.448, p < 0.001) and OLD (r = 0.685, p < 0.001). There was no significant correlation between ΔVLCSA and ΔQMVC at the whole-group level (r = 0.138, p = 0.085) or in YOUNG (r = 0.220, p = 0.078) or OLD (r = 0.150, p = 0.156). All of the above correlations and regression analyses were similar after normalizing for FFM.

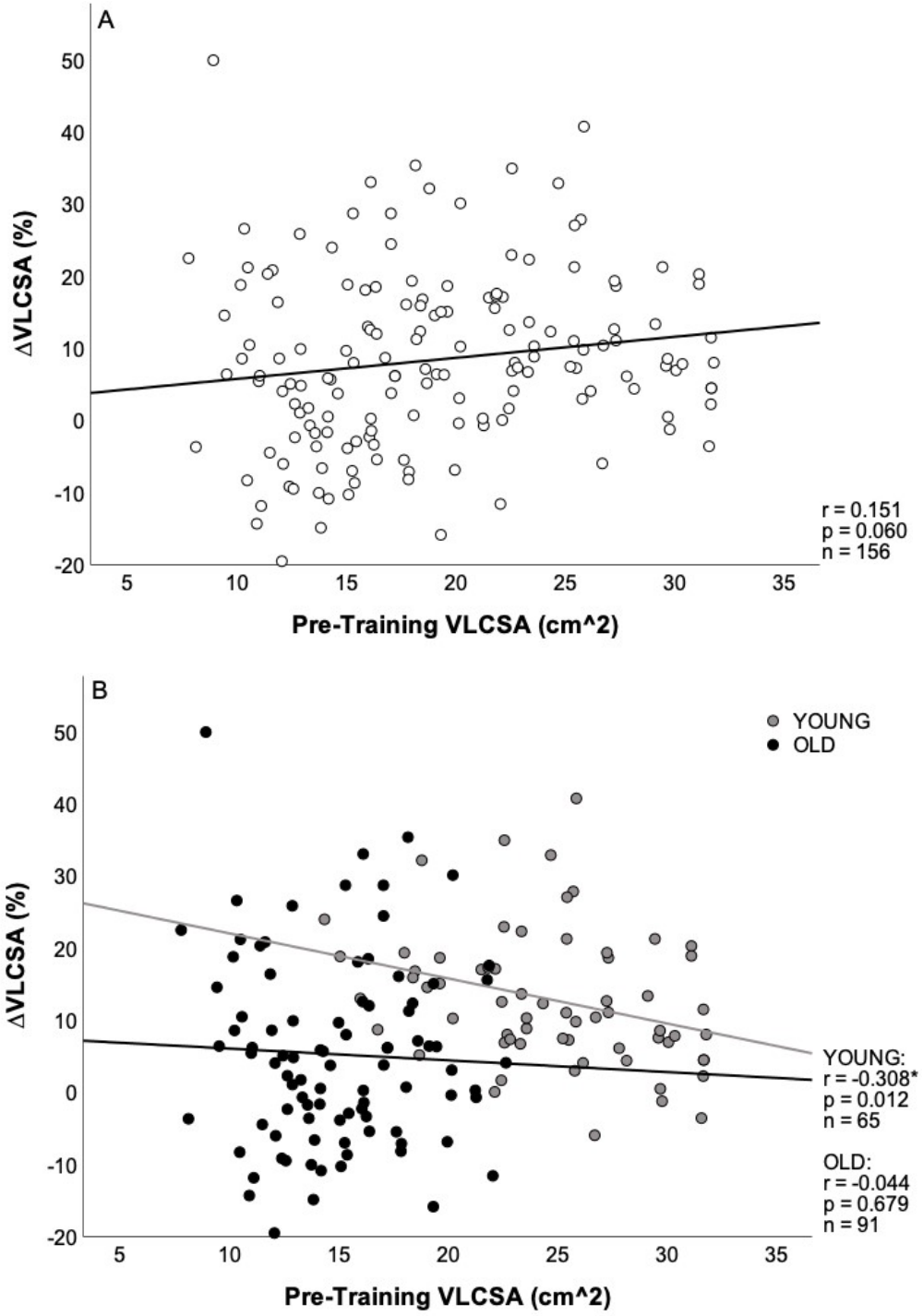

FIGURE 11. Relationship between pre-training muscle size and relative change in muscle size after 6-12 months of resistance training in all participants (n = 165) (A) and separated into younger (YOUNG, 20-45 years, n = 65) and older (OLD, 60-80 years, n = 91) participants (B). VLCSA, vastus lateralis cross-sectional area

