Adaptations to concurrent training in healthy active men: the role of exercise session order

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Abstract

Concurrently performing endurance and resistance exercise within the same training program presents a theoretically optimal training method for improving athletic performance, as well as attaining the multiple health benefits from both modes of training. However, many studies provide evidence demonstrating that concurrent training can attenuate the development of hallmark resistance training adaptations such as strength, muscle hypertrophy, and power, compared to performing resistance training alone. This phenomenon has been termed the "*interference effect*" or the "*concurrent training effect*". Whilst much research has been dedicated to understanding this effect, the precise causes are not well known, and are further confounded by a growing body of conflicting literature. Given that endurance and resistance exercise transiently induce distinct molecular responses that govern their respective mode-specific phenotypic adaptations, it has been proposed that some degree of molecular incompatibility between the different exercise modes may contribute to the interference effect; however, supportive evidence in human studies is lacking. Furthermore, the nature of the interference effect may largely be dictated by the manipulation of training variables (*e.g., exercise order, intensity, frequency, volume, mode, recovery duration*) and non-training variables (*e.g., training status, nutrient availability*).

The overarching aim of this thesis was to investigate the effects of concurrent endurance and resistance training on the development of hallmark resistance and endurance training adaptations, and the molecular responses that regulate them. A secondary aim was to investigate the effect of manipulating the order in which concurrent exercise sessions are performed. An in-depth review of the existing concurrent training literature was conducted (*Chapter 2*), followed by an original body of research designed to investigate how exercise-induced molecular responses to resistance-only and concurrent exercise differ before and after a period of a structured training (*Chapter 4*), whilst simultaneously assessing the effects of concurrent training (in both orders) on the development of whole-body training adaptations compared to resistance-only training (*Chapter 5*). As such, data in each chapter were derived from one major training study involving the same cohort of participants who performed acute, experimental exercise trials both before and after a 9-week period of training.

Following familiarisation and baseline fitness testing, twenty-nine healthy, active men were ranked according to their baseline levels of maximal strength, aerobic fitness, and lean body mass, and allocated to one of three training groups in a counterbalanced order: 1) *RO*, resistance-only exercise; 2) *ER*, endurance prior to resistance exercise; or 3) *RE*, resistance followed by endurance exercise. On the first training day in both Weeks 1 and 10, *twenty-five* of these participants completed an "*experimental*" training day, during which muscle biopsies were obtained

immediately before, after, and 3 hours after each exercise session, to characterise temporal changes in gene expression and protein phosphorylation across a full day in response to resistance-only and concurrent exercise, before and after a period of training. Between Weeks 1 and 10, all *twenty-nine* participants completed 8 weeks of structured training in their respective groups (Weeks 2 to 9). The training program was of a moderate frequency (3 days a week), and the same-day concurrent sessions were separated by 3 hours of recovery. The battery of anthropometric, physiological, and performance tests were repeated during, and after the training program to assess changes in whole-body adaptations in response to the different training programs.

Chapter 4 represents the first study of its kind that attempts to elucidate the extended time-course of molecular responses to both concurrent and resistance-only exercise when performed in the fed-state, in both the untrained (*Week 1*) and training-accustomed states (*Week 10*). Following training, all groups demonstrated comparable increases in resting muscle glycogen concentration. Despite concurrent exercise (regardless of the order) inducing greater muscle glycogen depletion than resistance-only exercise by the end of each day, as well as transiently upregulating purported inhibitors of anabolic signalling pathways, the findings in this study do not clearly support the premise that concurrent exercise induces a molecular interference effect. Novel findings include the similar, rather than divergent, patterns of expression between AMPK and Akt, as well as the characterisation of Mighty mRNA expression, which has not been previously reported in resistance and concurrent exercise models in human skeletal muscle. This study also provides supportive evidence for resistance exercise-induced increases in PGC-1α mRNA, contraction-induced reductions in myostatin mRNA, and the differential regulation of 'atrogenes' (MuRF1 and MAFbx) in response to endurance and resistance exercise. Finally, this study also provides support for training-induced changes in molecular responses to exercise, whereby several genes and proteins (related to mitochondrial biogenesis, protein degradation and translation) elicited more transient, and smaller perturbations in the training-accustomed, compared to untrained state.

Whilst the data gleaned from *Chapter 4* did not clearly indicate that performing concurrent exercise would 'acutely' interfere with the molecular responses governing resistance training adaptations, the relationship between exercise-induced molecular responses and training-induced adaptations is not always clear. Therefore, the aim of *Chapter 5* was to assess changes in hallmark endurance and resistance adaptations, following 9 weeks of resistance-only and concurrent training in both exercise orders. The main findings demonstrate that concurrent training, irrespective of the session order, led to comparable improvements in maximal strength and lean body mass to that of resistance-only training. Furthermore, independent of the session order, both concurrent groups similarly improved all markers of aerobic fitness more than resistance-only

training. However, performing endurance training *after* resistance training (i.e., *RE*) attenuated the development of countermovement jump displacement, force, and power compared to resistance-only training; the reverse exercise order (i.e., *ER*) possibly had a negative effect on these parameters. In addition, only the *RE* group displayed a meaningful reduction of total fat mass following training. This chapter also provides novel data regarding the participants subjective wellbeing and "readiness-to-train" prior to all exercise sessions, as well as their training load (both internal and external). In combination with the performance and physiological data, this study indicates that whilst all three groups completed similar volumes of resistance training, performing endurance training *before* resistance training may lead to greater perceptions of internal training load, and more negative perceptions of total wellbeing, muscle soreness, stress and mood.

Collectively, the results from this body of work do not support the premise of compromised molecular responses, or subsequent strength and lean mass gains, following concurrent training, compared to only performing resistance training. In healthy, active men, a short-term concurrent training program, regardless of exercise order, presents a viable strategy to improve lower-body maximal strength and total lean body mass comparably to resistance-only training, whilst also improving aerobic fitness. However, improvements in some measures of countermovement jump performance were attenuated with concurrent training, particularly when resistance exercise was performed first. There were also possible effects of exercise order on changes in countermovement jump performance (favouring *ER*) and reductions in fat mass (favouring *RE*); however, more data are required to determine the importance of these effects.

For healthy, active individuals engaging in same-day concurrent training, with short recovery durations, the choice of exercise order could be dictated by personal preference, given that the exercise order may affect perceptions of "readiness-to-train" prior to, and perceptions of effort after, resistance exercise. Perhaps more importantly, the exercise order should be periodised according to the specific goals of an individual training cycle. However, in environments where the exercise order may be dictated by external factors (e.g., congested competition schedules, restricted availability of training facilities), careful consideration should also be given to the effects of other training and non-training variables, to minimise potential interference effects and maximise concurrent training adaptations.

Student Declaration

I, Matthew Lee, declare that the PhD thesis entitled "*Adaptations to concurrent training in healthy active men: the role of exercise session order*" is no more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

Signature: _____

Date: _____

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And with that, I hope you all enjoy this thesis [1].

[1] *A thesis which has been described as, and I quote, 'lovely stuff'. Not my words, Cian, the words of Shakin' Stevens.*

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List of Publications, Conferences and Awards

Publications and conference presentations in support of this thesis

The following have been published in peer reviewed journals, books and/or presented at scientific meetings during candidature, in support of this thesis:

- **Lee MJ**, Ballantyne J, Chagolla J, Bishop DJ, and Bartlett JD. (2018). The effect of concurrent exercise order on training adaptations in active males. Oral presentation given at: *23rd Annual Congress of the European College of Sport Science*. July 4th-7th, 2018. Dublin, Ireland.
- Bishop DJ, Bartlett J, Fyfe J, and **Lee M.** (2019). Methodological considerations for concurrent training. In Schumann, M., Rønnestad, B. (Eds.), *Concurrent Aerobic and Strength Training: Scientific Basics and Practical Applications* (pp. 183-196). Cham, Switzerland: Springer. doi:10.1007/978-3-319-75547-2_13

Other publications and conference presentations arising during candidature

The following have been published in peer-reviewed journals and/or presented at scientific meetings during candidature, but are outside the scope of this thesis:

- Routledge HE, Leckey JJ, **Lee MJ**, Garnham A, Graham S, Burgess D, Burke LM, Erskine RM, Close GL, and Morton JP. (2018). Muscle Glycogen Utilisation during an Australian Rules Football Game. *International Journal of Sports Physiology and Performance*, 1-13. doi:10.1123/ijspp.2018-0106
- Pitchford NW, Bishop DJ, Bartlett JD, and **Lee MJ.** (2018). Does more sleep enhance recovery? Influence of post-exercise sleep extension on physiological, neuromuscular and perceptual recovery. Poster presentation given at: *Exercise and Sports Science Australia Conference.* March 27th-29th, 2018. Brisbane, Queensland, Australia.
- Bishop DJ, Botella J, Genders AJ, **Lee MJ**, Saner NJ, Kuang J, Yan X, and Granata C. (2019). High-Intensity Exercise and Mitochondrial Biogenesis: Current Controversies and Future Research Directions. *Physiology*, 34(1): 56-70. doi:10.1152/physiol.00038.2018

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List of Abbreviations

%	percentage
°	degree (angle)
°C	degree (Celsius)
1-RM	1-repetition maximum
4E-BP1	eukaryotic initiation factor 4E binding protein 1
5’-TOP	5’-tract of pyrimidine
90%CI	90% confidence interval
99%CI	99% confidence interval
ACC	acetyl-coA carboxylase
ACTB	beta actin
ADP	adenosine diphosphate
AMP	adenosine monophosphate
AMPK	adenosine monophosphate-dependent protein kinase
Atg	autophagy-related protein
ATP	adenosine triphosphate
BASE	baseline
BM	body mass
BMP	bone morphogenetic protein
BSA	bovine serum albumin
Ca2+	calcium ion
CaMK	Ca2+/calmodulin-dependent protein kinase
cDNA	complementary DNA
cm	centimetre
CMJ	countermovement jump
CREB	cyclic AMP response element-binding protein
CSA	cross-sectional area
CV	coefficient of variation
d	Cohen's effect size
d	day
DAG	diacylglycerol
DEPC	diethylpyrocarbonate-treated water
DEPTOR	dishevelled, eg1-10, pleckstrin domain containing mTOR-interacting protein
DGKζ	diacylglycerol kinase zeta
DM	dry mass
DNA	deoxyribonucleic acid

DXA	dual-energy x-ray absorptiometry
ECL	electrochemiluminescence
EDTA	ethylenediaminetetraacetic acid
eEF	eukaryotic elongation factor
eEF2K	eukaryotic elongation factor 2 kinase
eIF	eukaryotic initiation factor
END	endurance exercise
ER	endurance-resistance
eRF	eukaryotic release factor
ES	standardised effect size
FAM	familiarisation trial
FIP200	focal adhesion kinase family interacting protein of 200 kDa
FOXO	forkhead box-O
FRB	FKBP12-rapamycin-binding
FSR	fractional synthetic rate
g	grams
GAP	GTPase-activating protein
GAPDH	glyceraldeyde-3-phosphate dehydrogenase
GATOR	GAP Activity Towards Rags
GDP	guanosine diphosphate
GEF	guanine exchange factor
GTP	guanosine triphosphate
GXT	graded exercise test
h	hour
HCL	hydrochloric acid
HIIT	high-intensity interval training
ICC	intra-class correlation coefficient
IGF-1	insulin-like growth factor 1
IGF-BP3	insulin-like growth factor binding protein 3
IRS	insulin receptor substrates
JNK	c Jun N-terminal kinase
kcal	kilocalorie
kDa	kilodalton
kg	kilogram
kJ	kiloJoule
km	kilometre

L	litre
LRS	leucyl tRNA synthase
m	metre
MAFbx	muscle-specific atrophy F box
MAPK	mitogen activated protein kinase
MDM2	murine double minute 2
MEF2	myocyte enhancer factor-2
mg	milligram
MID	mid-training timepoint
min	minute
mL	millilitre
mLST8/GβL	mammalian lethal with SEC13 protein 8/G-protein beta subunit-like protein
mM	millimolar
mmol	millimole
MPB	muscle protein breakdown
MPS	muscle protein synthesis
mRNA	messenger ribonucleic acid
mSIN1	mammalian stress-activated protein kinase-interacting protein 1
mtDNA	mitochondrial DNA
mTOR(C1C2)	mechanistic target of rapamycin (complex 1 and 2)
MuRF1	muscle RING finger-1
MyoD	myogenic differentiation 1
N	newton
Na3VO4	sodium orthovanadate
Na4P2O7	sodium pyrophosphate tetrabasic
NaCl	sodium chloride
NAD+	oxidised nicotine adenine dinucleotide
NADH	reduced nicotine adenine dinucleotide
NaN3	sodium azide
NaOH	sodium hydroxide
nm	nanometre
nM	nanomolar
NP-40	nonyl phenoxypolyethoxylethanol
NRF 1/ 2	nuclear respiratory factor 1
NuGEMPs	nuclear genes encoding mitochondrial proteins
p-	phosphorylated

p70S6K	70 kilodalton ribosomal protein subunit kinase
PA	phosphatidic acid
PABP	poly(A) binding protein
PCR	polymerase chain reaction
PDCD4	programmed cell death protein 4
PDK1	phosphoinositol-dependent kinase-1
PGC-1α	peroxisome proliferator-activated receptor-γ coactivator-1α
pH	negative logarithm (base 10) hydrogen ion activity/concentration
PHF20	PHD finger protein 20
Pi	inorganic phosphate
PI3K	phosphatidylinositol 3-kinase
PIP2	phosphatidylinositol (4,5)-bisphosphate
PIP3	phosphatidylinositol (3,4,5)-trisphosphate
PKB/Akt	protein kinase B
PLD	phospholipase D
Plk2	polo-like kinase 2
POST	post-training timepoint
PP2A	protein phosphatase 2A
PRAS40	proline-rich Akt substrate of 40 kDa
PROTOR	protein observed with rictor
PTEN	phosphatase and tensin homologue
PVDF	polyvinylidine fluoride
Rag	ras-related guanosine triphosphate binding
raptor	regulatory associated protein of mTOR
RE	resistance-endurance
reps	repetitions
RES	resistance exercise
RFD	rate of force development
Rheb	ras homologue enriched in brain
rictor	rapamycin-insensitive companion of mTOR
RIR	repetitions in reserve
RM	repetition maximum
RNA	ribonucleic acid
RO	resistance-only
ROS	reactive oxygen species
RPE	rating of perceived exertion

RPM	revolutions per minute
rpS6	ribosomal protein S6
RQI	RNA quality indicator
rRNA	ribosomal ribonucleic acid
s	second
SD	standard deviation
SDS	sodium dodecyl sulphate
SDS-PAGE	sodium dodecyl sulphate–polyacrylamide gel electrophoresis
Ser	serine
SIRT	sirtuins
Smad	small mother of decapentaplegic
SCO2	synthesis of cytochrome c oxidase 2
sRPE	session rating of perceived exertion
TBP	TATA-binding-protein
TBS	tris-buffered saline
TBST	tris-buffered saline with Tween-20
TEM	typical error of measurement
Tfam	mitochondrial transcription factor A
TGF-β	transforming growth factor-β
Thr	threonine
TOS	TOR signalling
Tris	tris(hydroxymethyl)aminomethane
tRNA	transfer ribonucleic acid
TSC1/2	tuberous sclerosis complex (1/2)
UBF	upstream binding factor
ULK1	unc-51-like kinase 1
UTR	5’-untranslated region
V	volt
v-ATPase	vacuolar H+-adenosine triphosphatase
VCO_2	volume of carbon dioxide
VEGF	vascular endothelial growth factor
VO_2	volume of oxygen
$\dot{V}O_{2peak}$	peak rate of oxygen uptake
W	watt
$\dot{W}Ex$	relative exercise intensity
wk	week

$\dot{W}_{LT}$	power at the lactate threshold
$\dot{W}_{peak}$	peak aerobic power
WT	wild-type
y	year
β2M	β2-microglobin
μg	microgram
μL	microlitre

Chapter 1 General Introduction, Aims and Objectives

1.1 Introduction

A periodised training programme involving both endurance and resistance exercise sessions is termed concurrent training (Dudley and Djamil, 1985, Hickson, 1980). These sessions may be performed back-to-back (affording a time-efficient training method) or separated by hours or days of recovery. In theory, concurrent training represents an ideal training strategy for both athletes and non-elite, recreationally-active populations, to simultaneously develop divergent skeletal muscle adaptations (i.e., hypertrophy, strength, and power, as well as aerobic fitness). Furthermore, from a health perspective, regularly performing endurance and resistance exercises is widely recommended for healthy (American College of Sports Medicine, 2009, Garber et al., 2011), sedentary (Australian Government, 2014), overweight (Jakicic et al., 2001), and elderly populations (Chodzko-Zajko et al., 2009), as well as individuals with hypertension (Pescatello et al., 2004), diabetes (Colberg et al., 2010) and coronary artery disease (American College of Sports Medicine, 1994). In Australia, where 63% of the population are now overweight or obese (Leung et al., 2014), cardiovascular and musculoskeletal diseases were allocated the 1st and 4th highest health expenditure respectively between 2008-09 (Australian Institute of Health and Welfare, 2014). Thus, concurrent training may be useful not just for improving performance in sports which demand concomitantly-high levels of both endurance and resistance adaptations, but also for helping to prevent and combat several metabolic and musculoskeletal diseases that present an increasing burden on the healthcare system (Fyfe et al., 2014).

The malleability of skeletal muscle in response to a range of stimuli is well known, and adaptations to different modes of exercise, such as endurance or resistance, are highly specific to the stimulus applied (Fluck and Hoppeler, 2003, Hoppeler et al., 2011). Consequently, the divergent nature of these exercise modes raises the question: *can endurance and resistance adaptations be developed simultaneously to the same degree as with single-mode training?* This was first addressed in a seminal paper by Dr Robert Hickson (1980), an avid powerlifter who observed that his own strength and muscle mass gains were diminishing after having incorporated endurance running into his strength regimen (Baar, 2014). He investigated changes in maximal leg strength, body composition, and aerobic power ($\dot{V}O_{2max}$) over 10 weeks of training, in three groups of recreationally-active men and women: *(1)* strength-only [S]; *(2)* endurance-only [E]; and *(3)* concurrent strength-endurance [SE]. The strength programme, performed 5 $d \cdot wk^{-1}$, consisted of lower-body exercises in which participants were instructed to lift "*as much weight as possible*" (3-5 sets, 3-20 reps, ≥ 80% of their max). The endurance training, performed 6 $d \cdot wk^{-1}$, involved both high-intensity interval cycling (6 × 5 min bouts at ~$\dot{V}O_{2max}$, 3 $d \cdot wk^{-1}$) and continuous

running (30-40 $min \cdot d^{-1}$, performed "*as fast as possible*", 3 $d \cdot wk^{-1}$). The SE group completed both programs with at least 2 hours recovery between each mode. The strength group improved their lower-body strength each week, however the concurrent group paralleled these improvements only for the first 7 weeks, after which their strength plateaued, and subsequently declined over the last two weeks. Conversely, both the endurance and concurrent groups elicited similar improvements in $\dot{V}O_{2max}$ (measured on both a cycle ergometer and treadmill) and completed the same amount of work on the cycle ergometer each week. These results suggested that concurrent endurance and resistance exercise could selectively hinder resistance adaptations, with no negative effects on endurance parameters.

Since Hickson's work, several others have also shown that when combined, either in the same session (Babcock et al., 2012, Chtara et al., 2008, Coffey et al., 2009a, Coffey et al., 2009b, Sale et al., 1990a) or separate sessions/days (Bell et al., 2000, Dudley and Djamil, 1985, Häkkinen et al., 2003, Hennessy and Watson, 1994, Hickson, 1980, Kraemer et al., 1995), concurrent training can induce sub-optimal strength, power and/or hypertrophic adaptations in comparison to resistance-only training. This phenomenon is commonly known as the "*interference effect*" or the "*concurrent training effect*" (Baar, 2006, Hawley, 2009, Hickson, 1980, Nader, 2006). However, it should also be noted that there are also several studies that do not provide supporting evidence of an interference effect on resistance adaptations following concurrent training (McCarthy et al., 1995, McCarthy et al., 2002, Murach and Bagley, 2016, Sale et al., 1990b). Furthermore, whilst some studies have reported negative effects (Levin et al., 2009), the consensus is that endurance parameters are largely unaffected (Wilson et al., 2012), and in many cases improved, by the addition of resistance exercise (Irving et al., 2015, Ronnestad et al., 2015, Ronnestad and Mujika, 2014, Vikmoen et al., 2015, Wang et al., 2011).

The interference effect is suggested to occur as a result of both '*acute*' and '*chronic*' factors; residual fatigue, substrate depletion, muscle damage, and metabolite accumulation, coupled with the inherent dichotomy of endurance and resistance adaptations on a structural and functional level that prevent the muscle from simultaneously meeting the divergent metabolic and morphological demands of both exercise modes following training (reviewed in Leveritt et al. (1999) and Nader (2006)). However, the extent to which each of these factors (and others) contribute to the interference effect remains uncertain. Indeed, our understanding of the precise cause*(s)* of this "interference", and the extent to which training variables (such as exercise order, frequency, intensity, duration) may be manipulated to reduce it, require further research.

The growing use of molecular biology techniques in exercise science has shifted the search for mediators of an interference effect toward the different exercise-induced cell signalling pathways,

gene expression, and protein synthesis responses that dictate endurance and resistance training adaptations (Baar, 2014, Coffey and Hawley, 2007, Hawley, 2009). However, whilst potential molecular mechanisms orchestrating the interference effect have emerged over the last decade, much of our current understanding of the molecular events induced by endurance and resistance exercise is based on studies using pharmacological activation of signalling pathways in cell culture, or electrically-stimulated contractions in animal muscle (Atherton et al., 2005, Fyfe et al., 2014, Ogasawara et al., 2014); indeed, conclusive evidence of such mechanisms in human skeletal muscle remains elusive (Apró et al., 2015, Apró et al., 2013, Coffey et al., 2009a, Coffey et al., 2009b, Lundberg et al., 2012, Lundberg et al., 2013, Lundberg et al., 2014). This inconsistency is not helped by the myriad of training and non-training variables employed in concurrent training studies (e.g., exercise order, participant training status, nutrient availability, recovery duration, exercise frequency, intensity and modality, and dependent variable selection), precluding definitive conclusions being drawn from across the literature (Fyfe et al., 2014, Leveritt et al., 1999). Furthermore, whilst these studies provide important mechanistic insight into the acute molecular responses following a single bout of exercise, the extent to which these signalling events relate into the potential for, and magnitude of, training-induced phenotypic adaptations remains unclear (Fyfe et al., 2014, Mitchell et al., 2015). As such, there is a need for more research to elucidate the time-course of concurrent training adaptations and the relationship between acute post-exercise molecular signalling events and long-term phenotypic adaptations.

Careful consideration of how to manipulate the multitude of variables that impact the development of training adaptations is imperative to achieve the desired adaptation. Whilst the effect of concurrent exercise session order has received growing interest in recent years, it remains unclear whether performing endurance (Chtara et al., 2005, Enright et al., 2015) or resistance exercise first (Cadore et al., 2012, Cadore et al., 2013) offers a more favourable stimulus for concurrent training adaptations, whilst others have shown no order effect (Chtara et al., 2008, Collins and Snow, 1993, Davitt et al., 2014, Eklund et al., 2015, Gravelle and Blessing, 2000, MacNeil et al., 2014, Schumann et al., 2014a). Furthermore, much of this research has focussed on the development of whole-body adaptations following a period of training; few studies to date have investigated the molecular responses to concurrent exercise, and fewer still have specifically investigated their effects under alternate exercise orders (Coffey et al., 2009a, Coffey et al., 2009b, Jones et al., 2016). Consequently, more research is needed to investigate the role of concurrent exercise order on acute molecular responses and the subsequent development of whole-body endurance and resistance adaptations.

1.2 Aims and objectives

The aim of this thesis is to investigate how the order in which concurrent endurance and resistance exercise are performed affects different exercise-induced molecular responses, as well as the development of whole-body training adaptations, compared to resistance-only training, in healthy, active men, both before and after a 9-week training period, when sessions are performed in the fed-state and separated by 3 hours of recovery.

This was achieved by examining:

1. Acute changes in post-exercise molecular responses (mRNA expression and protein phosphorylation) after a single session of resistance-only or concurrent exercise performed in both orders (*i.e., resistance-only vs endurance→resistance vs resistance→endurance*), both before and after a training intervention (*Chapter 4*);
2. Training-induced changes in whole-body endurance and resistance adaptations (i.e., strength, power, muscle mass, and aerobic fitness) following 9 weeks of training (*Chapter 5*).

Given the popularity and relevance of concurrent training for improving exercise capacity, muscle mass, strength and power in a range of populations, these data may help to inform a better approach to concurrent training practice not only for more appropriate training program design in athletic populations, but may also have implications for further research involving concurrent exercise prescription for preventing and countering several metabolic, musculoskeletal, and aging-related diseases.

Chapter 2 Literature Review

2.1 The Specificity and Molecular Basis of Training Adaptations

Skeletal muscle is a highly malleable and abundant tissue, comprising around 45-55% of total body mass, and capable of responding to a range of stimuli (Fluck and Hoppeler, 2003, Goodman, 2014, Zierath and Hawley, 2004). In the context of exercise, the resulting structural and functional adaptations are highly specific to the type, intensity, volume and frequency of the stimulus imposed (Hawley, 2002, Hawley, 2009, Hoppeler et al., 2011). Endurance and resistance exercise represent divergent modalities, with contrasting phenotypes that sit at opposing ends of the adaptation spectrum (Hoppeler et al., 2011, Nader, 2006). Endurance training leads to an increase in oxidative capacity, mediated by mitochondrial biogenesis (Holloszy, 1967), changes in substrate utilisation toward a greater reliance on fats to fuel sub-maximal exercise (sparing carbohydrates at the same relative intensity (Hurley et al., 1986, Phillips et al., 1996)), and a greater proportion of fatigue-resistant muscle fibres (Andersen and Henriksson, 1977, Simoneau et al., 1985). Conversely, resistance training induces neuromuscular and morphological adaptations, such as increased muscle fibre size, recruitment, and force production, resulting in increases in hypertrophy, strength, and power (Folland and Williams, 2007).

Improvements in molecular biology techniques have enabled exercise physiology researchers to further our understanding of the acute cellular and molecular processes that govern training adaptations (Baar, 2014). It is now understood that exercise-induced homeostatic perturbations within the muscle milieu (e.g., changes in AMP:ATP, P_i, NAD^+:NADH, Ca^{2+}, ROS, mechanical stretch) are detected by various sensors, which initiate a cascade of transient molecular signalling events regulating gene expression, transcription, and translation of new proteins. With repeated stimulation through training, the cumulative effect of multiple exercise sessions increases protein content and enzyme activity, leading to a new steady-state, in turn promoting structural and functional adaptations that are representative of the stimulus (i.e., endurance or resistance), and resulting in a reduced homeostatic disturbance to subsequent sessions (Baar et al., 2002, Coffey and Hawley, 2007, Egan and Zierath, 2013, Perry et al., 2010).

Although endurance and resistance exercise are associated with distinct molecular signalling events, it should be noted that there is potential for "cross-over" between these divergent modes and their resulting adaptations. Indeed, endurance exercise can induce growth signalling and protein synthesis (Harber et al., 2010, Mascher et al., 2011), and result in skeletal muscle hypertrophy (Konopka and Harber, 2014). However, it should be noted that this may occur via different molecular mechanisms to resistance exercise, as endurance exercise has been shown to

stimulate protein synthesis in both myofibrillar and mitochondrial subfractions despite mTORC1 (a key regulator of skeletal muscle growth, subsequently discussed) being suppressed (Philp et al., 2015). Resistance exercise has also been shown to potentiate signalling associated with mitochondrial biogenesis (Wang et al., 2011) and improve whole-body aerobic capacity (Alvehus et al., 2014). This cross-over effect appears to be particularly dependent upon factors such as participant training status and the type of stimulus imposed (Coffey et al., 2006b, Wilkinson et al., 2008); the evidence for which will be discussed later this review. Nonetheless, given that the distinct molecular pathways governing endurance and resistance adaptations are energy-producing and energy-consuming respectively (Kimball, 2006), it is reasonable to suggest that simultaneously training these contrasting modes may result in some degree of molecular incompatibility, ultimately compromising training adaptations (Hawley, 2009). To better explore the notion of the interference effect between concurrent exercise modes, at both the molecular and whole-body levels, it is first prudent to understand the regulatory steps involved in the development of resistance and endurance phenotypes, respectively.

2.2 Resistance Exercise & Training Adaptations

The capacity to produce high levels of force, and the rate at which those forces are developed, are positively associated with the performance of several general and sport-specific skills, as well as a reduced risk of injury (Suchomel et al., 2016). From a health perspective, age-related declines in muscle mass and strength (respectively termed sarcopenia and dynapenia) can significantly impact daily physical function, overall quality of life, and are associated with several diseased states and adverse health outcomes (Beaudart et al., 2017, Clark and Manini, 2008, Winett and Carpinelli, 2001). Consequently, the development and maintenance of strength, muscle mass, and power are important not only for athletic populations, but also for general health and wellbeing. This can be achieved through regular resistance exercise, which is an effective mode of training for increasing strength, hypertrophy, and power, and is widely recommended by several health organisations for a range of populations (Kraemer et al., 2002).

The hallmark adaptation to resistance training is an increase in maximal strength, which is underpinned by both neural and morphological adaptations (Folland and Williams, 2007). Typically, neural adaptations are considered predominantly responsible for the rapid increases in strength observed during the early phases of a resistance training program (Sale, 1988), prior to notable changes in muscle mass (Seynnes et al., 2007). Neural mechanisms contributing to early improvements in strength with resistance training include improvements in co-ordination and motor learning (Rutherford and Jones, 1986), increased activation of specific agonist muscles (Hakkinen and Komi, 1983, Moritani and deVries, 1979, Narici et al., 1989) facilitated by changes

in motor unit recruitment and firing frequency (Van Cutsem et al., 1998, Vila-Cha et al., 2010), and a concomitant reduction in co-activation of antagonist muscles (Carolan and Cafarelli, 1992). Given that this body of work will largely focus on the development of overall strength and muscle mass, as well as the molecular regulation of muscle mass accretion in response to resistance-only and concurrent training, the neural adaptations to resistance training will not be reviewed here (see Gabriel et al. (2006) and Sale (1988)).

As training continues, further improvements in strength are associated with muscle hypertrophy. Resistance training-induced increases in whole-muscle size are facilitated by increases in muscle fibre cross-sectional area (CSA) (McDonagh and Davies, 1984), which have been suggested to occur through the increased production and parallel arrangement of contractile and structural proteins (rather than an increase in the *number* of muscle fibres, termed hyperplasia), subsequently increasing the contractile capacity of the muscle (Folland and Williams, 2007, Russell et al., 2000). Muscle hypertrophy appears to preferentially occur in type II fibres (Fry, 2004, Tesch, 1988); however, type I fibre hypertrophy has been observed, albeit to a lesser degree (Häkkinen et al., 1981). Indeed, this may largely depend on the training load and time under tension (Grgic et al., 2018a, Ogborn and Schoenfeld, 2014). In addition to fibre area, resistance training may also affect the proportion of fibre types, with evidence of transitions from type IIx to IIa (Staron et al., 1994, Staron et al., 1991, Staron et al., 1990). Indeed, cross-sectional analyses reveal a greater proportion and size of type II fibres in strength-trained individuals compared with untrained controls (Fry et al., 2003a, Fry et al., 2003b, Jürimäe et al., 1997), and these type II fibre characteristics have been correlated with various measures of strength (Dons et al., 1979, Fry et al., 2003a, Fry et al., 2003b, Jürimäe et al., 1997).

2.2.1 The regulation of skeletal muscle mass: protein turnover

Skeletal muscle of healthy active individuals turns over ~1 to 2% of muscle proteins per day, with the resulting muscle mass determined by the continuous daily flux of muscle protein synthesis (MPS) and breakdown (MPB) (Atherton and Smith, 2012, Rose and Richter, 2009). When MPB exceeds MPS, as is the case in the post-absorptive (*fasted*) state, the resulting net protein balance is negative, whilst feeding elevates MPS above MPB, eliciting a net gain (Rennie et al., 1982, Rennie et al., 2004). In addition to feeding, resistance exercise is a potent stimulator of MPS and can increase the fractional synthetic rate (FSR) above resting values for 48 hours post-exercise (Phillips et al., 1997). Following resistance exercise, there is short period of latency during which MPS is supressed. This duration appears dependent upon the degree of metabolic and mechanical stress imposed (Atherton and Smith, 2012), evidenced by a lack of change in MPS ~1 hour following lower-intensity resistance exercise (Kumar et al., 2009) and up to 3 hours after fatiguing and damaging eccentric contractions (Cuthbertson et al., 2006). Following this period, MPS

increases substantially, remaining elevated for ~4 hours in the fasted-state (Kumar et al., 2009), and for 24 to 48 hours with protein ingestion (Burd et al., 2011, Churchward-Venne et al., 2012), due to the heightened sensitivity of skeletal muscle to the anabolic effects of protein during this period (McGlory et al., 2017). However, despite the increase in MPS, resistance exercise also stimulates a rise in the rate of MPB, which remains elevated for ~24 hours post-exercise; thus, the resulting net protein balance after resistance exercise remains negative (Phillips et al., 1997). Only with increased amino acid availability following resistance exercise does the rate of MPS exceed MPB (Biolo et al., 1997). Consequently, increases in muscle mass are due to repeated, transient stimulations in MPS above MPB, via the additive effects of regular resistance exercise and increased amino acid availability, inducing a net positive protein balance (McGlory et al., 2017).

The precise mechanisms regulating skeletal muscle plasticity have been the subject of extensive research in recent decades. Protein synthesis, leading to an increase in contractile and structural proteins is dependent upon the capacity and efficiency of the translational machinery (Hoppeler, 2016). Protein translation occurs in 3 steps; initiation, elongation, and termination, and these processes are under the regulatory control of eukaryotic initiation (eIF), elongation (eEF), and release/termination factors (eRF) (Proud, 2007).

Translation initiation

Initiation is considered a major control site for protein synthesis (Proud, 2007, Rose and Richter, 2009) and involves several steps leading to the assembly of 80S ribosomes onto messenger RNA (mRNA), bound by base-pairing between a start codon on the mRNA and initiator transfer RNA (tRNA) within the ribosome (Jackson et al., 2010). Translation initiation commences with the formation of a ternary complex, comprising the initiation methionyl-tRNA (Met-tRNA) and GTP-(guanine triphosphate)-bound eukaryotic initiation factor 2 (eIF2) (Merrick and Pavitt, 2018). A small ribosomal subunit (40S) is recruited to the mRNA; this is considered a rate-limiting step of initiation (Hershey et al., 2012). With the assistance of several elongation factors, the eIF2/GTP/Met-tRNA complex then associates with the 40S ribosomal subunit, to form the 43S complex (Hinnebusch and Lorsch, 2012, Kapp and Lorsch, 2004). A complex of elongation factors (eIF-4F) forms and binds to the *5'*-end 7-methylguanosine cap (m^7G cap) of the mRNA, whilst poly(A) binding protein (PABP) binds to the *3'*-poly(A) tail of the mRNA (Merrick and Pavitt, 2018). eIF-4F and PABP interact to form a circularised, closed-loop (Hershey et al., 2012, Mangus et al., 2003). The eIF-4F complex is composed of several subunits (namely eIF-4E, -4G and -4A). eIF-4E is responsible for binding to the 5'-cap of the mRNA. eIF-4G is a 'scaffold' subunit, with binding domains for eIF-4E, -4A, eIF3, PABP. Finally, eIF-4A is an RNA helicase responsible for unravelling secondary structures in the *5'*-untranslated region (UTR) (Kapp and

Lorsch, 2004). The helicase activity is mediated by the formation of the eIF-4F complex as well as the binding of eIF4B, an accessory factor (Merrick and Pavitt, 2018). The 43S complex binds to the *5'*-end of the mRNA, mediated by PABP and the elongation factors eIF3, eIF-4B, -4H and -4F, and begins scanning downstream from the *5'*-end, in search of the AUG start codon (Hershey et al., 2012, Hinnebusch and Lorsch, 2012). Once identified, base-pairing commences between the start codon on the mRNA and the anticodon of initiator Met-tRNA (Kapp and Lorsch, 2004). Several elongation factors then dissociate from the complex, permitting the recruitment of the larger, 60S ribosomal subunit (bound to eIF6, and mediated by eIF5) to the 40S/Met-tRNA/mRNA complex, to form an 80S initiation complex, ready to commence elongation (Hinnebusch and Lorsch, 2012, Kapp and Lorsch, 2004).

Translation elongation & termination

During elongation, amino acyl-tRNAs are recruited to the A-site on the ribosome (mediated by eukaryotic elongation factors eEF-1A and eEF-1B), which subsequently migrates along the mRNA with the addition of each new amino acid to the growing peptide chain; this is facilitated by eEF2 (Browne and Proud, 2002). The process of polypeptide assembly requires a significant metabolic cost, consuming at least four high energy bonds per additional amino acid (Browne and Proud, 2002). Amino acyl-tRNAs are transported as a ternary complex with eEF-1A and GTP to an unoccupied A-site within the ribosome, adjacent to a peptidyl-tRNA located at the P-site. Codon-anticodon base pairing between the mRNA and tRNA commences at the P-site, and eEF-1A (now in its GDP-bound state) releases the amino acyl-tRNA into the A-site (Merrick and Pavitt, 2018). A peptide bond is formed between the new amino acid and the peptidyl-tRNA, catalysed by ribosomal peptidyl transferase (Kapp and Lorsch, 2004). Both tRNAs are now in hybrid states, whereby their acceptors and anticodons are split across the E- and P-sites (deacetylated-tRNA), and P- and A-sites (peptidyl-tRNA), respectively. As such, the entire complex requires translocation along the mRNA by three nucleotides, so that the deacetylated- and peptidyl-tRNAs are entirely within the E- and P-sites respectively, and the codon for the next amino acid is in the A-site (Kapp and Lorsch, 2004). This process requires GTP hydrolysis and is facilitated by eEF2 (Wang et al., 2001). The process of elongation is repeated until a stop codon is identified in the ribosomal A-site (UAA, UAG or UGA), at which point the termination process commences. Eukaryotic release factors 1 and 3 (eRF1 and eRF3) promote hydrolysis of the ester bond between the polypeptide chain and the peptidyl-tRNA in the P-site of the ribosome (Kapp and Lorsch, 2004).

Clearly, protein translation involves several intricate stages, dependent upon the co-ordinated efforts of numerous initiation, elongation, and release factors. The activity and capacity of these translation factors is in turn regulated by numerous 'upstream' intracellular pathways, which

transduce various stimuli and signals to the translational machinery, subsequently influencing protein synthesis (Proud, 2009). Whilst the molecular signalling responses to different stimuli are incompletely resolved, several recent advances have been made in our understanding of key pathways and proteins involved in the regulation of protein synthesis and skeletal muscle growth following resistance exercise and training.

2.2.2 The molecular control of load-induced muscle hypertrophy

The mechanistic (previously mammalian (Hall, 2013)) target of rapamycin (mTOR) is a highly-conserved serine/threonine protein kinase that forms part of a multicomponent protein complex that occurs as two distinct variants. Each variant is composed of different accessory proteins, which dictate their respective structure, function, and location (Hall, 2008). Both complexes 1 and 2 (mTORC1 and mTORC2) comprise mTOR, mLST8/GβL (mammalian lethal with SEC13 protein 8/G-protein beta subunit-like protein), and DEPTOR (dishevelled, eg1-10, pleckstrin domain containing mTOR-interacting protein), which respectively function as positive and negative regulators of mTOR (Baar, 2014, Goodman, 2014). mTORC1 also contains raptor (regulatory-associated protein of mTOR) which binds to TOS (TOR signalling) motifs on mTOR substrates in a rapamycin-sensitive manner, and PRAS40 (proline-rich Akt substrate of 40 kDa) which inhibits mTORC1 activity by interfering with raptor-substrate binding (Kim et al., 2002, Nojima et al., 2003, Sancak et al., 2007, Vander Haar et al., 2007). Conversely, mTORC2 contains rictor (rapamycin-insensitive companion of mTOR), PROTOR (protein observed with rictor), and mSIN1 (mammalian stress-activated protein kinase-interacting protein 1) (Frias et al., 2006, Pearce et al., 2007, Sarbassov et al., 2004). Both complexes differ structurally and functionally; mTORC1 plays a central role in regulating translation and cell growth, whilst mTORC2 regulates actin cytoskeleton organisation, cell proliferation and survival, and targets different proteins from mTORC1 (Goodman, 2014). Given its role in regulating the protein synthetic response to resistance exercise, the activation of mTORC1 and subsequent effects on several key downstream targets of the translational machinery will be the focus of this review.

The role of mTORC1 activity in resistance training-induced hypertrophy was first investigated in rodent skeletal muscle by Baar and Esser (1999). Six weeks of training (via high-resistance, electrically-stimulated contractions) induced muscle growth which correlated with the level of p70S6K phosphorylation observed after the first exercise bout (70 kDa ribosomal protein S6 kinase, a direct target of mTORC1 involved in translation initiation, subsequently discussed). This study highlighted a link between mTORC1 signalling and load-induced muscle hypertrophy, which was subsequently supported in other rodent studies (Goodman et al., 2011, Hornberger et al., 2005, Ogasawara et al., 2013, O'Neil et al., 2009, Spangenburg et al., 2008, You et al., 2012). However, the necessity of mTORC1 activity for load-induced hypertrophy, not merely their

association, was first established with the administration of rapamycin, a selective mTOR inhibitor (Bodine et al., 2001b). Bodine *et al.* (2001b) demonstrated that rapamycin treatment attenuated mTORC1 signalling and the hypertrophic response to synergistic ablation. Using a model of chronic mechanical loading via synergist ablation in transgenic mice expressing various mTOR mutations of rapamycin-resistance, Goodman *et al.* (2011) further elucidated that load-induced hypertrophy is dependent on skeletal muscle-specific mTORC1 activity, which in turn is rapamycin-sensitive. Other studies in rodents have also shown that acute mTORC1 signalling and protein synthesis stimulated in response to *ex vivo* passive stretch (Hornberger et al., 2004) and *in vivo* resistance exercise (Kubica et al., 2005) were attenuated by rapamycin treatment. This highlighted the need of mTORC1 signalling and activity for stimulating protein synthesis and hypertrophy in response to mechanical load (Goodman, 2014). Resistance exercise in humans has also been shown to stimulate robust increases in post-exercise mTORC1 signalling and MPS (Cuthbertson et al., 2006, Dreyer et al., 2006, Witard et al., 2009). In young men, transient increases in mTORC1 activity have been shown to correlate with subsequent changes in MPS observed 1-hour post-exercise (Kumar et al., 2009). Furthermore, and commensurate with the previous findings of Baar and Esser (1999), resistance training-induced changes in strength, muscle-mass, and type IIa muscle fibre CSA were shown to correlate with increases in p70S6K phosphorylation induced by the first resistance exercise session (Terzis et al., 2008). Whilst there are no training studies in humans using prolonged rapamycin treatment, acute resistance exercise-(Drummond et al., 2009) and amino acid-induced increases in MPS and markers of mTORC1 signalling were attenuated with rapamycin treatment (Dickinson et al., 2011), highlighting its importance in mediating the stimulation of MPS. Collectively, these studies highlight a fundamental role for mTORC1 activity in the regulation of skeletal muscle mass in response to acute and prolonged loading. As such, it is important to understand the mechanisms through which mTORC1 becomes activated, and subsequently exerts its effects on downstream targets involved in protein synthesis.

2.2.3 Upstream activators of mTORC1

Growth factors

mTORC1 regulates cell growth and metabolism in response to a range of stimuli (growth factors, nutrients, energy availability and stress) and as such serves as a nexus upon which several upstream targets converge (Hall, 2008, Watson and Baar, 2014). The canonical pathway of mTORC1 activation via growth factor-dependent signalling remains one of the most widely-studied. Briefly, growth factors such as insulin and insulin-like growth factor 1 (IGF-1) bind to receptor tyrosine kinases in the plasma membrane, which subsequently auto-phosphorylate. This permits binding of insulin receptor substrates (IRS), which translocate to the membrane and

interact with the regulatory protein phosphatidylinositol-3-kinase (PI3K) (Cohen et al., 1990). PI3K phosphorylates phospholipids residing in the plasma membrane, converting phosphatidylinositol (4,5)-bisphosphate (PIP_2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP_3) (Vanhaesebroeck et al., 1997). PIP_3 then recruits protein kinase B (PKB, also referred to as Akt) and its kinase, 3-phosphoinositide-dependent protein kinase-1 (PDK1) to the plasma membrane where, coupled with further phosphorylation by mTORC2, Akt becomes fully activated (Vanhaesebroeck et al., 1997). Akt phosphorylates several downstream targets including PRAS40 (Vander Haar et al., 2007) and the tuberous sclerosis complex (Inoki et al., 2002), both of which inhibit mTORC1 activity. The tuberous sclerosis complex is a heterodimeric complex, comprising the tumour suppressors TSC1 (hamartin), TSC2 (tuberin) (Huang and Manning, 2008). Rheb (Ras homologue enriched in brain) is a small G-protein substrate of mTORC1 that increases mTORC1 activity when bound to GTP. TSC2 inhibits mTORC1 through its function as a GTPase-activating protein (GAP) towards Rheb, by converting $Rheb^{-GTP}$ to $Rheb^{-GDP}$ (Inoki et al., 2003a). Akt-mediated phosphorylation of TSC2 on multiple residues results in its sequestration and binding to 14-3-3 protein, relieving its inhibition on Rheb, resulting in $Rheb^{-GTP}$ accumulation and mTORC1 activation (Li et al., 2002) (Figure 2.1).

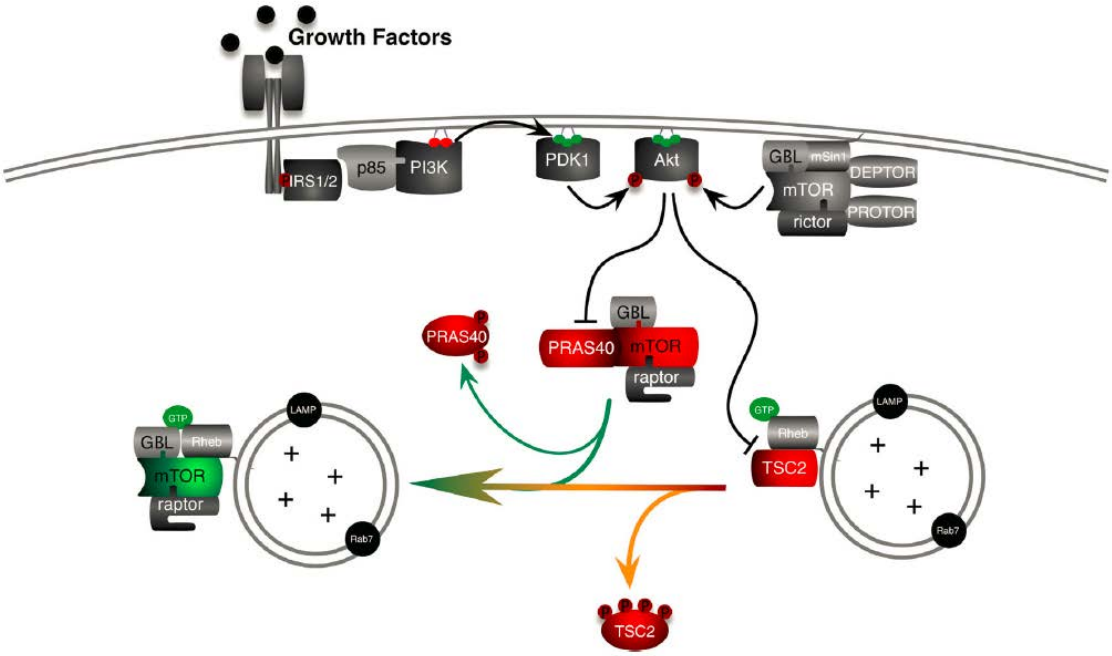


Figure 2.1 - Growth factor-mediated activation of mTORC1, from Marcotte et al. (2015).

Growth factor-independent mechanisms for load-induced hypertrophy

Whilst mechanical loading has been shown to increase the expression of growth factors (Greig et al., 2006, Hameed et al., 2003), which have been shown to stimulate protein synthesis (Gulve and Dice, 1989, Monier et al., 1983) and hypertrophy (Barton-Davis et al., 1998, Musaro et al., 2001,

Musaro et al., 1999), more recent lines of evidence suggest that the mechanical activation of mTORC1 and MPS are mediated by growth factor-independent pathways. For example, despite pharmacological inhibition of the PI3K-Akt-signalling axis, and the use of Akt1-knockout mice, mTORC1 signalling and protein synthesis were stimulated as normal by mechanical loading (Hornberger et al., 2004). Furthermore, the effects of locally-released growth factors were insufficient to stimulate mTORC1 signalling events (Hornberger et al., 2004). Subsequent work by Spangenburg *et al.* (2008) demonstrated that mice expressing a dominant-negative IGF-1 receptor mutation elicited comparable mTORC1 signalling and hypertrophy to wild-type mice in response to functional overloading. Indeed, unlike the established action of insulin and growth factors, resistance exercise (via electrical stimulation) did not increase IGF-1 receptor phosphorylation, nor subsequent IRS binding with PI3K (Hamilton et al., 2010). Furthermore, and similarly to Spangenburg *et al.* (2008), deleting a skeletal muscle-specific inhibitor of PI3K, PTEN (phosphatase and tensin homologue) did not lead to greater hypertrophy than wild-type mice, following synergist ablation (Hamilton et al., 2010). In humans, the questionable role of growth factors on mTORC1 signalling, MPS, and training-induced hypertrophy has also been investigated (West et al., 2010, West et al., 2009). Transient post-exercise increases in p70S6K phosphorylation and MPS (West et al., 2009) and subsequent hypertrophy (West et al., 2010) occurred regardless of whether resistance exercise was conducted under conditions of high or low circulating hormone concentrations. Collectively these studies question the role of IGF-PI3K-Akt signalling for regulating resistance exercise-induced stimulation of mTORC1 and suggest a contribution from other compensatory mechanisms that independent of the traditional growth-factor pathway.

Two key molecules implicated in the mechanical activation of mTORC1 are Rheb, and phosphatidic acid (PA) (Jacobs et al., 2014). In a series of experiments, Jacobs *et al.* (2013) demonstrated that at rest, Rheb, PA, mTOR and TSC2 are lysosome-bound in rodent skeletal muscle. In this arrangement, TSC2 exerts its inhibitory GAP activity upon Rheb, preventing it from binding with mTORC1. However, following eccentric contractions, phosphorylation of TSC2 at RxRxxS*/T* sites led to its dissociation and translocation away from the lysosome, relieving its inhibition on Rheb. Concurrently, colocalization of mTOR and the lysosome also increased, providing greater potential for mTOR-substrate binding (Jacobs et al., 2013). As such, it appears that not unlike the growth factor pathway, mechanical loading leads to mTORC1 activation via the inhibition of TSC2, removing its inhibitory effect on Rheb. However, given that previously highlighted studies have demonstrated mTORC1 activation, MPS and hypertrophy in the absence of PI3K-Akt signalling (Hamilton et al., 2010, Hornberger et al., 2004, Spangenburg et al., 2008) and a lack of an additive effect when combining resistance exercise and high levels of circulating growth factors (West et al., 2010, West et al., 2009), it is likely that the upstream

kinase mediating mechanical load-induced TSC2 phosphorylation and mTORC1 activation is distinct from the growth factor pathway; however, the precise protein(s) responsible remain to be identified (Marcotte et al., 2015).

In addition to Rheb, phosphatidic acid (PA) is a glycerophospholipid that can activate mTORC1 by directly binding to its rapamycin-sensitive FRB domain (Fang et al., 2001). Phosphatidic acid concentrations are regulated by a number of enzymes that affect its synthesis and breakdown (Goodman, 2014). Two noteworthy enzymes recently implicated in the mechanical stimulation of mTOR signalling are phospholipase D (PLD) (Hornberger et al., 2006, O'Neil et al., 2009) and diacylglycerol kinase zeta (DGKζ) (You et al., 2014). Hornberger *et al.* (2006) demonstrated that increased PA levels stimulate mTOR signalling in rodent skeletal muscle. Additionally, the load-induced activation of mTOR signalling (via *ex vivo* passive stretching) required a PLD-dependent increase in PA concentrations; a response which was subsequently attenuated with pharmacological inhibition of PLD (Hornberger et al., 2006). Further work by O'Neil *et al.* (2009) corroborated that mechanical activation of mTOR required PA synthesis by PLD and occurred through PI3K-Akt-independent mechanisms. However, as stated, other enzymes also regulate PA concentration and thus the effects may not be solely due to PLD. Indeed, Hornberger *et al.* (2006) did acknowledge the possible contribution of other regulatory enzymes, whilst others questioned the specificity of the PLD-inhibitor used in these previous studies (Goodman, 2014). Consequently, You *et al.* (2014) employed a more potent and specific PLD inhibitor than previously used, and whilst their results supported that PA was an upstream activator of mTOR in response to mechanical stimuli, PLD was not essential for the stretch-induced increase in PA or mTOR signalling. These events were instead attributed to the action of the enzyme DGKζ, which is responsible for PA synthesis from diacylglycerol (DAG) (Wang et al., 2006). You *et al.* (2014) and others (Cleland et al., 1989, Sadoshima and Izumo, 1993) have shown increases in DAG concentration with mechanical loading, which would provide DGKζ with more substrate. Indeed, membranous DGK activity increased biphasically following passive stretch. Furthermore, DGKζ overexpression enhanced serum-induced mTOR-signalling, and hypertrophy, whilst DGKζ knockout impaired these responses (You et al., 2014). Collectively, their findings suggest a role for DGKζ in the mechanical activation of mTOR signalling. However, whether this response is necessary for the stimulation of mTORC1 signalling following resistance exercise remains unknown and is area for further research. Consequently, whilst a growing body of literature suggests that mechanical loading, such as resistance-type contractions, stimulate mTORC1 activity, MPS and muscle growth via mechanisms independent of the canonical growth factor pathways, more research, particularly in human skeletal muscle, is needed to elucidate the upstream mechanisms leading to these signalling events.

Amino acids

Amino acids are potent stimulators of mTORC1 and MPS in skeletal muscle (Dickinson et al., 2011), and signal independently of the TSC2-Rheb axis implicated in growth factor signalling and mechanical loading (Bar-Peled and Sabatini, 2014). This is evident from studies using TSC2-null cells, which remain sensitive to changes in amino acid availability such that their withdrawal still impairs mTOR signalling (Roccio et al., 2006, Smith et al., 2005). In the absence of amino acids, mTORC1 is distributed across the cytoplasm (Sancak et al., 2008); however, with increased amino acid availability, mTORC1 translocates to the lysosome where it colocalises with Rheb (Sancak et al., 2010, Sancak et al., 2008). This amino acid-induced translocation is mediated by a nutrient-sensing complex composed of Vacuolar-type H^+-ATPase (v-ATPase), Ragulator, and Rags (Kim et al., 2008, Sancak et al., 2010, Sancak et al., 2008, Zhang et al., 2014a) (Figure 2.2).

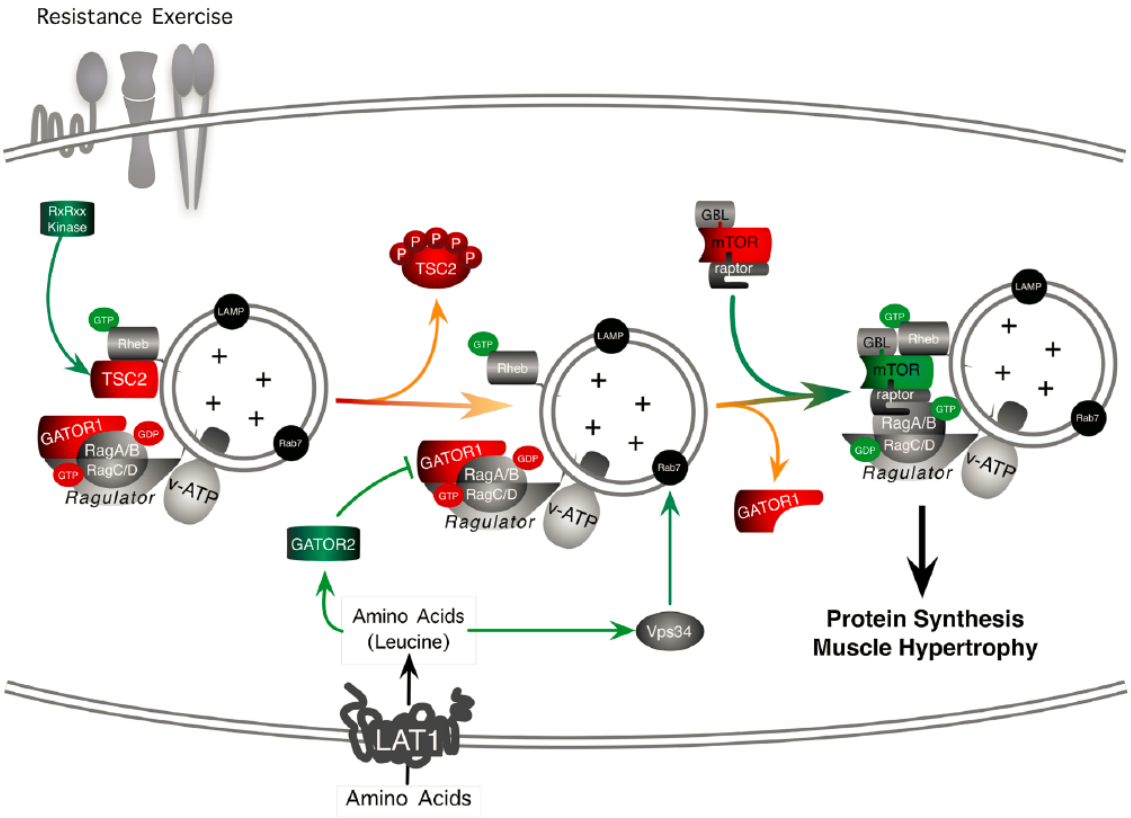


Figure 2.2 - Resistance exercise and amino acid-mediated activation of mTORC1, from Marcotte et al. (2015).

Rags (Ras-related GTPases) are small G-proteins expressed in four variants (A to D) that form heterodimeric complexes, comprising one of either RagA or B (RagA/B) with either RagC or D (RagC/D) (Sancak et al., 2008). Rag activity is dependent on their GTP-bound state; $RagA/B^{-GTP}$ and $RagC/D^{-GDP}$ promote mTORC1 translocation to the lysosome, where it is subsequently activated by Rheb (Bar-Peled and Sabatini, 2014, Bar-Peled et al., 2012, Chantranupong et al., 2014, Sancak et al., 2008). Conversely, in the absence of amino acids, GDP-bound RagA/B results

in mTORC1 dissociation from the lysosome, preventing its activation (Sancak et al., 2008). Ragulator functions as a guanine nucleotide exchange factor (GEF) that anchors the Rag proteins to the lysosomal membrane and mediates the conversion of the inactive RagA/B^{-GDP} to its active, GTP-bound state (Bar-Peled et al., 2012, Sancak et al., 2008, Zoncu et al., 2011). The v-ATPase functions as a nutrient and energy sensor, which promotes the GEF activity of Ragulator in response to amino acid availability (Bar-Peled et al., 2012, Zoncu et al., 2011). In addition, the tumour suppressor Folliculin (Tsun et al., 2013), and leucyl tRNA synthase (LRS) (Han et al., 2012), have been implicated as possible GAPs for RagC/D; however more research is required to elucidate their roles.

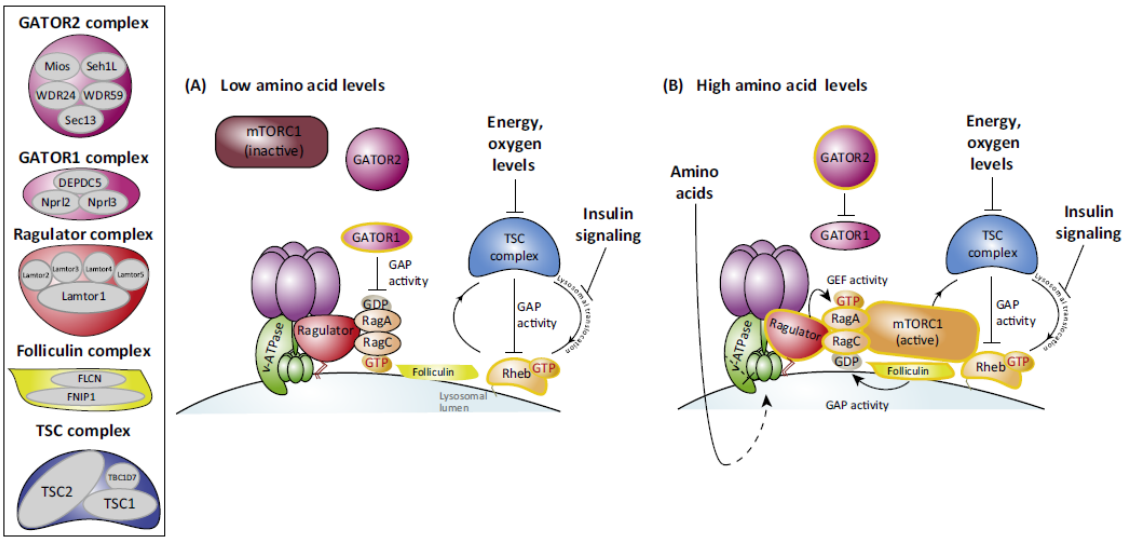


Figure 2.3 – The effect of low (A) and high (B) amino acid availability on the GATOR- and Rag-dependent regulation of mTORC1 activity, from Bar-Peled and Sabatini (2014).

In addition to the v-ATPase/Ragulator complex, Rag activity is also controlled by a super-complex termed GATOR, (GAP Activity Towards Rags), which is composed of two sub-complexes: GATOR1 and GATOR2 (Bar-Peled et al., 2013) (Figure 2.3). GATOR1 is a negative regulator of Rags that favours the hydrolysis of RagA/B^{-GTP} to its GDP-bound state (Bar-Peled et al., 2013). GATOR2, located upstream of GATOR1, relieves its inhibition on mTORC1 (Bar-Peled et al., 2013, Bar-Peled and Sabatini, 2014); however, its physiological function requires further research. The GATOR super-complex in turn is proposed to be regulated by Sestrins (Figure 2.4); these are stress-inducible proteins that are upregulated in response to a range of environmental stresses (Lee et al., 2016). There are three isoforms, Sestrin 1, 2, and 3, with Sestrin 1 shown to be highly expressed in rodent skeletal muscle (Xu et al., 2019). Various cell culture and *in vitro* models provide evidence that under conditions of low amino acid availability, Sestrins interact with GATOR2, removing its suppression on GATOR1, which in turn elicits inhibitory GAP activity towards the Rag heterodimers, preventing mTORC1 translocation to the

lysosome (Chantranupong et al., 2014, Parmigiani et al., 2014). Furthermore, Sestrins also possess guanine nucleotide dissociation inhibitor (GDI) motifs; as such, Sestrins may also function downstream of GATOR2, acting directly on the Rag complexes as GDIs (Peng et al., 2014). In skeletal muscle, Sestrin1 elicits a high affinity for leucine, and leucine administration results in Sestrin1 dissociation from GATOR2 (Xu et al., 2019). Thus, when amino acid (i.e., leucine) availability is high, the nutrient-sensitive mechanisms for increasing mTORC1 activity may result from Sestrin dissociating from GATOR2, thereby preventing GATOR1-mediated inhibition on the Rag complexes, which permits mTORC1 translocation to the lysosome where it can be activated by Rheb. Sestrin1 protein expression has been shown to increase after both a single resistance exercise session and 12 weeks of resistance training in active males (Zeng et al., 2017); this may provide some insight into the exercise-induced increase in skeletal muscle amino acid sensitivity, and presents an avenue for further exploration (Xu et al., 2019). Clearly, the distinct mechanisms through which amino acid availability promotes mTORC1 activation compared to growth factors and more importantly mechanical loading highlights the additive effects of combining resistance exercise and protein availability on maximising MPS post-exercise, and promoting skeletal muscle hypertrophy (Marcotte et al., 2015).

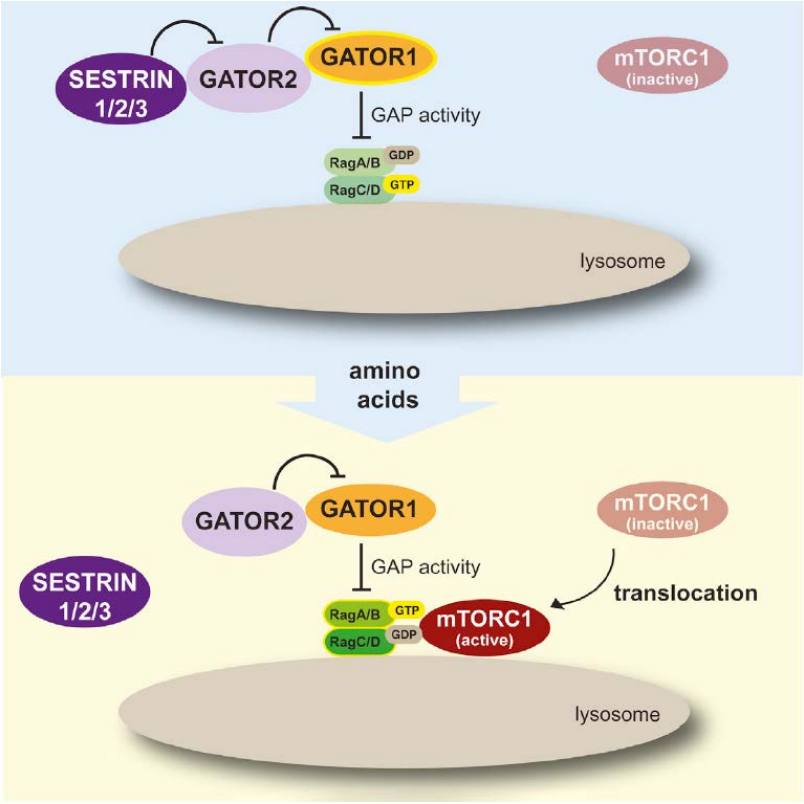


Figure 2.4 - Amino acid-dependent regulation of the GATOR super-complex by Sestrins, from Chantranupong et al. (2014)

2.2.4 Downstream targets of mTORC1

The two most widely researched downstream substrates of mTORC1 are 4E-BP1 (eukaryotic initiation factor-4E binding protein 1) and p70S6K1, due to their roles in regulating several factors affecting the translational machinery and ribosomal biogenesis (Goodman, 2014). Raptor, the scaffold protein on mTORC1, binds to the TOS motifs on these targets to allow subsequent phosphorylation (Nojima et al., 2003). 4E-BP1 regulates the assembly of the eIF-4F complex, acting as a repressor of cap-dependent translation initiation by obstructing the initiation factor eIF-4E from binding to the m^7G cap at the 5'-end of the mRNA, and to eIF-4G located in the eIF4F complex (Gingras et al., 2001). Activation of mTORC1 leads to direct phosphorylation of 4E-BP1 at multiple sites (initially via ^{Thr36} and ^{Thr45}, then ^{Thr70} and ^{Ser65}), upon which eIF-4E dissociates from 4E-BP1, relieving its inhibition on translation initiation (Gingras et al., 2001, Goodman, 2019).

For full activation, p70S6K1 requires phosphorylation on threonine residues ^{Thr389} and ^{Thr229}, by mTORC1 and PDK1, respectively (Alessi et al., 1998, Pearson et al., 1995, Pullen et al., 1998). The former (p70S6K1^{Thr389}) is often used as a proxy of mTORC1 activity, as post-exercise phosphorylation of p70S6K1^{Thr389} has been shown to correlate with resistance training-induced growth (Baar and Esser, 1999, Terzis et al., 2008). p70S6K can phosphorylate a range of downstream targets involved in translation initiation, elongation and ribosome biogenesis. Briefly, translation initiation is facilitated by p70S6K-mediated phosphorylation of eIF-4B^{Ser422}, enabling it to bind with the eIF3-preinitiation complex, as well as the RNA helicase eIF-4A (Holz et al., 2005, Shahbazian et al., 2006). The latter is also mediated by phosphorylation of another target of p70S6K, PDCD4^{Ser67} (programmed cell death protein 4), which inhibits eIF-4A binding (Loh et al., 2009, Suzuki et al., 2008). Phosphorylation by p70S6K1 targets PDCD4 to be broken down by the ubiquitin-proteasome system thereby relieving its inhibition on eIF-4A (Dorrello et al., 2006). Translation elongation is limited by the inhibition of elongation factor 2 (eEF2), by its kinase eEF2K (Wang et al., 2001). Phosphorylation of eEF2K^{Ser366} removes this suppression, permitting eEF2 to facilitate ribosomal translocation along the mRNA (Wang et al., 2001). Another key substrate for p70S6K1 phosphorylation is ribosomal protein S6 (rpS6), a component of the small 40S ribosomal subunit, which has been shown to interact with, and regulate the translation of *5'*-tract of pyrimidine (*5'*-TOP) mRNAs, to synthesise translation factors and ribosomal proteins (Jefferies et al., 1997, Nygard and Nilsson, 1990). As such, rpS6 phosphorylation, which occurs in sequence on five serine residues ($^{Ser235, Ser236, Ser240, Ser244, Ser247}$), is considered a positive regulator of protein synthesis and frequently measured as a surrogate for mTORC1 activity (Goodman, 2019, Krieg et al., 1988). However, its exact role and necessity in these processes is unclear (Ruvinsky and Meyuhas, 2006), owing to contradictory findings of

rpS6 phosphorylation on stimulating translational of *5'*-TOP mRNAs (Ruvinsky et al., 2005) and protein synthesis (Montine and Henshaw, 1990).

Finally, as well as the wide-ranging effects of mTORC1-mediated phosphorylation of p70S6K and 4E-BP1 on the translational machinery, mTORC1 *per se* can also directly phosphorylate some of its targets. For example, mTORC1 can directly phosphorylate eEF2K on multiple residues, relieving its inhibition on eEF2 (Browne and Proud, 2004). Furthermore, mTORC1 can also directly phosphorylate and inhibit PRAS40$^{Ser183,\ Ser221}$ (Oshiro et al., 2007, Wang et al., 2008), an accessory protein of the mTORC1 complex that inhibits its kinase activity through competitive-binding to raptor (Sancak et al., 2007).

2.2.5 The molecular control of muscle protein breakdown

Whilst the regulation MPS following exercise and nutritional interventions is better understood than MPB (partly due to the greater methodological challenges of accurately measuring MPB [see Tipton et al. (2018)]), the other half of the protein balance equation cannot be neglected. Muscle atrophy occurs when the rate of protein breakdown exceeds synthesis, leading to a reduction in contractile and structural proteins, muscle and fibre size, and force-generating capacity (Jackman and Kandarian, 2004, Schiaffino et al., 2013). Whilst muscle atrophy is a hallmark of several pathological states, such as ageing, cancer, diabetes, acquired immune deficiency syndrome, neuromuscular diseases and conditions of disuse (Jackman and Kandarian, 2004, Mitch and Goldberg, 1996), it is important to consider that the numerous environmental and physiological stimuli endured by skeletal muscle proteins can disrupt cellular homeostasis and induce significant damage; thus an increase in breakdown and subsequent re-synthesis of specific proteins is also necessary to preserve and maintain muscle tissue integrity (Bell et al., 2016). Consequently, an increase in the rate of MPB following resistance exercise for example, may instead reflect a need for repair and remodelling of damaged proteins, rather than excessive protein degradation often associated with disease (Bell et al., 2016, Tipton et al., 2018). Indeed, muscle protein breakdown has been shown to be elevated following resistance exercise in the post-absorptive state (Biolo et al., 1995, Biolo et al., 1997, Phillips et al., 1997). Muscle protein breakdown is posited to occur under the combined regulation of multiple degradation pathways, two of which include the ubiquitin/proteasome system and the autophagy/lysosomal system (Sandri, 2013, Schiaffino et al., 2013).

Ubiquitin/proteasome system

The ubiquitin/proteasome system is responsible for the degradation of most intracellular proteins (Rock et al., 1994). Briefly, through a cascade of enzyme-mediated reactions involving ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin-ligating (E3) enzymes (Jackman and

Kandarian, 2004), proteins requiring degradation are marked with ubiquitin, a highly-conserved 8.5 kDa polypeptide, and subsequently recognised and degraded by a 26 kDa proteasome complex (Glickman and Ciechanover, 2002). This process is regulated at the transcriptional level by atrophy-related genes (termed '*atrogenes*') that are upregulated in response to any atrophy stimulus (Rudrappa et al., 2016, Schiaffino et al., 2013). The final step involving E3-ubiquitin ligases is considered rate-limiting (Schiaffino et al., 2013), and two key atrogenes identified in several models of skeletal muscle atrophy which encode these ligases are muscle-specific atrophy F box (MAFbx; also termed atrogin-1) and muscle RING finger-1 (MuRF1) (Bodine et al., 2001a, Gomes et al., 2001). Both MAFbx- and MuRF1-null mice exhibit less muscle mass loss than wild-type mice (Bodine et al., 2001a) and consequently, these are often used as surrogate markers to infer skeletal muscle atrophy (Coffey and Hawley, 2007). Suggested targets of MuRF1 include thick filament myofibrillar proteins, including myosin-binding protein C, myosin light chains 1 and 2, and myosin heavy chain (Cohen et al., 2009), whilst MAFbx has been shown to target myogenic regulatory factor D (MyoD) and the initiation factor eIF-3F (Lagirand-Cantaloube et al., 2008, Tintignac et al., 2005). The expression of these atrogenes is regulated by class O-type forehead transcription factors, of which there are multiple isoforms (FOXO1, FOXO3a, FOXO 4) (Bodine and Baehr, 2014). These transcription factors are in turn regulated by Akt, whereby Akt-mediated phosphorylation retains FOXO within the cytoplasm, bound to a 14-3-3 binding protein, precluding its entry into the nucleus to upregulate atrogene expression (Brunet et al., 1999, Sandri et al., 2004, Stitt et al., 2004). Furthermore, the transcriptional activity of FOXO3a is also upregulated by AMPK (adenosine monophosphate kinase)-mediated phosphorylation (Greer et al., 2007).

In addition to MuRF1 and MAFbx, other E3 ligases have also been implicated in regulating skeletal muscle remodelling in response to atrophy and loading. Firstly, a novel f-box protein named MUSA1 (muscle ubiquitin ligase of SCF complex in atrophy-1) was shown to be increased in denervated and atrophying skeletal muscles (Sartori et al., 2013). MUSA1 expression is regulated by the bone morphogenic protein (BMP) signalling pathway (*discussed in section 2.4.2*), in which the competitive binding of Smad4 to either the Smad2/3 or Smad1/5/8 complexes determines the transcription of several growth-related and atrogenes (Sartori et al., 2014). Indeed, the inhibition of this pathway was shown to enhance MUSA1 expression, whilst the inhibition of MUSA1 was protective against denervation-induced atrophy (Sartori et al., 2013). As such, MUSA1 appears to play a key role in regulating skeletal muscle atrophy.

More recently, work by Seaborne *et al.* identified a role for the E3 ligase UBR5 (Ubiquitin protein ligase E3 component n-recognin 5) in skeletal muscle hypertrophy and recovery from atrophy (Seaborne et al., 2019, Seaborne et al., 2018). Firstly, in response to a single bout of resistance

exercise, subsequent resistance training, and re-training after a period of unloading, the authors identified that UBR5 becomes hypomethylated, a response which corresponded with increased UBR5 gene expression and protein abundance (Seaborne et al., 2019, Seaborne et al., 2018). Furthermore, during the period of re-training, UBR5 expression increased more than in response to the initial training stimulus, and was positively correlated with training-induced changes in lower-body lean mass (Seaborne et al., 2018). Genetic variations that relate to increased UBR5 gene expression were also highly prevalent in the muscles of strength and power athletes compared to control and endurance athletes, and were associated with superior weightlifting performance and greater fast-twitch muscle fibre CSA (Seaborne et al., 2019). In addition to its implicated role in muscle hypertrophy, UBR5 expression increased early in response to different models of atrophy, before returning to baseline, during which time MuRF1 and MAFbx were increased to a greater extent (Seaborne et al., 2019). However, during recovery from the atrophy stimulus, UBR5 was again hypomethylated, eliciting a trend for increased gene expression, whilst both MuRF1 and MAFbx were downregulated (Seaborne et al., 2019). Collectively these findings implicate UBR5 as a key mediator of skeletal muscle growth in response to training and recovery from atrophy, and appears to be regulated differently from atrogenes in response to growth and atrophy stimuli.

Autophagy/lysosomal system

The autophagy/lysosomal system controls the dynamic catabolic process in which damaged or dysfunctional proteins and organelles are engulfed by double-membrane vesicles (autophagosomes), which translocate and fuse with the lysosomes to initiate degradation (Vainshtein et al., 2014). The process of autophagy can be broken down into 5 steps; induction, nucleation and expansion, cargo selection, fusion, and degradation and efflux (Vainshtein and Hood, 2016). *In vitro*, the initiation of autophagy is regulated through the interactions between the mTORC1 and AMPK signalling pathways with ULK1 (Unc-51-like kinase 1), a serine/threonine protein kinase which facilitates initial autophagosome formation (Zachari and Ganley, 2017). Under conditions conducive to growth, such as nutrient availability, mTORC1 phosphorylates ULK1^{Ser757} (Kim et al., 2011). This prevents ULK1 from forming a complex with autophagy-related protein (Atg) Atg13, Atg101 and FIP200 (focal adhesion kinase family interacting protein of 200 kDa), which is the initial driver of autophagy initiation (Zachari and Ganley, 2017, Sanchez et al., 2012). However, cellular energy signals are also detected by AMPK (Hardie, 2011); under conditions of low energy availability, mTORC1 activity is attenuated via AMPK-mediated phosphorylation of TSC2 (Inoki et al., 2003a, Inoki et al., 2003b) and raptor (Gwinn et al., 2008); *discussed further in section 2.4.2*). Consequently, mTORC1 is removed from the lysosomal membrane, thus relieving its inhibition on ULK1 (Zachari and Ganley, 2017). AMPK can also increase ULK1 activity via direct phosphorylation on multiple sites (Egan et al.,

2011), and upregulate the transcriptional activity of FOXO3 which controls the expression of several autophagy-related genes (Mammucari et al., 2007, Sanchez et al., 2012, Zhao et al., 2007).

Resistance exercise and markers of protein breakdown

There is currently limited information regarding the extent to which both systems contribute to protein degradation and remodelling following resistance exercise and training. Following a resistance exercise session, MuRF1 mRNA and protein expression have been shown to be elevated, whilst MAFbx decreased or remained unchanged (Borgenvik et al., 2012, Dickinson et al., 2017, Fry et al., 2013, Glynn et al., 2010, Louis et al., 2007, Mascher et al., 2008, Nedergaard et al., 2007). This may indicate that the two proteolytic markers are differentially regulated following exercise and may play different roles. Regarding autophagy, despite some endurance exercise studies providing supportive evidence of AMPK-mediated phosphorylation of ULK1 (Fritzen et al., 2016, Moller et al., 2015, Schwalm et al., 2015) the necessity of this to increase autophagosome content remains unclear (Fritzen et al., 2016). Following resistance exercise, studies suggest that the autophagic response to resistance exercise may be downregulated <24 hours following resistance exercise, evident through reductions in LCB-II content and LCB-II/LC3-I ratios (Dickinson et al., 2017, Fry et al., 2013, Glynn et al., 2010, Ogborn et al., 2015); although a recent study demonstrated an increase in markers of autophagy 48 hours following an unaccustomed bout of resistance exercise (Hentila et al., 2018). Collectively these findings suggest a greater contribution of the ubiquitin/proteasome system to increases in MPB following resistance exercise, compared to the autophagy/lysosomal systems which may be suppressed (Glynn et al., 2010).

2.3 Endurance Exercise & Training Adaptations

Endurance exercise is characterised by submaximal, high-frequency contractions, which must be maintained for prolonged durations for successful endurance performance (Hawley, 2002, Hoppeler et al., 2011). Regular endurance training is associated with central and peripheral adaptations that facilitate greater oxygen delivery and extraction (Lundby et al., 2017) culminating in improvements in whole-body aerobic power and fatigue resistance. One of the hallmark adaptations of endurance training is an increased content and function of the mitochondrial reticulum, via mitochondrial biogenesis. While the most appropriate methods of defining and measuring mitochondrial biogenesis remain the subject of debate (Bishop et al., 2019b, Miller and Hamilton, 2012), the term encompasses the dynamic cellular processes involved in mitochondrial protein synthesis and degradation (Hood, 2001).

Interest into the study of exercise-induced mitochondrial biogenesis emerged from the seminal work of John Holloszy (1967). In rodent skeletal muscle, it was established that regular strenuous endurance training increased the concentration and activity of enzymes in the Krebs cycle and mitochondrial respiratory chain, which lead to an increase in maximal oxygen uptake and fatigue resistance (Holloszy, 1967). Subsequent studies in both rodent (Barnard et al., 1970, Gollnick and King, 1969) and human skeletal muscle (Gollnick et al., 1973, Henriksson and Reitman, 1977) demonstrated that regular endurance exercise elicits an increase in mitochondrial size and number, as well as the content and activity of key oxidative enzymes, improving the capacity of the mitochondria to aerobically generate ATP (Oscai and Holloszy, 1971), via an increased contribution of lipid oxidation (Henriksson, 1977, Hurley et al., 1986, Mole et al., 1971, Phillips et al., 1996) and a greater proportion of fatigue-resistant muscle fibres (Andersen and Henriksson, 1977, Simoneau et al., 1985).

Provided the exercise stimulus is of a sufficient intensity and dose, mitochondrial content can be increased by 50 to 100% within 6 weeks of regular endurance training (Hood, 2001). However, at the molecular level, the process of mitochondrial biogenesis is stimulated after a single exercise session (Baar et al., 2002, Perry et al., 2010, Pilegaard et al., 2003). The onset of muscular contraction induces perturbations to several primary signals, such as intracellular calcium (Ca^{2+}) release from the sarcoplasmic reticulum, lactate, muscle glycogen depletion and ATP turnover (elevating ADP and AMP concentrations), changes in redox state (increasing NAD+:NADH ratio), and reactive oxygen species (ROS) production (Hood, 2001, Ljubicic and Hood, 2009). These putative signals trigger the activation of various signalling proteins, notably Ca^{2+}/calmodulin-dependent protein kinase (CaMK), AMP-dependent protein kinase (AMPK), sirtuins (SIRT) and p38 mitogen-activated protein kinase (p38 MAPK) (Amat et al., 2009, Hood

et al., 2011, Zhang et al., 2014b). These signalling pathways converge at the nucleus and activate transcription factors that upregulate the expression of nuclear genes encoding mitochondrial proteins (NuGEMPs) (Hood et al., 2011). Following translation in the cytoplasm, the NuGEMPs are imported into the mitochondria to contribute to the formation of respiratory chain complexes, mitochondrial DNA (mtDNA) transcription factors, and mitochondrial import machinery (for more detail, see Hood et al. (2015), Kelly and Scarpulla (2004)).

In addition to nuclear DNA, mtDNA also encode 13 proteins involved in mitochondrial biogenesis, highlighting the need for a coordinated transcriptional response of both nuclear and mitochondrial genomes (Hood, 2001). This coordination is mediated by the transcriptional coactivator, peroxisome proliferator receptor-γ co-activator-1α (PGC-1α), which is widely regarded as the "master regulator" of mitochondrial biogenesis. Early cell culture studies identified a significant role for PGC-1α in coordinating mitochondrial biogenesis; PGC-1α overexpression increased the expression of nuclear and mitochondrial-encoded genes and transcription factors involved in oxidative phosphorylation and the respiratory chain, as well as an increase in mtDNA content, and an increase in mitochondrial respiration (Puigserver et al., 1998, Wu et al., 1999). This was associated with increased expression and co-activation of nuclear- (NRF-1/-2) and mitochondrial (Tfam) transcription factors (Wu et al., 1999). Further work in mouse skeletal muscle also implicated PGC-1α in mediating fibre-type transformations toward a fatigue-resistant, oxidative phenotype (Lin et al., 2002). In human skeletal muscle, PGC-1α expression is transiently increased following acute bouts of endurance exercise (Bartlett et al., 2012, Perry et al., 2010, Pilegaard et al., 2003), and training periods of varying intensities and volumes (Granata et al., 2016b, Granata et al., 2016a, Perry et al., 2010). The isoform of PGC-1α induced by exercise is transcribed from an alternative promoter situated ~14 kilobases upstream of the proximal promoter (Chinsomboon et al., 2009), and also lacks the inhibitory exon 8 (Baar et al., 2002).

Contraction-induced increases in PGC-1α mRNA expression and protein activity are activated by several signalling pathways, such as AMPK, CaMK and p38 MAPK (Zhang et al., 2014b). PGC-1α protein is activated via post-translational modifications, such as phosphorylation by AMPK (Jager et al., 2007) and p38 (Akimoto et al., 2005, Wright et al., 2007a), as well as via deacetylation by SIRT1 (Gerhart-Hines et al., 2007, Gurd, 2011). Upon activation, PGC-1α accumulates in both the nucleus (Little et al., 2011, Zhang et al., 2014b) and mitochondria (Safdar et al., 2011) where, rather than transcribing DNA *per se*, it interacts with and coactivates multiple transcription factors that upregulate the expression of nuclear and mitochondrial genomes (Hood et al., 2011). In a secondary response, PGC-1α gene expression is increased via an auto-regulatory feedback loop, in which co-activated transcription factors such as CREB, MEF2 and MyoD

activate PGC-1α promoter regions, thereby increasing PGC-1α protein abundance, and further enhancing mitochondrial biogenesis (Handschin et al., 2003, Wright et al., 2007b).

In conclusion, the expansion of the mitochondrial network requires the integration of multiple contraction-induced signals, mediated by transcription factors and transcriptional coactivators, to co-ordinate the expression of both nuclear- and mitochondrial-encoded genes involved in mitochondrial biogenesis, oxidative phosphorylation, substrate metabolism and utilisation, and angiogenesis (Hood, 2001, Lin et al., 2005, Ljubicic et al., 2010, Olesen et al., 2010) (Figure 2.5).

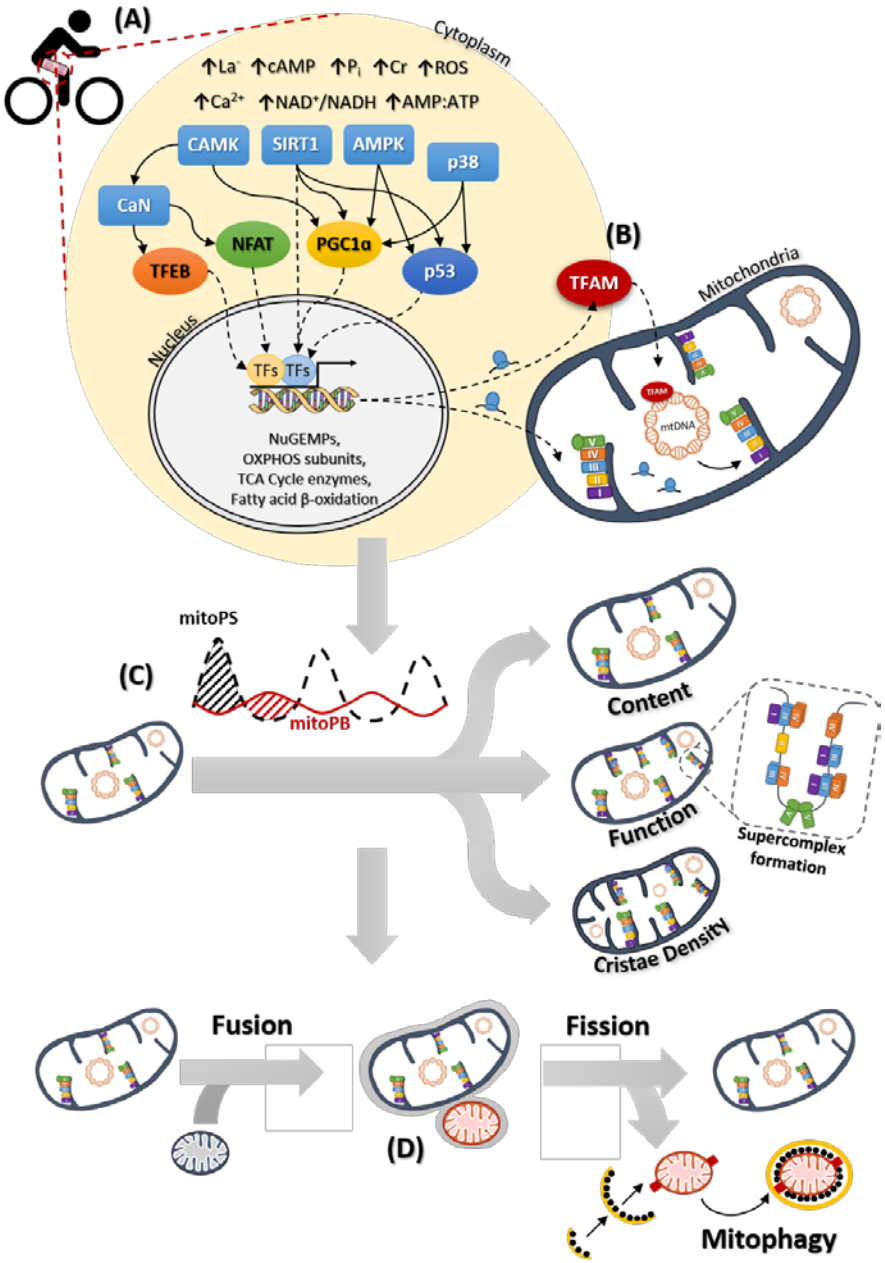


Figure 2.5 - Schematic representation of an overview of the effects of endurance exercise and training (specifically high-intensity) on mitochondrial adaptations. Produced by the author for Bishop et al. (2019b).

A: a single session of high-intensity exercise elevates cytosolic concentrations of several metabolites, which initiates a cascade of signalling events in numerous pathways, leading to the upregulated expression of genes encoding proteins for mitochondrial biogenesis, fatty acid oxidation, the Krebs cycle, and oxidative phosphorylation. This is facilitated by transcription factors, transcriptional co-activators, and transcriptional regulators, which translocate (broken lines) into the nucleus to modulate gene expression. B: mitochondrial transcription factors and other proteins encoded within the nucleus translocate into the mitochondria where they affect mitochondrial gene expression or are incorporated into the mitochondria. C: high-intensity exercise transiently upregulates mitochondrial protein synthesis (mitoPS). Repeated mitoPS stimulation through training, coupled with increases in fusion and fission, leads to expansion and remodelling of the mitochondrial reticulum, evident through changes in mitochondrial content, function, and cristae density. D: damaged mitochondria (in red, reflecting a loss of membrane potential) are isolated from the mitochondrial reticulum by fission proteins, and subsequently degraded via mitophagy. AMP, adenosine monophosphate; ATP, adenosine triphosphate; NAD, nicotinamide adenine dinucleotide; CaN, calcineurin; CAMK, Ca2 /calmodulin-dependent protein kinase; SIRT1, NAD-dependent deacetylase sirtuin-1; TFEB, transcription factor EB; PGC1α, peroxisome proliferator-activated receptor gamma co-activator 1-a; TFs, transcription factors; NUGEMPs, nuclear genes encoding mitochondrial proteins; OXPHOS, oxidative phosphorylation; TFAM, mitochondrial transcription factor A; mitoPS, mitochondrial protein synthesis; mitoPB, mitochondrial protein breakdown.

* * * * *

Based on the literature reviewed thus far, it is clear that endurance and resistance exercise induce distinct and divergent post-exercise molecular responses, and the cumulative effect of training results in the development of different phenotypes. Given that both exercise modes have the capacity to improve several aspects of health and wellbeing, and benefit performance in a range of sporting events, concurrently training for both modes offers an ideal strategy to maximise adaptations that are considered to sit at opposing ends of the spectrum (Fyfe et al., 2014, Nader, 2006). However, as will be discussed in the next section, under different conditions, concurrent training can induce both negative, and additive effects on the development of specific adaptations, and therefore a detailed understanding of the methodological considerations to concurrent training is necessary for those aiming to minimise the risk of interference to both training adaptations.

2.4 Concurrent Exercise & Training Adaptations

Interest into concurrent training began following the seminal work of Dr Robert Hickson, who demonstrated that improvements in lower-body strength were attenuated when heavy resistance training was combined with high-intensity, high-volume endurance training (Hickson, 1980). These initial findings have since been supported by several studies incorporating various training program designs, which show diminished gains in strength (Bell et al., 2000, Fyfe et al., 2016a, Gergley, 2009, Hickson, 1980, Kraemer et al., 1995, Ronnestad et al., 2012, Sale et al., 1990a), hypertrophy (Bell et al., 2000, Fyfe et al., 2016a, Kraemer et al., 1995, Ronnestad et al., 2012), and power (Dudley and Djamil, 1985, Häkkinen et al., 2003, Kraemer et al., 1995, Mikkola et al., 2012, Tsitkanou et al., 2017) when compared with performing resistance-only training; this has been termed the "*interference effect*" or the "*concurrent training effect*" (Baar, 2006, Hawley, 2009). A combination of *'acute'* and *'chronic'* factors have been suggested to mediate this effect, related to both the immediate impact of one exercise session on the quality of another, and the different demands for adaptation of each mode (reviewed in Leveritt et al. (1999) and Nader (2006)).

The interference effect, however, is not always observed, with mounting evidence that concurrent training does not inhibit gains in strength and muscle mass (de Souza et al., 2013, McCarthy et al., 1995, McCarthy et al., 2002). This is supported by several studies failing to report compromised mTORC1 signalling with concurrent training (Apró et al., 2015, Apró et al., 2013). However, it is also worth noting that whilst Apró *et al.* (2015) did not report a 'statistically significant' effect on mTORC1 signalling (e.g., p70S6K activity), there appears to be a strong trend for lower kinase activity in the concurrent group, and as such does not negate the possibility of a physiologically relevant effect. Nonetheless, others have shown augmented signalling responses associated with both muscle growth (Lundberg et al., 2012, Pugh et al., 2015), and mitochondrial biogenesis (Wang et al., 2011), as well as greater hypertrophic and oxidative adaptations compared to single-mode training (Kazior et al., 2016, Lundberg et al., 2013, Lundberg et al., 2014). It has also been proposed that power development may be more susceptible to the interference effect than strength and muscle mass (Kraemer et al., 1995, Wilson et al., 2012). Indeed, others have observed a selective interference effect, whereby power or the rate of force development was impaired by concurrent training, despite no interference to strength or muscle hypertrophy (Dudley and Djamil, 1985, Häkkinen et al., 2003, Kraemer et al., 1995, Mikkola et al., 2012, Tsitkanou et al., 2017). Such discrepancies are likely reflected by the marked differences in training program and study designs between concurrent training studies (Bishop et al., 2019a, Fyfe et al., 2014).

It appears that the development of hallmark resistance adaptations are primarily susceptible to the interference effect with the addition of endurance to resistance training. Conversely, the literature to date supports the notion that endurance performance and adaptations are largely unaffected (Wilson et al., 2012), and in many cases improved by the addition of resistance to endurance training (Irving et al., 2015, Ronnestad et al., 2015, Ronnestad and Mujika, 2014, Vikmoen et al., 2015, Wang et al., 2011). Such improvements are ascribed to fibre-type conversions from type IIx to fatigue-resistant type IIa fibres, alterations in muscle fibre recruitment patterns, and increases in maximum force-generating capacity and the rate of force development (Ronnestad and Mujika, 2014). As such, the principal foci of this review and subsequent original works relate to the potential negative effects of endurance training on the development of resistance training adaptations.

2.4.1 Suggested mechanisms of interference

The factors suggested to underpin the interference effect can be classified as *'acute'* and *'chronic'*, whereby the former relates to the effects of an endurance session on subsequent resistance exercise performance, and the latter concerns the different adaptive demands of long-term endurance and resistance training (Leveritt et al., 1999). More specifically, the *'acute'* hypothesis, originally proposed by Craig *et al.* (1991), suggests that the ability to produce force during a resistance session may be compromised by acute fatigue induced from a prior endurance exercise session (Leveritt et al., 1999). Indeed, reductions in force-generating capacity have been demonstrated after endurance sessions of various intensities and durations (Abernethy, 1993, Bentley et al., 1998, Bentley et al., 2000, Lepers et al., 2000, Leveritt and Abernethy, 1999). Furthermore, resistance exercise performance (i.e., the number of repetitions completed, or the maintenance of a required load) has been shown to be diminished when preceded by steady-state continuous and high-intensity interval cycling (Sporer and Wenger, 2003) and running (Inoue et al., 2016, Jones et al., 2017), with recovery durations ranging from <10 minutes (Inoue et al., 2016, Jones et al., 2017) to 4 and 8 hours (Sporer and Wenger, 2003). The quality of a resistance session may also be diminished due to an anticipatory reduction in effort or training volume if performed *before* an endurance session (Sale et al., 1990a). Given that the force-generating capacity of a muscle is an important factor in strength development (Leveritt et al., 1999), and that resistance training volume appears to be the key driver of both muscle hypertrophy (Schoenfeld et al., 2017) and strength adaptations (Colquhoun et al., 2018, Grgic et al., 2018b), reductions in either may increase the potential for an interference effect. These findings also highlight the potential importance of concurrent training organisation, with respect to the role of exercise order in mitigating any potential negative effects of acute fatigue on the stimulus for resistance adaptations; this will be discussed in more detail in subsequent sections.

The *'chronic'* hypothesis proposes that the inherent dichotomy of endurance and resistance adaptations, on a structural and functional level, may prevent the muscle from simultaneously meeting the divergent metabolic and morphological demands of each training mode (Leveritt et al., 1999, Nader, 2006). Given that endurance and resistance exercise induce distinct molecular events that govern their respective phenotypic adaptations, coupled with the increased availability and adoption of molecular biology techniques into exercise physiology research, increasing attention has been paid to the potential antagonism between concurrent exercise modes at the molecular level, which may, in part, explain the interference to whole-body adaptations.

2.4.2 Exploring the molecular interference effect

The precise molecular mechanisms governing endurance and resistance adaptations are incompletely resolved; however, several points of interference between their respective signalling pathways have been proposed (Figure 2.7). The purported antagonism between AMPK and mTORC1 signalling has received much attention (Kimball, 2006). AMPK functions as an energy sensor in response to changes in AMP:ATP ratios and cellular stress, and mediates the reduction in energy-consuming pathways, favouring energy production (Hardie, 2011). AMPK directly phosphorylates TSC2, which functions as a GTPase-activating protein (GAP) towards Rheb (Ras homologue enriched in brain), a key substrate for mTORC1 (Inoki et al., 2003a, Inoki et al., 2003b). AMPK-mediated phosphorylation of TSC2 converts Rheb to its inactive GDP-bound state, supressing mTORC1 signalling (Inoki et al., 2003a, Inoki et al., 2003b). However, TSC2 is also phosphorylated (and inactivated) by Akt, causing its association with 14-3-3 binding protein, thereby removing its inhibition on Rheb and mTOR (Li et al., 2002). Thus, the interaction between AMPK-TSC2-Rheb-mTORC1 serves as a potential point of divergence in the molecular control of concurrent training adaptations.

A key mechanistic step required to increase AMPK kinase activity is phosphorylation by the protein LKB1, which is bound to a scaffold protein called AXIN (Zhang et al., 2013). Conditions of metabolic stress, such as elevated AMP concentrations and glucose starvation, increase the affinity of AMPK for AXIN, which consequently form an AXIN/LKB1/AMPK complex, that promotes LKB1-mediated phosphorylation and activation of AMPK (Zhang et al., 2013). Furthermore, glucose starvation promotes AXIN/LKB1/AMPK translocation to the lysosome, where the nutrient-sensing v-ATPase/Ragulator complex undergoes a conformational change, rendering v-ATPase inactive. In this way, AXIN binds onto Ragulator, inhibiting its GEF activity to the Rag GTPases, resulting in mTORC1 dissociation from the lysosome (Efeyan et al., 2013, Zhang et al., 2014a) (Figure 2.6). Despite the apparent physiological paradox that mTORC1 and AMPK share a mutual activator, the differential regulation of the v-ATPase/Ragulator complex by both amino acid and energy availability may present a mechanism to explain the molecular

switch between anabolic and catabolic processes (Efeyan et al., 2013, Zhang et al., 2014a). This may be of particular importance to concurrent training, and the nutritional strategies to support adaptations, given that the additional training volume performed compared to resistance-only training may induce a greater energy deficit (Hughes et al., 2018). This highlights a need to maximise protein and energy availability; however, this has not yet been investigated.

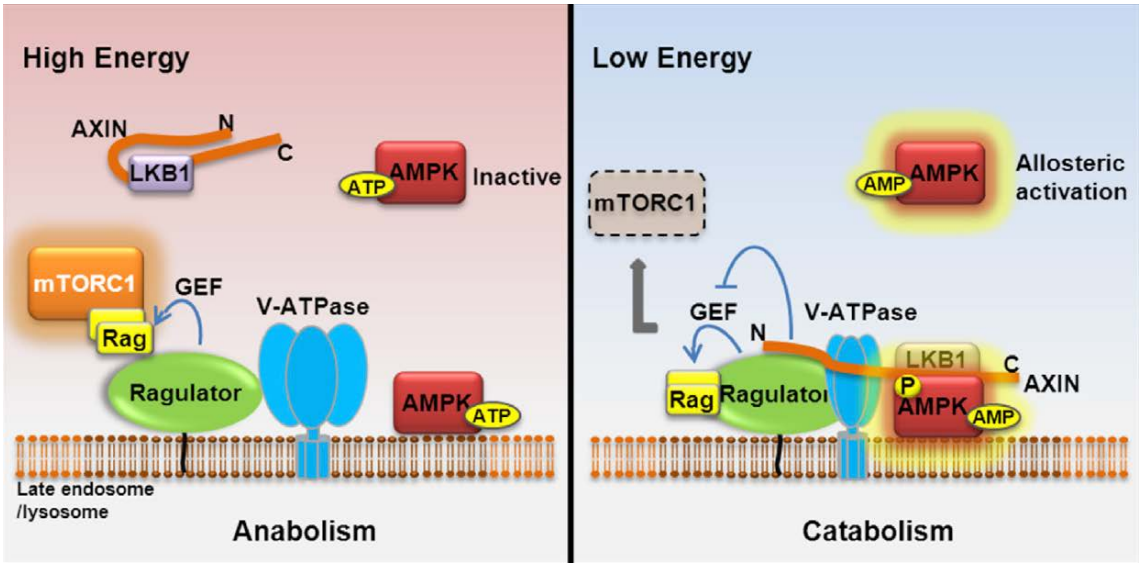


Figure 2.6 - The effect of high and low energy availability on AXIN/LKB1/AMPK-mediated regulation of v-ATPase/Ragulator/Rag dependent mTORC1 activity, from (Zhang et al., 2014a)

In addition to the above mechanisms, AMPK-mediated phosphorylation of raptor (a component of mTORC1, which recruits substrates to the complex for activation) results in its association with 14-3-3 binding protein, rendering it inactive; this suggests that AMPK may suppress mTORC1 signalling by negatively affecting multiple upstream targets (Gwinn et al., 2008). Further models of AMPK activation have demonstrated diminished mTORC1 signalling via: direct phosphorylation on mTORC1^{Thr2446}, which is inversely associated with Akt-mediated phosphorylation on ^{ser2448} (Cheng et al., 2004); suppression of regulatory proteins involved in translation initiation and elongation (e.g., p70S6K, 4E-BP1 and eEF2K) (Bolster et al., 2002, Rose and Richter, 2009, Thomson et al., 2008); increased association with the autophagy-inducing kinase ULK1 (Lee et al., 2010b); and increased FOXO-mediated transcription of their associated atrophy-inducing genes, MuRF1 and MAFbx (Krawiec et al., 2007, Nakashima and Yakabe, 2007). Consequently, mounting evidence implicates AMPK as a major point of molecular interference.

Early work in rodents proposed the notion of an "*AMPK-Akt switch*"-like mechanism to explain how endurance and resistance exercise induce mode-specific adaptations (Atherton et al., 2005). However, in humans, such a mechanism is too simplistic and remains to be confirmed (Fyfe et

al., 2014, Timmons, 2011, Hamilton and Philp, 2013). For instance, AMPK can respond to both endurance and resistance exercise (Dreyer et al., 2006, Koopman et al., 2006, Lundberg et al., 2014) in both untrained and trained participants, whilst mTOR signalling is selectively activated by resistance exercise following training (Vissing et al., 2013). Emerging evidence also suggests that endurance exercise can induce mTORC1 signalling in recreationally-active participants (Mascher et al., 2011) and with training, induce comparable MPS and hypertrophy, albeit to a lesser magnitude, to resistance exercise (Konopka and Harber, 2014, Ozaki et al., 2015). Conversely, resistance exercise has been shown, under certain conditions, to induce mitochondrial (Balakrishnan et al., 2010, Burd et al., 2012), oxidative (Tang et al., 2006) and cardiovascular adaptations (Lovell et al., 2009). These studies highlight the complexity of the molecular regulation of different training adaptations in human skeletal muscle and suggest other mechanisms may govern the interference effect in addition to, or instead of, the AMPK-mTOR signalling axis.

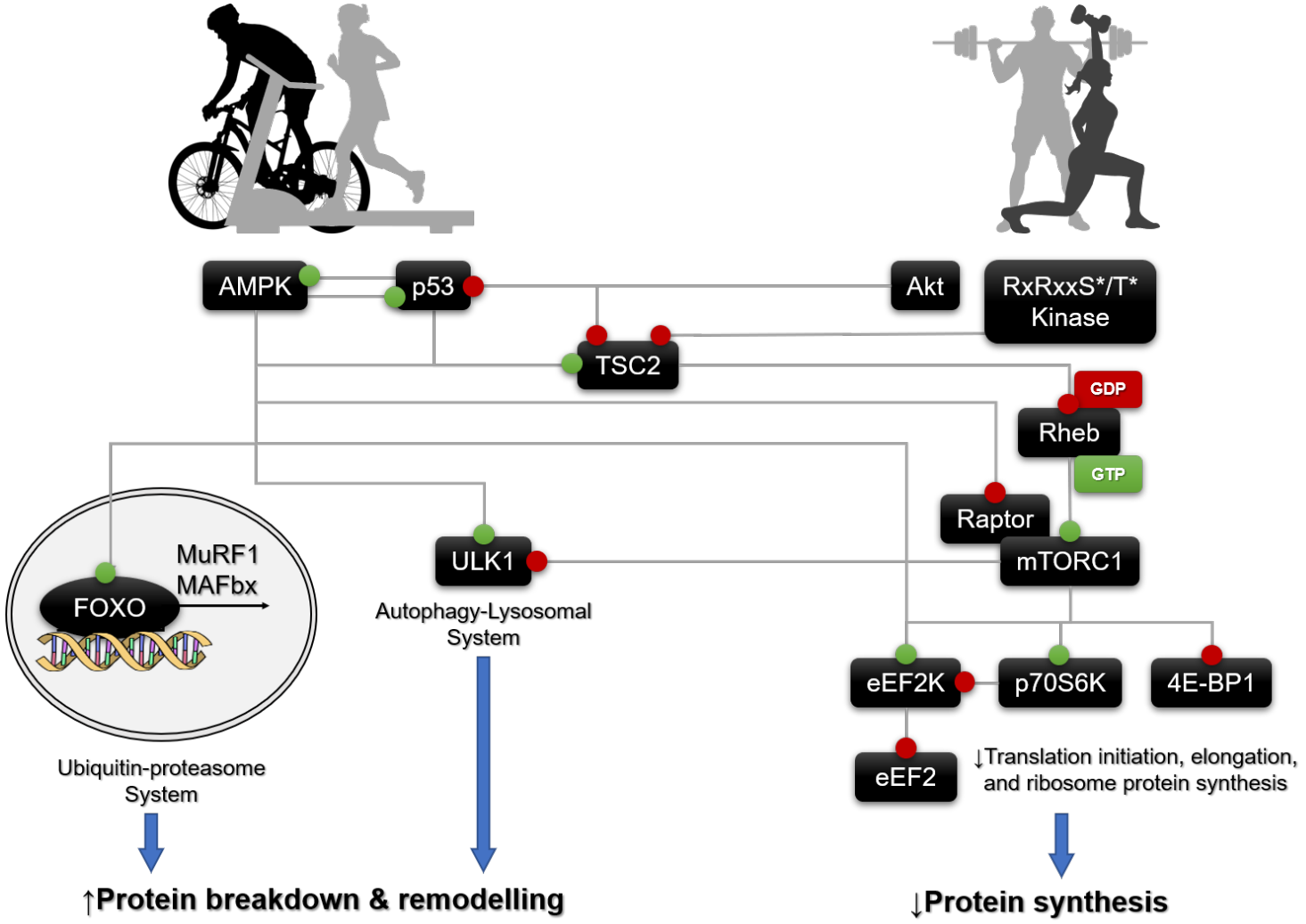


Figure 2.7 - The primary molecular mechanisms of suggested antagonism between the AMPK and mTORC1 signalling pathways, adapted from Fyfe et al. (2014).

A potential alternative "*molecular switch*" has recently emerged, involving the transforming growth factor-β (TGF-β) family of ligands and the mitogen-activated protein kinase (MAPK) c-Jun N-terminal kinase (JNK). TGF-β growth factors play a significant role in cell growth, proliferation, differentiation, and apoptosis, and regulate developmental and mature skeletal muscle mass (Kollias and McDermott, 2008). TGF-β ligands bind to, and activate, receptors in the plasma membrane, which subsequently phosphorylate small mother of decapentaplegic (Smad) proteins (Kollias and McDermott, 2008), which are transcription factors for numerous hypertrophy- and atrophy-related genes, depending on the initial ligand binding (Marcotte et al., 2015). The TGF-β ligand myostatin is of particular interest, given its capacity to inhibit mTORC1 by attenuating mTORC1 phosphorylation *per se*, as well as via several key upstream mediators of mTORC1 activation (Akt and TSC2) and downstream targets such as rpS6 and 4E-BP1 (Amirouche et al., 2009, Winbanks et al., 2012). Furthermore, myostatin binding leads to the phosphorylation of the Smad2/3 complex, promoting its association with Smad4, upon which this ternary complex translocates to the nucleus to upregulate the expression of target genes such as MuRF1 and MAFbx (Sartori et al., 2014), as well as repressing the transcription of Mighty, a downstream target of myostatin shown to positively correlate with resistance-training induced changes in muscle mass (MacKenzie et al., 2013, Marshall et al., 2008). Conversely, alternative ligands such as bone morphogenetic protein (BMP) activate the Smad1/5/8 complex, whose competing association with Smad4, and subsequent nuclear translocation, suppresses the expression of ubiquitin-ligases, and promotes protein synthesis (Sartori et al., 2014).

Two studies by Lessard and colleagues (Lessard et al., 2018, Lessard et al., 2013) identified a potential role of JNK in regulating myostatin/Smad signalling and subsequently mediating different adaptations to endurance and resistance exercise. Firstly, mice selectively-bred to be low-responders to endurance training exhibited compromised endurance adaptations characterised by impaired metabolic function and endurance capacity (Lessard et al., 2013). Mechanistically, these adaptations were associated with a greater exercise-induced phosphorylation of the linker region on Smad2 (Smad2-L); this was proposed to be mediated by the activity of upstream kinases JNK and p38 MAPK (Lessard et al., 2013). Thus, the phosphorylation of Smad2-L by JNK was suggested to compromise skeletal muscle adaptations to endurance training (Lessard et al., 2013). Further work by Lessard *et al.* explored the role of JNK/Smad signalling in facilitating adaptations to different exercise stimuli (Lessard et al., 2018). Following endurance training, JNK-null mice exhibited greater capillary density, type I fibre proportions, and reductions in fibre CSA, culminating in a greater endurance capacity than wild-type (WT) mice. Conversely, following synergist ablation-induced overload, JNK knockout attenuated the increases in muscle fibre size and mass observed in WT. Subsequent experiments revealed that contraction-stimulated activation of JNK leads to Smad2-L phosphorylation,

attenuating its translocation to the nucleus in the ternary complex with Smad3 and 4, and inhibiting its transcriptional activity in response to myostatin availability (Lessard et al., 2018). These findings were also supported in humans, whereby a single bout of resistance exercise induced robust, biphasic stimulation of JNK and Smad2-L phosphorylation, whilst the response to endurance exercise was substantially diminished (Lessard et al., 2018). Thus, whilst the AMPK-mTOR "*master switch*" hypothesis lacks support from exercise studies in human skeletal muscle, the JNK signalling pathway may offer an alternative explanation for competing adaptations with concurrent training (Figure 2.8). However, this has yet to be explored in a concurrent training model in human skeletal muscle.

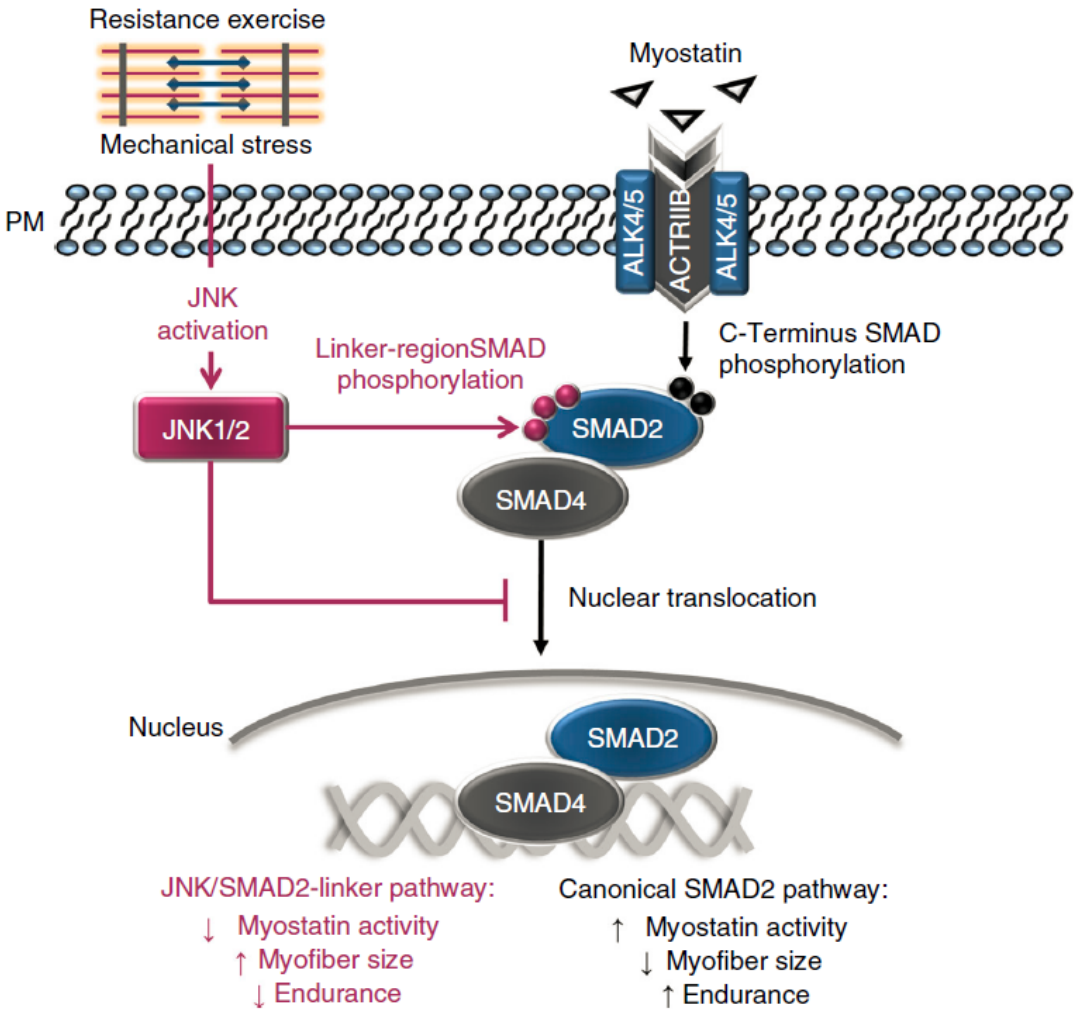


Figure 2.8 - Proposed mechanisms through which resistance exercise-induced activation of JNK signalling inhibits myostatin activity via Smad2-linker phosphorylation, preventing the subsequent translocation of the Smad protein complex into the nucleus, from Lessard et al. (2018).

Another potential mechanism that remains largely overlooked in the concurrent training literature is the influence of the tumour suppressor p53. Considered the "*guardian of the genome*", p53 functions as a transcription factor regulating the expression of genes involved in cell-cycle arrest, senescence, apoptosis, and autophagy (Levine et al., 2006, Bartlett et al., 2014). Recent evidence has also demonstrated a role for p53 in regulating metabolism (Berkers et al., 2013) and exercise-induced adaptations (Bartlett et al., 2014). p53-deficient rodent and human cells display elevated lactate and ROS production, reduced mitochondrial content and respiration, reduced mRNA and protein expression associated with mitochondrial biogenesis (i.e., PGC-1α, Tfam, SCO2, mtDNA), and transgenic mice elicit a reduced exercise capacity and fatigue resistance (Matoba et al., 2006, Park et al., 2009, Saleem et al., 2009, Saleem and Hood, 2013). In humans, work-matched high-intensity interval and moderate-intensity continuous running both induced phosphorylation of $p53^{Ser15}$ and signalling responses associated with mitochondrial biogenesis (Bartlett et al., 2012), which was further enhanced when endurance (Bartlett et al., 2013) and resistance exercise (Camera et al., 2015a) were commenced under conditions of low carbohydrate availability.

Studies in human and rodent cells have demonstrated that p53 can stimulate AMPK-mediated phosphorylation of TSC2, which subsequently disrupts Rheb co-localisation with mTORC1 (Feng et al., 2005). p53 also regulates the transcription of PTEN, IGF-binding protein 3 (IGF-BP3) and polo-like kinase 2 (Plk2) – all of which negatively influence the IGF-1/Akt/mTOR axis (Feng et al., 2007, Matthew et al., 2009). Furthermore, during energy stress, AMPK directly phosphorylates $p53^{ser15}$ (Feng et al., 2005, Imamura et al., 2001, Jones et al., 2005), highlighting that p53 can function both up- and downstream of AMPK to inhibit mTORC1 signalling (Berkers et al., 2013). Conversely, p53 is inactivated via Akt-mediated phosphorylation of MDM2 (murine double minute 2, an inhibitor of p53) (Gottlieb et al., 2002) and phosphorylation (and nuclear abrogation) of PHF20 (PHD Finger Protein 20, a transcription factor for p53) (Park et al., 2012), plus mTORC1-mediated phosphorylation of p53 phosphatase (α4 and PP2A (Protein Phosphatase 2A)) (Kong et al., 2004). In considering the purported roles of both p53 and mTORC1 respectively in coordinating both skeletal muscle oxidative adaptations (Bartlett et al., 2014, Saleem et al., 2011) and growth (Dreyer et al., 2010, Drummond et al., 2009), the differential regulation of the p53-mTOR signalling axis may contribute to the molecular incompatibility between divergent exercise modes (Figure 2.9).

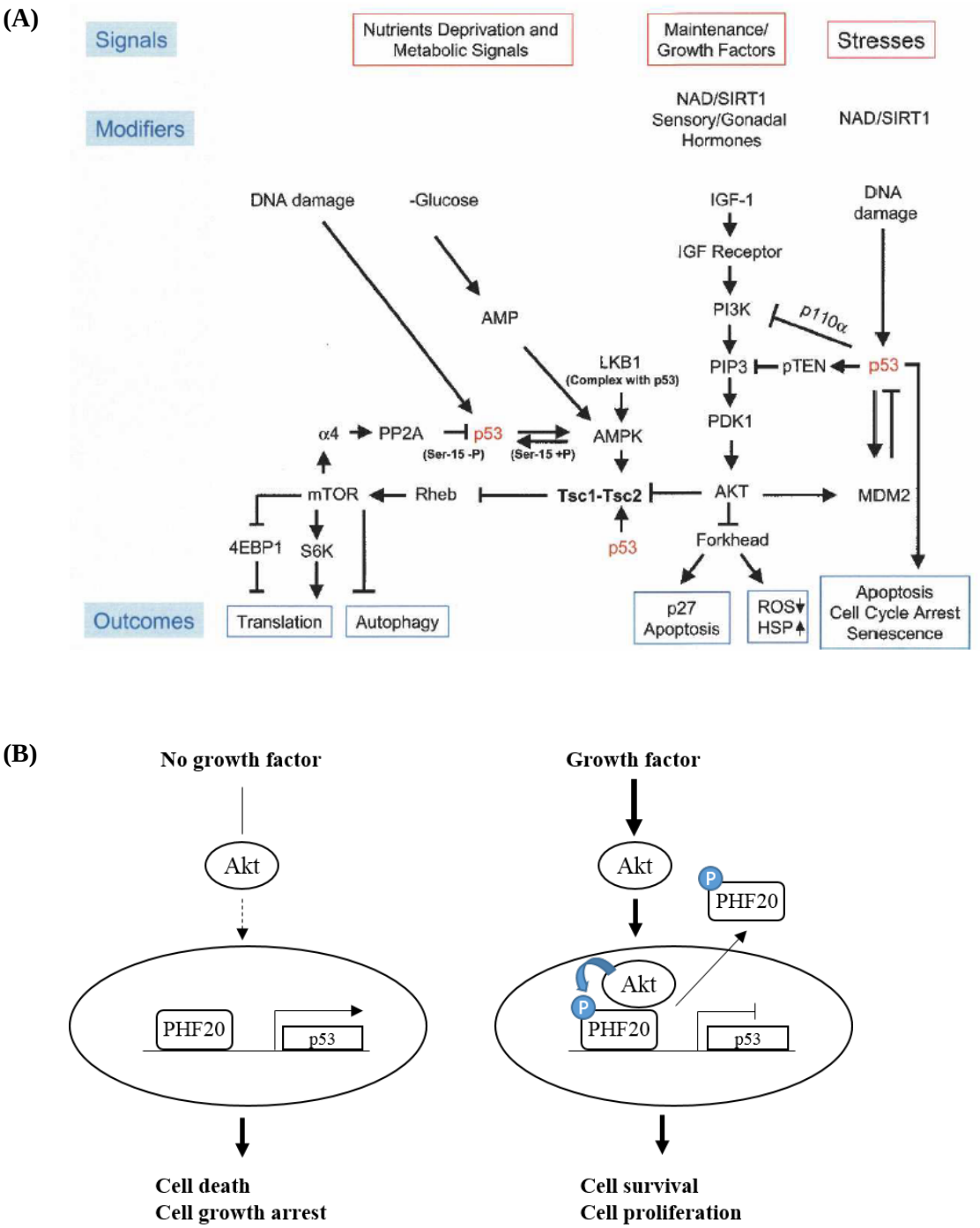


Figure 2.9 - (A) The communication between AMPK, p53 and mTOR signalling pathways in response to various stresses, from Levine et al. (2006); (B) Growth factor-induced, Akt-mediated, transcriptional regulation of p53 via the phosphorylation of PHF20, from Park et al. (2012).

More recently, the potential role of p53 in specifically regulating concurrent training adaptations has been further proposed, due to its involvement in both amino acid-stimulated activation of mTORC1 and ribosomal biogenesis (Ellefsen and Baar, 2019) (Figure 2.10). Briefly, the activation of mTORC1 by the amino acid leucine is negatively affected by Sestrins, which are stress-inducible proteins involved in the regulation of mTORC1 and AMPK signalling, and are

transcriptional targets for p53 and FOXO transcription factors (Lee et al., 2016). Sestrins can inhibit mTORC1 by stimulating both AMPK-mediated phosphorylation of the TSC2 complex (thereby inhibiting the mTORC1 substrate Rheb) (Budanov and Karin, 2008), as well as by binding to GATOR2, permitting GATOR1 to interact with, and exert inhibitory GAP activity towards the RagA/B complexes, compromising mTORC1 translocation to the lysosome (Chantranupong et al., 2014, Lee et al., 2016). Regarding its effect on ribosome biogenesis, activated p53 translocates to the nucleolus (the site of ribosomal RNA synthesis) and interferes with the interaction between two auxiliary factors of ribosomal RNA (rRNA) transcription, upstream binding factor (UBF) and selectivity factor SL1 (Zhai and Comai, 2000). This interference represses the transcriptional activity of RNA Polymerase I (Zhai and Comai, 2000). Consequently, in response to different stimuli, p53 may disrupt not only the efficiency of, but also the capacity for, protein synthesis, whereby endurance exercise-induced activation of p53 may lead to the suppression of mTORC1 as well as ribosome biogenesis, through a variety of the mechanisms described above. Whether any of these occur in human skeletal muscle in response to concurrent endurance and resistance stimuli remains to be tested.

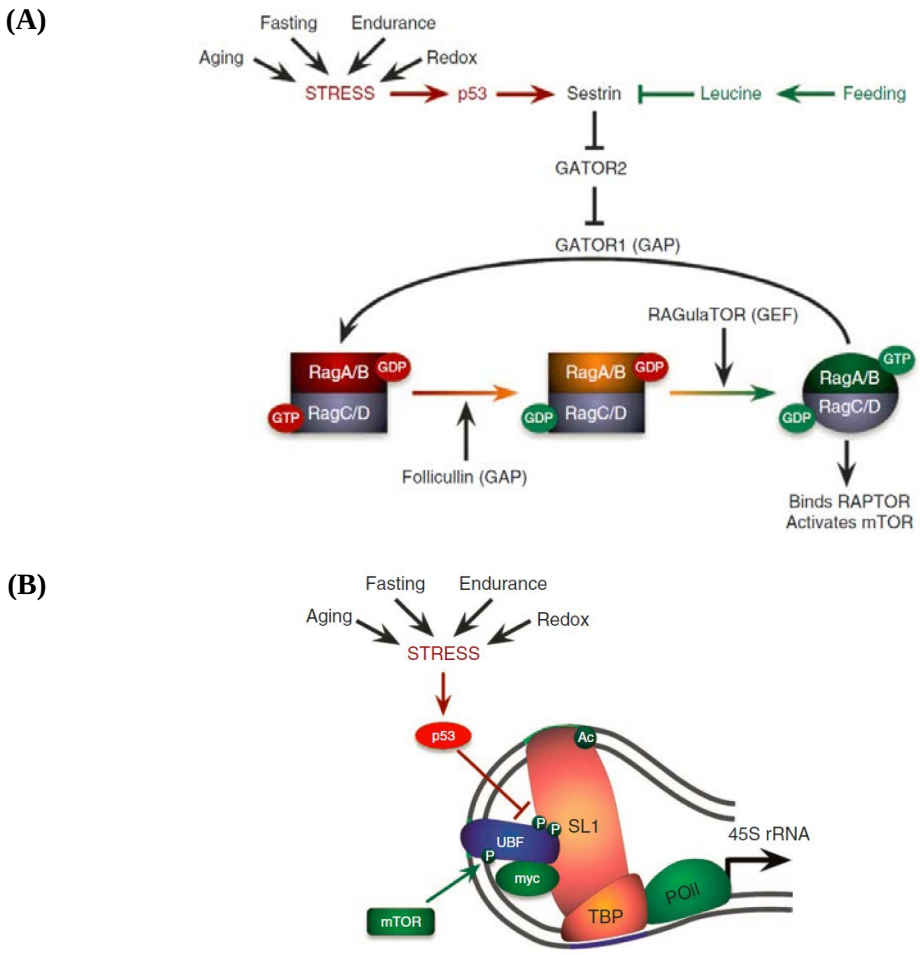


Figure 2.10 - Schematic representation of the involvement of p53 in inhibiting (A) amino acid-induced mTOR activation, and (B) ribosome biogenesis, from Ellefsen and Baar (2019).

2.4.3 Is there a molecular interference in humans?

Collectively, it appears that antagonism between the signalling pathways induced by endurance and resistance exercise may contribute to the compromised adaptations frequently observed following concurrent training (Coffey and Hawley, 2007). However, much of this evidence has been derived from experimental models employing pharmacological activation of signalling pathways in cell culture, artificially-induced contractions via electrical stimulation, and transgenic animals. In human skeletal muscle, under normal physiological conditions, our understanding of the molecular regulation of concurrent training adaptations remains in its infancy.

Few studies provide evidence of an interference to exercise-induced molecular responses with concurrent exercise (Babcock et al., 2012, Fyfe et al., 2018). One study demonstrated that concurrent exercise attenuated the resistance exercise-induced increase in satellite cells, in all muscle fibres (Babcock et al., 2012). More recently, after 8 weeks of training, a single resistance exercise session induced greater signalling associated with mTORC1 and ribosome biogenesis compared to concurrent exercise (Fyfe et al., 2018). Nonetheless, most other studies to date do not provide compelling evidence of a molecular interference effect. In healthy males, performing resistance exercise prior to both steady-state (Apró et al., 2013) and high-intensity interval cycling (Pugh et al., 2015) elicited comparable mTORC1 signalling to resistance-only exercise. Similar findings were also reported in sedentary middle-aged men, despite performing only 50% of the total endurance and resistance exercise volumes, respectively, in the concurrent training trial (Donges et al., 2012). Apró *et al.* (2013) also observed a decrease in AMPK phosphorylation concomitant with maximal p70S6K phosphorylation, suggesting that prior activation of mTORC1 signalling by resistance exercise may inhibit AMPK activity. However, given the temporal differences between AMPK signalling after endurance exercise, and resistance exercise-induced stimulations in mTORC1 and protein synthesis (<3 vs >24 hours, respectively), it has also been proposed that concurrently training in the reverse order may allow a greater anabolic response during recovery following resistance exercise (Fyfe et al., 2014). Indeed, prior endurance exercise did not compromise subsequent resistance exercise-induced mTORC1 signalling in active (Fyfe et al., 2016b, Wang et al., 2011) and trained individuals (Apró et al., 2015), and this was also demonstrated with both moderate- and high-intensity cycling (Fyfe et al., 2016b). In fact, Lundberg *et al.* (2012) observed greater mTORC1 and p70S6K phosphorylation with concurrent training compared to resistance-only exercise, and others have also shown greater expression of genes associated with mitochondrial biogenesis than single-mode exercise (Wang et al., 2011). Collectively it appears that concurrent training may amplify the molecular responses to both resistance and endurance exercise, compared to each mode performed separately. However, other factors, such as participant training status (*discussed further in section 2.4.5*), and small participant cohorts, may alter the interpretation of the training effect; e.g., the absence of

'statistical significance' despite a strong trend for lower p70S6K activity with concurrent training in trained individuals (Apró et al., 2015) may incorrectly negate reporting a potentially physiologically relevant effect. Furthermore, as these studies only compared one concurrent group to single-mode resistance exercise, it is difficult to speculate how the responses within each study may have differed had the concurrent exercise regime also been performed in the reverse order. Whilst a limited number of studies to date have investigated the effects of concurrent exercise on the adaptive molecular responses in humans, fewer still have specifically addressed the effect of concurrent exercise order.

Coffey *et al.* conducted the first two studies in humans to investigate the acute effects of concurrent exercise order on the expression of gene and proteins involved in endurance and resistance adaptations (Coffey et al., 2009a, Coffey et al., 2009b). Resistance exercise (8 × 5 leg extensions at 80% 1-repetition maximum [RM]) was performed concurrently with steady-state (30 minutes at 70% $\dot{V}O_{2peak}$ (Coffey et al., 2009b)) or repeated sprint cycling (10 × 6 seconds at 0.75 N·m torque·kg^{-1} (Coffey et al., 2009a)). When combined with steady-state cycling, mTORC1 signalling responses downstream of Akt occurred independent of exercise order (Coffey et al., 2009b). However, when cycling preceded resistance exercise, IGF-1 mRNA expression was reduced (suggestive of a diminished anabolic response), whilst the reverse order increased mRNA expression of the ubiquitin ligase MuRF-1 (associated with inflammation and muscle protein breakdown) (Coffey et al., 2009b). This was further exacerbated when the endurance modality involved repeated maximal sprints (Coffey et al., 2009a). Furthermore, the prior bout of maximal sprints also attenuated resistance exercise-induced p70S6K and rpS6 phosphorylation, both of which are integral to translation initiation (Coffey et al., 2009a). Evidently, neither order provided a desirable molecular environment for adaptation. However, these studies were conducted in the fasted-state, which has been shown to affect signalling associated with both growth (Creer et al., 2005) and mitochondrial adaptations (Bartlett et al., 2013). The lack of a resistance-only group also precludes interpretations about the degree of '*molecular*' interference from each exercise order versus single-mode resistance exercise.

More recently, Jones *et al.* (2016) investigated the potential antagonism between AMPK and mTORC1 signalling networks in resistance-trained men, in which resistance exercise (5 × 6 repetitions of leg press and leg extensions at 80% 1-RM) was performed in the fed-state before, after, and independent of steady-state cycling (30 minutes at 70% power at $\dot{V}O_{2max}$). Unlike the previous works (Coffey et al., 2009a, Coffey et al., 2009b), AMPK and mTORC1 signalling responses were similar between alternate exercise orders, *as well as* resistance-only exercise (Jones et al., 2016). However, this study only investigated the immediate post-exercise time-course (<1 hour); thus, it is possible that key signalling events may have been missed.

The current understanding of the molecular responses and adaptations to concurrent training is based on protocols in which concurrent modes were scheduled either within the same session, typically ≤ 15 to 20 minutes apart (Apró et al., 2015, Apró et al., 2013, Coffey et al., 2009a, Coffey et al., 2009b, de Souza et al., 2013, Lundberg et al., 2014, Pugh et al., 2015, Wang et al., 2011), or several (≥ 6) hours apart (Lundberg et al., 2012, Lundberg et al., 2013). However, the expression of several important regulatory genes and proteins involved in the crosstalk between endurance (AMPK, PGC-1α, p53) (Bartlett et al., 2012, Bartlett et al., 2013, Camera et al., 2015a, Gibala et al., 2009, Nordsborg et al., 2010, Norrbom et al., 2004, Pilegaard et al., 2003) and resistance signalling pathways (mTORC1, p70S6K) (Dreyer et al., 2010, Drummond et al., 2009, Vissing et al., 2013) are known to be upregulated ~2 to 4 hours post-exercise in human skeletal muscle. Given that it is also common practice, particularly within athletic environments, for concurrent sessions to be separated by short recovery periods of only a few hours (Cross et al., 2019, Enright et al., 2015, Enright et al., 2017, Robineau et al., 2016), no research to date has investigated how training in this way may modulate the molecular events orchestrating the development of endurance and resistance adaptations, and thus presents an avenue for further exploration.

2.4.4 Methodological considerations when interpreting concurrent training studies

Given the lack of evidence supporting a clear interference effect at the molecular level, it is also unsurprising to find a growing body of literature showing comparable gains in strength (Abernethy, 1993, Cantrell et al., 2014, Glowacki et al., 2004, Laird et al., 2016, McCarthy et al., 1995, Sale et al., 1990b, Volpe et al., 1993) and muscle hypertrophy (de Souza et al., 2013, Kazior et al., 2016, Lundberg et al., 2013, Lundberg et al., 2014, McCarthy et al., 2002, Sale et al., 1990b) with concurrent and resistance-only training. The presence and magnitude of the interference effect is likely dependent upon several methodological factors pertaining to the training program and study design (Bishop et al., 2019a). These include training variables such as the choice of exercise session order (i.e., endurance prior to, or after resistance exercise), between-session recovery duration, training frequency, volume, intensity, and exercise modality, plus other '*non-training*' variables such as the participant training status, nutrient availability, and individual responses to training (Figure 2.11).

Concurrent training offers a time-efficient alternative to single-mode training, particularly if both modes are performed within the same session or separated by short recovery periods. The '*acute*' interference hypothesis suggests that one exercise session may induce residual fatigue and substrate depletion, hindering the quality and performance of a subsequent bout, and may induce unfavourable neuromuscular, hormonal, and molecular milieus for adaptation (Fyfe et al., 2014,

Leveritt et al., 1999). Consequently, the choice of exercise order is an important consideration for maximising concurrent training adaptations and as such, is a major focus of this thesis.

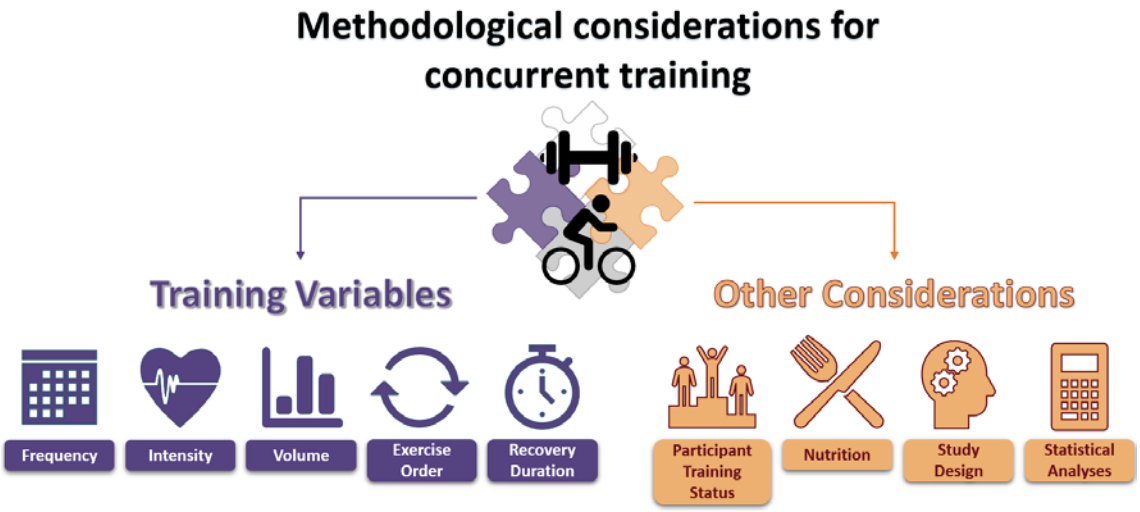


Figure 2.11 - Methodological considerations for concurrent training. A schematic highlighting the key training and 'non-training' variables that dictate the potential presence and magnitude of the interference effect. Produced by the author for Bishop et al., (2019a).

Exercise session order

Greater reductions in acute strength performance (i.e., the ability to maintain a required load or volume) have been observed when resistance exercise was conducted immediately (≤ 10 minutes) after both steady-state (Jones et al., 2017) and high-intensity intermittent running (Inoue et al., 2016), compared with the reverse order. As such, a reduction in the resistance training stimulus, such as the volume, may compromise the potential for adaptation (Colquhoun et al., 2018, Grgic et al., 2018b, Schoenfeld et al., 2017). Evidence in elderly men supports greater improvements in strength, muscle quality (force production per unit of active mass), and neuromuscular economy, plus a trend for greater resistance training load when resistance training precedes endurance (Cadore et al., 2012, Cadore et al., 2013). Similar findings were also reported in healthy young women, following a water-based concurrent training program, where greater improvements in maximal dynamic strength were observed in those who performed resistance training first (Pinto et al., 2014). However, conducting resistance exercise prior to endurance also attenuated running performance the following day to a greater extent than the reverse order, despite a 6-hour recovery window (Doma and Deakin, 2013). Furthermore, other indices of aerobic fitness and performance such as submaximal (Schumann et al., 2015) and maximal oxygen uptake, as well as running time-trial performance (Chtara et al., 2005) and cycling time to exhaustion (Kuusmaa et al., 2016) have been shown to improve to a greater extent when endurance training was performed prior to resistance training.

Collectively, these findings indicate some degree of exercise order-dependent adaptations, thus prioritising the exercise order according to the primary goals of training may help to maximise the quality of the exercise session and the stimulus for adaptation. Indeed, two recent meta-analyses concluded that for same-session concurrent training (<15 minutes of between-mode recovery), performing resistance exercise before endurance exercise has a greater effect on maximal dynamic strength compared to the reverse order (Eddens et al., 2018, Murlasits et al., 2018). However, no order effect was evident for changes in aerobic capacity (Eddens et al., 2018, Murlasits et al., 2018), nor static strength, hypertrophy, or body fat percentage (Eddens et al., 2018). Furthermore, others have reported no differences in acute strength performance between alternate orders, as well as compared to single-mode exercise (Jones et al., 2016). This study employed steady-state cycling, which may have resulted in less residual fatigue and muscle damage compared to studies involving running protocols (Jones et al., 2017), due to a reduced eccentric component and greater biomechanical similarities between cycling and the resistance exercises (Gergley, 2009, Wilson et al., 2012). Nevertheless, others have also shown similar fluctuations in post-exercise neuromuscular fatigue (Eklund et al., 2016, Taipale and Hakkinen, 2013), as well as comparable rates of oxygen consumption both during (Ferrari et al., 2018, Vilacxa Alves et al., 2012) and after concurrent sessions (Oliveira and Oliveira, 2011, Lamego et al., 2018) irrespective of the exercise order; these results would suggest similar demands of concurrent training regardless of the order in which sessions are performed.

Consequently, with limited evidence supporting acute order-dependent effects on exercise performance, more research is needed to determine if and how these findings may translate to order-dependent training effects, given that most training studies to date report comparable gains in dynamic and isometric strength (Collins and Snow, 1993, Davitt et al., 2014, Eklund et al., 2015, Eklund et al., 2016, Gravelle and Blessing, 2000, MacNeil et al., 2014, Makhlouf et al., 2016, McGawley and Andersson, 2013, Schumann et al., 2014b, Schumann et al., 2014a, Wilhelm et al., 2014), power (Wilhelm et al., 2014), hypertrophy (Davitt et al., 2014, Eklund et al., 2015, Eklund et al., 2016, Schumann et al., 2014a, Wilhelm et al., 2014), aerobic power and capacity (Davitt et al., 2014, Eklund et al., 2015, Eklund et al., 2016, MacNeil et al., 2014, Schumann et al., 2014a), endurance performance (Makhlouf et al., 2016, McGawley and Andersson, 2013, Schumann et al., 2014a), speed and agility (Makhlouf et al., 2016, McGawley and Andersson, 2013), irrespective of intra-session exercise order. This has been shown in a range of populations, including previously-untrained/recreationally-active men and women (Collins and Snow, 1993, Davitt et al., 2014, Eklund et al., 2015, Eklund et al., 2016, Gravelle and Blessing, 2000, Schumann et al., 2014b, Schumann et al., 2014a), elite soccer players (Makhlouf et al., 2016, McGawley and Andersson, 2013), and elderly men (Wilhelm et al., 2014).

Finally, in addition to exercise order, consideration must be given to both individual and collective roles of other training variables, as the interference effect is unlikely attributable to the manipulation of one training variable alone; a change to one may alter the effect of another. The effects of other training variables (such as exercise intensity, mode, frequency, volume, and recovery duration) have been extensively reviewed elsewhere (Bishop et al., 2019a, Fyfe et al., 2014, Fyfe and Loenneke, 2018);

2.4.5 The influence of 'non-training' variables

In addition to training variables, other factors inherent to training programs and research study designs also moderate the training effects and observed outcomes. Such '*non-training*' variables include the participant training status and nutrient availability, discussed below, as well as other factors such as the sample size, individual responses, and choice of statistical analyses (which have been discussed elsewhere (Bishop et al., 2019a).

Participant training status

The repeated, transient activation of the molecular responses that govern mode-specific training adaptations have previously been shown to be affected by training history. When endurance- and strength-trained athletes performed their habitual exercise mode, the respective phosphorylation of AMPK and Akt was diminished (Coffey et al., 2006b). However, when performing the nonhabitual exercise mode, AMPK phosphorylation increased in both groups, whilst Akt did not increase for either group after resistance exercise (Coffey et al., 2006b). Furthermore, when endurance-trained individuals performed resistance exercise, there were greater changes in the expression of metabolic and myogenic genes, highlighting greater demands for energy provision, repair and remodelling following an unfamiliar exercise stress (Coffey et al., 2006a).

Wilkinson *et al.* (2008) demonstrated that in untrained individuals, single-leg resistance exercise stimulated similar rates of both myofibrillar and mitochondrial protein synthesis. Following 10-weeks of training (during which each limb performed either endurance or resistance training), resistance exercise stimulated only myofibrillar protein synthesis. Conversely, both before and after training, unilateral endurance exercise only increased mitochondrial protein synthesis. Furthermore, when untrained, both endurance and resistance exercise similarly stimulated signalling through mTORC1. After training, this response was stimulated only by resistance exercise (Wilkinson et al., 2008). Others have also demonstrated both endurance and resistance exercise can stimulate mTORC1 signalling in recreationally-trained individuals (Camera et al., 2010), whilst in resistance-trained individuals, resistance exercise preferentially activates mTORC1 signalling, and AMPK responds similarly to both endurance and resistance exercise following training (Vissing et al., 2013). Collectively, these findings suggest that the acute

responses to different exercise stimuli are dictated by the participants' training history. In the untrained state, exercise promotes a generic response, unspecific to the exercise mode, while highly-trained individuals exhibit more selective molecular responses to different stimuli (Coffey and Hawley, 2016).

To date, much of the research in human concurrent training models has studied acute molecular responses in either untrained (Donges et al., 2012, Pugh et al., 2015), recreationally-active (Fyfe et al., 2016b, Lundberg et al., 2012, Wang et al., 2011), moderately-trained (Apró et al., 2015, Apró et al., 2013), or trained individuals (Coffey et al., 2009a, Coffey et al., 2009b, Jones et al., 2016). Fyfe *et al.* (2016b) previously reported uncompromised mTOR signalling in response to both concurrent and resistance-only exercise, in recreationally-active individuals. More recently, the same group demonstrated that resistance exercise induces greater signalling associated with mTORC1 and ribosome biogenesis than concurrent exercise in training-accustomed individuals (Fyfe et al., 2018). Whilst these results suggest that the presence of a '*molecular interference effect*' may manifest after a period of training, these two studies were conducted in separate cohorts of participants. Collectively, studies on participants of different training backgrounds have proved crucial in developing our understanding of the molecular blueprint of concurrent training adaptations. However, how such responses change after training within the same cohort of participants whose training has been controlled and monitored, remains poorly defined. Indeed, few studies have examined molecular adaptations following a period of concurrent training. De Souza *et al.* (2013) demonstrated that following 8 weeks of training, despite divergent changes in the content of various proteins following strength, endurance and concurrent training, the development of strength and muscle mass were not diminished in the latter. However, only resting biopsies were obtained before and after training, limiting insights into how the exercise-induced signalling responses may have changed with training. Other training studies assessing molecular adaptations to concurrent training have typically studied changes in basal gene and protein expression before and after training (Fyfe et al., 2018, Kazior et al., 2016, Lundberg et al., 2013), or assessed acute molecular responses *only* prior to (Lundberg et al., 2014) or after (Fyfe et al., 2018) a period of structured training.

To the author's knowledge, only one study to date has assessed changes in acute molecular responses to concurrent training, both before and after training (Fernandez-Gonzalo et al., 2013). For 5 weeks, moderately-active males performed unilateral concurrent training, whereby one limb performed cycle ergometry, whilst both legs performed unilateral knee extensions 6 hours later. Both before and after the training intervention, the participants completed an acute exercise bout during which muscle biopsies were sampled before and 3 hours after the resistance mode, to

characterise both acute and training-induced changes in molecular markers for mitochondrial biogenesis, angiogenesis, muscle protein synthesis and breakdown (Figure 2.12).

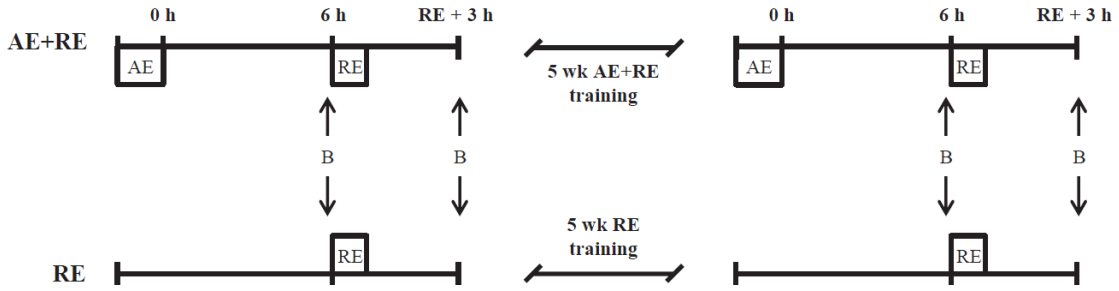


Figure 2.12 - Schematic overview of the study by Fernandez-Gonzalo et al. (2013). AE = aerobic exercise, RE = resistance exercise, B = muscle biopsy.

Both before and after training, PGC-1α expression was elevated after aerobic exercise (i.e., prior to the resistance exercise bout); however, the magnitude was lower in the trained state. In the untrained state, the resistance-only leg also increased PGC-1α expression; this response was attenuated with training. Similar patterns of expression were observed for vascular endothelial growth factor (VEGF). In the untrained state, the expression of atrogenes MuRF1 and MAFbx following concurrent exercise was greater than in the resistance-only leg; these responses were also diminished after training. Both conditions elicited similar p70S6K phosphorylation, and the response was augmented with training. Furthermore, regardless of training status, myostatin expression was lower with concurrent training. Collectively, this study supports prior evidence that exercise in the untrained state, regardless of mode, promotes generic molecular responses, which become more refined and mode-specific following a period of training. Furthermore, during the initial stages of a concurrent training program, the addition of aerobic exercise to resistance training provides a greater stimulus for molecular mediators of muscle protein synthesis and remodelling (Fernandez-Gonzalo et al., 2013). Whilst the authors should be commended for undertaking a demanding training study, which also involved multiple muscle biopsies, when considering that the interference effect may not manifest until after several weeks of concurrent training (Hickson, 1980) it is possible that a longer training period may provide further insight into the time course of molecular changes to concurrent training.

Nutrient availability

In addition to the training program design, nutrient availability can significantly modulate training adaptations (Hawley et al., 2011). Commencing exercise with low carbohydrate availability can enhance metabolic and mitochondrial-specific signalling responses (Bartlett et al., 2013, Camera et al., 2015a) and endurance adaptations (Chan et al., 2004, Hansen et al., 2005, Yeo et al., 2010, Yeo et al., 2008), whilst protein ingestion (either as whole protein or amino acids) can augment

MPS both in combination with, and independent of, exercise (Apró and Blomstrand, 2010, Karlsson et al., 2004, Tipton et al., 2007, Wilkinson et al., 2007). Nutrient provision also influences the expression of mRNA and proteins involved in catabolic pathways (Borgenvik et al., 2012). Furthermore, whilst a negative energy balance (through carbohydrate restriction) may potentiate the signalling responses to endurance exercise, energy restriction can also significantly affect the synthesis and remodelling of skeletal muscle proteins, by reducing post-absorptive rates of myofibrillar protein synthesis (Areta et al., 2014), and the basal content of autophagy-related gene (Atg) proteins (Smiles et al., 2015).

Given the effects of nutrient availability on molecular signalling responses and adaptations to both endurance and resistance exercise, controlling dietary intake can be problematic for concurrent training researchers, who are investigating both ends of the adaptation 'continuum'. In the existing literature, many sessions have been conducted in the fasted-state (Apró et al., 2015, Apró et al., 2013, Camera et al., 2015b, Coffey et al., 2009a, Coffey et al., 2009b, Vissing et al., 2013, Wang et al., 2011), which is often unrepresentative of athlete practices, whereby carbohydrates and protein are typically consumed before, during, and after training to facilitate performance, recovery and adaptation (Holway and Spriet, 2011). Nutritional recommendations for supporting concurrent training adaptations are based on studies of nutritional interventions during single-mode endurance or resistance training, respectively (Perez-Schindler et al., 2015). However, more recent work has investigated the effects of protein supplementation on the acute molecular and protein synthetic responses to concurrent training (Camera et al., 2016a, Camera et al., 2015b, Churchward-Venne et al., 2019). Compared to a placebo, post-exercise protein provision (25 g of whey protein) induced greater increases in Akt-mTOR-p70S6K phosphorylation and myofibrillar protein synthesis, as well as reductions in MuRF1 and MAFbx gene expression; there were, however, no effects on mitochondrial protein synthesis (Camera et al., 2015b). This was also accompanied by an increased abundance of select microRNAs involved in regulating translation initiation and mTORC1 signalling (Camera et al., 2016a). Further research also demonstrated that improvements in strength, lean mass, jump performance, and aerobic fitness were not compromised following 12 weeks of concurrent training supported by a high-protein diet (2 $g \cdot kg \cdot day^{-1}$); however, the lack of a placebo group provides limited insight into the discernible impact of a high protein diet *per se*, in addition to the effects of other training variables (Shamim et al., 2018). Recent evidence has also demonstrated that protein and carbohydrate co-ingestion induced greater increases in myofibrillar (but not mitochondrial) protein synthesis than carbohydrate-only, with no differential effects between types of protein (milk vs whey vs casein) (Churchward-Venne et al., 2019). Collectively, these findings support the co-ingestion of protein and carbohydrate, both as mixed meals and post-exercise supplements, in facilitating protein turnover and remodelling during recovery from concurrent training.

2.5 Summary

It is clear from the literature reviewed that skeletal muscle has the capacity to adapt to a range of stimuli. The resulting adaptations are highly specific to the stimulus imposed, and mediated by the repeated, transient activation of distinct molecular events. It is also evident that under certain conditions, the concurrent performance of endurance and resistance training may interfere with the adaptive potential of hallmark resistance training adaptations such as strength, muscle hypertrophy, and power. The precise causes of the interference effect remain a contentious area of research, but are likely the product of both '*acute*' and '*chronic*' factors, such as residual fatigue, potential incompatibility between the molecular pathways induced by endurance and resistance exercise respectively, and the distinct structural and functional adaptations to both modes. However, many studies do not support the notion of an interference effect, adding further complexity to the field. The presence and magnitude of an interference effect is likely mediated by the organisation of the training program, with respect to the manipulation of both training variables (e.g., exercise order, mode, intensity, frequency, volume, recovery duration) and non-training variables (e.g., nutrient availability and participant training status). From this review, the following points have been identified as key gaps in the literature that require further research:

- Despite evidence from cell culture and animal studies of mechanisms by which typical 'endurance' and 'resistance' signalling pathways may interact (*and interfere*) with each other, the molecular regulation of concurrent training adaptations in human skeletal muscle remains poorly understood.

- To date, most molecular studies in humans have employed designs in which: one concurrent group was compared to a resistance-only group (*limiting insight into the effect of exercise order*); two concurrent groups were compared without a resistance-only group (*limiting insight into the molecular interference effect*); exercise sessions were performed in a fasted-state (*unrepresentative of typical nutritional practices*); post-exercise molecular signalling responses were measured over short time frames, either before or after a period of training.

- No research to date has investigated the molecular responses to concurrent training when sessions are separated by a 3-hour recovery period, at which time several key molecular mediators of endurance and resistance adaptations have previously been shown to be upregulated.

- Finally, the role and importance of concurrent exercise order in exercise-induced molecular signalling events, and the subsequent development of training adaptations, remains unclear.

Chapter 3 General Methodology

Preface

This research project was designed to study how exercise-induced molecular responses to concurrent and resistance exercise change before and after a period of a structured training, with the aim of elucidating whether these acute molecular responses contribute to the concurrent training interference effect (*Chapter 4*). Furthermore, this project simultaneously investigated the effects of concurrent training on the development of whole-body adaptations compared with resistance-only training (*Chapter 5*), within the same cohort of participants. To achieve this, the objectives of each study were combined into one major training study, with the acute, 'experimental' trials conducted before and after training.

Therefore, this chapter provides extensive detail of all procedures conducted during this research project, relevant to both studies. Within each subsequent chapter, any details pertaining to the respective study that may differ from the overall general methodology are specified where necessary.

3.1 Research Design Overview

Following familiarisation trials and baseline fitness testing, twenty-nine healthy, active men were ranked according to baseline strength, aerobic fitness, and lean body mass, and allocated to one of three training groups in a counterbalanced order: 1) *RO*, resistance exercise only; 2) *ER*, endurance prior to resistance exercise; or 3) *RE*, resistance followed by endurance exercise. In Week 1, the participants performed an 'experimental' training session, during which muscle was sampled at various timepoints to characterise the temporal changes in gene and protein expression following resistance-only and concurrent exercise sessions. Following this, the participants continued 8 weeks of structured training in their respective groups (*Weeks 2 to 9*), before repeating the experimental session (*Week 10*). A battery of anthropometric, physiological, and performance tests were performed before (*PRE*), during (*MID*), and after training (*POST*) to monitor changes in whole-body training adaptations in response to the different training programs (Figure 3.1).

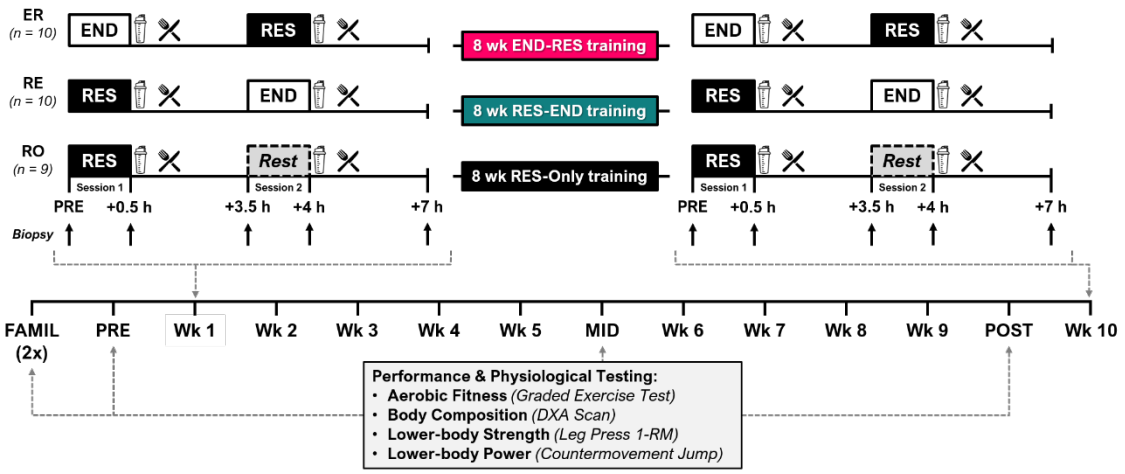


Figure 3.1 - Schematic representation of the experimental protocol. END = endurance session; RES = resistance session; ER = endurance-resistance; RE = resistance-endurance; RO = resistance-only; ↑ = muscle biopsy; = standardised meal (carbohydrate = 1.3 g·kg^{-1}; protein = 0.3 g·kg^{-1}; fat = 0.3 g·kg^{-1}); = whey protein (0.25 g·kg^{-1}); DXA = dual-energy x-ray absorptiometry; 1-RM = one repetition maximum; FAMIL = familiarisation trials.

3.2 Ethical Approval

This study was approved by the Victoria University Human Research Ethics Committee (*HRE15-292*). Participants were provided with comprehensive information about the study (see Appendix A) in both written and verbal formats, and screened for any pre-existing medical conditions that may have compromised their ability to participate in the project; after which, they provided written informed consent. All testing procedures and training sessions took place in the exercise physiology and muscle function laboratories at Victoria University, under the supervision of the student investigator.

3.3 Participant Characteristics

Participants were non-smokers, free from any pre-existing medical conditions, cardiovascular abnormalities, respiratory conditions, or musculoskeletal injuries, and were habitually engaging in endurance and/or resistance exercise for ≥30 minutes, 2 to 3 times per week, but were not currently following a structured training regimen. Figure 3.2 depicts the recruitment process leading to the final sample sizes for each training group. Out of 155 initial expressions of interest, forty-five healthy, active men volunteered to participate in the study. During the preliminary testing phase, fifteen participants withdrew for various reasons (e.g. changes in availability, time commitment, personal reasons). Thirty participants completed the baseline testing and were allocated to one of the three training groups. During the training phase, one participant withdrew due to an injury sustained outside of the study. Therefore, twenty-nine participants completed the training study (mean ± SD; *age* 24.5 ± 4.7 y; *height* 179.7 ± 6.5 cm; *weight* 74.9 ± 10.8 kg). Four of these participants were unable to complete the muscle biopsy procedures, and therefore only training and performance data are available for those participants. Table 3.1 contains the baseline characteristics and sample sizes of each group[2]. Effect size analysis revealed some small differences between groups at baseline (i.e. standardised effect size 0.2-0.6); these were accounted for prior to analysis.

3.4 Familiarisation and Baseline Testing

Prior to the baseline testing (*BASE*), participants completed two familiarisation trials of each test (*FAM1* and *FAM2*); these tests included a countermovement jump (*CMJ*), a leg press 1-repetition maximum (*1-RM*) and a graded exercise test (*GXT*). The CMJ and 1-RM leg press tests were performed during the same visit, with 5 mins of passive recovery between tests. The GXT was conducted on a separate day. Each testing session was separated by ≥24 hours of recovery. To minimise diurnal effects on exercise performance, test times were standardised for each participant and replicated on subsequent visits. At least 24 hours prior to all procedures, participants were requested to abstain from exercise, and the consumption of alcohol and caffeine. During the *MID* and *POST* testing weeks, an additional training session was performed at the end of the week (24 to 48 h after the last testing session). Thus, coupled with the two testing days during those weeks (which also served as an exercise stimulus), participants were still exercising three times per week, with the aim of minimising the possibility of training adaptations dissipating during these weeks. At least 48 hours rest was scheduled between the final training session of Week 9, and the *POST* testing sessions, to facilitate recovery from the penultimate training week in which the endurance and resistance intensities were the greatest.

[2] *Participant baseline data for Chapters 4 and 5 are available in Appendices B and C, respectively.*

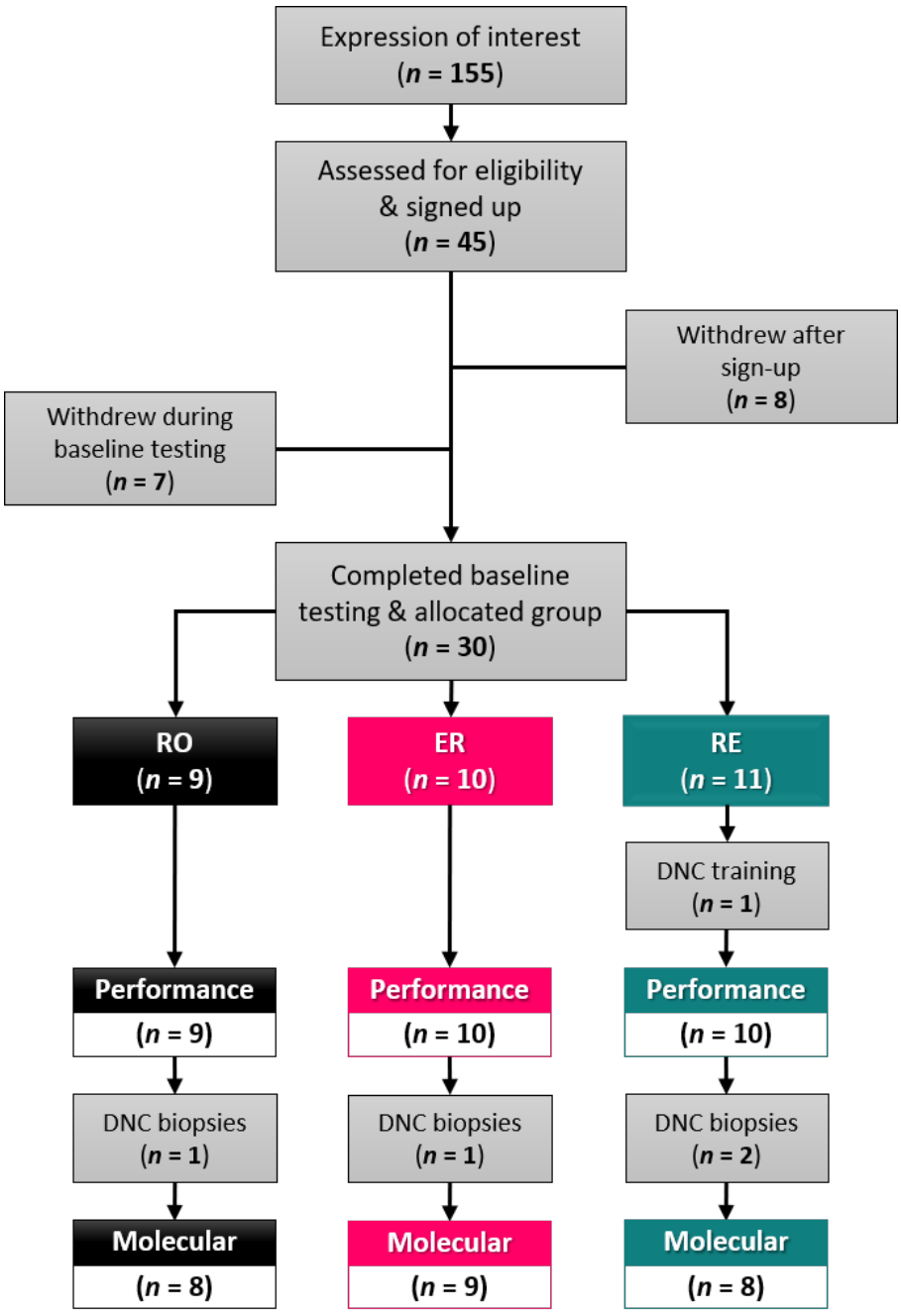


Figure 3.2 - Schematic representation of the recruitment process leading to the final sample sizes for each group, for both the performance measures and molecular analyses. RO = resistance-only group; ER = endurance-resistance group; RE = resistance-endurance group; DNC = did not complete.

Table 3.1 - Baseline characteristics of each training group for all participants (n = 29). Data are mean ± SD.

	Resistance-Only *(n = 9)*	**Endurance-Resistance** *(n = 10)*	**Resistance-Endurance** *(n = 10)*
Lower-Body Maximal Strength			
Leg press 1-RM (kg)	344 ± 100	329 ± 94	327 ± 90
Countermovement Jump Variables			
Peak Displacement (cm)	35.6 ± 7.0	35.2 ± 4.2	35.8 ± 5.9
Peak Velocity ($m \cdot s^{-1}$)	2.72 ± 0.24	2.71 ± 0.15	2.75 ± 0.20 □
Peak Force (N)	959 ± 227 □^	1037 ± 256	1014 ± 174
Peak Power (W)	3814 ± 689	3783 ± 720	3786 ± 712
Physical Characteristics and Body Composition			
Total Lean Body Mass [*LBM*] (kg)	57.7 ± 6.9	55.6 ± 8.3 ○^	57.7 ± 8.0
Upper body LBM (kg)	34.5 ± 3.9	33.1 ± 5.2 ○^	34.7 ± 4.8
Lower body LBM (kg)	19.6 ± 3.0	19.7 ± 3.2	19.8 ± 3.4
Fat Mass (kg)	14.8 ± 5.8	15.5 ± 6.8	13.5 ± 5.8 ○□
Aerobic Fitness			
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	3.33 ± 0.76	3.36 ± 0.62	3.24 ± 0.54
$\dot{V}O_{2peak}$ ($mL \cdot kg \cdot min^{-1}$)	44.2 ± 8.1	45.2 ± 7.2	43.7 ± 5.9 □
Lactate Threshold [$\dot{W}_{LT}$] (W)	157 ± 45	162 ± 38	153 ± 31 □
Peak Aerobic Power [$\dot{W}_{peak}$] (W)	215 ± 54	217 ± 46	205 ± 41 ○□

○small difference vs RO; □small difference vs ER; ^small difference vs RE. (i.e., standardised ES = 0.20-0.60); RM = repetition maximum.

3.4.1 Lower-body maximal strength and power

Assessments of lower-body maximal strength and power were conducted during the same visit. Upon arrival, participants completed a standardised warm up consisting of 10 sub-maximal repetitions of leg press, glute bridges, and unloaded body-weight squats, respectively. The participants then commenced the CMJ test, followed by the leg press 1-RM test. A 5-minute passive recovery period was allocated between each test to facility recovery of the phosphagen system, the dominant energy system for short-duration (< 10 s) high-intensity contractions (Harris et al., 1976).

Countermovement jump (CMJ)

Indices of lower-body power were assessed by a countermovement jump test, performed on a commercially-available force plate (400S, Fitness Technology, Adelaide, Australia). After completing a warm-up (three, submaximal jumps at 50%, 75%, and 90% of maximal effort respectively), participants performed three maximal countermovement jump efforts, each separated by 1-minute recovery periods (Fyfe et al., 2016a). Starting from a standing position, participants were instructed to perform the countermovement phase to a self-selected depth, from

which they subsequently accelerated as quickly as possible to achieve maximal jump height (Figure 3.3). Arm swing was minimised by participants firmly holding a light wooden pole (0.5 kg) across their shoulders. Force-time data was sampled at 600 Hz and analysed in Microsoft Excel to derive peak force, velocity, displacement and power (Chavda et al., 2018). Average CMJ height has been suggested to be more sensitive than the best jump height for determining the effects of training (Claudino et al., 2017). Therefore, an average of the three attempts per visit was used for analysis. The data were analysed using Excel spreadsheets specifically formulated for the analysis of countermovement jumps (Chavda et al., 2018).

a *– Starting position (stationary, body weight)*

b *– Countermovement (end of breaking, self-selected depth, start of propulsive phase)*

c *– Flight (peak jump height)*

Figure 3.3 - The key stages of the countermovement jump measurement

Leg press 1-repetition maximum (1-RM)

Lower-body dynamic strength was assessed by a 1-RM leg press test, performed on a plate-loaded 45° incline leg press (Hammer Strength Linear, Schiller Park, IL, USA). Participants performed 3 warm-up sets consisting of 5, 3, and 1 repetition at 50%, 70%, and 90% of the estimated 1-RM, respectively. Each set was separated by 2 minutes of passive recovery. Participants then attempted up to 5 single repetitions of increasing weight, until the maximal load for one successful repetition was achieved. Each attempt was separated by 2 minutes of passive recovery. For a successful repetition, participants were required to lower the sled from full knee extension through a range of motion eliciting 90° knee flexion, which was monitored by one investigator and confirmed using video footage (Figure 3.4). Failure was determined when the load could not be lifted through the required range of motion.

During *FAM1*, participants were asked of their previous leg press experience, and if so, the loads and repetitions they typically lifted. This information was used in conjunction with a 1-RM prediction table (Baechle and Earle, 2008) (see appendices) and a 10-point resistance exercise-specific RPE scale (Repetitions-in-Reserve, [*RIR*], (Zourdos et al., 2016), see appendices), to aid load prescription. For those without prior experience, 1-RM was estimated according to visual assessment of sled velocity during the movement, and participant feedback using the RIR scale. Therefore, during *FAM1* some participants required 2 to 3 additional attempts to reach 1-RM, due to initial trial and error. Predicted 1-RM and load progression for subsequent visits were based off data obtained in *FAM1*.

a *– Starting position* ***b*** *– Desired range of motion* ***c*** *– Finish position*

Figure 3.4 - The key stages of the leg press 1-RM test

3.4.2 Aerobic fitness

Peak oxygen uptake ($\dot{V}O_{2peak}$), power at the lactate threshold ($\dot{W}_{LT}$), and peak aerobic power ($\dot{W}_{peak}$) were determined from a graded exercise test (GXT), followed by a supramaximal, constant-workload verification bout. Both tests were performed to volitional exhaustion, on an electromagnetically-braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands), and separated by 5 minutes of active recovery.

Graded exercise test (GXT)

The test involved multiple 4-minute stages of constant workloads, during which participants were instructed to maintain a target cadence of 70 ± 10 RPM. During the initial visit (*FAM1*) demographic, anthropometric, and self-reported physical activity data (i.e., age, height, mass, sex, and physical activity rating) were used to estimate relative $\dot{V}O_{2peak}$ (Jackson et al., 1990), which was then used to estimate $\dot{W}_{peak}$ (Jamnick et al., 2016, Pescatello and Medicine, 2013). To ensure participants could complete 8 to 10 4-minute stages, the derived $\dot{W}_{peak}$ was then used to design a customised protocol, with a desired duration of 36 minutes (i.e., 9 × 4-minute stages). The initial workload and subsequent stage increments were calculated using the following calculations:

$$\text{Initial workload (W)} = \text{Predicted } \dot{W}_{peak} \times 25\% \quad \textbf{(1)}$$

$$\text{Stage increment (W)} = \frac{\text{Predicted } \dot{W}_{peak} - \text{Initial workload}}{8} \quad \textbf{(2)}$$

Participants were provided with consistent verbal encouragement by the investigators throughout the test, which was terminated either volitionally by the participant, or by the investigators if the participants could not maintain a cadence >60 RPM. If participants successfully completed 8 to 10 stages in *FAM1*, the protocol remained the same for all subsequent visits. If they completed <8 or >10 stages, their protocol was adjusted prior to *FAM2* to elicit volitional exhaustion and $\dot{W}_{peak}$ within the desired range of 8 to 10 stages. Thereafter, the protocol remained consistent for all subsequent visits. $\dot{W}_{peak}$ was determined from the following calculation, as previously used elsewhere (Granata et al., 2016b):

$$\dot{W}_{peak} \text{ (W)} = \text{Final stage completed (W)} + [\%\text{ into next stage} \times \text{Stage increments (W)}] \quad \textbf{(3)}$$

Prior to commencing the test, a 20-gauge intravenous catheter was inserted into an antecubital vein of the forearm by a trained phlebotomist. Approximately 1 mL of blood was sampled at rest and during the last 15 seconds of each 4-minute stage, and analysed immediately, in duplicate, for lactate concentration (2300 STAT Plus; YSI Inc., Yellow Springs, OH, USA). The lactate threshold ($\dot{W}_{LT}$) was determined by the modified Dmax method ($Dmax_{MOD}$) and calculated using Lactate-E Software (Newell et al., 2007). Heart rate (Polar FT1, Kempele, Finland) and rating of perceived exertion (RPE) (Borg, 1970) were recorded in the last 10 seconds of each stage. An automated metabolic system (Moxus Modular $\dot{V}O_2$ System, AEI Technologies, Pittsburgh, PA, USA) sampled expired VO_2 and VCO_2 every 15 seconds throughout. Before each test, the gas analysers (O_2: N-22M; CO_2: P-61B; AEI Technologies Pittsburgh, PA, USA) were calibrated against known gas concentrations (*Gas 1*: 21.0% O_2, 0.0% CO_2, *Gas 2*: 16.0% O_2, 4.0% CO_2; BOC Gases, Chatswood, NSW, Australia). The turbine flowmeter was calibrated using a 3-litre syringe (Hans Rudolph, Shawnee, KS, USA).

Peak oxygen uptake ($\dot{V}O_{2peak}$) test

After 5 minutes of active recovery (light cycling at 20 W, self-selected cadence), participants completed a supramaximal, steady-state cycle to volitional exhaustion, set at 105% of the $\dot{W}_{peak}$ achieved during the GXT. A similar protocol has previously been reported to elicit similar $\dot{V}O_{2peak}$ values to those determined during a ramp incremental test performed 5 min previously (Rossiter et al., 2006). Following a 5-second countdown, participants were instructed to accelerate to 90 to 100 RPM and to maintain a high, but not fixed cadence. The test was terminated volitionally by the participant, or by the investigators if the participants could not maintain a cadence >60 RPM.

Expired gases were sampled throughout (as previously described) and $\dot{V}O_{2peak}$ was defined as an average of the two-highest consecutive 15-second values elicited during the test.

3.4.3 Body composition

Body composition was determined via whole-body Dual-energy X-ray Absorptiometry (DXA) (GE Lunar iDXA, GE Lunar Corp, Madison WI, USA). The DXA scanner was calibrated prior to all scans, using a phantom with known values for fat mass, bone mineral content and fat-free soft tissue mass, as per manufacturer's guidelines. Each participants' scans were conducted and analysed by the same certified technician. To further reduce measurement errors within and between scans, and to minimise the effects of nutrition and activity levels, participants arrived following an overnight fast, and were requested to refrain from exercise 24 hours prior to all scans (Nana et al., 2012, Nana et al., 2013). Two scans were conducted at baseline (*BASE1* and *BASE2*), on separate days, to assess between-day reliability.

3.4.4 Reliability

The technical error of measurement (TEM), the coefficient of variation (CV), and the intra-class correlation coefficient were calculated for all primary variables, using data from *FAM2* and the *BASE* trials (Table 3.2). The reliability data were determined using Excel spreadsheets specifically formulated for the analysis of reliability (Hopkins, 2017). It should be noted that the data in Table 3.2 represent the reliability of these measures when the repeated tests were separated by 48 hours to 1 week. Given that these tests were used to assess changes in performance measures before and after 9 weeks of training, it would have been more appropriate to assess the reliability of the tests when separated by a 10-week control period; however, due to the time constraints of this project, this was not possible.

3.5 Muscle Biopsy Sampling

Muscle biopsies were sampled in Weeks 1 and 10 to characterise acute temporal changes in protein and gene expression to resistance-only and concurrent exercise sessions, both before and after a period of structured training. The biopsy procedure was performed under sterile conditions by a qualified, experienced medical doctor. Local anaesthetic (Xylocaine, 1%) was injected at the site of the biopsy (*vastus lateralis*) and once numb, a small incision (~ 0.5 to 1.0 cm) was made through the skin and muscle fascia. Muscle was sampled using the suction-modified Bergström technique (Shanely et al., 2014, Tarnopolsky et al., 2011). New incisions were made for each biopsy, which were distributed across both legs. The chosen limb for the first biopsy was randomised, counterbalanced, and crossed-over in Week 10, with the aim of sampling all resting biopsies, and biopsies around each exercise session from the same legs, respectively (Table 3.3).

Muscle samples (~ 180 ± 50 mg) were immediately frozen in liquid nitrogen and stored at -80°C until analysis. Participants were requested to refrain from strenuous exercise, and consumption of alcohol and caffeine at least 48 hours prior to all resting muscle biopsies. Participants were also provided with a standardised meal to consume the evening before, and on the morning of all resting biopsies (for details, see section *3.8. Exercise and Dietary Control*).

Table 3.2 - Technical error of measurement (TEM), the coefficient of variation (CV) and the intra-class correlation coefficient (ICC) for each primary variable, with lower and upper 90% confidence limits.

	TEM	CV (%)	ICC
Lower-Body Maximal Strength			
Leg press 1-RM (kg)	10.0 (*8.3 – 12.9*)	3.5 (*2.8 – 4.5*)	0.99 (*0.98 – 0.99*)
Countermovement Jump Variables			
Peak Displacement (m)	0.01 (*0.01 – 0.02*)	3.7 (*3.0 – 4.7*)	0.96 (*0.92 – 0.98*)
Peak Velocity (m/s)	0.05 (*0.04 – 0.06*)	1.7 (*1.4 – 2.2*)	0.95 (*0.90 – 0.97*)
Peak Force (N)	63 (*52 – 82*)	6.6 (*5.3 – 8.5*)	0.92 (*0.86 – 0.96*)
Peak Power (W)	116 (*95 – 149*)	3.2 (*2.6 – 4.2*)	0.97 (*0.95 – 0.99*)
Body Composition			
Total LBM (kg)	0.67 (*0.55 – 0.87*)	1.4 (*1.2 – 1.8*)	0.993 (*0.986 – 0.996*)
Upper LBM (kg)	0.49 (*0.40 – 0.63*)	1.5 (*1.2 – 2.0*)	0.990 (*0.981 – 0.994*)
Lower LBM (kg)	0.20 (*0.16 – 0.26*)	1.1 (*0.9 – 1.4*)	0.996 (*0.993 – 0.998*)
Total Fat Mass (kg)	0.39 (*0.32 – 0.50*)	2.9 (*2.4 – 3.8*)	0.996 (*0.993 – 0.998*)
Aerobic Fitness			
Absolute $\dot{V}O_{2peak}$ (L/min)	0.11 (*0.09 – 0.14*)	3.1 (*2.6 – 4.1*)	0.97 (*0.95 – 0.99*)
Relative $\dot{V}O_{2peak}$ (mL/kg/min)	1.4 (*1.2 – 1.9*)	3.1 (*2.5 – 4.0*)	0.96 (*0.93 – 0.98*)
Lactate Threshold, W_{LT} (W)	6 (*5 – 8*)	3.9 (*3.2 – 5.1*)	0.97 (*0.95 – 0.99*)
Peak Aerobic Power, W_{peak} (W)	7 (*6 – 9*)	3.2 (*2.6 – 4.1*)	0.98 (*0.96 – 0.99*)

Table 3.3 - An example of the muscle biopsy sample distribution across each leg. The initial leg in Week 1 was randomised and counterbalanced and crossed-over in Week 10 (L = left leg; R = right leg).

Timepoint		Abbreviation	Week 1	Week 10
Day 1	Pre-exercise session 1 (resting)	***PRE***	**L**	**R**
	Post-exercise session 1	***+0.5 h***	**L**	**R**
	+ 3 h post-session 1/Pre-exercise session 2	***+3.5 h***	**R**	**L**
	Post-exercise session 2	***+4 h***	**R**	**L**
	+ 3 h post-exercise session 2	***+7 h***	**R**	**L**

3.6 Week 1 and 10: Experimental Training Week

On Day 1 of the first experimental training week, the participants arrived at the laboratory following an overnight fast, having consumed a standardised meal the previous evening (see *3.8. Exercise and Dietary Control*). They were provided with a standardised breakfast on arrival at the lab. Two hours later, a resting pre-exercise muscle biopsy was taken, after which the participants began their first exercise session of either endurance or resistance exercise. Further

biopsies were sampled immediately post- and 3 hours post-exercise; the latter time-point also serving as the '*pre-exercise*' sample for the second exercise session of the day for the concurrent groups.

Subjective wellbeing and fatigue responses: Prior to each training session, participants were asked to complete a questionnaire (*see appendices*) to monitor potential changes in wellbeing and fatigue status (McLean et al., 2010). This questionnaire assessed perceived levels of fatigue, sleep quality, general muscle soreness, stress, and mood, using a five-point scale (each rated 1 to 5, with 0.5 increments). Scores were combined to provide an overall wellbeing score, out of a possible 25. A higher score indicates better overall wellbeing, mood, sleep quality, less fatigue and general muscle soreness. Furthermore, after each session, participants were asked to report their overall rating of perceived exertion for the entire training session (i.e., session RPE [*sRPE*], *see appendices*), using the CR1-10 scale (Foster et al., 2001). The total load for the session was calculated by multiplying sRPE by session duration. This is a valid and reliable method for monitoring training load for both aerobic and resistance training (Haddad et al., 2017).

Endurance exercise (END): After a standardised warm-up (5-minutes cycling at 75 W, ~70 RPM) participants performed 10 × 2-minute cycling intervals, separated by 1-minute rest periods, on an electromagnetically-braked cycle ergometer (Velotron, Racer-Mate, Seattle, WA, USA). Participants were instructed to maintain a cadence between 90 and 100 RPM during each interval. Heart rate (Polar FT1, Kempele, Finland) and rating of perceived exertion (RPE) (Borg, 1970) were recorded in the last 10 seconds of each interval. Untrained and trained individuals have been shown to elicit markedly different metabolic and cardiovascular responses when working at the same $\%\dot{V}O_{2peak}$ compared to $\%\dot{W}_{LT}$ (Baldwin et al., 2000). Furthermore, during previous concurrent training studies in our lab (Fyfe et al., 2016a, Fyfe et al., 2016b), in which endurance exercise intensity was determined relative only to $\%\dot{W}_{LT}$, it was noted that individuals with a higher baseline $\dot{W}_{LT}$ trained closer to their $\dot{W}_{peak}$ throughout the regime, compared to those less well-trained (*Fyfe, JJ, personal communication, 27/08/15*). Thus, in the present study, both $\dot{W}_{LT}$ and $\dot{W}_{peak}$ were used to determine relative exercise intensity ($\dot{W}_{Ex}$) to ensure participants experienced the same relative physiological stimulus. In Weeks 1 and 10, $\dot{W}_{Ex}$ was set at 40% of the difference between $\dot{W}_{LT}$ and $\dot{W}_{peak}$ (~84% $\dot{W}_{peak}$), and calculated as:

$$\dot{W}_{Ex} = \dot{W}_{LT} + [\chi\,\% \times (\dot{W}_{peak} - \dot{W}_{LT})] \quad \chi = \textit{desired \% of difference between } \dot{W}_{LT} \textit{ and } \dot{W}_{peak} \qquad \textbf{(4)}$$

Resistance exercise (RES): Following a standardised warm-up (one set of 5 reps at 50% 1-RM, then 3 repetitions at 60% 1-RM), participants performed 6 × 10 leg press repetitions at 70% 1-RM,

separated by 2-minute rest periods, on a plate-loaded 45° incline leg press (Hammer Strength Linear, Schiller Park, IL).

Three hours after completing their first exercise session, the participants in the *ER* and *RE* groups commenced their second exercise session, whist those in the *RO* group continued to rest quietly in the laboratory. Muscle was sampled immediately pre-, post-, and 3 hours post-exercise. Those in the *RO* group, whilst not exercising, still provided muscle biopsies to enable comparisons with the concurrent groups of the post-exercise time course of molecular responses to resistance-only exercise at the corresponding timepoints. Further standardised meals were provided one hour after each training session, during the 3-hour recovery period (Figure 3.6). For the remainder of the experimental training week, participants completed two more training days as described above, without muscle samples, or standardised meals (Figure 3.5).

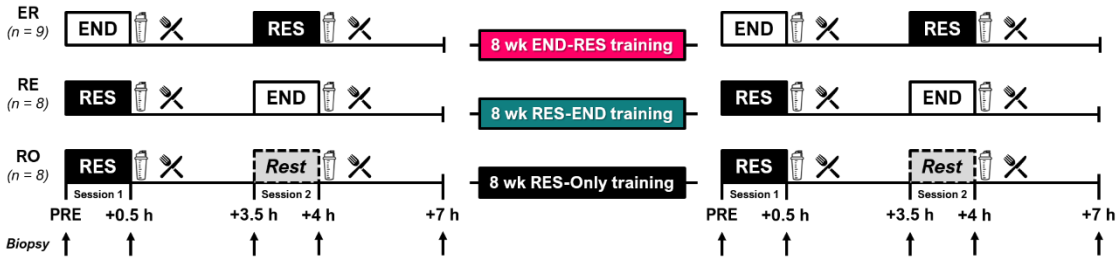


Figure 3.5 - Schematic overview of the experimental training day in Weeks 1 and 10. END = endurance session; RES = resistance session; RO = resistance-only, ER = endurance-resistance, RE = resistance-endurance; ↑ = muscle biopsy; ✕ = standardised meal (carbohydrate = 1.3 g·kg^{-1}; protein = 0.3 g·kg^{-1}; fat = 0.3 g·kg^{-1}); 🥛 = whey protein (0.25 g·kg^{-1}).