* correlation is significant at the $p < 0.05$ level

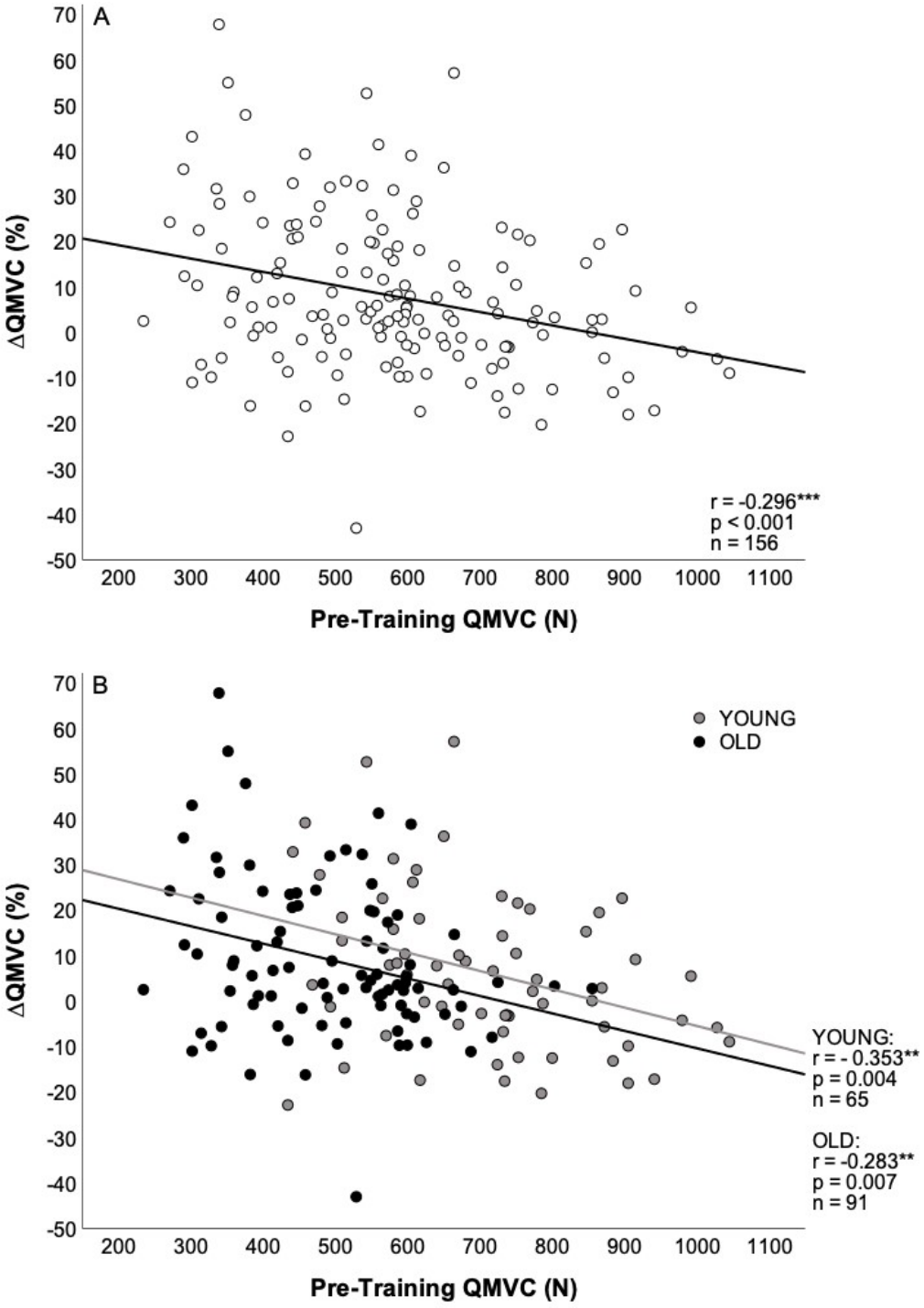

FIGURE 12. Relationship between pre-training muscle strength and relative change in muscle strength after 6-12 months of resistance training in all participants (n = 165) (A) and separated into younger (YOUNG, 20-45 years, n = 65) and older (OLD, 60-80 years, n = 91) participants (B). QMVC, quadriceps maximal voluntary contraction

** correlation is significant at the $p < 0.01$ level

*** correlation is significant at the $p < 0.001$ level

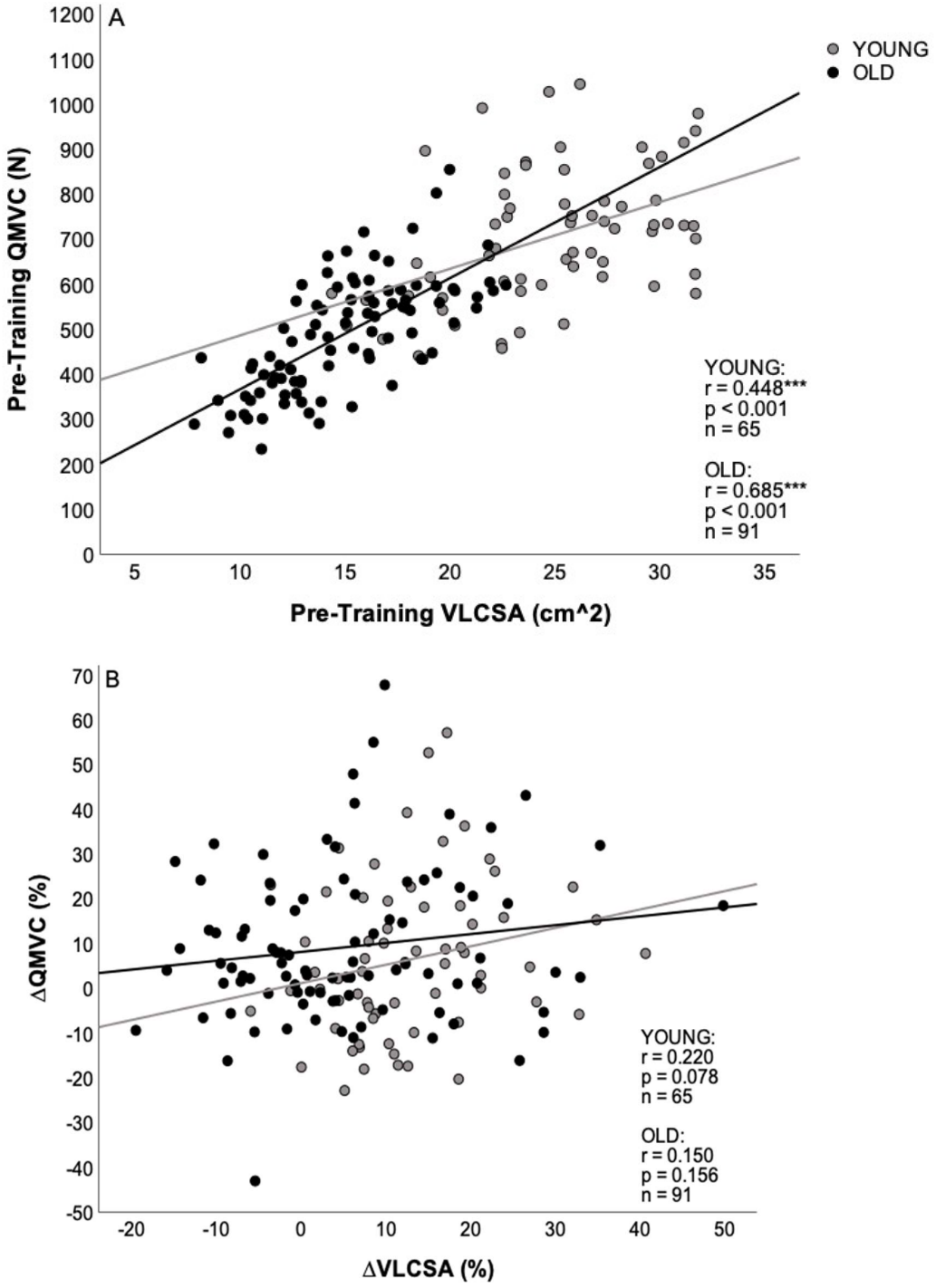

FIGURE 13. Relationships between pre-training muscle size and strength (A) and relative changes in muscle size and strength after 6-12 months of resistance training (B) in younger (YOUNG, 20-45 years, $n = 65$) and older (OLD, 60-80 years, $n = 91$) adults. QMVC, quadriceps maximal voluntary contraction; VLCSA, vastus lateralis cross-sectional area

*** correlation is significant at the $p < 0.001$ level

10 DISCUSSION

This investigation used a retrospective analysis of 156 participants from three studies to examine: the heterogeneity in responses to resistance training (RT) in younger and older adults, whether this variability differs between these two age groups, and whether pre-training muscle size or strength predicts an individual's level of responsiveness to long-term RT. The results of this study indicate that the variability in responses to prolonged RT differs between younger (20-45 years) and older (60-80 years) adults such that older adults are more likely to demonstrate hypertrophic non-response compared to younger adults. Secondly, pre-training muscle size is related to the individual hypertrophy response to RT in younger but not older individuals while pre-training strength is related to the individual strength response regardless of age. This study provides further information regarding the effects of aging on muscle size and strength responses to prolonged RT and the level of heterogeneity in these responses. It is one of the few studies to quantify and compare individual responses between younger and older adults and is the first, to this author's knowledge, to examine the effects of age on the relationship between pre-training muscle characteristics and responsiveness to RT.