3.7 Week 2 to 9: 8-week Training Program

Following the first experimental week, the participants continued to train in their respective groups three days per week for 8 weeks, with the battery of testing repeated after weeks 5 (*MID*) and 9 (*POST*). The training days followed a similar format to the experimental week, although no muscle tissue was sampled, and standardised meals were not provided during this period. Wellbeing scores and sRPE were recorded at the beginning and end of each session respectively, to monitor participants' readiness to train, perceptions of effort, and internal training load throughout the program. The target recovery period between concurrent sessions was 3 hours (*mean* ± *SD*, *ER* = 3.1 ± 0.2 hours; *RE* = 3.1 ± 0.5 hours).

Resistance training (RES): The resistance training intensity and volume progressed from 3 sets (*Weeks 2 to 5*) to 4 sets (*Weeks 6 to 9*), consisting of 12- to 6-RM for each exercise, with a 2-min rest between sets (Table 3.4). Warm-up sets (5 × ~75% training load) were performed prior to the

first 2 exercises of each session (*Session 1:* leg press and bench press; *Session 2:* leg press and dumbbell chest press). As 1-RM was only determined for the leg press, the weight for all other exercises was set according to the maximum number of repetitions possible for a given load (i.e., the *n*-RM). During the initial session (RM goal = 12-RM), starting loads for each exercise were adjusted until no more than 12 reps were possible. Throughout the training program, the loads were subsequently adjusted in accordance with the changes in *n*-RM prescription. As such, the final set of each exercise was not performed to failure, as the aim was to standardise the repetition volume between groups. An RM prediction table (Baechle and Earle, 2008) , and participant feedback using the RIR scale (Zourdos et al., 2016), were also used as accessory tools to aid load prescription.

Endurance training (END): The endurance training programme involved multiple 2-minute cycling intervals separated by 1-minute recovery periods, at relative intensities ranging from 40 to 90 % of the difference between $\dot{W}_{LT}$ and $\dot{W}_{peak}$ (~84 to 97% $\dot{W}_{peak}$). Each session commenced with a standardized warm-up (5 min cycling at 75 W, ~70 RPM). Progressive overload was achieved by modifying the volume and intensity of the intervals per session (Table 3.5). After the *MID*- and *POST*-testing GXTs, the relative exercise intensities for the subsequent sessions were adjusted according to the updated $\dot{W}_{LT}$ and $\dot{W}_{peak}$ data.

These training programs (including the experimental training sessions in Weeks 1 and 10) were adapted from previous concurrent training research conducted in our lab (Fyfe et al., 2016a, Fyfe et al., 2016b). As the previous study (Fyfe et al., 2016a) elicited minimal lower-body hypertrophy (*mean* ± *SD*: 1.8 ± 1.6 %; *standardised effect size [ES]* ±*90% confidence interval:* 0.13 ±0.12; *P* = 0.069) in their HIIT+RT group (high-intensity interval cycling combined with resistance exercise, comparable to the present *ER* group), the programme was modified in the present study to provide a greater hypertrophic stimulus, by adopting a higher rep range (12 to 6-RM vs 8 to 4-RM (Fyfe et al., 2016a)) and increasing the number of sets from 3 to 4 throughout Weeks 6 to 9. The endurance training programme was also modified by an additional 3 intervals on top of those prescribed in the previous study.

Table 3.4 - 8-week resistance training programme, adapted from (Fyfe et al., 2016a). RM = rep. max target

	Week:	**2**	**3**	**4**	**5**		**6**	**7**	**8**	**9**	**Exercises:**
MON and FRI	*Sets:*	3	3	3	3	**MID Testing**	4	4	4	4	*Leg press, bench press, seated row, leg extension, leg curl*
	RM:	12	10	8	6		12	10	8	6	
WED	*Sets:*	3	3	3	3		4	4	4	4	*Leg press, dumbbell chest press, lat. pulldown, lunges, leg curl*
	RM:	12	12	10	10		8	8	6	6	

Table 3.5 - 8-week endurance training programme, adapted from (Fyfe et al., 2016a).

Week . Session	No. of 2-min Intervals	Training Intensity ($\dot{W}_{Ex}$)†
2.1	8	
2.2	9	χ = 50-60%
2.3	10	
3.1	9	
3.2	11	χ = 55-65%
3.3	10	
4.1	11	
4.2	12	χ = 60-70%
4.3	11	
5.1	10	
5.2	9	χ = 65-75%
5.3	8	
*MID**	8	χ = 60% ‡
6.1	9	
6.2	10	χ = 65-75%
6.3	11	
7.1	10	
7.2	11	χ = 70-80%
7.3	12	
8.1	11	
8.2	13	χ = 75-85%
8.3	12	
9.1	11	
9.2	9	χ = 80-90%
9.3	8	
*POST**	8	χ = 80% ‡

† Training intensity calculated as: $\dot{W}_{LT} + (\chi\ \% \times [\dot{W}_{peak} - \dot{W}_{LT}])$.

** Additional training session added at the end of MID- and POST-testing weeks, respectively.*

‡ Training intensity re-calculated using updated data from MID- and POST-testing weeks, respectively.

3.8 Exercise and Dietary Control

Throughout the study, participants were instructed to maintain their habitual dietary intake and physical activity levels throughout the study, which were regularly monitored via self-reported diaries. Any additional, non-prescribed exercise performed outside of the study was recorded using an online training diary, in which participants were asked to record the type and duration of the exercise completed, and to provide an sRPE score.

As described previously, both carbohydrate and protein availability can modulate exercise-induced cell signalling events and muscle protein synthesis rates. Therefore, any dietary controls

employed when conducting concurrent training research require careful consideration. One goal of this study was to investigate the interference effect under conditions that better represent real-world nutritional practices, whereby carbohydrates and protein are often consumed before, during, and after training to facilitate recovery and adaptation (Holway and Spriet, 2011). Therefore, during the experimental training weeks, a standardised dinner and breakfast were provided prior to all resting biopsies, to be consumed ~15 to 16 hours, and ~2 hours prior, respectively. The target macronutrient content for these meals (expressed in grams per kilogram of body mass), was: carbohydrate (CHO) = 1.3 g·kg BM^{-1}; protein = 0.3 g·kg BM^{-1}; fat = 0.3 g·kg BM^{-1}. The total macronutrient intake for the experimental training days was: CHO = 4.0 g·kg BM^{-1}; protein = 1.5 g·kg BM^{-1}; fat = 1.0 g·kg BM^{-1}. These daily macronutrient targets are comparable to recently published intakes typical of Dutch endurance, strength, and team sport athletes (Wardenaar et al., 2017) and Australian Football League players (Bilsborough et al., 2016). During Weeks 2 to 9, the participants were requested to maintain their habitual dietary intake, which was assessed using a 3-day food diary (including one weekend day), conducted prior to the study. Food diaries were analysed using Cronometer, an online application for tracking nutrition data (https://cronometer.com/). A whey protein isolate supplement (BodyScience, QLD, Australia) was provided immediately after every training session throughout the study, providing 0.25 g·kg·BM^{-1} of protein, which has been shown to be an appropriate dose for maximising post-exercise MPS (Morton et al., 2015).

3.9 Muscle Analyses

3.9.1 Western blotting

Whole-muscle homogenisation and protein concentration assay

Approximately 20 mg of frozen muscle tissue was added to ice-cold Auwerx lysis buffer (20 µL/mg of tissue; 50 mM Tris-HCL, 150 mM NaCl, 1 mM EDTA, 5 mM $Na_4P_2O_7$, 1 mM Na_3VO_4, 1% NP-40, 1:100 protease/phosphatase inhibitor cocktail [#5872, Cell Signalling Technology (CST), Danvers, MA], adjusted to pH 7.4). Clean stainless-steel beads were added to all samples, which were homogenised at 30 Hz for 2×2 minutes in an automated homogeniser (TissueLyser II, Qiagen). Muscle homogenates were rotated end-over-end for 60 minutes at 4°C after which protein concentration was determined in triplicate against bovine serum albumin standards (BSA, Sigma-Aldrich, St. Louis, MI, #A9647) using a commercial colorimetric Bradford assay (Protein Assay kit-II; Bio-Rad, Gladesville, NSW, Australia).

Immunoblotting

Muscle homogenate was diluted in 4× Laemmli buffer (0.25 M Tris, 4% SDS, 20% glycerol, 0.015% bromophenol blue and 10% 2-mercaptoethanol), and stored at -80°C until subsequent

analysis. For all targets, samples were boiled at 95°C for 5 minutes prior to loading. Equal quantities of total protein from each sample (15-30 µg, depending on the target) were loaded into different wells on pre-cast 4–20% Criterion™ TGX Stain-Free™ gels (Bio-Rad, Hercules, CA, #5678095). All sample timepoints from each participant were loaded on the same gel in adjacent wells. Four lanes per gel were reserved for different volumes (7.5 µg, 15 µg, 30 µg, and 37.5 µg) of a mixed-homogenate internal standard, containing equal quantities of all samples collected. The standards were used to derive a calibration curve of signal intensity versus total protein loaded, from which protein abundance of each sample could then be calculated, using the linear regression equation and the band intensity (Murphy and Lamb, 2013). Proteins were separated via sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Gels were run for 20 minutes at 80 V, then at 100-120 V for a further 60 to 90 minutes in a 1× running buffer (25 mM Tris, 192 mM Glycine, 0.1% SDS). Once resolved, proteins were transferred onto polyvinylidene fluoride (PVDF) membranes (Bio-Rad, Hercules, CA, #1620264) in a commercially-available transfer buffer (Bio-Rad, Hercules, CA), using a semi-dry transfer system (Trans-Blot® Turbo™ Transfer System, Bio-Rad, Hercules, CA) for 10 minutes at 25 V. Stain-free images of the membranes were then taken using ChemiDoc™ MP imaging system (Bio-Rad, Hercules, CA), to determine the total protein loaded per lane, which was normalised to the calibration curve for each blot.

Membranes were then blocked for 60 minutes at room temperature with 3% BSA (Sigma-Aldrich, St. Louis, MI, #A9647), diluted in Tris-buffered saline with 0.1% Tween-20 (TBST: 150 mM NaCl, 20 mM Tris, 0.1% Tween-20, pH 7.6). Membranes were then washed (4×4 minutes rocking in TBST) and incubated overnight in primary antibodies at 4°C with gentle rocking. Primary antibodies were diluted in 5% BSA and 0.02% NaN_3 in TBST. Primary antibodies for monoclonal p-4EBP1$^{Thr37/46}$ #2855, p-AMPK^{Thr172} #2535, p-mTOR^{Ser2448} #5536, p-TSC2^{Thr1462} #3617, and polyclonal p-Akt^{Ser473} #9271, p-eEF2^{Thr56} #2331, p-p53^{Ser15} #9284, p-rpS6$^{Ser235/236}$ #4856 were from Cell Signaling Technology (Danvers, MA). The following morning, membranes were again washed (4×4 minutes in TBST) before incubation in a species-specific horseradish peroxidise-conjugated secondary antibody (Donkey Anti-Rabbit IgG, Ab6802, Abcam; or Goat Anti-Rabbit IgG, NEF812001EA, Perkin Elmer, Waltham, MA), for 90 minutes at room temperature. Membranes were then washed (4×4 minutes rocking in TBST) before being treated with a chemiluminescent solution (Clarity™ Western ECL Substrate, Bio-Rad, Hercules, CA; or SuperSignal™ West Femto Maximum Sensitivity Substrate, ThermoFischer Scientific, Wilmington, DE, depending on the target protein). Images were taken using ChemiDoc™ MP imaging system (Bio-Rad, Hercules, CA), and proteins were quantified via densitometry (Image Lab 5.0 software, Bio-Rad, Hercules, CA). Samples were normalised to both the internal

standards loaded on each gel, as well as the total protein content of each lane determined using the stain-free imaging system.

3.9.2 Real-time quantitative PCR (RT-qPCR)

RNA extraction

Frozen muscle samples (~20 mg) were removed from -80°C storage and placed on dry ice until 800 µL of TRIzol™ reagent (Invitrogen, Thermo Fisher Scientific, Waltham, USA, #15596018) and a new, stainless-steel metal bead was added to each sample. Samples were homogenised at 30 Hz for 2×2 minutes in an automated homogeniser (TissueLyser II, Qiagen), before being returned to -80°C storage overnight. Following overnight incubation, the samples were thawed on ice, then centrifuged from 15 minutes at 13,000 rpm and 4°C. The upper homogenate was aliquoted to a new, sterile tube containing 250 µL of chloroform, inverted briefly, then left on ice for 5 minutes. The samples were then centrifuged at 13,000 rpm for 15 minutes at 4°C, after which the top, aqueous phase was collected carefully (so not to disturb and aspirate any of the interphase, and contaminate the final sample with DNA and protein), and aliquoted to a new, sterile tube containing 400 µL of 2-Propanol (Sigma-Aldrich, St. Louis, MI, #19516) and 10 µL of 5 M NaCl, and left for 10 minutes at room temperature to precipitate. The samples were then centrifuged from 20 minutes at 13,000 rpm and 4°C, to pellet the RNA. Most of the isopropanol was aspirated, and the pellet was washed once with ~400 µL of 75% ethanol solution made with diethylpyrocarbonate-treated water (DEPC) (Invitrogen, Thermo Fisher Scientific, Waltham, USA) and centrifuged at 9,000 rpm for 8 minutes at 4°C. The ethanol was aspirated, and the pellet air-dried, before being re-suspended in 30 µL of DEPC.

RNA quantification and integrity testing

RNA concentration (ng/µL) was determined using 1 µL of sample via spectrophotometry (NanoDrop 2000, Thermo Fisher Scientific, Wilmington, DE) at 260 (A_{260}) and 280 (A_{280}) nm, with an A_{260}/A_{280} ratio of 1.84 ± 0.10. RNA integrity was assessed as per the manufacturers guidelines, using an automated electrophoresis system (Experion™, Bio-Rad, Hercules, CA), which provides an RNA Quality Indicator score (RQI) from 1 to 10. Samples with an RQI score > 7 were deemed to be of sufficient integrity for analysis (Kuang et al., 2018). Any samples that failed the integrity test required a new morsel of tissue to be re-chipped, re-homogenised and re-extracted. RNA samples were stored at -80°C until further analysis.

Reverse transcription

One microgram of RNA was combined with 4 µL of a commercially-available kit (iScript™ RT Supermix cDNA synthesis kit, Bio-Rad, Hercules, CA, #1708890), and topped up with DEPC for a total reaction volume of 20 µL. Using a thermal cycler (S1000™ Thermal Cycler, Bio-Rad,

Hercules, CA), the cDNA was synthesised by priming at 25°C for 5 minutes, reverse transcription at 46°C for 20 minutes, and inactivation at 95°C for 1 minutes. Following the reaction, 180 µL of DEPC was added to all samples, which were then stored at -20°C until further analysis.

Real-time quantitative PCR (RT-qPCR)

Relative mRNA expression of PGC-1α, MuRF1, MAFbx, Myostatin, Mighty, and the reference genes 18S, β2M, Cyclophilin, GAPDH, ACTB and TBP were measured via qPCR (QuantStudio 7 Flex, Applied Biosystems, Foster City, CA). Primers were either adapted from existing literature, or designed using Primer-BLAST (Ye et al., 2012) to include all splice variants, and were purchased from Sigma-Aldrich (details in Table 3.6). All reactions were performed in duplicate, on 384-well MicroAmp optical plates (Applied Biosystems™, #4309849) using an epMotion M5073 automated pipetting system (Eppendorf AG, Hamburg, Germany). The final reaction volume (5 µL) contained 2 µL of the cDNA template, 300 nM of each forward and reverse primer (Table 3.6) and 2X SsoAdvanced Universal SYBR Green Supermix (Bio-Rad, Hercules, CA), except when amplifying TBP, where 900 nM of each primer was used. Each plate was briefly centrifuged before loading into the PCR machine. The PCR reactions were conducted under the following conditions: 3 minutes at 95°C, 40 cycles of 15 seconds at 95°C/1 minute at 60°C, one cycle of 15 seconds at 95°C/15 seconds at 60°C, and a ramp for 20 minutes to 95°C. To account for variations in initial RNA concentrations and the efficiency of the reverse transcription, mRNA data were quantified using the $2^{-\Delta\Delta CT}$ method, where Ct is the quantification cycle (Schmittgen and Livak, 2008). Values were normalised to the geometric mean (Vandesompele et al., 2002) of the three most stable housekeeping genes analysed (ACTB, cyclophilin and 18S), which were determined using both *BestKeeper* (Pfaffl et al., 2004) and *NormFinder* (Andersen et al., 2004) software. Primer efficiency and single product amplification were confirmed prior, using standard and melting curves, respectively.

3.9.3 Muscle glycogen assay

Frozen muscle samples (~15 mg) were removed from -80°C storage and transferred on dry ice to a freeze drier for 24 hours (Heto PowerDry LL1500 Freeze Dryer, Thermo Electron Corporation). The freeze-dried muscle samples (2-3 mg dry mass [DM]) were dissected of visible blood and connective tissue, weighed, and subsequently extracted with 2 M HCl (50 µL/mg DM). The samples were incubated for 2 hours at 100°C, with gentle agitation every 15-20 minutes. Samples were then neutralised using 0.66 M NaOH (150 µL/mg DM). Glycogen content was subsequently assayed in triplicate via enzymatic analysis with fluorometric detection (calculations adapted from Harris et al. (1974)). Values are expressed as $mmol \cdot kg^{-1}$ DM.

Primers

Table 3.6 - Details of primer sequences used for RT-qPCR.

Target Gene	**Forward Primer** (*5'-3'*)	**Reverse Primer** (*5'-3'*)	**Primer efficiency**	**Product Size (bp)**	**Accession No.**
PGC-1α[3]	CAGCCTCTTTGCCCAGATCTT	TCACTGCACCACTTGAGTCCAC	104%	101	NM_013261.3
MuRF1	CCGTCGAGTGACCAAGGAGA	CCAGGATGGCATACAACGTG	99%	80	NM_032588
MAFbx (*Atrogin1*)	GCAGCTGAACAACATTCAGATCAC	CAGCCTCTGCATGATGTTCAGT	100%	97	NM_058229
Myostatin	GGAGAAGATGGGCTGAATCCG	GCATCGTGATTCTGTTGAGTGC	99%	111	NM_005259
Mighty (*Akirin-1*)	CCAACTCCGGAGCAAATTTTTCA	TCCGAAGCACAAGCTTCACT	95%	106	NM_024595
Housekeeping Genes					
18S	CTTAGAGGGACAAGTGGCG	GGACATCTAAGGGCATCACA	99%	71	NR_003286.2
ACTB	GAGCACAGAGCCTCGCCTTT	TCATCATCCATGGTGAGCTGGC	107%	70	NM_001101.3
β_2M	TGCTGTCTCCATGTTTGATGTATCT	TCTCTGCTCCCCACCTCTAAGT	98%	86	NM_004048.2
Cyclophilin	GTCAACCCCACCGTGTTCTTC	TTTCTGCTGTCTTTGGGACCTTG	100%	100	NM_021130.4
GAPDH	AATCCCATCACCATCTTCCA	TGGACTCCACGACGTACTCA	106%	82	NM_002046.7
TBP	CAGTGACCCAGCAGCATCACT	AGGCCAAGCCCTGAGCGTAA	99%	205	NM_003194.4

Abbreviations: PGC-1α = peroxisome proliferator-activated receptor gamma coactivator 1-alpha; MuRF1 = Muscle RING-finger protein-1; MAFbx = muscle-specific atrophy F box; 18S = 18S ribosomal RNA; ACTB = beta actin; β2M = β2-microglobin (β2M); GAPDH = glyceraldeyde-3-phosphate dehydrogenase; TBP = TATA-binding-protein.

[3] *This primer sequence is taken from Ruas et al. (2012), which targets exon 2, present in all isoforms (PGC-1α1, -1α2, -1α3, and -1α4).*

Chapter 4 New kids on the blot: investigating the molecular interference effect

Molecular responses to resistance-only and alternate orders of concurrent exercise, before and after 9 weeks of training, in healthy active men.

Preface

Endurance and resistance training are associated with different phenotypes that are regulated by cascades of transient, exercise-induced molecular signalling events, which are specific to the exercise mode. It has previously been proposed that concurrently stimulating the different molecular pathways typically induced by endurance and resistance exercise may result in some degree of molecular incompatibility (Coffey and Hawley, 2007), whereby each pathway is downregulated by the '*opposing*' exercise mode (Atherton et al., 2005).

However, supportive evidence for this in human studies is scarce; few studies have reported a molecular interference effect (Babcock et al., 2012, Fyfe et al., 2018), whilst most others do not (Apró et al., 2015, Apró et al., 2013, Lundberg et al., 2012, Lundberg et al., 2014, Pugh et al., 2015, Wang et al., 2011). The lack of consensus in the literature is likely due to the varying study designs employed. The training status of the participants may affect the observed molecular responses (Vissing et al., 2013, Wilkinson et al., 2008), and given the different signalling time-courses of specific proteins implicated in endurance and resistance adaptations, the order in which concurrent sessions are performed may also dictate the subsequent molecular response (Fyfe et al., 2014); however, few studies have specifically addressed this (Coffey et al., 2009a, Coffey et al., 2009b, Jones et al., 2016).

The following chapter will build on previous studies by investigating the molecular responses to resistance-only and concurrent exercise, in both the untrained and training-accustomed states, with a specific focus on the effect of concurrent exercise order.

4.1 Introduction

Skeletal muscle tissue is highly malleable and capable of adapting to a range of stimuli (Fluck and Hoppeler, 2003), and in the context of exercise, training adaptations are highly specific to the type, intensity, volume and frequency of stimulus imposed (Hawley, 2002, Hawley, 2009, Hoppeler et al., 2011). Endurance and resistance training represent different exercise modalities with distinct phenotypic adaptations that are considered to sit at opposing ends of the adaptation spectrum (Hoppeler et al., 2011, Nader, 2006). Both exercise modes transiently induce distinct molecular signalling events, which regulate gene expression, transcription, and translation of new proteins, and the cumulative effect of training results in structural and functional adaptations that are representative of each training mode (Coffey and Hawley, 2007, Egan and Zierath, 2013, Perry et al., 2010, Baar et al., 2002).

Integrating both endurance and resistance exercise within the same training program is called concurrent training (Fyfe et al., 2014). Whilst this appears to be an ideal training method for improving athletic performance, as well as attaining multiple health benefits from both modes, several studies have reported that concurrent training can compromise the development of hallmark resistance training adaptations, such as strength (Bell et al., 2000, Fyfe et al., 2016a, Gergley, 2009, Hickson, 1980, Kraemer et al., 1995, Ronnestad et al., 2012, Sale et al., 1990a), muscle hypertrophy (Bell et al., 2000, Fyfe et al., 2016a, Kraemer et al., 1995, Ronnestad et al., 2012) and power (Häkkinen et al., 2003, Mikkola et al., 2012, Tsitkanou et al., 2017, Dudley and Djamil, 1985, Kraemer et al., 1995). This has been termed the "*interference effect*" or the "*concurrent training effect*" (Hawley, 2009, Baar, 2006). Whilst the precise causes of the interference effect remain to be fully understood, given that endurance and resistance exercise induce distinct molecular events governing their respective phenotypic adaptations, increased attention has been paid to the potential antagonism between concurrent exercise modes at the molecular level to explain, in part, the interference to whole-body adaptations (Baar, 2014, Coffey and Hawley, 2007, Hawley, 2009).

The mechanistic target of rapamycin complex 1 (mTORC1) is a highly-conserved serine/threonine protein kinase that functions as a critical mediator of muscle protein synthesis (MPS) in response to mechanical load (Goodman, 2014). The ability of mTORC1 to interact both with its substrates and downstream targets has been shown to be inhibited by certain proteins typically induced by endurance exercise; one in particular is 5'-adenosine monophosphate-activated protein kinase (AMPK) a cellular energy sensor that mediates the reduction in energy-consuming pathways (such as protein synthesis) and favours energy production (Hardie, 2011). Several models of AMPK activation have been shown to suppress mTORC1 activity, by preventing its association with key substrates (Inoki et al., 2003a, Inoki et al., 2003b, Gwinn et

al., 2008) and suppressing target proteins involved in translation initiation and elongation (e.g. p70S6K, 4E-BP1 and eEF2) (Bolster et al., 2002, Thomson et al., 2008, Rose and Richter, 2009). AMPK also upregulates the autophagy-inducing kinase ULK1 (Lee et al., 2010a) and FOXO-mediated transcription of atrophy-inducing genes, such as MuRF1 and MAFbx (Krawiec et al., 2007, Nakashima and Yakabe, 2007). In addition to AMPK, the tumour suppressor p53 may also play a role owing to its ability to inhibit mTORC1 by stimulating AMPK-mediated mechanisms (Feng et al., 2005), whilst in turn being negatively regulated by components of the mTORC1 pathway, such as Akt (Gottlieb et al., 2002). More recently, the potential role for p53 in specifically regulating concurrent training adaptations was proposed (Ellefsen and Baar, 2019), firstly due to its role as a transcription factor for Sestrins (which inhibit amino acid-stimulated activation of mTORC1 (Budanov and Karin, 2008)), and secondly due to its interfering effect on the transcription of ribosomal RNA (Zhai and Comai, 2000). Consequently, in response to different stimuli, both AMPK and p53 may disrupt not only the efficiency of, but also the capacity for, protein synthesis, through a variety of the mechanisms. However, much of the supportive evidence for a molecular interference effect has been derived from experimental models employing pharmacological activation of signalling pathways in cell culture, artificially-induced contractions via electrical stimulation, and transgenic animals.

In human skeletal muscle, under normal physiological conditions, few studies provide evidence of a 'molecular interference effect'. Concurrent exercise has previously been shown to attenuate resistance-exercise induced satellite cell proliferation (Babcock et al., 2012), and signalling associated with mTORC1 and ribosomal biogenesis (Fyfe et al., 2018). On the contrary, most other human studies report comparable (Apró et al., 2015, Apró et al., 2013, Donges et al., 2012, Fyfe et al., 2016b, Pugh et al., 2015) or amplified (Lundberg et al., 2012, Wang et al., 2011) molecular responses to both resistance and endurance exercise, compared to each mode performed separately. This has been demonstrated when resistance exercise is performed both prior to (Apró et al., 2013, Pugh et al., 2015) and after (Apró et al., 2015, Wang et al., 2011) endurance exercise. However, as these studies only compared one concurrent group with single-mode exercise, it is difficult to speculate how the results of these studies may have differed had the concurrent exercise order been reversed; indeed, few studies have specifically investigated the effect of concurrent exercise order on the molecular mediators of endurance and resistance training adaptations in humans. Coffey *et al.* conducted two studies in which resistance exercise was combined with steady-state (Coffey et al., 2009b) and repeated-sprint cycling (Coffey et al., 2009a). With steady-state cycling, mTORC1 signalling responses occurred independent of exercise order (Coffey et al., 2009b). However, performing cycling first reduced IGF-1 mRNA expression (suggestive of a diminished anabolic response), whilst performing resistance exercise first increased mRNA expression of the ubiquitin ligase MuRF-1 (associated with inflammation

and muscle protein breakdown) (Coffey et al., 2009b). This was exacerbated when cycling involved repeated maximal sprints (Coffey et al., 2009a). Furthermore, performing the maximal sprints first attenuated resistance exercise-induced p70S6K and rpS6 phosphorylation, which are both integral to translation initiation (Coffey et al., 2009a). Whilst neither order provided a desirable molecular environment for adaptation, these studies were conducted in the fasted-state, which has been shown to affect signalling associated with both growth (Creer et al., 2005) and mitochondrial adaptations (Bartlett et al., 2013). Furthermore, the lack of a resistance-only group precludes interpretations about the degree of 'molecular interference' with each concurrent exercise order compared to resistance-only exercise. More recently, Jones *et al.* (2016) demonstrated comparable AMPK and mTORC1 signalling responses in resistance-trained men, when resistance exercise (in the fed-state) was performed before, after, *and without* steady-state cycling. However, only the immediate (<1 hour) post-exercise signalling responses were captured; thus, it is possible that key molecular events may have been missed.

The current understanding of molecular responses to concurrent training is also based on protocols in which both modes are performed either in close proximity (≤ 15-20 minutes (Apró et al., 2015, Apró et al., 2013, Coffey et al., 2009a, Coffey et al., 2009b, de Souza et al., 2013, Lundberg et al., 2014, Pugh et al., 2015, Wang et al., 2011)) or several (≥ 6) hours apart (Lundberg et al., 2012, Lundberg et al., 2013). However, in human skeletal muscle, the expression of several regulatory genes and proteins involved in both the endurance (AMPK, PGC-1α, p53) (Bartlett et al., 2012, Bartlett et al., 2013, Camera et al., 2015a, Gibala et al., 2009, Nordsborg et al., 2010, Norrbom et al., 2004, Pilegaard et al., 2003) and resistance signalling pathways (mTORC1, p70S6K) (Dreyer et al., 2010, Drummond et al., 2009, Vissing et al., 2013) are known to be upregulated ~2 to 4 hours post-exercise. It was previously suggested that a between-mode recovery period of at least 3 hours may allow any potential antagonism between different exercise-induced molecular responses to subdue (Baar, 2014); however, this has never been explicitly investigated. Given that it is also common practice, particularly within athletic environments, for concurrent sessions to be separated by recovery periods of only a few hours (Cross et al., 2019, Enright et al., 2015, Enright et al., 2017, Robineau et al., 2016) little is known about how training in this way may modulate the molecular events orchestrating the development of endurance and resistance adaptations, and thus presents an important avenue for further exploration.

Participant training status can also significantly modulate the signalling responses governing training adaptations. In the untrained state, exercise promotes a generic response, non-specific to the exercise mode, while training-accustomed individuals exhibit molecular responses that are more specific to the stimuli (Coffey and Hawley, 2016, Vissing et al., 2013, Wilkinson et al., 2008). Concurrent training studies to date have recruited untrained (Donges et al., 2012, Pugh et

al., 2015), recreationally-active (Fyfe et al., 2016b, Lundberg et al., 2012, Wang et al., 2011), moderately-trained (Apró et al., 2015, Apró et al., 2013), and trained individuals (Coffey et al., 2009a, Coffey et al., 2009b, Jones et al., 2016). Whilst collectively, these studies have developed our understanding of the molecular blueprint of concurrent training adaptations, how such responses change within the same cohort of participants after a period of training that has been controlled and monitored, remains poorly defined. That said, few studies have examined molecular adaptations following a period of concurrent training, and have typically assessed changes in basal gene and protein expression before and after training (Fyfe et al., 2018, Kazior et al., 2016, Lundberg et al., 2013), or measured acute molecular responses *only* before (Lundberg et al., 2014) or after (Fyfe et al., 2018) a period of training. To the author's knowledge, only one study has assessed changes in acute signalling responses to concurrent exercise, both before *and* after training, within the same participants (Fernandez-Gonzalo et al., 2013). This study demonstrated that prior to a 5-week concurrent training program, the addition of aerobic exercise to resistance training provided a greater stimulus for molecular mediators of protein synthesis and remodelling (Fernandez-Gonzalo et al., 2013). Furthermore, exercise in the untrained state, regardless of mode, promoted generic molecular responses that became 'dampened' and more mode-specific following training (Fernandez-Gonzalo et al., 2013). Whilst the authors should be commended for undertaking a demanding training study involving multiple muscle biopsies, considering that the interference effect may not manifest until after several weeks of training (Hickson, 1980), it is possible that a longer training period may further our insight into the time course of molecular adaptations to concurrent training.

Consequently, the aim of this study was to investigate the post-exercise molecular signalling responses to concurrent and resistance-only exercise, both before and after a 9-week training period. The intention was to provide novel information characterising the time course of acute molecular responses to concurrent and resistance only exercise, as well as the effect of training status on these responses, when exercise was performed in the fed-state, and concurrent sessions were separated by a 3-hour recovery period.

4.2 Materials and Methods

Full details of all experimental procedures can be found in *Chapter 3: General Methodology*; any differences from the general methodology that are pertinent to this chapter are outlined below.

Experimental Overview

Following familiarisation trials and baseline fitness testing, twenty-five healthy, active men were ranked according to baseline levels of maximal strength, aerobic fitness, and lean mass and allocated to one of three training groups, in a semi-randomised[4], counterbalanced order: 1) *ER*, endurance prior to resistance exercise (n = 9); 2) *RE*, resistance prior to endurance (n = 8); or 3) *RO*, resistance exercise only (n = 8). In Week 1, the participants performed three '*experimental*' training sessions; during the first session, muscle was sampled at various timepoints to characterise the temporal changes in gene and protein expression following resistance-only and concurrent exercise sessions. The experimental resistance sessions involved 6 sets of 10 leg press repetitions, at 70% 1-RM, with 2 min between sets. The endurance sessions involved performing 10 × 2-min cycling bouts, at 40% of the difference between the power at the lactate threshold ($\dot{W}_{LT}$) and peak aerobic power ($\dot{W}_{peak}$) (~84% $\dot{W}_{peak}$). Following this, the participants continued 8 weeks of structured training in their respective groups (*Weeks 2 to 9*), before repeating the experimental week (*Week 10*), at the same relative exercise intensities.

Figure 4.1 - Schematic overview of the experimental training day in Weeks 1 and 10. END = endurance session; RES = resistance session; RO = resistance-only, ER = endurance-resistance, RE = resistance-endurance; ↑ = muscle biopsy; ✕ = standardised meal (carbohydrate = 1.3 g·kg^{-1}; protein = 0.3 g·kg^{-1}; fat = 0.3 g·kg^{-1}); 🥤 = whey protein (0.25 g·kg^{-1}).

Statistical analyses

Prior to analysis, all dependent variables were log-transformed on the reasonable assumption that effects and errors are more uniform when expressed in percent or factor (fold-change) units, than in original raw units (Hopkins et al., 2009). A mixed model, realised with Proc Mixed in the

[4] *Group allocations were 'semi-randomised' in that not all 25 participants were recruited at once. However, once participants were recruited, and all baseline tests completed, they were allocated to a group with the aim of matching the groups primarily according to baseline levels of maximal strength, aerobic fitness and lean mass; where possible, I endeavoured to also match other baseline variables.*

Statistical Analysis System (University Edition of SAS Studio, Version 9.4, SAS Institute, Cary, NC), was used to analyse each dependent variable. To estimate the means of each group at each timepoint before and after training, the fixed effect in the model was the interaction of group (*three levels* representing each training group) with week (*two levels*: week 1 and 10), and timepoint (*five levels*: PRE, +0.5 h, +3.5 h, +4 h, and +7 h). The random effects were the participant identity (to estimate different overall mean values for each participant, and thereby account for repeated measurement), a dummy variable interacted with participant identity (to estimate overall individual responses to training, with different individual-response variances in each group), and dummy variables interacted with the interaction of participant identity and week (to estimate individual responses to the acute effects of exercise, with different individual-response variances in each group, and with an unstructured covariance matrix to allow for the individual responses to be correlated). The individual responses were included to account for different measurement errors in each group at different time points and thereby provide more trustworthy estimates for the uncertainty in the mean effects. The standard deviations representing individual responses are not presented.

Differences between groups at baseline were assessed for magnitude using standardisation; confidence intervals and *P*-values for the differences were not derived, because inferences about the differences are irrelevant for the allocation process, and any differences should be adjusted for (see appendices). However, adjusting for differences at baseline on the acute and chronic effects of exercise was not possible, owing to the limited sample size in each group.

Mean within-group changes and between-group differences in the changes were derived using estimate statements in Proc Mixed. As the majority of the effects and their uncertainties were in excess of 25%, outcome measures are presented as fold-changes with 90% *factor* confidence intervals (×/÷90%CI) (Hopkins et al., 2009). The between-subjects standard deviation at PRE (Week 1) was used to derive standardised effect sizes (ES) of the magnitude of the within- and between-group mean effects, where <0.20 = trivial, 0.20-0.60 = small, 0.60-1.2 = moderate, 1.2-2.0 = large, 2.0-4.0 = very large, >4.0 = extremely large; the 0.20 threshold defined smallest important effects (Hopkins et al., 2009). The standardizing standard deviation was derived from a sample size of 25, which is less than the sample size (n = 30) that results in negligible inflation of the confidence interval (Hopkins, 2019). For this reason, the 99% confidence intervals provide more trustworthy decisions about the magnitude of the standardised effects (see below).

Using the 90% confidence interval (90%CI), *non-clinical* thresholds were used to make decisions about the magnitude of the effects, according to the probability of being substantially positive or negative. Effects were deemed unclear if the probability for a substantially positive and negative

effect were both >5%. The probability thresholds for determining meaningful effects were as follows: 75-95% = *likely*, 95-99.5% = *very likely*, and >99.5% = *most likely*. All substantially positive (↑), negative (↓), or trivial effects were considered meaningful only if the probability was >75%. To account for inflation of error arising from multiple inferences, the thresholds for determining unclear effects were then adjusted to more conservative thresholds of 99% CI. Effects which remained clear after adjusting for multiple inferences are represented bold text in figures and tables**.** Precise *P*-values for the effects (unless $P < 0.001$) are also provided in the appendices.

4.3 Results [5]

Muscle glycogen

Resting content: In week 1, there were moderate differences in muscle glycogen content at rest between *RO* and both *ER* (ES = 0.88) and *RE* (ES = 1.03). The difference between *ER* and *RE* was trivial (ES = 0.15). In week 10, there was a moderate difference between *RO* and *ER* (ES = 0.81) and small differences between *RE* and both *RO* (ES = -0.51) and *ER* (ES = 0.30), at rest. All groups increased muscle glycogen content with training (*mean fold change ×/÷90%CI [ES ±90%CI]*; *RO:* 1.32 ×/÷1.20 [1.28 ±0.70]; *ER:* 1.30 ×/÷1.20 [1.23 ±0.71]; *RE:* 1.18 ×/÷1.17 [0.78 ±0.68]) with no clear differences between groups for the training-induced changes.

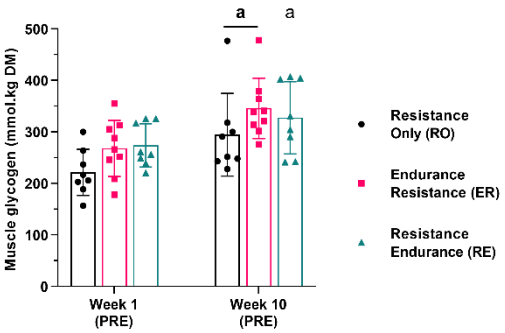


Figure 4.2 - Resting muscle glycogen content at rest in week 1 and week 10. Data are group mean ± SD in raw units. a = substantial change between week 1 and 10. Bold letter indicates effects remained clear after adjusting for multiple comparisons.

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, muscle glycogen increased above rest at +7 h (1.12 ×/÷1.17 [0.52 ±0.70]). In *ER*, muscle glycogen decreased from rest at all timepoints (*+0.5 h*: 0.84 ×/÷1.16 [-0.79 ±0.90]; *+3.5 h*: 0.80 ×/÷1.11 [-1.02 ±0.66]; *+4 h*: 0.73 ×/÷1.17 [-1.48 ±1.09]; *+7 h*: 0.81 ×/÷1.13 [-0.97 ±0.72]). In *RE*, muscle glycogen decreased from rest at +4 h (0.71 ×/÷1.17 [-1.60 ±1.07]). **Week 10:** In *RO*, there were no clear changes in muscle glycogen at any timepoint. In *ER*, muscle glycogen decreased from rest at +0.5 h (0.86 ×/÷1.17 [-0.73 ±0.90]) and +7 h (0.72 ×/÷1.11 [-1.54 ±0.72]). In *RE*, muscle glycogen decreased from rest at +4 h (0.79 ×/÷1.18 [-1.11 ±1.04]) and +7 h (0.81 ×/÷1.16 [-0.96 ±0.91]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: In *RO*, at +4 h, glycogen increased from rest in week 1, and decreased in week 10 (0.77 ×/÷1.23 [-1.20 ±1.36]). In *ER*, at +3.5 h, the glycogen depletion observed in week 1 was attenuated in week 10 (1.18 ×/÷1.24 [0.78 ±0.93]). There were no clear differences between weeks 1 and 10 for *RE*-induced changes to glycogen.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +3.5 h, muscle glycogen was reduced in *ER* compared to both *RO* (0.74 ×/÷1.15 [-1.40 ±0.94]) and *RE* (0.76 ×/÷1.27 [-1.26 ±0.94]). Compared to *RO*, at both +4 h and +7 h,

[5] *All raw data, and extended within- and between-group comparison data for this chapter are available in Appendix B*

muscle glycogen was reduced in both *ER* (*+4 h*: 0.62 ×/÷1.19 [-2.21 ±1.43]; *+7 h*: 0.73 ×/÷1.16 [-1.49 ±0.99]) and *RE* (*+4 h*: 0.61 ×/÷1.19 [-2.32 ±1.41]; *+7 h*: 0.80 ×/÷1.20 [-1.03 ±1.13]). **Week 10:** At +7 h, compared to *RO*, muscle glycogen was reduced in both *ER* (0.71 ×/÷1.15 [-1.62 ±0.99]) and *RE* (0.80 ×/÷1.20 [-1.03 ±1.13]).

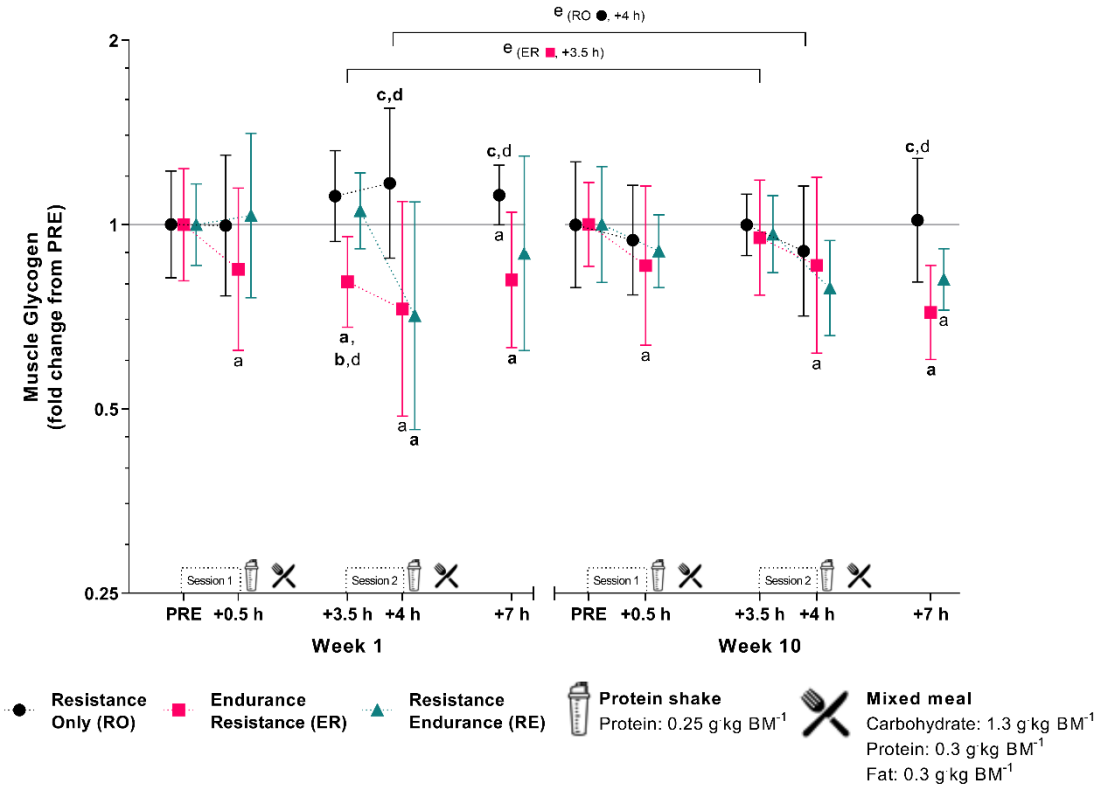


Figure 4.3 - The time-course of changes in muscle glycogen content following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses). Bold letters specify effects remained clear after adjusting for multiple comparisons.

Messenger RNA (mRNA) responses to exercise and training

PGC-1α

Basal expression: In week 1, there were small differences at rest between *ER* and both *RO* (ES = 0.49) and *RE* (ES = 0.44), whilst the difference between *RO* and *RE* was trivial (ES = -0.05). In week 10 there were small differences between *RO* and both *ER* (ES = -0.50) and *RE* (ES = -0.46), whilst the differences between *ER* and *RE* was trivial (ES = 0.04). There were no clear changes in basal PGC-1α expression between week 1 and 10.

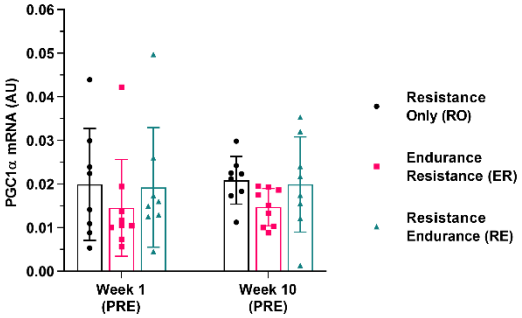


Figure 4.4 - Basal PGC-1α expression in week 1 and week 10. Data are group mean ± SD in arbitrary units.

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, PGC-1α expression increased at +3.5 h (4.42 ×/÷3.40 [2.21 ±0.77]), +4 h (1.91 ×/÷2.05 [0.96 ±0.78]) and +7 h (2.18 ×/÷2.25 [1.16 ±0.81]). In *ER*, PGC-1α increased at all timepoints (*+0.5 h*: 1.41 ×/÷1.57 [0.51 ±0.59]; *+3.5 h*: 5.23 ×/÷3.60 [2.46 ±0.71]; *+4 h*: 5.34 ×/÷3.17 [2.49 ±0.59]; *+7 h*: 3.45 ×/÷2.56 [1.84 ±0.65]). In *RE*, PGC-1α increased at +3.5 h (2.13 ×/÷2.24 [1.12 ±0.82]), +4 h (1.64 ×/÷1.71 [0.73 ±0.62]), and +7 h (2.47 ×/÷2.38 [1.34 ±0.79]). **Week 10:** In *RO*, PGC-1α increased at +3.5 h (2.12 ×/÷2.15 [1.12 ±0.77]) and +4 h (2.70 ×/÷2.48 [1.48 ±0.78]). In *ER*, PGC-1α increased at +3.5 h (2.92 ×/÷2.45 [1.59 ±0.71]), +4 h (3.03 ×/÷2.23 [1.65 ±0.59]) and +7 h (1.97 ×/÷1.89 [1.00 ±0.65]). In *RE*, PGC-1α increased at +0.5 h (1.40 ×/÷1.61 [0.50 ±0.62]), +4 h (1.90 ×/÷1.82 [0.95 ±0.62]) and +7 h (3.65 ×/÷3.05 [1.92 ±0.79]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, at +3.5 h, the increase in expression in week 10 was half that of week 1 (0.48 ×/÷1.39 [-1.09 ±1.09]). Likewise, for *ER*, the increase in expression was lower in week 10 than week 1 at +3.5 h (0.56 ×/÷1.41 [-0.87 ±1.01]), +4 h (0.57 ×/÷1.34 [-0.84 ±0.83]), and +7 h (0.57 ×/÷1.38 [-0.83 ±0.92]). There were no clear differences between weeks for the *RE*-induced changes in PGC-1α expression.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +0.5 h, PGC-1α expression was greater in *ER* than *RO* (1.81 ×/÷1.10 [0.88 ±0.86]). At +3.5 h, PGC-1α expression was lower in *RE* than both *RO* (0.48 ×/÷1.40 [-1.09 ±1.11]) and *ER* (0.41 ×/÷1.32 [-1.34 ±1.08]). At +4 h, PGC-1α expression in *ER* was greater than both *RO* (2.79 ×/÷1.94 [1.53 ±0.96]) and *RE* (3.23 ×/÷1.19 [1.76 ±0.86]). **Week 10:** At both +3.5 h and +4 h, PGC-1α expression was greater in *ER* than *RE* (+3.5 h: 1.96 ×/÷1.40 [1.01 ±1.08]; +4 h: 1.59

×/÷1.38 [0.69 ±0.86]). At +7 h, PGC-1α expression was greater in *RE* than both *RO* (2.98 ×/÷3.45 [1.62 ±1.12]) and *ER* (1.86 ×/÷1.36 [0.92 ±1.01]).

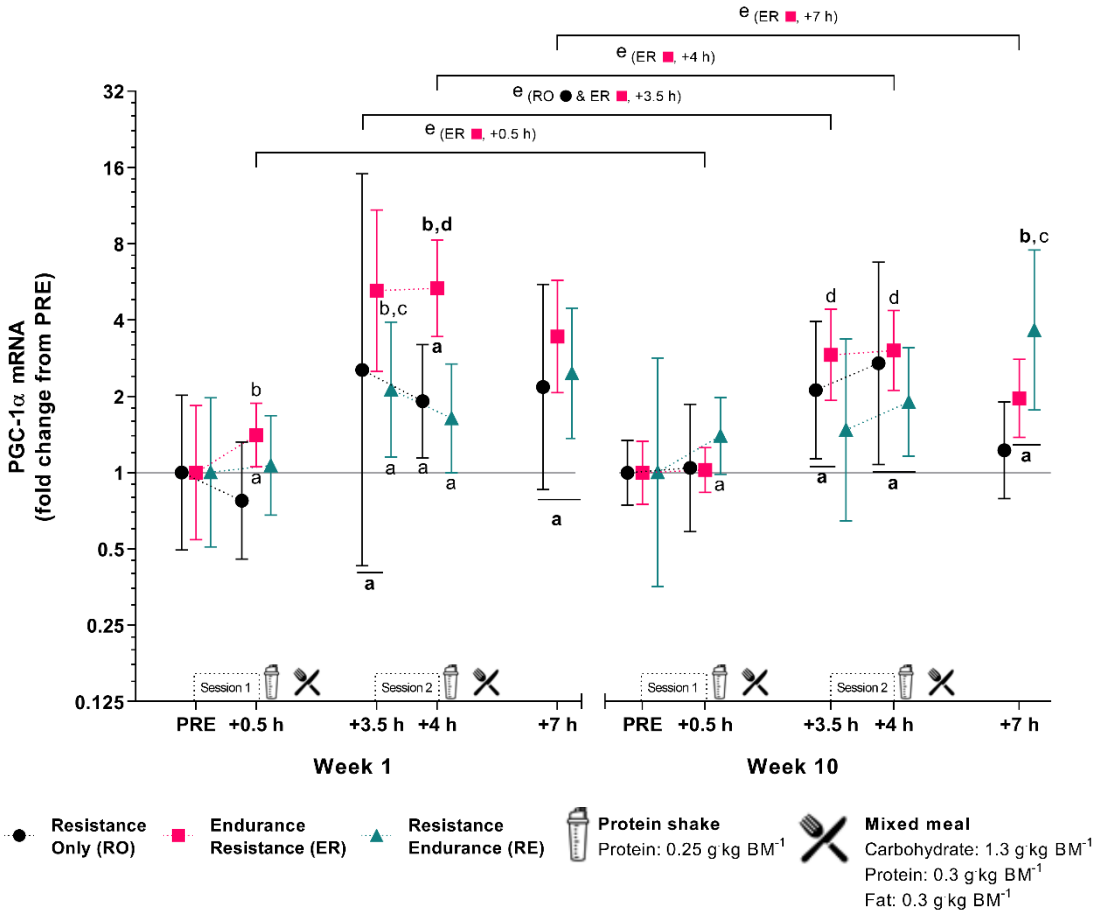


Figure 4.5 - The time-course of changes in PGC-1α expression content following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses). Bold letters specify effects remained clear after adjusting for multiple comparisons.

MuRF1

Basal expression: In both weeks 1 and 10, there were moderate differences at rest between *RE* and both *RO* (*Week 1*, ES = -1.04; *Week 10*, ES = -0.84) and *ER* (*Week 1*, ES = 0.60; *Week 10*, ES = 0.94), and large differences between *RO* and *ER* (*Week 1*, ES = -1.65; *Week 10*, ES = -1.78). There were no clear changes in basal MuRF1 expression between week 1 and 10 for any group.

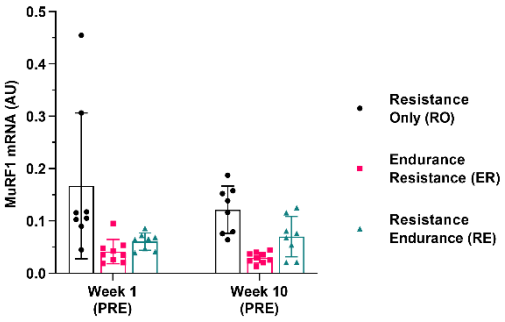


Figure 4.6 - Basal MuRF1 expression in weeks 1 and week 10. Data are group mean ± SD in arbitrary units.

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, MuRF1 increased at +3.5 h (1.43 ×/÷1.57 [0.47 ±0.50]) and decreased at +7 h (0.69 ×/÷1.35 [-0.49 ±0.64]). In *ER*, MuRF1 increased at +3.5 h (2.37 ×/÷1.86 [1.13 ±0.46]) and +4 h (2.23 ×/÷1.74 [1.05 ±0.43]). In *RE*, MuRF1 decreased at +4 h (0.70 ×/÷1.24 [-0.46 ±0.44]) and increased at +7 h (1.98 ×/÷1.68 [0.89 ±0.44]). **Week 10:** In *RO*, MuRF1 decreased at +7 h (0.48 ×/÷1.25 [-0.95 ±0.64]). In *ER*, MuRF1 increased at +3.5 h (1.63 ×/÷1.59 [0.64 ±0.46]) and +4 h (1.71 ×/÷1.57 [0.70 ±0.43]). In *RE*, MuRF1 decreased at +4 h (0.69 ×/÷1.24 [-0.49 ±0.44]) and increased at +7 h (1.59 ×/÷1.54 [0.60 ±0.44]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, at +4 h, MuRF1 expression was greater in week 10 than week 1 (1.66 ×/÷2.13 [0.66 ±0.83]). For *ER*, the increase in MuRF1 expression at +3.5 h in week 10 was lower than week 1 (0.69 ×/÷1.36 [-0.49 ±0.66]). There were no clear differences between weeks for *RE*-induced changes in MuRF1 expression.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At both +3.5 h and +4 h, MuRF1 expression was greater in *ER* than both *RO* (*+3.5 h*: 1.65 ×/÷1.89 [0.66 ±0.67]; *+4 h*: 3.09 ×/÷2.78 [1.47 ±0.72]) and *RE* (*+3.5 h*: 2.08 ×/÷1.31 [0.97 ±0.80]; *+4 h*: 3.23 ×/÷1.15 [1.51 ±0.61]). At +7 h, MuRF1 expression was greater in *RE* than both *RO* (2.88 ×/÷2.80 [1.38 ±0.77]) and *ER* (2.16 ×/÷2.12 [1.01 ±0.65]). **Week 10:** At +3.5 h, MuRF1 expression was greater in *ER* than both *RO* (1.57 ×/÷1.85 [0.59 ±0.67]) and *RE* (2.17 ×/÷1.30 [1.02 ±0.80]). At +4 h, MuRF1 expression was lower in *RE* than both *RO* (0.57 ×/÷1.33 [-0.73 ±0.73]) and *ER* (0.40 ×/÷1.19 [-1.19 ±0.61]). At +7 h, MuRF1 expression was greater in *RE* than both *RO* (3.28 ×/÷3.05 [1.55 ±0.77]) and *ER* (1.94 ×/÷2.01 [0.87 ±0.65]); MuRF1 expression was also greater in *ER* than *RO* (1.69 ×/÷2.09 [0.68 ±0.80]).

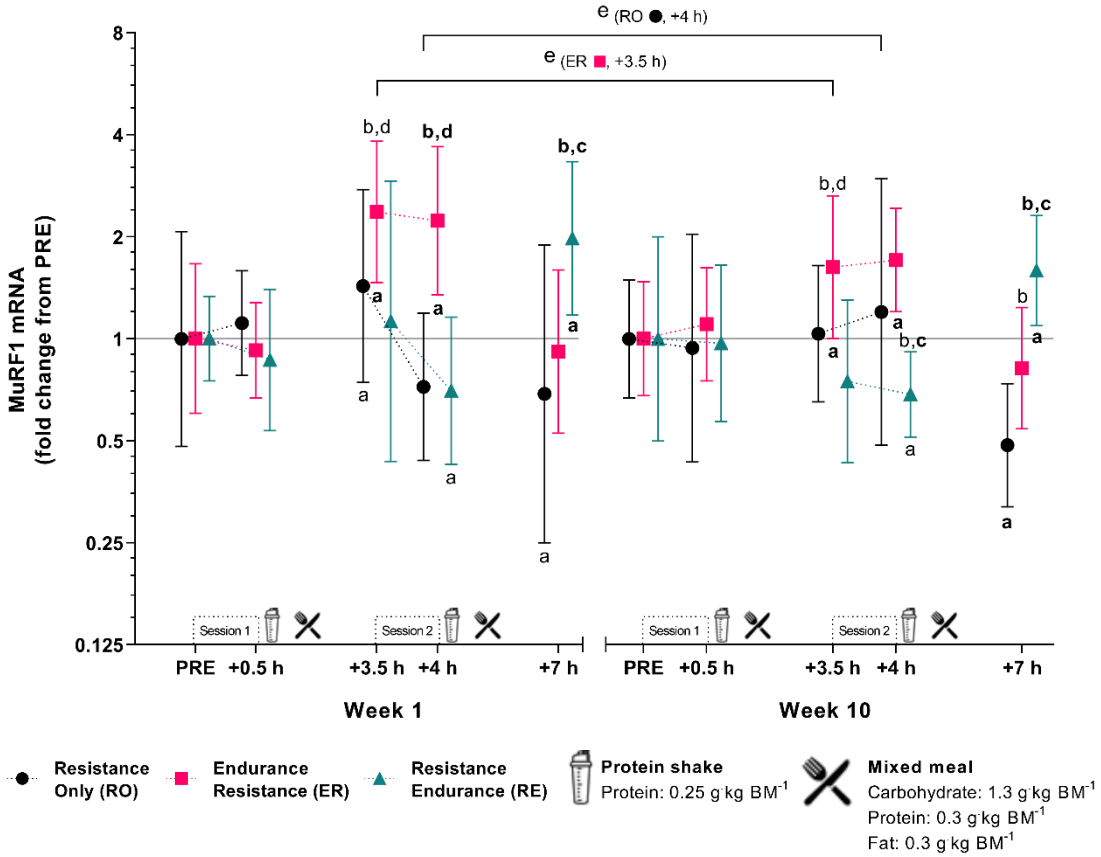


Figure 4.7 - The time-course of changes in MuRF1 expression following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses). ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

MAFbx

Basal expression: In weeks 1 and 10, there were moderate differences at rest between *RE* and both *RO* (*Week 1*, ES = 0.88; *Week 10*, ES = 1.00) and *ER* (*Week 1*, ES = -0.84; *Week 10*, ES = -0.79), and large differences between *RO* and *ER* (*Week 1*, ES = -1.72; *Week 10*, ES = -1.79). There was a small increase in basal MAFbx expression between weeks 1 and 10 for *ER* (1.38 ×/÷1.44 [0.37 ±0.36]), which was greater than the change in *RO* (1.66 ×/÷1.79 [0.58 ±0.53]).

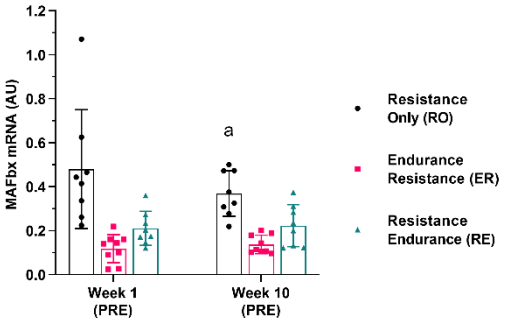


Figure 4.8 - Basal MAFbx expression in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10.

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, MAFbx decreased at +3.5 h (0.47 ×/÷1.26 [-0.87 ±0.60]), +4 h (0.23 ×/÷1.11 [-1.70 ±0.52]) and +7 h (0.17 ×/÷1.11 [-2.03 ±0.69]). In *ER*, MAFbx increased at +3.5 h (1.54 ×/÷1.79 [0.50 ±0.57]), +4 h (1.45 ×/÷1.67 [0.43 ±0.51]) and decreased at +7 h (0.58 ×/÷1.26 [-0.63 ±0.50]). In *RE*, MAFbx decreased at +3.5 h (0.44 ×/÷1.18 [-0.95 ±0.46]), +4 h (0.23 ×/÷1.08 [-1.70 ±0.38]), and +7 h (0.32 ×/÷1.16 [-1.31 ±0.56]). **Week 10:** In *RO*, MAFbx was reduced at +3.5 h (0.48 ×/÷1.26 [-0.84 ±0.60]), +4 h (0.52 ×/÷1.24 [-0.76 ±0.52]), and +7 h (0.25 ×/÷1.16 [-1.61 ±0.69]). In *ER*, MAFbx was reduced at +0.5 h (0.66 ×/÷1.25 [-0.48 ±0.42]) and +7 h (0.37 ×/÷1.17 [-1.31 ±0.56]). In *RE*, MAFbx was reduced at +3.5 h (0.41 ×/÷1.17 [-1.03 ±0.46]), +4 h (0.33 ×/÷1.11 [-1.27 ±0.38]), and +7 h (0.56 ×/÷1.29 [-0.66 ±0.56]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, MAFbx at +4 h was reduced more in week 1 than week 10 (2.25 ×/÷2.55 [0.93 ±0.74]). For *ER*, at +0.5 h, MAFbx was lower in week 10 compared to week 1 (0.56 ×/÷1.31 [-0.66 ±0.60]). For *RE*, MAFbx was reduced more in week 1 than week 10 at both +4 h (1.46 ×/÷1.72 [0.43 ±0.54]) and +7 h (1.76 ×/÷2.32 [0.65 ±0.80]).

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: MAFbx was greater in *ER* than both *RO* and *RE* at +3.5 h (*vs RO*: 3.28 ×/÷3.49 [1.37 ±0.81]; *vs RE*: 3.45 ×/÷1.19 [1.44 ±0.67]), +4 h (*vs RO*: 6.35 ×/÷523 [2.13 ±0.72]; *vs RE*: 6.25 ×/÷1.09 [2.13 ±0.63]), and +7 h (*vs RO*: 3.36 ×/÷3.68 [1.39 ±0.84]; *vs RE*: 1.79 ×/÷1.38 [0.68 ±0.74]). At +7 h, MAFbx was also reduced more in *RO* than *RE* (1.86 ×/÷2.55 [0.72 ±0.87]). **Week 10:** At +0.5h, MAFbx was lower in *ER* compared to *RE* (0.68 ×/÷1.75 [-0.44 ±0.57]). Compared to *ER*, MAFbx was lower in both *RO* and *RE* at +3.5 h (*vs RO*: 0.44 ×/÷2.72 [-0.94 ±0.81]; *vs RE*: 0.38 ×/÷1.25 [-1.13 ±0.67]), +4 h (*vs RO*: 0.47 ×/÷2.42 [-0.87 ±0.72]; *vs RE*: 0.30 ×/÷1.18 [-1.38 ±0.63]). At +4h, MAFbx was lower in *RE* than *RO* (0.64 ×/÷1.38 [-0.51 ±0.64]). At +7h, MAFbx was lower in *RO* than *RE* (0.44 ×/÷2.91 [-0.95 ±0.87]).

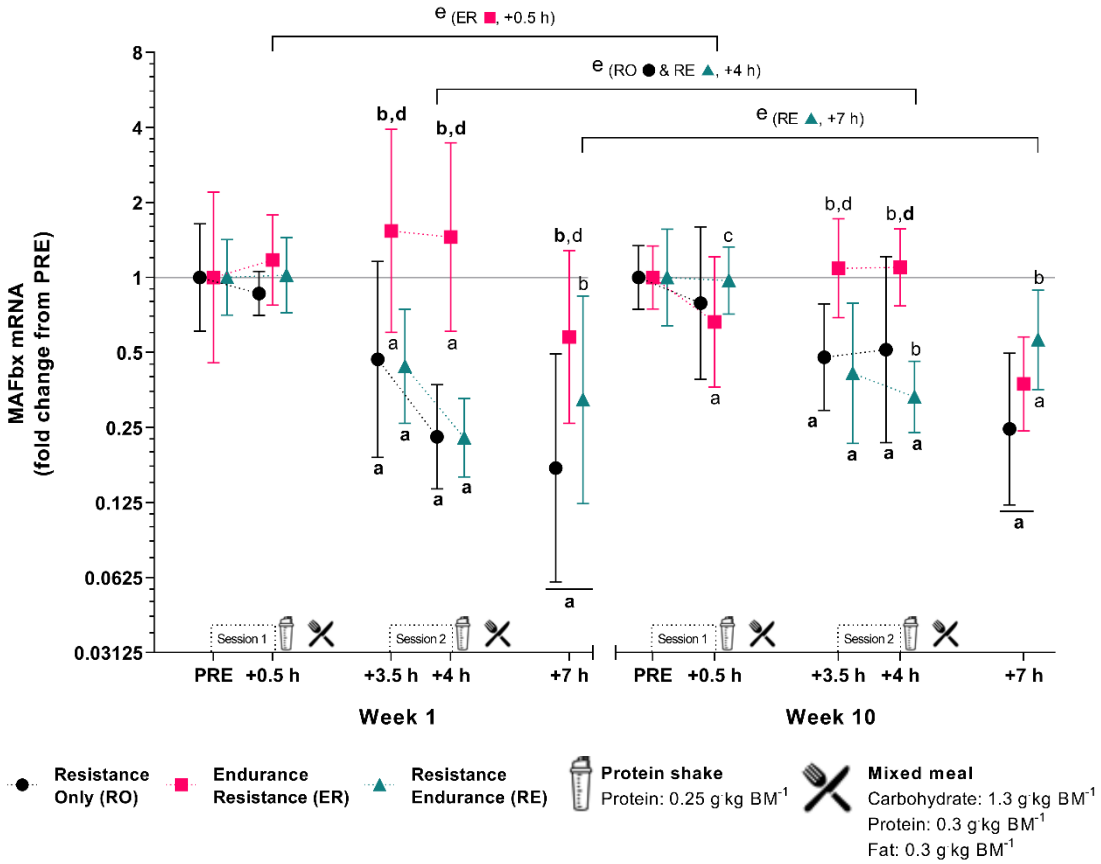


Figure 4.9 - The time-course of changes in MAFbx expression following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses). ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

Myostatin

Basal expression: In week 1, there were small differences at rest between *RO* and both *ER* and *RE* (both ES = 0.54); the difference between *ER* and *RE* was trivial (ES = 0.00). In week 10, there were moderate differences at rest between *RO* and both *ER* (ES = 0.77) and *RE* (ES = 0.80); the difference between *ER* and *RE* was trivial (ES = -0.03). There were no clear changes in basal myostatin expression between weeks for any group.

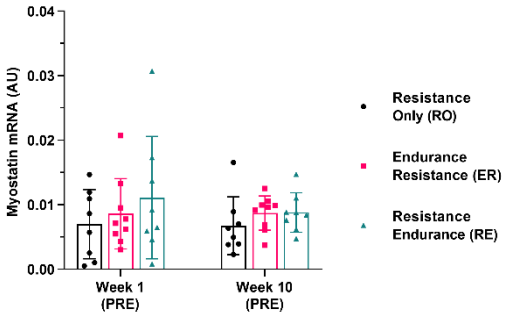


Figure 4.10 - Basal myostatin expression in week 1 and week 10. Data are group mean ± SD in arbitrary units.

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, there were no clear changes in myostatin expression at any timepoint. In *ER*, myostatin decreased at +4 h (0.65 ×/÷1.32 [-0.42 ±0.47]). In *RE*, myostatin increased at +0.5 h (1.56 ×/÷1.83 [0.43 ±0.49]) and decreased at +7 h (0.38 ×/÷1.20 [-0.94 ±0.49]). **Week 10:** In *RO*, myostatin decreased at +3.5 h (0.45 ×/÷1.24 [-0.78 ±0.49]), +4 h (0.58 ×/÷1.31 [-0.52 ±0.49]) and +7 h (0.46 ×/÷1.31 [-0.75 ±0.60]). In *ER*, myostatin decreased at +3.5 h (0.57 ×/÷1.29 [-0.55 ±0.48]), +4 h (0.52 ×/÷1.26 [-0.63 ±0.47]), and +7 h (0.62 ×/÷1.34 [-0.47 ±0.51]). In *RE*, myostatin decreased at +7 h (0.65 ×/÷1.35 [-0.41 ±0.49]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, myostatin was reduced at +3.5 h in week 10 compared to week 1 (0.38 ×/÷1.30 [-0.93 ±0.70]). For *RE*, the changes in myostatin were lower in week 10 than week 1 at +0.5 h (0.58 ×/÷1.45 [-0.53 ±0.70]), +3.5 h (0.56 ×/÷1.47 [-0.56 ±0.73]) and +7 h (0.58 ×/÷2.36 [-0.53 ±0.70]). There were no clear differences between weeks for any *ER*-induced changes in myostatin.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +0.5 h, myostatin was increased in *RE* compared to *RO* (*+0.5 h*: 2.10 ×/÷3.03 [0.72 ±0.83]). At +7 h, myostatin was lower in *RE* than both *RO* (0.54 ×/÷1.48 [-0.60 ±0.77]) and *ER* (0.44 ×/÷1.35 [-0.79 ±0.70]), respectively. **Week 10:** There were no clear between-group differences for the changes in myostatin at any timepoint.

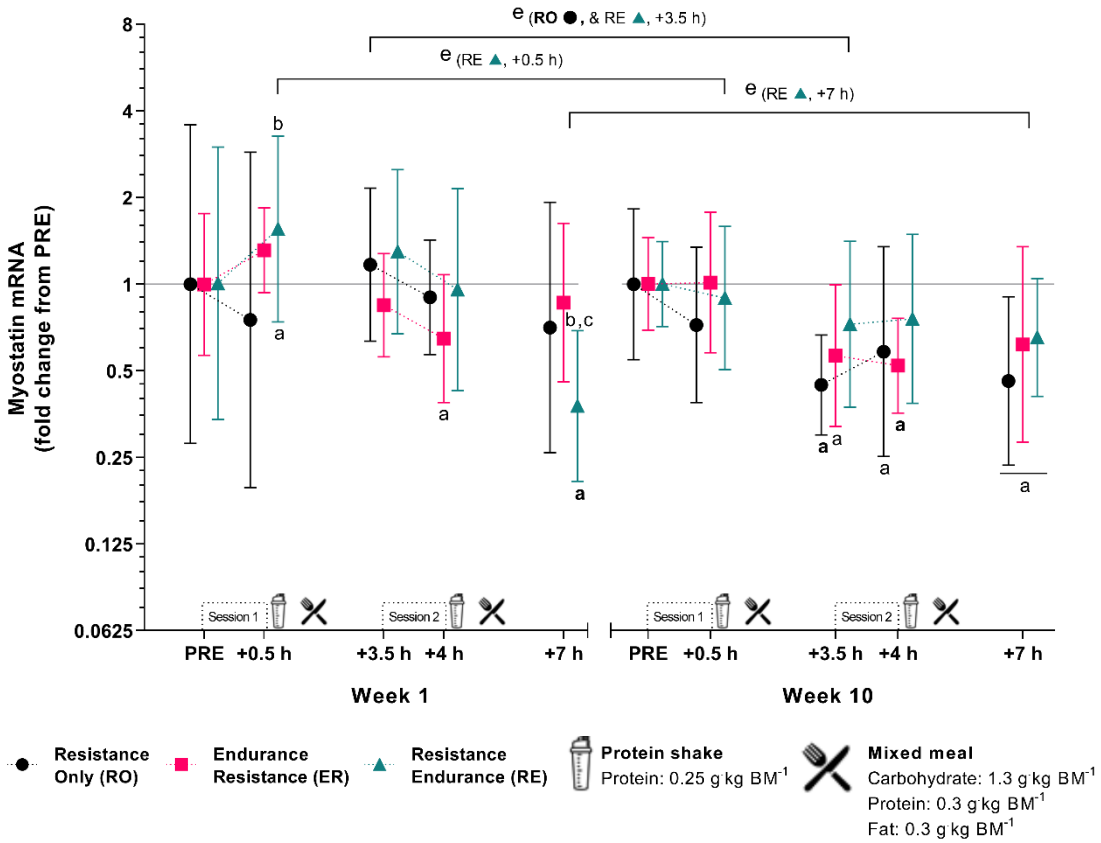


Figure 4.11 - The time-course of changes in myostatin expression following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses). ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

Mighty (akirin-1)

Basal expression: In week 1 there were moderate differences at rest between *RO* and both *ER* (ES = -1.02) and *RE* (ES = -0.68), and a small difference between *ER* and *RE* (ES = 0.34). In week 10, there were moderate differences at rest between *RO* and both *ER* (ES = -1.07) and *RE* (ES = -1.06); the difference between *ER* and *RE* was trivial (ES = 0.01). There was a small increase in basal mighty expression between weeks 1 and 10 for *ER* (1.22 ×/÷1.24 [0.40 ±0.39]); there were no clear differences between groups for any changes in basal might expression.

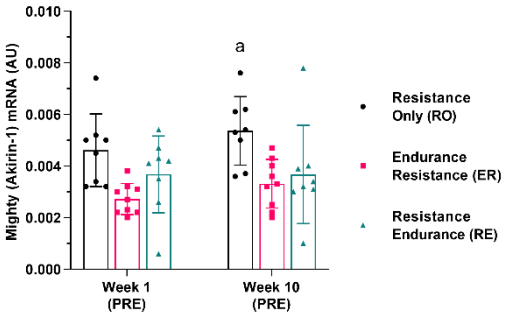


Figure 4.12 - Basal mighty expression in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10.

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, mighty increased at +3.5 h (1.83 ×/÷1.38 [1.20 ±0.41]), +4 h (1.61 ×/÷1.56 [0.94 ±0.68]) and +7 h (2.17 ×/÷1.71 [1.53 ±0.64]). In *ER*, mighty increased at all timepoints (*+0.5 h:* 1.24 ×/÷1.24 [0.43 ±0.39]; *+3.5 h*: 1.48 ×/÷1.31 [0.77 ±0.41]; *+4 h*: 1.49 ×/÷1.29 [0.79 ±0.39]; *+7 h*: 1.72 ×/÷1.34 [1.07 ±0.39]). In *RE*, mighty increased at +3.5 h (1.34 ×/÷1.30 [0.58 ±0.44]). **Week 10:** In *RO*, mighty decreased at +0.5 h (0.69 ×/÷1.23 [-0.75 ±0.65]) and increased at both +4 h (1.42 ×/÷1.49 [0.69 ±0.68]) and +7 h (1.43 ×/÷1.47 [0.71 ±0.64]). In *ER*, mighty was increased at +7 h (1.42 ×/÷1.28 [0.70 ±0.39]). In *RE*, mighty was increased at +7 h (1.73 ×/÷1.69 [1.08 ±0.77]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, the change in mighty was lower in week 10 than week 1 at +0.5 h (0.68 ×/÷1.33 [-0.78 ±0.92]), +3.5 h (0.62 ×/÷1.18 [-0.95 ±0.58]), and +7 h (0.66 ×/÷1.31 [-0.82 ±0.90]). For *ER*, the change in mighty was also lower in week 10 than week 1, at +0.5 h (0.72 ×/÷1.20 [-0.64 ±0.55]), +3.5 h (0.76 ×/÷1.22 [-0.55 ±0.57]), and +4 h (0.75 ×/÷1.21 [-0.56 ±0.55]). There were no clear differences between weeks for *RE*-induced changes in mighty.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +3.5 h, the increased in mighty following *RE* was lower than *RO* (0.73 ×/÷1.22 [-0.62 ±0.60]). Mighty was reduced in *RE* compared to both *RO* and *ER* at +4 h (*vs RO*: 0.53 ×/÷1.27 [-1.26 ±0.99]; *vs ER*: 0.57 ×/÷1.25 [-1.12 ±0.84]) and +7 h (*vs RO*: 0.55 ×/÷1.28 [-1.18 ±0.98]; *vs ER*: 0.70 ×/÷1.31 [-0.72 ±0.85]), respectively. **Week 10:** There were no clear between-group differences for the changes in mighty at any timepoint.

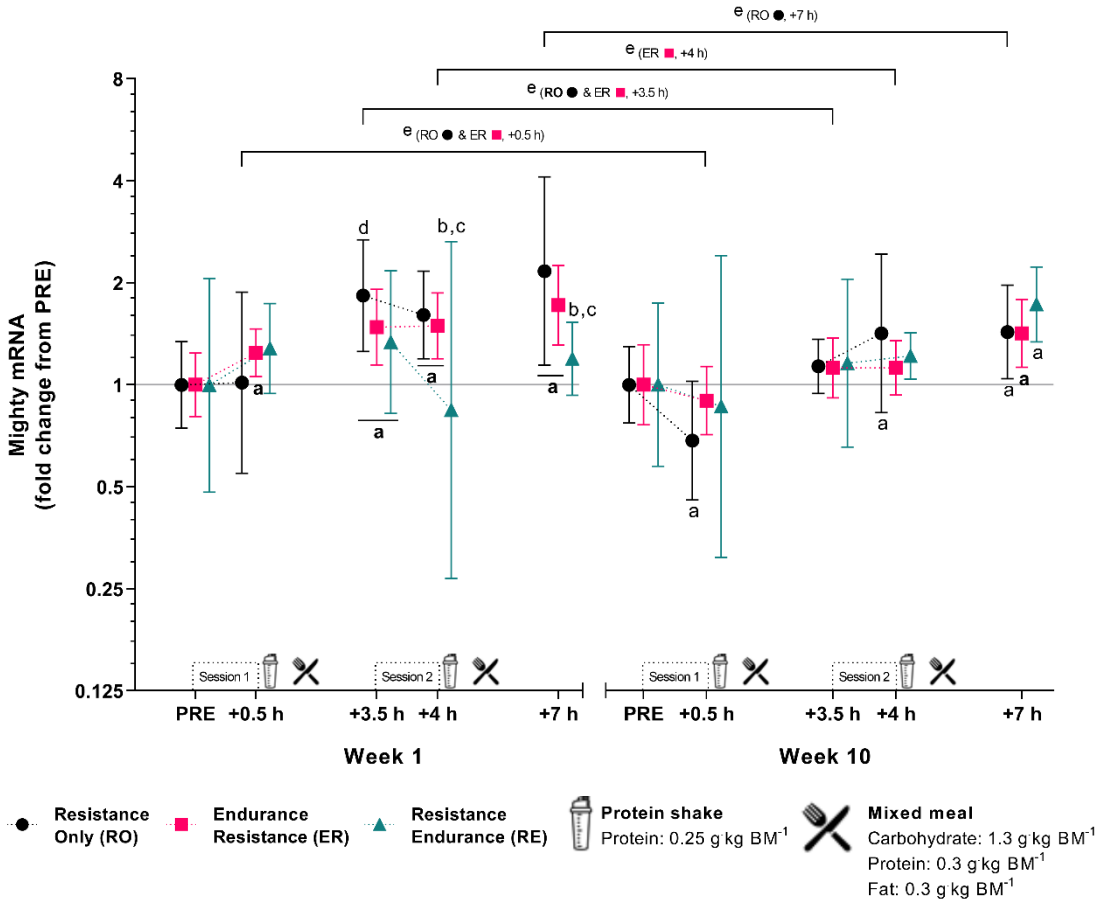


Figure 4.13 - The time-course of changes in mighty expression following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses). ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

Protein phosphorylation responses to exercise and training

p-Akt^{ser473}

Basal phosphorylation: In week 1 there were small differences at rest between *RO* and both *ER* (ES = -0.48), and *RE* (ES = 0.28), and a moderate difference between *ER* and *RE* (ES = -0.76). In week 10, there were small differences at rest between *ER* and both *RO* (ES = 0.34) and *RE* (ES = -0.56), and a moderate difference between *RO* and *RE* (ES = 0.89). Both *RO* (0.38 ×/÷1.18 [-0.92 ±0.44]) and *RE* (0.65 ×/÷1.36 [-0.40 ±0.49]) elicited reductions in basal p-Akt with training. The *RO* training-induced change in basal p-Akt was greater than both *ER* (2.27 ×/÷2.47 [0.78 ±0.58]) and *RE* (1.73 ×/÷2.26 [0.52 ±0.64]).

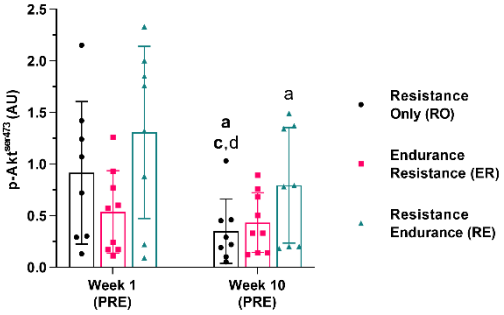


Figure 4.14 - Basal p-Akt^{ser473} abundance in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. ***Bold*** *letter indicates effects remained clear after adjusting for multiple comparisons.*

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, p-Akt decreased at +3.5 h (0.38 ×/÷1.15 [-0.91 ±0.35]) and +4 h (0.66 ×/÷1.31 [-0.39 ±0.43]). In *ER*, p-Akt increased at +4 h (2.00 ×/÷1.72 [0.66 ±0.33]) and +7 h (1.84 ×/÷1.66 [0.58 ±0.33]). In *RE*, p-Akt decreased at +3.5 h (0.40 ×/÷1.15 [-0.87 ±0.35]). **Week 10:** In *RO*, p-Akt increased at +7 h (2.36 ×/÷1.90 [0.81 ±0.35]). In *ER*, p-Akt increased at +0.5 h (1.69 ×/÷1.61 [0.50 ±0.33]), +4 h (1.91 ×/÷1.68 [0.61 ±0.33]), and +7 h (2.18 ×/÷1.78 [0.74 ±0.33]). In *RE*, p-Akt increased at +4 h (1.51 ×/÷1.61 [0.39 ±0.37]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, p-Akt was lower in week 1 than week 10 at +3.5 h (3.47 ×/÷2.92 [1.18 ±0.50]), +4 h (1.89 ×/÷2.30 [0.60 ±0.61]), and +7 h (2.38 ×/÷2.32 [0.82 ±0.50]). For *ER*, at +3.5 h, p-Akt was reduced in week 1 and increased in week 10 (1.67 ×/÷1.87 [0.48 ±0.47]). For *RE*, the reduction of p-Akt in week 1 was attenuated in week 10, at +3.5 h (2.23 ×/÷2.23 [0.76 ±0.50]) and +4 h (1.69 ×/÷1.99 [0.50 ±0.53]).

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: p-Akt was greater in *ER* than both *RO* and *RE* at +3.5 h (*vs RO:* 1.97 ×/÷2.06 [0.64 ±0.48]; *vs RE:* 1.89 ×/÷1.28 [0.61 ±0.48]), +4 h (*vs RO:* 3.02 ×/÷2.80 [1.04 ±0.53]; *vs RE:* 2.27 ×/÷1.24 [0.77 ±0.49]), and +7 h (*vs RO:* 1.86 ×/÷1.99 [0.58 ±0.48]; *vs RE:* 1.79 ×/÷1.41 [0.54 ±0.63]). **Week 10:** At +7 h p-Akt was lower in *RE* than both *RO* (0.40 ×/÷1.30 [-0.86 ±0.65]) and *ER* (0.43 ×/÷1.31 [-0.79 ±0.63]).

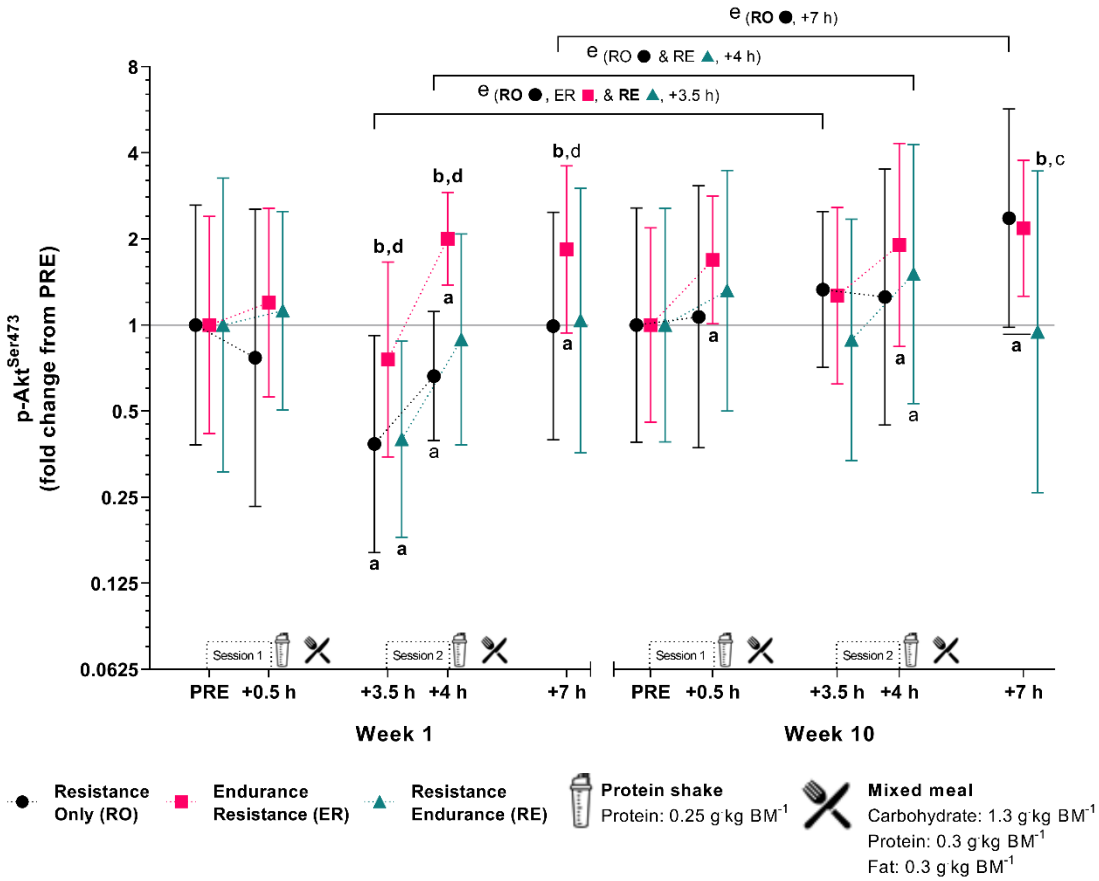


Figure 4.15 - The time-course of changes in p-Akt^{ser473} phosphorylation following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses). ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

p-mTOR^{ser2448}

Basal phosphorylation: In week 1 there were moderate differences at rest between *ER* and both *RO* (ES = 0.65) and *RE* (ES = 0.97), and a small difference between RO and RE (ES = 0.31). In week 10, there were moderate differences at rest between *RE* and both *RO* (ES = -0.64) and *ER* (ES = -0.67), and a trivial difference between *RO* and *ER* (ES = -0.02). *RO* training led to a reduction in basal p-mTOR (0.64 ×/÷1.29 [-0.67 ±0.66]).

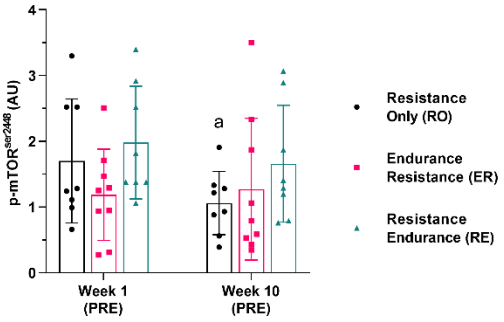


Figure 4.16 - Basal p-mTOR^{ser2448} in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10.

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, p-mTOR decreased at +0.5 h (0.61 ×/÷1.21 [-0.76 ±0.52]), increased at +4 h (1.47 ×/÷1.51 [0.59 ±0.52]), and decreased at +7 h (0.43 ×/÷1.33 [-1.28 ±1.08]). In *ER*, p-mTOR decreased at +7 h (0.47 ×/÷1.40 [-1.14 ±1.17]). In *RE*, p-mTOR decreased at +0.5 h (0.60 ×/÷1.24 [-0.78 ±0.59]), +4 h (0.62 ×/÷1.30 [-0.73 ±0.72]), and +7 h (0.54 ×/÷1.36 [-0.94 ±0.96]). **Week 10:** In *RO*, p-mTOR decreased at +0.5 h (0.74 ×/÷1.26 [-0.47 ±0.52]) and increased at +4 h (1.49 ×/÷1.52 [0.61 ±0.52]). In *ER*, p-mTOR decreased at +0.5 h (0.70 ×/÷1.24 [-0.55 ±0.51]) and +7 h (0.31 ×/÷1.26 [-1.77 ±1.17]). In *RE*, p-mTOR decreased at +0.5 h (0.66 ×/÷1.26 [-0.63 ±0.59]). **Week 1 vs Week 10:** There were no clear differences between weeks in any group for the exercise-induced changes in p-mTOR.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +0.5 h, compared to *ER*, p-mTOR was lower in both *RO* (0.63 ×/÷1.79 [-0.71 ±0.72]) and *RE* (0.61 ×/÷1.32 [-0.74 ±0.76]). At +4 h, compared to *RO*, p-mTOR was lower in both *ER* (0.69 ×/÷1.33 [-0.58 ±0.71]) and *RE* (0.42 ×/÷1.26 [-1.32 ±0.88]); p-mTOR was also lower in the *RE* group than *ER* (0.61 ×/÷1.37 [-0.75 ±0.86]). **Week 10:** At +4 h, compared to *RO*, p-mTOR was lower in *ER* (0.66 ×/÷1.32 [-0.62 ±0.71]) and *RE* (0.51 ×/÷1.31 [-1.03 ±0.88]). At +7 h, p-mTOR was also greater in the *RE* group than *ER* (3.02 ×/÷4.39 [1.68 ±1.47]).

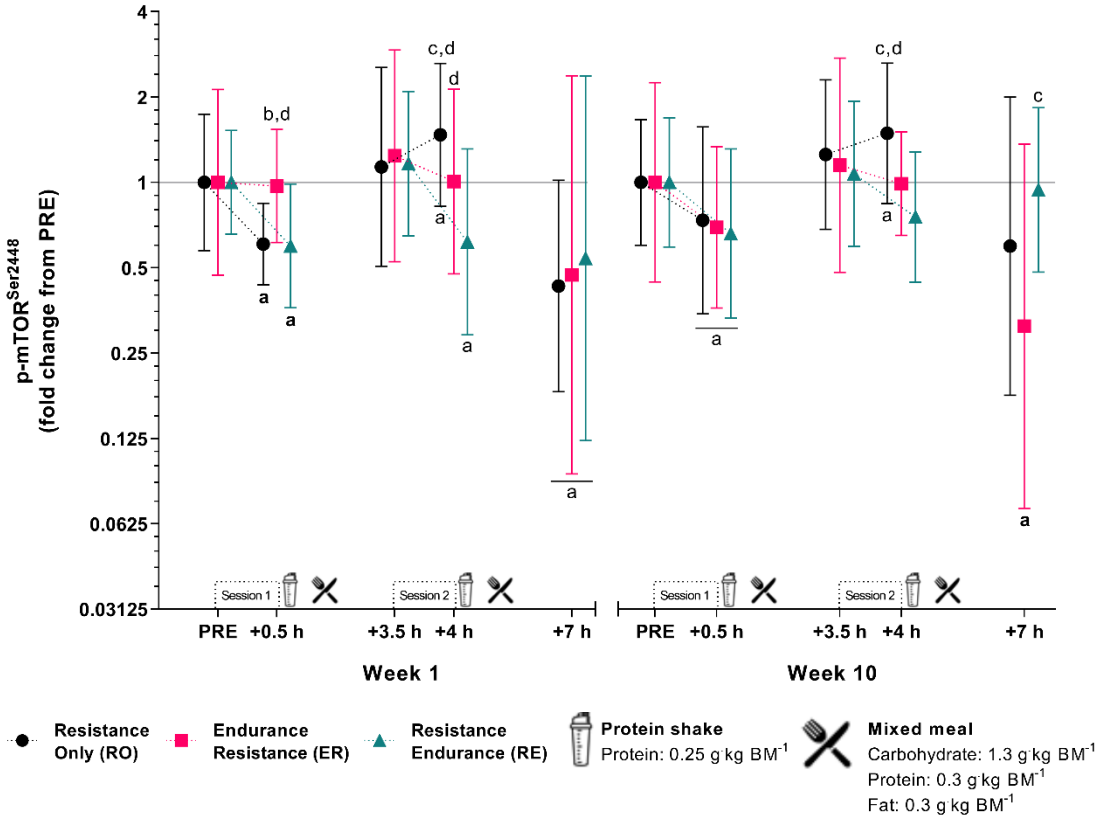


Figure 4.17 - The time-course of changes in p-mTOR^{ser2448} phosphorylation *following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses).* ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

p-eEF2^{thr56}

Basal phosphorylation: In week 1 there were small differences at rest between *RE* and both *RO* (ES = -0.25) and *RE* (ES = 0.39), and a trivial difference between *RO* and *ER* (ES = -0.14). In week 10, there were moderate differences at rest between *ER* and both *RO* (ES = 0.71) and *RE* (ES = -1.17), and a small difference between *RO* and *ER* (ES = 0.46). All groups elicited reductions in basal p-eEF2 following training (*RO:* 0.50 ×/÷1.23 [-0.98 ±0.64]; *ER*: 0.26 ×/÷1.20 [-1.96 ±1.03]; *RE:* 0.70 ×/÷1.29 [-0.51 ±0.58]). The training-induced reduction in p-eEF2 was greater in *ER* than *RO* (0.51 ×/÷1.45 [-0.98 ±1.14]) and *RE* (0.36 ×/÷3.38 [-1.45 ±1.12]).