10.1 Age differences in resistance training responses

At the group level, older men and women exhibited lower muscle size and strength at pre-training compared to younger men. This finding is consistent with the gradual declines in muscle mass and strength that occur as a result of age-related muscle atrophy and motor unit loss (Lavin et al., 2019). While both age groups demonstrated significant increases in muscle size and strength from pre- to post-training, the relative increases in OLD were significantly less than those of YOUNG following 6-12 months of RT. Strength increases, however, were similar between groups. These findings are consistent with previous research showing diminished muscle growth but not strength responses to RT in older versus younger adults. For example, Ahtiainen et al. (2011) and Mero et al. (2013) both showed similar improvements in leg extension strength but smaller relative increases in fCSA in older versus younger subjects after 21 weeks of whole-body RT. Studies focused specifically on RT-induced hypertrophy have also shown diminished responses in older compared to younger adults (Brook et al., 2016; Welle et al., 1996) while those focused on strength have shown no differences between age groups (Häkkinen et al., 2000, 2001; Newton et al., 2002).

Potential explanations for the diminished hypertrophic responses of older individuals are several-fold but likely relate to age-related decrements in hypertrophy signalling mechanisms such as post-exercise MPS (Kumar et al., 2009), mTOR activation (Greig et al., 2011), ribosome biogenesis (Stec et al., 2015), SC proliferation and MN counts (Petrella et al., 2006, 2008), and IGF-1 concentrations (Petrella et al., 2006). Increased inflammatory markers and decreased muscle capillarization could also play a role in the reduced hypertrophic capacities of older individuals (Merritt et al., 2013; Ryan et al., 2006). While many factors influence the RT-induced increases in muscle strength, the similar increases observed between age groups can be explained by improvements in motor unit activation in older adults that are similar to if not greater than those in younger adults (Knight & Kamen, 2001; Walker & Häkkinen, 2014). Greater decreases in antagonist coactivation in older compared to younger adults following RT could also play a role in their similar rates of strength improvements (Häkkinen et al., 1998). Measures of the above-mentioned hypertrophic biomarkers or agonist-antagonist activation were not included in this analysis. As such, the degree to which any or all of these factors played a role in the RT adaptations between younger and older adults herein are unknown. Nonetheless, the finding that older adults demonstrate similar strength but lesser muscle size gains following prolonged RT compared to younger adults is consistent with the existing literature and indicates that aging impairs the muscle size but not strength adaptative response to RT.

10.2 **Individual variability in resistance training responses**

The range of relative changes in muscle size and strength between individuals in this study demonstrates the considerable variability that exists in RT adaptations and indicates that persons who perform the same RT program do not necessarily experience the same post-training adaptations. The response variability in muscle size and strength in this study is greater than that which has been observed previously (Ahtiainen et al., 2016; Balshaw et al., 2017; Erskine et al., 2010). The longer duration of RT in this study (6-12 months) compared to others (2-6 months) could explain this increased variability. Indeed, the results from this study could simply be a continuation of what would have been observed in previous studies had they been of longer duration. Evidence for this comes from a recent investigation in older women by Nunes et al. (2020) who showed that responders and non-responders in terms of muscle size after 12 weeks of RT continued their response patterns after an additional 12 weeks of training. Whether this same pattern occurs for measures of physical function such as strength, however, is questionable (Barbalho et al., 2017; Churchward-Venne et al., 2015). Nonetheless, it is clear

that a high degree of inter-individual variability exists for the changes in muscle size and strength brought about by RT. The magnitude of this variability might depend on the duration of the RT intervention.

Between age groups, the variability in muscle size was significantly greater in OLD compared to YOUNG while that of muscle strength was similar. These findings likely relate to variability in the magnitude of age-related declines in muscle size and function. Indeed, the rate of age-related muscle deterioration has been shown to differ considerably between older individuals (Degens & Korhonen, 2012). This is supported by the relatively small number of participants in this investigation who were classified as sarcopenic despite many being upwards of 70 years old at the time of participation. Interestingly, the majority of these sarcopenic participants were classified as muscle size non-responders. This agrees with recent research from Negaresh et al. (2019) who showed decreased levels of muscle growth following RT in sarcopenic vs. non-sarcopenic older men. On the other hand, many older individuals in this study demonstrated changes in muscle size of over 20 % (Figure 8). In fact, the highest muscle size responder, with a relative change in VLCSA from pre-post training of almost 50 %, was 74 years old. It can be hypothesized then, that the hypertrophic response of older individuals is highly dependent on their stage of age-related muscular decline (Negaresh et al., 2019).

As for muscle strength, aging does not appear to detrimentally affect its response to RT. Accordingly, Clark & Manini (2008) showed that age-related muscle loss does not correlate with declines in muscle function. This is evidenced by the relatively few sarcopenic individuals in this study who were classified as strength non-responders. Hence, the similar variability in strength responses between younger and older participants in this study is not unexpected. Altogether, the larger variability in muscle size but not strength responses in the older group in this study is likely a reflection of the large inter-individual variability in the magnitude of age-related muscle loss rather than function.