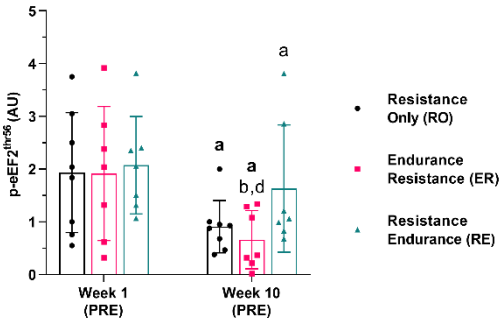


Figure 4.18 - Basal p-eEF2^{thr56} in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10; b = change from PRE is substantially different from RO; d = change from PRE is substantially different from RE. ***Bold*** *letter indicates effects remained clear after adjusting for multiple comparisons.*

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, p-eEF2 decreased at +0.5 h (0.43 ×/÷1.22 [-1.20 ±0.69]), +4 h (0.62 ×/÷1.19 [-0.68 ±0.42]), and +7 h (0.32 ×/÷1.22 [-1.64 ±0.93]). In *ER*, p-eEF2 decreased at +3.5 h (0.52 ×/÷1.33 [-0.94 ±0.86]), and +7 h (0.21 ×/÷1.22 [-2.25 ±1.32]). In *RE*, p-eEF2 decreased at +3.5 h (0.71 ×/÷1.19 [-0.49 ±0.37]), and +7 h (0.26 ×/÷1.19 [-1.95 ±0.98]). **Week 10:** In *RO*, p-eEF2 increased at +0.5 h (1.56 ×/÷1.38 [0.64 ±0.35]) and decreased at +7 h (0.58 ×/÷1.41 [-0.78 ±0.93]). In *ER*, p-eEF2 increased at +0.5 h (2.47 ×/÷2.14 [1.30 ±0.64]) and +4 h (1.59 ×/÷2.00 [0.66 ±0.85]). There were no clear *RE*-induced changes in p-eEF2 at any timepoint. **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, p-eEF2 was greater in week 10 than week 1 at +0.5 h (1.54 ×/÷1.54 [0.62 ±0.49]), +3.5 h (2.90 ×/÷3.12 [1.53 ±0.97]), and +4 h (1.81 ×/÷1.77 [0.85 ±0.59]). For *ER*, p-eEF2 was greater in week 10 than week 1 at +0.5 h (2.11 ×/÷2.42 [1.07 ±0.90]) and +3.5 h (2.91 ×/÷3.78 [1.53 ±1.22]). For *RE*, p-eEF2 was lower in week 1 than week 10 at +3.5 h (0.74 ×/÷1.50 [-0.43 ±0.52]) and +7 h (0.29 ×/÷4.88 [-1.76 ±1.39]).

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +3.5 h, p-eEF2 was greater in *RE* than *RO* (1.64 ×/÷1.92 [0.71 ±0.77]). At +4 h, compared to *RO*, p-eEF2 was greater in both *ER* (1.72 ×/÷2.19 [0.77 ±0.93]) and *RE* (1.59 ×/÷1.94 [0.67 ±0.80. **Week 10:** At +0.5 h, p-eEF2 was greater in *ER* than *RO* (1.58 ×/÷1.81 [0.66 ±0.71]) and *RE* (2.70 ×/÷1.19 [1.44 ±0.72]); p-eEF2 was also greater in *RO* than *RE* (1.72 ×/÷1.21 [0.79 ±0.51]).

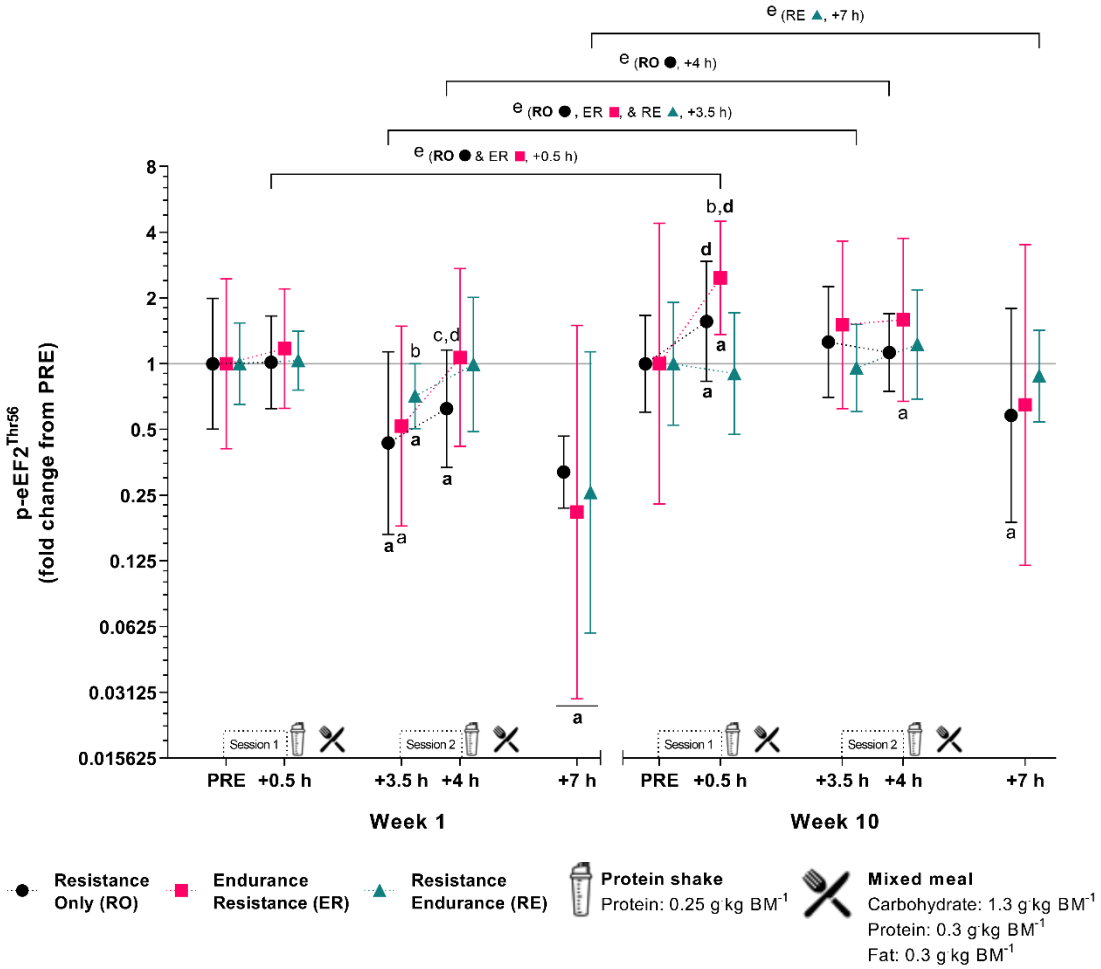


Figure 4.19 - The time-course of changes in p-eEF2^{thr56} phosphorylation *following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses).* ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

p-4E-BP1$^{thr37/46}$

Basal phosphorylation: In week 1 there were moderate differences at rest between *ER* and both *RO* (ES = -0.67) and *RE* (ES = -0.99), and a small difference between *RO* and *RE* (ES = 0.32). In week 10, there were small differences at rest between *RO* and both *ER* (ES = -0.32) and *RE* (ES = 0.36), and a moderate difference between *ER* and *RE* (ES = -0.68). Both *RO* (0.66 ×/÷1.14 [-0.71 ±0.36]) and *RE* (0.63 ×/÷1.12 [-0.78 ±0.33]) elicited reductions in basal p-4E-BP1 with training. The *RE*-induced change in basal p-4E-BP1 was different from *ER* (0.74 ×/÷1.29 [-0.52 ±0.65]).

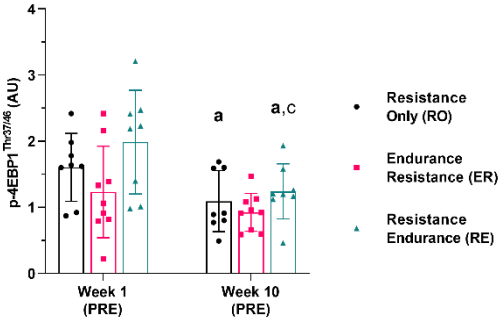


*Figure 4.20 - Basal p-4EBP1$^{thr37/46}$ abundance in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10; c = change from PRE is substantially different from ER. **Bold** letter indicates effects remained clear after adjusting for multiple comparisons.*

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, p-4E-BP1 decreased at all timepoints (*+0.5 h:* 0.41 ×/÷1.16 [-1.53 ±0.65]; *+3.5 h*: 0.69 ×/÷1.25 [-0.64 ±0.61]; *+4 h*: 0.68 ×/÷1.14 [-0.67 ±0.35]; *+7 h*: 0.65 ×/÷1.13 [-0.73 ±0.33]). In *ER*, p-4E-BP1 decreased at +0.5 h (0.32 ×/÷1.08 [-1.98 ±0.45]), +3.5 h (0.73 ×/÷1.16 [-0.53 ±0.37]) and +4 h (0.34 ×/÷1.09 [-1.85 ±0.46]). In *RE*, p-4E-BP1 decreased at all timepoints (*+0.5 h:* 0.34 ×/÷1.08 [-1.84 ±0.42]; *+3.5 h*: 0.62 ×/÷1.22 [-0.81 ±0.60]; *+4 h*: 0.23 ×/÷1.08 [-2.50 ±0.59]; *+7 h*: 0.62 ×/÷1.16 [-0.82 ±0.45]). **Week 10:** In *RO*, p-4E-BP1 decreased at both +0.5 h (0.50 ×/÷1.19 [-1.20 ±0.65]) and +3.5 h (0.75 ×/÷1.28 [-0.48 ±0.61]). In *ER*, p-4E-BP1 decreased at both +0.5 h (0.39 ×/÷1.60 [-1.60 ±0.45]), and +4 h (0.66 ×/÷1.18 [-0.71 ±0.46]) and increased at +7 h (1.35 ×/÷1.34 [0.52 ±0.42]). In *RE*, p-4E-BP1 was reduced at both +0.5 h (0.56 ×/÷1.14 [-1.00 ±0.42]), and +4 h (0.43 ×/÷1.15 [-1.46 ±0.59]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, p-4E-BP1 was reduced less in week 10 than week 1 at +4 h (1.26 ×/÷1.37 [0.40 ±0.49]) and +7 h (1.48 ×/÷1.40 [0.67 ±0.46]). For *ER*, p-4E-BP1 was reduced less in week 10 than week 1 at +3.5 h (1.29 ×/÷1.41 [0.43 ±0.53]) and +4 h (1.95 ×/÷1.76 [1.14 ±0.65]) and increased more at +7 h (1.51 ×/÷1.53 [0.70 ±0.59]). For *RE*, p-4E-BP1 was reduced less in week 10 at +0.5 h (1.63 ×/÷1.57 [0.84 ±59]), +4 h (1.83 ×/÷1.94 [1.04 ±0.84]), and +7 h (1.48 ×/÷1.56 [0.68 ±0.63]).

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +4 h, compared to *RO*, p-4E-BP1 was lower in *ER* (0.50 ×/÷1.17 [-1.19 ±0.56]) and *RE* (0.34 ×/÷1.14 [-1.83 ±0.67]); p-4E-BP1 was also lower in *RE* than *ER* (0.69 ×/÷1.30 [-0.64 ±0.73]). At +7 h, p-4E-BP1 greater in *ER* than *RO* (1.38 ×/÷1.43 [0.54 ±0.52]) and *RE* (1.45 ×/÷1.25

[0.63 ±0.60]). **Week 10:** At +0.5 h, p-4E-BP1 was greater in *RE* than *ER* (1.42 ×/÷1.51 [0.60 ±0.60]). At +4 h, compared to *RO*, p-4E-BP1 was lower in *ER* (0.77 ×/÷1.26 [-0.44 ±0.56]) and *RE* (0.50 ×/÷1.20 [-1.19 ±0.67]); p-4E-BP1 was also lower in *RE* than *ER* (0.65 ×/÷1.28 [-0.75 ±0.73]). At +7 h, p-4E-BP1 was greater in *ER* compared to both *RO* (1.41 ×/÷1.43 [0.58 ±0.52]) and *RE* (1.47 ×/÷1.24 [0.66 ±0.60]).

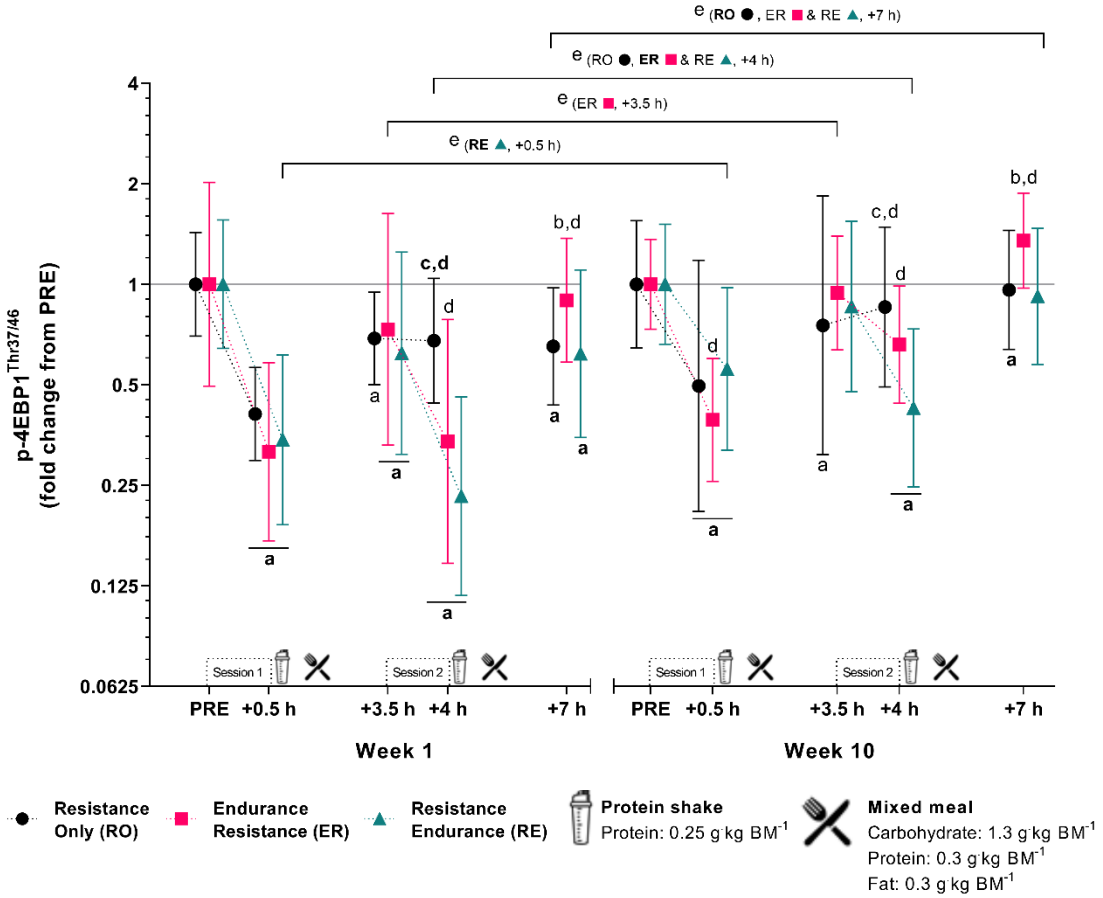


Figure 4.21 - The time-course of changes in p-4E-BP1$^{thr37/46}$ phosphorylation *following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses).* ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

p-rpS6$^{ser235/236}$

Basal phosphorylation: In week 1 there were small differences at rest between *RO* and both *ER* (ES = -0.59) and *RE* (ES = 0.53), and a trivial difference between *ER* and *RE* (ES = -0.05). In week 10, there were trivial differences at rest between *RE* and both *RO* (ES = -0.16) and *ER* (ES = -0.17), and a small difference between *RO* and *ER* (ES = -0.24). All groups elicited moderate-to-large reductions in basal p-rpS6 (*RO*: 0.29 ×/÷1.22 [-1.45 ±0.83]; *ER*: 0.38 ×/÷1.29 [-1.14 ±0.82]; *RE*: 0.39 ×/÷1.24 [-1.10 ±0.69]), with no clear differences between groups for the training-induced changes.

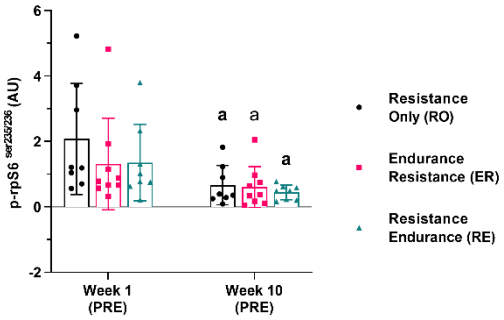


Figure 4.22 - Basal p-rpS6$^{ser235/236}$ abundance in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10. ***Bold*** *letter indicates effects remained clear after adjusting for multiple comparisons.*

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, p-rpS6 decreased at +0.5 h (0.53 ×/÷1.32 [-0.75 ±0.67]). In *ER*, p-rpS6 increased at +7 h (2.55 ×/÷3.09 [1.10 ±0.88]). There were no clear *RE*-induced changes in p-rpS6. **Week 10:** In *RO*, p-rpS6 increased at +3.5 h (1.81×/÷2.46 [0.70 ±0.87]), +4 h (1.87 ×/÷2.45 [0.74 ±0.88]), and +7 h (1.81 ×/÷2.09 [0.70 ±0.67]). In *ER*, p-rpS6 increased at +7 h (2.60 ×/÷3.14 [1.13 ±0.88]). There were no clear *RE*-induced changes in p-rpS6. **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, p-rpS6 was reduced in week 1 and increased in week 10, with moderate differences between weeks at +0.5 h (2.60 ×/÷3.33 [1.13 ±0.95]) and +7 h (2.26 ×/÷3.02 [0.96 ±0.95]). For both *ER* and *RE*, there were no clear differences between weeks for the exercise-induced changes in p-rpS6.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +0.5 h, p-rpS6 was greater in *ER* than *RO* (2.07 ×/÷2.93 [0.86 ±0.98]). At +7 h, p-rpS6 was greater in *ER* compared to both *RO* (3.18 ×/÷4.40 [1.36 ±1.09]) and *RE* (2.33 ×/÷1.51 [1.01 ±1.19]). **Week 10:** There were no clear differences between groups at any timepoint.

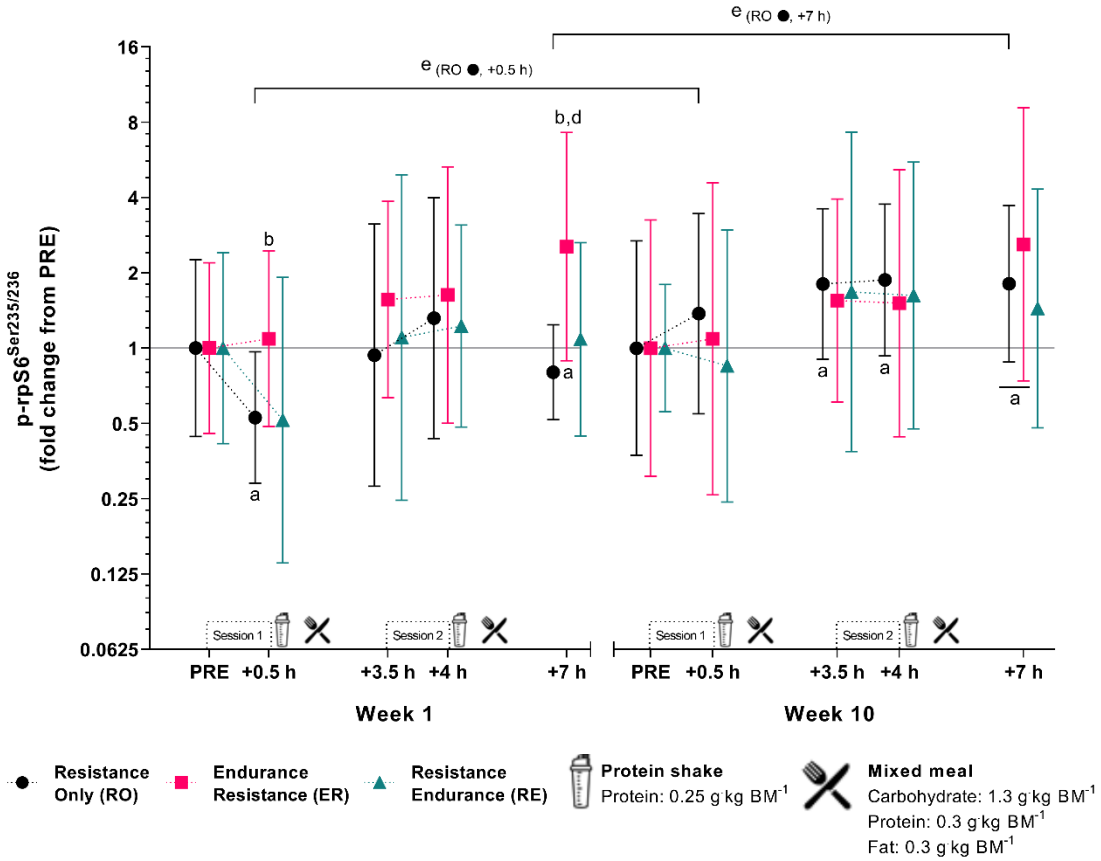


Figure 4.23 - The time-course of changes in p-rpS6$^{ser235/236}$ phosphorylation *following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses).* ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

p-TSC2^{thr1462}

Basal phosphorylation: In week 1 there were small differences at rest between *RO* and both *ER* (ES = -0.26) and *RE* (ES = 0.42), and a moderate difference between *ER* and *RE* (ES = -0.68). In week 10, there were small differences at between *RE* and both *RO* (ES = -0.53) and *ER* (ES = 0.53), and a trivial difference between *RO* and *RE* (ES = -0.10). There were no clear training-induced changes in basal p-TSC2 phosphorylation or any group.

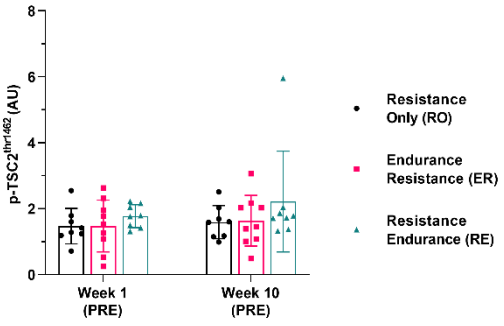


Figure 4.24 - Basal p-TSC2^{thr1462} abundance in week 1 and week 10. Data are group mean ± SD in arbitrary units.

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, p-TSC2 decreased at +7 h (0.26 ×/÷1.29 [-2.53 ±1.78]). In both *ER* and *RE*, p-TSC2 decreased at +4 h (*ER*: 0.50 ×/÷1.35 [-1.32 ±1.25]; *RE*: 0.51 ×/÷1.29 [-1.25 ±1.02]) and +7 h (*ER*: 0.10 ×/÷1.15 [-4.31 ±2.28]; *RE*: 0.16 ×/÷1.19 [-3.49 ±1.96]). **Week 10:** There were no clear changes in p-TSC2 in *RO*. In *ER*, p-TSC2 decreased at +0.5 h (0.51 ×/÷1.17 [-1.28 ±0.61]) and +7 h (-0.05 ×/÷1.08 [-5.53 ±2.28]). In *RE*, p-TSC2 was reduced at +0.5 h (0.67 ×/÷1.20 [-0.74 ±0.55]) and +4 h (-0.54 ×/÷1.31 [-1.16 ±1.02]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *ER*, at +0.5 h, p-TSC2 was reduced in week 10 compared to week 1 (0.49 ×/÷1.23 [-1.35 ±0.86]). For both *RO* and *RE*, there were no clear differences between weeks for any exercise-induced changes in p-TSC2.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: There no clear differences between any of the groups at any timepoint, for the changes in p-TSC2. **Week 10:** At +3.5 h, p-TSC2 was reduced more in both concurrent groups than *RO* (*vsER*: 0.75 ×/÷1.28 [-0.55 ±0.69]; *vsRE*: 0.78 ×/÷1.27 [-0.47 ±0.65]). At +7 h, p-TSC2 was reduced more in *ER* than both *RO* (0.11 ×/÷1.19 [-4.10 ±2.44]) and *RE* (0.12 ×/÷20.30 [-4.03 ±2.91]).

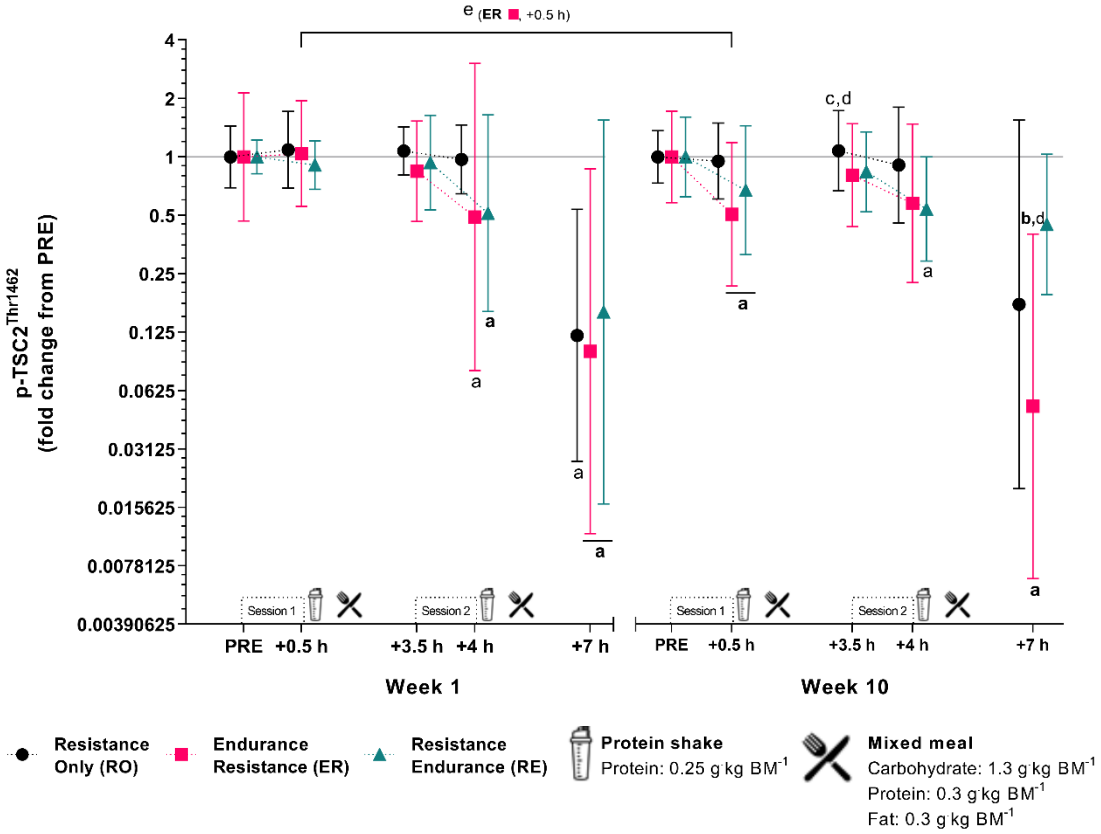


Figure 4.25 - The time-course of changes in p-TSC2^{thr1462} phosphorylation *following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses).* ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

p-AMPKα^{thr172}

Basal phosphorylation: In week 1 there were moderate differences at rest between *ER* and both *RO* (ES = -0.80) and *RE* (ES = -0.61), and a trivial difference between *RO* and *RE* (ES = -0.19). In week 10, there was a trivial difference at rest between *RO* and *ER* (ES = 0.14), and small differences between *ER* and both *RO* (ES = -0.55) *RE* (ES = 0.41). Both *RO* (0.44 ×/÷1.18 [-1.11 ±0.53]) and *RE* (0.71 ×/÷1.28 [-0.48 ±0.52]) elicited reductions in basal p-AMPKα with training. The *RO* training-induced change in basal p-AMPKα was greater than both *ER* (1.95 ×/÷1.10 [0.91 ±0.71]) and *RE* (1.59 ×/÷1.90 [0.64 ±0.74]).

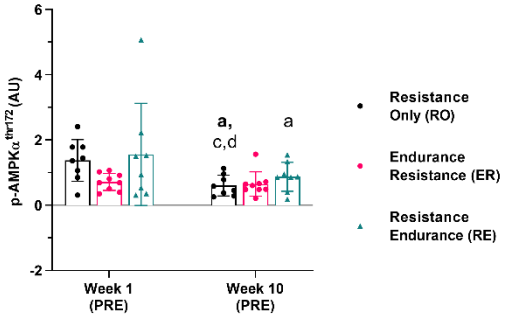


*Figure 4.26 - Basal p-AMPKα$^{thr1/2}$ abundance in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. **Bold** letter indicates effects remained clear after adjusting for multiple comparisons.*

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, p-AMPKα decreased at +3.5 h (0.36 ×/÷1.14 [-1.39 ±0.51]) and +4 h (0.71 ×/÷1.36 [-0.46 ±0.66]). In *ER*, p-AMPKα increased at +4 h (2.13 ×/÷1.77 [1.03 ±0.48]) and +7 h (1.59 ×/÷1.69 [0.64 ±0.57]). In *RE*, p-AMPKα decreased at +3.5 h (0.43 ×/÷1.17 [-1.16 ±0.51]) and increased at +7 h (1.42 ×/÷1.55 [0.96 ±0.57]). **Week 10:** In *RO*, p-AMPKα increased at both +0.5 h (1.42 ×/÷1.63 [0.48 ±0.58]) and +7 h (1.91 ×/÷1.92 [0.88 ±0.63]). In both *ER* and *RE*, p-AMPKα increased at +0.5 h (*ER*: 1.59 ×/÷1.59 [0.63 ±0.49]; *RE*: 1.44 ×/÷1.56 [0.50 ±0.51]), +4 h (*ER*: 1.95 ×/÷1.71 [0.91 ±0.48]; *RE*: 1.80 ×/÷1.69 [0.80 ±0.51]), and +7 h (*ER*: 2.02 ×/÷1.88 [0.96 ±0.57]; *RE*: 1.53 ×/÷1.59 [0.58 ±0.51]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, p-AMPKα decreased from rest in week 1 and was increased in week 10 at both +0.5 h (1.94 ×/÷2.25 [0.90 ±0.83]) and +3.5 h (3.27 ×/÷2.82 [1.62 ±0.73]). For *RE*, the suppression of p-AMPKα at +3.5 h in week 1 was attenuated in week 10 (2.31 ×/÷2.29 [1.14 ±0.73]), and the increase in p-AMPKα at +4 h was greater in week 10 (1.59 ×/÷1.89 [0.64 ±0.73]). There were no clear differences between weeks for *ER*-induced changes in p-AMPKα.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +0.5 h, compare to *RO*, p-AMPKα was elevated in both *ER* (1.79 ×/÷2.04 [0.79 ±0.75]) and *RE* (1.79 ×/÷2.07 [0.79 ±0.77]). At +3.5 h, p-AMPKα was reduced in both *RO* (0.38 ×/÷2.43 [-1.33 ±0.71]) and *RE* (0.45 ×/÷1.24 [-1.09 ±0.71]) compared to *ER*. At +4 h, p-AMPKα was increased in *ER* compared to both *RO* (2.99 ×/÷2.88 [1.49 ±0.81]) and *RE* (1.89 ×/÷1.29 [0.87 ±0.71]); there was also a moderate difference between *RO* and *RE* (1.58 ×/÷2.02 [0.63 ±0.83]).

Week 10: At +4 h the increase in p-AMPKα was greater in *ER* than *RO* (1.66 ×/÷2.04 [0.69 ±0.81]).

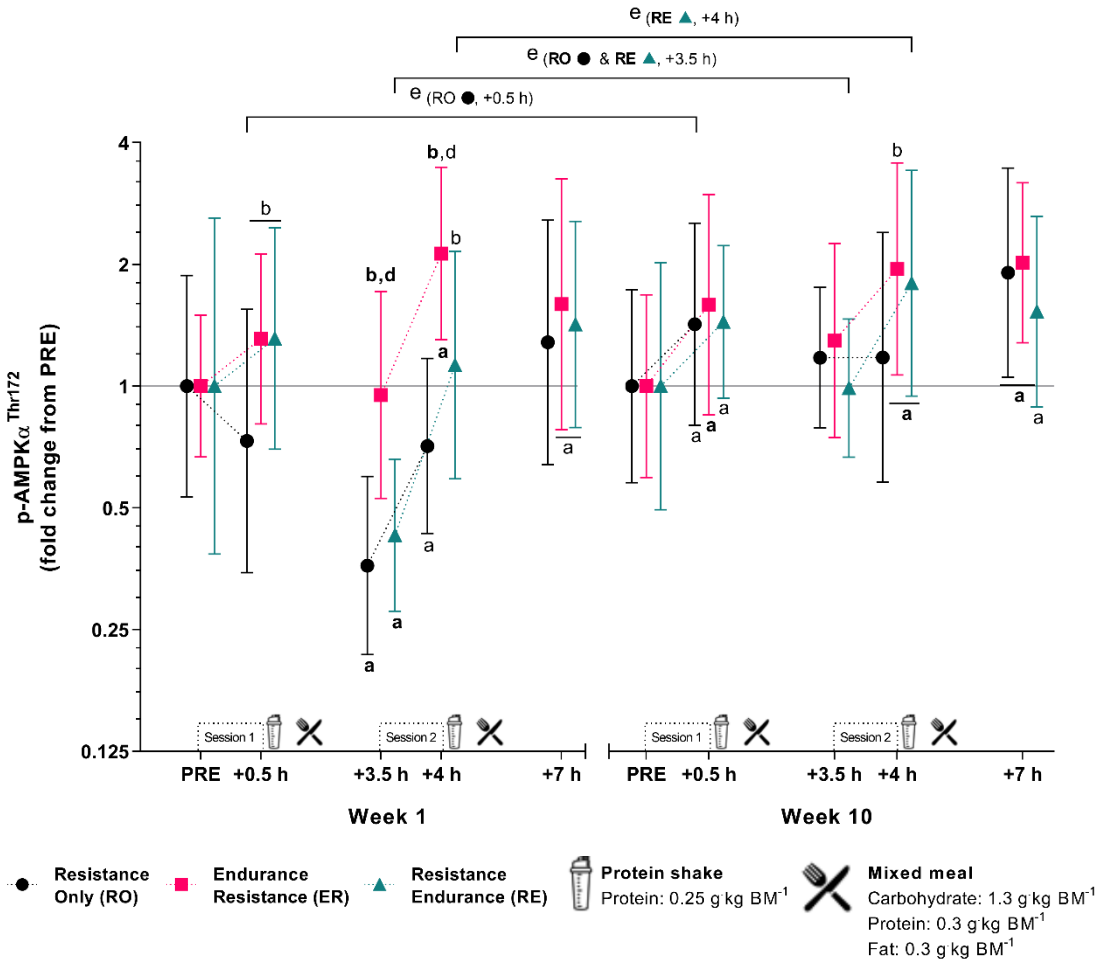


Figure 4.27 - The time-course of changes in p-AMPKα^{thr172} phosphorylation *following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses).* ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

p-p53^{ser15}

Basal phosphorylation: In week 1 there was a moderate difference at rest between *RO* and *ER* (ES = -0.62), a trivial difference between *RO* and *RE* (ES = -0.10), and a small difference between *ER* and *RE* (ES = 0.52). In week 10, there were small differences at rest between *ER* and both *RO* (ES = 0.35) and *RE* (ES = -0.44), and a moderate difference between *RO* and *RE* (ES = 0.79). Both *RO* training led to reductions in basal p-p53 (0.37 ×/÷1.19 [-0.85 ±0.43]). The *RO* training-induced change in basal p-p53 was greater than both *ER* (2.75 ×/÷2.95 [0.87 ±0.57]) and *RE* (2.18 ×/÷2.53 [0.67 ±0.56]).

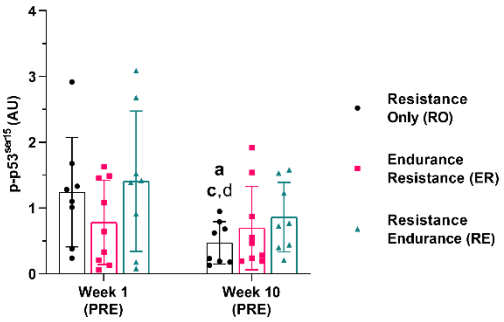


*Figure 4.28 - Basal p-p53^{ser15} abundance in week 1 and week 10. Data are group mean ± SD in arbitrary units. a = substantial change between week 1 and 10; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. **Bold** letter indicates effects remained clear after adjusting for multiple comparisons.*

Exercise-induced responses (mean fold change ×/÷90%CI [ES ±90%CI]):

Week 1: In *RO*, p-p53 decreased at +3.5 h (0.37 ×/÷1.16 [-0.86 ±0.37]) and +4 h (0.63 ×/÷1.29 [-0.40 ±0.39]). In *ER*, p-p53 increased at +4 h (2.25 ×/÷1.93 [0.70 ±0.35]) and +7 h (1.75 ×/÷1.74 [0.48 ±0.36]). In *RE*, p-p53 decreased at +3.5 h (0.48 ×/÷1.21 [-0.64 ±0.37]). **Week 10:** In *RO*, p-p53 increased at +7 h (2.31 ×/÷2.02 [0.72 ±0.37]). In *ER*, p-p53 increased at +0.5 h (1.61 ×/÷1.67 [0.41 ±0.35]), +4 h (1.67 ×/÷1.69 [0.44 ±0.35]), and +7 h (1.89 ×/÷1.08 [0.55 ±0.36]). In *RE*, p-p53 increased at +4 h (1.52 ×/÷1.67 [0.21 ±0.37]). **Week 1 vs Week 10** *(mean difference ×/÷90%CI [ES ±90%CI])*: For *RO*, p-p53 was lower in week 1 at all timepoints (*+0.5 h:* 1.88 ×/÷2.21 [0.55 ±0.52]; *+3.5 h*: 3.33 ×/÷3.14 [1.04 ±0.52]; *+4 h*: 2.14 ×/÷2.44 [0.66 ±0.55]; *+7 h*: 2.22 ×/÷2.43 [0.69 ±0.52]). For *RE*, the reduction in p-p53 in week 1 at +3.5 h was attenuated in week 10 (2.13 ×/÷2.37 [0.65 ±0.52]). There were no clear differences between weeks for *ER*-induced changes in p-p53.

Between-group differences for exercise-induced responses (mean diff ×/÷90% CI [ES ±90% CI]):

Week 1: At +0.5 h, compared to *RO*, p-p53 was greater in both *ER* (1.61 ×/÷2.00 [0.41 ±0.51]) and *RE* (1.83 ×/÷2.17 [0.52 ±0.52]). At +3.5 h, p-p53 was reduced in both *RO* (0.40 ×/÷2.55 [-0.79 ±0.51]) and *RE* (0.52 ×/÷1.32 [-0.57 ±0.51]) compared to *ER*. At +4 h, p-p53 was elevated in *ER* than both *RO* (3.57 ×/÷3.25 [1.10 ±0.51]) and *RE* (1.85 ×/÷1.33 [0.54 ±0.51]); there was also a small difference between *RO* and *RE* (1.91 ×/÷2.24 [0.56 ±0.53]). At +7 h, p-p53 was increased in *ER* compared to *RO* (1.69 ×/÷2.05 [-0.45 ±0.51]). **Week 10:** At +7 h p-p53 was lower in *RE* than *RO* (0.55 ×/÷1.35 [-0.52 ±0.52]).

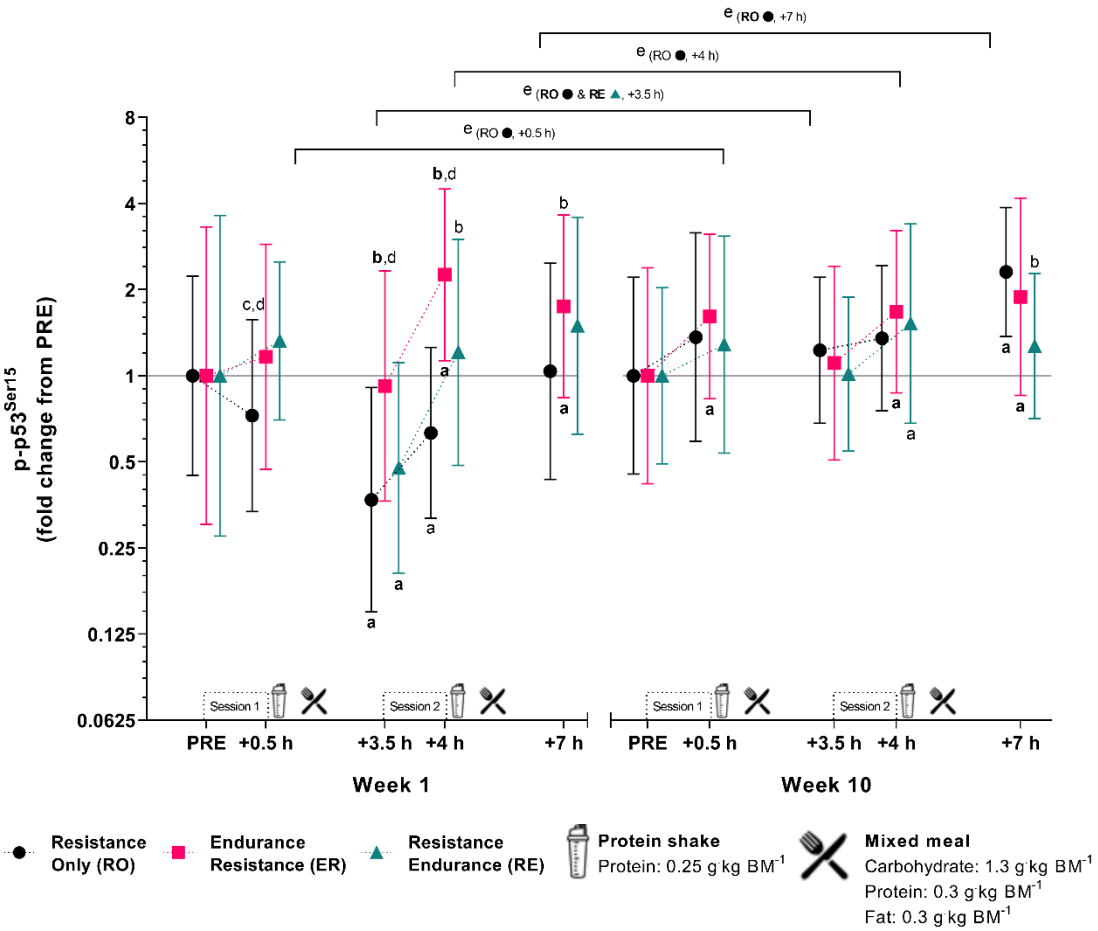


Figure 4.29 - The time-course of changes in p-p53^{ser15} phosphorylation *following resistance-only (RO, ●) and concurrent exercise (ER, endurance-resistance ■; RE, resistance-endurance ▲), both before (Week 1) and after (Week 10) training. In both weeks, muscle samples were taken at rest (PRE) and at +0.5 h, 3.5 h, 4 h, and 7 h after starting the first exercise session (the RO group rested during 'session 2'). Data are geometric mean fold change ± SD. Within-week changes: a = substantial change from PRE; b = change from PRE is substantially different from RO; c = change from PRE is substantially different from ER; d = change from PRE is substantially different from RE. Between-week comparisons: e = substantial difference between week 1 and 10 for the change from PRE at the designated timepoint (within-group, relevant groups indicated in parentheses).* ***Bold*** *letters specify effects remained clear after adjusting for multiple comparisons.*

4.4 Discussion

The aim of the present study was to elucidate the time-course of exercise-induced molecular responses to alternate concurrent exercise orders, and resistance-only exercise, performed in the fed-state, both before and after 9 weeks of structured training. The main findings were that *1)* resting muscle glycogen concentrations increased with training, irrespective of the training mode. Furthermore, muscle glycogen utilisation during resistance exercise was limited, whilst endurance exercise reduced muscle glycogen, irrespective of the order, culminating in similar overall levels of depletion in both concurrent groups. *2)* The time-course of p-AMPKα elicited some divergent between-group responses in both weeks, which also corresponded with the changes in muscle glycogen. *3)* Exercise-induced changes p-Akt mimicked p-AMPKα and appeared discordant from the time-course of p-mTOR, which remained unchanged or suppressed after the initial exercise session, regardless of mode. *4)* After the second session, p-mTOR remained unchanged or suppressed in the concurrent groups, but increased in *RO*, suggestive of a molecular interference to mTOR; however, whilst p-TSC2 was also reduced, p-AMPKα, p-Akt, and p-p53 were all elevated at the same timepoint, and p-mTOR was subsequently reduced in all groups by the end of the training day. *5)* In Week 10, myostatin was reduced over the course of the day by all exercise interventions, whilst its target of inhibition, Mighty, was similarly elevated in all groups by the end of the training day. *6)* Changes in MuRF1 and MAFbx expression immediately post-exercise elicited some divergent between-group responses; *ER* increased MuRF1 expression immediately after both modes, whilst *RE* decreased MAFbx expression after endurance exercise more so during the 3-hour recovery period. *7)* Both exercise modes increased PGC-1α expression; in Week 1 the increase was greater in *ER* than *RE* following the endurance session; this order effect was not apparent in Week 10. *8)* At both the transcriptional and post-translational levels, the time-course and magnitude of expression for several genes and proteins were diminished in Week 10, compared to Week 1.

Muscle Glycogen

Resting muscle glycogen concentrations increased after training in all groups, regardless of the mode. This has been previously demonstrated following both short-term, intense endurance training (Benziane et al., 2008) and a prolonged period of heavy resistance training (MacDougall et al., 1977). Another study also reported increased resting muscle glycogen concentrations after 5 weeks of concurrent, but not resistance-only, training (Lundberg et al., 2014). As such, the present study also supports that following both resistance-only and concurrent training (irrespective of order), the capacity to store muscle glycogen is increased.

In both weeks, the initial leg press session had no clear effect on muscle glycogen; this was also reported in a similar study from our lab, in which muscle glycogen remained unchanged in the 3

hours following resistance exercise (Fyfe et al., 2016b). In the present study, the cycling sessions induced similar levels of glycogen depletion in both groups (~20 to 30%) in both weeks, and these changes are comparable to other concurrent training studies (Apró et al., 2015, Lundberg et al., 2014). In Week 1, despite having consumed a mixed meal during the 3-hour recovery period after the initial exercise session, muscle glycogen was lower at +3.5 hours in the *ER* group than both *RE* and *RO*, indicative of greater muscle glycogen utilisation during the endurance session than the resistance session. However, this response was diminished at the same time-point in Week 10, where muscle glycogen was restored to near-resting levels in *ER* group (Figure 4.2); this suggests an improved capacity to restore muscle glycogen post-exercise following training.

In Weeks 1 and 10, both concurrent groups displayed a similar level of muscle glycogen depletion at the end of each day, whilst muscle glycogen in the *RO* group remained elevated (Week 1) or unchanged (Week 10) from baseline. These discrepancies may reflect an insufficiency of the prescribed diet to meet the demands of the concurrent sessions, compared to the single resistance exercise session. Indeed, the concurrent groups performed a greater total volume of work than the *RO* group – an inherent factor of concurrent training research investigating the effects of additional endurance exercise on resistance training adaptations. The three standardised meals (expressed in grams per kilogram of body mass) provided ~1.3 g·kg BM^{-1} carbohydrate, ~0.3 g·kg BM^{-1} protein, and ~0.3 g·kg BM^{-1} fat, for a total daily intake of ~4.0 g·kg BM^{-1} carbohydrate; ~1.5 g·kg BM^{-1} protein, and ~1.0 g·kg BM^{-1} fat. These values are comparable to typical intakes of endurance, strength, and team sport (i.e. concurrent) athletes (Bilsborough et al., 2016, Wardenaar et al., 2017). The greater daily energy expenditure in the concurrent groups could induce an energy deficit, which has been previously shown to reduce post-absorptive rates of myofibrillar protein synthesis (Areta et al., 2014) and may compromise training-induced gains in muscle mass and strength (Hughes et al., 2018). Indeed, muscle glycogen depletion and residual fatigue induced by a prior endurance session may contribute to the interference effect, by compromising the capacity for ATP re-synthesis during subsequent high-intensity contractions in the resistance sessions, limiting resistance exercise performance, and attenuating anabolic signalling responses to mechanical loading. However, whilst low muscle glycogen availability may serve as a putative signal for molecular responses to endurance exercise (Hawley and Morton, 2014), the effect of performing resistance exercise with reduced muscle glycogen availability on anabolic signalling is uncertain. Some evidence supports attenuated Akt-mTOR phosphorylation (Creer et al., 2005), whilst others show no compromising effects on hypertrophy signalling (Churchley et al., 2007) or rates of muscle protein synthesis (Camera et al., 2012)). In the present work, despite divergent responses in muscle glycogen depletion over the course of a training day between the *RO* and concurrent groups, improvements in muscle strength and hypertrophy were not compromised in any group (explored in *Chapter 5*). Whilst the standardised meals provided on the '*experimental*'

days may not have adequately met the energy demands of both concurrent sessions, it is possible the participants' habitual diets and nutritional practices beyond the 7-hour measurement period, and throughout the training study may have negated this deficit. Unfortunately, information regarding habitual dietary intake was only available at baseline, prior to commencing the study (*see appendices*). Nonetheless, the divergent fluctuations in muscle glycogen concentration between single-mode and concurrent training further highlight the need to periodise nutrient availability according to the requirements of training (Impey et al., 2018).

AMPKα

AMPK phosphorylation has been previously associated with reductions in muscle glycogen, given its glycogen-binding domain (McBride et al., 2009). In the present study, the time-course of p-AMPKα signalling appears to correspond with the observed changes in muscle glycogen, supporting its role as an energy sensor. In Week 1, some divergent between-group responses were evident; 3 hours after the initial session, p-AMPKα was unchanged in *ER*, and reduced in both *RO* and *RE*. Reductions in p-AMPKα 3 hours after resistance exercise have also been reported elsewhere in moderately-trained individuals (Apró et al., 2013); however, others have shown resistance exercise-induced increases in AMPK phosphorylation and activity in both untrained (Coffey et al., 2006b, Dreyer et al., 2006, Wilkinson et al., 2008) and training-accustomed individuals (Vissing et al., 2013, Wilkinson et al., 2008). In the present study, exercise was performed in the fed-state, with subsequent nutrients provided during the 3-hour post-exercise recovery period. It is possible that performing the initial leg press session under such conditions did not induce sufficient metabolic stress to stimulate AMPK signalling, and the subsequent ingestion of a mixed meal may have contributed to its further suppression. Indeed, increasing amino acid and carbohydrate availability can reduce p-AMPKα (Fujita et al., 2007), and Lundberg *et al.* (2014) observed unchanged p-AMPK following resistance exercise performed in the fed-state. After training, in Week 10, the initial time-course of p-AMPKα was similar between all groups, regardless of the mode; p-AMPKα increased immediately post-exercise, before returning to baseline 3 hours later. Others have also reported signalling through AMPK (Vissing et al., 2013, Wilkinson et al., 2008) and its downstream target p-ACC (Vissing et al., 2013) to similarly increase following both endurance and resistance exercise in training-accustomed individuals.

In Week 1, after the second concurrent session, p-AMPKα was substantially elevated in the *ER* group, whilst in *RO* and *RE* p-AMPKα remained depressed and unchanged, respectively. Again, given that the *ER* group commenced their leg press session with greater muscle glycogen depletion than the *RE* group did their cycling session, the *ER* group may have experienced a greater metabolic stress than the other groups, reflected by greater elevations in p-AMPKα. However, once both concurrent groups had completed the same total volume of contractile work,

p-AMPKα increased and remained similarly elevated at +7 hours (in both weeks). This likely indicates the additional metabolic stress endured with concurrent training and corresponds with the reductions in muscle glycogen elicited at the same timepoints. The secondary rise in p-AMPKα elicited by the *RO* group in Week 10 at +7 hours was unexpected, as typically, AMPK signalling and activity are transiently increased 0-3 hours following resistance exercise (Camera et al., 2010, Dreyer et al., 2006, Drummond et al., 2008, Koopman et al., 2006, Vissing et al., 2013, Wilkinson et al., 2008), returning to baseline levels within 2.5-6 hours (Drummond et al., 2008, Vissing et al., 2013, Wilkinson et al., 2008). Furthermore, this group did not show any substantial glycogen depletion at this point, providing further confusion to this finding, for which there is no current explanation.

Akt-mTOR signalling (Akt, mTOR, 4EBP1, eEF2, rpS6)

The seminal work by Atherton *et al.* (2005), in which rodent muscle was electrically-stimulated to mimic endurance and resistance exercise, proposed that different exercise modes may selectively activate AMPK and Akt-mTOR signalling pathways respectively, and that this molecular "switch-like" mechanism may explain the attenuated resistance adaptations with concurrent training. However, in the present study, the time-course of Akt phosphorylation followed a similar pattern to that of p-AMPKα, contradicting the previous notion. However, the larger variation in individual responses elicited for this protein, indicated by the large standard deviations at several timepoints, likely resulted in fewer clear within- and between-group effects being observed. Nonetheless, in humans, evidence for selective AMPK-Akt signalling in response to different exercise modes remains elusive. Indeed, others have demonstrated comparable increases in p-Akt after endurance and resistance exercise during the early (< 4 hours) recovery period (Camera et al., 2010, Wilkinson et al., 2008), and between concurrent (*ER*) and single-mode endurance (Wang et al., 2011) and resistance exercise (Apró et al., 2015). However, similar to the results in Week 1, transient reductions in p-Akt have also been reported following both resistance-only (Apró et al., 2013, Pugh et al., 2015) and concurrent (*RE*) exercise (Pugh et al., 2015).

When interpreting the mode-specific responses in the present study, both before and after training, p-Akt was elevated 0-3 hours after the leg press session in *ER*, compared to both the *RO* and *RE*, suggesting that a prior bout of endurance exercise does not inhibit subsequent resistance-exercise induced stimulation of Akt, and may provide an additive stimulus. This is consistent with the work of Coffey *et al.*, in which *ER* induced a greater change in p-Akt than *RE* immediately after resistance exercise, when preceded by both steady-state (Coffey et al., 2009b), and repeated-sprint cycling (Coffey et al., 2009a). Given its role in activating mTORC1 signalling, by phosphorylating (and inhibiting) downstream targets such as TSC2, which represses mTORC1

activity (Inoki et al., 2002), it might be speculated that a greater resistance exercise-induced elevation in p-Akt in the *ER* group may lead to greater mTOR signalling, MPS, and ultimately hypertrophy. However, in both Weeks 1 and 10, p-mTOR remained unchanged from rest immediately after the *ER* group completed the leg press session and decreased over the subsequent 3-hour recovery period. Furthermore, in *RE* and *RO*, p-Akt remained unchanged immediately after the leg press and was reduced 3 hours later. The necessity of Akt in mediating mechanical load-induced mTOR signalling has indeed been previously questioned in both rodent (Hamilton et al., 2010, Hornberger et al., 2004, Spangenburg et al., 2008) and human models (West et al., 2010, West et al., 2009), and the present results do not suggest a clear relationship between the time course of p-Akt and mTOR signalling.

The reported time-course of mTOR phosphorylation in response to different exercise modes in humans is conflicting. Resistance exercise transiently increases p-mTOR 1 to 6 hours post-exercise (Dreyer et al., 2008, Dreyer et al., 2006, Dreyer et al., 2010, Drummond et al., 2008, Wilkinson et al., 2008) with sustained elevations evident 22 hours post-exercise in training-accustomed individuals (Vissing et al., 2013). Elevations in p-mTOR have also been reported during the early recovery period (< 4 hours) following concurrent exercise (Apró et al., 2015, Apró et al., 2013, Wang et al., 2011), as well as greater *overall* levels of p-mTOR compared to single-mode resistance exercise despite no changes over time (Fyfe et al., 2016b, Lundberg et al., 2012, Pugh et al., 2015). However, not all studies demonstrate acute changes in p-mTOR following resistance and concurrent exercise (Donges et al., 2012, Fyfe et al., 2016b), irrespective of the exercise order (Coffey et al., 2009a, Coffey et al., 2009b, Jones et al., 2016) and participant training status (Fernandez-Gonzalo et al., 2013, Wilkinson et al., 2008). In the present study, p-mTOR remained unchanged (Week 1: *ER*) or depressed (Week 1: *RO* & *RE*; Week 10: *all groups*) immediately after the first exercise bout, before returning to resting levels 3 hours later. This may reflect a temporary reduction in energy-consuming processes such as protein synthesis, which has previously been shown to be suppressed during exercise (Dreyer et al., 2006, Dreyer et al., 2008). This is supported in the present study by reductions in p-4EBP1 immediately after exercise, in both weeks. A target of mTOR, 4EBP1 represses the initiation of cap-dependent translation; hypo-phosphorylated 4EBP1 binds to eIF-4E, obstructing the assembly of the eIF-4F initiation complex, whilst p-4EBP1 dissociates from eIF-4E, relieving its inhibition on translation initiation (Gingras et al., 2001, Goodman, 2019). This study and others (Apró et al., 2015, Apró et al., 2013, Dreyer et al., 2008, Dreyer et al., 2006, Koopman et al., 2007, Koopman et al., 2006) have shown transient, exercise-induced reductions in p-4EBP1.

In addition to translation initiation, eEF2 (a marker of translation elongation) was also measured. eEF2 facilitates ribosomal translocation along mRNA, and is inhibited when phosphorylated by

its kinase, eEF2K (Wang et al., 2001). In the present study, most notably in Week 1, reductions in p-eEF2 were observed in all groups, 3 hours after both exercise sessions; this is indicative of greater eEF2 activity, and thus elongation rate. Others have also shown reductions in p-eEF2 following concurrent and resistance-only exercise (Apró et al., 2015, Apró et al., 2013, Wang et al., 2011). In Week 10, the changes in p-eEF2 from resting levels were less clear, although p-eEF2 increased immediately after the initial bout of endurance (*ER*) and resistance exercise (*RO*) respectively, which may suggest a reduction in translation elongation (Rose et al., 2005). However, in the same week, p-rpS6 was elevated from +3.5 to 7 hours after the initial resistance session in *RO*, and by +7 hours in *ER*. Phosphorylation of rpS6 has been previously shown to correlate with the efficiency of translation initiation and protein synthesis – although its exact role and necessity in these processes has been questioned (Ruvinsky and Meyuhas, 2006). Nonetheless, both resistance and concurrent exercise-induced increases in p-rpS6 have been shown to occur alongside increases in MPS, without a simultaneous increase in p-mTOR (Donges et al., 2012). It has been proposed that training alters the sensitivity and timing of anabolic signalling responses, whereby key mediators of MPS are upregulated more transiently than before training (Wilkinson et al., 2008). As such, it is possible that the timing of the muscle biopsies around each exercise session in Week 10 (+0 and +3 hours post-exercise) may not have been appropriate to capture exercise-induced changes in all markers of mTOR signalling, compared to in Week 1. Nonetheless, in line with previous literature, it appears that translational signalling before and after training, may be transiently suppressed during and immediately after exercise, regardless of the mode. Indeed, in Week 1 of the present study, p-rpS6 was suppressed immediately following *RO*, and returned to baseline 3 hours later. By the end of the day (+7 hours), only the *ER* group elicit a substantial increase in p-rpS6, compared to PRE, as well as both the *RO* and *RE* groups (Figure 4.23); this suggests that in the untrained state, performing endurance exercise before resistance exercise had a more positive effect on p-rpS6 than the reverse order and single-mode resistance exercise. However, in both weeks, many of the changes were unclear in all 3 groups, likely due to the large variation in the individual responses elicited at each time-point, and as such more data are required to further elucidate the response of p-rpS6 to concurrent training.

Attenuated mTOR signalling with concurrent exercise? (AMPKa, TSC2, p53)

In both the untrained (Week 1), and training-accustomed states (Week 10), some divergent, between-group differences in p-mTOR were evident 4 hours after the initial exercise bout; p-mTOR was increased only in *RO*, whilst changes in both concurrent groups were either unclear or supressed. Consequently, this could suggest a time-point at which concurrent exercise may have attenuated p-mTOR signalling. Indeed, at the same time (which corresponded with the end of the second concurrent session), p-AMPKa was elevated in *ER* (Week 1 and 10) and *RE* (Week

10). AMPK has been shown in cell culture to suppress mTORC1 activity, by phosphorylating TSC2, which subsequently disrupts mTORC1 binding with its activator, Rheb (Inoki et al., 2003a, Inoki et al., 2003b). Conversely, Akt can also phosphorylate TSC2 on different residues (e.g., Threonine 1462) to AMPK to remove this inhibition (Inoki et al., 2002, Li et al., 2002). In the present study, at +4 hours, p-TSC2^{Thr1462} (the site of Akt-mediated phosphorylation) was suppressed in both concurrent groups in Week 1, and in *RE* in Week 10, at which point p-AMPK was also elevated. This could suggest greater AMPK-mediated phosphorylation of TSC2, resulting in attenuated p-mTOR signalling. However, at the same time, p-Akt was also elevated in *ER* (Week 1) and both concurrent groups in Week 10. As it was not possible to measure all sites at which AMPK and Akt phosphorylate TSC2, it would be difficult to speculate whether one may have had an overriding effect on TSC2 activity than the other.

The tumour suppressor p53 has recently been hypothesised to play a potential role in the molecular interference effect (Ellefsen and Baar, 2019), as p53 is a transcription factor for Sestrins, which inhibit amino acid-stimulated activation of mTORC1 (Budanov and Karin, 2008), and can also interfere with the transcription of ribosomal RNA (Zhai and Comai, 2000). Furthermore, p53 can stimulate AMPK-mediated phosphorylation of TSC2 (Feng et al., 2005), and is also directly phosphorylated *per se* by AMPK (Feng et al., 2005, Imamura et al., 2001, Jones et al., 2005). Conversely, p53 is inactivated via Akt-mediated phosphorylation of MDM2 (murine double minute 2, an inhibitor of p53) (Gottlieb et al., 2002) and PHF20 (PHD Finger Protein 20, a transcription factor for p53) (Park et al., 2012), as well as mTORC1-mediated phosphorylation of p53 phosphatase (α4 and PP2A [Protein phosphatase 2A]) (Kong et al., 2004). In the present study, p-p53 followed a similar time-course to both p-AMPKα and p-Akt, confounding the interpretation of its opposing interactions on the AMPK and Akt-mTORC1 pathways previously highlighted in cell culture and rodent models. Whilst a role has emerged for p53 in regulating endurance training adaptations such as mitochondrial biogenesis (Bartlett et al., 2014) less is known about its role in resistance and concurrent training (Smiles and Camera, 2018). Indeed, other than the present work, to the author's knowledge, only one study has measured changes in p53 following concurrent (*RE*) exercise, demonstrating an increase in nuclear p53 abundance, and whole-muscle p-p53^{Ser15}, 8 hours after concurrent exercise combined with post-exercise whey protein (Smiles et al., 2016). Evidently, more research is required to investigate the effects of different concurrent exercise models on p53 and elucidate its potential role in regulating concurrent training adaptations.

Whilst it may be tempting to infer these data as evidence for attenuated or suppressed mTOR signalling with concurrent exercise in humans, the above timepoint simply represents a snapshot of the phosphorylation status of the measured targets, and it is worth noting that by the end of the

training day in both weeks, p-mTOR was reduced or unchanged in *all training groups* and there were large variations in the individual responses. Most studies to date in human skeletal muscle do not support an interference effect, demonstrating comparable (Apró et al., 2015, Apró et al., 2013, Donges et al., 2012, Fyfe et al., 2016b, Pugh et al., 2015) or indeed amplified (Lundberg et al., 2012, Wang et al., 2011) molecular responses to concurrent exercise, compared to each mode performed separately. A similar concurrent training model to the present study previously demonstrated comparable mTOR signalling following both concurrent and resistance-only exercise in recreationally-active individuals (Fyfe et al., 2016b), whilst signalling associated with mTORC1 and ribosome biogenesis was greater with resistance exercise-only, when performed by training-accustomed individuals (Fyfe et al., 2018). These results suggest a role for participant training status in dictating the presence of a 'molecular interference effect' (discussed later); however, these studies were conducted in separate cohorts of participants. In the present study, despite some potential evidence for attenuated p-mTOR at the +4 h timepoint with concurrent training (irrespective of exercise order), in *both* untrained and training-accustomed states, the implications of these findings are unclear, particularly when considering that the overall training-induced increases in lean mass were comparable between all three groups (*Chapter 5*).

Regulation of MPS at the transcriptional level (Myostatin & Mighty)

At the transcriptional level, the TGF-β ligand myostatin is a potent, negative regulator of muscle mass, and highly-expressed in skeletal muscle (Lee, 2004, McPherron et al., 1997). Myostatin has the capacity to inhibit mTORC1 signalling by attenuating mTORC1 phosphorylation *per se*, as well as via several key upstream effectors (Akt and TSC2), and downstream targets (rpS6 and 4EBP1) (Amirouche et al., 2009, Winbanks et al., 2012). Furthermore, through its interactions with Smad protein complexes, myostatin binding can upregulate the expression of atrogenes such as MuRF1 and MAFbx (Sartori et al., 2014). In the present study, in Week 1, there were few clear changes in myostatin mRNA following exercise, likely due to the large individual variations in its expression at baseline, precluding clear changes at the subsequent timepoints. However, in Week 10, myostatin mRNA was reduced 3 to 4 hours after the first exercise bout, regardless of mode, and was reduced in all groups by +7 hours. This is supported by existing studies demonstrating myostatin expression to be transiently reduced following resistance (Dalbo et al., 2013, Hulmi et al., 2007, Kim et al., 2005, Louis et al., 2007), endurance (Louis et al., 2007), and concurrent exercise in humans (Fernandez-Gonzalo et al., 2013, Lundberg et al., 2012, Lundberg et al., 2014, Pugh et al., 2015). Collectively, it appears that myostatin is acutely reduced in response to contractile activity *per se*, independent of the exercise mode. Whether a reduction in myostatin provides an indication for increased MPS and growth requires further research, as some research indicates comparable training-induced reductions in myostatin across individuals with varying levels of training-induced hypertrophy (Kim et al., 2007), whilst others suggest a

relationship between exercise-induced suppressions of myostatin mRNA and training-induced increases in strength and muscle cross-sectional area (Raue et al., 2012).

Myostatin has also been shown to suppress the transcription of Mighty, a novel downstream target shown to positively correlate with hypertrophy elicited in myotubes (Marshall et al., 2008, Mobley et al., 2014), and following resistance training in rodents (MacKenzie et al., 2013). Elevations in Mighty mRNA were evident in Week 1 in both *RO* and *ER*, between the +3.5 and +7 hour time-points. These findings are commensurate with previous research showing an increase in Mighty mRNA 6 hours after resistance exercise in rodents (MacKenzie et al., 2013). In Week 1, at +7 hours, Mighty expression in *RE* was not clearly increased from baseline and was substantially lower than both *RO* and *ER* at the same timepoint. This could suggest that the subsequent endurance session may have attenuated the resistance exercise-induced increase in Mighty expression. However, myostatin mRNA was also reduced to a greater extent in the *RE* group than *RO* and *ER* at this same timepoint. There was also greater variation in the *RE* group at baseline in Week 1, which may have contributed to the lack of clear changes in this group. Conversely, in Week 10, at +7 hours, Mighty mRNA was elevated in all groups. Clearly more research is required to elucidate the time-course, and roles, of both myostatin and Mighty expression in response to different exercise modes. Indeed, to the author's knowledge, the present study represents the first of its kinds to characterise the transcriptional response of Mighty to resistance-only and concurrent exercise in human skeletal muscle, in both untrained and training-accustomed states. Collectively, these findings may suggest that the regulation of muscle growth at the transcriptional level is not negatively affected by concurrent exercise, which largely elicited comparable responses to resistance-only exercise, regardless of the exercise order.

Protein degradation (MuRF1, MAFbx)

As well as the purported attenuation to protein synthesis, concurrent training may interfere with load-induced hypertrophy by inducing the expression of markers of protein degradation, such as the 'atrogenes' MAFbx (also termed atrogin-1) and MuRF1 (Apró et al., 2015). These E3 ligases are responsible for 'tagging' specific proteins requiring degradation (Murton et al., 2008). In the present study, in both weeks, MuRF1 mRNA was similarly elevated in both concurrent groups 3 hours after their respective cycling bouts. However, there was a difference between exercise orders immediately after both their respective leg press (Weeks 1 and 10) and cycling sessions (Week 10), whereby MuRF1 expression was greater in *ER* than *RE*. Previously, Coffey *et al.* (2009b) reported greater MuRF1 expression when resistance exercise was performed first; this may be due to the different exercise protocols employed from the present study (i.e., 30-minutes steady state cycling versus 20-minutes high-intensity interval exercise). Indeed, when the endurance mode involved repeated sprint cycling, both orders increased MuRF1 expression

(Coffey et al., 2009a). The latter study also reported no order effect on MAFbx expression, attributed to the large variation in individual responses (Coffey et al., 2009a). In the present study, MAFbx expression increased 3 hours after the initial cycling session in *ER* (Week 1) and concomitantly decreased after the leg press session in *RO* and *RE* (Weeks 1 and 10). When the concurrent groups performed their second session, the direction of the change in expression was altered (i.e., reduced in *ER*, whilst the *RE* group became less negative) (Figure 4.9). There was no clear effect of exercise order regarding the changes in MAFbx expression after their respective leg press sessions. However, in both weeks, MAFbx expression was greater in *ER* than *RE* during the 3-hour recovery period after cycling. Whereas the previous work of Coffey *et al.* only measured changes in MuRF1 and MAFbx expression 3 hours after both concurrent sessions had been completed (Coffey et al., 2009a, Coffey et al., 2009b), the present study provides a greater temporal resolution of the changes in atrogene expression throughout the training day, by taking measurements before, immediately after, and 3 hours after each mode respectively.

The present findings are similar to previous work in our lab, which showed an increase in MuRF1 mRNA 3 hours after concurrent (*ER*) exercise involving both high- and moderate-intensity cycling, whilst MAFbx mRNA was unaltered by either *RO* or concurrent exercise (Fyfe et al., 2016b). Others have reported increases in MuRF1 and MAFbx expression after concurrent (*ER*) exercise, with no changes or reductions after resistance exercise (Apró et al., 2015, Lundberg et al., 2014, Pugh et al., 2015). Pugh *et al.* (2015) reported reductions in MAFbx expression 2 to 6 hours following both *RO* and concurrent (*RE*) exercise, and suggested that exercising in the fed-state may have contributed to this reduction. Indeed, the provision of amino acids has previously been shown to suppress atrogene expression (Borgenvik et al., 2012). In the present study, the exercise sessions were also conducted in the fed-state, which may have influenced the observed reductions in MAFbx mRNA; however, without fasted-controls, this remains speculative.

Collectively, these results indicate that these markers of protein degradation may be differentially regulated by endurance, resistance, and concurrent exercise. Performing endurance exercise first may increase MuRF1 and MAFbx expression immediately after both modes, whilst the reverse order may lead to a reduction in MAFbx expression over the 3-hour recovery period after the endurance session. Given the lack of interference to muscle hypertrophy observed in *Chapter 5*, and the limited data currently available on atrogene expression following concurrent training, the implications of these findings are currently unclear. However, it is also important to consider that the numerous environmental and physiological stimuli endured by skeletal muscle proteins can disrupt cellular homeostasis and induce significant damage; thus an increase in breakdown and subsequent re-synthesis of specific proteins is also necessary to preserve and maintain muscle tissue integrity (Bell et al., 2016). Therefore, changes in expression of proteolytic markers may

simply reflect a necessary adaptive response for skeletal muscle repair and remodelling, as opposed to a 'molecular interference' to skeletal muscle growth.

Signalling associated with mitochondrial biogenesis (PGC-1α)

High-intensity endurance training is a powerful stimulus for mitochondrial biogenesis (Bishop et al., 2019b) and is typically associated with the transient upregulation of the 'master regulator' PGC-1α (Lira et al., 2010, Perry et al., 2010). In the present study, PGC-1α was increased 3 to 4 hours after the first exercise session, regardless of the mode, and remained elevated throughout. The finding that resistance exercise can increase PGC-1α expression is not unexpected, as some (Fernandez-Gonzalo et al., 2013, Lundberg et al., 2012, Lundberg et al., 2014), but not all (Fyfe et al., 2016b, Pugh et al., 2015), have also reported increases in PGC-1α mRNA after resistance exercise. This may represent a generic stress response to an unfamiliar exercise bout. In Week 1, 3 hours after the leg press session, PGC-1α expression was greater in *RO* compared to *RE*. This finding was unexpected given both groups performed identical sessions first. However, this difference is likely due to the greater range of individual responses in the *RO* group at the +3.5 h timepoint (Figure 4.5).

Previous research has also suggested that concurrent training may potentiate PGC-1α expression more than both single-mode endurance (Wang et al., 2011) and resistance exercise (Apró et al., 2013, Pugh et al., 2015). The present study did not include an endurance-only group, based on the rationale that limited data support attenuations to endurance adaptations with concurrent training (Fyfe et al., 2014). However, compared to both *RO* and *RE*, the increase in PGC-1α mRNA immediately after the leg press session was greater in *ER* (in Weeks 1 and 10), and is likely due to the residual effects of the prior endurance session. Indeed, Lundberg *et al.* reported that PGC-1α mRNA was increased 6 hours after an endurance session and remained elevated immediately after resistance exercise (Lundberg et al., 2012). When the concurrent sessions were separated by 15 minutes (Lundberg et al., 2014), the increase in PGC-1α 3 hours after the resistance exercise was also greater in *ER* than *RO*. These results suggest that a subsequent resistance session does not attenuate PGC-1α expression induced by a prior endurance exercise session. Furthermore, in relation to exercise order, previous work has shown concurrent exercise to increase PGC-1α expression after 3 hours, independent of exercise order when resistance exercise was combined with steady state cycling (Coffey et al., 2009b), and only a modest order effect (favouring *RE*) when combined with repeated-sprint cycling (Coffey et al., 2009a). In the present study, PGC-1α expression was greater in *ER* than *RE* immediately after their leg press sessions (Week 1 and 10), and 3 hours after the cycling sessions (Week 1). However, in Week 10, there was no order effect for the increase in PGC-1α expression 3 hours after the respective cycling sessions. These results would suggest that in the untrained state, performing endurance

exercise prior to resistance may permit greater elevations of PGC-1α following both sessions, compared to the reverse order. In the training-accustomed state (discussed in more detail below), both exercise orders induced comparable increases in PGC-1α mRNA following their respective endurance and resistance sessions. It is worth noting that due to the study design, PGC-1α expression was measured over 7 hours after the initial endurance session of the *ER* group, whereas data for the *RE* group are only available over the initial 3 hours post-endurance exercise. Thus, whilst it appears that the *ER* exercise order may induce a greater cumulative expression of PGC-1α over the course of the training day, it remains unclear whether the *RE* group would have elicited a similar pattern of expression after the endurance session, beyond the 3 hours measured. Nonetheless it appears that both resistance-only and concurrent training, regardless of the order, are potent stimulators for signalling associated with mitochondrial biogenesis.

The role of training status on molecular responses to exercise

Participant training status can substantially affect the molecular responses to different exercise modes. Typically, in the untrained state, the molecular responses appear less representative of the exercise mode, whilst exercise in training-accustomed or highly-trained state promotes dampened, more refined, mode-specific molecular responses (Coffey and Hawley, 2016, Vissing et al., 2013, Wilkinson et al., 2008). The present study provides further evidence for this, at both the transcriptional and post-translational levels, as the expression of several genes and proteins differed in magnitude between Weeks 1 and 10. For example, following the initial cycling session in *ER*, the elevations in MuRF1 and MAFbx expression at +3.5 to +4 hours were lower in Week 10 than Week 1. The reductions in MAFbx in both *RO* and *RE* at the corresponding timepoint were also less in Week 10 than Week 1. Furthermore, in *RO*, despite an initial increase at +3.5 hours in Week 1, MuRF1 expression was reduced by +7 hours in both weeks (Figure 4.7). Similar findings have been reported elsewhere (Fernandez-Gonzalo et al., 2013), and may indicate that an unfamiliar exercise bout provides a greater stimulus for skeletal muscle remodelling than when performed at the same relative intensity in the training-accustomed state (Bishop et al., 2019b). Furthermore, whilst both endurance and resistance exercise increased PGC-1α expression before and after training, the increase in Week 10 was lower in both *ER* and *RO*. These findings are also commensurate with the work of Fernandez-Gonzalo et al. (2013), in which endurance and resistance exercise-induced elevations in PGC-1α mRNA were respectively dampened and attenuated following 5 weeks of training. Others have also shown diminished PGC-1α transcriptional responses to repeated exercise bouts performed at the same relative intensity (Perry et al., 2010).

At the post-translational level, several proteins show altered patterns and levels of phosphorylation between Weeks 1 and 10. As highlighted previously, in Week 10 p-4EBP1 was

reduced less at both +4 and +7 hour timepoints, in all groups. Furthermore, in Week 1 p-eEF2 was also reduced in all groups at +3.5 hours, and unchanged from baseline in Week 10. Collectively, the present results suggest that following a short-term training period, molecular responses to exercise performed at the same relative intensity appear more transient and short-lived, and the magnitude of certain transcriptional and translational signalling responses are reduced. These results also further highlight the need for caution when interpreting molecular responses to concurrent and single-mode exercise in the untrained state to infer a 'molecular interference effect', as these responses may simply reflect a generic response to an unfamiliar exercise stress.

4.5 Conclusions

In conclusion, this study represents the first of its kind to elucidate the extended time-course of molecular signalling events that govern endurance and resistance adaptations, following both concurrent and resistance-only exercise performed in the fed-state, in both the untrained and training-accustomed states. Despite greater muscle glycogen depletion, and transient increases in suggested inhibitors of mTOR signalling, the present data do not provide clear evidence of a 'molecular interference' to anabolic signalling with concurrent exercise compared to performing resistance alone. This study provides new information regarding of time-course of expression of novel targets previously-understudied in concurrent and resistance exercise models in human skeletal muscle, such as p53 and Mighty. Furthermore, this study supports previous research demonstrating that many molecular responses at the transcriptional and post-translational level are reduced following training. This also highlights the need for further research on the molecular responses elicited by highly-trained individuals in response to different and concurrent exercise modes, in whom the interference effect at the phenotypic level is more likely to be observed.

Chapter 5 To lift first, or to cycle, that is the question.

No interference to strength, lean mass, or aerobic fitness in healthy, active men following short-term concurrent training, regardless of exercise order [6]

Preface

The previous chapter did not demonstrate a clear ability of concurrent exercise, regardless of the order, to compromise anabolic signalling responses compared to resistance exercise. Whilst such molecular responses are often used to infer or predict subsequent training adaptations (Camera et al., 2016b), there is often a discordance between molecular signalling events, protein synthesis and training adaptations (Atherton et al., 2010, Mayhew et al., 2009, Mitchell et al., 2014, Mitchell et al., 2012, Phillips et al., 2013).

Nonetheless, from the review of literature it is clear that concurrently performing endurance and resistance training has the potential to interfere with the development of strength (Hickson, 1980), hypertrophy (Bell et al., 2000), and power (Häkkinen et al., 2003). Whilst this "*interference effect*" is not always observed (McCarthy et al., 1995, McCarthy et al., 2002), the potential for, and magnitude of, this effect is likely dictated by the manipulation of several training and non-training variables (Bishop et al., 2019a).

Deciding which exercise mode to perform first is an important methodological consideration when designing any concurrent training program. Some studies advocate performing resistance exercise first (Cadore et al., 2012, Cadore et al., 2013, Pinto et al., 2014), and others endurance (Chtara et al., 2005, Kuusmaa et al., 2016, Schumann et al., 2015), to induce superior improvements in their respective adaptations. However, other studies do not support such an order effect (Collins and Snow, 1993, Eklund et al., 2015, Eklund et al., 2016, Schumann et al., 2014a). Furthermore, many of these studies do not include a resistance-only training group, limiting insights into the interference effect, regardless of whether one exercise order is more beneficial for adaptation than the other.

The following chapter will expand on these previous studies, and simultaneously investigate the interference effect (*i.e. concurrent training vs resistance-only training*), and the effect of concurrent exercise order (*i.e. endurance prior to resistance vs resistance prior to endurance*) on the development of strength, hypertrophy, power and aerobic fitness in healthy active men.

[6] *Preliminary findings from this study were presented at the 23rd annual Congress of the European College of Sport Science - ECSS Dublin 2018.*

5.1 Introduction

Skeletal muscle adaptations to training are highly specific to the type of the stimulus imposed (Hoppeler et al., 2011). For example, endurance and resistance exercise represent different stimuli that induce distinct phenotypes (Nader, 2006). Regular endurance training is predominantly associated with central and peripheral adaptations that facilitate greater oxygen delivery and extraction within skeletal muscle (Lundby et al., 2017), as well as alterations in substrate utilisation (Hurley et al., 1986, Phillips et al., 1996), culminating in improvements in whole-body aerobic power and fatigue resistance. Instead, resistance training is best known for inducing neuromuscular and morphological adaptations, such as increased muscle fibre hypertrophy, recruitment, and force production, contributing to increases in muscle size, strength, and power (Folland and Williams, 2007). A periodised training program involving both exercise modes is termed "*concurrent training*" and presents an approach to obtain concomitantly high levels of endurance, strength, and power, which may be beneficial for both health and performance (Fyfe et al., 2014).

The divergent nature of adaptations to these exercise modes raises the question of whether endurance and resistance adaptations can be developed simultaneously to the same degree as with single-mode training. This has become an area of growing interest over the last four decades, inspired by the seminal work of Dr. Robert Hickson who demonstrated that, when compared to performing resistance-only training, concurrent endurance and resistance training attenuated strength development (Hickson, 1980). The results of other studies also support the conclusion that concurrent training, either in the same session (Cadore et al., 2010, Craig et al., 1991, Dolezal and Potteiger, 1998, Fyfe et al., 2016a, Kraemer et al., 1995, Ronnestad et al., 2012, Sale et al., 1990a) or on separate days (Bell et al., 2000, Dudley and Djamil, 1985, Häkkinen et al., 2003, Hennessy and Watson, 1994, Horne et al., 1997), can compromise strength, as well as power and/or hypertrophic adaptations, compared to resistance-only training; this phenomenon is commonly referred to as the "*interference effect*" or the "*concurrent training effect*" (Baar, 2006, Hawley, 2009, Hickson, 1980, Nader, 2006). Additionally, whilst there is potential for resistance exercise to also acutely hinder endurance performance (Doma et al., 2017), endurance training adaptations appear largely unaffected (Wilson et al., 2012) or improved (Chtara et al., 2005, Irving et al., 2015, Ronnestad et al., 2015, Ronnestad and Mujika, 2014, Vikmoen et al., 2015, Wang et al., 2011) by the addition of resistance training.

Despite many supportive studies, the prevalence of the interference effect is not consistent throughout the literature. Several studies report improvements in strength and muscle mass following concurrent training commensurate with resistance-only training (Cantrell et al., 2014, Donges et al., 2013, Glowacki et al., 2004, Laird et al., 2016, LeMura et al., 2000, McCarthy et

al., 1995, McCarthy et al., 2002), as well as comparable improvements in aerobic fitness to single-mode endurance training (McCarthy et al., 1995). Other research suggests that certain variables may be more susceptible to inhibition than others. For example, concurrent training has been shown to attenuate improvements in the rate of force development, despite inducing similar strength and hypertrophic adaptations to resistance-only training (Häkkinen et al., 2003, Mikkola et al., 2012, Ronnestad et al., 2012). Indeed, the choice of dependent variable and the sensitivity of a test may also affect whether an interference effect is observed (Leveritt et al., 2003). The equivocal nature of the research investigating the interference phenomenon may also be due to the diverse experimental procedures and training programs employed between studies (Bishop et al., 2019a). As such, the potential for, and degree of, interference is likely related to the manipulation of both training variables (e.g., exercise order, between-mode recovery duration, exercise mode, frequency, intensity, volume, (Fyfe et al., 2014, Murach and Bagley, 2016, Wilson et al., 2012)) and 'non-training' variables (such as participant training status and nutrient availability (Fyfe and Loenneke, 2018, Leveritt et al., 2003, Sale et al., 1990b)), all of which require careful consideration when prescribing training.

Concurrent sessions are typically performed either within the same-session (affording a time-efficient alternative to single-mode training) or on separate days (allowing greater recovery between modes). However, it is also common practice, particularly within athletic environments, for concurrent sessions to be separated by shorter recovery periods of only a few hours (Cross et al., 2019, Enright et al., 2015, Enright et al., 2017, Robineau et al., 2016). Thus, a key consideration central to any same-day concurrent training program design is the choice of exercise session order, given factors such as residual fatigue and substrate depletion induced during exercise may negatively impact the quality and performance of a subsequent session (Leveritt et al., 1999). Studies have shown both endurance (Doma and Deakin, 2013) and resistance exercise performance (Inoue et al., 2016, Jones et al., 2017, Sporer and Wenger, 2003) may be impaired when preceded by a prior bout of the contrasting exercise mode. This may reduce the training stimulus, and compromise the potential for adaptation (Colquhoun et al., 2018, Grgic et al., 2018b, Schoenfeld et al., 2017).

To date, investigations into the effect of exercise order on training adaptations have yielded inconsistent results. Some research indicates that performing endurance sessions first may favour greater improvements in submaximal (Schumann et al., 2015) and maximal oxygen uptake (Chtara et al., 2005), 4-km time-trial running performance (Chtara et al., 2005), and cycling time to exhaustion (Kuusmaa et al., 2016). Conversely, performing resistance sessions first has been shown to elicit greater improvements in lower-body strength, muscle quality (i.e., force per unit of active mass), and neuromuscular economy (Cadore et al., 2013, Cadore et al., 2012, Pinto et

al., 2014). Collectively, these findings are indicative of order-dependent concurrent training adaptations. Indeed, two recent meta-analyses also concluded that for same-session concurrent training (< 15 min of between-mode recovery), prioritising resistance before endurance exercise produces a greater effect on maximal dynamic strength compared to the reverse order; however, no order effect was evident for changes in aerobic capacity (Murlasits et al., 2018, Eddens et al., 2018), nor static strength, hypertrophy, or body fat percentage (Eddens et al., 2018). Only a finite sample of eligible studies were available (n = 17 combined), many of which included small numbers of participants, and were of varying quality and design (Murlasits et al., 2018), with moderate-to-substantial heterogeneity reported for certain variables (Eddens et al., 2018). More research is warranted to further our understanding of the effects of concurrent exercise order on various training outcomes, given that these findings are not universal. Many studies report similar improvements in dynamic and isometric strength (Collins and Snow, 1993, Davitt et al., 2014, Eklund et al., 2016, Eklund et al., 2015, Gravelle and Blessing, 2000, MacNeil et al., 2014, Makhlouf et al., 2016, McGawley and Andersson, 2013, Schumann et al., 2014b, Schumann et al., 2014a, Wilhelm et al., 2014), power (Wilhelm et al., 2014), hypertrophy (Eklund et al., 2015, Eklund et al., 2016, Davitt et al., 2014, Wilhelm et al., 2014, Schumann et al., 2014a), aerobic power and capacity (Davitt et al., 2014, Eklund et al., 2015, Eklund et al., 2016, MacNeil et al., 2014, Schumann et al., 2014a), endurance performance (Makhlouf et al., 2016, McGawley and Andersson, 2013, Schumann et al., 2014a), speed and agility (Makhlouf et al., 2016, McGawley and Andersson, 2013), irrespective of intra-session exercise order. This has been shown in a range of populations, including previously-untrained/recreationally-active men and women (Collins and Snow, 1993, Davitt et al., 2014, Eklund et al., 2015, Eklund et al., 2016, Gravelle and Blessing, 2000, Schumann et al., 2014b, Schumann et al., 2014a), elite soccer players (Makhlouf et al., 2016, McGawley and Andersson, 2013) and elderly men (Wilhelm et al., 2014). Furthermore, many studies investigating the effect of concurrent exercise order do not include a single-mode, resistance-only training group, thereby precluding inferences about whether an interference effect had occurred with the addition of endurance training, regardless of whether one exercise order induced superior adaptations than the reverse.

Consequently, the aims of this study were two-fold. The first aim was to investigate how nine weeks of concurrent training (with sessions separated by a 3-hour recovery window) might hinder the development of strength, muscle mass and power, in healthy, active men, compared to resistance-only training (i.e., *the extent to which there an interference effect*). The second aim was to investigate differences in the magnitude of concurrent training adaptations when altering the exercise order (i.e., *the extent to which there is an exercise order effect*).

5.2 Materials and Methods

Full details of all experimental procedures can be found in *Chapter 3: General Methodology*; any differences from the general methodology that are pertinent to this chapter are outlined below.

Experimental Overview

After familiarisation trials and baseline assessments of 1 repetition maximum (1-RM) leg press strength, countermovement jump (CMJ) performance, body composition, and aerobic fitness, twenty-nine healthy, active men were ranked according to baseline levels of maximal strength, aerobic fitness, and lean mass and allocated to one of three training groups, in a semi-randomised[7], counterbalanced order: *1) ER*, endurance prior to resistance exercise (n = 10); *2) RE*, resistance prior to endurance exercise (n = 10); or *3) RO*, resistance exercise only (n = 9). Baseline characteristics for each group are displayed in Table 3.1 (in *Chapter 3*). Participants trained for 3 days a week for 9 weeks in their respective groups. Concurrent training sessions were separated by a 3-hour recovery period. The battery of fitness testing was repeated after weeks 5 (*MID*) and 9 (*POST*) of training (Figure 5.1).

Week 1 differed slightly from the subsequent 8 weeks of training, as this week also formed part of an acute experimental trial investigating molecular responses to concurrent training (*see Chapter 4*). The participants performed three '*experimental*' training sessions. During the first session, muscle biopsies were sampled at various timepoints to characterise temporal changes to protein and gene expression following resistance-only and concurrent exercise sessions. The experimental resistance sessions involved 6 sets of 10 leg press repetitions, at 70% 1-RM, with 2 minutes between sets, whilst the endurance sessions involved performing 10 × 2-minute cycling bouts, at 40% of the difference between the power at the lactate threshold ($\dot{W}_{LT}$) and peak aerobic power ($\dot{W}_{peak}$) (~84% $\dot{W}_{peak}$). The molecular data are outside the scope of this chapter and will not be discussed here. However, this was illustrated in to highlight the differences between Week 1 and the rest of the training program.