After classifying participants as responders or non-responders based on their training-induced changes being above or below the smallest worthwhile change (SWC) threshold for each measurement, OLD made up a greater proportion of muscle size non-responders compared to YOUNG. Among strength non-responders, the proportion of YOUNG to OLD was similar (51 and 49 % for young and old, respectively). Older participants exhibiting greater muscle size non-response to RT has been observed previously. Indeed, Bamman et al. (2007) showed that

more than one-third of the older men and women in their study demonstrated hypertrophic non-response compared to 16 % of younger men and women following 16 weeks of RT. Other studies have shown that between 30 to 60 % of older adults demonstrate hypertrophic non-responses to RT (Blocquiaux et al., 2020; Churchward-Venne et al., 2015; Nunes et al., 2020; Stec et al., 2016, 2017) compared to only 15 to 25 % of younger participants (Davidsen et al., 2011; Mobley et al., 2018). On the other hand, Ahtiainen et al. (2016) found no age or sex differences in the number of muscle size or strength non-responders in their retrospective analysis of younger, middle-aged, and older men and women following 21-24 weeks of RT. However, the inclusion of different measures of muscle size in their analysis (ultrasound, MRI, and/or DXA) makes it difficult to interpret whether their results truly represent the variability in muscle size across ages and genders given the lack of agreement across these different measures of muscle size within the same individual (Ahtiainen et al., 2016; Haun et al., 2019b).

The work by Ahtiainen et al. (2016) is the only study, to this author's knowledge, to analyze age differences in the number of responders and non-responders to RT in terms of strength. Studies undertaken in young or old subjects show that approximately 15 % of young subjects exhibit strength non-response following training (Erskine et al., 2010) compared to 15 to 30 % of older participants (Bechshøft et al., 2017; Chmelo et al., 2015; Karavirta et al., 2011). This contrasts with the 42 % of younger and 29 % of older strength non-responders observed in this study. Mechanisms explaining these disparate findings are unknown and future research should aim to determine the true proportion of strength responders and non-responders between younger and older subjects and the mechanisms at play. Altogether, the findings from this study and others indicate that older adults performing RT are more likely to demonstrate non-response in terms of muscle size but not strength compared to younger adults.

The literature is scarce regarding the potential explanatory mechanisms behind RT non-response and why it is more common in older individuals. Research in endurance-type exercise points to genetic factors playing a role in those who respond adversely to this type of training (Bouchard et al., 2012; Stephens & Sparks, 2015). The same is likely true for RT as highlighted by the litany of studies that have identified genetic markers differentiating between low and high muscle size responders to RT (section 4.2). As discussed, RT-induced hypertrophy and age-related muscle loss appear to be two distinct genetic processes (Phillips et al., 2013). However, many of the processes involved in RT-induced muscle growth are compromised with aging. It is plausible to theorize, then, that the increased rate of non-response in older

populations is due to the detrimental effects of aging on the muscle growth process. Further research is required, however, to identify the factors that predispose an individual to muscle size non-response and the degree to which these factors differ between younger and older participants.

While speculative, these findings could explain the diminished hypertrophic responses of older adults seen at the group level. Indeed, all else being equal, a group with more non-responders will likely demonstrate a lower group mean compared to a group with fewer non-responders. This does not necessarily mean, however, that the group means differed among those who did respond to the intervention. A cursory look at this data shows that the group-level relative change in VLCSA was still lower in the older versus the younger group when only muscle size responders were analyzed (p = 0.048). It is unknown, however, whether this difference is physiologically relevant. Thus, whether the diminished hypertrophic capabilities of older adults at the group level can be explained by the higher number of non-responders in this population is speculative and requires further investigation.

Finally, it is important to note that a relatively small proportion of individuals demonstrated non-response to both muscle size and strength in this investigation. The minimal amount of "global" exercise non-responders – those that do not exhibit a response in any measured physiological variable from pre- to post-training – is a common finding within the literature (Pickering & Kiely, 2019). Indeed, several RT studies in young individuals have shown that few, if any, muscle size non-responders are also muscle strength non-responders (Ahtiainen et al., 2016; Damas et al., 2019b; Erskine et al., 2010). Accordingly, only 8 (12 %) participants in the younger group fit this description in the current study. While a greater number of older subjects demonstrated global non-response (n = 16, 18 %), similar investigations in older adults have failed to show global non-response to RT when measures of functional performance such as the chair-rise test are included (Barbalho et al., 2017; Chmelo et al., 2015; Churchward-Venne et al., 2015; Stec et al., 2017). This is important given this population's increased risk of injury resulting from the reduced ability to perform activities of daily living (Lavin et al., 2019). It is thus possible that the number of global non-responders in the current study would have been less having included more measures of functional performance. Accordingly, the likelihood of an individual not gaining any physiological, psychological, or social benefit from RT is extremely small and should not prohibit persons from participating in this form of exercise. Taken together, the above findings show that older adults demonstrate greater

variability and non-response in terms of muscle size but not strength compared to younger adults following prolonged RT. This indicates that RT prescriptions may need to be differentiated for older adults to limit hypertrophic non-response, maximize muscle growth, and limit age-related muscle atrophy in this population.

10.3 **Predictability of pre-training characteristics**

10.3.1 **Muscle size**

The finding that pre-training muscle size relates to RT-induced muscle growth in younger but not older adults is novel and indicates that this relationship could be mediated by age. The relationship between smaller pre-training muscle size and greater levels of growth in YOUNG agrees with the above-mentioned works from Roberts' lab showing significant, albeit moderate, negative correlations between various measures of muscle size at pre-training and RT-induced growth in their studies in younger men (Haun et al., 2019a; Mobley et al., 2018; Roberts et al., 2018b). Why smaller pre-training muscle size predicts greater RT-induced muscle growth in this population is as yet unknown but could relate to those with smaller pre-training muscle sizes possessing an enhanced capacity for muscle plasticity and/or smaller extracellular matrices allowing them to experience greater levels of muscle growth during RT (Mobley et al., 2018). Among older adults, our findings contrast with those of Bechshøft et al. (2017), who showed that those with smaller pre-training quadriceps CSAs demonstrated greater relative increases after 12 weeks of RT. The more advanced age of the participants in that study (86.9 ± 3.2 years) compared to ours (69.2 ± 2.7 years), however, makes them difficult to compare. In a similarly-aged cohort to ours (65.9 ± 1.1 years), Stec et al. (2016) showed no differences in pre-training muscle fCSA between hypertrophic responders and non-responders to a short RT program.

Why smaller pre-training muscle size indicates greater potential for growth in younger but not older individuals has not been explored in the literature. Speculatively, the greater variability in muscle size adaptations to RT in older adults likely contributes to their lesser relationship between pre-training size and training-induced growth. Indeed, correlations between pre-training characteristics and muscle growth in older adults are likely complicated by the greater range of muscle size responses to RT in this population and the consequences of aging on RT-induced muscle growth.

Interestingly, several studies using cohorts made up of *both* younger and older participants have shown that pre-training muscle size did not differ between hypertrophic responders and non-responders to RT (Bamman et al., 2007; Petrella et al., 2008; Phillips et al., 2013). Since participants were not separated by age in these studies, it cannot be determined whether pre-training muscle size differed between responders and non-responders of different ages. The results from our study demonstrate the importance of distinguishing between younger and older individuals when performing these types of analyses. Indeed, contrary to the relationship in YOUNG, when YOUNG and OLD were grouped, pre-training muscle size did not correlate with muscle growth. Thus, since the relationship between pre-training muscle size and RT-induced muscle growth differs between younger and older participants, these individuals should not be grouped when examining the hypertrophic predictability of this characteristic.

It should be noted that the correlation between pre-training muscle size and RT-induced muscle growth in YOUNG was relatively weak (r = -0.308) and accounted for less than 10 % of the variance in muscle growth. This may explain the insignificant differences in pre-training muscle size between muscle size responders and non-responders (Table 6) and the trend for high hypertrophic responders exhibiting smaller pre-training muscle sizes in some studies as noted in Table 2. Indeed, pre-training muscle size is likely just one of many factors that interact to differentiate between muscle size responders and non-responders (Roberts et al., 2018a). Furthermore, it is conceivable that an individual expressing several of the above-mentioned hypertrophic biomarkers, despite having a larger relative muscle size at baseline, would still demonstrate an increased hypertrophic response – increasing the average pre-training muscle size of responders. Conversely, an individual with few hypertrophic biomarkers *and* smaller relative muscle size at baseline would likely demonstrate a diminished hypertrophic response – decreasing the average pre-training muscle size of non-responders. Altogether, these results indicate that smaller pre-training muscle size signals a greater potential for muscle growth in younger but not older adults. The magnitude of this relationship, however, is small and many other factors likely contribute to one's RT-induced muscle size responsiveness.