[7] *Group allocations were 'semi-randomised' in that not all 29 participants were recruited at once. However, once participants were recruited, and all baseline tests completed, they were allocated to a group with the aim of matching the groups primarily according to baseline levels of maximal strength, aerobic fitness and lean mass; where possible, I endeavoured to also match other baseline variables.*

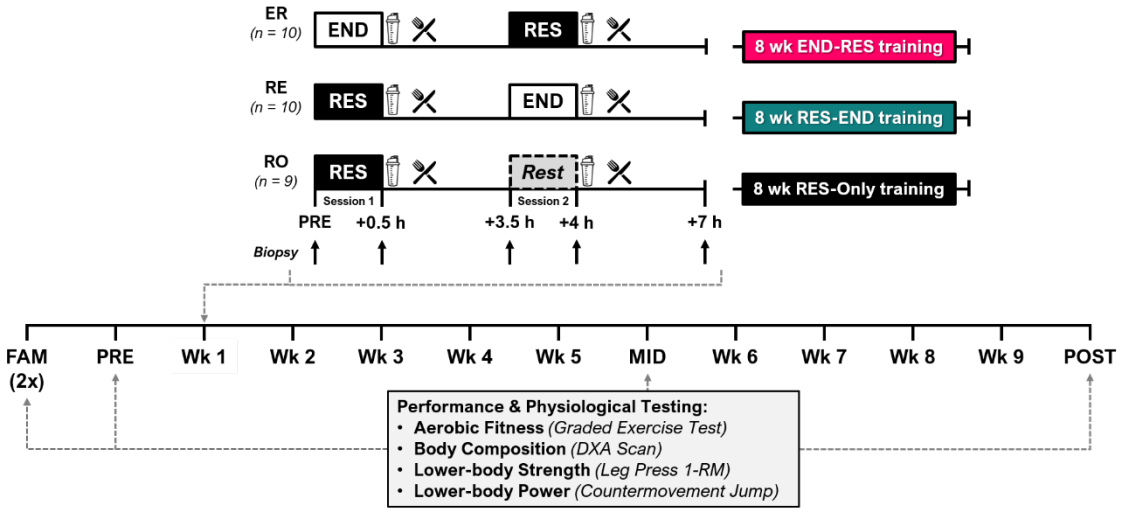


Figure 5.1 - Schematic representation of the experimental protocol. END = endurance session; RES = resistance session; ER = endurance-resistance; RE = resistance-endurance; RO = resistance-only; ↑ = muscle biopsy; ✕ = standardised meal (carbohydrate = 1.3 g·kg^{-1}; protein = 0.3 g·kg^{-1}; fat = 0.3 g·kg^{-1}); 🥛 = whey protein (0.25 g·kg^{-1}); DXA = dual-energy x-ray absorptiometry; 1-RM = one repetition maximum; FAMIL = familiarisation trials.

Statistical Analyses

Prior to analysis, all dependent variables (excluding the wellbeing questionnaires) were log-transformed on the reasonable assumption that effects and errors are more uniform when expressed in factor or percent units, than in original raw units (Hopkins et al., 2009). To improve the precision of the estimate, the mean of the second familiarisation (*FAM2*) and *PRE*-trials were used as each participants' baseline value. A mixed model realised with Proc Mixed in the Statistical Analysis System (University Edition of SAS Studio, Version 9.4, SAS Institute, Cary, NC) was used to analyse change scores from baseline (*PRE*) at the *MID* and *POST*-training assessment time-points. The fixed effects were the interaction of group (*three levels* representing the training groups) with time (*two levels*: *MID* and *POST*), and the interaction of group with the baseline score (linear numeric, to adjust for any differences between the groups at baseline). The random effects specified different residual variances (of the change scores) at the *MID* and *POST* time-points in each group, allowing for correlations between the *MID* and *POST* residuals within each group (in SAS code: repeated Time/subject=Participant type=un group=Training group). The residuals were back-transformed to give standard deviations of the change scores, in percent units.

Differences between groups at baseline were assessed for magnitude using standardisation; confidence intervals and *P*-values for the differences were not derived, because inferences about the differences are irrelevant for the allocation process, and any differences need to be adjusted for (*see* *appendices*). To account for any differences between groups at baseline, all effects were then adjusted to the grand baseline mean, pooled from the entire participant cohort (Figure 5.2).

Mean within-group percent changes, and between-group differences for the changes were derived using estimate statements in Proc Mixed. The residual variances were back-transformed to standard deviations of change scores in percent units. Training load and wellbeing data were analysed with a reliability mixed model, in which fixed effects accounted for session and weekly means, and random effects accounted for within-subject variability within and between weeks, in each of the three groups. The between-subjects standard deviation at baseline was used to derive standardised effect sizes (ES) of the magnitude of the within- and between-group mean effects, where <0.20 = trivial, 0.20-0.60 = small, 0.60-1.2 = moderate, >1.2 = large; the 0.20 threshold defined smallest important effects (Hopkins et al., 2009). Given the typical magnitude and uncertainty of the ES on performance (trivial-to-moderate effects, with 90%CI ranging from ±0.05 to ±0.50) a spreadsheet for simulating standardised effects (Hopkins, 2019) showed that any additional uncertainty in the standardised effect arising from the uncertainty in the standardising standard deviation from a sample size of 29, had a negligible impact on the decisions about the magnitude.

Using the 90%CI, decisions about the magnitude of the effects were made according to the probability of being substantially beneficial/positive or harmful/negative. For clarity, and to standardise terminology across *clinical* and *non-clinical* effects, substantially beneficial/positive and harmful/negative effects are respectively qualified as improvements or impairments. *Clinical* thresholds regarding the probability of benefit and harm were used for comparisons between each concurrent training group with the resistance-only (i.e., control) training group, to assess the interference effect. These effects were deemed unclear if there was a >25% probability of improvement with an unacceptable risk [>0.5%] of impairment. *Non-clinical* thresholds for positive and negative effects were used for comparisons between the concurrent training groups (i.e., the assessment of the exercise order), as well as analysis of training load and wellbeing data. These effects were deemed unclear if the probability for a substantial improvement and impairment were both >5%. The probability thresholds for determining meaningful effects were as follows: 75-95% = *likely*, 95-99.5% = *very likely*, and >99.5% = *most likely*. All substantial improvements (↑), impairments (↓), or trivial effects were considered meaningful only if the probability was >75%. To account for inflation of error arising from multiple inferences, the thresholds for determining unclear effects were then adjusted to more conservative thresholds (i.e., *clinical*: >0.1% risk of impairment with >5% chance of improvement; *non-clinical*: ±99%CI). Effects which remained clear after adjusting for multiple inferences are represented in by upper case letters in figures, and bold text in tables**.** Precise *P*-values for the effects (unless *P* < 0.001) are also provided in the appendices.

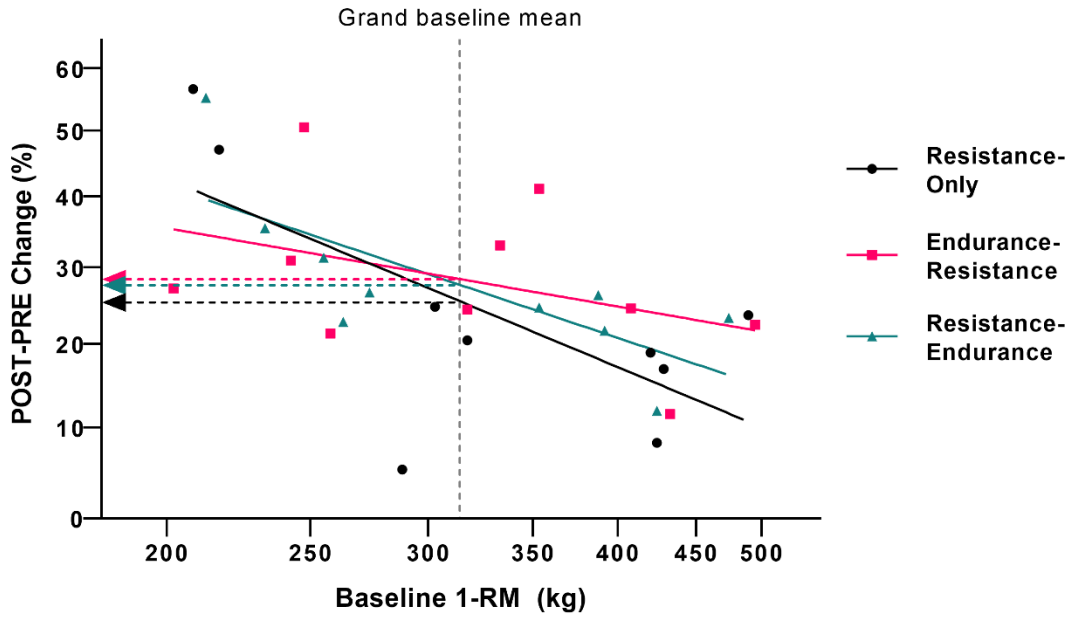


Figure 5.2 - An example scatter plot depicting how all effects were adjusted for any differences between groups at baseline, using the baseline 1-RM leg press data. For each participant, a baseline 1-RM value was derived by calculating the mean of their FAM2 and PRE trials. A baseline grand mean pooled from all 3 groups was then calculated (represented by the dashed vertical line). Participants' baseline values were plotted against their respective percent change in leg press 1-RM from PRE to POST training. The point of intersect between each groups' regression line and the grand baseline mean represents the adjusted group mean change.

5.3 Results [8]

Training Compliance

All participants adhered sufficiently (>85 %) to the prescribed training programs (*mean ± SD, RO* 98 ± 2.6 %; *ER* 96 ± 4.4 %; *RE* 95 ± 4.7 %).

Training Load

Internal Load

Internal training load was determined following all training sessions, and weekly averages were calculated for each group (Table 5.1). Throughout the study, the *ER* group reported a greater weekly internal load during the resistance training sessions than both the *RO* (*mean diff ± 90%CI* 25 ± 20 %, *ES ±90% CI* 0.84 ±0.60) and *RE* groups (-18 ± 9.3 %, -0.76 ±0.44). There was no clear difference between *RO* and *RE*. There was no clear difference between the concurrent training groups for the average weekly internal load perceived in the endurance sessions.

External Load

External training load was determined following all training sessions, and weekly averages were calculated for each group (Table 5.1**)**. There were no clear differences for any between-group comparison for average weekly external load completed in both the resistance and endurance sessions, quantified as absolute volume load lifted (in kg) and absolute work done (in kJ), respectively.

Table 5.1 - Average weekly training loads for the prescribed sessions (mean ± SD).

	Resistance-Only	**Endurance-Resistance**	**Resistance-Endurance**
Internal Load			
Resistance Sessions	269 ± 100 □	337 ± 84	275 ± 76 □
Endurance Sessions	-	218 ± 71	217 ± 49
External Load			
Absolute Volume Load Lifted (kg)	14,800 ± 3,900	14,200 ± 4,500	14,600 ± 3,400
Absolute Work Done (kJ)	-	993 ± 230	929 ± 190

□ *meaningful difference vs ER (i.e. ES ≥ 0.2, likelihood ≥75%).*

[8] *All raw data, and extended within- and between-group comparison data for this chapter are available in Appendix B*

Wellbeing and readiness to train

Wellbeing scores were determined prior to all training sessions, and weekly averages were calculated for each group (Table 5.2). A higher score indicates better overall perceptions of wellbeing, mood, and sleep quality, as well as less fatigue and general muscle soreness. On average, prior to the resistance sessions, the *ER* group reported lower total wellbeing scores than *RO* (*mean difference [raw]* ± *90% CI* -1.8 ± 1.4, *ES* ±*90% CI* -0.60 ±0.46). This was also reflected in lower scores for general muscle soreness (-0.6 ± 0.4, -0.62 ±0.46), stress (-0.4 ± 0.3, -0.51 ±0.40), and mood (-0.4 ± 0.2, -0.68 ±0.39). Differences between these groups for fatigue (-0.3 ± 0.4, -0.36 ±0.43) and sleep quality (-0.2 ± 0.3, -0.21 ±0.32) were not determined as meaningful. There were no clear differences between *RO* and *RE* for total wellbeing, fatigue, sleep, stress and mood; there was a small difference for general muscle soreness (-0.3 ± 0.5, -0.37 ±0.55), which was not considered meaningful. There were no clear differences between *RE* and *ER* for any measure, other than mood, which was greater in *RE* than *ER* (0.4 ± 0.3, 0.65 ±0.47).

There were no clear differences between *ER* and *RE* for the wellbeing scores prior to the endurance sessions. The *RE* group did report a *possibly* lower score for soreness (-0.3 ± 0.5, -0.32 ±0.51), a greater mood (0.2 ± 0.3, 0.34 ±0.45) than *ER*; however, these differences were no considered meaningful.

Table 5.2 - Average weekly scores for wellbeing and readiness to train (mean ± SD).

	Resistance-Only	**Endurance-Resistance**	**Resistance-Endurance**
Resistance Sessions			
Total score	18.1 ± 2.7	16.3 ± 2.9 °	17.5 ± 3.4
Fatigue	3.3 ± 0.8	3.0 ± 0.8	3.2 ± 1.0
Sleep	3.6 ± 0.8	3.4 ± 0.8	3.5 ± 0.9
General Muscle Soreness	3.4 ± 0.9	2.9 ± 0.8 °	3.1 ± 1.0
Stress	3.8 ± 0.6	3.4 ± 0.8 °	3.7 ± 0.7
Mood	4.0 ± 0.5	3.6 ± 0.7 ° ^	4.0 ± 0.6
Endurance Sessions			
Total score	-	17.1 ± 3.0	17.3 ± 3.3
Fatigue	-	3.2 ± 0.9	3.2 ± 0.9
Sleep	-	3.4 ± 0.8	3.5 ± 0.9
General Muscle Soreness	-	3.3 ± 0.9	3.0 ± 0.9
Stress	-	3.5 ± 0.8	3.7 ± 0.7
Mood	-	3.7 ± 0.7	3.9 ± 0.6

○ meaningful difference vs RO; ^ meaningful difference vs RE (i.e. ES ≥ 0.2, likelihood ≥75%)

Habitual Dietary Intake

Habitual baseline dietary intake data are presented in Table 5.3**.** At baseline, there were small differences for absolute daily energy intake between *RO* and both *ER* (*ES* = 0.26) and *RE* (*ES* = 0.30). There were also small differences between all groups for daily carbohydrate intake (*ES* ranging from 0.14 to 0.58). For daily protein intake there were small differences between *ER* and both *RO* (*ES* -0.25) and *RE* (*ES* = -0.40). There were also small differences between all groups for daily fat intake (*ES* ranging from 0.23 to 0.51). Similar differences were observed when values were expressed relative to body mass.

Table 5.3 - Differences in habitual dietary intake at baseline (mean ± SD).

	1. Resistance-Only	**2. Endurance-Resistance**	**3. Resistance-Endurance**
Absolute			
Energy Intake (kcal·d^{-1})	2,457 ± 519 □^	2,649 ± 617	2,691 ± 703
Carbohydrate (g·d^{-1})	235 ± 87 ■^	285 ± 97 ^	266 ± 71
Protein (g·d^{-1})	153 ± 56	137 ± 34 °^	156 ± 45
Fat (g·d^{-1})	88 ± 24 ■^	110 ± 41 ^	100 ± 32
Relative to body mass			
Energy Intake (kcal·kg·day^{-1})	33 ± 8 □^	36 ± 11	36 ± 9
Carbohydrate (g·kg·day^{-1})	3.2 ± 1.3 ■^	4.0 ± 1.9 ^	3.6 ± 1.0
Protein (g·kg·day^{-1})	2.0 ± 0.7	1.9 ± 0.6 °^	2.1 ± 0.6
Fat (g·kg·day^{-1})	1.2 ± 0.4 □^	1.5 ± 0.4 ^	1.4 ± 0.4

○ *small difference vs RO;* □ *small difference vs ER;* ■ *moderate difference vs ER;* ^ *small difference vs RE.*

Performance measures

Leg press 1-RM Strength

There were small improvements in leg press 1-RM strength following the initial 5 weeks of *RO* (*mean* ± *SD* 15.1 ± 4.6 %, *ES* ±*90% CI* 0.49 ±0.14), *ER* (17.7 ± 7.0 %, 0.56 ±0.18) and *RE* (16.9 ± 3.1 %, 0.54 ±0.14). There were further small improvements following the last 4 weeks of training (*RO:* 7.7 ± 8.4 %, 0.26 ±0.18; *ER:* 8.9 ± 2.8 %, 0.29 ±0.08; *RE:* 8.9 ± 5.1 %, 0.30 ±0.12). Together, this resulted in moderate improvements in leg press 1-RM strength following 9 weeks of training in all groups (*RO:* 23.9 ± 12.4 %, 0.74 ±0.29; *ER:* 28.1 ± 8.3 %, 0.86 ±0.24; *RE:* 27.4 ± 7.9 %, 0.84 ±0.24; Figure 5.3). There were no meaningful between-group differences for the changes in leg press 1-RM between any time-points (Table 5.4).

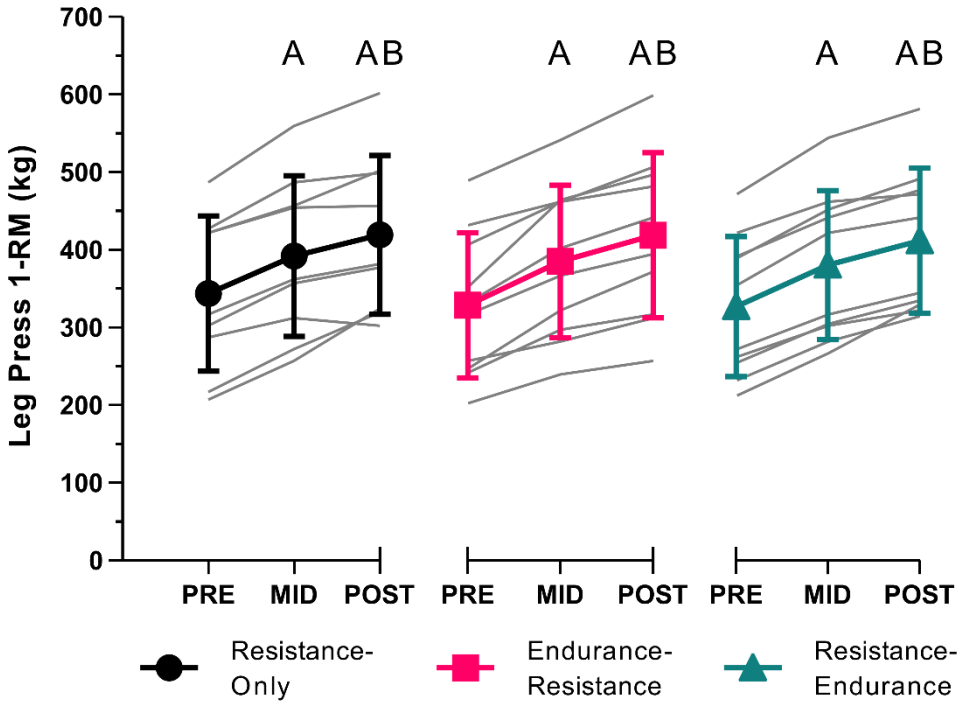


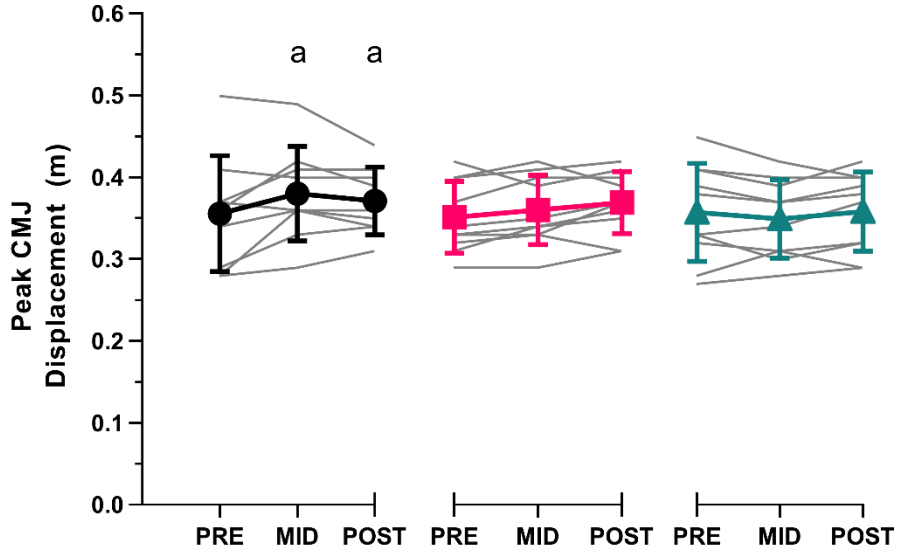
Figure 5.3 - Within-group changes in leg press 1-RM strength at PRE-, MID- (+5 weeks) and POST-training (+9 weeks). Data are group mean ± SD, plus individual participant data (grey lines). A = meaningful change from PRE; B = meaningful change from MID; (i.e. ES ≥ 0.2, plus ≥ 75% chance that the true change between time-points is substantial). Capital letter denotes effect remained clear after adjustment for multiple comparisons. For between-group comparisons, see Table 5.4.

Countermovement Jump (CMJ) Performance

During weeks 1 to 5 *RO* training induced small improvements in all CMJ parameters (*mean* ± *SD*, *peak displacement*: 6.9 ± 9.8 %, *ES* ±*90% CI* 0.41 ±0.40; *peak velocity:* 3.0 ± 4.2 %, 0.42 ±0.40; *peak force:* 8.7 ± 9.6 %, 0.37 ±0.28; *peak power:* 9.7 ± 5.5 %, 0.50 ±0.21), but there were no meaningful changes in any CMJ performance measures following *ER* and *RE* training during this period (i.e., all effects were either possibly improved, trivial or unclear). For all groups, there were also no meaningful changes to any CMJ variable following weeks 6 to 9 of training. Overall, from *PRE* to *POST* training, *RO* training induced small improvements in all CMJ parameters (*peak displacement*: 5.3 ± 6.3 %, 0.32 ±0.26; *peak velocity:* 2.2 ± 2.7 %, 0.31 ±0.25; *peak force:* 10.1 ± 10.1 %, 0.43 ±0.29; *peak power:* 9.8 ± 7.6 %, 0.50 ±0.26). *ER* training also induced a small meaningful improvement in peak velocity (2.2 ± 2.7 %, 0.31 ±0.23). All other changes from *PRE* to *POST* training for both concurrent groups were either trivial or not meaningful (Figure 5.4 and Figure 5.5).

From *PRE* to *MID* training, *RO* training induced greater improvements in peak displacement (*ES* ±*90% CI*, *ROvsRE* -0.55 ±0.42) and velocity (*ROvsRE* -0.57 ±0.42) compared to *RE*, plus greater improvements in peak force (*ROvsER* -0.37 ±0.37; *ROvsRE* -0.35 ±0.37) and peak power (*ROvsER* -0.40 ±0.22; *RO vs RE* -0.53 ±0.24) than both concurrent training groups. The change in peak velocity was also greater following *ER* than *RE* (*ERvsRE* -0.33 ±0.23); however, there were no other meaningful differences in CMJ adaptations between the concurrent groups after 5 weeks of training. From *MID* to *POST*, there were no meaningful between-group differences for changes in any CMJ performance measure, regardless of comparisons between concurrent vs resistance-only training, or between concurrent exercise orders. Overall, from *PRE* to *POST*, *RO* training induced a greater change in peak CMJ displacement (-0.33 ±0.29), force (-0.38 ±0.35) and power (-0.33 ±0.28) than *RE*. There were no other meaningful between-group differences for changes in any other CMJ performance measure, whether comparing concurrent to single-mode training, or between concurrent exercise orders (Table 5.4).

(i)



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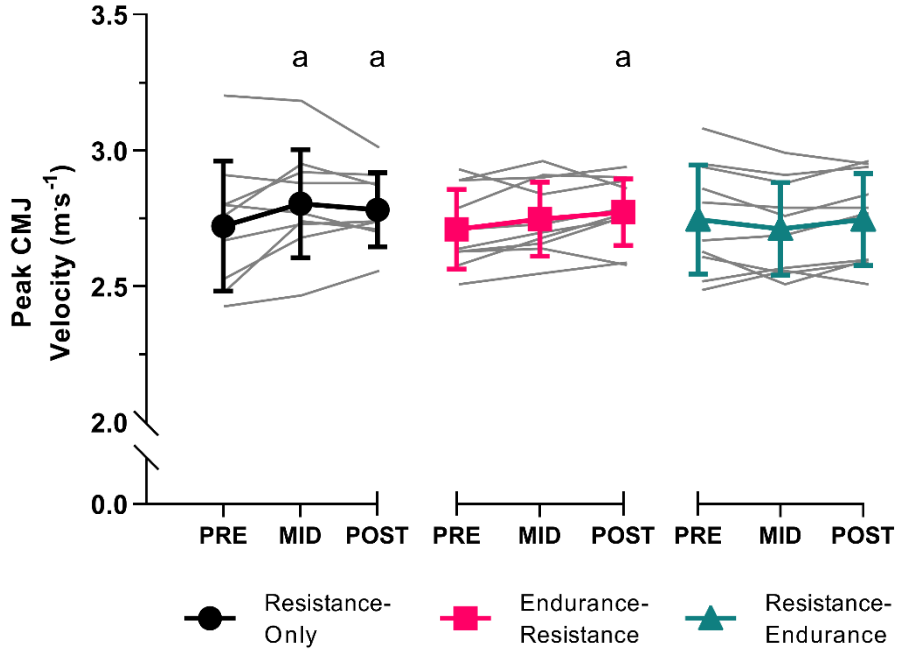
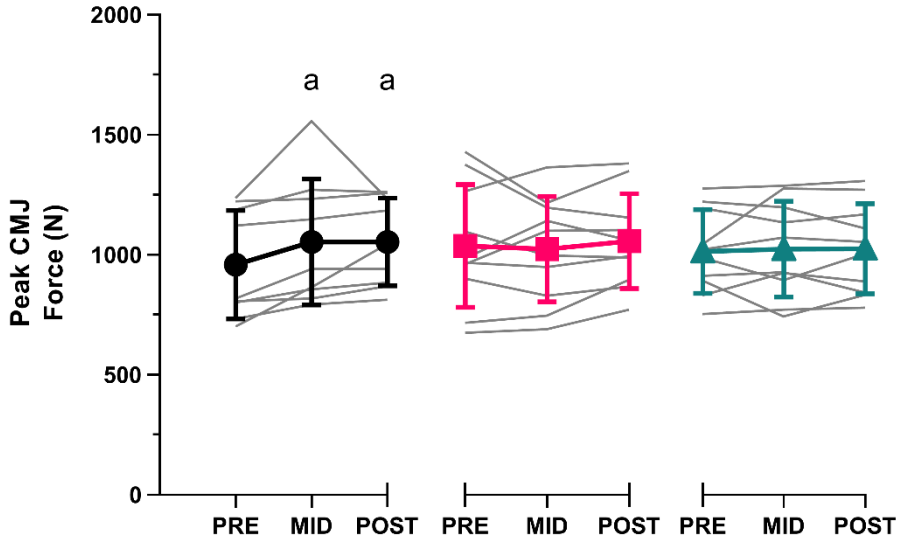


Figure 5.4 - Within-group changes in (i) peak CMJ displacement and (ii) peak CMJ velocity at PRE-, MID-(+5 weeks) and POST-training (+9 weeks). Data are group mean ± SD, plus individual participant data (grey lines). a = meaningful change from PRE (i.e. ES ≥ 0.2, plus ≥ 75% chance that the true change between time-points is substantial). For between-group comparisons, see Table 5.4.

(i)



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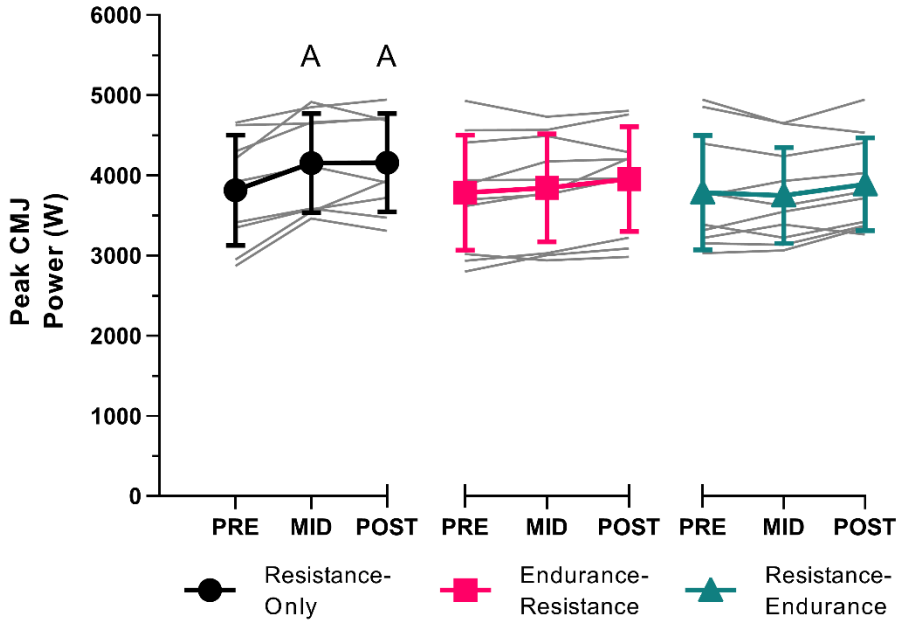


Figure 5.5 - Within-group changes in (i) peak CMJ force and (ii) peak CMJ power, at PRE-, MID- (+5 weeks) and POST-training (+9 weeks). Data are group mean ± SD, plus individual participant data (grey lines). a/A = meaningful change from PRE (i.e. ES ≥ 0.2, plus ≥ 75% chance that the true change between time-points is substantial). Capital letter denotes effect remained clear after adjustment for multiple comparisons. For between-group comparisons, see Table 5.4.

Body Composition

When analysing changes from *PRE* to *MID*, and *MID* to *POST* training, all effects for total, upper, and lower-body lean mass, as well as total fat mass, were either clearly trivial or not meaningful in all groups. Overall, nine weeks of training led to small increases in total-body lean mass following *ER* (*mean* ± *SD* 3.7 ± 2.4 %, *ES* ±*90% CI* 0.27 ±0.11) and *RE* (3.5 ± 1.4 %, 0.25 ±0.08), with the latter group also eliciting small increases in upper-body lean mass (3.5 ± 1.6 %, 0.24 ±0.07) and reductions in total fat mass (-10.5 ± 11 %, -0.27 ±0.16). All other within-group changes were either clearly trivial, or not meaningful, for all groups (Figure 5.6 and Figure 5.7). Only the difference between *RO* and *RE* for the change in total fat mass from *PRE* to *POST* training was meaningful (*ES* ±*90%CI* -0.32 ±0.18), in favour of *RE*. All other between-group differences for changes in body composition parameters were either clearly trivial or not meaningful (Table 5.4).

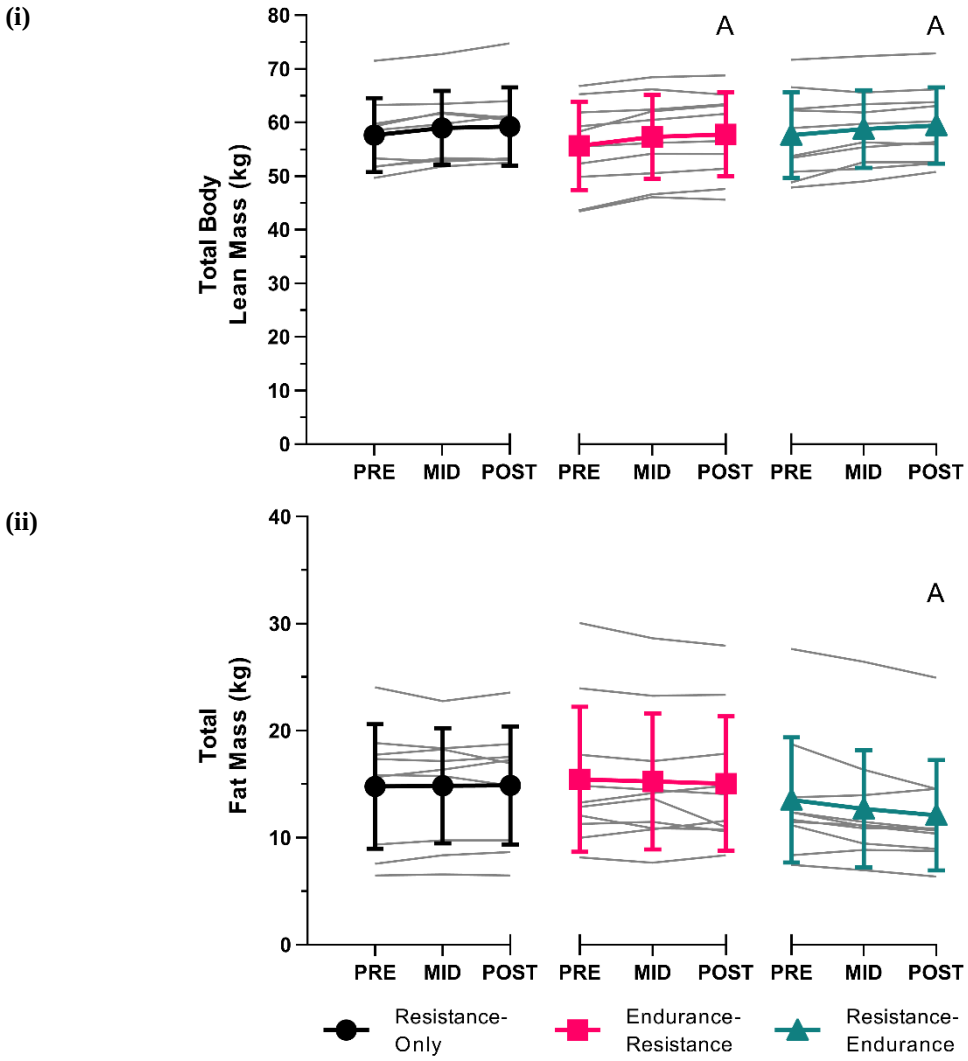


Figure 5.6 - Within-group changes in (i) total lean body mass and (ii) total fat mass at PRE-, MID- (+5 weeks) and POST-training (+9 weeks). Data are group mean ± SD, plus individual participant data (grey lines). A = meaningful change from PRE; (i.e. ES ≥ 0.2, plus ≥ 75% chance that the true change between time-points is substantial). Capital letter denotes effect remained clear after adjustment for multiple comparisons. For between-group comparisons, see Table 5.4.

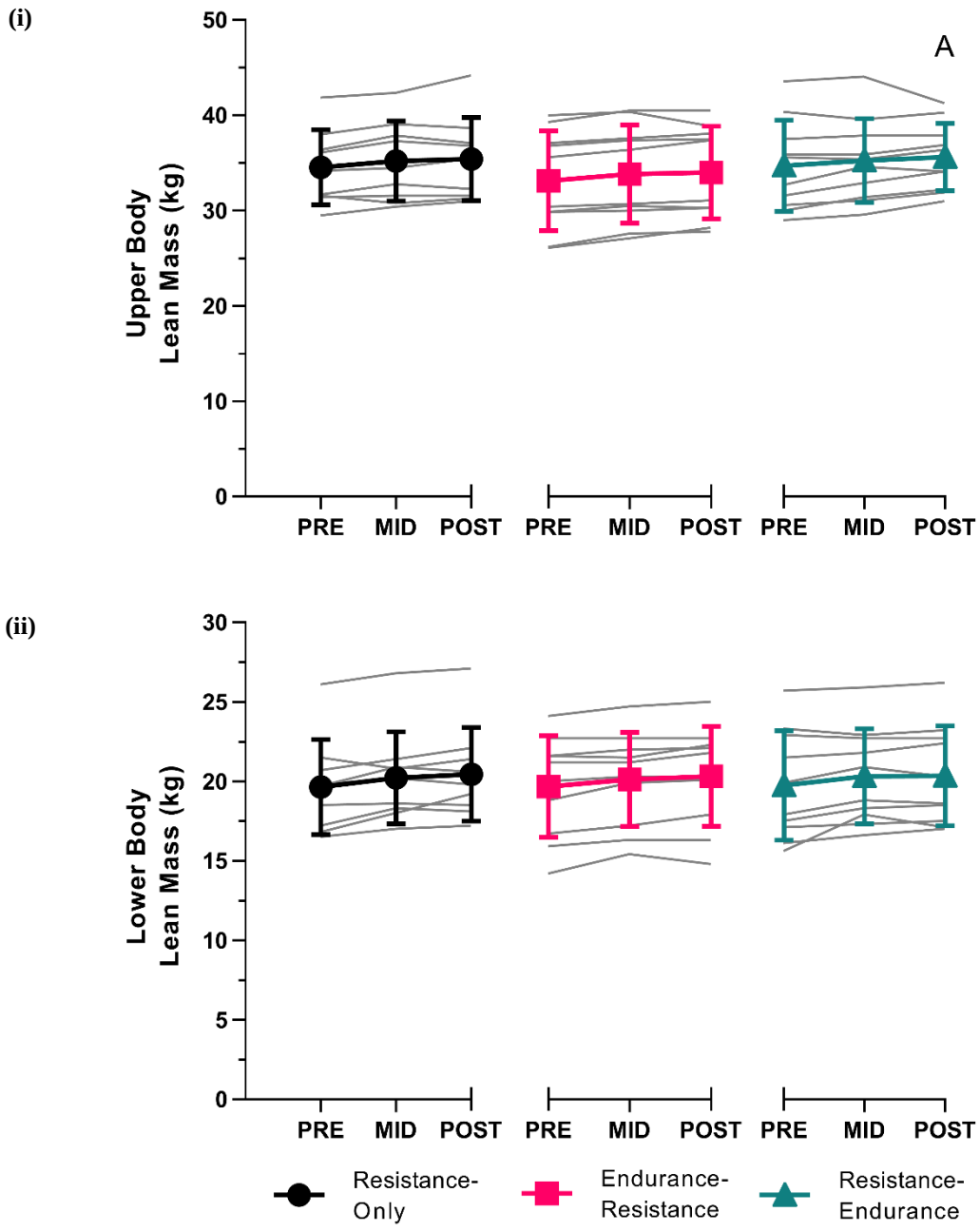


Figure 5.7 - Within-group changes in (i) upper lean body mass and (ii) lower lean body mass at PRE-, MID- (+5 weeks) and POST-training (+9 weeks). Data are group mean ± SD, plus individual participant data (grey lines). A = meaningful change from PRE (i.e. ES ≥ 0.2, plus ≥ 75% chance that the true change between time-points is substantial). Capital letter denotes effect remained clear after adjustment for multiple comparisons. For between-group comparisons, see Table 5.4.

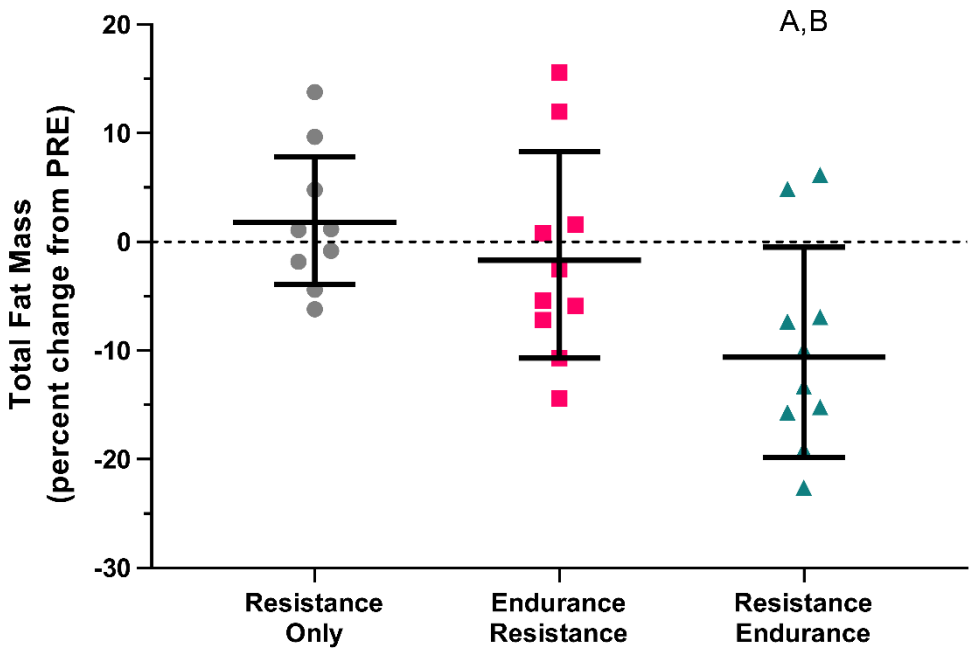


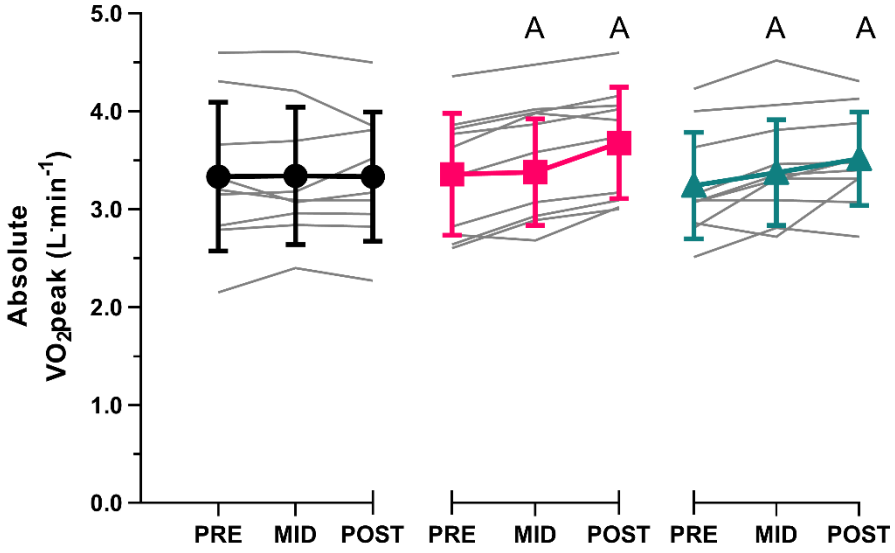
Figure 5.8 – Percent changes in total fat mass from PRE- to POST-training. Data are group mean ± SD, with individual change scores. A = meaningful change from PRE (i.e. ES ≥ 0.2, plus ≥ 75% chance that the true change between time-points is substantial). B = change in RE is substantially different from RO. Capital letter denotes effect remained clear after adjustment for multiple comparisons.

Aerobic Fitness

The first 5 weeks of concurrent training elicited small, meaningful improvements in $\dot{V}O_{2peak}$ in both absolute (*mean ± SD, ER* 6.7 ± 5.0 %, *ES ±90%CI* 0.33 ±0.17; *RE* 6.3 ± 6.7 %, 0.32 ±0.22) and relative terms (*ER* 5.4 ± 4.8 %, 0.31 ±0.18; *RE* 5.5 ± 7.0 %, 0.31 ±0.25). Further changes during weeks 6 to 9 were either not meaningful or clearly trivial. Overall, from *PRE* to *POST* training, both *ER* and *RE* training led to small improvements in both absolute (*ER* 10.7 ± 1.9 %, 0.53 ±0.13; *RE* 8.7 ± 5.0 %, 0.43 ±0.17) and relative $\dot{V}O_{2peak}$ (*ER* 8.6 ± 3.4 %, 0.48 ±0.15; *RE* 7.6 ± 4.2 %, 0.43 ±0.17) (Figure 5.9). Initial improvements (weeks 1-5) to the lactate threshold with concurrent training were small (*RE* 9.7 ± 7.9 %, 0.40 ±0.21) to moderate (*ER* 15.0 ± 4.7 %, 0.60 ±0.17). For all 3 groups, changes to the lactate threshold during weeks 6 to 9 were either not meaningful or unclear. Overall, nine weeks of concurrent training induced moderate improvements in the lactate threshold (*ER* 19.6 ± 5.5 %, 0.77 ±0.21; *RE* 16.1 ± 12.8 %, 0.64 ±0.33) (Figure 5.10). Concurrent training also improved peak aerobic power from weeks 1 to 5 (*ER* 8.8 ± 7.6 %, 0.39 ±0.21; *RE* 7.7 ± 5.0 %, 0.35 ±0.15) and weeks 6 to 9 (*ER*: 5.2 ± 2.5 %, 0.24 ±0.08; *RE* 5.7 ± 4.5 %, 0.26 ±0.13), culminating in moderate improvements following 9 weeks of training (*ER* 14.5 ± 7.1 %, 0.63 ±0.23; *RE* 13.9 ± 7.5 %, 0.61 ±0.23). Changes to peak aerobic power following *RO* training were clearly trivial throughout (Figure 5.10).

From *PRE* to *MID*, both concurrent groups elicited greater improvements than *RO* for relative $\dot{V}O_{2peak}$ (*ES ±90% CI, ROvsER* 0.44 ±0.24; *ROvsRE* 0.45 ±0.29), the lactate threshold (*ROvsER* 0.61 ±0.35; *ROvsRE* 0.41 ±0.36) and peak aerobic power (*ROvsER* 0.49 ±0.28; *ROvsRE* 0.44 ±0.24). Only *ER* showed a small meaningful difference from *RO* for absolute $\dot{V}O_{2peak}$ (*ROvsER* 0.29 ±0.21). From *MID* to *POST,* there were no meaningful between-group differences for any comparison of changes in aerobic fitness (i.e., all differences were either clearly trivial, or not meaningful, or not clear). Overall, from *PRE* to *POST*, compared to *RO*, both concurrent training groups elicited greater improvements in both absolute (*ROvsER* 0.49 ±0.21; *ROvsRE* 0.40 ±0.24) and relative $\dot{V}O_{2peak}$ (*ROvsER* 0.61 ±0.22; *ROvsRE* 0.56 ±0.23), as well as the lactate threshold (*ROvsER* 0.87 ±0.47; *ROvsRE* 0.74 ±0.51) and peak aerobic power (*ROvsER* 0.68 ±0.29; *ROvsRE* 0.65 ±0.29). There were no clear differences between concurrent exercise orders (Table 5.4).

(i)



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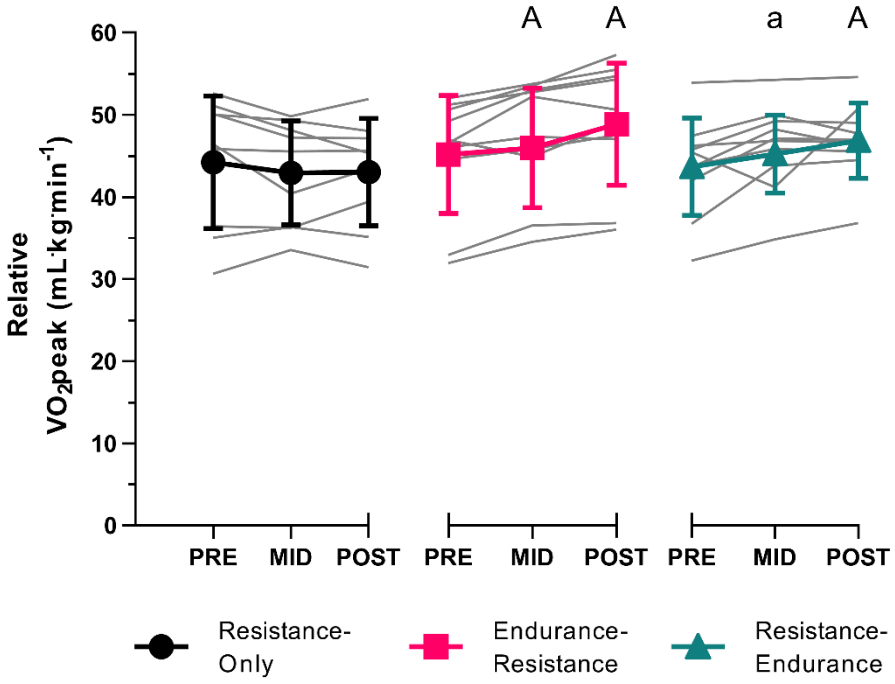

Figure 5.9 - Within-group changes in (i) absolute $\dot{V}O_{2peak}$ and (ii) relative $\dot{V}O_{2peak}$ at PRE-, MID- (+5 weeks) and POST-training (+9 weeks). Data are group mean ± SD, plus individual participant data (grey lines). a/A = meaningful change from PRE; (i.e. ES ≥ 0.2, plus ≥ 75% chance that the true change between time-points is substantial). Capital letter denotes effect remained clear after adjustment for multiple comparisons. For between-group comparisons, see Table 5.4.

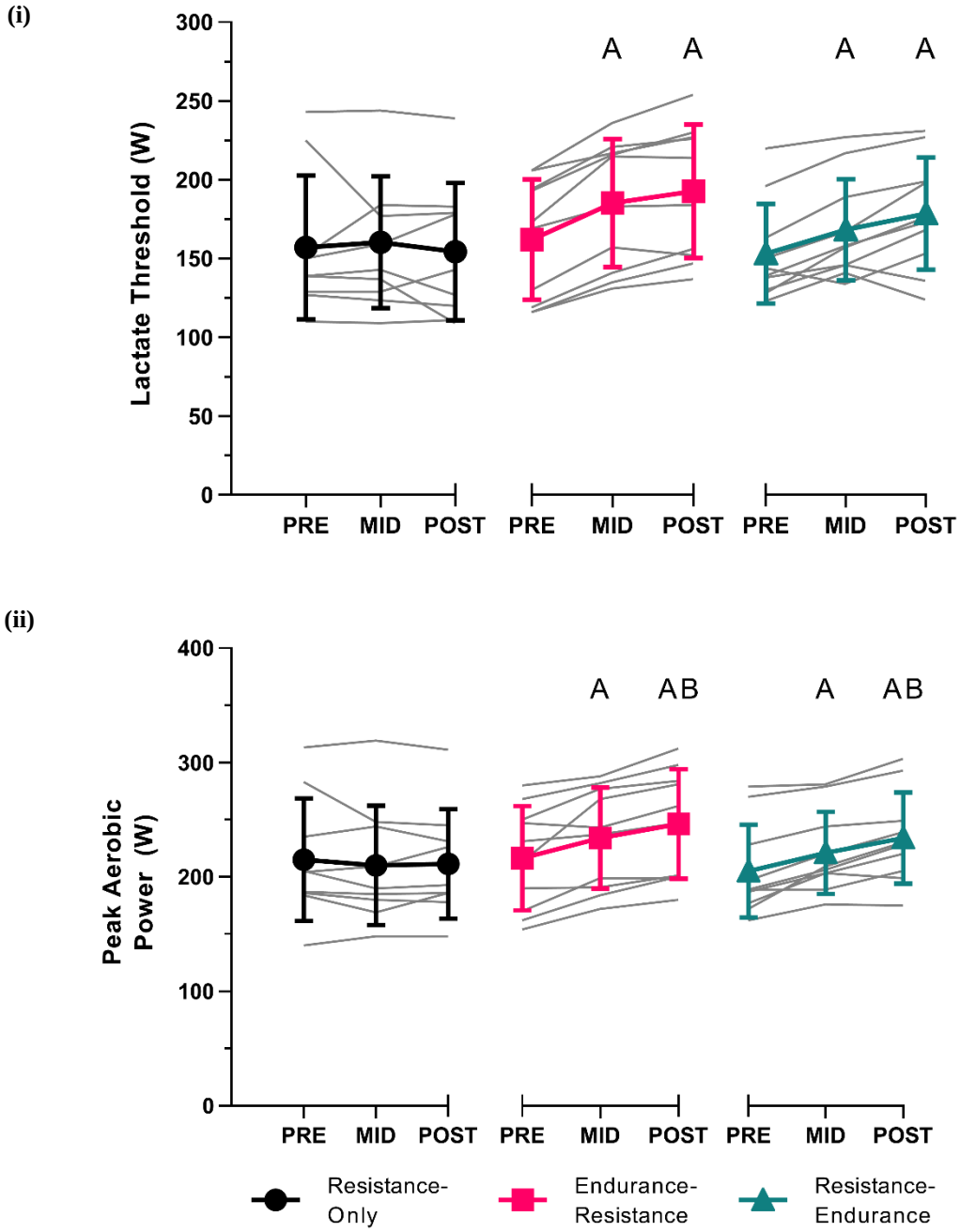

Figure 5.10 - Within-group changes in (i) lactate threshold, and (ii) peak aerobic power, at PRE-, MID-(+5 weeks) and POST-training (+9 weeks). Data are group mean ± SD, plus individual participant data (grey lines). A = meaningful change from PRE; B = meaningful change from MID; (i.e. ES ≥ 0.2, plus ≥ 75% chance that the true change between time-points is substantial). Capital letter denotes effect remained clear after adjustment for multiple comparisons. For between-group comparisons, see Table 5.4.

Table 5.4 - Between-group comparisons of percent changes in all performance measures, from PRE to MID, MID to POST, and PRE to POST training. Data are mean percent differences with 90% confidence intervals (90%CI), plus magnitude-based decisions regarding standardised effect sizes (ES) and qualitative likelihoods†

	PRE to MID			**MID to POST**			**PRE to POST**		
	'Interference Effect'		***'Order Effect'***	***'Interference Effect'***		***'Order Effect'***	***'Interference Effect'***		***'Order Effect'***
	RO vs ER	**RO vs RE**	**ER vs RE**	**RO vs ER**	**RO vs RE**	**ER vs RE**	**RO vs ER**	**RO vs RE**	**ER vs RE**
Lower-Body Maximal Strength									
Leg Press 1-Rep. Max	2.2, ±4.7	1.6, ±3.3	-0.6, ±4.2	1.1, ±5.2	1.1, ±5.6	0.0, ±3.2	3.4, ±8.5	2.8, ±8.4	-0.6, ±6.0
	Trivial, •	***Trivial,*** •	*Trivial,* •	*Trivial,* •	*Trivial,* •	***Trivial,*** •	*Trivial*	*Trivial*	*Trivial,* •
Lower-Body Maximal Power									
Peak CMJ Displacement	-4.2, ±6.3	-8.4, ±6.0	-4.4, ±3.4	3.5, ±4.4	3.6, ±4.3	0.1, ±4.0	-0.8, ±5.0	-5.1, ±4.3	-4.3, ±4.1
	Small, •↓	***Small,*** •↓	***Small,*** °↓	*Small,* °↑	*Small,* °↑	*Trivial*	*Trivial,* °	***Small,*** •↓	***Small,*** °↓
Peak CMJ Velocity	-1.7, ±2.8	-3.9, ±2.8	-2.3, ±1.5	1.7, ±2.0	2.0, ±1.9	0.3, ±1.6	0.0, ±2.2	-2.0, ±1.9	-2.0, ±1.8
	Small, °↓	***Small,*** •↓	***Small,*** •↓	*Small,* °↑	*Small,* °↑	*Trivial,* •	*Trivial,* °	***Small,*** °↓	***Small,*** °↓
Peak CMJ Force	-8.0, ±7.4	-7.4, ±7.6	0.5, ±8.5	2.6, ±7.9	-0.8, ±7.5	-3.3, ±5.5	-5.6, ±7.4	-8.2, ±7.1	-2.7, ±7.0
	Small, •↓	***Small,*** °↓	*Trivial*	*Trivial*	*Trivial,* °	*Trivial,* °↓	***Trivial,*** °↓	***Small,*** •↓	*Trivial,* °↓
Peak CMJ Power	-7.1, ±3.5	-9.4, ±3.5	-2.5, ±2.9	2.9, ±3.9	3.8, ±3.9	0.9, ±3.2	-4.4, ±5.1	-6.0, ±4.7	-1.6, ±3.9
	Small, •↓	***Small,*** •↓	***Trivial,*** °↓	*Trivial,* °↑	*Small,* °↑	*Trivial,* •	***Small,*** °↓	***Small,*** •↓	*Trivial,* •
Body Composition									
Total Lean Mass	0.7, ±1.5	0.0, ±1.6	-0.7, ±1.5	0.3, ±1.2	0.7, ±1.2	0.4, ±1.0	0.9, ±1.7	0.7, ±1.4	-0.2, ±1.5
	Trivial, •	*Trivial,* •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •
Upper Body Lean Mass	0.2, ±1.4	0.3, ±1.8	0.1, ±1.6	0.1, ±1.7	0.7, ±2.2	0.6, ±2.1	0.3, ±1.8	1.1, ±1.5	0.8, ±1.7
	Trivial, •	*Trivial,* •	***Trivial,*** •	*Trivial,* •	*Trivial,* •	*Trivial,* •	*Trivial,* •	***Trivial,*** •	***Trivial,*** •
Lower Body Lean Mass	-0.4, ±2.2	0.2, ±2.6	0.6, ±2.2	-0.2, ±2.0	-0.9, ±2.0	-0.7, ±1.8	-0.7, ±2.7	-0.7, ±2.7	-0.1, ±1.7
	Trivial, •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •
Total Fat Mass	-2.1, ±4.0	-7.7, ±4.1	-5.7 ±5.0	-1.5, ±5.4	-4.7, ±3.4	-3.3, ±5.3	-3.5, ±5.9	-12.0, ±5.9	-8.8, ±7.0
	Trivial, •	***Small,*** °↑	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	***Trivial,*** •	*Trivial,* •	***Small,*** •↑	***Small,*** °↑
Maximal Aerobic Fitness									
$\dot{V}O_{2peak}$ - Absolute	5.8, ±4.1	5.4, ±4.9	-0.4, ±4.8	3.9, ±4.1	2.4, ±5.3	-1.4, ±4.8	10.0, ±4.0	8.0, ±4.7	-1.8, ±2.9
	Small, •↑	*Small,* °↑	*Trivial*	*Small,* °↑	*Trivial*	*Trivial,* •	***Small,*** •↑	***Small,*** •↑	***Trivial,*** •
$\dot{V}O_{2peak}$ - Relative	7.9, ±4.1	8.0, ±5.2	0.1, ±4.9	2.8, ±4.1	1.8, ±5.5	-1.0, ±5.0	11.0, ±3.5	10.0, ±3.7	-0.9, ±2.9
	Small, •↑	***Small,*** •↑	*Trivial*	*Small,* °↑	*Trivial*	*Trivial*	***Moderate,*** •↑	***Small,*** •↑	*Trivial,* •
Lactate Threshold	15.2, ±8.9	9.9, ±9.1	-4.6, ±4.8	6.2, ±7.8	8.0, ±9.3	1.7, ±6.0	22.3, ±12.4	18.7, ±13.6	-3.0, ±7.2
	Moderate, •↑	*Small* •↑	***Small,*** °↓	*Small,* °↑	*Small,* °↑	*Trivial,* •	***Moderate,*** •↑	*Moderate,* •↑	*Trivial,* °↓
Peak Aerobic Power	11.0, ±6.2	9.8, ±5.2	-1.0, ±4.9	4.3, ±3.3	4.8, ±3.8	0.5, ±2.8	15.7, ±6.2	15.1, ±6.4	-0.5, ±5.5
	Small, •↑	***Small,*** •↑	*Trivial,* •	***Small,*** °↑	***Small,*** °↑	***Trivial,*** •	***Moderate,*** •↑	***Moderate,*** •↑	*Trivial*

*†ES thresholds: <0.20 = trivial; 0.20-0.60 = small; 0.60-1.2 = moderate. 0.20 defined smallest important effects. •meaningful difference (i.e., ≥ 75 % chance the true difference is substantial); °possible difference (i.e. 25-75% chance; not meaningful). Unclear comparisons have no symbol. Effects that remained clear after adjustment for multiple inferences are in **bold**. ↓ = interference; ↑ = improvement.*

5.4 Discussion

The purpose of this study was to investigate the interference effect in healthy, active men, with an additional focus on the influence of the concurrent session order on training adaptations. The 9-week training program was of a moderate frequency (3 days a week) and the same-day concurrent sessions were separated by 3 hours of recovery. The main findings were that concurrent training, irrespective of the session order, led to improvements in maximal strength and lean body mass comparable to that of resistance-only training. Furthermore, independent of the session sequence, both concurrent groups similarly improved all markers of aerobic fitness, more than *RO*. However, compared to resistance-only training, performing endurance after resistance training (*RE*) attenuated the development of CMJ displacement, force, and power; the reverse order had a possibly negative effect on these parameters. Finally, only the RE group displayed a meaningful reduction of total fat mass.

Concurrent exercise session order

The present concurrent training program induced comparable improvements in dynamic strength, lean-body mass, and aerobic fitness, regardless of the order in which the sessions were performed. Some studies have previously reported greater strength adaptations when resistance exercise is performed first, attributed to superior neural (Cadore et al., 2012, Cadore et al., 2013) and hypertrophic adaptations (Pinto et al., 2014); this was also recently supported by two meta-analyses (Eddens et al., 2018, Murlasits et al., 2018). Others have also shown superior improvements in endurance adaptations and performance when aerobic sessions were prioritised (Chtara et al., 2005, Kuusmaa et al., 2016, Schumann et al., 2015). However, these studies performed concurrent training within the same session, compared to the present study which employed a 3-hour recovery window between modes, during which any potentially adverse effects of a prior bout of endurance exercise on subsequent resistance exercise performance, such as residual fatigue, may have been mitigated. The present findings are also supported by several studies reporting no order effect on dynamic strength (Chtara et al., 2008, Collins and Snow, 1993, Eklund et al., 2016, Gravelle and Blessing, 2000, Schumann et al., 2014a), various measures of muscle mass (Cadore et al., 2012, Cadore et al., 2013, Davitt et al., 2014, Schumann et al., 2014a), aerobic capacity (Cadore et al., 2012, Collins and Snow, 1993, Davitt et al., 2014, MacNeil et al., 2014, Schumann et al., 2014a), and aerobic power (Cadore et al., 2012, Eklund et al., 2015, Eklund et al., 2016, Schumann et al., 2014a, Schumann et al., 2014b). Indeed, other than dynamic strength development, both previous meta-analyses also reported no order effect on aerobic capacity (Murlasits et al., 2018, Eddens et al., 2018), static strength, hypertrophy, or body fat percentage (Eddens et al., 2018). Whilst there were *possible* order effects for changes in countermovement jump performance (favouring *ER*) and fat mass loss (favouring *RE*) in the present study, more data are required to gain clarity on the importance of these effects, which

were likely confounded by the large variation in individual responses for these measures. Indeed, adequate estimation and interpretation of individual responses requires a much larger sample size ($6.5 \times n^2$, where n is the sample size required for the mean effect), as well as repeating post-intervention assessments (Hopkins, 2018); neither of which were feasible at the time of conducting this study. As such and given the similar training adaptations to both concurrent interventions, this discussion will largely focus on the comparison between resistance-only and concurrent training, regardless of the order.

Maximal lower-body dynamic strength

Whilst previous work from our lab (Fyfe et al., 2016a) reported attenuated strength gains when resistance training was preceded by high-intensity interval cycling (similar to the present *ER* group), the lack of interference to strength in the present study is commensurate with several other reports of comparable strength gains with concurrent and single-mode resistance training (Balabinis et al., 2003, de Souza et al., 2013, Donges et al., 2013, Glowacki et al., 2004, Sale et al., 1990b, Volpe et al., 1993, Tsitkanou et al., 2017). The relative change in strength following *RO* training in the present study (23.9 ± 12.4 %) was lower than previously reported in our lab (38.5 ± 8.5 %, (Fyfe et al., 2016a)); this difference is likely due to variations between the respective resistance training program designs. Indeed, during the last 4 weeks of training, Fyfe *et al.* (2016a) adopted a lower repetition volume (~120-80 reps per session) and progressed to a higher intensity (9-RM to 4-RM), typical of maximal strength training (Kraemer and Ratamess, 2004), whilst the present study employed a higher repetition volume (~240-120 reps per session) and a lower intensity (12-RM to 6-RM), directed more towards hypertrophy. This may also reflect the minor discrepancies in total lean mass gains between the two studies (1.6 ± 1.4 % vs 2.8 ± 2.0 %). Nonetheless, the degree of improvement observed herein (~24-28 %) is typical of previously-reported 1-RM leg press gains in untrained and recreationally-active individuals (Gravelle and Blessing, 2000, Karavirta et al., 2011, Mikkola et al., 2012).

According to the 'acute interference hypothesis', the quality of a resistance session may be reduced when performed concurrently with endurance exercise, due to either an anticipatory reduction in effort and training volume if performed first, or due to residual fatigue induced by a prior endurance session (Sale et al., 1990a, Leveritt and Abernethy, 1999, Leveritt et al., 1999). As such, a reduction in effort or training volume may increase the possibility of an interference effect. In the present study, no clear differences were observed between any of the groups for resistance training volume throughout the program. This may be attributed to the 3-hour recovery period separating the concurrent sessions, which may have been sufficient for the participants to recover, and afforded the opportunity to implement nutritional strategies to support subsequent exercise performance and training adaptations (i.e., replacement of carbohydrates, protein and

fluids). Consequently, it appears the quality of the second session (indicated by the matched external load between groups), and thus the stimulus for adaptation, was not diminished, thereby reducing the likelihood of observing an interference effect. However, the *internal* load data suggest the *ER* group perceived the resistance sessions to be harder than both groups who commenced with resistance exercise. Furthermore, compared to the *RO* group, the *ER* group also scored lower (i.e., worse) for perceptions of total wellbeing, as well as general muscle soreness, stress and mood before their afternoon resistance training sessions. Having already completed an endurance session earlier that day, they may have been experiencing some residual soreness from that session. The *RO* group also had a greater recovery period between their training sessions, and a lower total training volume than the *ER* group due to the nature of the study design, which together may also have contributed to the lower perceptions of soreness. Whether extending the duration of the current training program beyond 9 weeks would have led to more observable differences in resistance training loads and subsequent strength adaptations remains speculative; however, similar findings have been observed elsewhere (Izquierdo et al., 2005, Cadore et al., 2013). In elderly men, the group who performed resistance training *first* showed a greater increase in training load over 12 weeks compared to the reverse order (Cadore et al., 2013), and others have only observed an interference to strength after periods longer than 8 weeks (Hickson, 1980, Izquierdo et al., 2005). However, it is also worth noting that the "readiness-to-train" questionnaire was conducted on arrival to each session, prior to any exercise taking place; whether the responses would have differed had the questionnaire been completed after a warm-up is worth considering if using this questionnaire again. Nonetheless, the present concurrent training program did not limit the development of maximal, lower-body dynamic strength, compared to resistance-only training.

Lean body mass

Concurrent training has previously been shown to attenuate hypertrophy at the individual myofiber (Kraemer et al., 1995, Bell et al., 2000, Putman et al., 2004), whole-muscle (Ronnestad et al., 2012), and whole-body level (Fyfe et al., 2016a), which may contribute to reductions in strength development. Using a similar training protocol to the present study, Fyfe *et al.* (2016a) reported attenuated lower-body lean mass (measured via DXA) when resistance sessions were preceded by HIIT cycling (4.1 ± 2.0 % vs 1.8 ± 1.6 %). In the present study, all groups showed small, positive changes in DXA-derived lean-body mass. However, changes in total lean mass were only considered meaningful for *ER* (3.7 ± 2.4 %) and *RE* (3.5 ± 1.4 %), with *RO* training inducing a *possible* improvement (2.8 ± 2.0 %). Importantly, all between-group comparisons were trivial (i.e., ES < 0.2; likelihood ≥ 75 %) indicating that over the 9-week period there was little difference between the concurrent and resistance-only training groups. McCarthy *et al.* (2002) demonstrated comparable myofiber and whole-muscle hypertrophy with concurrent and

resistance-only training, in sedentary healthy men who trained for 3 days a week for 10 weeks. Others have also shown equivalent (de Souza et al., 2014, Häkkinen et al., 2003) and greater (Lundberg et al., 2013, Mikkola et al., 2012) hypertrophic adaptations with concurrent, compared to resistance-only training. A recent meta-analysis also reported no significant interference effect of concurrent HIIT and resistance training on both total and lower-body lean muscle mass (Sabag et al., 2018). In support of this, the present concurrent training program also did not interfere with lean-body mass gains compared to resistance-only training.

There are several possible explanations why concurrent training did not interfere with lean-body mass gains in the present study. High-intensity interval (HIIT) cycling was employed as the endurance exercise modality, which is more biomechanically similar to the lower-body resistance exercises (Gergley, 2009) and may potentially induce less eccentric muscle damage compared to running (Wilson et al., 2012). Furthermore, given that greater recruitment of higher-threshold, fast-twitch motoneurons occurs with high-intensity contractions than low-intensity contractions (Duchateau et al., 2006) it is possible that the nature of the HIIT cycling bouts provided a synergistic, rather than antagonistic, hypertrophic stimulus to a greater range of muscle fibres (Murach and Bagley, 2016, Sabag et al., 2018). Furthermore, the participants' training status likely contributed to the lack of interference, as growing lines of evidence suggest endurance training alone can induce some degree of hypertrophic adaptations in untrained populations (Konopka and Harber, 2014). Finally, in line with nutritional recommendations for maximising post-exercise protein synthesis (Morton et al., 2015), all participants were given a protein supplement after every training session, providing 0.25 $g \cdot kg^{-1}$ of protein (~20 g whey, ~2 g leucine per serving). Furthermore, the food diary data suggest that participants in all groups habitually consumed ~1.9-2.1 $g \cdot kg \cdot d^{-1}$ of protein, which is greater than the upper limit for maximising changes in DXA-derived fat-free mass with resistance training (Morton et al., 2018). When considering the existing literature, few studies provide supportive evidence for an interference effect to hypertrophy (Murach and Bagley, 2016). Indeed attenuations to strength have been observed without interference to hypertrophy, including the original work of Hickson (1980), which showed comparable gains in thigh girth. Furthermore, consideration must also be given to the different methods by which hypertrophic adaptations are detected (e.g. MRI, CT, ultrasound, DXA, skinfolds), regarding their respective strengths, limitations, sensitivity and error in measuring training-induced changes in muscle mass, often over short training periods (Aragon et al., 2017, Lundberg, 2019). Nonetheless, the present findings further support that concurrent training does not interfere with lean-body mass gains. This may have been a product of the training program design, the biomechanical similarities between the endurance and resistance modes, the participants' training status, and their habitual protein intake.

Countermovement jump performance

Despite no between-group differences to changes in lean-body mass or strength, there may have been some attenuations to neuromuscular adaptations, reflected by changes in countermovement jump (CMJ) performance. Indeed, it has been posited that power development may be more susceptible to the interference effect (Kraemer et al., 1995, Wilson et al., 2012), and others have observed '*selective'* attenuations to power or the rate of force development with concurrent training, despite no interference to strength or hypertrophy (Dudley and Djamil, 1985, Häkkinen et al., 2003, Kraemer et al., 1995, Mikkola et al., 2012, Tsitkanou et al., 2017). In the present study, nine weeks of *RO* training induced small improvements in all measures of CMJ performance, despite not completing any specific power or explosive strength training. This is consistent with resistance training-unaccustomed men who improved jump performance after both heavy strength and ballistic resistance training (Cormie et al., 2010). Only *ER* training induced comparable improvements in CMJ velocity to *RO*, whilst *RE* training interfered with CMJ displacement, force and power development, and possibly impaired CMJ velocity. Our findings are comparable to Fyfe *et al.* (2016a), who reported attenuated improvements in CMJ force, and to others who reported impaired jump performance following concurrent training (Hennessy and Watson, 1994, Ronnestad et al., 2012). Given that there was no interference to hypertrophic adaptations, the interference to CMJ force and power may have resulted from other neuromuscular mechanisms. Such mechanisms may relate to differential fibre-type transformations between concurrent and single-mode training, subsequently limiting the contractile capacity of the muscle (Kraemer et al., 1995), or attenuated neural adaptations such as reductions in rapid voluntary activation of the trained muscles (Häkkinen et al., 2003). However, it should be noted that changes at the muscle fibre level do not always represent changes at the whole-muscle or whole-body level (de Souza et al., 2014, de Souza et al., 2013, McCarthy et al., 2002). In the present study neither fibre-type changes nor voluntary activation were measured, making it difficult to speculate the exact mechanisms contributing to the divergent changes in CMJ parameters between groups. Nonetheless, the present data give some credence to the notion that measures pertaining to rapid force and power production may be more susceptible to the interference effect than strength and muscle mass. However, as alluded to previously, more research with a larger sample size is required to better elucidate both the interference and order effects of this current training program, as the large variability in individual responses likely contributed to many of the effects being interpreted as only *possible* changes or differences.

Aerobic fitness

Unlike strength, muscle hypertrophy and power, improvements in endurance do not appear to be as susceptible to the interference effect (Wilson et al., 2012). Indeed, the present concurrent training program, regardless of exercise order, induced small-to-moderate improvements in all

variables pertaining to aerobic fitness ($\dot{V}O_{2peak}$, $\dot{W}_{LT}$ and $\dot{W}_{peak}$), whilst resistance-only training did not. These findings are not unexpected, given the lack of differences between groups in both internal and external training loads to the endurance training program. The observed improvements in relative $\dot{V}O_{2peak}$ (~8 to 9%) are commensurate with similar studies in untrained or recreationally-active populations, showing no interference (Bell et al., 2000, Dudley and Djamil, 1985, Hickson, 1980, Leveritt et al., 2003), nor an effect of exercise order on endurance capacity (Cadore et al., 2012, Collins and Snow, 1993, MacNeil et al., 2014, Schumann et al., 2014a, Schumann et al., 2015). Chtara *et al.* (2005) observed superior improvements in $\dot{V}O_{2peak}$ and 4 km time-trial running performance when endurance exercise was performed prior to resistance, and greater percent changes in $\dot{V}O_{2peak}$ than those reported in the present study. This is likely due to differences in the training protocols employed, as the former study involved HIIT running combined with a circuit-based resistance regime that also improved endurance performance and capacity, without the addition of endurance training (Chtara et al., 2005). Some studies have reported an interference effect to the development of aerobic capacity (Dolezal and Potteiger, 1998, Glowacki et al., 2004, Nelson et al., 1990). Whilst the mechanisms contributing to attenuated aerobic development with concurrent training have received less attention in the concurrent training literature, previous studies have shown attenuated changes in oxidative enzymes, and dilutions in mitochondrial volume in type IIa muscle fibres, attributed to resistance training-induced hypertrophy (MacDougall et al., 1979, Nelson et al., 1990). However, more recent data in recreationally-active participants support that mitochondrial respiration, protein abundance and signalling responses associated with mitochondrial biogenesis are potentiated with concurrent training (Irving et al., 2015, Wang et al., 2011). Whilst the mechanisms contributing to the improved aerobic fitness in the present study were not determined, both concurrent groups displayed robust increases in aerobic capacity and power, supporting the view that endurance adaptations are not limited with the addition of resistance training.

Fat Mass

Concurrent training can reduced fat mass, and more-so when incorporating high-intensity interval training as the endurance mode (Wilson et al., 2012). Indeed, performing resistance exercise prior to endurance (*RE*) led to substantial reductions in fat mass (-10.5 ± 11 %). Similar values (-16.2 %) were reported in sedentary men who trained 3 days a week for 8 weeks, with resistance sessions performed 15-20 minutes prior to running-based endurance sessions (Ghahramanloo et al., 2009). However, in the present study, both *ER* and *RO* training induced trivial changes in fat mass (-1.8 ± 9.8 % and 1.8 ± 5.6 %, respectively). The reason for this discrepancy, particularly between the two concurrent groups is unclear, given that both groups completed similar training volumes. Whilst speculative, different exercise orders may have induced divergent effects on fat

metabolism and energy expenditure. Previous research in healthy active participants has shown that a prior bout of high-intensity resistance exercise (similar to that employed in the present study) can increase the availability, oxidation, and contribution of fat to energy provision during a subsequent endurance session (Goto et al., 2007, Kang et al., 2009). This may be due to elevated plasma concentrations of free fatty acids, glycerol and lipolytic hormones such as growth hormone and catecholamines (Goto et al., 2007). However, these studies only compared the effects to endurance-only exercise, and not the reverse concurrent exercise order. Nonetheless, others have reported greater elevations in oxygen uptake (Drummond et al., 2005, Taipale et al., 2015) and energy expenditure (Beltz et al., 2014) during endurance sessions when performed after resistance exercise, compared to the reverse order. Contrasting this, others have found no effect of exercise order on oxygen consumption both during (Ferrari et al., 2018, Vilacxa Alves et al., 2012) and after concurrent sessions (Oliveira and Oliveira, 2011, Lamego et al., 2018). Recent evidence in older men with type 2 diabetes supports that performing HIIT in the afternoon is more beneficial for lowering blood glucose levels than morning exercise (Savikj et al., 2019). Given endurance training-induced improvements in insulin sensitivity are associated with increased rates of fat oxidation (Goodpaster et al., 2003, Hawley and Lessard, 2008), performing the HIIT endurance sessions in the afternoon may have resulted in greater fat loss through improved glycaemic control mediating increases in fat oxidation. However, none of the above measures were taken during this study, and therefore it is difficult to ascertain the exact mechanisms contributing to the different rates of fat loss in the present study.

It is clear when inspecting the individual changes for each group (Figure 5.8), four participants in the *ER* group increased total fat mass following training, two of whom by as much as 12 to 16% (both 1.6 kg). Although two participants in the *RE* group also increased fat mass following training, the increases were smaller (5 to 6%, 0.4 to 0.9 kg). Whilst the overall small participant cohort, and single DXA measurement taken post-training preclude exact quantification of individual changes (Hopkins, 2015), their potential effect on the divergent group responses cannot be ignored. In conclusion, performing resistance exercise prior to endurance resulted in substantial fat mass reductions, compared to both the reverse exercise order and resistance-only training. Whilst the mechanisms for this divergent response between groups cannot be determined precisely from the available data, differential effects on fat metabolism and energy expenditure may have played a role, as well as the confounding effect of different individual responses.

Other considerations

Whilst one aim of this study was to investigate the role of concurrent exercise order on training adaptations, the potentially confounding effects of other training and non-training variables employed in the study design cannot be ignored when interpreting the results (Bishop et al.,

2019a). For example, this study employed a moderate training frequency of 3 days per week, above which an interference effect may be more likely to occur (Hickson, 1980, Jones et al., 2013, Wilson et al., 2012). Concurrent sessions were performed on the same day, as is customary in many sporting environments (Enright et al., 2015, Enright et al., 2017). However, some research suggests prolonging the recovery duration between concurrent sessions (>8 to 24 hours) may benefit resistance exercise performance (Sporer and Wenger, 2003), as well as strength (McCarthy et al., 1995, Sale et al., 1990a), hypertrophic (McCarthy et al., 1995, McCarthy et al., 2002), and aerobic adaptations (Schumann et al., 2015). The short-term training period (9 weeks), and participant training status will also have likely affected the training outcomes. When untrained or unaccustomed to exercise, several nonspecific adaptive responses are induced, regardless of the type of stimulus (Coffey et al., 2006a, Coffey et al., 2006b, Vissing et al., 2013, Wilkinson et al., 2008). For more highly-trained individuals with prolonged training backgrounds (for whom the potential for adaptation is comparatively lower) an interference effect may become more apparent (Coffey and Hawley, 2016). Consequently, whilst our data do not support the notion of an interference effect, nor a clear effect of exercise order, for improvements in strength, lean body mass, or aerobic fitness, these outcomes cannot be solely attributed to the manipulation of one training variable; a change to one may alter the effect of another. Careful consideration of the individual and collective roles of all training and non-training variables is required by anyone engaging in concurrent training to achieve the desired adaptations.

5.5 Conclusions

In conclusion, the present study does not support the premise of attenuated strength and lean mass gains following concurrent training. In healthy, active men, a 9-week concurrent training program, regardless of exercise order, presents a viable strategy to improve lower-body maximal strength and total lean body mass comparable to resistance-only training, whilst also improving aerobic fitness. However, improvements in some measures of countermovement jump performance were attenuated with concurrent training, particularly when resistance exercise was performed first. There were also possible effects of exercise order on changes in countermovement jump performance (favouring *ER*) and reductions in fat mass (favouring *RE*); however, more data are required to determine the importance of these effects. For healthy, active individuals engaging in same-day concurrent training, with short recovery durations, the choice of exercise order could be dictated by personal preference, or more importantly, periodised according to the goals of a specific training phase. However, careful consideration should also be given to the effects of other training and non-training variables, to minimise potential interference effects and maximise concurrent training adaptations.

Chapter 6 General Discussion and Conclusions

Preface

The following section provides a summary of the main findings from this thesis related to the original aims and objectives outlined in *Chapter 1*. These findings are then discussed in relation to their relevance to advancing the current understanding of molecular responses and whole-body adaptations to concurrent and resistance-only training. Finally, following a brief discussion of the limitations of the current work, practical applications of the findings and directions for future research are also presented.

6.1 Summary of key findings

The overarching aim of this thesis was to investigate the extent to which the addition of endurance exercise to a resistance training program might attenuate the development of hallmark resistance training adaptations. Furthermore, this work sought to elucidate the effect of concurrent exercise order on exercise-induced molecular signalling responses and whole-body training adaptations, compared to resistance-only training.

These aims were achieved by examining:

1. *Acute changes in post-exercise molecular responses (mRNA expression and protein phosphorylation) following a single session of resistance-only or concurrent exercise, performed in different orders (i.e., resistance-only vs endurance → resistance vs resistance → endurance), both before and after a training intervention (Chapter 4)*

This chapter presents the first attempt to characterise the time-course of molecular responses to resistance-only and concurrent exercise (in alternate orders), over an extended recovery period, when exercise was performed in the fed-state, both before and after a training period. During the first (*Week 1*) and last week of training (*Week 10*), twenty-five healthy, active males completed an '*experimental*' training session of resistance-only or concurrent exercise (performing either endurance or resistance exercise first). Over a 7-hour duration, muscle biopsies were sampled at rest, and both immediately and 3 hours after each exercise session. The main findings from this study were that both orders of concurrent training resulted in comparable muscle glycogen depletion compared to resistance-only exercise, and transient changes in purported inhibitors of growth signalling, such as AMPKα and p53 which were elevated at similar timepoints. However, despite some indication that concurrent exercise may have inhibited resistance exercise-induced mTOR signalling during the extended recovery period (4 hours after the initial exercise bout), the present data do not provide clear evidence of a 'molecular interference' to anabolic signalling

with concurrent exercise compared to performing resistance alone. Importantly, new information about the time-course of p53 signalling and Mighty gene expression in the context of resistance and concurrent exercise are provided. Furthermore, when the same exercise sessions were conducted in the training-accustomed state, the magnitude of change in the expression of several genes and proteins was reduced.

2. *Training-induced changes in whole-body endurance and resistance adaptations (i.e., strength, power, muscle mass, endurance capacity and performance) following 9 weeks of training (Chapter 5)*

Twenty-nine healthy, active males completed 9 weeks of training, performing either resistance-only or concurrent training for 3 days a week. Measures of maximal strength, countermovement jump performance, body composition and aerobic fitness were obtained before, mid-way through, and after the training period. These data showed that performing resistance-only and concurrent training (irrespective of exercise order) resulted in comparable improvements in maximal strength and lean-body mass. Furthermore, concurrent training in either order led to similar improvements in maximal aerobic capacity and power, and the lactate threshold. However, the addition of endurance exercise *after* resistance training did attenuate improvements in countermovement jump displacement, force and power, compared to resistance-only training; performing the reverse order also possibly interfered with the development of countermovement jump force and power. Finally, performing endurance exercise *after* resistance exercise lead to greater reductions in total fat mass than both the reverse order and resistance-only training.

6.2 General discussion of key findings

It is clear from the existing literature that adaptations to concurrent endurance and resistance exercise are dependent upon the manipulation of, and interactions between, both training and non-training variables (Bishop et al., 2019a). Whereas much of the previous literature has investigated the effects of one variable whilst attempting to control for the rest, the present work adopted an integrated approach to researching the interference effect. Indeed, the novel study design simultaneously assessed both one training and one non-training variable respectively; namely, the effect of exercise order and participant training status, whilst also providing nutritional support in accordance with recommended guidelines and real-world practices. In doing so, this thesis builds on the current body of literature by providing new information about the effects of concurrent training on post-exercise molecular responses *and* phenotypic adaptations, in human skeletal muscle, with a specific focus on the effect of concurrent exercise order, compared to resistance-only exercise.

The effect of concurrent exercise order and training status on molecular responses

Despite limited evidence supporting molecular mechanisms of an interference effect in humans (Babcock et al., 2012, Fyfe et al., 2018), most studies refuting this notion in human skeletal muscle assessed only one order of concurrent exercise against a single-mode resistance (Apró et al., 2015, Apró et al., 2013, Donges et al., 2012, Fernandez-Gonzalo et al., 2013, Fyfe et al., 2016b, Pugh et al., 2015) or endurance exercise group (Donges et al., 2012, Wang et al., 2011), precluding inferences about whether the alternate exercise order may have altered the molecular responses. Even at the molecular level, the choice of exercise order may be an important methodological consideration, given the typical time-course of AMPK signalling and protein synthetic pathways following exercise (Fyfe et al., 2014). Prior to the present work, only three studies had specifically addressed the effect of concurrent exercise order on molecular responses to concurrent exercise in humans (Coffey et al., 2009a, Coffey et al., 2009b, Jones et al., 2016). The initial work by Coffey *et al.* demonstrated no effect of exercise order on mTORC1 signalling when resistance exercise was combined with steady-state cycling (Coffey et al., 2009b); however, performing endurance exercise first reduced IGF-1 expression, and the reverse order exacerbated MuRF1 expression. When combined with repeated-sprint cycling, subsequent resistance exercise-induced phosphorylation of p70S6K and rpS6 were compromised (Coffey et al., 2009a). However, these studies were conducted in the fasted-state, which may have altered the signalling responses governing hypertrophic (Creer et al., 2005) and aerobic pathways (Bartlett et al., 2013, Hawley and Morton, 2014). Whilst the authors concluded that neither exercise order promoted an optimal anabolic milieu for adaptation (Coffey et al., 2009a), a resistance-only group was also not included. To address these points, Jones *et al.* (2016) measured signalling responses to alternate orders of concurrent exercise, and resistance exercise, performed in the fed-state. Whilst Jones et al. demonstrated comparable AMPK and mTORC1 signalling between groups, only the immediate (0-1 h) recovery period was assessed, possibly missing molecular events that may have subsequently occurred.

The present work extends the findings of these previous studies, by assessing changes in gene and protein expression to concurrent and resistance-only exercise, performed in the fed-state, over an extended measurement period, to provide a greater temporal resolution of the signalling responses over a typical training day. Herein, these data do not provide clear evidence of a molecular interference effect when concurrent endurance and resistance sessions are performed in the fed-state and separated by a 3-hour recovery period, compared to resistance-only exercise. Previous work in our lab has demonstrated uncompromised mTOR signalling in the untrained state (Fyfe et al., 2016b), whilst resistance exercise preferentially stimulated mTOR signalling compared to concurrent exercise in a training-accustomed state (Fyfe et al., 2018). In the present study, in both the untrained and training-accustomed states, p-mTOR was elevated 4 hours after

resistance exercise only, whilst both concurrent exercise orders elicited unchanged, or reduced phosphorylation. Whilst some purported inhibitors of mTORC1 were simultaneously increased (e.g., AMPK, p53, TSC2), so to were other molecular mediators of anabolic signalling (e.g. Akt, Mighty), whilst other inhibitors of muscle growth were concomitantly downregulated (e.g. myostatin). Collectively, the present data do not lend clear support to the notion of a molecular interference effect with concurrent exercise (Figure 6.1), nor a clear effect of exercise order.

Despite the lack of clear interference, the current data do support the notion that compared to performing an unfamiliar exercise session, exercise-induced molecular responses are dampened in the training-accustomed state. This was particularly evident from the reduced changes in atrogene expression (MuRF1 and MAFbx), which likely indicates a reduced need for skeletal muscle repair and remodelling when exercise was performed at the same relative intensity. Furthermore, both the resistance and endurance exercise sessions displayed a reduced capacity to upregulate the transcriptional response of PGC-1α, whilst specific markers of translational signalling (i.e., 4EBP1 and eEF2) elicited smaller and more transient perturbations in the training-accustomed state.

Whilst neither an interference effect, nor an exercise order effect were clear at the molecular level, the extent to which single measures of changes in molecular responses to exercise can explain, or indeed predict subsequent training adaptations has been questioned. Previous research has highlighted the lack of relationship between translational signalling responses and rates of protein synthesis (Atherton et al., 2010, Wilkinson et al., 2008) and training-induced hypertrophy (Fernandez-Gonzalo et al., 2013, Mitchell et al., 2014, Phillips et al., 2013). As such, it was important to also measure changes in whole-body training adaptations to concurrent and resistance-only exercise, to provide a broader perspective of the relevance of the observed signalling responses.

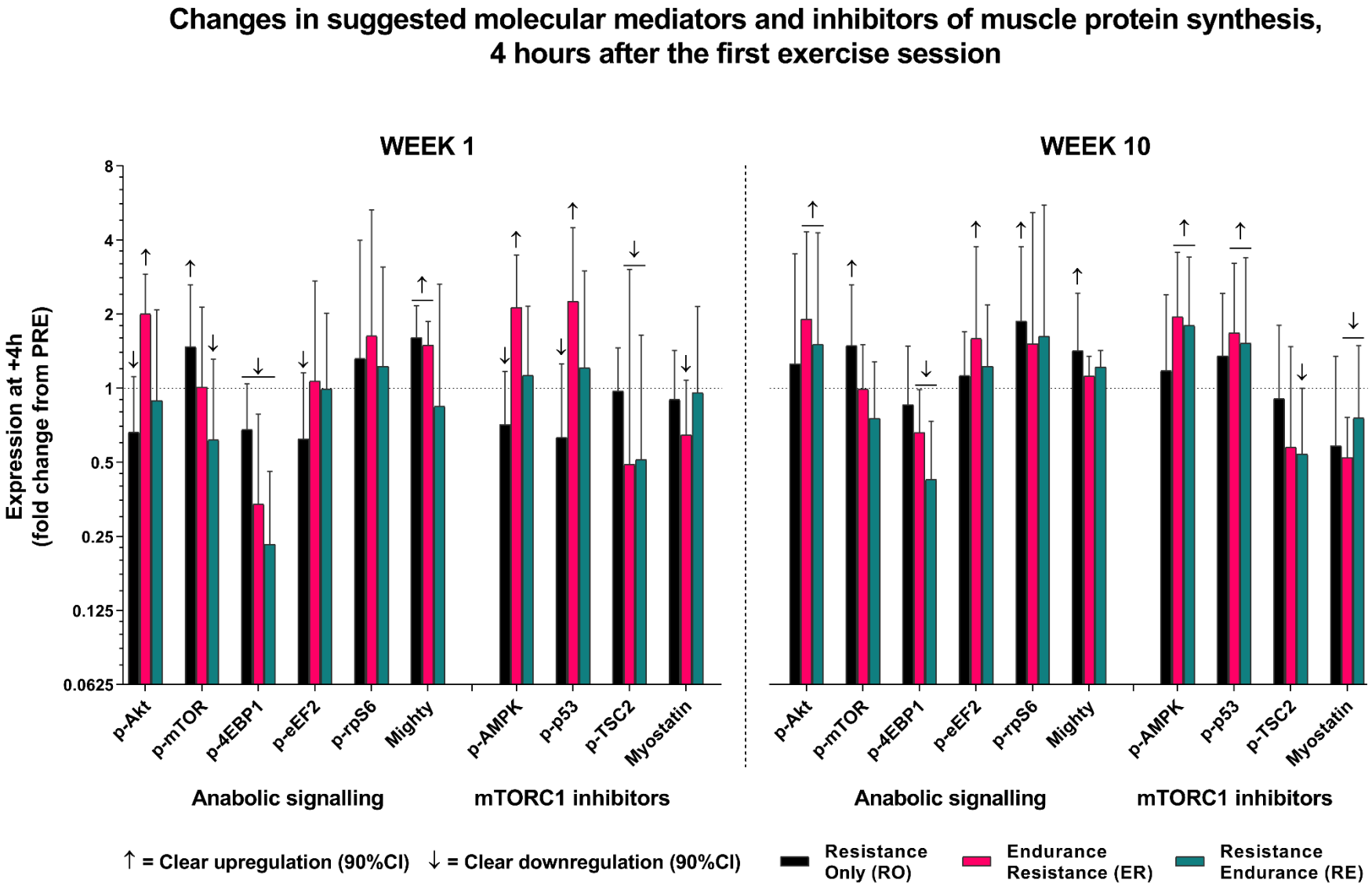

Figure 6.1 - Changes in suggested molecular mediators and inhibitors of muscle protein synthesis, 4 hours after the initial exercise session.

Training adaptations to alternate concurrent exercise orders

Unlike at the molecular level, investigations into the effect of concurrent exercise order on whole-body, phenotypic adaptations have received wider attention. Some studies have demonstrated that performing resistance exercise first may benefit strength adaptations (Cadore et al., 2012, Cadore et al., 2013, Eddens et al., 2018, Murlasits et al., 2018, Pinto et al., 2014), and that prioritising endurance exercise may augment the development of submaximal (Schumann et al., 2015) and maximal oxygen uptake (Chtara et al., 2005), as well as endurance exercise performance (Chtara et al., 2005) and capacity (Kuusmaa et al., 2016). The aim of *Chapter 5* was therefore to elucidate whether *a)* concurrent training would induce the classic interference effect to resistance adaptations, and *b)* whether the order in which concurrent training was performed would affect the magnitude of endurance and resistance adaptations. The present findings do not indicate an interference to the development of strength and muscle hypertrophy with concurrent training (irrespective of order) compared to resistance-only training. Furthermore, adaptations to endurance training were comparable between the concurrent training groups, regardless of the order. These findings are consistent with several studies reporting no order effect on improvements in dynamic strength (Chtara et al., 2008, Collins and Snow, 1993, Eklund et al., 2016, Gravelle and Blessing, 2000, Schumann et al., 2014a), various measures of muscle mass gain (Cadore et al., 2012, Cadore et al., 2013, Davitt et al., 2014, Eddens et al., 2018, Murlasits et al., 2018, Schumann et al., 2014a), aerobic capacity (Cadore et al., 2012, Collins and Snow, 1993, Davitt et al., 2014, Eddens et al., 2018, MacNeil et al., 2014, Murlasits et al., 2018, Schumann et al., 2014a), and aerobic power (Cadore et al., 2012, Eklund et al., 2015, Eklund et al., 2016, Schumann et al., 2014a, Schumann et al., 2014b). However, compared to resistance-only training, attenuations to the development of CMJ force and power were observed when resistance training was followed by endurance training; the reverse exercise order also possibly interfered with these variables. These findings are consistent with existing studies demonstrating a selective interference to improvements in power or the rate of force development (Dudley and Djamil, 1985, Häkkinen et al., 2003, Kraemer et al., 1995, Mikkola et al., 2012, Tsitkanou et al., 2017), and support the notion that the ability to rapidly produce force may be more susceptible to the interference effect than strength and muscle mass.