10.3.2 **Muscle strength**

The relationship between pre-training muscle strength and RT-induced strength improvements in this study indicates that those with lower strength at the beginning of an intervention improve strength more than those with higher pre-training strength. This relationship was similar in both

YOUNG and OLD which is unsurprising given that younger and older adults experience similar strength adaptations to RT (see above). These findings agree with those of Newton et al. (2002) who showed that pre-training isometric squat strength correlated negatively with relative strength improvements after 10 weeks of RT in untrained younger and older men. The authors hypothesised that there are diminishing returns in terms of strength improvements following RT such that those with greater initial strength have a reduced window for training adaptations and vice versa (Newton et al., 2002). This is supported by studies showing significantly greater strength improvements in untrained compared to trained individuals following the same RT program (Ahtiainen et al., 2003). While these results are at odds with the previously mentioned studies showing no relationship between pre-training strength and RT-induced improvements (Chmelo et al., 2015; Erskine et al., 2010; Karavirta et al., 2011), the discrepancy likely relates to the differences in strength assessments (i.e., 1RM vs. MVC) described above.

Correlations between pre-training strength and RT-induced improvements, if they do exist, are typically weak and only account for a small proportion of the variance in relative strength increases (Balshaw et al., 2017; Erskine et al., 2014; Hubal et al., 2005; Lexell et al., 1995; Newton et al., 2002). This study showed that the correlation between pre-training strength and relative strength improvements was similarly weak (r = -0.296) and pre-training strength accounted for less than 9 % of the variance in strength improvements overall. Similar to that for muscle size, there were minimal differences between strength responders and non-responders in terms of pre-training strength. This indicates that many factors other than pre-training strength delineate strength responders from non-responders. Thus, while a relatively weaker individual may experience slightly greater improvements in strength during RT compared to one who is stronger, many other factors play a role in strength improvements, complicating the predictability of RT-induced strength outcomes based on pre-training level.

Despite the strong correlation between muscle size and strength at pre-training, no relationship was observed between the relative changes in muscle size and strength over the course of training. This finding contradicts what many believe about RT-induced strength improvements – that increases in muscle size play a role (Loenneke et al., 2019). While early researchers suggested that muscle growth plays an integral part in late-stage strength adaptations to RT (after the initial neural adaptations plateau) (Ikai & Fukunaga, 1970; Moritani & DeVries, 1979), these were largely speculative and based on the relationship between muscle size and strength at pre-training. Recent works showing marked improvements in one outcome (strength or

hypertrophy) in the absence of the other, however, challenge this assumption (Loenneke et al., 2019). Additionally, a correlation between muscle size and strength at baseline does not imply that their relative changes with training will correlate (Dankel et al., 2018). While a subject of great debate currently (Taber et al., 2019), increases in muscle size may not play as large a role in the RT-induced increases in muscle strength as previously assumed. The lack of correlation between the relative changes in muscle size and strength in this study and many others (Loenneke et al., 2019) adds to this debate and suggests that RT-induced increases in muscle size and strength are not as interconnected as once thought.

10.4 **Strengths and limitations**

There are many strengths of this investigation. First, the amalgamation of participants from three separate studies who underwent similar RT protocols and identical muscle size and strength measurements allowed for the effects of RT on muscle size and strength to be analyzed in a large sample of younger and older adults. The inclusion of both younger and older adults allowed for the determination of the differential effects of age on RT response heterogeneity. Although older men and women may exhibit differential responses to RT (Jones et al., 2021), this was not seen in the current investigation as relative changes in muscle size or strength did not differ between the two older sexes ($p > 0.05$). Thus, combining the older sexes into one group, which some may see as a limitation, did not adversely affect the analysis and increased the sample size of OLD, improving this study's statistical power. Additionally, the highly controlled, supervised, and progressive RT protocols that were used – designed according to the ACSM recommendations – maximized the likelihood of muscle mass and strength gain in each participant (Garber et al., 2011; Ratamess et al., 2009). The relatively long durations of these RT interventions are another strength of this investigation. Indeed, 6-12 months is ample time for RT adaptations to occur, minimizing the chance of "slow-responders" being mislabelled as non-responders (Churchward-Venne et al., 2015; Pickering & Kiely, 2019).

The main limitation of this investigation is the different lengths of RT protocols of the included studies. Indeed, since the duration of an exercise intervention plays a large role in the magnitude of training adaptations (Garber et al., 2011), it is plausible to assume that those in the 12-month interventions experienced greater adaptations than those in the 6-month interventions. While this is likely the case, evidence from older individuals undergoing 12 months of RT shows that the rate of adaptations slows considerably after the initial 3-4 months (Pyka et al., 1994). Thus,

the difference in RT adaptations between 6- and 12-month exercisers may be minimal. This cannot be assumed, however, and the discrepancies in intervention duration between the three studies is recognized as a major limitation. Another major limitation is the absence of a non-exercise, time-matched control group. The inclusion of a control group would have allowed a more precise detection of true score change among RT participants and a more precise estimation of SWC taking into account measurement accuracy and day-to-day biological variability in muscle size and strength among controls (Ahtiainen et al., 2016; Swinton et al., 2018). The absence of a group comprising of younger, adult women is also a limitation. Unfortunately, at the time of writing, no study from our laboratory had carried out the same measurements of muscle size and strength in younger women undergoing prolonged RT. This prohibited their inclusion in the analysis and prevented the examination of the differential effects of age *and* sex on RT response heterogeneity. Additionally, while dietary intake was logged in two of the included studies (Ahtiainen et al., 2015; Hulmi et al., 2015), nutritional information was not available for all participants in this investigation. Thus, the influence of dietary factors such as protein intake on RT adaptations could not be determined. This is a key limitation given that decreased protein intake among older populations may contribute to their diminished RT-induced muscle growth response compared to younger individuals (Mero et al., 2013). It should also be noted that changes in muscle CSA may differ along the length of a muscle following RT (Earp et al., 2015). Measuring muscle size at one point along a muscle then, as was done in the studies in this investigation, may not accurately reflect the changes induced by RT (Earp et al., 2015). Lastly, the current findings can only be generalized to the quadriceps muscles of previously untrained, apparently healthy younger men and older men and women. Future research should aim to determine the heterogeneity in RT adaptations among trained individuals, younger women, and in different muscle groups.

10.5 **Conclusions**

This retrospective analysis showed that, while the majority of younger men (20-45 years) and older men and women (60-80 years) experience increases in muscle size and strength following RT, there is a considerable level of inter-individual variation in these responses. Indeed, over one-third of participants were classified as strength non-responders while nearly half were muscle size non-responders following 6-12 months of supervised, progressive RT. Importantly, only a small proportion of participants (15 %) were classified as non-responders for both muscle size and strength indicating that most individuals gain at least some benefit from RT.

When compared to younger adults, older adults showed diminished levels of muscle growth but similar improvements in strength at the group level. Older adults also demonstrated greater variability and higher levels of non-response in terms of muscle size but not strength changes following training compared to younger adults. This indicates that aging impairs the muscle size but not strength response to RT. The higher degree of variability in muscle size adaptations in older adults is likely due to large inter-individual variation in age-related muscle decline (Degens & Korhonen, 2012). Further research is required, however, to confirm this.

Pre-training muscle size was moderately related to RT-induced changes in muscle size in younger but not older adults. This discrepancy likely arises from the high variability in muscle size adaptations among older adults. Pre-training strength, on the other hand, was moderately related to RT-induced strength changes in both age groups, indicative of the similar strength adaptations between younger and older individuals. Interestingly, RT-induced changes in muscle size were not related to changes in muscle strength regardless of age, indicating that muscle growth may not be required to increase strength during long-term RT in previously untrained individuals.

This investigation shows that RT adaptations differ considerably between individuals performing the same training program, regardless of age. Furthermore, older individuals exhibit diminished and more variable muscle size but not strength responses to RT compared to younger adults. While pre-training value may be related to the RT-induced changes in muscle size and strength, it only explains a small proportion of the variance in these outcomes indicating that many other factors contribute to the inter-individual variation in muscle size and strength.

10.6 **Practical applications**

The range of individual responses observed in this study demonstrates the importance of individualization when designing and progressing resistance training programs. Exercise participants, especially those new to resistance training, should be continually monitored to ensure that they are responding appropriately and according to their training goal(s). If an individual is not responding appropriately or is demonstrating non-response, steps should be taken to alter their training program to maximize responsiveness (changing the exercise

intensity, volume, and/or frequency for example). This is especially important for practitioners working with older adults as they may be at a greater risk of muscle size non-response compared to younger adults. Accordingly, resistance training prescriptions aimed at maximizing muscle growth may need to be differentiated for older adults. Lastly, practitioners should be aware that those with relatively weaker and/or smaller muscles at the beginning of a resistance training program may improve more rapidly than those with relatively stronger and/or larger muscles. These individuals may need to be progressed more quickly to ensure they are provided with sufficient stimulus for continued neuromuscular adaptations.

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APPENDICES

APPENDIX 1: Example 2 day/week resistance training protocol

	Sets	Reps	Intensity	Inter-Set Rest
Primary Exercises				
Leg Press	3-4	8-12 or UCF	75-85 % of 1RM	1 minute
Knee Flexion	3-4	8-12 or UCF	75-85 % of 1RM	1 minute
Knee Extension	2-3	10-15 or UCF	75-85 % of 1RM	1 minute
Secondary Exercises (alternated each session)				
Bench Press (Day 1) / Lat Pulldown (Day 2)	3-4	10-15 or UCF	70-85 % of 1RM	1 minute
Accessory Exercises	2-4	8-15 or UCF	70-85 % of 1RM	1 minute

Day 1 accessory exercises: shoulder press, elbow extensors, upper-back/rear deltoideus, hip abductors and adductors.

Day 2 accessory exercises: horizontal row, elbow flexors, torso rotators, abdominals, back extensions

UCF until concentric failure, RM repetition maximum. Adapted from Hulmi et al. (2015)