Whilst the main outcomes of this study are largely supported by existing literature, the novelty of this research comes from the additional, secondary measures obtained throughout the training period, relating to internal and external training load, and subjective perceptions of wellbeing and readiness to train, which are rarely reported within concurrent training literature. It is often cited that the quality of resistance training may be reduced when performed in close proximity to an endurance exercise bout, due to either a preventive reduction in effort (and consequently training

volume) if performed first, or due to endurance exercise-induced residual fatigue if performed afterwards (Sale et al., 1990a, Leveritt and Abernethy, 1999, Leveritt et al., 1999). In the present study, all three groups completed a similar resistance training volume, regardless of the order in which concurrent training was performed. However, whilst the external load was comparable across the groups, the internal load data suggested that performing endurance exercise first leads to a greater perception of effort in a subsequent resistance bout, than if the resistance exercise was performed first. Furthermore, the *ER* group elicited lower (i.e., worse) scores for total wellbeing/readiness to train, and specifically worse general muscle soreness, stress, and mood, compared to those who performed resistance exercise only. Although most adaptations over the 9-week duration of the present study were similar across all groups, a longer-duration study may have led to more noticeably compromised adaptations in this group, who were generally commencing each session in a lower mood state and perceiving the sessions to be harder.

Summary

This thesis has provided new knowledge regarding the time-course of several molecular responses in response to both resistance-only and concurrent training, both before and after a training period. Whilst the specific role of concurrent exercise order remains unclear in relation to the presence of a molecular interference effect, at the whole-body level, concurrent training sessions irrespective of exercise order can induce comparable improvements in muscular strength and hypertrophy to resistance-only training, whilst concomitantly improving indices of aerobic fitness.

6.3 Limitations of the present work and recommendations for future research

Typically, improvements in strength elicited during the initial stages of a resistance training program are associated with neural adaptations (Sale, 1988), prior to increases in muscle hypertrophy (Seynnes et al., 2007); although the contributory effect of the latter has recently been contested (Loenneke et al., 2019). Nonetheless, given the lack of noticeable interference to DXA-derived estimated of lean mass (which, within-group effects were only *moderate*), nor a conclusive molecular interference effect (discussed below), coupled with the attenuated development of countermovement jump force and power, it is possible that the present study was insufficient in duration to detect an interference to muscle hypertrophy, and its associated molecular mediators. Furthermore, whilst DXA is appropriate as a criterion measure for assessing changes in whole- and segmental body composition with a high level of accuracy and reproducibility (Aragon et al., 2017), it is not without its limitations. Results may be confounded by between-measurement variations in hydration status, muscle glycogen and creatine concentrations (Bone et al., 2017, Toomey et al., 2017), as well as prior exercise and typical daily activities and meals (Nana et al., 2012, Nana et al., 2013); as such, the participants were assessed in the rested and fasted state, in an attempt to diminish these effects (Nana et al., 2013), outlined in *Chapter 3*. DXA-derived lean mass has been shown to correlate with the gold-standard measure of magnetic resonance imaging (MRI), however the latter permits the detection of changes within and between individual muscles, whilst the former may underestimate muscle mass in comparison (Maden-Wilkinson et al., 2013). Furthermore, it is also important to consider the appropriate definition of, and measures used to detect hypertrophy, given that changes in muscle size are reflected by changes in both mass and volume, which may exert different effects on overall function (Taber et al., 2019). Indeed, in the general context of concurrent training adaptations, it has previously been demonstrated that the choice of dependent variable may affect the interpretation of an interference effect (Leveritt et al., 2003).

Changes in gene expression, protein abundance, and post-translational modifications (such as phosphorylation status) are often used to infer changes in protein synthesis, and to predict or explain changes in muscle hypertrophy (Camera et al., 2016b). However, changes in mRNA content are not always succeeded by corresponding changes in protein content (Hornberger et al., 2016), nor are post-translational modifications indicative of protein activity (McGlory et al., 2014). Furthermore, whilst some research has reported relationships between acute mTORC1 signalling responses, changes in protein synthesis (Kumar et al., 2009) and muscle hypertrophy (Mitchell et al., 2013), these results are not globally supported (Atherton et al., 2010, Mayhew et al., 2009, Mitchell et al., 2014, Mitchell et al., 2012, Phillips et al., 2013). There is a considerable level of “cross-talk” between different molecular pathways, in which proteins may elicit an array of functions in response to different stimuli, over a specific time-course, meaning the

interpretation may be limited by the chosen biopsy time-points (Camera et al., 2016b). As such, acute transient changes in the abundance or phosphorylation of molecular markers may not specifically reflect their functional relevance or determine phenotypic outcome measures. Furthermore, in the present study, the sample size (discussed below) was deemed too small to precisely estimate correlations between changes in the molecular targets and the performance measures. Additionally, due to the considerable number of muscle samples (n = 250), and limitations in time and available antibodies, the present phosphorylation data are not expressed relative to the total abundance of each specific protein. This is an important consideration, given changes in a phospho-protein may reflect changes in either post-translational modifications, or the total content of each specific protein (Bass et al., 2017). Nonetheless, in line with recommended best practice, the present data are expressed normalised to the total protein loaded on in each well, and corrected against a standard curve using a control sample pooled from all samples, to correct for between-gel variations in loading, separation, transfer and detection, permitting between-gel comparisons to be made (Bass et al., 2017). Furthermore, similar methods for presenting western blot data have been reported in other published concurrent training studies (Apró et al., 2013, Fernandez-Gonzalo et al., 2013, Lundberg et al., 2012, Lundberg et al., 2014, Pugh et al., 2015). Nonetheless, whilst it is not expected that there would be substantial changes in total protein content over the 7-hour measurement period on each experimental day, this remains a limitation that should be considered when interpreting the results.

> *Collectively, future research should look to adopt an integrated approach, combining assessments of acute molecular responses with measures of protein synthesis, as well as multiple measures of hypertrophy (assessing whole-body, muscle- and fibre-specific changes mass, volume and area), taken over a longer training period, to provide greater insight into the temporal relationship between exercise-induced responses and skeletal muscle adaptations to concurrent training.*

It is also worth considering that the original study by Hickson (Hickson, 1980) demonstrated the interference to strength occurred after the first 7-weeks of training, which involved high-intensity endurance and resistance training, performed 5 to 6 days per week:

> "*All exercises were performed with as much weight as possible; initially the subjects exercised at approx. 80% of maximum weight. As strength increased, additional weight was added to maintain maximal resistance for the required repetitions. . . The interval training consisted of six 5-min sessions of bicycling at a work rate that approached the subjects'* $\dot{V}O_{2max}$ *. . . The running program consisted of continuous running as fast as possible for 30 min/day during the 1st week, 35 min/day during the 2nd week, and 40 min/day thereafter*" (**p. 256**, Hickson (1980)).

To date, no other concurrent study has replicated such extreme training methods, which are also not reflective of real-world training practices. Whilst the present study may have been insufficient in duration to elicit more discernible changes in muscle mass (in all groups), it is also possible that the present training *volume* was not severe enough to induce an interference to training adaptations. Indeed, whilst this research endeavoured to elucidate the role of concurrent exercise order on training adaptations, the confounding effects of the other training and non-training variables employed cannot be ignored when interpreting the results (Bishop et al., 2019a). This study employed a moderate training frequency of 3 days per week, above which an interference effect may be more likely to occur (Hickson, 1980, Jones et al., 2013, Wilson et al., 2012). Concurrent sessions were also performed on the same day, as is customary in many sporting environments (Enright et al., 2015, Enright et al., 2017). However, some research suggests prolonging the recovery duration between concurrent sessions (>8 to 24 hours) may benefit resistance exercise performance (Sporer and Wenger, 2003), as well as strength (McCarthy et al., 1995, Sale et al., 1990a), hypertrophic (McCarthy et al., 1995, McCarthy et al., 2002), and aerobic adaptations (Schumann et al., 2015). Furthermore, compared to running, cycling has been suggested to induce less eccentric muscle damage (Wilson et al., 2012). Owing to its biomechanical similarities to the lower-body resistance exercises (Gergley, 2009), as well as the greater recruitment of higher-threshold, fast-twitch motoneurons with high-intensity compared to low-intensity contractions (Duchateau et al., 2006), the HIIT cycling sessions employed in the present study may have provided a synergistic, rather than antagonistic, hypertrophic stimulus to a greater range of muscle fibres (Murach and Bagley, 2016, Sabag et al., 2018). Whether comparable results would have been observed with a HIIT running protocol remain uncertain. Finally, as previously discussed, the short-term training period (9 weeks) and participant initial training status will also have affected the training outcomes, as more highly-trained individuals with prolonged training backgrounds (for whom the potential for adaptation is comparatively lower) an interference effect may become more apparent (Coffey and Hawley, 2016). Consequently, whilst our data do not support the notion of an interference effect, nor a clear effect of exercise order, for improvements in strength, lean body mass, or aerobic fitness, these outcomes cannot be solely attributed to the manipulation of one training variable; a change to one may alter the effect of another. Careful consideration of the individual and collective roles of all training and non-training variables is required by anyone engaging in concurrent training to achieve the desired adaptations.

The work in both chapters of this thesis is undoubtedly limited by the small sample sizes of 8 to 10 in each group, and the magnitude of the error of measurement in relation to the smallest worthwhile change (SWC). Table 6.1 summarizes the values of the SWC and the error of measurement for each of the molecular targets from *Chapter 4*. The combined between-subject

standard deviation (SD) at rest in Week 1 was used to define the SWC in the mean of each target: the usual default via standardisation, 0.2 of the standard deviation. The SWC and other magnitude thresholds for standard deviations are half those for changes in means (Smith and Hopkins, 2011). From the statistical model, the error of measurement was derived as the residual variation in all three groups combined, because the residual variation was expected to be similar across all groups. As can be seen in the final column of Table 6.1, all targets exhibited moderate-to-large errors of measurement, ranging from 2× (p-4EBP1) to 5.2× (p-rpS6) the SWC. There appear to be no published values for errors of measurement derived either from reliability studies or from the statistical model of experimental studies with which to compare the present errors in Table 6.1. Whilst the contributions of technical error and biological variation to the error is therefore unclear, published recommendations to help reduce the technical error in Western blotting (Bass et al., 2017) and PCR (Kuang et al., 2018) were followed.

Table 6.1 - Between-subject standard deviation, smallest worthwhile change and error of measurement for each molecular target, presented in percent (%) and standardised (ES) units.

Variable	Between-Subject SD (%) [a]	SWC (%)	Error of Measurement					Error ÷SWC
			%	×/÷90%CI	ES	±90%CI	Magnitude[b]	
Glycogen	23	4.4	**19**	*1.17*	**0.84**	*0.12*	Large	4.3
PGC-1α	92	14	**66**	*1.18*	**0.77**	*0.1*	Large	4.6
MuRF1	110	17	**50**	*1.20*	**0.54**	*0.08*	Moderate	3.0
MAFbx	132	19	**49**	*1.23*	**0.47**	*0.08*	Moderate	2.6
Myostatin	172	23	**85**	*1.18*	**0.61**	*0.07*	Large	3.7
Mighty	63	11	**28**	*1.18*	**0.51**	*0.07*	Moderate	2.7
p-Akt	179	24	**57**	*1.17*	**0.44**	*0.06*	Moderate	2.4
p-mTOR	89	14	**50**	*1.24*	**0.64**	*0.11*	Large	3.5
p-4EBP1	76	12	**25**	*1.25*	**0.40**	*0.08*	Moderate	2.0
p-eEF2	96	15	**33**	*1.28*	**0.42**	*0.09*	Moderate	2.2
p-rpS6	127	19	**97**	*1.29*	**0.82**	*0.15*	Large	5.2
p-AMPKα	103	16	**57**	*1.20*	**0.64**	*0.09*	Large	3.6
p-p53	207	26	**67**	*1.17*	**0.46**	*0.06*	Moderate	2.6
p-TSC2	68	11	**26**	*1.51*	**0.45**	*0.17*	Moderate	2.3

Btwn-SD, between-subject standard deviation; SWC, smallest worthwhile change; 90%CI, 90% confidence interval.

[a]Used to determine smallest worthwhile change in the mean for each variable (0.2 × BtwnSD)

[b]Standardised thresholds for interpreting SDs are half those for means (Smith and Hopkins, 2011): 0.1-0.3, small; 0.3-0.6, moderate; 0.6-1.0, large.

The model also allowed for individual responses to differ between each group, at each time-point. Individual responses arise from variation additional to the error of measurement (Hopkins, 2018), and were evident via larger standard deviations around the group mean responses, in both the

exercise-induced molecular responses and the training-induced changes in performance measures. Individual responses for the molecular targets are available in *Appendix C*; in the performance chapter, the individual changes for each measure are presented in the figures. Adequate estimation and interpretation of individual responses requires a much larger sample size ($6.5 \times n^2$, where n is the sample size required for the mean effect), and it is also recommended to obtain multiple pre- and post-intervention assessments, to improve the precision of the estimate (Hopkins, 2018).

> *To appropriately account for, and quantify individual responses, future studies should endeavour to recruit larger participant cohorts, and obtain repeated assessments of dependent variables both before and after the intervention, to improve the precision of the estimate.*

Finally, the molecular data were derived using mixed, whole-muscle homogenates, with no distinction between muscle fibre types or subcellular fractions. Previous research has demonstrated mTORC1 signalling (Koopman et al., 2006, Parkington et al., 2003, Sakamoto et al., 2003) and hypertrophy may be preferentially stimulated in type II fibres (Fry, 2004, Tesch, 1988), whilst others have also shown selective interference to growth in Type I muscle fibres with concurrent training (Bell et al., 2000, Fyfe et al., 2018, Kraemer et al., 1995). Furthermore, upon stimulation, many genes and proteins alter their subcellular locations to exert their effects, such as PGC-1a (Little et al., 2011, Little et al., 2010) p53 (Saleem and Hood, 2013, Tachtsis et al., 2016), and mTOR (Hodson et al., 2017, Song et al., 2017). As such, the current study is unable to provide information regarding potential fibre type and subcellular location-specific responses.

6.4 If the 1% differences mattered?

The present data do not provide evidence for any differences between the concurrent exercise orders for any of the performance variables. However, given the small sample size (*n* = 9-10 per group), it cannot be overlooked that the analyses may lack sufficient power, and that despite the absence of "significant" effects, some between-group differences may still be physiologically and/or performance relevant. In the present thesis, a range of statistical approaches using effect sizes and confidences intervals, as well as reporting precise *P*-values, were used in an attempt to make more conservative decisions and to provide the reader with a wider range of information to decide whether or not to adopt a particular training approach.

Non-clinical thresholds were used for comparisons between the concurrent groups, whereby effects were deemed unclear if there was a >5% likelihood the true effect was substantial in both groups. The probability thresholds for determining meaningful effects were as follows: 75-95% = *likely*, 95-99.5% = *very likely*, and >99.5% = *most likely*. In the present study, the criteria for a meaningful effect/difference required a standardised effect size ≥ 0.2, with a ≥ 75% likelihood that the true effect is either substantially positive or negative, as has been previously adopted in our lab (Fyfe et al., 2016a). Accordingly, the only effects that met these criteria are those that were *likely, very likely* or *most likely* trivial (Table 6.2). For $\dot{W}_{peak}$, the mean difference of -0.5% lower in *RE* than *ER* was deemed unclear as all three likelihoods were greater than 5%; there was a 12.7% chance that the true effect is lower in *RE* than *ER*, an 80% of being trivial, and 7.3% chance that *ER* is greater than *RE*.

Table 6.2 - Between-group differences in the performance variables from Chapter 5, presented as percent and standardised effects with 90% confidence intervals, plus the likelihoods of the magnitude of the true effect, and the qualitative inference.

					Chance (%) true difference is:			
	%diff	90%CI	**ES**	90%CI	**ER>RE**	**Trivial**	**ER<RE**	**Outcome**
Leg Press 1-RM	**-0.6**	6.0	**-0.02**	0.21	7.8 %	87.9 %	4.3 %	Likely trivial
Peak Displacement	**-4.3**	4.1	**-0.28**	0.27	68.6 %	31.0 %	0.4 %	Possibly ER > RE
Peak Velocity	**-2.0**	1.8	**-0.28**	0.26	70.3 %	29.5 %	0.3 %	Possibly ER > RE
Peak Force	**-2.7**	7.0	**-0.12**	0.32	34.5 %	60.6 %	4.9 %	Possibly ER > RE
Peak Power	**-1.6**	3.9	**-0.09**	0.22	19.0 %	79.3 %	1.6 %	Likely trivial
Total Lean Mass	**-0.2**	1.5	**-0.02**	0.11	0.6 %	99.2 %	0.2 %	Very likely trivial
Upper Lean Mass	**0.8**	1.7	**0.05**	0.12	0.1 %	97.2 %	2.7 %	Very likely trivial
Lower Lean Mass	**-0.1**	1.7	**0.00**	0.10	0.2 %	99.6 %	0.2 %	Most likely trivial
Total Fat Mass	**8.8**	7.0	**0.23**	0.20	0.1 %	40.6 %	59.3 %	Possibly RE > ER
$\dot{V}O_{2peak}^{ABS}$	**-1.8**	2.9	**-0.09**	0.15	12.1 %	87.6 %	0.3 %	Likely trivial
$\dot{V}O_{2peak}^{REL}$	**-0.9**	2.9	**-0.05**	0.17	7.8 %	91.1 %	1.1 %	Likely trivial
$\dot{W}_{LT}$	**-3.0**	7.2	**-0.13**	0.32	35.0 %	60.4 %	4.6 %	Possibly ER > RE
$\dot{W}_{peak}$	**-0.5**	5.5	**-0.03**	0.26	12.7 %	80.0 %	7.3 %	*Unclear, need more data*

There are however, several effects which were *possibly* greater in one group over another. For example, the improvement in peak CMJ velocity was 4.3% lower in *RE* than *ER*, with a 70% likelihood that the true effect was greater in *ER* than *RE*. The differences in peak CMJ displacement and force, and $\dot{W}_{LT}$ were also possibly more beneficial in the *ER* order than *RE*. Conversely, the reduction in total fat mass was 8.8% greater in *RE*, with a 59% likelihood that the true change was greater in *RE* than *ER*. Collectively, when interpreting the likelihoods for strength, CMJ performance, and aerobic development (including the overall trivial differences), the chances of attaining superior training adaptations appear greater in the *ER* group than *RE* (Figure 6.2). Consequently, using the information above, practitioners working with populations for whom small percent differences in training-specific adaptations between conditions may translate to meaningful differences in competition performance, and who may be willing to accept a lower threshold for a meaningful difference between groups (i.e., < 75%), may wish to consider scheduling endurance exercise prior resistance exercise sessions. However, the present data were obtained from non-athletic populations, and as the range of uncertainty in the true value of the between-group difference (particularly for $\dot{W}_{LT}$ and $\dot{W}_{peak}$) was too large to provide a clear outcome based on the definition of a meaningful difference herein, it appeared appropriate to conclude that in healthy active males, either exercise order would result in similar endurance adaptations.

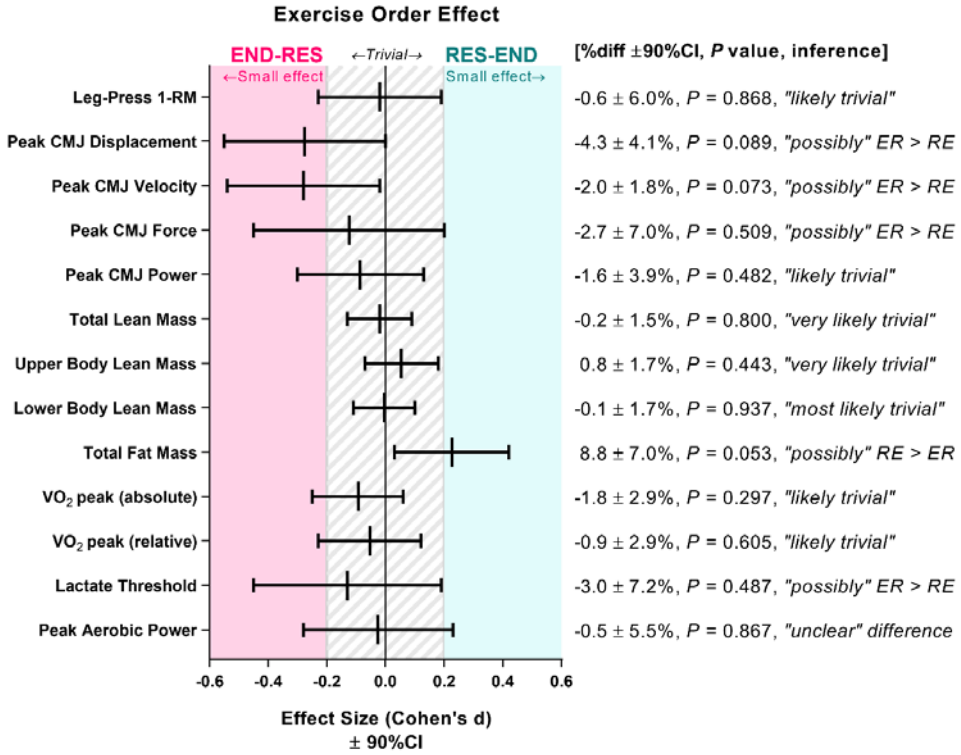

Figure 6.2 - Forrest plot depicting the differences in training adaptations between the concurrent exercise orders groups. To show all variables on one figure, the standardised effect sizes (Cohen's d) have been plotted with 90% confidence intervals, rather than percent units, as the smallest important percent effect would differ for each variable. Percent differences, precise P values, and the qualitative inference based on the likelihoods are also provided.

6.5 Practical applications

Typically, concurrent training sessions are performed within in the same session (affording a time-efficient training method), or on alternate days (providing greater recovery between modes). However, it is also common practice, particularly within athletic environments, for concurrent sessions to be separated by short recovery periods of only a few hours (Cross et al., 2019, Enright et al., 2015, Enright et al., 2017, Robineau et al., 2016). In the present study, the concurrent training program was designed to investigate molecular and whole-body adaptations to concurrent training, when sessions were separated by a 3-hour recovery period, at which point several key molecular mediators of endurance and resistance adaptations are known to be upregulated, and therefore could increase the potential for molecular incompatibility between modes.

Despite the lack of clear evidence for an interference or exercise order effect at the molecular level, the data from *Chapter 5* suggest that over a short-term period of training, concurrent exercise order does not appear to be a critical mediator of the interference to hallmark resistance (or endurance) adaptations. However, the exercise order may alter the participants' motivation to train, by negatively affecting their subjective wellbeing and perceptions of effort if the resistance exercise sessions are performed *after* endurance exercise. Whilst the long-term implications of training in this way are unclear from the present thesis, where possible, it may be prudent to choose the exercise order according to the participant or athletes' personal preference. Given that regularly engaging in both endurance and resistance exercise are widely recommended for a range of populations (American College of Sports Medicine, 1994, American College of Sports Medicine, 2009, Australian Government, 2014, Chodzko-Zajko et al., 2009, Colberg et al., 2010, Garber et al., 2011, Jakicic et al., 2001, Pescatello et al., 2004), organising concurrent training around individual preference to maximise motivation, enjoyment, and adherence is vital.

The organisation of training may also be dictated by factors outside the control of the practitioner, particularly within elite sport, where training schedules are often based around what is easiest and most logistically feasible to 'get the work done'. This is even more pronounced in team sports where large squads exist, and space, time, and staff availability may be limiting factors. Indeed, Enright *et al.* recently highlighted some logistical challenges faced by coaches in professional soccer, such as demanding competition schedules and restricted availability of training facilities, which can subsequently alter training session order, inter-session recovery duration, and affect the timing, type and total amount of nutrients consumed around training sessions (Enright et al., 2017). Thus, when the individuals' personal preference, or perhaps more importantly, the specific goals of the training phase cannot dictate the exercise order, careful consideration should be given to the effects of other training and non-training variables, to minimise potential interference effects, and maximise concurrent training adaptations.

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Appendices

Appendix A – Participant Documentation

Participant information sheet

INFORMATION TO PARTICIPANTS INVOLVED IN RESEARCH

You are invited to participate

You are invited to participate in a research project entitled *"The effect of concurrent endurance and resistance exercise order on genotypic and phenotypic adaptations in previously-untrained males, following a single bout, one week, and 10-week training period"*.

This project is being conducted by lead student investigator Mr Matthew Lee as part of a PhD study at Victoria University under the supervision of Dr Jon Bartlett and Prof David Bishop from the Institute of Sport, Exercise and Active Living (ISEAL). Dr Aaron Peterson, and student investigators Mr Nick Saner, Mr Nathan Pitchford, and Mr James Ballantyne and will assist with the research in this study.

Project explanation

Concurrent training involves performing both resistance (RES, e.g. weights) and endurance (END, e.g. cardio) exercises in the same training program. While this is a common training approach for many populations to combine the benefits of both exercise modes, several studies have shown that concurrent training can lead to an "*interference effect*" – gains in muscle mass, strength and power are reduced, compared to performing resistance-only.

Exercise order (i.e. END→RES or RES→END) is an important consideration when designing a concurrent training programme. However, it is currently unclear whether performing endurance before or after resistance exercise is best to maximise training adaptations and minimise the interference effect.

This project will investigate the effect of concurrent endurance and resistance exercise order on the interference effect, both at a cellular and whole-body level, compared to undertaking resistance exercise alone.

You are eligible to participate in this study if you are:

- Healthy, recreationally active males aged 18-40 years old
- *"Healthy"* = Non-smoker, free from pre-existing medical conditions (e.g., heart rhythm disturbance, elevated blood pressure, diabetes), cardiovascular abnormalities, respiratory conditions and musculoskeletal injuries. Further target criteria include:
    - VO2peak = ≥40 ml/kg/min
    - 1-Rep. Max. Leg Press Strength = ≥2.5 x body mass
    - Body Fat % = ≤24%
    - BMI = 18-25
- *"Recreationally active"* = currently exercising 2-3 times per week, >30 min, of exercise involving aerobic and/or resistance exercise, not currently participating in any high-level sporting competitions

What will I be asked to do?

After reading this document, you will meet with Matthew Lee, who will answer any questions you may have about your role in the study. You will be asked to fill out some short questionnaires about your family medical history and exercise habits, to assess your eligibility to participate in this study. After confirming your eligibility and providing written informed consent, you will undertake the following procedures (*summarised in figure 1*) all conducted in Building P at Victoria University, Footscray Park campus.

1. Familiarisation

During the two weeks prior to starting the study, you will visit the laboratory on 4 occasions to practice the exercise tests. Each session will be separated by at least 48 hours recovery. Each session will last ~1 hour (*see figure 2*).

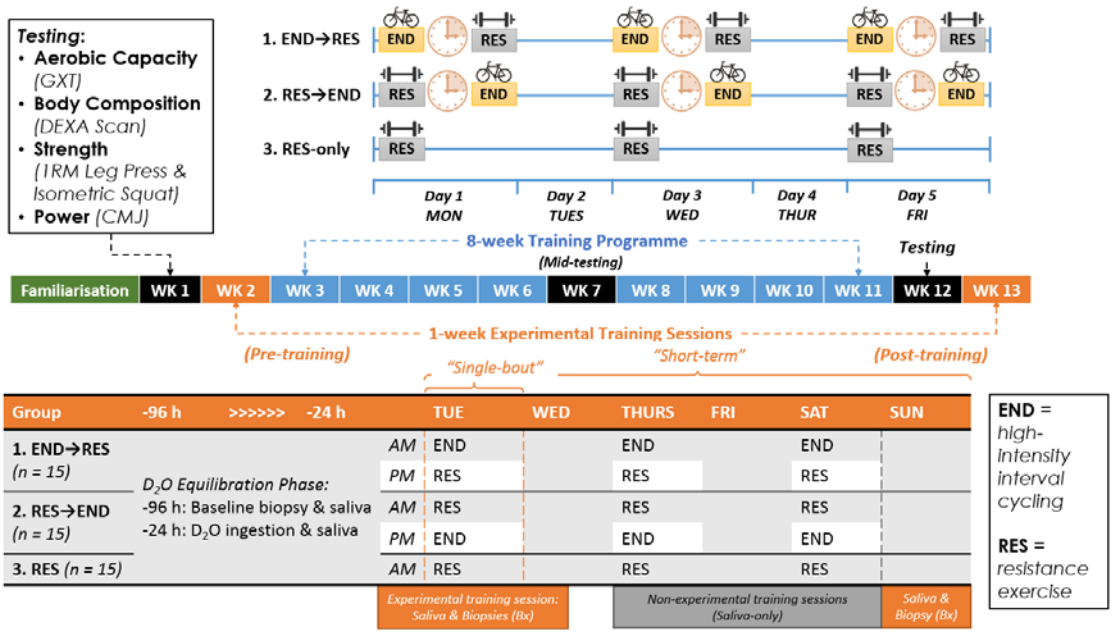

Figure 1 – An overview of the entire study design.

- The graded incremental exercise test (GXT) is an endurance test to exhaustion. It consists of multiple 4-minute stages at increasing workloads, separated by 30 seconds recovery. The test will finish when you can no longer complete the desired workload. In order to measure blood lactate concentrations, blood samples (~1 mL) will be taken via a cannula inserted into the vein in the forearm, and sampled at rest, and immediately after each stage. After 5 minutes recovery, you will again cycle against a high resistance until you cannot continue any further and expired gases will be measured via a mouthpiece to measure your maximal oxygen consumption (VO_{2max}).

- The one repetition maximum strength test (1RM) will be conducted on a seated leg press machine. After a standard warm-up, you will attempt to lift increasing weights until only one, but not a second, repetition is possible. Three minutes recovery will be allowed between 1RM attempts.

- The isometric squat test involves performing the upwards phase of a squat, pushing upwards against a fixed bar. This procedure is performed in a squat rack, stood on a force plate, with the bar fixed at 85% of your standing height. The protocol will involve 3 maximal attempts (i.e., push up as hard and fast as you can, and hold for 3 seconds), separated by 1 minute of recovery.

- The maximal power (countermovement jump) test involves performing body-weight jumps on a force plate to measure your ability to produce force and power. The protocol will involve 3 maximal jumps (i.e., as high as you can), separated by 1 minute of recovery.

2. <u>Baseline Testing</u>

Once you have been familiarised with all the testing procedures, you will then undertake these baseline tests across the next two sessions to evaluate various aspects of your fitness (*see figure 2*). The first session (~1 hour) will involve 1-repetition maximum (1RM) leg-press, isometric squat and countermovement jump (CMJ) test for power. The second session (~1 hour) involves a graded exercise test (GXT) performed to exhaustion on a cycle ergometer to determine your aerobic fitness.

On the morning of *both* sessions, a DEXA scan will be performed to estimate your body composition (i.e., lean mass vs. fat mass). This procedure is not invasive and involves lying still on the DEXA scanner for approximately 7 minutes while the scanner passes over you to assess your body composition.

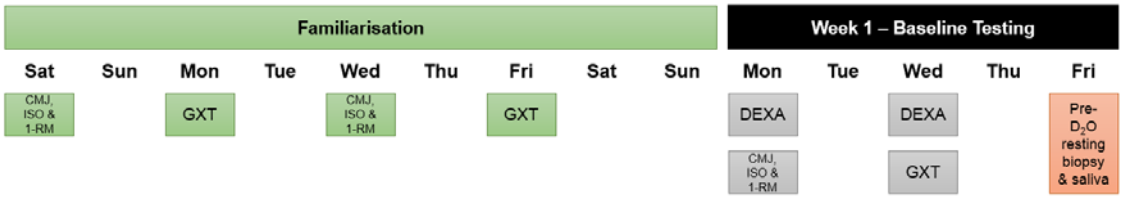

Figure 2 – An overview of the familiarisation and baseline testing phase. Note – the exact days may be altered according to your availability.

3. D_2O Drink

We are interested in how concurrent training affects the rate at which the body can build and repair proteins following exercise (i.e. muscle protein synthesis). In order to do this, you will be asked to drink 150 ml of deuterium oxide (also known as D_2O, or heavy water), which is water (H_2O) that has been labelled with deuterium – this tastes exactly the same as normal water. Calculating the rate at which water labelled with D_2O is incorporated into new proteins give us a measure of the rate of protein synthesis.

Before you start your first exercise session (*figure 2 & 3*) you will be asked to come into the lab to provide a resting, pre-D_2O muscle biopsy and saliva sample. You will be given a standardised meal the night before, and on the morning of the biopsy. The day before you start exercise, you will drink 150 ml of D_2O provided to you. You may experience a bit of dizziness shortly after drinking the D_2O, but this will subside; though we'll need to keep an eye on you for 1-2 h after drinking. We will also collect daily saliva samples into a plastic tube, to measure how much of the D_2O has been incorporated into the body (*figure 3*).

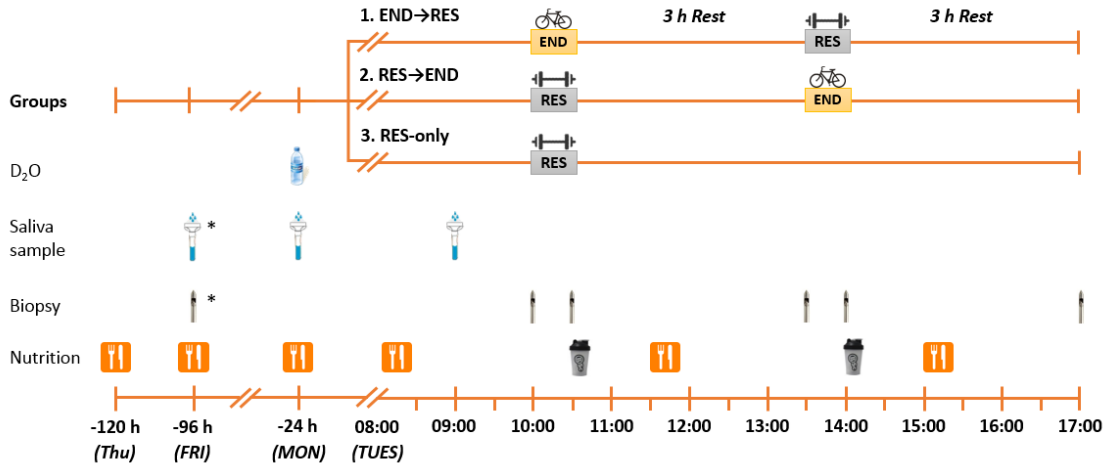

Figure 3 – An overview of the first stage of the experimental training week, from -96 h to the end of day 1. (*) means this biopsy and saliva sample will not be needed in week 10.

After you have completed the baseline testing, and the D_2O phase, you will begin the 10-week training program. You will be RANDOMLY allocated to one of three training groups: 1) high-intensity interval exercise on a stationary bike, followed by resistance exercise [*END→RES*]; 2) the reverse [*RES→END*]; or 3) resistance exercise-only [*RES-only*]. Training sessions will be performed 3 times per week (*i.e. Mon-Wed-Fri*). Each training session will last between ~40-110 minutes. For groups 2 & 3, there will be a 3 hour recovery period between the two exercise sessions. The first and last week of the 10-week training programme are "*experimental*" training weeks, during which muscle biopsies and saliva will be sampled (described in more detail below).

4. Experimental Training Week (Figures 3 & 4)

- *Day 1 (i.e. Tuesday):* You will arrive at the laboratory in a fasted state (i.e. having not had breakfast before you arrive). We will provide you with a standardised breakfast when you arrive. Two hours later, you will then

provide a resting muscle biopsy, after which you will begin your first exercise session (according to whichever group you are in). The sessions will consist of the following:

- High-intensity interval cycling [END]: On a stationary bike, you will perform 10 x 2-min intervals at 40% of the difference between your power at lactate threshold (W_{LT}) and peak power (W_{peak}), separated by 1 min of recovery.
- Resistance exercise [RES]: You will perform 6 x 10 leg press at 70% of your maximum.

Immediately after you finish your first exercise session, you will provide another muscle biopsy, before drinking a protein shake. One hour later, you will be given another standardised meal.

3 hours after finishing your first session, you will then begin the second; the RES-only group will not perform the cycling session, but still be required to provide the subsequent muscle biopsies. Again, muscle biopsies will be required immediately before, after, and 3 hours after the exercise session, and you will be given another protein shake and standardised meal after the second exercise session, like the first.

- *Day 2 (i.e. Wednesday):* REST DAY.

- *Days 3 & 5 (i.e. Thurs/Sat):* You will perform two more training days during the week, in the same order as you did on the first day. However, you will *not* be asked to provide any muscle biopsies on these two days. You will be asked to provide a saliva sample, and will receive *similar* nutritional support as Day 1. However, *on day 3 standardised meals will not be provided*, as there are no biopsies. *They will be provided on day 5*, as we want to control nutrition the day before the final biopsy (*see figure 4*).

- Day 4 (*i.e. Friday*): REST DAY.

- *Day 6 (i.e. Sunday): You* will be asked to come into the lab to provide one final resting muscle biopsy, 24 hours after the last training session on day 5 (see figure 4). *You will be given a standardised breakfast/lunch to eat beforehand.*

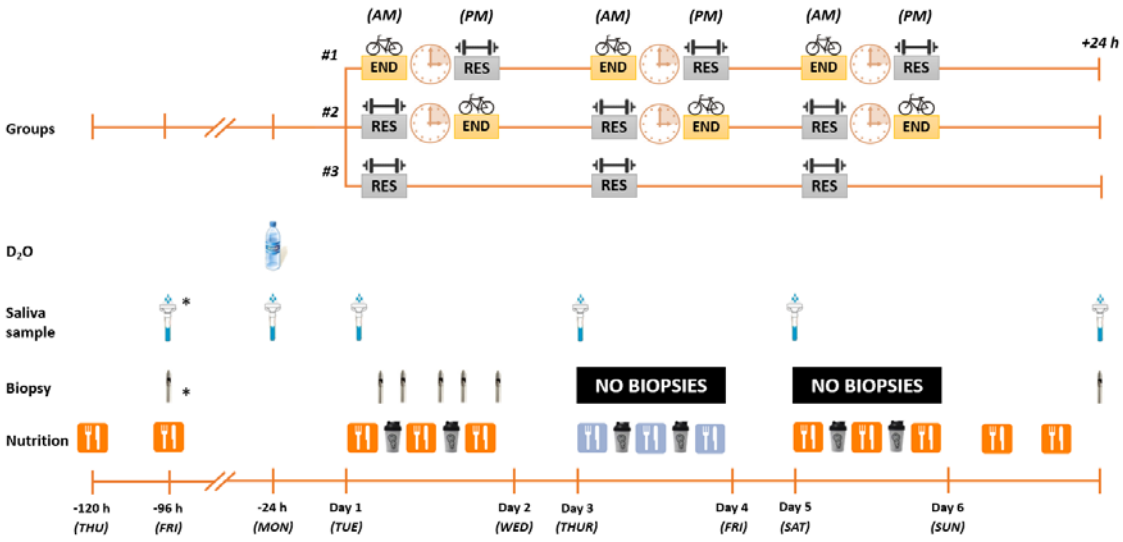

***Figure 4** – An overview of the entire experimental training week, from -96 h to day 6. (*) means this biopsy and saliva sample will not be needed in week 10.*

Throughout the entire study, the training days will typically begin at 08:00 AM, and finish at 05:00 PM - *however this can vary depending on your availability*. On Day 1 of the experimental week, you will be requested to stay in the lab and rest quietly for the full duration between and after the exercise session, due to the multiple biopsies required.

During the recovery periods you will be able to complete quiet activities (e.g., study, read, watch movies, listen to music, etc.). On all other training days, you will be allowed to leave the labs in between the training sessions, provided that you log all nutritional intake and physical activity in your diaries (described below).

8-week training block

After completing the first experimental week, you will then undergo an 8-week training block. During this time, you will continue to train 3 days a week (i.e. Mon-Wed-Fri), in the same format as the experimental week. The only differences are that there will be no muscle biopsies or saliva samples, and you will be asked to provide your own meals before/between/after each exercise session. You will still receive a protein supplement immediately after your exercise sessions.

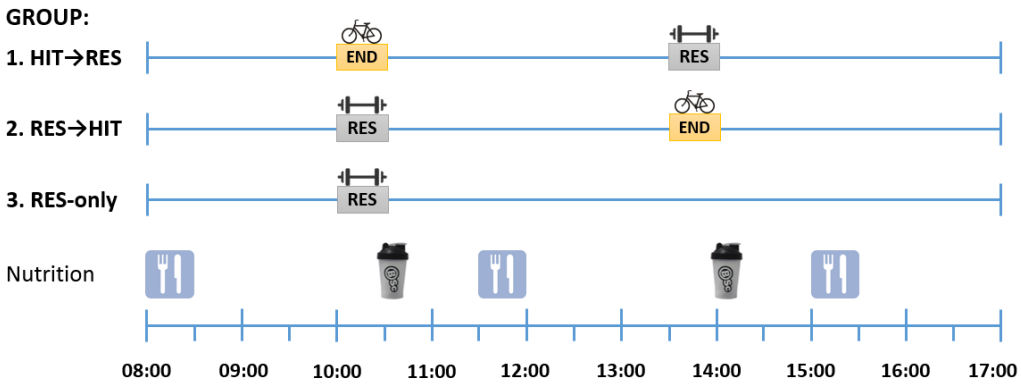

Figure 5 – An overview of a typical training day during the 8-week training block.

Mid-way through the study and at the end of the 8-week training block (*figure 1, weeks 7 & 12*), you will repeat all of the baseline tests so that we can monitor your progress, re-adjust the training intensities for remainder of the training program, and evaluate how you have responded to the training program. During these two weeks, you will perform an additional training session on the Friday (*see figure 6 below*) – this is to ensure that any molecular adaptations aren't lost by having an extended break between training weeks.

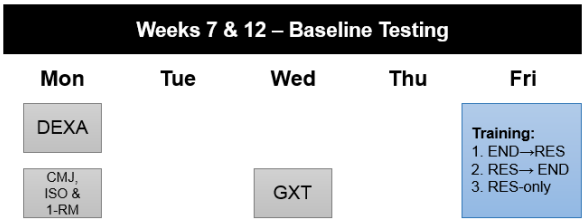

Figure 6 – An overview of the mid- and post-training testing weeks.

5. Exercise and diet control

Diet: Before starting the study you will complete a 3-day food diary during a normal week. During the study, you will be asked to complete another food diary, for one 3-day period in the first training block (Weeks 1-5), and another 3-day period in the second training block (Weeks 6-10). These will be used to determine whether your habitual diet changed during the training period. You will also need to keep a record of the food you eat 24 h before the baseline tests, so that you can replicate this diet when you repeat the tests again.

During the two experimental weeks (1 & 10) standardised meals will be provided (*Lite n'Easy*), to tightly control nutrition around the muscle biopsies. The following meals will be provided on the following days:

- Pre-D2O biopsy: Dinner (the night before) & Breakfast (on the morning of)
- Day 1 (5 x biopsies): Dinner (the night before) & Breakfast, Lunch, Dinner (on the day of)
- Day 3 (no biopsies): *No meals, participant will provide their own*
- Day 5 (no biopsies): Breakfast, Lunch, Dinner
- Day 6 (+24 h biopsy): Breakfast, Lunch

During the 8-week training block, you will be requested to provide your own meals. You will still receive a protein supplement after each training session.

Exercise: You must refrain from exercise 24-48 h before all testing and exercise sessions. You will wear a portable accelerometer on the following days to monitor your normal physical activity levels:

- 1-week prior to starting the study
- A 3-day period in the first training block (Weeks 1-5)
- A 3-day period in the second training block (Weeks 6-10)

You will record your habitual exercise patterns or any additional, non-prescribed training performed outside of the study using a simple, online training diary for 2-weeks prior to commencing the study. This is important to measure how much extra exercise participants do outside of the study.This will need to be completed as soon as possible (within 30 minutes) after any exercise session performed outside of the study. However, *you are requested not to take on any additional, new training or exercise programmes.*

What will I gain from participating?

Whilst we cannot guarantee that you will gain any benefits from your participation in this study, you will receive:

- High-quality exercise training supervised by sport scientists in a state-of-the-art research facility
- The training may improve various aspects of your health and fitness
- You will also receive potentially valuable information regarding your aerobic fitness and strength levels
- You will also receive an individualised report on your potential fitness improvements following the training period
- On the 3 training days during the 2 experimental weeks, all meals will be provided

How will the information I give be used?

All data collected will be stored under alphanumeric codes (i.e. without your name or personal details) which will only be identifiable by the researchers. All muscle samples collected will be used to analyse some proteins and genes involved with adaptations to training. The data that will be collected during the study may be used in a thesis, at conference presentations and published in peer-reviewed scientific journals. All data will be de-identified so your confidentiality is maintained.

With your written consent, photographs or videos may be taken during experimental trials for use in presentations or to assist in future experimental set-ups. Any images will only be taken with your written consent and in all cases you will be de-identified.

What are the potential risks of participating in this project?

The procedures involved in participating in this study are of low risk. Nevertheless, as with any invasive methods and exercise procedures, there are small risks and some discomfort that may be experienced:

Exercise testing and training: You will experience the fatigue associated with strenuous exercise, particularly during the GXT and 1RM. Nevertheless, as in any physical activity, there is a very small possibility of injuries that include, but are not restricted to; muscle, ligament or tendon damage, breathing irregularities and dizziness. There is a high probability that you might experience mild muscle soreness for 2-3 days following the 1RM test, however this will not be more severe than is typically experienced after unaccustomed resistance exercise. There is also a small risk of muscle, ligament or tendon injury during the 1RM test. However, all protocols are commonly performed in exercise physiology laboratories and potential risks to participants have been minimised by employing appropriate warm-up procedures and researcher supervision.

Intravenous cannulation/venepuncture: During the GXT, we will need to insert a cannula into a vein in the forearm, to sample blood. During the needle insertion you will feel minor-to-moderate discomfort or pain. However, the needle is quickly removed and only a flexible plastic tube remains in your vein for the duration of blood sampling (approximately 45 min). When the cannula is removed, direct pressure will be applied to the area to reduce the chances of bruising.

Cannulas are routinely placed into veins of participants in clinical research studies and in hospital patients. The risks of IV cannulation are low, but very occasionally significant bruising or infection can occur. The researchers are qualified and experienced in venous cannula placement, venepuncture, and the use of sterile techniques.

Muscle biopsy: This is required to take small samples of your muscle tissue for analysis of proteins, genes and energy sources. The biopsy will be performed under sterile conditions by a qualified, experienced medical doctor. Local anaesthetic (Xylocaine) is injected at the site of the muscle biopsy (vastus lateralis – mid/outer thigh) then a small incision (approx. 0.6 cm long) is made in the skin. The anaesthetic may burn or sting when injected before the area becomes numb. The biopsy needle is then inserted to extract a small muscle sample (approx. 3-4 rice grains in size). During this part of the procedure you will feel pressure, and this will be quite uncomfortable. You may experience some pain but will last for only about 1-2 seconds. When the piece of muscle is removed you may also experience a mild muscle cramp, but this only persists for a few seconds. This poses no long-term effects for your muscle and will not be noticeable to others apart from a small scar on the skin for a few months. The incision will be closed using a steri-strip and covered by a transparent waterproof dressing. Then a pressure bandage will be applied, which should be maintained for 24-48 hours. The steri-strip closure should be maintained for a few days. It is possible that you might experience some muscle soreness (due to slight bleeding within the muscle) for the next 2-3 days, however this will pass, and does not restrict movement. This is best treated with ice, compression and elevation. Ice will be applied to the biopsy site after the procedure to minimise any bleeding and soreness. In rare cases haematomas have been reported, although these symptoms typically disappear within a week. On very rare occasions, altered sensations on the skin near the site of the biopsy have been reported (numbness or tingling). This is due to a very small nerve being cut, but this sensation disappears over a period of a few weeks-to-months. Although the possibility of infection, significant bruising and altered sensation is quite small, if by chance it does eventuate, please inform us immediately and we will immediately consult the doctor who performed the biopsy to review the reported problems and recommend appropriate action.

Seven biopsies will be taken across Week 1, and six in Week 10 of training (13 in total):

- Wk 1: *-4 d ex 1, Pre-ex 1, Post-ex 1, +3h ex 1/Pre-ex 2, Post-ex 2, +3 h ex 2, +5 d ex 2*
- Wk 10: *n/a, Pre-ex 1, Post-ex 1, +3h ex 1/Pre-ex 2, Post-ex 2, +3 h ex 2, +5 d ex 2*

DEXA scan: This procedure involves exposure to a very small amount of radiation (less than 0.01 millisievert (mSv) per examination). This is substantially less than the radiation experienced during a 7-hour plane flight or a standard chest x-ray. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 mSv each year. The effective dose of radiation you will be exposed to across the four DEXA scans in this study is less than 0.04 mSv. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. This study has been assessed by a Medical Physicist and the radiation dose determined to be of minimal risk.

D_2O: This procedure involves drinking 150 ml of water that has been enriched with deuterium. Deuterated water is becoming more commonly used in studies to measure rates of protein synthesis. Some previous studies have reported short-term side effects of drink large volumes (~400 ml) of D_2O, such as dizziness and nausea. This dizziness is suspected to be due to the water across the inner ear not equilibrating rapidly, and the membranes reacting to the heavier water. This study is using smaller dose (150 ml), however you may still experience some short-term dizziness after drinking the water. Therefore, we will keep you in the lab for ~1 h after, to monitor you before letting you go.

Counselling and independent follow-up:

Your participation in this study is voluntary. You are free to change your mind and withdraw from participating at any time should you so wish, or if you develop any conditions which would require you to withdraw from the study. Should you experience any psychological distress as a result of your participation in this study and wish to speak to someone, one of the investigators will assist with arrangement of a consultation with a psychologist if needed (Janet Young, janet.young@vu.edu.au).

Who is conducting this study?

To express your interest in participating, or further information regarding this research, please contact:

Dr. Jon Bartlett
Chief Investigator
Mob: 0424 980 643
Email: jon.bartlett@vu.edu.au

Mr Matthew Lee
PhD Candidate
Mob: 0432 043 596
Email: matthew.lee10@live.vu.edu.au

Any queries about your participation in this project may be directed to the Chief Investigator listed above. If you have any queries or complaints about the way you have been treated, you may contact the Ethics Secretary, Victoria University Human Research Ethics Committee, Office for Research, Victoria University, PO Box 14428, Melbourne, VIC, 8001 or phone (03) 9919 4781.

Participant consent form

CONSENT FORM FOR PARTICIPANTS INVOLVED IN RESEARCH

You are invited to participate in research entitled *"The effect of concurrent endurance and resistance exercise order on genotypic and phenotypic adaptations in previously-untrained males, following a single bout, one week, and 10-week training period."*

Aims of project

Concurrent training involves simultaneously performing both resistance (RES, e.g. weights) and endurance (END, e.g. cardio) exercises in the same training program. While this is a common training approach for many populations to combine the benefits of both exercise modes, several studies have shown that concurrent training can lead to an "*interference effect*" – gains in muscle mass, strength and power are reduced, compared to performing resistance-only.

Exercise order (i.e. END→RES or RES→END) is an important consideration when designing a concurrent training programme. However, it is currently unclear whether performing endurance before or after resistance exercise is best to maximise training adaptations and minimise the interference effect.

This project will investigate the effect of concurrent endurance and resistance exercise order on the interference effect, both at a cellular and whole-body level, compared to performing resistance exercise only.

Procedures involved

- 4 x Familiarisation **sessions (separated by ≥ 48 h):**
  - 2 sessions involving: Leg press 1-RM test for max. strength; isometric squat test for max. isometric strength; and countermovement jump test (CMJ) for max. power
  - 2 sessions involving: Graded incremental exercise test to exhaustion (GXT) to measure aerobic fitness
- 2 x Baseline Testing sessions (repeated pre-, mid, & post-training, i.e. 6 in total):
  - Day 1: DEXA scan (for body composition), leg press 1-RM, isometric squat, and CMJ tests
  - Day 2: DEXA scan, and GXT
- Venous blood samples: taken from the forearm at rest and at the end of each stage during the GXT, to assess blood lactate concentrations
- 10-week training programme, 3 days per week, (in one of 3 groups):
  1. High-intensity interval exercise on a bike, followed by resistance exercise *[END→RES];*
  2. The reverse *[RES→END];*
  3. Resistance exercise-only *[RES-only].*
- Muscle biopsies: Sampled during the first and last weeks of training. Seven biopsies will be taken across Week 1, and six in Week 10 of training (13 in total):
  - Wk 1: *-4 d ex 1, Pre-ex 1, Post-ex 1, +3h ex 1/Pre-ex 2, Post-ex 2, +3 h ex 2, +5 d ex 2*
  - Wk 10: *n/a, Pre-ex 1, Post-ex 1, +3h ex 1/Pre-ex 2, Post-ex 2, +3 h ex 2, +5 d ex 2*
- Saliva: Obtained daily during the first and last weeks of training. These are required to analyse how much of the D_2O drink has been incorporated into the body's water pool.

Risks involved

The procedures involved in participating in this study are of low risk. Nevertheless, as in any invasive and exercise procedure, there are small risks of some pain and discomfort that may be experienced.

All potential risks associated with participation in this study are fully explained in the 'INFORMATION TO PARTICIPANTS INVOLVED IN RESEARCH' form.

CERTIFICATION BY SUBJECT

I, _____ (*Full Name*)
of _____ (*Street Address*)
_____ (*Suburb*) _____ (*Postcode*)
Phone: _____ *Email*: _____

certify that I am at least 18 years old and that I am voluntarily giving my consent to participate in the study: *"The effect of concurrent endurance and resistance exercise order on genotypic and phenotypic adaptations in previously-untrained males, following a single bout, one week, and 10-week training period."* being conducted at Victoria University by Mr Matthew Lee as part of a PhD study at Victoria University under the supervision of Dr Jon Bartlett and Prof David Bishop from the Institute of Sport, Exercise and Active Living (ISEAL). Dr Aaron Peterson, and student investigators Mr Nick Saner, Mr Nathan Pitchford, and Mr James Ballantyne and will assist with the research in this study.

I certify that the objectives of the study, together with any risks and safeguards associated with the procedures listed hereunder to be carried out in the research, have been fully explained to me by *Mr Matthew Lee* and that I freely consent to participating in all of the following mentioned procedures:

- Graded exercise test (GXT)
- Maximal leg press strength (1RM), isometric squat, and power (jump) testing
- DEXA scan
- 10-week training program conducted three (3) times per week
- Blood, saliva and muscle sampling

I certify that I have had the opportunity to have any questions answered and that I understand that I can withdraw my participation and my data from this study at any time, and that this withdrawal will not jeopardise me in any way.

ADDITIONAL CONSENT

I also agree to allow photographs or video of me without identifying features to be used in publications or conference presentations. I understand that I am free to withdraw my consent for this at any time without prejudice.

☐ Yes ☐ No

I have been informed that the information I provide will be kept confidential.

Signed: _____ Date: _____

Any queries about your participation in this project may be directed to the lead student researcher:
Mr Matthew Lee
Mob: 0432 043 596
Email: matthew.lee10@live.vu.edu.au

If you have any queries or complaints about the way you have been treated, you may contact the Research Ethics and Biosafety Manager, Victoria University Human Research Ethics Committee, Victoria University, PO Box 14428, Melbourne, VIC, 8001 or phone (03) 9919 4148.

Additional consent form

CONSENT TO BE RE-CONTACTED FOR DATA TO BE USED IN ADDITIONAL RESEARCH

The study entitled *"The effect of concurrent endurance and resistance exercise order on genotypic and phenotypic adaptations in previously-untrained males, following a single bout, one week, and 10-week training period"* may present opportunities for tissue samples and data from this study to be incorporated into other related studies and research publications.

Principal Investigator

I, Mr Matthew Lee, request permission to re-contact _____ (participant)

if opportunities arise to use tissue samples and data obtained in this study in other related studies and/or research publications.

Signed: _____ *Date*: _____

The person giving consent

I, _____ (*Full Name*)

of _____ (*Street Address*)

_____ (*Suburb*) _____ (*Postcode*)

Phone: _____ *Email*: _____

agree to be re-contacted to provide my consent should opportunities arise for my tissue samples and data to be incorporated into other research projects and publications.

I understand that I am free to withdraw my consent for this data at any time without prejudice.

Signed: _____ *Date*: _____

Cardiovascular and risk factor questionnaire

CARDIOVASCULAR AND OTHER RISK FACTOR QUESTIONNAIRE

In order to be eligible to participate in the study entitled: *"The effect of concurrent endurance and resistance exercise order on genotypic and phenotypic adaptations in previously-untrained males, following a single bout, one week, and 10-week training period"*, you are required to complete the following questionnaire which is designed to assess the risk of you having a cardiovascular event occurring during an exhaustive exercise bout.

Name: _____ Date of birth: _____

Address: _____ Phone: _____

Age: _____ years Weight: _____ kg Height: _____ cm Gender: M F

EMERGENCY CONTACT INFORMATION:

Name: _____ Relationship to you: _____

Address: _____

Post Code: _____ Phone (home): _____ (mobile): _____

Phone (other): _____

PHYSICAL ACTIVITY LEVELS:

Please give a brief description of your average physical activity/exercise pattern in the past 3 months

	Sedentary	*Light*	*Moderate*	*Vigorous*	*High*
Please tick (✓)	☐	☐	☐	☐	☐
Frequency (sessions per week)					
Duration (minutes per week)					
Type of activity *(e.g. endurance, resistance, gym, soccer, etc.)*					

Intensity Guidelines *(Based on ESSA Adult Pre-exercise Screening tool)*:

Sedentary: <40% max HR – "*Very, very light*" RPE ≤ 1 (e.g. activities that usually involve sitting or lying and that have little additional movement and a low energy requirement)

Light: 40-55% max HR – "*Very light*" to "*Light*" RPE 1-2 (e.g. an aerobic activity that does not cause a noticeable change in breathing rate; an intensity that can be sustained for at least 60 minutes)

Moderate: 55-70% max HR – "*Moderate*" to "*Somewhat hard*" RPE 3-4 (e.g. an aerobic activity that is able to be conducted whilst maintaining a conversation uninterrupted; an intensity that may last between 30 and 60 minutes)

Vigorous: 70-90% max HR – "*Hard*" RPE 5-6 (e.g. an aerobic activity in which a conversation generally cannot be maintained uninterrupted; an intensity that may last up to about 30 minutes)

High: ≥90% max HR – "*Very hard*" RPE ≥7 (e.g. an intensity that generally cannot be sustained for longer than about 10 minutes)

Please circle the appropriate response to the following questions.

1.	Are you overweight?	Yes	No	Don't know
2.	Do you smoke?	Yes	No	Social
3.	Are you an asthmatic?	Yes	No	Don't know
4.	Are you a diabetic?	Yes	No	Don't know
5.	Does your family have a history of diabetes?	Yes	No	Don't know
6.	Do you have a thyroid disorder?	Yes	No	Don't know
7.	Does your family have a history of thyroid disorders?	Yes	No	Don't know
8.	Do you have a pituitary disorder?	Yes	No	Don't know
9.	Does your family have a history of pituitary disorders?	Yes	No	Don't know
10.	Do you have a heart rhythm disturbance?	Yes	No	Don't know
11.	Do you have a high blood cholesterol level?	Yes	No	Don't know
12.	Do you have elevated blood pressure?	Yes	No	Don't know
13.	Are you being treated with diuretics?	Yes	No	
14.	Are you on any other medications?	Yes	No	

Please list all/any medications:

……

……

……

15. Do you think you have any medical complaint or any other reason which you know of which you think may prevent you from participating in strenuous exercise? (*please circle*) Yes No

If "*Yes*", please elaborate ……

……

……

16. Have you had any musculoskeletal problems that have required medical treatment (e.g., broken bones, joint reconstruction etc.)? (*please circle*) Yes No

If "*Yes*", please elaborate ……

……

……

17. Does your family have a history of premature cardiovascular problems (e.g. heart attack, stroke)? (*please circle*) Yes No Don't know

I, _____, believe that the answers to these questions are true and correct.

Signed: _____ Date: _____

Muscle biopsy & venous catheterisation questionnaire

MUSCLE BIOPSY & VENOUS CATHETERISATION QUESTIONNAIRE

For the study entitled: "The effect of concurrent endurance and resistance exercise order on genotypic and phenotypic adaptations in previously-untrained males, following a single bout, one week, and 10-week training period".

Name: _____ Date of birth: _____

Address: _____ Phone: _____

Age: _____ years Weight: _____ kg Height: _____ cm Gender: M F

1. Have you or your family suffered from any tendency to bleed excessively (e.g. haemophilia) or bruise very easily? Yes No Don't Know
   If yes, please elaborate
   _____

2. Are you allergic to local anaesthetic? Yes No Don't Know
   If yes, please elaborate
   _____

3. Do you have any skin allergies? Yes No Don't Know
   If yes, please elaborate
   _____

4. Have you any other allergies? Yes No Don't Know
   If yes, please elaborate
   _____

5. Are you currently on any medication? Yes No
   If yes, what is the medication?
   _____

6. Do you have any other medical problems? Yes No
   If yes, please elaborate
   _____

7. Have you ever fainted when you had an injection or blood sample taken?
   Yes No Don't know
   If yes, please elaborate
   _____

8. Have you previously had heparin infused or injected?

   Yes No Don't know

   If yes, please elaborate

   _____

9. Do you or other members of your family have Raynaud's disease, or suffer from very poor circulation in the fingers, leading to painful fingers that turn white/blue?

   Yes No Don't know

   If yes, please elaborate

   _____

I, _____, believe that the answers to these questions are true and correct.

Signed: _____ Date: _____

Appendix B – Chapter 4 Resources & Data

Participant characteristics

		WEEK 1								WEEK 10					
		Age (y)	Height (cm)	Body Mass (kg)	Lean Mass (kg)	Fat Mass (kg)	1-RM Leg Press (kg)	$\dot{V}O_{2peak}$ (ml/kg/min)	W_{peak} (W)	Body Mass (kg)	Lean Mass (kg)	Fat Mass (kg)	1-RM Leg Press (kg)	$\dot{V}O_{2peak}$ (ml/kg/min)	W_{peak} (W)
END-RES	1	29.8	176	79.5	52.3	24.0	240.50	32.9	154	80.6	54.1	23.4	373.00	36.8	180
	2	22.6	179	88.6	55.5	30.1	315.50	31.9	170	87.6	56.6	28.0	395.50	36.0	199
	3	26.4	193	84.0	65.3	14.9	433.00	51.2	280	83.3	65.2	14.1	483.00	54.3	312
	4	19.9	182	74.2	59.3	11.3	328.00	52.0	247	75.8	61.6	10.6	498.00	55.5	262
	5	18.8	182	58.5	43.6	10.0	193.00	46.9	190	62.2	47.6	11.6	258.00	49.0	201
	6	29.0	182	65.6	49.9	12.9	233.00	50.6	231	65.3	51.4	11.0	318.00	57.3	247
	7	18.5	179	77.8	58.3	12.1	333.00	46.5	213	77.1	63.2	10.8	443.00	50.6	281
	8	26.0	179	83.3	61.9	17.8	395.50	44.6	250	85.0	63.4	17.9	508.00	47.5	284
	9	18.4	169	54.1	43.4	8.2	251.75	49.2	162	56.5	45.6	8.4	313.00	54.7	200
MEAN		23.3	180.0	73.9	54.4	15.7	302.6	45.1	211	74.8	56.5	15.1	398.8	49.1	241
SD		4.6	6.3	12.0	7.7	7.2	79.6	7.6	44	11.0	7.3	6.7	90.3	7.9	47

		WEEK 1								WEEK 10					
		Age (y)	Height (cm)	Body Mass (kg)	Lean Mass (kg)	Fat Mass (kg)	1-RM Leg Press (kg)	$\dot{V}O_{2peak}$ (ml/kg/min)	W_{peak} (W)	Body Mass (kg)	Lean Mass (kg)	Fat Mass (kg)	1-RM Leg Press (kg)	$\dot{V}O_{2peak}$ (ml/kg/min)	W_{peak} (W)
RES-END	1	22.6	166	58.1	47.9	7.5	253.00	43.6	162	59.9	50.8	6.4	335.50	46.2	175
	2	18.8	174	63.1	48.8	11.5	218.00	45.4	189	66.0	52.6	10.7	330.50	50.7	205
	3	23.2	174	74.4	59.0	12.4	423.00	42.0	177	73.6	60.2	10.4	473.00	46.9	220
	4	23.7	177	81.0	66.6	11.2	468.00	45.7	228	78.5	66.2	9.0	583.00	49.0	249
	5	23.6	182	70.8	53.7	13.8	228.00	43.8	189	73.8	55.9	14.6	315.50	45.5	228
	6	28.9	181	75.4	53.4	18.8	263.00	36.7	172	74.0	56.4	14.6	323.00	44.5	230
	7	28.6	190	93.4	62.3	27.7	344.25	32.2	197	91.4	63.1	25.0	443.00	36.8	239
	8	18.4	179	74.1	62.5	8.4	381.75	53.9	270	75.0	63.8	8.8	493.00	54.6	293
MEAN		23.5	177.8	73.8	56.8	13.9	322.4	42.9	198	74.0	58.6	12.4	412.1	46.8	229.7
SD		3.9	7.0	10.8	6.8	6.6	95.2	6.4	35	9.2	5.6	5.8	100.2	5.2	34.1

(continued)

				WEEK 1						WEEK 10					
		Age (y)	**Height (cm)**	**Body Mass (kg)**	**Lean Mass (kg)**	**Fat Mass (kg)**	**1-RM Leg Press (kg)**	**$\dot{V}O_{2peak}$ (ml/kg/min)**	**W_{peak} (W)**	**Body Mass (kg)**	**Lean Mass (kg)**	**Fat Mass (kg)**	**1-RM Leg Press (kg)**	**$\dot{V}O_{2peak}$ (ml/kg/min)**	**W_{peak} (W)**
RES-ONLY	1	27.5	177	85.1	63.3	17.8	418.00	51.1	283	84.9	64.0	17.0	503.00	45.3	245
	2	22.6	185	70.7	59.8	7.6	206.75	52.6	235	72.5	60.5	8.7	325.50	51.9	231
	3	22.4	186	70.2	49.7	17.4	201.75	30.6	140	73.2	52.5	17.6	320.50	31.4	148
	4	38.2	176	86.5	59.3	24.1	423.00	36.4	204	87.7	60.9	23.6	500.50	39.4	226
	5	27.6	182	80.6	58.6	18.9	398.00	35.0	186	83.2	61.3	18.8	458.00	35.1	178
	6	28.9	177	63.6	51.7	9.4	300.50	50.1	205	65.5	53.1	9.8	378.00	47.1	193
	7	21.3	182	71.8	53.3	15.7	275.50	46.4	184	73.3	53.3	17.3	303.00	43.4	186
	8	28.0	175	61.1	51.8	6.5	318.00	45.8	187	62.3	53.0	6.5	383.00	45.6	186
MEAN		27.1	180.0	73.7	55.9	14.7	317.7	43.5	203	75.3	57.3	14.9	396.4	42.4	199
SD		5.4	4.1	9.5	4.9	6.2	89.0	8.3	42	9.2	4.8	5.9	81.1	6.7	32

Heart rate responses during END session

(% max. heart rate)

		WEEK 1			WEEK 10		
		1.1	**1.2**	**1.3**	**10.1**	**10.2**	**10.3**
END-RES	1	93%	88%	89%	86%	86%	87%
	2	92%	89%	92%	82%	81%	89%
	3	90%	96%	89%	92%	94%	95%
	4	95%	94%	96%	92%	99%	95%
	5	92%	96%	95%	93%	92%	92%
	6	91%	90%	88%	87%	85%	88%
	7	86%	87%	88%	87%	93%	89%
	8	92%	93%	90%	95%	94%	95%
	9	89%	93%	92%	94%	91%	90%
	MEAN	91%	92%	91%	90%	91%	91%
	SD	2%	3%	3%	4%	5%	3%
RES-END	1	91%	87%	82%	76%	75%	79%
	2	96%	91%	92%	87%	87%	90%
	3	89%	87%	90%	88%	90%	87%
	4	82%	86%	82%	85%	85%	85%
	5	94%	90%	89%	86%	84%	83%
	6	97%	92%	90%	86%	86%	85%
	7	87%	83%	78%	85%	87%	84%
	8	86%	88%	83%	97%	95%	95%
	9	86%	83%	83%	83%	83%	82%
	MEAN	90%	87%	85%	86%	86%	85%
	SD	5%	3%	5%	5%	5%	5%

Molecular data & statistical analyses

Muscle glycogen

Endurance-Resistance

RAW UNITS (mmol·kg·DM^{-1})

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	266	309	267	309	298	321	290	443	468	268
2	288	182	202	181	142	339	434	318	385	244
3	209	194	159	119	168	478	372	324	200	225
4	305	128	172	106	204	276	194	273	208	181
5	355	252	247	366	223	364	303	442	378	349
6	246	265	201	178	273	302	240	285	315	228
7	313	291	217	214	279	314	251	382	381	263
8	178	165	206	162	170	341	444	282	240	260
9	252	290	254	214	218	379	214	243	202	225
Geomean	**262.7**					**342.2**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.01	1.17	1.01	1.18	1.13	0.94	0.85	1.30	1.37	0.78
2	1.09	0.69	0.77	0.69	0.54	0.99	1.27	0.93	1.12	0.71
3	0.80	0.74	0.61	0.45	0.64	1.40	1.09	0.95	0.58	0.66
4	1.16	0.49	0.66	0.40	0.78	0.81	0.57	0.80	0.61	0.53
5	1.35	0.96	0.94	1.39	0.85	1.06	0.89	1.29	1.10	1.02
6	0.93	1.01	0.77	0.68	1.04	0.88	0.70	0.83	0.92	0.67
7	1.19	1.11	0.83	0.82	1.06	0.92	0.73	1.12	1.11	0.77
8	0.68	0.63	0.79	0.62	0.65	1.00	1.30	0.82	0.70	0.76
9	0.96	1.11	0.97	0.82	0.83	1.11	0.63	0.71	0.59	0.66
MEAN	1.00	0.84	0.80	0.73	0.81	1.00	0.86	0.95	0.86	0.72
SD	0.21	0.25	0.14	0.32	0.21	0.17	0.27	0.22	0.29	0.13

Resistance-Endurance

RAW UNITS (mmol·kg·DM^{-1})

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	220	215	323	139	129	404	374	374	322	256
2	261	357	249	83	170	304	267	293	285	332
3	256	267	323	208	228	290	251	285	199	272
4	325	307	252	236	284	241	318	388	301	264
5	249	465	251	316	247	407	316	286	224	234
6	325	304	339	233	434	402	290	302	221	242
7	317	168	251	162	261	242	253	317	219	235
8	239	260	320	278	306	330	277	253	280	266
Geomean	**271.3**					**320.7**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.81	0.79	1.19	0.51	0.48	1.26	1.17	1.17	1.00	0.80
2	0.96	1.32	0.92	0.31	0.63	0.95	0.83	0.91	0.89	1.04
3	0.94	0.98	1.19	0.77	0.84	0.90	0.78	0.89	0.62	0.85
4	1.20	1.13	0.93	0.87	1.05	0.75	0.99	1.21	0.94	0.82
5	0.92	1.71	0.92	1.16	0.91	1.27	0.98	0.89	0.70	0.73
6	1.20	1.12	1.25	0.86	1.60	1.25	0.90	0.94	0.69	0.75
7	1.17	0.62	0.92	0.60	0.96	0.76	0.79	0.99	0.68	0.73
8	0.88	0.96	1.18	1.02	1.13	1.03	0.86	0.79	0.87	0.83
MEAN	1.00	1.04	1.05	0.71	0.90	1.00	0.91	0.97	0.79	0.81
SD	0.15	0.33	0.15	0.28	0.34	0.22	0.13	0.14	0.14	0.10

Resistance-Only

RAW UNITS (mmol·kg·DM^{-1})

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	237	235	246	261	288	318	265	272	211	217
2	189	157	188	146	210	228	378	274	394	464
3	206	268	241	340	228	300	262	326	273	346
4	300	273	237	288	254	477	321	344	320	293
5	217	273	300	332	211	243	201	271	195	254
6	264	214	197	205	267	248	312	240	206	295
7	203	234	295	294	262	252	235	274	294	257
8	157	135	210	235	237	291	231	301	237	264
Geomean	**217.7**					**286.8**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.09	1.08	1.13	1.20	1.32	1.11	0.92	0.95	0.74	0.76
2	0.87	0.72	0.86	0.67	0.97	0.79	1.32	0.96	1.37	1.62
3	0.95	1.23	1.11	1.56	1.05	1.05	0.91	1.14	0.95	1.21
4	1.38	1.25	1.09	1.32	1.16	1.66	1.12	1.20	1.12	1.02
5	1.00	1.25	1.38	1.53	0.97	0.85	0.70	0.95	0.68	0.88
6	1.21	0.98	0.91	0.94	1.23	0.86	1.09	0.84	0.72	1.03
7	0.93	1.07	1.36	1.35	1.20	0.88	0.82	0.95	1.03	0.90
8	0.72	0.62	0.96	1.08	1.09	1.01	0.81	1.05	0.83	0.92
MEAN	1.00	1.00	1.08	1.17	1.12	1.00	0.94	1.00	0.90	1.02
SD	0.21	0.24	0.19	0.30	0.13	0.28	0.20	0.12	0.24	0.27

RT qPCR

PGC-1a

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0056	0.0118	0.0383	0.0400	0.0395	0.0175	0.0151	0.0327	0.0266	0.0224
2	0.0422	0.0241	0.0671	0.0905	0.0749	0.0133	0.0144	0.0380	0.0409	0.0341
3	0.0105	0.0206	0.0477	0.0548	0.0730	0.0103	0.0118	0.0233	0.0343	0.0184
4	0.0137	0.0216	0.1446	0.1288	0.0412	0.0193	0.0174	0.0703	0.0586	0.0545
5	0.0104	0.0194	0.0124	0.0309	0.0214	0.0195	0.0117	0.0605	0.0802	0.0249
6	0.0194	0.0145	0.0862	0.0794	0.0209	0.0186	0.0215	0.0617	0.0523	0.0196
7	0.0073	0.0112	0.0641	0.0476	0.0358	0.0151	0.0146	0.0252	0.0284	0.0265
8	0.0117	0.0122	0.0785	0.0673	0.0278	0.0088	0.0126	0.0390	0.0429	0.0319
9	0.0073	0.0188	0.1299	0.0758	0.0739	0.0132	0.0179	0.0605	0.0572	0.0406
Geomean	**0.012**					**0.015**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.47	1.01	3.26	3.40	3.36	1.20	1.04	2.24	1.83	1.54
2	3.59	2.05	5.71	7.70	6.37	0.91	0.99	2.61	2.81	2.34
3	0.90	1.75	4.06	4.66	6.21	0.71	0.81	1.60	2.36	1.27
4	1.17	1.84	12.30	10.96	3.51	1.33	1.19	4.83	4.03	3.74
5	0.89	1.65	1.06	2.63	1.82	1.34	0.80	4.16	5.51	1.71
6	1.65	1.23	7.33	6.75	1.78	1.27	1.47	4.24	3.59	1.34
7	0.62	0.96	5.46	4.05	3.05	1.04	1.00	1.73	1.95	1.82
8	1.00	1.04	6.68	5.73	2.37	0.60	0.87	2.67	2.94	2.19
9	0.62	1.60	11.06	6.45	6.29	0.91	1.23	4.16	3.93	2.79
MEAN	1.00	1.41	5.23	5.34	3.45	1.00	1.03	2.92	3.03	1.97
SD	0.96	0.41	3.58	2.54	1.92	0.27	0.22	1.21	1.18	0.79

PGC-1a

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0260	0.0241	0.0596	0.0344	0.0882	0.0240	0.0173	0.0117	0.0234	0.0403
2	0.0160	0.0181	0.0499	0.0324	0.0301	0.0174	0.0192	0.0163	0.0201	0.0706
3	0.0149	0.0140	0.0907	0.0510	0.0719	0.0121	0.0170	0.0498	0.0363	0.0572
4	0.0173	0.0162	0.0215	0.0156	0.0521	0.0217	0.0162	0.0131	0.0127	0.0545
5	0.0129	0.0108	0.0135	0.0130	0.0133	0.0353	0.0285	0.0485	0.0384	0.0999
6	0.0497	0.0316	0.0277	0.0155	0.0286	0.0320	0.0331	0.0570	0.0667	0.0967
7	0.0125	0.0081	0.0306	0.0342	0.0383	0.0155	0.0133	0.0058	0.0252	0.0107
8	0.0045	0.0241	0.0245	0.0325	0.0368	0.0013	0.0322	0.0280	0.0307	0.0864
Geomean	**0.016**					**0.015**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.65	1.52	3.77	2.18	5.58	1.61	1.15	0.78	1.57	2.70
2	1.02	1.14	3.16	2.05	1.91	1.16	1.29	1.09	1.34	4.72
3	0.95	0.88	5.74	3.23	4.56	0.81	1.13	3.33	2.42	3.82
4	1.10	1.03	1.36	0.99	3.30	1.45	1.08	0.88	0.85	3.64
5	0.81	0.69	0.86	0.83	0.84	2.36	1.90	3.24	2.57	6.68
6	3.15	2.00	1.75	0.98	1.81	2.14	2.21	3.81	4.46	6.46
7	0.79	0.51	1.94	2.17	2.42	1.04	0.89	0.39	1.68	0.72
8	0.29	1.53	1.55	2.06	2.33	0.09	2.15	1.87	2.05	5.78
MEAN	1.00	1.07	2.13	1.64	2.47	1.00	1.40	1.47	1.90	3.65
SD	0.87	0.49	1.62	0.82	1.56	0.73	0.53	1.35	1.10	2.03

PGC-1a

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0224	0.0187	0.0442	0.0112	0.0221	0.0242	0.0244	0.0281	0.0312	0.0265
2	0.0299	0.0102	0.2266	0.0281	0.1142	0.0223	0.0176	0.0846	0.0870	0.0241
3	0.0239	0.0102	0.0283	0.0226	0.0177	0.0212	0.0170	0.0150	0.0215	0.0361
4	0.0088	0.0173	0.0524	0.0345	0.0138	0.0112	0.0153	0.0400	0.0355	0.0157
5	0.0141	0.0120	0.2555	0.0605	0.0485	0.0183	0.0192	0.0335	0.0321	0.0148
6	0.0439	0.0132	0.0671	0.0472	0.0330	0.0173	0.0172	0.0550	0.3780	0.0276
7	0.0109	0.0272	0.0754	0.0418	0.0155	0.0298	0.0819	0.1069	0.0822	0.0534
8	0.0053	0.0046	0.0381	0.0306	0.1642	0.0225	0.0129	0.0396	0.0374	0.0175
Geomean	**0.016**					**0.020**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.38	1.15	2.71	0.69	1.36	1.20	1.21	1.39	1.55	1.32
2	1.83	0.63	13.89	1.72	7.00	1.11	0.87	4.20	4.32	1.20
3	1.47	0.62	1.73	1.39	1.09	1.05	0.84	0.74	1.07	1.79
4	0.54	1.06	3.21	2.11	0.85	0.55	0.76	1.98	1.76	0.78
5	0.87	0.73	15.66	3.71	2.98	0.91	0.95	1.66	1.59	0.73
6	2.69	0.81	4.11	2.89	2.02	0.86	0.85	2.73	18.76	1.37
7	0.67	1.67	4.62	2.56	0.95	1.48	4.07	5.31	4.08	2.65
8	0.32	0.28	2.34	1.88	10.07	1.12	0.64	1.97	1.86	0.87
MEAN	1.00	0.78	4.42	1.91	2.18	1.00	1.05	2.12	2.70	1.23
SD	0.78	0.42	5.49	0.94	3.41	0.27	1.14	1.53	5.94	0.64

MuRF1

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0187	0.0281	0.0639	0.0543	0.0319	0.0294	0.0302	0.0361	0.0246	0.0250
2	0.0350	0.0281	0.0696	0.1197	0.0686	0.0132	0.0215	0.0239	0.0386	0.0193
3	0.0536	0.0321	0.0597	0.0440	0.0524	0.0401	0.0467	0.0338	0.0479	0.0235
4	0.0202	0.0339	0.1356	0.2081	0.0245	0.0252	0.0405	0.1056	0.0701	0.0185
5	0.0424	0.0528	0.0368	0.0442	0.0370	0.0367	0.0161	0.0530	0.0832	0.0464
6	0.0481	0.0324	0.0953	0.0929	0.0140	0.0352	0.0485	0.0716	0.0518	0.0100
7	0.0951	0.0638	0.1181	0.0866	0.0249	0.0237	0.0303	0.0255	0.0520	0.0287
8	0.0341	0.0287	0.1146	0.1049	0.0213	0.0444	0.0398	0.0544	0.0415	0.0215
9	0.0264	0.0231	0.1696	0.0765	0.0726	0.0197	0.0224	0.0516	0.0437	0.0281
Geomean										

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.51	0.76	1.74	1.47	0.87	1.05	1.08	1.29	0.88	0.90
2	0.95	0.76	1.89	3.25	1.86	0.47	0.77	0.86	1.38	0.69
3	1.46	0.87	1.62	1.20	1.42	1.43	1.67	1.21	1.71	0.84
4	0.55	0.92	3.68	5.65	0.67	0.90	1.45	3.78	2.51	0.66
5	1.15	1.43	1.00	1.20	1.00	1.31	0.57	1.89	2.98	1.66
6	1.31	0.88	2.59	2.52	0.38	1.26	1.73	2.56	1.85	0.36
7	2.58	1.73	3.21	2.35	0.68	0.85	1.08	0.91	1.86	1.03
8	0.93	0.78	3.11	2.85	0.58	1.59	1.42	1.94	1.48	0.77
9	0.72	0.63	4.61	2.08	1.97	0.71	0.80	1.85	1.56	1.01
MEAN	1.00	0.93	2.37	2.23	0.92	1.00	1.11	1.63	1.71	0.82
SD	0.63	0.36	1.15	1.38	0.58	0.36	0.42	0.92	0.62	0.36

MuRF1

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0724	0.0766	0.1332	0.0336	0.2564	0.0675	0.0413	0.0174	0.0357	0.0664
2	0.0684	0.0632	0.0429	0.0221	0.1179	0.0540	0.0742	0.0293	0.0349	0.0952
3	0.0472	0.0671	0.2598	0.0995	0.2348	0.0806	0.0974	0.0861	0.0417	0.1174
4	0.0858	0.0724	0.0634	0.0415	0.1239	0.0759	0.0398	0.0403	0.0524	0.1089
5	0.0412	0.0408	0.0263	0.0432	0.0714	0.0211	0.0261	0.0484	0.0528	0.1109
6	0.0658	0.0216	0.0136	0.0214	0.0614	0.0208	0.0390	0.0320	0.0247	0.0567
7	0.0390	0.0290	0.0971	0.0576	0.0993	0.1156	0.1155	0.0908	0.0583	0.0651
8	0.0645	0.0709	0.1102	0.0487	0.0839	0.1251	0.0804	0.0544	0.0335	0.1731
Geomean	**0.058**					**0.059**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.24	1.31	2.28	0.58	4.38	1.15	0.70	0.30	0.61	1.13
2	1.17	1.08	0.73	0.38	2.02	0.92	1.26	0.50	0.59	1.62
3	0.81	1.15	4.44	1.70	4.02	1.37	1.66	1.47	0.71	2.00
4	1.47	1.24	1.08	0.71	2.12	1.29	0.68	0.69	0.89	1.85
5	0.70	0.70	0.45	0.74	1.22	0.36	0.44	0.82	0.90	1.89
6	1.13	0.37	0.23	0.37	1.05	0.35	0.66	0.55	0.42	0.97
7	0.67	0.50	1.66	0.98	1.70	1.97	1.97	1.55	0.99	1.11
8	1.10	1.21	1.88	0.83	1.43	2.13	1.37	0.93	0.57	2.95
MEAN	1.00	0.86	1.13	0.70	1.98	1.00	0.97	0.75	0.69	1.59
SD	0.28	0.37	1.35	0.43	1.27	0.65	0.55	0.45	0.20	0.65

MuRF1

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.1158	0.1793	0.0899	0.0579	0.0565	0.1162	0.0371	0.0497	0.0755	0.0363
2	0.1051	0.1091	0.3299	0.0547	0.0349	0.0640	0.0470	0.1574	0.2114	0.0780
3	0.1029	0.1310	0.1158	0.1063	0.0988	0.1524	0.1154	0.0978	0.0788	0.0771
4	0.0446	0.1174	0.1594	0.1134	0.0493	0.0755	0.0762	0.0846	0.0616	0.0760
5	0.1173	0.1095	0.6278	0.1646	0.0711	0.1579	0.1130	0.1253	0.0916	0.0849
6	0.4546	0.1541	0.2536	0.1770	0.0953	0.1386	0.1388	0.1341	0.9772	0.0518
7	0.0899	0.1209	0.1098	0.0496	0.0658	0.0795	0.4520	0.1442	0.0953	0.0300
8	0.3064	0.3126	0.1515	0.1109	0.9478	0.1874	0.1548	0.2358	0.1828	0.0385
Geomean	**0.130**					**0.114**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.89	1.38	0.69	0.44	0.43	1.02	0.33	0.44	0.66	0.32
2	0.81	0.84	2.54	0.42	0.27	0.56	0.41	1.38	1.86	0.69
3	0.79	1.01	0.89	0.82	0.76	1.34	1.02	0.86	0.69	0.68
4	0.34	0.90	1.23	0.87	0.38	0.66	0.67	0.74	0.54	0.67
5	0.90	0.84	4.82	1.27	0.55	1.39	0.99	1.10	0.81	0.75
6	3.49	1.18	1.95	1.36	0.73	1.22	1.22	1.18	8.59	0.46
7	0.69	0.93	0.84	0.38	0.51	0.70	3.97	1.27	0.84	0.26
8	2.36	2.40	1.16	0.85	7.28	1.65	1.36	2.07	1.61	0.34
MEAN	1.00	1.11	1.43	0.72	0.69	1.00	0.94	1.04	1.20	0.48
SD	1.07	0.53	1.38	0.37	2.40	0.40	1.16	0.49	2.73	0.20

MAFbx

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0279	0.2012	0.2393	0.3342	0.1697	0.2018	0.0990	0.1079	0.0610	0.0176
2	0.1600	0.1543	0.2182	0.2771	0.0558	0.0961	0.1029	0.1086	0.1682	0.0557
3	0.1442	0.1156	0.0444	0.1005	0.0674	0.1069	0.0819	0.0652	0.1454	0.0487
4	0.0243	0.1130	0.2635	0.2458	0.0372	0.1011	0.1141	0.3004	0.1848	0.0579
5	0.0909	0.0987	0.0238	0.0279	0.0280	0.1888	0.0185	0.1692	0.2160	0.0623
6	0.1606	0.0658	0.1035	0.1428	0.0125	0.1792	0.1387	0.1825	0.1361	0.0404
7	0.2197	0.1688	0.2094	0.1447	0.0602	0.1435	0.1089	0.1072	0.1414	0.0790
8	0.1401	0.1188	0.3938	0.3174	0.0690	0.1147	0.1176	0.1808	0.1561	0.0562
9	0.0996	0.0570	0.2705	0.0481	0.1434	0.1073	0.0978	0.1991	0.1615	0.0577
Geomean	**0.096**					**0.132**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.29	2.09	2.49	3.48	1.77	1.52	0.75	0.81	0.46	0.13
2	1.67	1.61	2.27	2.88	0.58	0.73	0.78	0.82	1.27	0.42
3	1.50	1.20	0.46	1.05	0.70	0.81	0.62	0.49	1.10	0.37
4	0.25	1.18	2.74	2.56	0.39	0.76	0.86	2.27	1.40	0.44
5	0.95	1.03	0.25	0.29	0.29	1.43	0.14	1.28	1.63	0.47
6	1.67	0.68	1.08	1.49	0.13	1.35	1.05	1.38	1.03	0.31
7	2.29	1.76	2.18	1.51	0.63	1.08	0.82	0.81	1.07	0.60
8	1.46	1.24	4.10	3.30	0.72	0.87	0.89	1.37	1.18	0.42
9	1.04	0.59	2.82	0.50	1.49	0.81	0.74	1.50	1.22	0.44
MEAN	1.00	1.18	1.54	1.45	0.58	1.00	0.66	1.09	1.10	0.37
SD	0.67	0.49	1.24	1.20	0.54	0.32	0.25	0.53	0.32	0.13

MAFbx

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.1213	0.1292	0.0434	0.0262	0.0964	0.2002	0.1824	0.0599	0.0621	0.0953
2	0.1750	0.1750	0.0884	0.0538	0.0447	0.1320	0.1859	0.0239	0.0507	0.1476
3	0.2348	0.2016	0.1074	0.0570	0.1553	0.2355	0.2828	0.1227	0.0864	0.2016
4	0.2732	0.1714	0.1131	0.0569	0.1398	0.2842	0.2364	0.1306	0.1058	0.2006
5	0.1716	0.2336	0.2056	0.0389	0.0095	0.1217	0.1190	0.0829	0.0691	0.0928
6	0.3609	0.2791	0.0399	0.0276	0.0273	0.1225	0.1449	0.0566	0.0417	0.0936
7	0.1467	0.1533	0.0986	0.0680	0.1271	0.3118	0.2875	0.1200	0.0962	0.0521
8	0.2035	0.3810	0.0936	0.0543	0.0910	0.3741	0.2189	0.1926	0.0563	0.1206
Geomean	**0.200**					**0.205**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.61	0.65	0.22	0.13	0.48	0.98	0.89	0.29	0.30	0.47
2	0.88	0.88	0.44	0.27	0.22	0.65	0.91	0.12	0.25	0.72
3	1.18	1.01	0.54	0.29	0.78	1.15	1.38	0.60	0.42	0.99
4	1.37	0.86	0.57	0.29	0.70	1.39	1.16	0.64	0.52	0.98
5	0.86	1.17	1.03	0.19	0.05	0.59	0.58	0.41	0.34	0.45
6	1.81	1.40	0.20	0.14	0.14	0.60	0.71	0.28	0.20	0.46
7	0.74	0.77	0.49	0.34	0.64	1.52	1.40	0.59	0.47	0.25
8	1.02	1.91	0.47	0.27	0.46	1.83	1.07	0.94	0.28	0.59
MEAN	1.00	1.02	0.44	0.23	0.32	1.00	0.97	0.41	0.33	0.56
SD	0.39	0.41	0.26	0.08	0.27	0.47	0.30	0.26	0.11	0.26

MAFbx

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.4651	0.4474	0.0946	0.0926	0.0301	0.3758	0.0958	0.0713	0.0892	0.0253
2	0.2610	0.2494	0.5960	0.0643	0.1904	0.2193	0.1274	0.3647	0.2751	0.0759
3	0.4432	0.4779	0.1188	0.1102	0.0683	0.3256	0.3068	0.1367	0.0684	0.1871
4	0.2241	0.4043	0.0766	0.0602	0.0251	0.4739	0.3118	0.1681	0.1633	0.2133
5	0.4143	0.3719	1.0230	0.2260	0.1176	0.3087	0.2881	0.1747	0.1995	0.0996
6	1.0714	0.3327	0.1886	0.1723	0.0609	0.4724	0.3734	0.2587	1.1366	0.1228
7	0.3364	0.3809	0.1410	0.0798	0.0247	0.2776	0.9918	0.2090	0.1607	0.0767
8	0.6254	0.3403	0.1905	0.0691	0.4940	0.5003	0.3085	0.1294	0.1275	0.0484
Geomean	**0.428**					**0.356**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.09	1.05	0.22	0.22	0.07	1.06	0.27	0.20	0.25	0.07
2	0.61	0.58	1.39	0.15	0.44	0.62	0.36	1.02	0.77	0.21
3	1.04	1.12	0.28	0.26	0.16	0.91	0.86	0.38	0.19	0.53
4	0.52	0.94	0.18	0.14	0.06	1.33	0.88	0.47	0.46	0.60
5	0.97	0.87	2.39	0.53	0.27	0.87	0.81	0.49	0.56	0.28
6	2.50	0.78	0.44	0.40	0.14	1.33	1.05	0.73	3.19	0.34
7	0.79	0.89	0.33	0.19	0.06	0.78	2.79	0.59	0.45	0.22
8	1.46	0.80	0.44	0.16	1.15	1.41	0.87	0.36	0.36	0.14
MEAN	1.00	0.86	0.47	0.23	0.17	1.00	0.79	0.48	0.51	0.25
SD	0.63	0.17	0.78	0.14	0.37	0.29	0.78	0.25	0.99	0.18

Myostatin

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0043	0.0176	0.0079	0.0082	0.0073	0.0091	0.0049	0.0021	0.0036	0.0021
2	0.0207	0.0133	0.0063	0.0041	0.0042	0.0105	0.0106	0.0101	0.0060	0.0135
3	0.0095	0.0124	0.0084	0.0077	0.0041	0.0061	0.0057	0.0043	0.0051	0.0030
4	0.0078	0.0079	0.0037	0.0037	0.0062	0.0096	0.0064	0.0026	0.0021	0.0070
5	0.0055	0.0087	0.0114	0.0064	0.0044	0.0099	0.0315	0.0064	0.0046	0.0028
6	0.0133	0.0056	0.0040	0.0030	0.0025	0.0037	0.0066	0.0024	0.0027	0.0023
7	0.0071	0.0079	0.0046	0.0025	0.0091	0.0125	0.0096	0.0062	0.0049	0.0115
8	0.0062	0.0101	0.0101	0.0101	0.0133	0.0100	0.0058	0.0076	0.0070	0.0037
9	0.0032	0.0091	0.0049	0.0030	0.0183	0.0069	0.0089	0.0063	0.0051	0.0140
Geomean	**0.007**					**0.008**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.58	2.36	1.06	1.10	0.98	1.11	0.60	0.25	0.43	0.25
2	2.78	1.79	0.84	0.55	0.56	1.27	1.29	1.22	0.73	1.64
3	1.28	1.66	1.12	1.04	0.55	0.74	0.69	0.52	0.61	0.37
4	1.05	1.06	0.50	0.49	0.84	1.16	0.77	0.31	0.26	0.85
5	0.74	1.16	1.53	0.85	0.59	1.20	3.82	0.77	0.56	0.34
6	1.78	0.75	0.53	0.41	0.33	0.45	0.80	0.29	0.33	0.28
7	0.96	1.07	0.61	0.34	1.22	1.52	1.17	0.75	0.59	1.39
8	0.83	1.36	1.35	1.36	1.79	1.21	0.71	0.92	0.85	0.45
9	0.43	1.22	0.66	0.40	2.45	0.84	1.07	0.77	0.61	1.69
MEAN	1.00	1.31	0.85	0.65	0.86	1.00	1.01	0.57	0.52	0.62
SD	0.73	0.48	0.37	0.37	0.69	0.32	1.00	0.33	0.19	0.61

Myostatin

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0092	0.0130	0.0103	0.0101	0.0016	0.0076	0.0072	0.0042	0.0063	0.0081
2	0.0173	0.0127	0.0134	0.0057	0.0021	0.0111	0.0109	0.0108	0.0122	0.0071
3	0.0137	0.0091	0.0096	0.0090	0.0032	0.0147	0.0231	0.0053	0.0047	0.0039
4	0.0046	0.0034	0.0061	0.0051	0.0030	0.0047	0.0046	0.0065	0.0046	0.0074
5	0.0065	0.0391	0.0221	0.0094	0.0051	0.0062	0.0080	0.0088	0.0127	0.0060
6	0.0307	0.0236	0.0110	0.0108	0.0011	0.0088	0.0049	0.0024	0.0037	0.0021
7	0.0059	0.0072	0.0025	0.0013	0.0028	0.0088	0.0039	0.0031	0.0022	0.0046
8	0.0008	0.0095	0.0151	0.0193	0.0074	0.0084	0.0080	0.0179	0.0150	0.0082
Geomean	**0.007**					**0.008**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.24	1.75	1.38	1.36	0.22	0.91	0.86	0.51	0.75	0.97
2	2.33	1.71	1.81	0.77	0.28	1.32	1.30	1.29	1.46	0.84
3	1.84	1.23	1.29	1.22	0.43	1.76	2.76	0.63	0.56	0.46
4	0.62	0.45	0.82	0.69	0.40	0.57	0.54	0.77	0.55	0.89
5	0.88	5.26	2.96	1.26	0.68	0.75	0.96	1.05	1.51	0.72
6	4.13	3.17	1.48	1.45	0.15	1.06	0.58	0.29	0.44	0.25
7	0.80	0.97	0.34	0.17	0.38	1.05	0.46	0.37	0.27	0.56
8	0.11	1.28	2.03	2.59	1.00	1.00	0.96	2.14	1.79	0.98
MEAN	1.00	1.56	1.30	0.96	0.38	1.00	0.90	0.73	0.76	0.65
SD	1.28	1.54	0.79	0.71	0.28	0.36	0.74	0.61	0.58	0.26

Myostatin

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0086	0.0041	0.0066	0.0041	0.0044	0.0038	0.0026	0.0025	0.0028	0.0027
2	0.0119	0.0077	0.0068	0.0047	0.0052	0.0070	0.0066	0.0047	0.0021	0.0009
3	0.0057	0.0066	0.0039	0.0061	0.0019	0.0165	0.0096	0.0020	0.0089	0.0071
4	0.0025	0.0058	0.0055	0.0040	0.0011	0.0023	0.0013	0.0017	0.0011	0.0021
5	0.0109	0.0065	0.0112	0.0032	0.0020	0.0063	0.0047	0.0046	0.0074	0.0040
6	0.0147	0.0030	0.0030	0.0016	0.0017	0.0039	0.0044	0.0024	0.0097	0.0012
7	0.0010	0.0036	0.0016	0.0027	0.0016	0.0050	0.0035	0.0019	0.0015	0.0030
8	0.0005	0.0001	0.0072	0.0069	0.0251	0.0089	0.0054	0.0021	0.0023	0.0042
Geomean	**0.004**					**0.006**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	2.03	0.95	1.56	0.95	1.04	0.67	0.45	0.44	0.50	0.48
2	2.80	1.80	1.61	1.11	1.22	1.23	1.16	0.83	0.37	0.16
3	1.34	1.54	0.92	1.44	0.45	2.90	1.69	0.35	1.56	1.25
4	0.59	1.36	1.29	0.93	0.26	0.40	0.22	0.29	0.20	0.38
5	2.56	1.54	2.63	0.75	0.47	1.11	0.83	0.81	1.30	0.70
6	3.45	0.71	0.71	0.39	0.40	0.69	0.78	0.43	1.70	0.21
7	0.23	0.86	0.37	0.64	0.38	0.87	0.62	0.33	0.26	0.52
8	0.11	0.03	1.70	1.63	5.89	1.56	0.94	0.37	0.40	0.73
MEAN	1.00	0.74	1.17	0.90	0.71	1.00	0.72	0.45	0.58	0.46
SD	1.26	0.58	0.70	0.41	1.90	0.79	0.45	0.22	0.63	0.35

Mighty

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0022	0.0034	0.0050	0.0043	0.0073	0.0040	0.0036	0.0035	0.0036	0.0048
2	0.0038	0.0036	0.0036	0.0051	0.0043	0.0022	0.0021	0.0031	0.0034	0.0038
3	0.0031	0.0041	0.0028	0.0031	0.0052	0.0033	0.0038	0.0031	0.0040	0.0048
4	0.0027	0.0033	0.0037	0.0044	0.0033	0.0036	0.0032	0.0035	0.0029	0.0049
5	0.0020	0.0039	0.0049	0.0046	0.0056	0.0047	0.0025	0.0058	0.0052	0.0052
6	0.0032	0.0029	0.0026	0.0029	0.0031	0.0043	0.0041	0.0040	0.0032	0.0034
7	0.0023	0.0024	0.0040	0.0029	0.0042	0.0032	0.0026	0.0029	0.0031	0.0036
8	0.0022	0.0029	0.0057	0.0049	0.0041	0.0025	0.0025	0.0038	0.0043	0.0047
9	0.0028	0.0034	0.0039	0.0042	0.0054	0.0024	0.0024	0.0037	0.0038	0.0073
Geomean	**0.003**					**0.003**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.84	1.30	1.88	1.64	2.74	1.22	1.12	1.08	1.11	1.49
2	1.43	1.37	1.35	1.91	1.63	0.68	0.66	0.94	1.06	1.18
3	1.18	1.53	1.06	1.15	1.96	1.02	1.16	0.96	1.23	1.47
4	1.00	1.25	1.41	1.66	1.24	1.12	0.99	1.08	0.88	1.51
5	0.74	1.47	1.85	1.73	2.09	1.46	0.78	1.79	1.59	1.59
6	1.22	1.08	1.00	1.11	1.16	1.31	1.26	1.24	0.97	1.03
7	0.88	0.92	1.51	1.10	1.57	1.00	0.81	0.91	0.94	1.12
8	0.83	1.10	2.17	1.84	1.54	0.76	0.76	1.17	1.32	1.45
9	1.07	1.30	1.47	1.58	2.04	0.73	0.74	1.13	1.16	2.25
MEAN	1.00	1.24	1.48	1.49	1.72	1.00	0.90	1.12	1.12	1.42
SD	0.23	0.19	0.39	0.32	0.49	0.27	0.22	0.27	0.22	0.36

Mighty

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0043	0.0042	0.0068	0.0047	0.0046	0.0040	0.0037	0.0040	0.0039	0.0040
2	0.0035	0.0033	0.0048	0.0032	0.0025	0.0031	0.0035	0.0028	0.0033	0.0069
3	0.0047	0.0035	0.0059	0.0032	0.0052	0.0030	0.0043	0.0043	0.0035	0.0049
4	0.0041	0.0025	0.0038	0.0023	0.0032	0.0039	0.0036	0.0037	0.0036	0.0062
5	0.0042	0.0043	0.0024	0.0029	0.0034	0.0032	0.0035	0.0037	0.0042	0.0050
6	0.0054	0.0041	0.0044	0.0045	0.0031	0.0034	0.0048	0.0043	0.0047	0.0070
7	0.0006	0.0070	0.0018	0.0002	0.0045	0.0010	0.0002	0.0013	0.0038	0.0081
8	0.0026	0.0049	0.0071	0.0090	0.0043	0.0078	0.0052	0.0107	0.0052	0.0043
Geomean	**0.003**					**0.003**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.37	1.34	2.16	1.48	1.47	1.23	1.13	1.23	1.20	1.22
2	1.11	1.03	1.51	1.00	0.80	0.94	1.08	0.87	1.00	2.10
3	1.48	1.11	1.86	1.01	1.66	0.93	1.31	1.33	1.07	1.51
4	1.30	0.78	1.20	0.74	1.00	1.21	1.10	1.15	1.09	1.91
5	1.34	1.37	0.77	0.93	1.09	0.97	1.08	1.13	1.28	1.54
6	1.71	1.29	1.38	1.44	1.00	1.04	1.46	1.31	1.45	2.13
7	0.18	2.21	0.58	0.06	1.41	0.32	0.07	0.41	1.16	2.49
8	0.81	1.54	2.27	2.86	1.37	2.40	1.58	3.27	1.59	1.31
MEAN	1.00	1.28	1.34	0.85	1.19	1.00	0.86	1.16	1.22	1.73
SD	0.47	0.42	0.61	0.80	0.29	0.58	0.46	0.84	0.20	0.45

Mighty

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.0052	0.0057	0.0124	0.0122	0.0096	0.0053	0.0020	0.0053	0.0045	0.0091
2	0.0074	0.0100	0.0124	0.0075	0.0111	0.0054	0.0044	0.0085	0.0089	0.0122
3	0.0050	0.0077	0.0074	0.0089	0.0080	0.0076	0.0063	0.0061	0.0076	0.0103
4	0.0032	0.0045	0.0063	0.0056	0.0112	0.0050	0.0033	0.0046	0.0047	0.0054
5	0.0032	0.0035	0.0114	0.0048	0.0046	0.0061	0.0050	0.0066	0.0099	0.0055
6	0.0045	0.0039	0.0047	0.0069	0.0055	0.0036	0.0042	0.0056	0.0223	0.0053
7	0.0050	0.0049	0.0091	0.0078	0.0078	0.0037	0.0022	0.0052	0.0051	0.0079
8	0.0034	0.0013	0.0054	0.0057	0.0381	0.0062	0.0032	0.0059	0.0055	0.0068
Geomean	**0.004**					**0.005**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.18	1.28	2.80	2.76	2.17	1.01	0.38	1.03	0.86	1.74
2	1.66	2.26	2.78	1.69	2.51	1.04	0.84	1.63	1.72	2.34
3	1.12	1.74	1.66	2.00	1.80	1.46	1.21	1.16	1.46	1.97
4	0.71	1.02	1.41	1.26	2.53	0.95	0.64	0.88	0.89	1.03
5	0.73	0.78	2.58	1.08	1.04	1.18	0.96	1.28	1.90	1.06
6	1.02	0.88	1.07	1.55	1.24	0.69	0.81	1.08	4.29	1.02
7	1.13	1.10	2.06	1.76	1.76	0.70	0.41	1.01	0.99	1.51
8	0.76	0.29	1.23	1.29	8.59	1.20	0.61	1.14	1.06	1.31
MEAN	1.00	1.02	1.83	1.61	2.17	1.00	0.69	1.13	1.42	1.43
SD	0.32	0.60	0.71	0.53	2.44	0.26	0.28	0.23	1.14	0.49

Western Blots

p-Akt^{Ser437}

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.57	0.92	0.21	0.96	0.22	0.12	0.33	0.14	0.13	0.68
2	0.17	0.19	0.21	0.87	1.31	0.33	0.80	0.38	0.71	0.56
3	0.60	0.37	0.64	1.05	0.77	0.33	0.44	0.39	0.43	0.81
4	0.24	0.32	0.17	0.34	0.35	0.14	0.73	0.17	0.55	0.63
5	0.11	0.13	0.08	0.69	0.58	0.14	0.22	0.44	0.33	0.26
6	0.17	0.70	0.19	1.27	1.15	0.68	0.91	1.35	1.57	0.90
7	0.93	1.04	0.70	0.70	0.62	0.50	0.73	0.54	1.41	0.59
8	0.77	0.84	0.55	0.82	0.93	0.76	1.03	0.85	1.09	1.37
9	1.26	0.78	0.70	0.81	1.94	0.89	0.52	0.52	1.19	1.74
Geomean	**0.40**					**0.34**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.448	2.327	0.543	2.436	0.560	0.342	0.978	0.415	0.375	2.016
2	0.420	0.469	0.536	2.211	3.305	0.982	2.361	1.126	2.095	1.661
3	1.508	0.926	1.608	2.651	1.936	0.976	1.301	1.147	1.255	2.402
4	0.597	0.810	0.419	0.855	0.877	0.418	2.158	0.488	1.611	1.868
5	0.286	0.321	0.202	1.739	1.466	0.418	0.639	1.310	0.965	0.767
6	0.435	1.759	0.473	3.220	2.896	2.004	2.678	3.969	4.632	2.667
7	2.363	2.630	1.780	1.779	1.565	1.474	2.147	1.577	4.158	1.751
8	1.941	2.134	1.392	2.083	2.343	2.253	3.050	2.518	3.198	4.025
9	3.194	1.964	1.758	2.053	4.906	2.624	1.543	1.534	3.512	5.127
MEAN	1.00	1.20	0.76	2.00	1.84	1.00	1.69	1.26	1.91	2.18
SD	1.01	0.86	0.65	0.66	1.35	0.86	0.81	1.10	1.51	1.33

p-Akt^{Ser437}

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.22	0.84	0.21	0.26	0.79	0.20	0.66	0.39	0.58	0.38
2	1.32	1.22	0.50	0.57	2.01	1.34	1.53	1.01	0.81	0.59
3	1.76	1.70	0.17	1.13	0.28	0.20	0.26	0.25	0.30	0.58
4	0.09	0.18	0.09	0.20	0.16	0.18	0.15	0.08	0.20	0.03
5	2.00	2.29	0.81	1.43	3.11	1.37	2.52	1.59	5.65	2.05
6	0.88	1.22	0.52	2.22	2.78	0.78	1.78	0.84	1.78	1.90
7	1.85	1.62	0.88	1.04	1.18	0.79	0.99	1.03	0.80	0.93
8	2.33	0.64	0.37	1.26	0.64	1.49	0.62	0.43	1.36	0.51
Geomean	**0.88**					**0.57**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.251	0.954	0.239	0.296	0.896	0.340	1.144	0.674	1.011	0.654
2	1.496	1.384	0.570	0.650	2.289	2.338	2.666	1.760	1.408	1.034
3	1.999	1.929	0.192	1.289	0.322	0.349	0.445	0.441	0.530	1.008
4	0.105	0.203	0.107	0.228	0.184	0.313	0.264	0.136	0.351	0.056
5	2.277	2.598	0.923	1.630	3.529	2.381	4.394	2.763	9.839	3.561
6	1.002	1.388	0.588	2.520	3.161	1.356	3.103	1.459	3.103	3.300
7	2.098	1.844	1.005	1.187	1.342	1.375	1.722	1.796	1.392	1.620
8	2.651	0.726	0.417	1.428	0.731	2.590	1.083	0.748	2.372	0.884
MEAN	1.00	1.12	0.40	0.89	1.04	1.00	1.32	0.89	1.51	0.95
SD	0.95	0.76	0.33	0.76	1.29	0.98	1.43	0.88	3.10	1.26

p-Akt^{Ser437}

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.24	0.49	0.58	0.28	0.58	0.45	0.39	0.33	0.33	0.71
2	0.30	0.35	0.24	0.43	0.47	0.46	0.46	0.30	0.32	0.99
3	0.72	0.28	0.11	0.33	0.27	0.10	0.10	0.12	0.28	0.30
4	0.13	0.05	0.06	0.21	0.23	0.05	0.14	0.17	0.08	0.11
5	0.29	0.76	0.14	0.33	0.35	0.22	0.14	0.65	0.70	1.07
6	1.42	2.51	0.49	0.96	3.02	1.03	1.35	0.77	0.82	1.77
7	2.15	0.75	0.48	0.73	1.66	0.29	0.06	0.47	0.99	0.40
8	1.07	1.30	0.54	0.63	1.06	0.19	0.71	0.27	0.06	0.78
Geomean	**0.65**					**0.25**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.896	0.744	0.883	0.434	0.894	1.814	1.574	1.352	1.327	2.882
2	0.464	0.536	0.363	0.659	0.715	1.853	1.877	1.217	1.307	3.997
3	1.101	0.429	0.163	0.510	0.414	0.421	0.420	0.495	1.151	1.208
4	0.202	0.070	0.089	0.321	0.346	0.201	0.586	0.698	0.344	0.441
5	0.436	1.162	0.219	0.503	0.531	0.909	0.587	2.647	2.820	4.328
6	2.176	3.831	0.753	1.469	4.620	4.195	5.465	3.124	3.326	7.160
7	3.285	1.141	0.737	1.115	2.536	1.186	0.252	1.891	4.003	1.613
8	1.636	1.986	0.827	0.964	1.628	0.777	2.876	1.106	0.235	3.157
MEAN	1.00	0.77	0.38	0.66	0.99	1.00	1.07	1.33	1.25	2.36
SD	1.05	1.20	0.33	0.40	1.48	1.27	1.77	0.92	1.40	2.13

p-mTOR^{Ser2448}

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.94	1.11	1.38	1.72	0.84	1.06	1.09	2.22	0.80	0.24
2	2.51	1.78	2.67	1.25	0.22	0.79	0.36	1.71	1.17	1.93
3	0.27	0.94	1.26	0.21	0.38	0.35	0.31	0.59	0.47	0.13
4	1.47	0.85	1.40	0.89	2.51	0.59	1.14	0.79	0.62	0.61
5	1.25	1.15	1.70	1.81	2.09	1.87	1.02	1.40	1.09	0.99
6	1.71	1.67	1.46	1.38	0.19	2.33	0.50	2.29	1.50	0.15
7	0.95	0.74	1.48	2.23	4.13	3.50	1.85	2.19	1.72	1.19
8	1.29	0.60	1.67	0.72	0.05	0.53	0.56	1.09	0.72	0.15
9	0.31	0.43	0.13	0.49	0.06	0.43	0.30	0.16	0.97	0.02
Geomean	**0.97**					**0.94**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.975	1.147	1.425	1.776	0.872	1.128	1.159	2.355	0.844	0.259
2	2.595	1.836	2.760	1.291	0.228	0.833	0.386	1.813	1.241	2.040
3	0.274	0.968	1.305	0.216	0.392	0.367	0.329	0.624	0.494	0.141
4	1.513	0.878	1.442	0.920	2.594	0.630	1.203	0.833	0.661	0.642
5	1.296	1.186	1.755	1.872	2.156	1.983	1.084	1.479	1.159	1.046
6	1.763	1.722	1.507	1.427	0.200	2.470	0.530	2.421	1.589	0.162
7	0.986	0.763	1.533	2.303	4.265	3.712	1.962	2.322	1.819	1.262
8	1.333	0.618	1.727	0.747	0.048	0.557	0.588	1.154	0.767	0.157
9	0.318	0.445	0.135	0.510	0.065	0.454	0.322	0.166	1.032	0.017
MEAN	1.00	0.97	1.24	1.01	0.47	1.00	0.69	1.15	0.99	0.31
SD	0.72	0.47	0.67	0.69	1.48	1.14	0.55	0.83	0.43	0.69

p-mTOR^{Ser2448}

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.82	1.76	3.64	3.25	1.28	1.29	0.37	2.65	0.45	0.96
2	1.06	1.81	1.81	1.05	1.03	1.87	2.93	1.54	0.98	1.77
3	3.40	1.68	3.38	1.45	7.87	2.89	2.09	2.61	1.44	3.51
4	1.38	1.46	1.26	1.02	1.43	1.20	0.66	0.86	0.72	0.87
5	1.38	0.71	2.04	1.35	0.17	0.79	0.93	0.59	0.91	0.53
6	1.38	0.51	0.71	0.23	0.08	0.76	0.95	1.14	1.59	0.84
7	2.52	1.09	2.86	0.98	2.00	3.07	1.15	2.88	2.45	2.73
8	2.92	0.66	3.71	1.74	2.35	1.41	0.52	2.15	1.44	2.15
Geomean	**1.83**					**1.47**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.992	0.962	1.983	1.774	0.696	0.878	0.251	1.804	0.305	0.653
2	0.580	0.986	0.986	0.575	0.563	1.269	1.994	1.050	0.663	1.203
3	1.857	0.915	1.842	0.792	4.295	1.963	1.421	1.777	0.981	2.385
4	0.754	0.797	0.687	0.557	0.779	0.818	0.448	0.583	0.488	0.592
5	0.752	0.389	1.114	0.735	0.091	0.539	0.630	0.401	0.618	0.358
6	0.753	0.279	0.387	0.125	0.043	0.519	0.645	0.774	1.082	0.569
7	1.375	0.594	1.561	0.533	1.093	2.085	0.785	1.956	1.662	1.853
8	1.596	0.360	2.024	0.951	1.283	0.958	0.355	1.458	0.982	1.463
MEAN	1.00	0.60	1.16	0.62	0.54	1.00	0.66	1.07	0.75	0.94
SD	0.47	0.29	0.62	0.48	1.36	0.60	0.60	0.60	0.43	0.72

p-mTOR^{Ser2448}

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.24	0.87	4.31	5.47	1.06	1.91	1.94	2.07	2.79	0.68
2	2.52	1.55	0.99	2.48	3.69	1.22	0.66	1.26	0.98	0.07
3	1.28	0.53	1.28	1.94	0.44	0.56	0.34	0.37	0.62	0.32
4	3.30	0.66	5.11	3.65	0.36	0.93	0.67	1.90	1.34	1.64
5	0.66	0.82	0.49	0.77	0.35	0.39	0.21	0.64	0.92	0.15
6	0.99	1.02	1.44	1.51	0.67	0.88	0.71	1.30	1.22	1.20
7	2.52	1.02	1.11	2.35	0.24	1.28	0.72	1.58	2.83	2.02
8	1.11	1.12	3.04	2.03	0.82	1.33	1.93	1.83	2.42	1.22
Geomean	**1.49**					**0.96**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.830	0.581	2.896	3.669	0.710	1.993	2.017	2.161	2.910	0.704
2	1.691	1.041	0.665	1.663	2.475	1.276	0.688	1.313	1.018	0.075
3	0.862	0.354	0.861	1.300	0.297	0.580	0.356	0.381	0.642	0.338
4	2.216	0.444	3.430	2.452	0.242	0.973	0.698	1.980	1.400	1.705
5	0.446	0.548	0.326	0.519	0.233	0.411	0.219	0.668	0.958	0.156
6	0.665	0.684	0.969	1.015	0.447	0.916	0.743	1.358	1.275	1.255
7	1.694	0.688	0.748	1.574	0.163	1.330	0.754	1.648	2.953	2.108
8	0.742	0.749	2.038	1.364	0.552	1.391	2.015	1.905	2.524	1.267
MEAN	1.00	0.61	1.13	1.47	0.43	1.00	0.73	1.25	1.49	0.60
SD	0.63	0.21	1.15	0.97	0.76	0.50	0.69	0.63	0.93	0.75

p-4E-BP1$^{Thr37/46}$

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.91	0.44	0.46	0.51	0.46	0.92	0.54	1.00	0.72	1.12
2	2.42	0.22	1.01	0.80	0.76	1.08	0.36	1.12	0.51	1.37
3	2.16	0.59	2.18	0.29	1.15	0.91	0.37	0.68	0.42	1.07
4	1.39	0.43	1.30	0.27	1.12	1.13	0.32	1.29	0.52	1.47
5	1.06	0.24	1.36	0.47	1.15	1.47	0.50	1.57	0.95	1.83
6	0.22	0.14	0.14	0.05	0.72	0.60	0.16	0.54	0.40	1.00
7	0.82	0.39	0.56	0.43	0.92	0.59	0.31	0.59	0.48	0.82
8	0.79	0.15	0.76	0.28	0.69	0.66	0.23	0.71	0.43	0.75
9	1.33	0.84	0.77	0.85	2.08	0.96	0.58	0.57	1.27	1.89
Geomean	**1.03**					**0.89**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.879	0.428	0.443	0.495	0.445	1.033	0.609	1.122	0.814	1.260
2	2.341	0.209	0.976	0.780	0.738	1.222	0.405	1.262	0.578	1.541
3	2.095	0.574	2.111	0.284	1.112	1.026	0.419	0.766	0.472	1.208
4	1.347	0.421	1.261	0.259	1.084	1.277	0.363	1.458	0.589	1.660
5	1.028	0.233	1.319	0.454	1.117	1.657	0.568	1.770	1.068	2.061
6	0.213	0.135	0.133	0.049	0.695	0.676	0.178	0.609	0.447	1.132
7	0.794	0.375	0.540	0.416	0.890	0.666	0.348	0.668	0.546	0.926
8	0.769	0.147	0.741	0.267	0.672	0.746	0.254	0.799	0.483	0.842
9	1.287	0.814	0.748	0.824	2.012	1.087	0.656	0.640	1.433	2.126
MEAN	1.00	0.31	0.73	0.34	0.90	1.00	0.39	0.94	0.66	1.35
SD	0.67	0.22	0.59	0.25	0.45	0.32	0.16	0.41	0.33	0.46

p-4E-BP1$^{Thr37/46}$

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	2.19	0.43	1.01	0.18	1.47	1.12	0.62	0.75	0.41	0.96
2	2.41	0.83	2.02	0.31	1.31	1.17	0.58	0.89	0.41	1.39
3	1.40	1.10	1.04	0.39	1.36	1.26	1.46	1.44	0.76	1.35
4	2.23	0.95	1.88	0.33	1.63	1.20	0.79	1.76	0.54	1.29
5	3.21	1.12	3.25	0.95	2.49	1.93	0.87	2.12	0.40	2.00
6	0.98	0.21	0.51	0.22	0.39	0.46	0.20	0.49	0.21	0.55
7	1.01	0.41	1.07	0.58	1.04	1.21	0.67	1.33	0.46	1.30
8	2.47	0.66	0.41	1.26	0.66	1.58	0.66	0.43	1.39	0.53
Geomean	**1.84**					**1.16**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.192	0.234	0.549	0.096	0.800	0.960	0.530	0.645	0.350	0.822
2	1.313	0.454	1.099	0.171	0.713	1.006	0.498	0.761	0.348	1.191
3	0.763	0.601	0.565	0.211	0.739	1.082	1.255	1.236	0.650	1.158
4	1.214	0.517	1.023	0.179	0.888	1.028	0.678	1.509	0.462	1.110
5	1.750	0.607	1.773	0.517	1.356	1.657	0.747	1.822	0.342	1.713
6	0.534	0.115	0.275	0.121	0.210	0.399	0.171	0.417	0.184	0.473
7	0.549	0.226	0.582	0.314	0.568	1.039	0.577	1.138	0.394	1.114
8	1.346	0.358	0.224	0.687	0.359	1.353	0.565	0.371	1.189	0.451
MEAN	1.00	0.34	0.62	0.23	0.62	1.00	0.56	0.86	0.43	0.92
SD	0.43	0.19	0.51	0.21	0.35	0.36	0.31	0.52	0.31	0.41

p-4E-BP1$^{Thr37/46}$

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.98	1.07	1.04	0.84	1.11	0.91	0.62	0.80	0.77	0.67
2	1.62	0.47	0.85	1.38	1.78	1.69	1.06	1.33	1.72	1.20
3	2.42	0.60	1.27	1.19	1.31	1.60	0.52	1.18	1.07	0.89
4	1.60	0.56	0.84	0.83	0.86	0.89	0.46	0.72	1.05	0.94
5	0.87	0.50	0.62	0.44	0.46	0.49	0.34	0.37	0.35	0.48
6	1.64	0.88	1.72	1.81	1.27	1.59	1.84	2.46	1.48	1.87
7	1.78	0.43	1.09	1.09	0.85	0.77	0.42	0.13	0.45	1.04
8	0.92	0.71	1.33	1.29	0.83	0.80	0.09	1.01	0.89	1.24
Geomean	**1.52**					**1.01**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.301	0.701	0.684	0.553	0.729	0.901	0.613	0.797	0.768	0.666
2	1.062	0.308	0.561	0.903	1.168	1.677	1.049	1.321	1.707	1.192
3	1.591	0.394	0.834	0.784	0.863	1.582	0.513	1.170	1.060	0.883
4	1.053	0.368	0.554	0.542	0.566	0.887	0.453	0.716	1.041	0.930
5	0.569	0.327	0.405	0.289	0.305	0.488	0.341	0.366	0.345	0.476
6	1.076	0.579	1.128	1.191	0.832	1.575	1.827	2.444	1.471	1.852
7	1.167	0.280	0.713	0.718	0.561	0.769	0.418	0.131	0.443	1.030
8	0.604	0.469	0.876	0.848	0.547	0.798	0.094	1.005	0.879	1.235
MEAN	1.00	0.41	0.69	0.68	0.65	1.00	0.50	0.75	0.86	0.96
SD	0.34	0.15	0.23	0.27	0.26	0.46	0.54	0.71	0.47	0.42

p-rpS6$^{Ser235/236}$

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.78	5.91	1.73	19.03	1.19	0.17	0.10	1.05	0.06	0.19
2	0.57	0.49	6.73	3.09	2.78	0.05	0.06	0.48	0.11	2.87
3	0.32	0.36	0.96	0.54	9.26	0.11	0.57	0.66	0.46	2.25
4	0.66	0.74	0.50	0.50	3.08	0.37	0.67	0.35	0.64	0.96
5	4.83	0.95	2.02	1.59	11.42	0.97	2.37	0.97	2.07	1.38
6	0.88	0.89	5.29	2.44	2.32	0.64	0.38	0.81	0.46	1.73
7	0.67	1.18	0.96	0.62	0.34	0.34	0.46	0.36	1.23	0.07
8	1.15	1.85	0.91	2.05	1.88	2.05	3.26	2.10	2.11	2.00
9	1.93	0.92	0.64	0.61	1.64	0.74	0.06	0.08	0.88	1.40
Geomean	**0.94**					**0.36**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.822	6.260	1.832	20.169	1.266	0.474	0.288	2.920	0.160	0.536
2	0.604	0.518	7.130	3.272	2.948	0.126	0.176	1.320	0.318	7.976
3	0.339	0.379	1.019	0.575	9.811	0.303	1.570	1.842	1.284	6.255
4	0.701	0.782	0.527	0.532	3.260	1.033	1.863	0.968	1.776	2.668
5	5.125	1.009	2.137	1.688	12.105	2.686	6.586	2.689	5.762	3.820
6	0.928	0.945	5.605	2.592	2.463	1.778	1.046	2.248	1.266	4.817
7	0.714	1.246	1.015	0.656	0.364	0.949	1.289	0.990	3.415	0.190
8	1.222	1.964	0.964	2.169	1.994	5.705	9.063	5.828	5.846	5.562
9	2.044	0.973	0.680	0.649	1.736	2.068	0.180	0.215	2.457	3.897
MEAN	1.00	1.09	1.56	1.63	2.55	1.00	1.09	1.55	1.51	2.60
SD	1.48	1.82	2.38	6.30	4.08	1.74	3.17	1.65	2.13	2.56

p-rpS6$^{Ser235/236}$

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.77	0.35	12.28	3.02	1.11	0.62	0.04	4.48	0.05	0.07
2	0.63	0.79	4.86	3.34	0.97	0.48	0.59	2.56	0.84	0.92
3	1.31	0.59	2.26	1.24	1.36	0.58	0.74	1.43	1.16	1.17
4	0.21	0.14	0.65	0.30	0.44	0.16	0.08	0.14	0.23	0.30
5	3.80	0.99	0.32	0.57	2.12	0.20	0.31	0.41	0.92	0.46
6	0.76	1.65	0.51	2.91	3.37	0.49	1.35	0.64	2.15	2.49
7	2.32	2.59	1.10	1.53	1.77	0.77	0.97	0.96	0.84	0.98
8	1.02	0.05	0.12	0.47	0.21	0.23	0.25	0.05	1.39	0.38
Geomean	**0.99**					**0.39**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.782	0.355	12.448	3.064	1.126	1.593	0.098	11.603	0.121	0.172
2	0.636	0.797	4.924	3.383	0.987	1.251	1.522	6.638	2.166	2.389
3	1.330	0.593	2.289	1.262	1.376	1.511	1.922	3.707	2.994	3.022
4	0.210	0.138	0.660	0.307	0.449	0.425	0.202	0.356	0.603	0.782
5	3.856	1.000	0.324	0.579	2.146	0.520	0.814	1.064	2.373	1.178
6	0.767	1.672	0.518	2.948	3.412	1.268	3.507	1.658	5.563	6.446
7	2.354	2.622	1.112	1.549	1.797	1.990	2.498	2.488	2.177	2.534
8	1.032	0.049	0.126	0.479	0.212	0.595	0.651	0.142	3.585	0.988
MEAN	1.00	0.52	1.10	1.23	1.08	1.00	0.85	1.68	1.62	1.44
SD	1.19	0.87	4.20	1.26	1.02	0.57	1.19	3.91	1.70	1.98

p-rpS6$^{Ser235/236}$

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.70	0.38	6.79	10.55	0.88	0.09	0.34	1.18	2.91	1.06
2	3.71	0.77	0.70	1.63	1.37	0.90	0.53	1.68	0.81	0.94
3	2.96	0.39	4.41	4.46	0.75	0.39	0.23	1.45	0.57	0.55
4	1.21	0.70	1.40	1.61	1.68	0.36	0.41	0.43	0.56	0.51
5	0.56	0.76	6.03	5.53	0.97	1.82	1.84	1.18	1.04	3.03
6	1.04	2.27	0.79	1.70	1.89	1.23	3.18	1.20	1.39	1.39
7	5.22	1.24	0.42	0.77	2.46	0.25	0.31	0.42	0.87	0.29
8	1.19	1.21	0.34	0.34	0.83	0.28	0.73	0.27	0.28	0.57
Geomean	**1.55**					**0.45**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.454	0.244	4.376	6.800	0.565	0.189	0.744	2.602	6.446	2.350
2	2.392	0.495	0.452	1.050	0.881	1.983	1.172	3.712	1.794	2.078
3	1.910	0.249	2.845	2.875	0.485	0.862	0.500	3.203	1.266	1.208
4	0.782	0.449	0.904	1.037	1.083	0.804	0.905	0.948	1.230	1.137
5	0.358	0.489	3.886	3.566	0.626	4.021	4.068	2.604	2.303	6.704
6	0.670	1.462	0.509	1.097	1.219	2.728	7.044	2.662	3.085	3.087
7	3.367	0.801	0.273	0.495	1.582	0.562	0.691	0.928	1.930	0.653
8	0.764	0.781	0.218	0.221	0.535	0.624	1.623	0.597	0.611	1.265
MEAN	1.00	0.53	0.94	1.32	0.80	1.00	1.37	1.81	1.87	1.81
SD	1.09	0.40	1.74	2.21	0.39	1.33	2.31	1.17	1.82	1.94

p-eEF2^{Thr56}

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	3.92	3.46	1.17	3.81	0.84	1.29	1.73	1.76	1.37	0.51
2	2.04	2.04	1.17	5.84	1.13	0.37	1.21	1.13	0.17	0.21
3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
4	2.38	1.78	1.13	1.39	1.39	0.32	0.91	0.34	0.69	0.87
5	2.83	2.98	2.29	2.26	2.40	1.08	1.64	1.12	1.59	2.04
6	1.32	2.15	1.01	1.24	0.01	1.34	1.04	0.47	0.48	0.38
7	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
8	0.62	0.83	0.44	0.51	0.05	0.02	0.37	0.33	0.22	0.02
9	0.32	0.64	0.09	0.51	0.11	0.22	0.45	0.14	0.90	0.03
Geomean	**1.46**					**0.37**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	2.688	2.371	0.803	2.609	0.579	3.462	4.656	4.729	3.698	1.370
2	1.402	1.402	0.804	4.004	0.772	1.007	3.247	3.049	0.462	0.572
3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
4	1.631	1.218	0.772	0.950	0.951	0.873	2.446	0.929	1.864	2.346
5	1.938	2.046	1.570	1.550	1.646	2.913	4.428	3.021	4.296	5.491
6	0.903	1.477	0.692	0.853	0.009	3.606	2.799	1.261	1.289	1.021
7	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
8	0.423	0.571	0.299	0.346	0.037	0.054	1.007	0.895	0.598	0.061
9	0.220	0.438	0.062	0.347	0.075	0.583	1.223	0.387	2.436	0.076
MEAN	1.00	1.17	0.52	1.07	0.21	1.00	2.47	1.51	1.59	0.65
SD	0.87	0.71	0.47	1.35	0.60	1.49	1.42	1.59	1.48	1.91

p-eEF2^{Thr56}

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.32	1.03	0.74	1.48	0.29	0.68	0.44	0.73	0.72	0.71
2	2.40	2.00	2.00	4.00	0.39	0.83	1.00	0.79	1.00	0.84
3	2.35	2.40	1.43	0.78	0.81	1.06	0.71	1.17	1.12	0.86
4	2.06	2.63	1.98	3.57	3.24	3.81	2.61	2.15	2.53	2.91
5	1.51	1.87	1.45	4.25	0.03	2.86	1.58	2.35	2.04	1.49
6	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
7	1.07	2.12	1.16	1.20	0.66	1.21	2.41	1.05	3.58	1.03
8	3.82	2.29	1.20	1.05	1.27	0.99	1.22	1.58	2.19	1.39
Geomean	**1.91**					**1.34**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.691	0.536	0.389	0.771	0.150	0.507	0.331	0.547	0.537	0.525
2	1.254	1.045	1.045	2.090	0.204	0.620	0.745	0.592	0.745	0.627
3	1.225	1.256	0.748	0.410	0.424	0.791	0.527	0.870	0.832	0.639
4	1.074	1.373	1.035	1.863	1.693	2.842	1.942	1.599	1.887	2.165
5	0.787	0.978	0.760	2.222	0.015	2.134	1.180	1.750	1.516	1.114
6	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
7	0.559	1.109	0.607	0.628	0.343	0.901	1.794	0.783	2.664	0.766
8	1.994	1.199	0.628	0.550	0.661	0.736	0.906	1.181	1.635	1.039
MEAN	1.00	1.03	0.71	0.99	0.26	1.00	0.90	0.96	1.23	0.88
SD	0.48	0.27	0.24	0.80	0.57	0.90	0.62	0.48	0.75	0.57

p-eEF2^{Thr56}

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	2.04	1.70	1.08	1.17	0.34	0.88	1.64	0.81	0.70	0.27
2	1.00	2.40	0.07	1.00	0.86	2.00	2.00	1.00	0.96	0.05
3	3.05	1.94	1.05	1.88	0.52	0.68	0.60	1.75	0.78	0.35
4	2.50	1.82	1.04	1.74	0.74	0.93	1.77	1.50	0.76	1.44
5	0.55	0.62	0.55	0.53	0.37	0.38	0.56	0.41	0.49	0.36
6	0.76	1.08	0.86	0.63	0.37	0.47	0.69	0.49	1.02	0.87
7	3.75	3.00	1.00	2.00	0.41	1.00	3.00	2.00	1.25	2.00
8	1.84	1.76	1.43	0.40	0.77	0.95	1.65	1.36	1.92	0.51
Geomean	**1.61**					**0.81**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.270	1.058	0.671	0.728	0.212	1.091	2.024	1.002	0.860	0.338
2	0.621	1.491	0.044	0.621	0.534	2.467	2.467	1.233	1.189	0.066
3	1.892	1.205	0.650	1.171	0.325	0.837	0.734	2.161	0.961	0.435
4	1.551	1.128	0.647	1.078	0.461	1.144	2.186	1.856	0.933	1.772
5	0.342	0.386	0.341	0.329	0.227	0.465	0.696	0.510	0.610	0.447
6	0.475	0.672	0.533	0.392	0.227	0.580	0.847	0.602	1.252	1.073
7	2.330	1.864	0.621	1.242	0.258	1.233	3.700	2.467	1.542	2.467
8	1.142	1.093	0.890	0.246	0.476	1.166	2.040	1.676	2.366	0.629
MEAN	1.00	1.02	0.43	0.62	0.32	1.00	1.56	1.26	1.12	0.58
SD	0.71	0.45	0.25	0.40	0.13	0.61	1.04	0.72	0.54	0.82

p-AMPKa^{Thr172}

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.92	1.40	0.36	1.27	0.29	0.21	0.50	0.28	0.38	1.13
2	0.40	0.57	0.70	2.12	2.62	0.49	1.26	0.60	1.09	0.63
3	0.69	0.60	1.12	1.73	1.09	0.48	0.58	0.61	1.29	1.38
4	0.81	0.98	0.53	1.11	0.46	0.48	2.31	0.39	1.18	1.34
5	0.50	0.73	0.28	2.01	1.85	0.65	0.80	1.10	1.31	1.06
6	0.35	0.66	0.50	1.08	0.75	0.60	0.70	0.91	1.06	0.72
7	1.02	1.80	1.96	2.84	1.50	1.56	1.92	1.20	3.20	0.78
8	1.07	1.53	0.80	1.41	1.24	0.72	1.35	1.38	1.71	2.27
9	0.69	0.48	0.53	0.53	1.80	0.66	0.37	1.09	0.59	2.17
Geomean	**0.67**					**0.58**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.374	2.092	0.536	1.895	0.430	0.369	0.864	0.482	0.661	1.958
2	0.592	0.849	1.041	3.172	3.917	0.844	2.191	1.037	1.886	1.096
3	1.027	0.895	1.671	2.587	1.637	0.834	1.000	1.065	2.233	2.402
4	1.211	1.470	0.799	1.669	0.692	0.832	4.007	0.672	2.052	2.335
5	0.741	1.089	0.418	3.014	2.776	1.132	1.382	1.913	2.280	1.833
6	0.530	0.993	0.742	1.611	1.116	1.050	1.221	1.576	1.839	1.258
7	1.521	2.700	2.929	4.247	2.246	2.703	3.335	2.090	5.564	1.350
8	1.597	2.286	1.192	2.110	1.857	1.251	2.349	2.403	2.977	3.948
9	1.037	0.717	0.788	0.790	2.700	1.151	0.644	1.901	1.021	3.774
MEAN	1.00	1.31	0.95	2.13	1.59	1.00	1.59	1.30	1.95	2.02
SD	0.39	0.73	0.77	1.03	1.11	0.65	1.17	0.67	1.41	1.04

p-AMPKa^{Thr172}

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.31	1.26	0.23	0.35	0.99	0.18	0.50	0.62	0.45	0.56
2	1.52	1.50	0.60	0.75	2.07	1.34	1.25	0.87	0.83	0.76
3	1.50	2.14	0.29	2.36	1.01	0.40	0.95	0.89	1.35	1.52
4	0.36	1.26	0.35	1.09	0.97	1.54	1.00	0.39	1.08	1.45
5	5.07	4.65	0.87	2.23	3.46	0.87	1.51	0.91	3.88	1.34
6	0.94	1.19	0.41	2.12	3.25	0.86	2.03	0.89	2.20	2.64
7	0.53	0.65	0.52	0.94	1.41	0.95	1.24	1.21	1.31	1.38
8	2.22	0.68	0.60	1.23	0.75	0.85	0.74	0.44	1.58	0.57
Geomean	**1.05**					**0.74**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.296	1.206	0.223	0.339	0.943	0.239	0.674	0.844	0.606	0.762
2	1.449	1.438	0.577	0.716	1.983	1.814	1.693	1.179	1.122	1.029
3	1.432	2.044	0.282	2.255	0.970	0.540	1.283	1.211	1.833	2.066
4	0.346	1.201	0.331	1.044	0.923	2.092	1.353	0.530	1.461	1.963
5	4.846	4.447	0.832	2.132	3.309	1.180	2.051	1.230	5.266	1.822
6	0.900	1.140	0.395	2.027	3.106	1.160	2.747	1.201	2.984	3.573
7	0.508	0.620	0.498	0.900	1.352	1.295	1.684	1.634	1.772	1.865
8	2.125	0.653	0.572	1.175	0.713	1.153	0.998	0.593	2.141	0.769
MEAN	1.00	1.31	0.43	1.13	1.42	1.00	1.44	0.99	1.80	1.53
SD	1.50	1.24	0.20	0.72	1.03	0.60	0.64	0.37	1.44	0.92

p-AMPKa^{Thr172}

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.44	0.58	0.81	0.42	1.72	0.96	1.08	1.02	1.06	2.60
2	0.31	0.32	0.16	0.48	0.52	0.58	0.59	0.45	0.52	1.59
3	1.78	1.05	0.33	1.02	0.91	0.38	0.58	0.66	1.16	1.07
4	1.78	0.62	0.66	1.85	1.80	0.46	1.19	0.92	0.38	0.86
5	0.85	1.13	0.46	1.01	1.22	0.78	0.57	0.86	0.90	1.16
6	1.06	4.10	0.49	1.30	5.66	1.13	1.52	0.61	0.48	1.18
7	2.41	0.60	0.31	0.64	2.22	0.26	0.26	0.51	1.34	0.38
8	1.36	1.04	0.58	0.86	1.42	0.28	1.07	0.31	0.16	0.56
Geomean	**1.20**					**0.53**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.202	0.481	0.678	0.351	1.432	1.810	2.028	1.924	1.997	4.902
2	0.262	0.270	0.137	0.404	0.431	1.085	1.117	0.848	0.986	2.997
3	1.488	0.880	0.278	0.847	0.759	0.724	1.101	1.237	2.192	2.020
4	1.487	0.516	0.547	1.543	1.499	0.865	2.246	1.732	0.725	1.615
5	0.706	0.940	0.382	0.841	1.014	1.474	1.076	1.618	1.689	2.189
6	0.888	3.418	0.412	1.087	4.721	2.125	2.857	1.141	0.902	2.219
7	2.014	0.503	0.260	0.536	1.851	0.490	0.482	0.963	2.535	0.714
8	1.134	0.868	0.488	0.721	1.183	0.529	2.016	0.590	0.306	1.058
MEAN	1.00	0.73	0.36	0.71	1.28	1.00	1.42	1.18	1.18	1.91
SD	0.54	1.01	0.17	0.39	1.33	0.61	0.79	0.46	0.80	1.30

p-p53^{Ser15}

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.49	1.08	0.56	1.69	0.38	0.28	0.46	0.34	0.33	1.05
2	0.21	0.30	0.40	1.58	2.25	0.24	1.14	0.41	1.02	0.67
3	0.33	0.32	0.92	3.35	1.19	1.92	1.10	1.18	0.93	2.41
4	0.64	0.65	0.26	0.39	0.39	0.19	0.97	0.13	0.65	0.82
5	0.06	0.11	0.08	0.46	0.45	0.19	0.28	0.33	0.32	0.36
6	0.13	0.30	0.17	1.05	0.49	0.47	0.61	0.81	0.65	0.27
7	1.08	1.40	1.15	0.87	0.66	0.55	1.00	0.69	2.15	0.74
8	1.63	1.85	1.04	1.82	1.73	1.54	2.65	1.87	1.57	2.22
9	1.46	0.89	0.78	0.74	2.05	0.87	0.49	0.55	1.21	2.26
Geomean	**0.48**					**0.49**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	3.093	2.255	1.168	3.530	0.798	0.570	0.930	0.695	0.667	2.140
2	0.443	0.616	0.825	3.300	4.679	0.497	2.325	0.826	2.086	1.358
3	0.679	0.676	1.911	6.987	2.470	3.905	2.232	2.407	1.900	4.906
4	1.331	1.349	0.543	0.821	0.820	0.395	1.983	0.272	1.332	1.666
5	0.128	0.238	0.158	0.963	0.945	0.392	0.564	0.672	0.644	0.739
6	0.273	0.627	0.355	2.189	1.017	0.949	1.246	1.653	1.321	0.553
7	2.244	2.917	2.400	1.821	1.369	1.111	2.031	1.402	4.367	1.505
8	3.386	3.852	2.172	3.786	3.601	3.133	5.396	3.799	3.193	4.516
9	3.040	1.857	1.626	1.540	4.265	1.767	0.991	1.125	2.458	4.601
MEAN	1.00	1.16	0.92	2.25	1.75	1.00	1.61	1.11	1.67	1.89
SD	1.33	1.22	0.82	1.92	1.58	1.29	1.44	1.09	1.21	1.74

p-p53^{Ser15}

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.18	0.67	0.23	0.31	0.62	0.21	0.47	0.69	0.48	0.62
2	0.91	0.95	0.36	0.50	2.28	1.58	1.78	0.80	0.72	0.75
3	1.42	1.61	0.44	1.72	0.80	0.44	0.75	0.81	1.11	1.04
4	0.08	0.43	0.09	0.43	0.40	0.40	0.19	0.22	0.31	0.48
5	1.39	1.33	0.46	1.13	1.86	0.77	1.48	0.97	3.25	1.34
6	1.52	2.60	1.15	4.94	5.92	1.53	3.06	1.24	2.62	2.46
7	3.09	2.54	1.28	1.67	2.04	1.23	1.38	1.49	1.10	1.27
8	2.68	0.82	0.40	1.43	0.84	0.73	0.63	0.40	1.62	0.44
Geomean	**0.87**					**0.71**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	0.209	0.767	0.261	0.360	0.704	0.301	0.659	0.967	0.677	0.879
2	1.039	1.091	0.415	0.567	2.613	2.235	2.505	1.131	1.021	1.062
3	1.627	1.837	0.508	1.966	0.911	0.628	1.053	1.149	1.566	1.464
4	0.094	0.493	0.104	0.488	0.457	0.571	0.274	0.312	0.444	0.680
5	1.590	1.517	0.526	1.292	2.133	1.086	2.091	1.368	4.585	1.888
6	1.744	2.978	1.321	5.647	6.776	2.152	4.317	1.756	3.699	3.473
7	3.537	2.909	1.469	1.916	2.335	1.733	1.944	2.099	1.552	1.793
8	3.064	0.943	0.452	1.641	0.961	1.025	0.886	0.562	2.284	0.618
MEAN	1.00	1.32	0.48	1.21	1.49	1.00	1.28	1.01	1.52	1.27
SD	1.22	0.95	0.49	1.71	2.05	0.74	1.30	0.58	1.47	0.94

p-p53^{Ser15}

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.33	0.55	1.07	0.36	0.94	0.68	0.64	0.48	0.49	1.48
2	0.38	0.55	0.28	0.56	0.78	0.62	0.63	0.44	0.51	1.44
3	1.10	0.38	0.15	0.65	0.64	0.19	0.30	0.33	0.50	0.62
4	1.28	0.55	0.72	1.60	1.60	0.95	1.55	1.55	0.62	1.11
5	0.24	0.26	0.07	0.16	0.19	0.13	0.11	0.31	0.39	0.45
6	1.01	2.71	0.39	0.93	3.44	0.79	1.03	0.44	0.44	1.29
7	2.92	0.84	0.48	0.82	1.96	0.23	0.28	0.54	1.51	0.42
8	1.68	1.73	0.70	0.84	1.23	0.18	0.65	0.21	0.18	0.71
Geomean	**0.98**					**0.37**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.357	0.558	1.085	0.370	0.957	1.869	1.752	1.314	1.341	4.043
2	0.389	0.557	0.288	0.573	0.791	1.705	1.728	1.206	1.384	3.955
3	1.125	0.387	0.149	0.658	0.647	0.510	0.818	0.896	1.360	1.692
4	1.302	0.565	0.730	1.625	1.626	2.588	4.235	4.256	1.686	3.034
5	0.248	0.269	0.072	0.166	0.192	0.366	0.297	0.856	1.072	1.229
6	1.026	2.763	0.399	0.943	3.503	2.162	2.833	1.203	1.210	3.545
7	2.974	0.861	0.489	0.837	1.997	0.625	0.760	1.467	4.140	1.141
8	1.710	1.758	0.713	0.852	1.248	0.481	1.789	0.565	0.491	1.952
MEAN	1.00	0.73	0.37	0.63	1.04	1.00	1.36	1.23	1.35	2.30
SD	0.85	0.86	0.34	0.44	1.03	0.89	1.27	1.16	1.09	1.21

p-TSC2^{Thr1462}

Endurance-Resistance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.77	0.96	1.05	1.42	0.65	1.46	1.02	1.05	0.78	0.01
2	0.53	0.46	0.39	0.77	0.01	1.39	0.34	0.28	0.14	0.84
3	0.25	0.91	0.60	0.01	0.05	0.49	0.52	0.92	0.68	0.01
4	1.08	0.69	1.05	1.12	0.86	1.01	0.35	1.30	0.31	0.09
5	1.95	1.77	1.48	0.80	0.99	1.08	0.38	1.28	1.43	0.72
6	1.26	1.26	1.27	0.28	0.00	2.03	0.33	1.67	2.15	0.06
7	1.52	1.60	1.89	1.65	1.35	2.03	1.24	1.19	0.72	1.28
8	2.63	2.64	2.38	1.89	0.03	2.17	2.46	2.20	2.06	0.03
9	2.32	3.16	0.58	1.86	0.12	3.06	2.62	2.06	2.00	0.01
Geomean	**1.22**					**1.45**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.453	0.786	0.866	1.170	0.538	1.003	0.703	0.723	0.533	0.005
2	0.440	0.376	0.317	0.633	0.006	0.954	0.235	0.192	0.095	0.576
3	0.205	0.750	0.491	0.005	0.045	0.333	0.355	0.636	0.466	0.006
4	0.888	0.568	0.862	0.923	0.709	0.694	0.243	0.893	0.212	0.059
5	1.606	1.457	1.215	0.654	0.811	0.742	0.261	0.881	0.986	0.493
6	1.038	1.039	1.043	0.228	0.004	1.393	0.224	1.150	1.480	0.040
7	1.246	1.312	1.554	1.355	1.108	1.394	0.854	0.820	0.493	0.883
8	2.163	2.175	1.957	1.556	0.027	1.488	1.690	1.515	1.419	0.017
9	1.911	2.597	0.477	1.529	0.097	2.103	1.804	1.414	1.373	0.009
MEAN	1.00	1.04	0.84	0.50	0.10	1.00	0.51	0.80	0.58	0.05
SD	0.65	0.75	0.54	0.56	0.43	0.53	0.63	0.40	0.54	0.33

p-TSC2^{Thr1462}

Resistance-Endurance

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.76	1.32	1.93	1.07	0.52	1.32	0.24	0.82	0.47	0.88
2	1.79	1.61	2.32	1.92	0.12	1.72	1.82	1.12	0.93	0.76
3	2.16	2.31	1.28	0.30	1.70	1.78	1.85	2.00	0.42	0.66
4	1.50	1.76	1.77	1.94	1.52	2.04	1.62	2.22	1.85	1.90
5	2.22	1.22	2.51	2.29	0.01	1.37	0.84	2.28	1.21	0.45
6	1.42	1.24	0.47	0.09	0.01	1.86	1.56	0.94	1.25	0.22
7	1.31	1.22	1.60	0.80	0.96	1.71	1.89	1.98	1.21	1.32
8	2.04	2.48	2.62	2.13	2.46	5.96	2.82	2.98	2.51	3.19
Geomean	**1.74**					**1.96**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.009	0.760	1.108	0.616	0.300	0.676	0.123	0.418	0.240	0.448
2	1.024	0.925	1.330	1.103	0.068	0.881	0.928	0.575	0.475	0.388
3	1.241	1.323	0.733	0.170	0.973	0.908	0.943	1.021	0.212	0.336
4	0.858	1.007	1.018	1.115	0.869	1.045	0.828	1.134	0.943	0.969
5	1.270	0.699	1.438	1.314	0.005	0.698	0.428	1.166	0.618	0.229
6	0.813	0.713	0.267	0.050	0.006	0.951	0.795	0.481	0.638	0.114
7	0.753	0.700	0.916	0.461	0.548	0.875	0.965	1.013	0.617	0.675
8	1.169	1.419	1.503	1.221	1.413	3.044	1.439	1.525	1.285	1.632
MEAN	1.00	0.91	0.93	0.51	0.16	1.00	0.67	0.84	0.54	0.45
SD	0.20	0.29	0.41	0.50	0.52	0.78	0.39	0.39	0.35	0.50

p-TSC2^{Thr1462}

Resistance-Only

RAW UNITS (AU)

	WEEK 1					WEEK 10				
Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.42	1.87	1.44	1.41	0.03	0.99	0.79	0.80	0.36	0.02
2	1.19	1.98	1.33	0.87	0.76	1.18	1.15	1.79	1.31	0.01
3	0.72	1.24	1.19	1.51	0.06	1.15	1.05	0.82	1.01	0.09
4	1.79	1.21	1.40	1.12	0.02	1.60	2.00	2.04	0.94	1.77
5	1.28	2.01	1.10	2.28	1.46	1.69	0.92	1.55	2.46	0.25
6	1.60	1.54	1.53	1.10	0.30	2.03	2.12	2.95	2.80	1.52
7	2.55	2.70	2.80	2.52	0.12	2.51	2.55	2.41	2.39	3.05
8	1.24	0.61	1.66	0.85	0.36	1.59	2.07	2.01	1.86	0.77
Geomean	**1.39**					**1.53**				

NORMALISED TO GROUP GEOMEAN AT PRE OF RESPECTIVE WEEK

Participant	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**	**PRE**	**+0.5 h**	**+3.5 h**	**+4 h**	**+7 h**
1	1.022	1.344	1.035	1.011	0.022	0.651	0.520	0.524	0.234	0.015
2	0.854	1.418	0.953	0.625	0.543	0.771	0.755	1.175	0.856	0.005
3	0.514	0.889	0.856	1.083	0.041	0.751	0.686	0.539	0.661	0.060
4	1.288	0.866	1.007	0.805	0.018	1.050	1.310	1.336	0.616	1.158
5	0.922	1.440	0.791	1.638	1.049	1.105	0.606	1.015	1.613	0.161
6	1.147	1.106	1.096	0.790	0.212	1.333	1.391	1.933	1.835	0.997
7	1.832	1.938	2.006	1.812	0.086	1.646	1.670	1.579	1.568	2.002
8	0.893	0.437	1.194	0.612	0.260	1.042	1.356	1.317	1.216	0.502
MEAN	1.00	1.09	1.07	0.97	0.12	1.00	0.95	1.08	0.91	0.18
SD	0.39	0.46	0.38	0.45	0.36	0.33	0.44	0.48	0.57	0.72

Differences at baseline

		Week 1			Week 10			Between-group	Standardised Effect Size (ES) Week 1		Week 10	
	Group	Mean	±	*SD*	Mean	±	*SD*	**comparisons**	ES	Magnitude	ES	Magnitude
Muscle glycogen	RES-Only	**222**	±	*45*	**295**	±	*80*	RES-Only vs END-RES	0.88	Moderate	0.81	Moderate
	END-RES	**268**	±	*54*	**346**	±	*59*	RES-Only vs RES-END	1.03	Moderate	0.51	Small
	RES-END	**274**	±	*42*	**327**	±	*70*	END-RES vs RES-END	-0.15	Trivial	0.30	Small
PGC-1α	RES-Only	**0.020**	±	*0.013*	**0.021**	±	*0.005*	RES-Only vs END-RES	-0.49	Small	-0.50	Small
	END-RES	**0.014**	±	*0.011*	**0.015**	±	*0.004*	RES-Only vs RES-END	-0.05	Trivial	-0.46	Small
	RES-END	**0.019**	±	*0.014*	**0.020**	±	*0.011*	END-RES vs RES-END	-0.44	Small	-0.04	Trivial
MuRF1	RES-Only	**0.17**	±	*0.14*	**0.12**	±	*0.05*	RES-Only vs END-RES	-1.65	Large	-1.78	Large
	END-RES	**0.04**	±	*0.02*	**0.03**	±	*0.01*	RES-Only vs RES-END	-1.04	Moderate	-0.84	Moderate
	RES-END	**0.06**	±	*0.02*	**0.07**	±	*0.04*	END-RES vs RES-END	-0.60	Moderate	-0.94	Moderate
MAFbx	RES-Only	**0.48**	±	*0.27*	**0.37**	±	*0.10*	RES-Only vs END-RES	-1.72	Large	-1.79	Large
	END-RES	**0.12**	±	*0.06*	**0.14**	±	*0.04*	RES-Only vs RES-END	-0.88	Moderate	-1.00	Moderate
	RES-END	**0.21**	±	*0.08*	**0.22**	±	*0.10*	END-RES vs RES-END	-0.84	Moderate	-0.79	Moderate
Myostatin	RES-Only	**0.007**	±	*0.005*	**0.007**	±	*0.004*	RES-Only vs END-RES	0.54	Small	0.77	Moderate
	END-RES	**0.009**	±	*0.005*	**0.009**	±	*0.003*	RES-Only vs RES-END	0.54	Small	0.80	Moderate
	RES-END	**0.011**	±	*0.009*	**0.009**	±	*0.003*	END-RES vs RES-END	0.00	Trivial	-0.03	Trivial
Mighty	RES-Only	**0.005**	±	*0.001*	**0.005**	±	*0.001*	RES-Only vs END-RES	-1.02	Moderate	-1.07	Moderate
	END-RES	**0.003**	±	*0.001*	**0.003**	±	*0.001*	RES-Only vs RES-END	-0.68	Moderate	-1.06	Moderate
	RES-END	**0.004**	±	*0.001*	**0.004**	±	*0.002*	END-RES vs RES-END	-0.34	Small	-0.01	Trivial

[a]Standardised thresholds for interpreting means: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

(continued)

		Week 1			Week 10			Between-group	Standardised Effect Size (ES) Week 1		Week 10	
	Group	Mean	±	*SD*	Mean	±	*SD*	**comparisons**	ES	Magnitude[a]	ES	Magnitude
p-Akt *ser473*	RES-Only	0.92	±	*0.69*	0.35	±	*0.31*	RES-Only vs END-RES	-0.48	Small	0.34	Small
	END-RES	0.54	±	*0.40*	0.43	±	*0.29*	RES-Only vs RES-END	0.28	Small	0.89	Moderate
	RES-END	1.31	±	*0.83*	0.79	±	*0.56*	END-RES vs RES-END	-0.76	Moderate	-0.56	Small
p-mTOR *ser2448*	RES-Only	1.70	±	*0.94*	1.06	±	*0.48*	RES-Only vs END-RES	-0.65	Moderate	-0.02	Trivial
	END-RES	1.19	±	*0.69*	1.27	±	*1.08*	RES-Only vs RES-END	0.31	Small	0.64	Moderate
	RES-END	1.98	±	*0.86*	1.66	±	*0.89*	END-RES vs RES-END	-0.97	Moderate	-0.67	Moderate
p-4E-BP1 *thr37/46*	RES-Only	1.09	±	*0.46*	0.67	±	*0.55*	RES-Only vs END-RES	-0.67	Moderate	-0.32	Small
	END-RES	0.93	±	*0.29*	0.38	±	*0.14*	RES-Only vs RES-END	0.32	Small	0.36	Small
	RES-END	1.24	±	*0.42*	0.73	±	*0.36*	END-RES vs RES-END	-0.99	Moderate	-0.68	Moderate
p-rpS6	RES-Only	2.08	±	*1.70*	0.67	±	*0.60*	RES-Only vs END-RES	-0.59	Small	-0.24	Small
	END-RES	1.31	±	*1.40*	0.61	±	*0.63*	RES-Only vs RES-END	-0.53	Small	-0.16	Trivial
	RES-END	1.35	±	*1.17*	0.44	±	*0.22*	END-RES vs RES-END	-0.05	Trivial	-0.07	Trivial
p-eEF2 *thr56*	RES-Only	1.94	±	*1.14*	0.91	±	*0.50*	RES-Only vs END-RES	-0.14	Trivial	-0.71	Moderate
	END-RES	1.92	±	*1.27*	0.66	±	*0.55*	RES-Only vs RES-END	0.25	Small	0.46	Small
	RES-END	2.07	±	*0.92*	1.64	±	*1.21*	END-RES vs RES-END	-0.39	Small	-1.17	Moderate
p-AMPK	RES-Only	1.38	±	*0.65*	0.60	±	*0.32*	RES-Only vs END-RES	-0.80	Moderate	0.14	Trivial
	END-RES	0.72	±	*0.26*	0.65	±	*0.37*	RES-Only vs RES-END	-0.19	Trivial	0.55	Small
	RES-END	1.56	±	*1.57*	0.87	±	*0.45*	END-RES vs RES-END	-0.61	Moderate	-0.41	Small
p-p53	RES-Only	1.24	±	*0.83*	0.47	±	*0.32*	RES-Only vs END-RES	-0.62	Moderate	0.35	Small
	END-RES	0.78	±	*0.64*	0.69	±	*0.63*	RES-Only vs RES-END	-0.10	Trivial	0.79	Moderate
	RES-END	1.41	±	*1.07*	0.86	±	*0.52*	END-RES vs RES-END	-0.52	Small	-0.44	Small
p-TSC2	RES-Only	1.48	±	*0.54*	1.59	±	*0.50*	RES-Only vs END-RES	-0.26	Small	-0.10	Trivial
	END-RES	1.48	±	*0.79*	1.63	±	*0.77*	RES-Only vs RES-END	0.42	Small	0.53	Small
	RES-END	1.77	±	*0.35*	2.22	±	*1.53*	END-RES vs RES-END	-0.68	Moderate	-0.63	Small

[a]*Standardised thresholds for interpreting means: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.*

Within-group changes in resting content

		Fold change from Week 1			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**		***Threshold for clear effect:***	***P* value**
	Group	mean	±	*90%CI*	ES *(d)*	±	*90%CI*	Magnitude				
Muscle glycogen	RES-Only	1.32	±	*1.20*	1.28	±	*0.70*	Large	***very likely***	↑	***@99%***	0.003
	END-RES	1.30	±	*1.20*	1.23	±	*0.71*	Large	***very likely***	↑	***@99%***	0.006
	RES-END	1.18	±	*1.17*	0.78	±	*0.68*	Moderate	*likely*	↑	*@90%*	0.059
PGC-1α	RES-Only	1.24	±	*1.64*	0.31	±	*0.73*	Small			*unclear*	0.477
	END-RES	1.24	±	*1.50*	0.32	±	*0.59*	Small			*unclear*	0.370
	RES-END	0.95	±	*1.44*	-0.08	±	*0.67*	Trivial			*unclear*	0.841
MuRF1	RES-Only	0.87	±	*1.30*	-0.18	±	*0.44*	Trivial			*unclear*	0.505
	END-RES	0.76	±	*1.25*	-0.36	±	*0.43*	Small	*possibly*	↓	*@90%*	0.166
	RES-END	1.01	±	*1.37*	0.01	±	*0.47*	Trivial			*unclear*	0.983
MAFbx	RES-Only	0.83	±	*1.28*	-0.21	±	*0.38*	Small	*possibly*	↓	*@90%*	0.360
	END-RES	1.38	±	*1.44*	0.37	±	*0.36*	Small	*likely*	↑	*@90%*	0.094
	RES-END	1.03	±	*1.35*	0.03	±	*0.39*	Trivial			*unclear*	0.902
Myostatin	RES-Only	1.34	±	*1.78*	0.28	±	*0.54*	Small			*unclear*	0.384
	END-RES	1.11	±	*1.55*	0.10	±	*0.47*	Trivial			*unclear*	0.723
	RES-END	1.13	±	*1.60*	0.11	±	*0.49*	Trivial			*unclear*	0.703
Mighty	RES-Only	1.17	±	*1.26*	0.32	±	*0.43*	Small	*possibly*	↑	*@90%*	0.224
	END-RES	1.22	±	*1.24*	0.40	±	*0.39*	Small	*likely*	↑	*@90%*	0.089
	RES-END	1.03	±	*1.22*	0.06	±	*0.41*	Trivial			*unclear*	0.793

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		Fold change from Week 1			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓		Threshold for clear effect:	*P* value
	Group	mean	±	*90%CI*	ES *(d)*	±	*90%CI*	Magnitude				
p-Akt *ser473*	RES-Only	0.38	±	*1.18*	-0.92	±	*0.44*	Moderate	***most likely***	↓	**@99%**	0.001
	END-RES	0.86	±	*1.35*	-0.15	±	*0.38*	Trivial			*unclear*	0.522
	RES-END	0.65	±	*1.36*	-0.40	±	*0.49*	Small	*likely*	↓	*@90%*	0.168
p-mTOR *ser2448*	RES-Only	0.64	±	*1.29*	-0.67	±	*0.66*	Moderate	*likely*	↓	*@90%*	0.096
	END-RES	0.97	±	*1.33*	-0.04	±	*0.51*	Trivial			*unclear*	0.898
	RES-END	0.80	±	*1.33*	-0.33	±	*0.61*	Small			*unclear*	0.360
p-4E-BP1 *thr37/46*	RES-Only	0.66	±	*1.14*	-0.71	±	*0.36*	Moderate	***very likely***	↓	**@99%**	0.003
	END-RES	0.86	±	*1.30*	-0.26	±	*0.58*	Small			*unclear*	0.441
	RES-END	0.63	±	*1.12*	-0.78	±	*0.33*	Moderate	***most likely***	↓	**@99%**	0.000
p-rpS6	RES-Only	0.29	±	*1.22*	-1.45	±	*0.83*	Large	***very likely***	↓	**@99%**	0.007
	END-RES	0.38	±	*1.29*	-1.14	±	*0.82*	Moderate	*very likely*	↓	*@90%*	0.026
	RES-END	0.39	±	*1.24*	-1.10	±	*0.69*	Moderate	***very likely***	↓	**@99%**	0.011
p-eEF2 *thr56*	RES-Only	0.50	±	*1.23*	-0.98	±	*0.64*	Moderate	***very likely***	↓	**@99%**	0.020
	END-RES	0.26	±	*1.20*	-1.96	±	*1.03*	Large	***very likely***	↓	**@99%**	0.011
	RES-END	0.70	±	*1.29*	-0.51	±	*0.58*	Small	*likely*	↓	*@90%*	0.147
p-AMPK	RES-Only	0.44	±	*1.18*	-1.11	±	*0.53*	Moderate	***most likely***	↓	**@99%**	0.001
	END-RES	0.86	±	*1.32*	-0.20	±	*0.49*	Small			*unclear*	0.491
	RES-END	0.71	±	*1.28*	-0.48	±	*0.52*	Small	*likely*	↓	*@90%*	0.130
p-p53	RES-Only	0.37	±	*1.19*	-0.85	±	*0.43*	Moderate	***very likely***	↓	**@99%**	0.002
	END-RES	1.02	±	*1.46*	0.02	±	*0.38*	Trivial			*unclear*	0.931
	RES-END	0.81	±	*1.36*	-0.18	±	*0.37*	Trivial	*possibly*	↓	*@90%*	0.416
p-TSC2	RES-Only	1.10	±	*1.26*	0.17	±	*0.43*	Trivial			*unclear*	0.501
	END-RES	1.20	±	*1.28*	0.34	±	*0.44*	Small	*possibly*	↑	*@90%*	0.198
	RES-END	1.12	±	*1.36*	0.22	±	*0.59*	Small			*unclear*	0.518

Mean, mean fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely.

↑ = increased; ↓ = decreased;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

Between-group differences for changes in resting content

	Between group comparison	**Difference (fold)** mean	±	*90%CI*	**Standardised Effect Size (ES)** ES (*d*)	±	*90%CI*	Magnitude	**Likelihood true effect is substantially ↑/↓**	***Threshold for clear effect***	***P* value**
Muscle glycogen	RES-Only vs END-RES	0.99	±	*1.21*	-0.05	±	*1.00*	Trivial		*unclear*	0.930
	RES-Only vs RES-END	0.90	±	*1.19*	-0.51	±	*0.97*	Small		*unclear*	0.390
	END-RES vs RES-END	0.91	±	*1.19*	-0.45	±	*0.98*	Small		*unclear*	0.442
PGC-1α	RES-Only vs END-RES	1.00	±	*1.68*	0.01	±	*0.94*	Trivial		*unclear*	0.992
	RES-Only vs RES-END	0.77	±	*1.55*	-0.39	±	*0.99*	Small		*unclear*	0.508
	END-RES vs RES-END	0.77	±	*1.49*	-0.40	±	*0.89*	Small		*unclear*	0.457
MuRF1	RES-Only vs END-RES	0.87	±	*1.42*	-0.18	±	*0.61*	Trivial		*unclear*	0.620
	RES-Only vs RES-END	1.15	±	*1.59*	0.18	±	*0.64*	Trivial		*unclear*	0.638
	END-RES vs RES-END	1.32	±	*1.67*	0.36	±	*0.64*	Small		*unclear*	0.341
MAFbx	RES-Only vs END-RES	1.66	±	*1.79*	0.58	±	*0.53*	Moderate	*likely* ↑	*@90%*	0.071
	RES-Only vs RES-END	1.23	±	*1.61*	0.24	±	*0.55*	Small		*unclear*	0.463
	END-RES vs RES-END	0.74	±	*1.36*	-0.34	±	*0.53*	Small	*possibly* ↓	*@90%*	0.288
Myostatin	RES-Only vs END-RES	0.83	±	*1.66*	-0.18	±	*0.71*	Trivial		*unclear*	0.670
	RES-Only vs RES-END	0.84	±	*1.69*	-0.17	±	*0.73*	Trivial		*unclear*	0.701
	END-RES vs RES-END	1.02	±	*1.77*	0.01	±	*0.68*	Trivial		*unclear*	0.973
Mighty	RES-Only vs END-RES	1.04	±	*1.31*	0.08	±	*0.58*	Trivial		*unclear*	0.813
	RES-Only vs RES-END	0.88	±	*1.27*	-0.25	±	*0.59*	Small		*unclear*	0.479
	END-RES vs RES-END	0.84	±	*1.24*	-0.34	±	*0.56*	Small		*unclear*	0.324

(continued)

	Between group comparison	**Difference (fold)** mean	±	*90%CI*	**Standardised Effect Size (ES)** ES (*d*)	±	*90%CI*	Magnitude	**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
p-Akt *ser473*	RES-Only vs END-RES	2.27	±	*2.47*	0.78	±	*0.58*	Moderate	***very likely*** ↑	***@99%***	0.028
	RES-Only vs RES-END	1.73	±	*2.26*	0.52	±	*0.64*	Small	*likely* ↑	*@90%*	0.178
	END-RES vs RES-END	0.76	±	*1.52*	-0.26	±	*0.60*	Small		*unclear*	0.470
p-mTOR *ser2448*	RES-Only vs END-RES	1.51	±	*1.87*	0.63	±	*0.83*	Moderate		*unclear*	0.212
	RES-Only vs RES-END	1.25	±	*1.78*	0.33	±	*0.90*	Small		*unclear*	0.534
	END-RES vs RES-END	0.82	±	*1.45*	-0.29	±	*0.79*	Small		*unclear*	0.534
p-4E-BP1 *thr37/46*	RES-Only vs END-RES	1.30	±	*1.52*	0.45	±	*0.66*	Small		*unclear*	0.258
	RES-Only vs RES-END	0.96	±	*1.27*	-0.07	±	*0.48*	Trivial		*unclear*	0.798
	END-RES vs RES-END	0.74	±	*1.29*	-0.52	±	*0.65*	Small	*likely* ↓	*@90%*	0.183
p-rpS6	RES-Only vs END-RES	1.31	±	*2.49*	0.32	±	*1.15*	Small		*unclear*	0.642
	RES-Only vs RES-END	1.35	±	*2.40*	0.35	±	*1.07*	Small		*unclear*	0.583
	END-RES vs RES-END	1.03	±	*2.05*	0.03	±	*1.06*	Trivial		*unclear*	0.962
p-eEF2 *thr56*	RES-Only vs END-RES	0.51	±	*1.45*	-0.98	±	*1.14*	Moderate	*likely* ↓	*@90%*	0.151
	RES-Only vs RES-END	1.39	±	*1.85*	0.47	±	*0.83*	Small		*unclear*	0.334
	END-RES vs RES-END	2.75	±	*3.38*	1.45	±	*1.12*	Large	*very likely* ↑	*@90%*	0.040
p-AMPK	RES-Only vs END-RES	1.95	±	*2.07*	0.91	±	*0.71*	Moderate	*likely* ↑	*@90%*	0.037
	RES-Only vs RES-END	1.59	±	*1.90*	0.64	±	*0.74*	Moderate	*likely* ↑	*@90%*	0.154
	END-RES vs RES-END	0.82	±	*1.45*	-0.27	±	*0.71*	Small		*unclear*	0.524
p-p53	RES-Only vs END-RES	2.75	±	*2.95*	0.87	±	*0.57*	Moderate	***very likely*** ↑	***@99%***	0.012
	RES-Only vs RES-END	2.18	±	*2.53*	0.67	±	*0.56*	Moderate	*likely* ↑	*@90%*	0.051
	END-RES vs RES-END	0.79	±	*1.52*	-0.20	±	*0.53*	Small		*unclear*	0.529
p-TSC2	RES-Only vs END-RES	1.09	±	*1.35*	0.17	±	*0.60*	Trivial		*unclear*	0.640
	RES-Only vs RES-END	1.03	±	*1.39*	0.05	±	*0.70*	Trivial		*unclear*	0.912
	END-RES vs RES-END	0.94	±	*1.36*	-0.12	±	*0.70*	Trivial		*unclear*	0.770

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely.
↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

Within-group exercise-induced changes

Muscle Glycogen

Group	Week	Time	Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
			mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	1	+ 0.5 h	1.00	±	*1.18*	-0.01	±	*0.85*	Trivial		*unclear*	0.990
		+ 3.5 h	1.08	±	*1.16*	0.38	±	*0.68*	Small		*unclear*	0.355
		+ 4.0 h	1.17	±	*1.24*	0.73	±	*0.96*	Moderate		*unclear*	0.207
		+ 7.0 h	1.12	±	*1.17*	0.52	±	*0.70*	Small	*likely* ↑	*@90%*	0.217
	10	+ 0.5 h	0.94	±	*1.17*	-0.28	±	*0.85*	Small		*unclear*	0.585
		+ 3.5 h	1.00	±	*1.15*	-0.01	±	*0.68*	Trivial		*unclear*	0.981
		+ 4.0 h	0.90	±	*1.19*	-0.47	±	*0.96*	Small		*unclear*	0.405
		+ 7.0 h	1.02	±	*1.15*	0.07	±	*0.70*	Trivial		*unclear*	0.859
END-RES	1	+ 0.5 h	0.84	±	*1.16*	-0.79	±	*0.90*	Moderate	*likely* ↓	*@90%*	0.147
		+ 3.5 h	0.80	±	*1.11*	-1.02	±	*0.66*	Moderate	***very likely*** ↓	***@99%***	0.013
		+ 4.0 h	0.73	±	*1.17*	-1.48	±	*1.09*	Large	*very likely* ↓	*@90%*	0.029
		+ 7.0 h	0.81	±	*1.13*	-0.97	±	*0.72*	Moderate	***very likely*** ↓	***@99%***	0.030
	10	+ 0.5 h	0.86	±	*1.17*	-0.73	±	*0.90*	Moderate	*likely* ↓	*@90%*	0.180
		+ 3.5 h	0.95	±	*1.14*	-0.23	±	*0.66*	Small		*unclear*	0.552
		+ 4.0 h	0.86	±	*1.20*	-0.71	±	*1.09*	Moderate		*unclear*	0.280
		+ 7.0 h	0.72	±	*1.11*	-1.54	±	*0.72*	Large	***most likely*** ↓	***@99%***	0.001
RES-END	1	+ 0.5 h	1.04	±	*1.19*	0.16	±	*0.83*	Trivial		*unclear*	0.740
		+ 3.5 h	1.05	±	*1.15*	0.24	±	*0.68*	Small		*unclear*	0.548
		+ 4.0 h	0.71	±	*1.17*	-1.60	±	*1.07*	Large	***very likely*** ↓	***@99%***	0.018
		+ 7.0 h	0.90	±	*1.18*	-0.51	±	*0.91*	Small		*unclear*	0.349
	10	+ 0.5 h	0.91	±	*1.16*	-0.46	±	*0.83*	Small		*unclear*	0.355
		+ 3.5 h	0.97	±	*1.14*	-0.17	±	*0.68*	Trivial		*unclear*	0.683
		+ 4.0 h	0.79	±	*1.18*	-1.11	±	*1.07*	Moderate	*likely* ↓	*@90%*	0.090
		+ 7.0 h	0.81	±	*1.16*	-0.96	±	*0.91*	Moderate	*likely* ↓	*@90%*	0.084

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑ & ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

PGC-1α

Group	Week	Time	Fold change from PRE mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
RES-Only	1	+ 0.5 h	0.78	±	*1.34*	-0.37	±	*0.62*	Small		*unclear*	0.321
		+ 3.5 h	4.42	±	*3.40*	2.21	±	*0.77*	Very large	***most likely*** ↑	***@99%***	0.000
		+ 4.0 h	1.91	±	*2.05*	0.96	±	*0.78*	Moderate	*likely* ↑	*@90%*	0.044
		+ 7.0 h	2.18	±	*2.25*	1.16	±	*0.81*	Moderate	***very likely*** ↑	***@99%***	0.023
	10	+ 0.5 h	1.05	±	*1.45*	0.07	±	*0.62*	Trivial		*unclear*	0.859
		+ 3.5 h	2.12	±	*2.15*	1.12	±	*0.77*	Moderate	***very likely*** ↑	***@99%***	0.020
		+ 4.0 h	2.70	±	*2.48*	1.48	±	*0.78*	Large	***most likely*** ↑	***@99%***	0.003
		+ 7.0 h	1.23	±	*1.70*	0.30	±	*0.81*	Small		*unclear*	0.531
END-RES	1	+ 0.5 h	1.41	±	*1.57*	0.51	±	*0.59*	Small	*likely* ↑	*@90%*	0.156
		+ 3.5 h	5.23	±	*3.60*	2.46	±	*0.71*	Very large	***most likely*** ↑	***@99%***	0.000
		+ 4.0 h	5.34	±	*3.17*	2.49	±	*0.59*	Very large	***most likely*** ↑	***@99%***	0.000
		+ 7.0 h	3.45	±	*2.56*	1.84	±	*0.65*	Large	***most likely*** ↑	***@99%***	0.000
	10	+ 0.5 h	1.03	±	*1.42*	0.04	±	*0.59*	Trivial		*unclear*	0.914
		+ 3.5 h	2.92	±	*2.45*	1.59	±	*0.71*	Large	***most likely*** ↑	***@99%***	0.001
		+ 4.0 h	3.03	±	*2.23*	1.65	±	*0.59*	Large	***most likely*** ↑	***@99%***	0.000
		+ 7.0 h	1.97	±	*1.89*	1.00	±	*0.65*	Moderate	***very likely*** ↑	***@99%***	0.016
RES-END	1	+ 0.5 h	1.07	±	*1.46*	0.10	±	*0.62*	Trivial		*unclear*	0.795
		+ 3.5 h	2.13	±	*2.24*	1.12	±	*0.82*	Moderate	*very likely* ↑	*@90%*	0.028
		+ 4.0 h	1.64	±	*1.71*	0.73	±	*0.62*	Moderate	*likely* ↑	*@90%*	0.054
		+ 7.0 h	2.47	±	*2.38*	1.34	±	*0.79*	Large	***very likely*** ↑	***@99%***	0.008
	10	+ 0.5 h	1.40	±	*1.61*	0.50	±	*0.62*	Small	*likely* ↑	*@90%*	0.188
		+ 3.5 h	1.47	±	*1.86*	0.58	±	*0.82*	Small		*unclear*	0.243
		+ 4.0 h	1.90	±	*1.82*	0.95	±	*0.62*	Moderate	***very likely*** ↑	***@99%***	0.013
		+ 7.0 h	3.65	±	*3.05*	1.92	±	*0.79*	Large	***most likely*** ↑	***@99%***	0.000

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

MuRF1

Group	Week	Time	Fold change from PRE mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
RES-Only	1	+ 0.5 h	1.11	±	*1.48*	0.14	±	*0.55*	Trivial		*unclear*	0.669
		+ 3.5 h	1.43	±	*1.57*	0.47	±	*0.50*	Small	*likely* ↑	*@90%*	0.124
		+ 4.0 h	0.72	±	*1.34*	-0.42	±	*0.59*	Small	*possibly* ↓	*@90%*	0.228
		+ 7.0 h	0.69	±	*1.35*	-0.49	±	*0.64*	Small	*likely* ↓	*@90%*	0.204
	10	+ 0.5 h	0.94	±	*1.40*	-0.08	±	*0.55*	Trivial		*unclear*	0.799
		+ 3.5 h	1.04	±	*1.41*	0.05	±	*0.50*	Trivial		*unclear*	0.878
		+ 4.0 h	1.20	±	*1.56*	0.24	±	*0.59*	Small		*unclear*	0.493
		+ 7.0 h	0.48	±	*1.25*	-0.95	±	*0.64*	Moderate	***very likely*** ↓	***@99%***	0.019
END-RES	1	+ 0.5 h	0.93	±	*1.30*	-0.10	±	*0.41*	Trivial		*unclear*	0.689
		+ 3.5 h	2.37	±	*1.86*	1.13	±	*0.46*	Moderate	***most likely*** ↑	***@99%***	0.000
		+ 4.0 h	2.23	±	*1.74*	1.05	±	*0.43*	Moderate	***most likely*** ↑	***@99%***	0.000
		+ 7.0 h	0.92	±	*1.35*	-0.12	±	*0.49*	Trivial		*unclear*	0.692
	10	+ 0.5 h	1.11	±	*1.36*	0.13	±	*0.41*	Trivial		*unclear*	0.597
		+ 3.5 h	1.63	±	*1.59*	0.64	±	*0.46*	Moderate	***likely*** ↑	***@99%***	0.027
		+ 4.0 h	1.71	±	*1.57*	0.70	±	*0.43*	Moderate	***very likely*** ↑	***@99%***	0.009
		+ 7.0 h	0.82	±	*1.31*	-0.26	±	*0.49*	Small		*unclear*	0.367
RES-END	1	+ 0.5 h	0.86	±	*1.30*	-0.19	±	*0.45*	Trivial		*unclear*	0.478
		+ 3.5 h	1.13	±	*1.61*	0.16	±	*0.67*	Trivial		*unclear*	0.691
		+ 4.0 h	0.70	±	*1.24*	-0.46	±	*0.44*	Small	*likely* ↓	*@90%*	0.082
		+ 7.0 h	1.98	±	*1.68*	0.89	±	*0.44*	Moderate	***very likely*** ↑	***@99%***	0.001
	10	+ 0.5 h	0.97	±	*1.34*	-0.04	±	*0.45*	Trivial		*unclear*	0.886
		+ 3.5 h	0.75	±	*1.40*	-0.38	±	*0.67*	Small		*unclear*	0.339
		+ 4.0 h	0.69	±	*1.24*	-0.49	±	*0.44*	Small	*likely* ↓	*@90%*	0.065
		+ 7.0 h	1.59	±	*1.54*	0.60	±	*0.44*	Moderate	***likely*** ↑	***@99%***	0.025

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑ & ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

MAFbx

Group	Week	Time	Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓		Threshold for clear effect	*P* value
			mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude				
RES-Only	1	+ 0.5 h	0.86	±	*1.34*	-0.17	±	*0.45*	Trivial			*unclear*	0.524
		+ 3.5 h	0.47	±	*1.26*	-0.87	±	*0.60*	Moderate	***very likely***	↓	***@99%***	0.021
		+ 4.0 h	0.23	±	*1.11*	-1.70	±	*0.52*	Large	***most likely***	↓	***@99%***	0.000
		+ 7.0 h	0.17	±	*1.11*	-2.03	±	*0.69*	Very large	***most likely***	↓	***@99%***	0.000
	10	+ 0.5 h	0.79	±	*1.31*	-0.27	±	*0.45*	Small	*possibly*	↓	*@90%*	0.307
		+ 3.5 h	0.48	±	*1.26*	-0.84	±	*0.60*	Moderate	***very likely***	↓	***@99%***	0.024
		+ 4.0 h	0.52	±	*1.24*	-0.76	±	*0.52*	Moderate	***very likely***	↓	***@99%***	0.020
		+ 7.0 h	0.25	±	*1.16*	-1.61	±	*0.69*	Large	***most likely***	↓	***@99%***	0.001
END-RES	1	+ 0.5 h	1.18	±	*1.44*	0.19	±	*0.42*	Trivial			*unclear*	0.459
		+ 3.5 h	1.54	±	*1.79*	0.50	±	*0.57*	Small	*likely*	↑	*@90%*	0.148
		+ 4.0 h	1.45	±	*1.67*	0.43	±	*0.51*	Small	*likely*	↑	*@90%*	0.165
		+ 7.0 h	0.58	±	*1.26*	-0.63	±	*0.50*	Moderate	***likely***	↓	***@99%***	0.042
	10	+ 0.5 h	0.66	±	*1.25*	-0.48	±	*0.42*	Small	*likely*	↓	*@90%*	0.066
		+ 3.5 h	1.09	±	*1.56*	0.10	±	*0.57*	Trivial			*unclear*	0.766
		+ 4.0 h	1.10	±	*1.51*	0.11	±	*0.51*	Trivial			*unclear*	0.725
		+ 7.0 h	0.37	±	*1.17*	-1.13	±	*0.50*	Moderate	***most likely***	↓	***@99%***	0.001
RES-END	1	+ 0.5 h	1.02	±	*1.35*	0.02	±	*0.38*	Trivial			*unclear*	0.917
		+ 3.5 h	0.44	±	*1.18*	-0.95	±	*0.46*	Moderate	***very likely***	↓	***@99%***	0.002
		+ 4.0 h	0.23	±	*1.08*	-1.70	±	*0.38*	Large	***most likely***	↓	***@99%***	0.000
		+ 7.0 h	0.32	±	*1.16*	-1.31	±	*0.56*	Large	***most likely***	↓	***@99%***	0.001
	10	+ 0.5 h	0.97	±	*1.33*	-0.03	±	*0.38*	Trivial			*unclear*	0.890
		+ 3.5 h	0.41	±	*1.17*	-1.03	±	*0.46*	Moderate	***most likely***	↓	***@99%***	0.001
		+ 4.0 h	0.33	±	*1.11*	-1.27	±	*0.38*	Large	***most likely***	↓	***@99%***	0.000
		+ 7.0 h	0.56	±	*1.29*	-0.66	±	*0.56*	Moderate	*likely*	↓	*@90%*	0.056

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

Myostatin

Group	Week	Time	Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
			mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	1	+ 0.5 h	0.74	±	*1.56*	-0.29	±	*0.67*	Small		*unclear*	0.470
		+ 3.5 h	1.17	±	*1.62*	0.15	±	*0.49*	Trivial		*unclear*	0.615
		+ 4.0 h	0.90	±	*1.48*	-0.10	±	*0.49*	Trivial		*unclear*	0.730
		+ 7.0 h	0.71	±	*1.47*	-0.34	±	*0.60*	Small		*unclear*	0.350
	10	+ 0.5 h	0.72	±	*1.55*	-0.31	±	*0.67*	Small		*unclear*	0.433
		+ 3.5 h	0.45	±	*1.24*	-0.78	±	*0.49*	Moderate	***very likely*** ↓	***@99%***	0.010
		+ 4.0 h	0.58	±	*1.31*	-0.52	±	*0.49*	Small	*likely* ↓	*@90%*	0.082
		+ 7.0 h	0.46	±	*1.31*	-0.75	±	*0.60*	Moderate	*likely* ↓	*@90%*	0.044
END-RES	1	+ 0.5 h	1.31	±	*1.66*	0.26	±	*0.47*	Small		*unclear*	0.351
		+ 3.5 h	0.85	±	*1.44*	-0.16	±	*0.48*	Trivial		*unclear*	0.576
		+ 4.0 h	0.65	±	*1.32*	-0.42	±	*0.47*	Small	*likely* ↓	*@90%*	0.137
		+ 7.0 h	0.86	±	*1.48*	-0.14	±	*0.51*	Trivial		*unclear*	0.634
	10	+ 0.5 h	1.01	±	*1.51*	0.01	±	*0.47*	Trivial		*unclear*	0.967
		+ 3.5 h	0.57	±	*1.29*	-0.55	±	*0.48*	Small	*likely* ↓	*@90%*	0.060
		+ 4.0 h	0.52	±	*1.26*	-0.63	±	*0.47*	Moderate	***likely*** ↓	***@99%***	0.027
		+ 7.0 h	0.62	±	*1.34*	-0.47	±	*0.51*	Small	*likely* ↓	*@90%*	0.130
RES-END	1	+ 0.5 h	1.56	±	*1.83*	0.43	±	*0.49*	Small	*likely* ↑	*@90%*	0.154
		+ 3.5 h	1.30	±	*1.73*	0.25	±	*0.52*	Small		*unclear*	0.420
		+ 4.0 h	0.96	±	*1.58*	-0.04	±	*0.55*	Trivial		*unclear*	0.894
		+ 7.0 h	0.38	±	*1.20*	-0.94	±	*0.49*	Moderate	***very likely*** ↓	***@99%***	0.002
	10	+ 0.5 h	0.90	±	*1.48*	-0.11	±	*0.49*	Trivial		*unclear*	0.722
		+ 3.5 h	0.73	±	*1.41*	-0.31	±	*0.52*	Small		*unclear*	0.322
		+ 4.0 h	0.76	±	*1.46*	-0.27	±	*0.55*	Small		*unclear*	0.419
		+ 7.0 h	0.65	±	*1.35*	-0.41	±	*0.49*	Small	*likely* ↓	*@90%*	0.169

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓= increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

Mighty

Group	Week	Time	Fold change from PRE mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
RES-Only	1	+ 0.5 h	1.02	±	*1.34*	0.03	±	*0.65*	Trivial		*unclear*	0.935
		+ 3.5 h	1.83	±	*1.38*	1.20	±	*0.41*	Large	***most likely*** ↑	***@99%***	0.000
		+ 4.0 h	1.61	±	*1.56*	0.94	±	*0.68*	Moderate	***very likely*** ↑	***@99%***	0.027
		+ 7.0 h	2.17	±	*1.71*	1.53	±	*0.64*	Large	***most likely*** ↑	***@99%***	0.001
	10	+ 0.5 h	0.69	±	*1.23*	-0.75	±	*0.65*	Moderate	*likely* ↓	*@90%*	0.063
		+ 3.5 h	1.13	±	*1.24*	0.24	±	*0.41*	Small	*possibly* ↑	*@90%*	0.323
		+ 4.0 h	1.42	±	*1.49*	0.69	±	*0.68*	Moderate	*likely* ↑	*@90%*	0.092
		+ 7.0 h	1.43	±	*1.47*	0.71	±	*0.64*	Moderate	*likely* ↑	*@90%*	0.068
END-RES	1	+ 0.5 h	1.24	±	*1.24*	0.43	±	*0.39*	Small	***likely*** ↑	***@99%***	0.068
		+ 3.5 h	1.48	±	*1.31*	0.77	±	*0.41*	Moderate	***very likely*** ↑	***@99%***	0.003
		+ 4.0 h	1.49	±	*1.29*	0.79	±	*0.39*	Moderate	***very likely*** ↑	***@99%***	0.001
		+ 7.0 h	1.72	±	*1.34*	1.07	±	*0.39*	Moderate	***most likely*** ↑	***@99%***	0.000
	10	+ 0.5 h	0.90	±	*1.18*	-0.21	±	*0.39*	Small	*possibly* ↓	*@90%*	0.371
		+ 3.5 h	1.12	±	*1.23*	0.23	±	*0.41*	Small	*possibly* ↑	*@90%*	0.355
		+ 4.0 h	1.12	±	*1.22*	0.23	±	*0.39*	Small	*possibly* ↑	*@90%*	0.326
		+ 7.0 h	1.42	±	*1.28*	0.70	±	*0.39*	Moderate	***very likely*** ↑	***@99%***	0.004
RES-END	1	+ 0.5 h	1.28	±	*1.55*	0.49	±	*0.83*	Small		*unclear*	0.317
		+ 3.5 h	1.34	±	*1.30*	0.58	±	*0.44*	Small	***likely*** ↑	***@99%***	0.034
		+ 4.0 h	0.85	±	*1.33*	-0.32	±	*0.75*	Small		*unclear*	0.466
		+ 7.0 h	1.19	±	*1.48*	0.35	±	*0.77*	Small		*unclear*	0.440
	10	+ 0.5 h	0.86	±	*1.37*	-0.30	±	*0.83*	Small		*unclear*	0.543
		+ 3.5 h	1.16	±	*1.26*	0.29	±	*0.44*	Small	*possibly* ↑	*@90%*	0.274
		+ 4.0 h	1.22	±	*1.47*	0.39	±	*0.75*	Small		*unclear*	0.385
		+ 7.0 h	1.73	±	*1.69*	1.08	±	*0.77*	Moderate	*very likely* ↑	*@90%*	0.027

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-Akt

			Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓		Threshold for clear effect	*P* value
Group	**Week**	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude				
RES-Only	1	+ 0.5 h	0.77	±	*1.45*	-0.25	±	*0.53*	Small			*unclear*	0.418
		+ 3.5 h	0.38	±	*1.15*	-0.91	±	*0.35*	Moderate	***most likely***	↓	***@99%***	0.000
		+ 4.0 h	0.66	±	*1.31*	-0.39	±	*0.43*	Small	*likely*	↓	*@90%*	0.133
		+ 7.0 h	0.99	±	*1.38*	-0.01	±	*0.35*	Trivial			*unclear*	0.966
	10	+ 0.5 h	1.07	±	*1.62*	0.06	±	*0.53*	Trivial			*unclear*	0.839
		+ 3.5 h	1.33	±	*1.51*	0.27	±	*0.35*	Small	*possibly*	↑	*@90%*	0.206
		+ 4.0 h	1.25	±	*1.59*	0.21	±	*0.43*	Small			*unclear*	0.401
		+ 7.0 h	2.36	±	*1.90*	0.81	±	*0.35*	Moderate	***most likely***	↑	***@99%***	0.000
END-RES	1	+ 0.5 h	1.20	±	*1.43*	0.17	±	*0.33*	Trivial	*possibly*	↑	*@90%*	0.394
		+ 3.5 h	0.76	±	*1.27*	-0.26	±	*0.33*	Small	*possibly*	↓	*@90%*	0.192
		+ 4.0 h	2.00	±	*1.72*	0.66	±	*0.33*	Moderate	***very likely***	↑	***@99%***	0.001
		+ 7.0 h	1.84	±	*1.66*	0.58	±	*0.33*	Small	***very likely***	↑	***@99%***	0.005
	10	+ 0.5 h	1.69	±	*1.61*	0.50	±	*0.33*	Small	***likely***	↑	***@99%***	0.015
		+ 3.5 h	1.27	±	*1.45*	0.22	±	*0.33*	Small	*possibly*	↑	*@90%*	0.270
		+ 4.0 h	1.91	±	*1.68*	0.61	±	*0.33*	Moderate	***very likely***	↑	***@99%***	0.003
		+ 7.0 h	2.18	±	*1.78*	0.74	±	*0.33*	Moderate	***most likely***	↑	***@99%***	0.000
RES-END	1	+ 0.5 h	1.12	±	*1.47*	0.11	±	*0.39*	Trivial			*unclear*	0.632
		+ 3.5 h	0.40	±	*1.15*	-0.87	±	*0.35*	Moderate	***most likely***	↓	***@99%***	0.000
		+ 4.0 h	0.89	±	*1.36*	-0.11	±	*0.37*	Trivial			*unclear*	0.611
		+ 7.0 h	1.04	±	*1.64*	0.03	±	*0.55*	Trivial			*unclear*	0.916
	10	+ 0.5 h	1.32	±	*1.56*	0.26	±	*0.39*	Small	*possibly*	↑	*@90%*	0.255
		+ 3.5 h	0.89	±	*1.34*	-0.11	±	*0.35*	Trivial			*unclear*	0.597
		+ 4.0 h	1.51	±	*1.61*	0.39	±	*0.37*	Small	*likely*	↑	*@90%*	0.088
		+ 7.0 h	0.95	±	*1.58*	-0.05	±	*0.55*	Trivial			*unclear*	0.870

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-mTOR

Group	Week	Time	Fold change from PRE mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
RES-Only	1	+ 0.5 h	0.61	±	*1.21*	-0.76	±	*0.52*	Moderate	***very likely*** ↓	***@99%***	0.018
		+ 3.5 h	1.13	±	*1.57*	0.19	±	*0.73*	Trivial		*unclear*	0.650
		+ 4.0 h	1.47	±	*1.51*	0.59	±	*0.52*	Small	*likely* ↑	*@90%*	0.063
		+ 7.0 h	0.43	±	*1.33*	-1.28	±	*1.08*	Large	*very likely* ↓	*@90%*	0.056
	10	+ 0.5 h	0.74	±	*1.26*	-0.47	±	*0.52*	Small	*likely* ↓	*@90%*	0.135
		+ 3.5 h	1.25	±	*1.63*	0.34	±	*0.73*	Small		*unclear*	0.420
		+ 4.0 h	1.49	±	*1.52*	0.61	±	*0.52*	Moderate	*likely* ↑	*@90%*	0.055
		+ 7.0 h	0.60	±	*1.46*	-0.79	±	*1.08*	Moderate		*unclear*	0.218
END-RES	1	+ 0.5 h	0.97	±	*1.33*	-0.04	±	*0.51*	Trivial		*unclear*	0.881
		+ 3.5 h	1.24	±	*1.49*	0.33	±	*0.59*	Small		*unclear*	0.346
		+ 4.0 h	1.01	±	*1.33*	0.01	±	*0.49*	Trivial		*unclear*	0.969
		+ 7.0 h	0.47	±	*1.40*	-1.14	±	*1.17*	Moderate	*likely* ↓	*@90%*	0.108
	10	+ 0.5 h	0.70	±	*1.24*	-0.55	±	*0.51*	Small	*likely* ↓	*@90%*	0.073
		+ 3.5 h	1.15	±	*1.45*	0.21	±	*0.59*	Small		*unclear*	0.539
		+ 4.0 h	0.99	±	*1.32*	-0.02	±	*0.49*	Trivial		*unclear*	0.954
		+ 7.0 h	0.31	±	*1.26*	-1.77	±	*1.17*	Large	***very likely*** ↓	***@99%***	0.017
RES-END	1	+ 0.5 h	0.60	±	*1.24*	-0.78	±	*0.59*	Moderate	***likely*** ↓	***@99%***	0.032
		+ 3.5 h	1.16	±	*1.40*	0.23	±	*0.52*	Small		*unclear*	0.457
		+ 4.0 h	0.62	±	*1.30*	-0.73	±	*0.72*	Moderate	*likely* ↓	*@90%*	0.094
		+ 7.0 h	0.54	±	*1.36*	-0.94	±	*0.96*	Moderate	*likely* ↓	*@90%*	0.108
	10	+ 0.5 h	0.66	±	*1.26*	-0.63	±	*0.59*	Moderate	*likely* ↓	*@90%*	0.080
		+ 3.5 h	1.07	±	*1.37*	0.10	±	*0.52*	Trivial		*unclear*	0.735
		+ 4.0 h	0.76	±	*1.37*	-0.43	±	*0.72*	Small		*unclear*	0.317
		+ 7.0 h	0.94	±	*1.63*	-0.09	±	*0.96*	Trivial		*unclear*	0.868

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓= increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-4E-BP1

Group	Week	Time	Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
			mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	1	+ 0.5 h	0.41	±	*1.16*	-1.53	±	*0.65*	Large	***most likely*** ↓	***@99%***	0.001
		+ 3.5 h	0.69	±	*1.25*	-0.64	±	*0.61*	Moderate	*likely* ↓	*@90%*	0.087
		+ 4.0 h	0.68	±	*1.14*	-0.67	±	*0.35*	Moderate	***very likely*** ↓	***@99%***	0.003
		+ 7.0 h	0.65	±	*1.13*	-0.73	±	*0.33*	Moderate	***most likely*** ↓	***@99%***	0.001
	10	+ 0.5 h	0.50	±	*1.19*	-1.20	±	*0.65*	Large	***very likely*** ↓	***@99%***	0.006
		+ 3.5 h	0.75	±	*1.28*	-0.48	±	*0.61*	Small	*likely* ↓	*@90%*	0.186
		+ 4.0 h	0.86	±	*1.17*	-0.27	±	*0.35*	Small	*possibly* ↓	*@90%*	0.197
		+ 7.0 h	0.96	±	*1.19*	-0.07	±	*0.33*	Trivial		*unclear*	0.731
END-RES	1	+ 0.5 h	0.32	±	*1.08*	-1.98	±	*0.45*	Large	***most likely*** ↓	***@99%***	0.000
		+ 3.5 h	0.73	±	*1.16*	-0.53	±	*0.37*	Small	***likely*** ↓	***@99%***	0.025
		+ 4.0 h	0.34	±	*1.09*	-1.85	±	*0.46*	Large	***most likely*** ↓	***@99%***	0.000
		+ 7.0 h	0.90	±	*1.22*	-0.19	±	*0.42*	Trivial		*unclear*	0.444
	10	+ 0.5 h	0.39	±	*1.10*	-1.60	±	*0.45*	Large	***most likely*** ↓	***@99%***	0.000
		+ 3.5 h	0.94	±	*1.21*	-0.10	±	*0.37*	Trivial		*unclear*	0.637
		+ 4.0 h	0.66	±	*1.18*	-0.71	±	*0.46*	Moderate	***very likely*** ↓	***@99%***	0.015
		+ 7.0 h	1.35	±	*1.34*	0.52	±	*0.42*	Small	***likely*** ↑	***@99%***	0.047
RES-END	1	+ 0.5 h	0.34	±	*1.08*	-1.84	±	*0.42*	Large	***most likely*** ↓	***@99%***	0.000
		+ 3.5 h	0.62	±	*1.22*	-0.81	±	*0.60*	Moderate	***very likely*** ↓	***@99%***	0.030
		+ 4.0 h	0.23	±	*1.08*	-2.50	±	*0.59*	Very large	***most likely*** ↓	***@99%***	0.000
		+ 7.0 h	0.62	±	*1.16*	-0.82	±	*0.45*	Moderate	***very likely*** ↓	***@99%***	0.005
	10	+ 0.5 h	0.56	±	*1.14*	-1.00	±	*0.42*	Moderate	***most likely*** ↓	***@99%***	0.001
		+ 3.5 h	0.86	±	*1.31*	-0.26	±	*0.60*	Small		*unclear*	0.454
		+ 4.0 h	0.43	±	*1.15*	-1.46	±	*0.59*	Large	***most likely*** ↓	***@99%***	0.001
		+ 7.0 h	0.92	±	*1.24*	-0.14	±	*0.45*	Trivial		*unclear*	0.586

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑ & ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-eEF2

Group	Week	Time	Fold change from PRE mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
RES-Only	1	+ 0.5 h	1.02	±	*1.25*	0.02	±	*0.35*	Trivial		*unclear*	0.914
		+ 3.5 h	0.43	±	*1.22*	-1.20	±	*0.69*	Large	***very likely*** ↓	***@99%***	0.009
		+ 4.0 h	0.62	±	*1.19*	-0.68	±	*0.42*	Moderate	***very likely*** ↓	***@99%***	0.012
		+ 7.0 h	0.32	±	*1.22*	-1.64	±	*0.93*	Large	***very likely*** ↓	***@99%***	0.009
	10	+ 0.5 h	1.56	±	*1.38*	0.64	±	*0.35*	Moderate	***very likely*** ↑	***@99%***	0.004
		+ 3.5 h	1.26	±	*1.63*	0.33	±	*0.69*	Small		*unclear*	0.409
		+ 4.0 h	1.12	±	*1.34*	0.17	±	*0.42*	Trivial		*unclear*	0.497
		+ 7.0 h	0.58	±	*1.41*	-0.78	±	*0.93*	Moderate	*likely* ↓	*@90%*	0.163
END-RES	1	+ 0.5 h	1.17	±	*1.54*	0.23	±	*0.64*	Small		*unclear*	0.534
		+ 3.5 h	0.52	±	*1.33*	-0.94	±	*0.86*	Moderate	*likely* ↓	*@90%*	0.075
		+ 4.0 h	1.07	±	*1.67*	0.09	±	*0.85*	Trivial		*unclear*	0.848
		+ 7.0 h	0.21	±	*1.22*	-2.25	±	*1.32*	Very large	***very likely*** ↓	***@99%***	0.010
	10	+ 0.5 h	2.47	±	*2.14*	1.30	±	*0.64*	large	***very likely*** ↑	***@99%***	0.004
		+ 3.5 h	1.51	±	*1.96*	0.59	±	*0.86*	Small		*unclear*	0.247
		+ 4.0 h	1.59	±	*2.00*	0.66	±	*0.85*	Moderate	*likely* ↑	*@90%*	0.190
		+ 7.0 h	0.65	±	*1.68*	-0.62	±	*1.32*	Moderate		*unclear*	0.417
RES-END	1	+ 0.5 h	1.03	±	*1.27*	0.05	±	*0.37*	Trivial		*unclear*	0.832
		+ 3.5 h	0.71	±	*1.19*	-0.49	±	*0.37*	Small	***likely*** ↓	***@99%***	0.032
		+ 4.0 h	0.99	±	*1.51*	-0.01	±	*0.71*	Trivial		*unclear*	0.977
		+ 7.0 h	0.26	±	*1.19*	-1.95	±	*0.98*	Large	***most likely*** ↓	***@99%***	0.004
	10	+ 0.5 h	0.90	±	*1.24*	-0.15	±	*0.37*	Trivial		*unclear*	0.503
		+ 3.5 h	0.96	±	*1.25*	-0.06	±	*0.37*	Trivial		*unclear*	0.769
		+ 4.0 h	1.23	±	*1.63*	0.29	±	*0.71*	Small		*unclear*	0.474
		+ 7.0 h	0.88	±	*1.65*	-0.19	±	*0.98*	Trivial		*unclear*	0.744

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓= increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-rpS6

Group	Week	Time	Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
			mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	1	+ 0.5 h	0.53	±	*1.32*	-0.75	±	*0.67*	Moderate	*likely* ↓	*@90%*	0.066
		+ 3.5 h	0.94	±	*1.76*	-0.08	±	*0.87*	Trivial		*unclear*	0.883
		+ 4.0 h	1.32	±	*2.09*	0.33	±	*0.88*	Small		*unclear*	0.533
		+ 7.0 h	0.80	±	*1.48*	-0.26	±	*0.67*	Small		*unclear*	0.515
	10	+ 0.5 h	1.37	±	*1.83*	0.37	±	*0.67*	Small		*unclear*	0.354
		+ 3.5 h	1.81	±	*2.46*	0.70	±	*0.87*	Moderate	*likely* ↑	*@90%*	0.184
		+ 4.0 h	1.87	±	*2.54*	0.74	±	*0.88*	Moderate	*likely* ↑	*@90%*	0.165
		+ 7.0 h	1.81	±	*2.09*	0.70	±	*0.67*	Moderate	*likely* ↑	*@90%*	0.087
END-RES	1	+ 0.5 h	1.09	±	*1.72*	0.10	±	*0.73*	Trivial		*unclear*	0.814
		+ 3.5 h	1.56	±	*2.06*	0.53	±	*0.75*	Small		*unclear*	0.239
		+ 4.0 h	1.63	±	*2.25*	0.58	±	*0.83*	Small		*unclear*	0.248
		+ 7.0 h	2.55	±	*3.09*	1.10	±	*0.88*	Moderate	*very likely* ↑	*@90%*	0.043
	10	+ 0.5 h	1.09	±	*1.72*	0.10	±	*0.73*	Trivial		*unclear*	0.818
		+ 3.5 h	1.55	±	*2.05*	0.52	±	*0.75*	Small		*unclear*	0.249
		+ 4.0 h	1.51	±	*2.16*	0.49	±	*0.83*	Small		*unclear*	0.326
		+ 7.0 h	2.60	±	*3.14*	1.13	±	*0.88*	Moderate	*very likely* ↑	*@90%*	0.039
RES-END	1	+ 0.5 h	0.52	±	*1.49*	-0.78	±	*1.00*	Moderate		*unclear*	0.192
		+ 3.5 h	1.10	±	*2.24*	0.11	±	*1.14*	Trivial		*unclear*	0.863
		+ 4.0 h	1.23	±	*2.02*	0.24	±	*0.89*	Small		*unclear*	0.650
		+ 7.0 h	1.08	±	*1.83*	0.10	±	*0.83*	Trivial		*unclear*	0.845
	10	+ 0.5 h	0.85	±	*1.81*	-0.19	±	*1.00*	Trivial		*unclear*	0.741
		+ 3.5 h	1.68	±	*2.89*	0.61	±	*1.14*	Moderate		*unclear*	0.364
		+ 4.0 h	1.63	±	*2.35*	0.57	±	*0.89*	Small		*unclear*	0.284
		+ 7.0 h	1.44	±	*2.10*	0.43	±	*0.83*	Small		*unclear*	0.383

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-AMPKα

Group	Week	Time	Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓		Threshold for clear effect	*P* value
			mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude				
RES-Only	1	+ 0.5 h	0.73	±	*1.32*	-0.42	±	*0.58*	Small	*possibly*	↓	*@90%*	0.226
		+ 3.5 h	0.36	±	*1.14*	-1.39	±	*0.51*	Large	***most likely***	↓	***@99%***	0.000
		+ 4.0 h	0.71	±	*1.36*	-0.46	±	*0.66*	Small	*likely*	↓	*@90%*	0.238
		+ 7.0 h	1.28	±	*1.62*	0.34	±	*0.63*	Small			*unclear*	0.364
	10	+ 0.5 h	1.42	±	*1.63*	0.48	±	*0.58*	Small	*likely*	↑	*@90%*	0.172
		+ 3.5 h	1.18	±	*1.45*	0.22	±	*0.51*	Small			*unclear*	0.474
		+ 4.0 h	1.18	±	*1.59*	0.22	±	*0.66*	Small			*unclear*	0.566
		+ 7.0 h	1.91	±	*1.92*	0.88	±	*0.63*	Moderate	***very likely***	↑	***@99%***	0.027
END-RES	1	+ 0.5 h	1.31	±	*1.49*	0.37	±	*0.49*	Small	*possibly*	↑	*@90%*	0.218
		+ 3.5 h	0.95	±	*1.35*	-0.07	±	*0.49*	Trivial			*unclear*	0.814
		+ 4.0 h	2.13	±	*1.77*	1.03	±	*0.48*	Moderate	***most likely***	↑	***@99%***	0.001
		+ 7.0 h	1.59	±	*1.69*	0.64	±	*0.57*	Moderate	*likely*	↑	*@90%*	0.069
	10	+ 0.5 h	1.59	±	*1.59*	0.63	±	*0.49*	Moderate	***likely***	↑	***@99%***	0.038
		+ 3.5 h	1.30	±	*1.48*	0.35	±	*0.49*	Small	*possibly*	↑	*@90%*	0.231
		+ 4.0 h	1.95	±	*1.71*	0.91	±	*0.48*	Moderate	***very likely***	↑	***@99%***	0.003
		+ 7.0 h	2.02	±	*1.88*	0.96	±	*0.57*	Moderate	***very likely***	↑	***@99%***	0.008
RES-END	1	+ 0.5 h	1.31	±	*1.51*	0.37	±	*0.51*	Small	*possibly*	↑	*@90%*	0.234
		+ 3.5 h	0.43	±	*1.17*	-1.16	±	*0.51*	Large	***most likely***	↓	***@99%***	0.000
		+ 4.0 h	1.13	±	*1.43*	0.16	±	*0.51*	Trivial			*unclear*	0.597
		+ 7.0 h	1.42	±	*1.55*	0.48	±	*0.51*	Small	*likely*	↑	*@90%*	0.124
	10	+ 0.5 h	1.44	±	*1.56*	0.50	±	*0.51*	Small	*likely*	↑	*@90%*	0.109
		+ 3.5 h	0.99	±	*1.38*	-0.02	±	*0.51*	Trivial			*unclear*	0.961
		+ 4.0 h	1.80	±	*1.69*	0.80	±	*0.51*	Moderate	***very likely***	↑	***@99%***	0.012
		+ 7.0 h	1.53	±	*1.59*	0.58	±	*0.51*	Small	*likely*	↑	*@90%*	0.065

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-p53

			Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect	Threshold for clear	
Group	**Week**	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude	**is substantially ↑/↓**	**effect**	***P* value**
RES-Only	1	+ 0.5 h	0.73	±	*1.32*	-0.28	±	*0.37*	Small	*possibly* ↓	*@90%*	0.214
		+ 3.5 h	0.37	±	*1.16*	-0.86	±	*0.37*	Moderate	***most likely*** ↓	***@99%***	0.000
		+ 4.0 h	0.63	±	*1.29*	-0.40	±	*0.39*	Small	*likely* ↓	*@90%*	0.091
		+ 7.0 h	1.04	±	*1.46*	0.03	±	*0.37*	Trivial		*unclear*	0.887
	10	+ 0.5 h	1.36	±	*1.60*	0.27	±	*0.37*	Small	*possibly* ↑	*@90%*	0.230
		+ 3.5 h	1.23	±	*1.54*	0.18	±	*0.37*	Trivial	*possibly* ↑	*@90%*	0.427
		+ 4.0 h	1.35	±	*1.62*	0.26	±	*0.39*	Small	*possibly* ↑	*@90%*	0.259
		+ 7.0 h	2.31	±	*2.02*	0.72	±	*0.37*	Moderate	***very likely*** ↑	***@99%***	0.002
END-RES	1	+ 0.5 h	1.17	±	*1.48*	0.13	±	*0.35*	Trivial		*unclear*	0.531
		+ 3.5 h	0.92	±	*1.38*	-0.07	±	*0.35*	Trivial		*unclear*	0.733
		+ 4.0 h	2.25	±	*1.93*	0.70	±	*0.35*	Moderate	***very likely*** ↑	***@99%***	0.001
		+ 7.0 h	1.75	±	*1.74*	0.48	±	*0.36*	Small	***likely*** ↑	***@99%***	0.028
	10	+ 0.5 h	1.61	±	*1.67*	0.41	±	*0.35*	Small	***likely*** ↑	***@99%***	0.052
		+ 3.5 h	1.11	±	*1.46*	0.09	±	*0.35*	Trivial		*unclear*	0.675
		+ 4.0 h	1.67	±	*1.69*	0.44	±	*0.35*	Small	***likely*** ↑	***@99%***	0.036
		+ 7.0 h	1.89	±	*1.80*	0.55	±	*0.36*	Small	***likely*** ↑	***@99%***	0.014
RES-END	1	+ 0.5 h	1.32	±	*1.58*	0.24	±	*0.37*	Small	*possibly* ↑	*@90%*	0.279
		+ 3.5 h	0.48	±	*1.21*	-0.64	±	*0.37*	Moderate	***very likely*** ↓	***@99%***	0.005
		+ 4.0 h	1.21	±	*1.53*	0.16	±	*0.37*	Trivial		*unclear*	0.467
		+ 7.0 h	1.49	±	*1.66*	0.35	±	*0.37*	Small	*possibly* ↑	*@90%*	0.122
	10	+ 0.5 h	1.29	±	*1.57*	0.22	±	*0.37*	Small	*possibly* ↑	*@90%*	0.333
		+ 3.5 h	1.01	±	*1.45*	0.01	±	*0.37*	Trivial		*unclear*	0.960
		+ 4.0 h	1.52	±	*1.67*	0.36	±	*0.37*	Small	*likely* ↑	*@90%*	0.105
		+ 7.0 h	1.27	±	*1.56*	0.21	±	*0.37*	Small	*possibly* ↑	*@90%*	0.356

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑& ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-TSC2

Group	Week	Time	Fold change from PRE			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* value
			mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	1	+ 0.5 h	1.47	±	*4.85*	0.72	±	*3.17*	Moderate		*unclear*	0.386
		+ 3.5 h	1.07	±	*1.22*	0.13	±	*0.38*	Trivial		*unclear*	0.549
		+ 4.0 h	2.40	±	*152.74*	1.64	±	*9.08*	Large		*unclear*	0.458
		+ 7.0 h	0.26	±	*1.29*	-2.53	±	*1.78*	Very large	*very likely* ↓	*@90%*	0.059
	10	+ 0.5 h	1.40	±	*4.66*	0.63	±	*3.17*	Moderate		*unclear*	0.430
		+ 3.5 h	1.08	±	*1.22*	0.14	±	*0.38*	Trivial		*unclear*	0.533
		+ 4.0 h	2.87	±	*183.78*	1.98	±	*9.09*	Large		*unclear*	0.400
		+ 7.0 h	0.47	±	*1.55*	-1.43	±	*1.87*	Large		*unclear*	0.145
END-RES	1	+ 0.5 h	1.04	±	*1.34*	0.07	±	*0.61*	Trivial		*unclear*	0.840
		+ 3.5 h	0.84	±	*1.27*	-0.32	±	*0.59*	Small		*unclear*	0.360
		+ 4.0 h	0.50	±	*1.35*	-1.32	±	*1.25*	Large	*likely* ↓	*@90%*	0.083
		+ 7.0 h	0.10	±	*1.15*	-4.31	±	*2.28*	Extremely large	***most likely*** ↓	***@99%***	0.004
	10	+ 0.5 h	0.51	±	*1.17*	-1.28	±	*0.61*	Large	***most likely*** ↓	***@99%***	0.002
		+ 3.5 h	0.80	±	*1.26*	-0.41	±	*0.59*	Small	*possibly* ↓	*@90%*	0.248
		+ 4.0 h	0.58	±	*1.41*	-1.03	±	*1.25*	Moderate		*unclear*	0.167
		+ 7.0 h	0.05	±	*1.08*	-5.53	±	*2.28*	Extremely large	***most likely*** ↓	***@99%***	0.001
RES-END	1	+ 0.5 h	0.91	±	*1.27*	-0.18	±	*0.55*	Trivial		*unclear*	0.574
		+ 3.5 h	0.93	±	*1.28*	-0.13	±	*0.54*	Trivial		*unclear*	0.689
		+ 4.0 h	0.51	±	*1.29*	-1.25	±	*1.02*	Large	*very likely* ↓	*@90%*	0.048
		+ 7.0 h	0.16	±	*1.19*	-3.49	±	*1.96*	Very large	***very likely*** ↓	***@99%***	0.007
	10	+ 0.5 h	0.67	±	*1.20*	-0.74	±	*0.55*	Moderate	***likely*** ↓	***@99%***	0.032
		+ 3.5 h	0.84	±	*1.25*	-0.33	±	*0.54*	Small		*unclear*	0.301
		+ 4.0 h	0.54	±	*1.31*	-1.16	±	*1.02*	Moderate	*likely* ↓	*@90%*	0.066
		+ 7.0 h	0.45	±	*1.56*	-1.50	±	*1.96*	Large		*unclear*	0.198

90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);

Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.

Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely; ↑ & ↓ = increased & decreased expression;

Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits

***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

Between-group differences in exercise-induced changes

Muscle glycogen

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	0.85	±	*1.22*	-0.78	±	*1.22*	Moderate		*unclear*	0.286
		RES-Only vs RES-END	1.04	±	*1.26*	0.17	±	*1.17*	Trivial		*unclear*	0.808
		END-RES vs RES-END	1.23	±	*1.32*	0.95	±	*1.20*	Moderate		*unclear*	0.191
	+3.5 h	RES-Only vs END-RES	0.74	±	*1.15*	-1.40	±	*0.94*	Large	***very likely*** ↓	***@99%***	0.015
		RES-Only vs RES-END	0.97	±	*1.20*	-0.13	±	*0.96*	Trivial		*unclear*	0.818
		END-RES vs RES-END	1.31	±	*1.27*	1.26	±	*0.94*	Large	*very likely* ↑	*@90%*	0.028
	+4 h	RES-Only vs END-RES	0.62	±	*1.19*	-2.21	±	*1.43*	Very Large	***very likely*** ↓	***@99%***	0.013
		RES-Only vs RES-END	0.61	±	*1.19*	-2.32	±	*1.41*	Very Large	***very likely*** ↓	***@99%***	0.008
		END-RES vs RES-END	0.98	±	*1.32*	-0.11	±	*1.50*	Trivial		*unclear*	0.899
	+7 h	RES-Only vs END-RES	0.73	±	*1.16*	-1.49	±	*0.99*	Large	***very likely*** ↓	***@99%***	0.015
		RES-Only vs RES-END	0.80	±	*1.20*	-1.03	±	*1.13*	Moderate	*likely* ↓	*@90%*	0.134
		END-RES vs RES-END	1.10	±	*1.27*	0.46	±	*1.15*	Small		*unclear*	0.504
10	+0.5 h	RES-Only vs END-RES	0.91	±	*1.24*	-0.45	±	*1.22*	Small		*unclear*	0.536
		RES-Only vs RES-END	0.96	±	*1.24*	-0.18	±	*1.17*	Trivial		*unclear*	0.794
		END-RES vs RES-END	1.06	±	*1.28*	0.27	±	*1.20*	Small		*unclear*	0.709
	+3.5 h	RES-Only vs END-RES	0.95	±	*1.19*	-0.22	±	*0.94*	Small		*unclear*	0.692
		RES-Only vs RES-END	0.97	±	*1.20*	-0.16	±	*0.96*	Trivial		*unclear*	0.786
		END-RES vs RES-END	1.02	±	*1.21*	0.07	±	*0.94*	Trivial		*unclear*	0.904
	+4 h	RES-Only vs END-RES	0.95	±	*1.30*	-0.23	±	*1.43*	Small		*unclear*	0.786
		RES-Only vs RES-END	0.87	±	*1.27*	-0.64	±	*1.41*	Moderate		*unclear*	0.452
		END-RES vs RES-END	0.92	±	*1.30*	-0.40	±	*1.50*	Small		*unclear*	0.653
	+7 h	RES-Only vs END-RES	0.71	±	*1.15*	-1.62	±	*0.99*	Large	***very likely*** ↓	***@99%***	0.008
		RES-Only vs RES-END	0.80	±	*1.20*	-1.03	±	*1.13*	Moderate	*likely* ↓	*@90%*	0.132
		END-RES vs RES-END	1.13	±	*1.28*	0.59	±	*1.15*	Small		*unclear*	0.396

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

PGC-1α

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.81	±	*2.10*	0.88	±	*0.86*	Moderate	*likely* ↑	*@90%*	0.092
		RES-Only vs RES-END	1.37	±	*1.87*	0.47	±	*0.88*	Small		*unclear*	0.376
		END-RES vs RES-END	0.76	±	*1.46*	-0.41	±	*0.86*	Small		*unclear*	0.431
	+3.5 h	RES-Only vs END-RES	1.18	±	*1.89*	0.25	±	*1.04*	Small		*unclear*	0.689
		RES-Only vs RES-END	0.48	±	*1.40*	-1.09	±	*1.11*	Moderate	*likely* ↓	*@90%*	0.108
		END-RES vs RES-END	0.41	±	*1.32*	-1.34	±	*1.08*	Large	*very likely* ↓	*@90%*	0.043
	+4 h	RES-Only vs END-RES	2.79	±	*2.94*	1.53	±	*0.96*	Large	***very likely*** ↑	***@99%***	0.011
		RES-Only vs RES-END	0.86	±	*1.61*	-0.23	±	*0.99*	Small		*unclear*	0.697
		END-RES vs RES-END	0.31	±	*1.19*	-1.76	±	*0.86*	Large	***most likely*** ↓	***@99%***	0.001
	+7 h	RES-Only vs END-RES	1.58	±	*2.18*	0.68	±	*1.02*	Moderate		*unclear*	0.267
		RES-Only vs RES-END	1.13	±	*1.94*	0.19	±	*1.12*	Trivial		*unclear*	0.779
		END-RES vs RES-END	0.72	±	*1.52*	-0.50	±	*1.01*	Small		*unclear*	0.411
10	+0.5 h	RES-Only vs END-RES	0.98	±	*1.60*	-0.03	±	*0.86*	Trivial		*unclear*	0.956
		RES-Only vs RES-END	1.34	±	*1.84*	0.43	±	*0.88*	Small		*unclear*	0.419
		END-RES vs RES-END	1.36	±	*1.83*	0.46	±	*0.86*	Small		*unclear*	0.375
	+3.5 h	RES-Only vs END-RES	1.38	±	*2.04*	0.47	±	*1.04*	Small		*unclear*	0.447
		RES-Only vs RES-END	0.70	±	*1.57*	-0.54	±	*1.11*	Small		*unclear*	0.418
		END-RES vs RES-END	0.51	±	*1.40*	-1.01	±	*1.08*	Moderate	*likely* ↓	*@90%*	0.120
	+4 h	RES-Only vs END-RES	1.12	±	*1.78*	0.17	±	*0.96*	Trivial		*unclear*	0.768
		RES-Only vs RES-END	0.70	±	*1.50*	-0.52	±	*0.99*	Small		*unclear*	0.378
		END-RES vs RES-END	0.63	±	*1.38*	-0.69	±	*0.86*	Moderate	*likely* ↓	*@90%*	0.182
	+7 h	RES-Only vs END-RES	1.60	±	*2.19*	0.70	±	*1.02*	Moderate		*unclear*	0.254
		RES-Only vs RES-END	2.98	±	*3.45*	1.62	±	*1.12*	Large	***very likely*** ↑	***@99%***	0.019
		END-RES vs RES-END	1.86	±	*2.36*	0.92	±	*1.01*	Moderate	*likely* ↑	*@90%*	0.131

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

MuRF1

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	0.83	±	*1.45*	-0.24	±	*0.68*	Small		*unclear*	0.560
		RES-Only vs RES-END	0.78	±	*1.44*	-0.33	±	*0.70*	Small		*unclear*	0.433
		END-RES vs RES-END	0.93	±	*1.45*	-0.09	±	*0.61*	Trivial		*unclear*	0.803
	+3.5 h	RES-Only vs END-RES	1.65	±	*1.89*	0.66	±	*0.67*	Moderate	*likely* ↑	*@90%*	0.108
		RES-Only vs RES-END	0.79	±	*1.53*	-0.31	±	*0.83*	Small		*unclear*	0.530
		END-RES vs RES-END	0.48	±	*1.31*	-0.97	±	*0.80*	Moderate	*likely* ↓	*@90%*	0.050
	+4 h	RES-Only vs END-RES	3.09	±	*2.78*	1.47	±	*0.72*	Large	***most likely*** ↑	***@99%***	0.001
		RES-Only vs RES-END	0.97	±	*1.57*	-0.04	±	*0.73*	Trivial		*unclear*	0.926
		END-RES vs RES-END	0.31	±	*1.15*	-1.51	±	*0.61*	Large	***most likely*** ↓	***@99%***	0.000
	+7 h	RES-Only vs END-RES	1.33	±	*1.86*	0.38	±	*0.80*	Small		*unclear*	0.432
		RES-Only vs RES-END	2.88	±	*2.80*	1.38	±	*0.77*	Large	***very likely*** ↑	***@99%***	0.004
		END-RES vs RES-END	2.16	±	*2.12*	1.01	±	*0.65*	Moderate	***very likely*** ↑	***@99%***	0.012
10	+0.5 h	RES-Only vs END-RES	1.18	±	*1.64*	0.21	±	*0.68*	Small		*unclear*	0.600
		RES-Only vs RES-END	1.03	±	*1.58*	0.04	±	*0.70*	Trivial		*unclear*	0.916
		END-RES vs RES-END	0.88	±	*1.42*	-0.17	±	*0.61*	Trivial		*unclear*	0.641
	+3.5 h	RES-Only vs END-RES	1.57	±	*1.85*	0.59	±	*0.67*	Small	*likely* ↑	*@90%*	0.149
		RES-Only vs RES-END	0.72	±	*1.49*	-0.43	±	*0.83*	Small		*unclear*	0.388
		END-RES vs RES-END	0.46	±	*1.30*	-1.02	±	*0.80*	Moderate	*very likely* ↓	*@90%*	0.040
	+4 h	RES-Only vs END-RES	1.42	±	*1.82*	0.46	±	*0.72*	Small		*unclear*	0.285
		RES-Only vs RES-END	0.57	±	*1.33*	-0.73	±	*0.73*	Moderate	*likely* ↓	*@90%*	0.097
		END-RES vs RES-END	0.40	±	*1.19*	-1.19	±	*0.61*	Moderate	***most likely*** ↓	***@99%***	0.002
	+7 h	RES-Only vs END-RES	1.69	±	*2.09*	0.68	±	*0.80*	Moderate	*likely* ↑	*@90%*	0.157
		RES-Only vs RES-END	3.28	±	*3.05*	1.55	±	*0.77*	Large	***most likely*** ↑	***@99%***	0.002
		END-RES vs RES-END	1.94	±	*2.01*	0.87	±	*0.65*	Moderate	***very likely*** ↑	***@99%***	0.030

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

MAFbx

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.36	±	*1.75*	0.36	±	*0.61*	Small		*unclear*	0.329
		RES-Only vs RES-END	1.18	±	*1.63*	0.19	±	*0.58*	Trivial		*unclear*	0.581
		END-RES vs RES-END	0.87	±	*1.44*	-0.16	±	*0.57*	Trivial		*unclear*	0.633
	+3.5 h	RES-Only vs END-RES	3.28	±	*3.49*	1.37	±	*0.81*	Large	***very likely*** ↑	***@99%***	0.007
		RES-Only vs RES-END	0.94	±	*1.64*	-0.08	±	*0.74*	Trivial		*unclear*	0.865
		END-RES vs RES-END	0.29	±	*1.19*	-1.44	±	*0.72*	Large	***most likely*** ↓	***@99%***	0.002
	+4 h	RES-Only vs END-RES	6.35	±	*5.23*	2.13	±	*0.72*	Very large	***most likely*** ↑	***@99%***	0.000
		RES-Only vs RES-END	0.99	±	*1.58*	-0.01	±	*0.64*	Trivial		*unclear*	0.986
		END-RES vs RES-END	0.16	±	*1.09*	-2.13	±	*0.63*	Very large	***most likely*** ↓	***@99%***	0.000
	+7 h	RES-Only vs END-RES	3.36	±	*3.68*	1.39	±	*0.84*	Large	***very likely*** ↑	***@99%***	0.008
		RES-Only vs RES-END	1.86	±	*2.55*	0.72	±	*0.87*	Moderate	*likely* ↑	*@90%*	0.175
		END-RES vs RES-END	0.56	±	*1.38*	-0.68	±	*0.74*	Moderate	*likely* ↓	*@90%*	0.132
10	+0.5 h	RES-Only vs END-RES	0.84	±	*1.46*	-0.20	±	*0.61*	Small		*unclear*	0.581
		RES-Only vs RES-END	1.23	±	*1.65*	0.24	±	*0.58*	Small		*unclear*	0.492
		END-RES vs RES-END	1.47	±	*1.75*	0.44	±	*0.57*	Small	*likely* ↑	*@90%*	0.196
	+3.5 h	RES-Only vs END-RES	2.27	±	*2.72*	0.94	±	*0.81*	Moderate	*likely* ↑	*@90%*	0.056
		RES-Only vs RES-END	0.86	±	*1.59*	-0.18	±	*0.74*	Trivial		*unclear*	0.682
		END-RES vs RES-END	0.38	±	*1.25*	-1.13	±	*0.72*	Moderate	*very likely* ↓	*@99%*	0.012
	+4 h	RES-Only vs END-RES	2.13	±	*2.42*	0.87	±	*0.72*	Moderate	*likely* ↑	*@90%*	0.048
		RES-Only vs RES-END	0.64	±	*1.38*	-0.51	±	*0.64*	Small	*likely* ↓	*@90%*	0.192
		END-RES vs RES-END	0.30	±	*1.18*	-1.38	±	*0.63*	Large	***most likely*** ↓	***@99%***	0.001
	+7 h	RES-Only vs END-RES	1.52	±	*2.21*	0.48	±	*0.84*	Small		*unclear*	0.340
		RES-Only vs RES-END	2.29	±	*2.91*	0.95	±	*0.87*	Moderate	*likely* ↑	*@90%*	0.074
		END-RES vs RES-END	1.51	±	*2.04*	0.47	±	*0.74*	Small		*unclear*	0.291

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

Myostatin

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.77	±	*2.67*	0.55	±	*0.81*	Small		*unclear*	0.259
		RES-Only vs RES-END	2.10	±	*3.03*	0.72	±	*0.83*	Moderate	*likely* ↑	*@90%*	0.153
		END-RES vs RES-END	1.19	±	*1.90*	0.16	±	*0.68*	Trivial		*unclear*	0.687
	+3.5 h	RES-Only vs END-RES	0.73	±	*1.56*	-0.31	±	*0.68*	Small		*unclear*	0.453
		RES-Only vs RES-END	1.11	±	*1.89*	0.10	±	*0.71*	Trivial		*unclear*	0.814
		END-RES vs RES-END	1.53	±	*2.21*	0.41	±	*0.70*	Small		*unclear*	0.330
	+4 h	RES-Only vs END-RES	0.72	±	*1.55*	-0.32	±	*0.68*	Small		*unclear*	0.438
		RES-Only vs RES-END	1.06	±	*1.89*	0.06	±	*0.74*	Trivial		*unclear*	0.894
		END-RES vs RES-END	1.48	±	*2.20*	0.38	±	*0.72*	Small		*unclear*	0.385
	+7 h	RES-Only vs END-RES	1.22	±	*2.09*	0.19	±	*0.78*	Trivial		*unclear*	0.680
		RES-Only vs RES-END	0.54	±	*1.48*	-0.60	±	*0.77*	Moderate	*likely* ↓	*@90%*	0.197
		END-RES vs RES-END	0.44	±	*1.35*	-0.79	±	*0.70*	Moderate	*likely* ↓	*@90%*	0.064
10	+0.5 h	RES-Only vs END-RES	1.40	±	*2.32*	0.33	±	*0.81*	Small		*unclear*	0.504
		RES-Only vs RES-END	1.24	±	*2.20*	0.21	±	*0.83*	Small		*unclear*	0.675
		END-RES vs RES-END	0.89	±	*1.67*	-0.12	±	*0.68*	Trivial		*unclear*	0.774
	+3.5 h	RES-Only vs END-RES	1.27	±	*1.98*	0.23	±	*0.68*	Small		*unclear*	0.580
		RES-Only vs RES-END	1.63	±	*2.31*	0.47	±	*0.71*	Small		*unclear*	0.275
		END-RES vs RES-END	1.28	±	*2.01*	0.24	±	*0.70*	Small		*unclear*	0.566
	+4 h	RES-Only vs END-RES	0.89	±	*1.68*	-0.11	±	*0.68*	Trivial		*unclear*	0.790
		RES-Only vs RES-END	1.30	±	*2.09*	0.25	±	*0.74*	Small		*unclear*	0.567
		END-RES vs RES-END	1.46	±	*2.18*	0.36	±	*0.72*	Small		*unclear*	0.402
	+7 h	RES-Only vs END-RES	1.34	±	*2.20*	0.28	±	*0.78*	Small		*unclear*	0.547
		RES-Only vs RES-END	1.42	±	*2.25*	0.34	±	*0.77*	Small		*unclear*	0.469
		END-RES vs RES-END	1.06	±	*1.84*	0.05	±	*0.70*	Trivial		*unclear*	0.897

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

Mighty

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.22	±	*1.47*	0.40	±	*0.75*	Small		*unclear*	0.371
		RES-Only vs RES-END	1.26	±	*1.68*	0.46	±	*1.03*	Small		*unclear*	0.453
		END-RES vs RES-END	1.03	±	*1.49*	0.06	±	*0.91*	Trivial		*unclear*	0.909
	+3.5 h	RES-Only vs END-RES	0.81	±	*1.24*	-0.43	±	*0.57*	Small	*possibly* ↓	*@90%*	0.219
		RES-Only vs RES-END	0.73	±	*1.22*	-0.62	±	*0.60*	Moderate	*likely* ↓	*@90%*	0.088
		END-RES vs RES-END	0.91	±	*1.28*	-0.19	±	*0.59*	Trivial		*unclear*	0.587
	+4 h	RES-Only vs END-RES	0.93	±	*1.37*	-0.15	±	*0.77*	Trivial		*unclear*	0.746
		RES-Only vs RES-END	0.53	±	*1.27*	-1.26	±	*0.99*	Large	*very likely* ↓	*@90%*	0.037
		END-RES vs RES-END	0.57	±	*1.25*	-1.12	±	*0.84*	Moderate	*very likely* ↓	*@90%*	0.031
	+7 h	RES-Only vs END-RES	0.79	±	*1.30*	-0.46	±	*0.74*	Small		*unclear*	0.299
		RES-Only vs RES-END	0.55	±	*1.28*	-1.18	±	*0.98*	Moderate	*very likely* ↓	*@90%*	0.049
		END-RES vs RES-END	0.70	±	*1.31*	-0.72	±	*0.85*	Moderate	*likely* ↓	*@90%*	0.162
10	+0.5 h	RES-Only vs END-RES	1.31	±	*1.51*	0.54	±	*0.75*	Small		*unclear*	0.230
		RES-Only vs RES-END	1.26	±	*1.68*	0.45	±	*1.03*	Small		*unclear*	0.462
		END-RES vs RES-END	0.96	±	*1.45*	-0.09	±	*0.91*	Trivial		*unclear*	0.870
	+3.5 h	RES-Only vs END-RES	0.99	±	*1.29*	-0.02	±	*0.57*	Trivial		*unclear*	0.954
		RES-Only vs RES-END	1.02	±	*1.31*	0.05	±	*0.60*	Trivial		*unclear*	0.899
		END-RES vs RES-END	1.03	±	*1.31*	0.07	±	*0.59*	Trivial		*unclear*	0.854
	+4 h	RES-Only vs END-RES	0.79	±	*1.32*	-0.46	±	*0.77*	Small		*unclear*	0.315
		RES-Only vs RES-END	0.86	±	*1.44*	-0.30	±	*0.99*	Small		*unclear*	0.604
		END-RES vs RES-END	1.08	±	*1.47*	0.16	±	*0.84*	Trivial		*unclear*	0.751
	+7 h	RES-Only vs END-RES	0.99	±	*1.38*	-0.02	±	*0.74*	Trivial		*unclear*	0.968
		RES-Only vs RES-END	1.21	±	*1.62*	0.37	±	*0.98*	Small		*unclear*	0.526
		END-RES vs RES-END	1.22	±	*1.54*	0.39	±	*0.85*	Small		*unclear*	0.445

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-Akt^{Ser473}

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.56	±	*2.09*	0.42	±	*0.61*	Small	*possibly* ↑	*@90%*	0.253
		RES-Only vs RES-END	1.46	±	*2.06*	0.36	±	*0.63*	Small		*unclear*	0.345
		END-RES vs RES-END	0.94	±	*1.52*	-0.06	±	*0.50*	Trivial		*unclear*	0.833
	+3.5 h	RES-Only vs END-RES	1.97	±	*2.06*	0.64	±	*0.48*	Moderate	***likely*** ↑	***@99%***	0.030
		RES-Only vs RES-END	1.04	±	*1.57*	0.04	±	*0.50*	Trivial		*unclear*	0.904
		END-RES vs RES-END	0.53	±	*1.28*	-0.61	±	*0.48*	Moderate	***likely*** ↓	***@99%***	0.040
	+4 h	RES-Only vs END-RES	3.02	±	*2.80*	1.04	±	*0.53*	Moderate	***very likely*** ↑	***@99%***	0.002
		RES-Only vs RES-END	1.34	±	*1.83*	0.28	±	*0.55*	Small		*unclear*	0.400
		END-RES vs RES-END	0.44	±	*1.24*	-0.77	±	*0.49*	Moderate	***very likely*** ↓	***@99%***	0.012
	+7 h	RES-Only vs END-RES	1.86	±	*1.99*	0.58	±	*0.48*	Small	***likely*** ↑	***@99%***	0.048
		RES-Only vs RES-END	1.05	±	*1.77*	0.04	±	*0.65*	Trivial		*unclear*	0.911
		END-RES vs RES-END	0.56	±	*1.41*	-0.54	±	*0.63*	Small	*likely* ↓	*@90%*	0.158
10	+0.5 h	RES-Only vs END-RES	1.58	±	*2.10*	0.43	±	*0.61*	Small	*possibly* ↑	*@90%*	0.240
		RES-Only vs RES-END	1.23	±	*1.89*	0.20	±	*0.63*	Small		*unclear*	0.599
		END-RES vs RES-END	0.78	±	*1.43*	-0.23	±	*0.50*	Small		*unclear*	0.435
	+3.5 h	RES-Only vs END-RES	0.95	±	*1.51*	-0.05	±	*0.48*	Trivial		*unclear*	0.870
		RES-Only vs RES-END	0.67	±	*1.37*	-0.38	±	*0.50*	Small	*possibly* ↓	*@90%*	0.205
		END-RES vs RES-END	0.70	±	*1.38*	-0.33	±	*0.48*	Small	*possibly* ↓	*@90%*	0.254
	+4 h	RES-Only vs END-RES	1.52	±	*1.91*	0.40	±	*0.53*	Small	*possibly* ↑	*@90%*	0.219
		RES-Only vs RES-END	1.20	±	*1.74*	0.18	±	*0.55*	Trivial		*unclear*	0.595
		END-RES vs RES-END	0.79	±	*1.43*	-0.22	±	*0.49*	Small		*unclear*	0.452
	+7 h	RES-Only vs END-RES	0.92	±	*1.49*	-0.08	±	*0.48*	Trivial		*unclear*	0.796
		RES-Only vs RES-END	0.40	±	*1.30*	-0.86	±	*0.65*	Moderate	***very likely*** ↓	***@99%***	0.030
		END-RES vs RES-END	0.43	±	*1.31*	-0.79	±	*0.63*	Moderate	*likely* ↓	*@90%*	0.044

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-mTOR^{Ser2448}

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.60	±	*1.79*	0.71	±	*0.72*	Moderate	*likely* ↑	*@90%*	0.102
		RES-Only vs RES-END	0.98	±	*1.52*	-0.03	±	*0.77*	Trivial		*unclear*	0.956
		END-RES vs RES-END	0.61	±	*1.32*	-0.74	±	*0.76*	Moderate	*likely* ↓	*@90%*	0.111
	+3.5 h	RES-Only vs END-RES	1.09	±	*1.70*	0.14	±	*0.92*	Trivial		*unclear*	0.800
		RES-Only vs RES-END	1.03	±	*1.63*	0.04	±	*0.89*	Trivial		*unclear*	0.939
		END-RES vs RES-END	0.94	±	*1.50*	-0.10	±	*0.77*	Trivial		*unclear*	0.833
	+4 h	RES-Only vs END-RES	0.69	±	*1.33*	-0.58	±	*0.71*	Small	*likely* ↓	*@90%*	0.180
		RES-Only vs RES-END	0.42	±	*1.26*	-1.32	±	*0.88*	Large	***very likely*** ↓	***@99%***	0.016
		END-RES vs RES-END	0.61	±	*1.37*	-0.75	±	*0.86*	Moderate	*likely* ↓	*@90%*	0.152
	+7 h	RES-Only vs END-RES	1.10	±	*2.31*	0.14	±	*1.54*	Trivial		*unclear*	0.878
		RES-Only vs RES-END	1.25	±	*2.32*	0.34	±	*1.40*	Small		*unclear*	0.678
		END-RES vs RES-END	1.14	±	*2.29*	0.20	±	*1.47*	Small		*unclear*	0.817
10	+0.5 h	RES-Only vs END-RES	0.95	±	*1.46*	-0.08	±	*0.72*	Trivial		*unclear*	0.844
		RES-Only vs RES-END	0.90	±	*1.48*	-0.16	±	*0.77*	Trivial		*unclear*	0.725
		END-RES vs RES-END	0.95	±	*1.50*	-0.08	±	*0.76*	Trivial		*unclear*	0.864
	+3.5 h	RES-Only vs END-RES	0.92	±	*1.59*	-0.13	±	*0.92*	Trivial		*unclear*	0.809
		RES-Only vs RES-END	0.86	±	*1.53*	-0.24	±	*0.89*	Small		*unclear*	0.647
		END-RES vs RES-END	0.93	±	*1.49*	-0.11	±	*0.77*	Trivial		*unclear*	0.815
	+4 h	RES-Only vs END-RES	0.66	±	*1.32*	-0.62	±	*0.71*	Moderate	*likely* ↓	*@90%*	0.148
		RES-Only vs RES-END	0.51	±	*1.31*	-1.03	±	*0.88*	Moderate	*likely* ↓	*@90%*	0.055
		END-RES vs RES-END	0.76	±	*1.46*	-0.41	±	*0.86*	Small		*unclear*	0.424
	+7 h	RES-Only vs END-RES	0.52	±	*1.62*	-0.98	±	*1.54*	Moderate		*unclear*	0.286
		RES-Only vs RES-END	1.58	±	*2.67*	0.69	±	*1.40*	Moderate		*unclear*	0.404
		END-RES vs RES-END	3.02	±	*4.39*	1.68	±	*1.47*	Large	*very likely* ↑	*@90%*	0.062

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-4E-BP1$^{Thr37/46}$

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	0.77	±	*1.36*	-0.45	±	*0.77*	Small		*unclear*	0.332
		RES-Only vs RES-END	0.84	±	*1.38*	-0.31	±	*0.75*	Small		*unclear*	0.495
		END-RES vs RES-END	1.09	±	*1.39*	0.14	±	*0.60*	Trivial		*unclear*	0.693
	+3.5 h	RES-Only vs END-RES	1.06	±	*1.45*	0.10	±	*0.70*	Trivial		*unclear*	0.800
		RES-Only vs RES-END	0.90	±	*1.45*	-0.18	±	*0.83*	Trivial		*unclear*	0.720
		END-RES vs RES-END	0.85	±	*1.35*	-0.28	±	*0.69*	Small		*unclear*	0.492
	+4 h	RES-Only vs END-RES	0.50	±	*1.17*	-1.19	±	*0.56*	Moderate	***most likely*** ↓	***@99%***	0.001
		RES-Only vs RES-END	0.34	±	*1.14*	-1.83	±	*0.67*	Large	***most likely*** ↓	***@99%***	0.000
		END-RES vs RES-END	0.69	±	*1.30*	-0.64	±	*0.73*	Moderate	*likely* ↓	*@90%*	0.145
	+7 h	RES-Only vs END-RES	1.38	±	*1.43*	0.54	±	*0.52*	Small	*likely* ↑	*@90%*	0.086
		RES-Only vs RES-END	0.95	±	*1.31*	-0.08	±	*0.54*	Trivial		*unclear*	0.794
		END-RES vs RES-END	0.69	±	*1.25*	-0.63	±	*0.60*	Moderate	*likely* ↓	*@90%*	0.083
10	+0.5 h	RES-Only vs END-RES	0.79	±	*1.37*	-0.40	±	*0.77*	Small		*unclear*	0.382
		RES-Only vs RES-END	1.12	±	*1.51*	0.20	±	*0.75*	Small		*unclear*	0.654
		END-RES vs RES-END	1.42	±	*1.51*	0.60	±	*0.60*	Moderate	*likely* ↑	*@90%*	0.097
	+3.5 h	RES-Only vs END-RES	1.25	±	*1.53*	0.38	±	*0.70*	Small		*unclear*	0.361
		RES-Only vs RES-END	1.14	±	*1.57*	0.22	±	*0.83*	Small		*unclear*	0.653
		END-RES vs RES-END	0.91	±	*1.38*	-0.16	±	*0.69*	Trivial		*unclear*	0.696
	+4 h	RES-Only vs END-RES	0.77	±	*1.26*	-0.44	±	*0.56*	Small	*likely* ↓	*@90%*	0.190
		RES-Only vs RES-END	0.50	±	*1.20*	-1.19	±	*0.67*	Moderate	***very likely*** ↓	***@99%***	0.006
		END-RES vs RES-END	0.65	±	*1.28*	-0.75	±	*0.73*	Moderate	*likely* ↓	*@90%*	0.092
	+7 h	RES-Only vs END-RES	1.41	±	*1.43*	0.58	±	*0.52*	Small	*likely* ↑	*@90%*	0.067
		RES-Only vs RES-END	0.96	±	*1.31*	-0.08	±	*0.54*	Trivial		*unclear*	0.815
		END-RES vs RES-END	0.68	±	*1.24*	-0.66	±	*0.60*	Moderate	*likely* ↓	*@90%*	0.071

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-eEF2^{Thr56}

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.16	±	*1.59*	0.21	±	*0.71*	Small		*unclear*	0.620
		RES-Only vs RES-END	1.02	±	*1.37*	0.02	±	*0.51*	Trivial		*unclear*	0.935
		END-RES vs RES-END	0.88	±	*1.46*	-0.18	±	*0.72*	Trivial		*unclear*	0.667
	+3.5 h	RES-Only vs END-RES	1.20	±	*1.97*	0.26	±	*1.06*	Small		*unclear*	0.681
		RES-Only vs RES-END	1.64	±	*1.92*	0.71	±	*0.77*	Moderate	*likely* ↑	*@90%*	0.128
		END-RES vs RES-END	1.37	±	*1.94*	0.45	±	*0.92*	Small		*unclear*	0.407
	+4 h	RES-Only vs END-RES	1.72	±	*2.19*	0.77	±	*0.93*	Moderate	*likely* ↑	*@90%*	0.166
		RES-Only vs RES-END	1.59	±	*1.94*	0.67	±	*0.80*	Moderate	*likely* ↑	*@90%*	0.164
		END-RES vs RES-END	0.93	±	*1.75*	-0.10	±	*1.06*	Trivial		*unclear*	0.867
	+7 h	RES-Only vs END-RES	0.65	±	*1.86*	-0.61	±	*1.56*	Moderate		*unclear*	0.507
		RES-Only vs RES-END	0.81	±	*1.84*	-0.31	±	*1.30*	Small		*unclear*	0.687
		END-RES vs RES-END	1.23	±	*2.66*	0.30	±	*1.59*	Small		*unclear*	0.748
10	+0.5 h	RES-Only vs END-RES	1.58	±	*1.81*	0.66	±	*0.71*	Moderate	*likely* ↑	*@90%*	0.125
		RES-Only vs RES-END	0.58	±	*1.21*	-0.79	±	*0.51*	Moderate	***very likely*** ↓	***@99%***	0.013
		END-RES vs RES-END	0.37	±	*1.19*	-1.44	±	*0.72*	Large	***most likely*** ↓	***@99%***	0.002
	+3.5 h	RES-Only vs END-RES	1.20	±	*1.97*	0.26	±	*1.06*	Small		*unclear*	0.680
		RES-Only vs RES-END	0.76	±	*1.43*	-0.39	±	*0.77*	Small		*unclear*	0.385
		END-RES vs RES-END	0.63	±	*1.44*	-0.65	±	*0.92*	Moderate		*unclear*	0.234
	+4 h	RES-Only vs END-RES	1.41	±	*1.98*	0.50	±	*0.93*	Small		*unclear*	0.367
		RES-Only vs RES-END	1.09	±	*1.64*	0.12	±	*0.80*	Trivial		*unclear*	0.792
		END-RES vs RES-END	0.77	±	*1.62*	-0.37	±	*1.06*	Small		*unclear*	0.552
	+7 h	RES-Only vs END-RES	1.12	±	*2.47*	0.16	±	*1.56*	Trivial		*unclear*	0.864
		RES-Only vs RES-END	1.51	±	*2.58*	0.59	±	*1.30*	Small		*unclear*	0.443
		END-RES vs RES-END	1.36	±	*2.83*	0.44	±	*1.59*	Small		*unclear*	0.641

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-rpS6$^{Ser235/236}$

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	2.07	±	*2.93*	0.86	±	*0.98*	Moderate	*likely* ↑	*@90%*	0.150
		RES-Only vs RES-END	0.98	±	*2.16*	-0.03	±	*1.19*	Trivial		*unclear*	0.970
		END-RES vs RES-END	0.47	±	*1.58*	-0.88	±	*1.21*	Moderate		*unclear*	0.228
	+3.5 h	RES-Only vs END-RES	1.67	±	*2.85*	0.60	±	*1.13*	Moderate		*unclear*	0.374
		RES-Only vs RES-END	1.18	±	*2.75*	0.19	±	*1.40*	Trivial		*unclear*	0.820
		END-RES vs RES-END	0.71	±	*1.98*	-0.41	±	*1.34*	Small		*unclear*	0.605
	+4 h	RES-Only vs END-RES	1.24	±	*2.47*	0.25	±	*1.19*	Small		*unclear*	0.725
		RES-Only vs RES-END	0.93	±	*2.16*	-0.09	±	*1.23*	Trivial		*unclear*	0.907
		END-RES vs RES-END	0.75	±	*1.90*	-0.34	±	*1.20*	Small		*unclear*	0.639
	+7 h	RES-Only vs END-RES	3.18	±	*4.40*	1.36	±	*1.09*	Large	*very likely* ↑	*@90%*	0.042
		RES-Only vs RES-END	1.35	±	*2.38*	0.36	±	*1.05*	Small		*unclear*	0.571
		END-RES vs RES-END	0.43	±	*1.51*	-1.01	±	*1.19*	Moderate	*likely* ↓	*@90%*	0.162
10	+0.5 h	RES-Only vs END-RES	0.79	±	*1.74*	-0.27	±	*0.98*	Small		*unclear*	0.641
		RES-Only vs RES-END	0.62	±	*1.73*	-0.57	±	*1.19*	Small		*unclear*	0.424
		END-RES vs RES-END	0.78	±	*1.95*	-0.29	±	*1.21*	Small		*unclear*	0.686
	+3.5 h	RES-Only vs END-RES	0.86	±	*1.95*	-0.18	±	*1.13*	Trivial		*unclear*	0.790
		RES-Only vs RES-END	0.93	±	*2.39*	-0.08	±	*1.40*	Trivial		*unclear*	0.919
		END-RES vs RES-END	1.08	±	*2.51*	0.09	±	*1.34*	Trivial		*unclear*	0.905
	+4 h	RES-Only vs END-RES	0.81	±	*1.96*	-0.25	±	*1.19*	Small		*unclear*	0.724
		RES-Only vs RES-END	0.87	±	*2.08*	-0.17	±	*1.23*	Trivial		*unclear*	0.820
		END-RES vs RES-END	1.07	±	*2.29*	0.08	±	*1.20*	Trivial		*unclear*	0.906
	+7 h	RES-Only vs END-RES	1.44	±	*2.53*	0.43	±	*1.09*	Small		*unclear*	0.515
		RES-Only vs RES-END	0.80	±	*1.81*	-0.27	±	*1.05*	Small		*unclear*	0.670
		END-RES vs RES-END	0.55	±	*1.66*	-0.70	±	*1.19*	Moderate		*unclear*	0.330

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-AMPKα^{Thr172}

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.79	±	*2.04*	0.79	±	*0.75*	Moderate	*likely* ↑	*@90%*	0.085
		RES-Only vs RES-END	1.79	±	*2.07*	0.79	±	*0.77*	Moderate	*likely* ↑	*@90%*	0.090
		END-RES vs RES-END	1.00	±	*1.54*	0.00	±	*0.71*	Trivial		*unclear*	0.993
	+3.5 h	RES-Only vs END-RES	2.64	±	*2.43*	1.33	±	*0.71*	Large	***most likely*** ↑	***@99%***	0.003
		RES-Only vs RES-END	1.19	±	*1.66*	0.24	±	*0.73*	Small		*unclear*	0.589
		END-RES vs RES-END	0.45	±	*1.24*	-1.09	±	*0.71*	Moderate	***very likely*** ↓	***@99%***	0.012
	+4 h	RES-Only vs END-RES	2.99	±	*2.88*	1.49	±	*0.81*	Large	***very likely*** ↑	***@99%***	0.004
		RES-Only vs RES-END	1.58	±	*2.02*	0.63	±	*0.83*	Moderate	*likely* ↑	*@90%*	0.208
		END-RES vs RES-END	0.53	±	*1.29*	-0.87	±	*0.71*	Moderate	*likely* ↓	*@90%*	0.045
	+7 h	RES-Only vs END-RES	1.24	±	*1.81*	0.30	±	*0.84*	Small		*unclear*	0.555
		RES-Only vs RES-END	1.11	±	*1.69*	0.14	±	*0.81*	Trivial		*unclear*	0.773
		END-RES vs RES-END	0.89	±	*1.53*	-0.16	±	*0.76*	Trivial		*unclear*	0.732
10	+0.5 h	RES-Only vs END-RES	1.12	±	*1.65*	0.15	±	*0.75*	Trivial		*unclear*	0.738
		RES-Only vs RES-END	1.01	±	*1.60*	0.02	±	*0.77*	Trivial		*unclear*	0.967
		END-RES vs RES-END	0.91	±	*1.49*	-0.13	±	*0.71*	Trivial		*unclear*	0.756
	+3.5 h	RES-Only vs END-RES	1.10	±	*1.60*	0.13	±	*0.71*	Trivial		*unclear*	0.756
		RES-Only vs RES-END	0.84	±	*1.47*	-0.24	±	*0.73*	Small		*unclear*	0.588
		END-RES vs RES-END	0.76	±	*1.41*	-0.37	±	*0.71*	Small		*unclear*	0.387
	+4 h	RES-Only vs END-RES	1.66	±	*2.04*	0.69	±	*0.81*	Moderate	*likely* ↑	*@90%*	0.160
		RES-Only vs RES-END	1.53	±	*1.98*	0.58	±	*0.83*	Small		*unclear*	0.247
		END-RES vs RES-END	0.92	±	*1.50*	-0.11	±	*0.71*	Trivial		*unclear*	0.794
	+7 h	RES-Only vs END-RES	1.06	±	*1.69*	0.08	±	*0.84*	Trivial		*unclear*	0.878
		RES-Only vs RES-END	0.80	±	*1.50*	-0.30	±	*0.81*	Small		*unclear*	0.529
		END-RES vs RES-END	0.76	±	*1.45*	-0.38	±	*0.76*	Small		*unclear*	0.409

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑= increased; ↓= decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-p53^{Ser15}

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	1.61	±	*2.00*	0.41	±	*0.51*	Small	*likely* ↑	*@90%*	0.183
		RES-Only vs RES-END	1.83	±	*2.17*	0.52	±	*0.52*	Small	*likely* ↑	*@90%*	0.102
		END-RES vs RES-END	1.14	±	*1.71*	0.11	±	*0.51*	Trivial		*unclear*	0.719
	+3.5 h	RES-Only vs END-RES	2.50	±	*2.55*	0.79	±	*0.51*	Moderate	***very likely*** ↑	***@99%***	0.011
		RES-Only vs RES-END	1.29	±	*1.83*	0.22	±	*0.52*	Small		*unclear*	0.486
		END-RES vs RES-END	0.52	±	*1.32*	-0.57	±	*0.51*	Small	*likely* ↓	*@90%*	0.065
	+4 h	RES-Only vs END-RES	3.57	±	*3.25*	1.10	±	*0.51*	Moderate	***most likely*** ↑	***@99%***	0.001
		RES-Only vs RES-END	1.91	±	*2.24*	0.56	±	*0.53*	Small	*likely* ↑	*@90%*	0.082
		END-RES vs RES-END	0.54	±	*1.33*	-0.54	±	*0.51*	Small	*likely* ↓	*@90%*	0.081
	+7 h	RES-Only vs END-RES	1.69	±	*2.05*	0.45	±	*0.51*	Small	*likely* ↑	*@90%*	0.144
		RES-Only vs RES-END	1.44	±	*1.92*	0.32	±	*0.52*	Small		*unclear*	0.318
		END-RES vs RES-END	0.85	±	*1.53*	-0.14	±	*0.51*	Trivial		*unclear*	0.659
10	+0.5 h	RES-Only vs END-RES	1.18	±	*1.73*	0.14	±	*0.51*	Trivial		*unclear*	0.639
		RES-Only vs RES-END	0.94	±	*1.60*	-0.05	±	*0.52*	Trivial		*unclear*	0.869
		END-RES vs RES-END	0.80	±	*1.50*	-0.20	±	*0.51*	Small		*unclear*	0.523
	+3.5 h	RES-Only vs END-RES	0.90	±	*1.56*	-0.09	±	*0.51*	Trivial		*unclear*	0.771
		RES-Only vs RES-END	0.83	±	*1.53*	-0.17	±	*0.52*	Trivial		*unclear*	0.599
		END-RES vs RES-END	0.92	±	*1.57*	-0.08	±	*0.51*	Trivial		*unclear*	0.802
	+4 h	RES-Only vs END-RES	1.24	±	*1.78*	0.18	±	*0.51*	Trivial		*unclear*	0.553
		RES-Only vs RES-END	1.13	±	*1.73*	0.10	±	*0.53*	Trivial		*unclear*	0.748
		END-RES vs RES-END	0.91	±	*1.57*	-0.08	±	*0.51*	Trivial		*unclear*	0.790
	+7 h	RES-Only vs END-RES	0.82	±	*1.51*	-0.17	±	*0.51*	Trivial		*unclear*	0.575
		RES-Only vs RES-END	0.55	±	*1.35*	-0.52	±	*0.52*	Small	*likely* ↓	*@90%*	0.104
		END-RES vs RES-END	0.67	±	*1.42*	-0.34	±	*0.51*	Small	*possibly* ↓	*@90%*	0.267

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

p-TSC2^{Thr1462}

Week	Time	Between-group comparison	Difference (fold) mean	±	*90%CI*	Standardised Effect Size (ES) ES (*d*)	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑/↓	Threshold for clear effect	*P* Value
1	+0.5 h	RES-Only vs END-RES	0.71	±	*3.73*	-0.65	±	*3.87*	Moderate		*unclear*	0.480
		RES-Only vs RES-END	0.62	±	*3.22*	-0.91	±	*3.74*	Moderate		*unclear*	0.369
		END-RES vs RES-END	0.87	±	*1.38*	-0.25	±	*0.80*	Small		*unclear*	0.596
	+3.5 h	RES-Only vs END-RES	0.79	±	*1.29*	-0.46	±	*0.69*	Small		*unclear*	0.271
		RES-Only vs RES-END	0.87	±	*1.31*	-0.26	±	*0.65*	Small		*unclear*	0.500
		END-RES vs RES-END	1.11	±	*1.48*	0.19	±	*0.78*	Trivial		*unclear*	0.677
	+4 h	RES-Only vs END-RES	0.21	±	*23.93*	-2.96	±	*10.14*	Very large		*unclear*	0.316
		RES-Only vs RES-END	0.21	±	*20.77*	-2.90	±	*9.80*	Very large		*unclear*	0.313
		END-RES vs RES-END	1.04	±	*1.97*	0.06	±	*1.57*	Trivial		*unclear*	0.945
	+7 h	RES-Only vs END-RES	0.39	±	*1.66*	-1.78	±	*2.43*	Large		*unclear*	0.220
		RES-Only vs RES-END	0.60	±	*1.85*	-0.96	±	*2.15*	Moderate		*unclear*	0.446
		END-RES vs RES-END	1.55	±	*4.50*	0.82	±	*2.91*	Moderate		*unclear*	0.635
10	+0.5 h	RES-Only vs END-RES	0.36	±	*2.40*	-1.91	±	*3.87*	Large		*unclear*	0.198
		RES-Only vs RES-END	0.48	±	*2.74*	-1.37	±	*3.74*	Large		*unclear*	0.260
		END-RES vs RES-END	1.33	±	*1.58*	0.54	±	*0.80*	Small		*unclear*	0.265
	+3.5 h	RES-Only vs END-RES	0.75	±	*1.28*	-0.55	±	*0.69*	Small	*likely* ↓	*@90%*	0.187
		RES-Only vs RES-END	0.78	±	*1.27*	-0.47	±	*0.65*	Small	*likely* ↓	*@90%*	0.225
		END-RES vs RES-END	1.04	±	*1.45*	0.08	±	*0.78*	Trivial		*unclear*	0.871
	+4 h	RES-Only vs END-RES	0.20	±	*23.42*	-3.01	±	*10.15*	Very large		*unclear*	0.312
		RES-Only vs RES-END	0.19	±	*18.49*	-3.14	±	*9.81*	Very large		*unclear*	0.293
		END-RES vs RES-END	0.94	±	*1.88*	-0.12	±	*1.57*	Trivial		*unclear*	0.894
	+7 h	RES-Only vs END-RES	0.11	±	*1.19*	-4.10	±	*2.44*	Extremely large	***very likely*** ↓	***@99%***	0.009
		RES-Only vs RES-END	0.96	±	*2.36*	-0.08	±	*2.16*	Trivial		*unclear*	0.951
		END-RES vs RES-END	8.55	±	*20.30*	4.03	±	*2.91*	Extremely large	*very likely* ↑	*@90%*	0.026

Mean, mean difference as fold change; 90%CI, 90% factor confidence interval; ES, standardised effect size (Cohen's d);
Standardised thresholds for interpreting ES: < 0.2, trivial; 0.2-0.6, small; 0.6-1.2, moderate; 1.2-2.0, large; 2.0-4.0 very large; > 4.0, extremely large.
Thresholds for interpreting likelihoods: 25-75 %, possibly; 75-95 %, likely; 95-99.5 %, very likely; > 99.5%, most likely. ↑ = increased; ↓ = decreased;
Non-clinical thresholds: @90%, 90% confidence limits; @99%, 99% confidence limits.
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @99%), after adjusting for multiple inferences.*

Between-week differences for exercise-induced changes (Week 1 vs Week 10)

Muscle Glycogen		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	0.94	±	*1.25*	-0.27	±	*1.20*	Small		*unclear*	0.706
	+ 3.5 h	0.92	±	*1.19*	-0.39	±	*0.96*	Small		*unclear*	0.502
	+ 4.0 h	0.77	±	*1.23*	-1.20	±	*1.36*	Large	*likely* ↓	*@90%*	0.143
	+ 7.0 h	0.91	±	*1.19*	-0.44	±	*0.98*	Small		*unclear*	0.451
END-RES	+ 0.5 h	1.01	±	*1.28*	0.06	±	*1.27*	Trivial		*unclear*	0.934
	+ 3.5 h	1.18	±	*1.24*	0.78	±	*0.93*	Moderate	*likely* ↑	*@90%*	0.163
	+ 4.0 h	1.18	±	*1.40*	0.78	±	*1.55*	Moderate		*unclear*	0.397
	+ 7.0 h	0.88	±	*1.20*	-0.57	±	*1.02*	Small		*unclear*	0.349
RES-END	+ 0.5 h	0.88	±	*1.22*	-0.62	±	*1.17*	Moderate		*unclear*	0.375
	+ 3.5 h	0.92	±	*1.19*	-0.41	±	*0.96*	Small		*unclear*	0.476
	+ 4.0 h	1.11	±	*1.37*	0.49	±	*1.52*	Small		*unclear*	0.585
	+ 7.0 h	0.91	±	*1.25*	-0.45	±	*1.29*	Small		*unclear*	0.556

PGC-1α		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	1.35	±	*1.85*	0.44	±	*0.88*	Small		*unclear*	0.408
	+ 3.5 h	0.48	±	*1.39*	-1.09	±	*1.09*	Moderate	*likely* ↓	*@90%*	0.100
	+ 4.0 h	1.41	±	*2.14*	0.51	±	*1.10*	Small		*unclear*	0.431
	+ 7.0 h	0.56	±	*1.48*	-0.85	±	*1.15*	Moderate		*unclear*	0.216
END-RES	+ 0.5 h	0.73	±	*1.43*	-0.47	±	*0.83*	Small		*unclear*	0.353
	+ 3.5 h	0.56	±	*1.41*	-0.87	±	*1.01*	Moderate	*likely* ↓	*@90%*	0.155
	+ 4.0 h	0.57	±	*1.34*	-0.84	±	*0.83*	Moderate	*likely* ↓	*@90%*	0.096
	+ 7.0 h	0.57	±	*1.38*	-0.83	±	*0.92*	Moderate	*likely* ↓	*@90%*	0.134
RES-END	+ 0.5 h	1.31	±	*1.82*	0.40	±	*0.88*	Small		*unclear*	0.453
	+ 3.5 h	0.69	±	*1.60*	-0.55	±	*1.16*	Small		*unclear*	0.431
	+ 4.0 h	1.16	±	*1.73*	0.22	±	*0.88*	Small		*unclear*	0.677
	+ 7.0 h	1.48	±	*2.23*	0.58	±	*1.12*	Small		*unclear*	0.384

MuRF1		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	0.84	±	*1.53*	-0.22	±	*0.77*	Small		*unclear*	0.630
	+ 3.5 h	0.72	±	*1.41*	-0.42	±	*0.71*	Small		*unclear*	0.321
	+ 4.0 h	1.66	±	*2.13*	0.66	±	*0.83*	Moderate	*likely* ↑	*@90%*	0.185
	+ 7.0 h	0.71	±	*1.53*	-0.46	±	*0.91*	Small		*unclear*	0.399
END-RES	+ 0.5 h	1.19	±	*1.55*	0.23	±	*0.58*	Small		*unclear*	0.512
	+ 3.5 h	0.69	±	*1.36*	-0.49	±	*0.66*	Small	*likely* ↓	*@90%*	0.214
	+ 4.0 h	0.77	±	*1.37*	-0.35	±	*0.60*	Small		*unclear*	0.336
	+ 7.0 h	0.89	±	*1.50*	-0.15	±	*0.69*	Trivial		*unclear*	0.717
RES-END	+ 0.5 h	1.12	±	*1.57*	0.15	±	*0.64*	Trivial		*unclear*	0.688
	+ 3.5 h	0.66	±	*1.53*	-0.54	±	*0.95*	Small		*unclear*	0.340
	+ 4.0 h	0.98	±	*1.48*	-0.03	±	*0.62*	Trivial		*unclear*	0.940
	+ 7.0 h	0.80	±	*1.40*	-0.29	±	*0.62*	Small		*unclear*	0.442

MAFbx		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	0.91	±	*1.53*	-0.10	±	*0.63*	Trivial		*unclear*	0.782
	+ 3.5 h	1.02	±	*1.82*	0.03	±	*0.85*	Trivial		*unclear*	0.958
	+ 4.0 h	2.25	±	*2.55*	0.93	±	*0.74*	Moderate	*likely* ↑	*@90%*	0.041
	+ 7.0 h	1.43	±	*2.37*	0.41	±	*0.98*	Small		*unclear*	0.475
END-RES	+ 0.5 h	0.56	±	*1.31*	-0.66	±	*0.60*	Moderate	*likely* ↓	*@90%*	0.069
	+ 3.5 h	0.71	±	*1.54*	-0.40	±	*0.80*	Small		*unclear*	0.407
	+ 4.0 h	0.76	±	*1.51*	-0.32	±	*0.73*	Small		*unclear*	0.455
	+ 7.0 h	0.65	±	*1.43*	-0.50	±	*0.71*	Small		*unclear*	0.243
RES-END	+ 0.5 h	0.95	±	*1.47*	-0.06	±	*0.54*	Trivial		*unclear*	0.863
	+ 3.5 h	0.93	±	*1.56*	-0.08	±	*0.65*	Trivial		*unclear*	0.837
	+ 4.0 h	1.46	±	*1.72*	0.43	±	*0.54*	Small	*likely* ↑	*@90%*	0.188
	+ 7.0 h	1.76	±	*2.32*	0.65	±	*0.80*	Moderate	*likely* ↑	*@90%*	0.175

Myostatin		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	0.98	±	*2.13*	-0.02	±	*0.95*	Trivial		*unclear*	0.965
	+ 3.5 h	0.38	±	*1.30*	-0.93	±	*0.70*	Moderate	***very likely*** ↓	***@99%***	0.030
	+ 4.0 h	0.65	±	*1.51*	-0.42	±	*0.70*	Small		*unclear*	0.321
	+ 7.0 h	0.65	±	*1.65*	-0.41	±	*0.85*	Small		*unclear*	0.418
END-RES	+ 0.5 h	0.77	±	*1.57*	-0.25	±	*0.66*	Small		*unclear*	0.528
	+ 3.5 h	0.67	±	*1.51*	-0.39	±	*0.68*	Small		*unclear*	0.338
	+ 4.0 h	0.81	±	*1.59*	-0.21	±	*0.66*	Small		*unclear*	0.597
	+ 7.0 h	0.72	±	*1.58*	-0.32	±	*0.72*	Small		*unclear*	0.454
RES-END	+ 0.5 h	0.58	±	*1.45*	-0.53	±	*0.70*	Small	*likely* ↓	*@90%*	0.207
	+ 3.5 h	0.56	±	*1.47*	-0.56	±	*0.73*	Small	*likely* ↓	*@90%*	0.206
	+ 4.0 h	0.79	±	*1.72*	-0.22	±	*0.78*	Small		*unclear*	0.631
	+ 7.0 h	1.73	±	*2.36*	0.53	±	*0.70*	Small	*likely* ↑	*@90%*	0.212

Mighty		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	0.68	±	*1.33*	-0.78	±	*0.92*	Moderate	*likely* ↓	*@90%*	0.160
	+ 3.5 h	0.62	±	*1.18*	-0.95	±	*0.58*	Moderate	***very likely*** ↓	***@99%***	0.008
	+ 4.0 h	0.88	±	*1.44*	-0.25	±	*0.95*	Small		*unclear*	0.656
	+ 7.0 h	0.66	±	*1.31*	-0.82	±	*0.90*	Moderate	*likely* ↓	*@90%*	0.134
END-RES	+ 0.5 h	0.72	±	*1.20*	-0.64	±	*0.55*	Moderate	*likely* ↓	*@90%*	0.055
	+ 3.5 h	0.76	±	*1.22*	-0.55	±	*0.57*	Small	*likely* ↓	*@90%*	0.116
	+ 4.0 h	0.75	±	*1.21*	-0.56	±	*0.55*	Small	*likely* ↓	*@90%*	0.090
	+ 7.0 h	0.83	±	*1.23*	-0.38	±	*0.55*	Small	*possibly* ↓	*@90%*	0.257
RES-END	+ 0.5 h	0.67	±	*1.42*	-0.79	±	*1.17*	Moderate		*unclear*	0.259
	+ 3.5 h	0.86	±	*1.28*	-0.29	±	*0.63*	Small		*unclear*	0.440
	+ 4.0 h	1.43	±	*1.81*	0.71	±	*1.06*	Moderate		*unclear*	0.263
	+ 7.0 h	1.45	±	*1.84*	0.73	±	*1.10*	Moderate		*unclear*	0.260

p-Akt^{Ser473}		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	1.39	±	*2.21*	0.31	±	*0.74*	Small		*unclear*	0.474
	+ 3.5 h	3.47	±	*2.92*	1.18	±	*0.50*	Moderate	***most likely*** ↑	***@99%***	0.000
	+ 4.0 h	1.89	±	*2.30*	0.60	±	*0.61*	Moderate	*likely* ↑	*@90%*	0.102
	+ 7.0 h	2.38	±	*2.32*	0.82	±	*0.50*	Moderate	***very likely*** ↑	***@99%***	0.007
END-RES	+ 0.5 h	1.41	±	*1.73*	0.32	±	*0.47*	Small	*possibly* ↑	*@90%*	0.254
	+ 3.5 h	1.67	±	*1.87*	0.48	±	*0.47*	Small	*likely* ↑	*@90%*	0.090
	+ 4.0 h	0.95	±	*1.49*	-0.05	±	*0.47*	Trivial		*unclear*	0.868
	+ 7.0 h	1.19	±	*1.61*	0.16	±	*0.47*	Trivial		*unclear*	0.571
RES-END	+ 0.5 h	1.18	±	*1.72*	0.15	±	*0.55*	Trivial		*unclear*	0.631
	+ 3.5 h	2.23	±	*2.23*	0.76	±	*0.50*	Moderate	***very likely*** ↑	***@99%***	0.013
	+ 4.0 h	1.69	±	*1.99*	0.50	±	*0.53*	Small	*likely* ↑	*@90%*	0.118
	+ 7.0 h	0.91	±	*1.84*	-0.09	±	*0.78*	Trivial		*unclear*	0.849

p-mTOR^{Ser2448}		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	1.21	±	*1.61*	0.29	±	*0.73*	Small		*unclear*	0.507
	+ 3.5 h	1.11	±	*1.82*	0.15	±	*1.04*	Trivial		*unclear*	0.798
	+ 4.0 h	1.01	±	*1.51*	0.02	±	*0.73*	Trivial		*unclear*	0.966
	+ 7.0 h	1.38	±	*2.63*	0.49	±	*1.52*	Small		*unclear*	0.575
END-RES	+ 0.5 h	0.72	±	*1.35*	-0.51	±	*0.72*	Small		*unclear*	0.238
	+ 3.5 h	0.93	±	*1.53*	-0.12	±	*0.83*	Trivial		*unclear*	0.813
	+ 4.0 h	0.98	±	*1.46*	-0.03	±	*0.69*	Trivial		*unclear*	0.946
	+ 7.0 h	0.66	±	*1.87*	-0.63	±	*1.65*	Moderate		*unclear*	0.516
RES-END	+ 0.5 h	1.11	±	*1.64*	0.15	±	*0.84*	Trivial		*unclear*	0.755
	+ 3.5 h	0.92	±	*1.46*	-0.13	±	*0.73*	Trivial		*unclear*	0.773
	+ 4.0 h	1.22	±	*1.88*	0.31	±	*1.02*	Small		*unclear*	0.608
	+ 7.0 h	1.74	±	*2.77*	0.84	±	*1.36*	Moderate		*unclear*	0.293

p-4E-BP1$^{Thr37/46}$		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**		**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude				
RES-Only	+ 0.5 h	1.21	±	*1.69*	0.33	±	*0.92*	Small			*unclear*	0.538
	+ 3.5 h	1.09	±	*1.58*	0.15	±	*0.86*	Trivial			*unclear*	0.759
	+ 4.0 h	1.26	±	*1.37*	0.40	±	*0.49*	Small	*likely*	↑	*@90%*	0.176
	+ 7.0 h	1.48	±	*1.40*	0.67	±	*0.46*	Moderate	***very likely***	↑	***@99%***	0.020
END-RES	+ 0.5 h	1.25	±	*1.47*	0.38	±	*0.63*	Small			*unclear*	0.316
	+ 3.5 h	1.29	±	*1.41*	0.43	±	*0.53*	Small	*likely*	↑	*@90%*	0.175
	+ 4.0 h	1.95	±	*1.76*	1.14	±	*0.65*	Moderate	***very likely***	↑	***@99%***	0.007
	+ 7.0 h	1.51	±	*1.53*	0.70	±	*0.59*	Moderate	*likely*	↑	*@90%*	0.054
RES-END	+ 0.5 h	1.63	±	*1.57*	0.84	±	*0.59*	Moderate	***very likely***	↑	***@99%***	0.024
	+ 3.5 h	1.38	±	*1.71*	0.55	±	*0.84*	Small			*unclear*	0.271
	+ 4.0 h	1.83	±	*1.94*	1.04	±	*0.84*	Moderate	*likely*	↑	*@90%*	0.046
	+ 7.0 h	1.48	±	*1.56*	0.68	±	*0.63*	Moderate	*likely*	↑	*@90%*	0.080

p-eEF2^{Thr56}		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**		**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude				
RES-Only	+ 0.5 h	1.54	±	*1.54*	0.62	±	*0.49*	Moderate	***likely***	↑	***@99%***	0.041
	+ 3.5 h	2.90	±	*3.12*	1.53	±	*0.97*	Large	***very likely***	↑	***@99%***	0.016
	+ 4.0 h	1.81	±	*1.77*	0.85	±	*0.59*	Moderate	***very likely***	↑	***@99%***	0.024
	+ 7.0 h	1.82	±	*2.93*	0.86	±	*1.32*	Moderate			*unclear*	0.270
END-RES	+ 0.5 h	2.11	±	*2.42*	1.07	±	*0.90*	Moderate	*likely*	↑	*@90%*	0.058
	+ 3.5 h	2.91	±	*3.78*	1.53	±	*1.22*	Large	*very likely*	↑	*@90%*	0.045
	+ 4.0 h	1.49	±	*2.41*	0.57	±	*1.20*	Small			*unclear*	0.415
	+ 7.0 h	3.11	±	*6.30*	1.63	±	*1.86*	Large			*unclear*	0.146
RES-END	+ 0.5 h	0.87	±	*1.33*	-0.19	±	*0.52*	Trivial			*unclear*	0.533
	+ 3.5 h	1.35	±	*1.50*	0.43	±	*0.52*	Small	*likely*	↑	*@90%*	0.179
	+ 4.0 h	1.24	±	*1.94*	0.30	±	*1.00*	Small			*unclear*	0.596
	+ 7.0 h	3.42	±	*4.88*	1.76	±	*1.39*	Large	*very likely*	↑	*@90%*	0.043

p-rpS6$^{Ser235/236}$		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	2.60	±	*3.33*	1.13	±	*0.95*	Moderate	*likely* ↑	*@90%*	0.052
	+ 3.5 h	1.92	±	*3.40*	0.77	±	*1.23*	Moderate		*unclear*	0.294
	+ 4.0 h	1.42	±	*2.81*	0.41	±	*1.25*	Small		*unclear*	0.575
	+ 7.0 h	2.26	±	*3.02*	0.96	±	*0.95*	Moderate	*likely* ↑	*@90%*	0.096
END-RES	+ 0.5 h	1.00	±	*1.99*	0.00	±	*1.03*	Trivial		*unclear*	0.997
	+ 3.5 h	0.99	±	*2.01*	-0.01	±	*1.05*	Trivial		*unclear*	0.987
	+ 4.0 h	0.93	±	*2.09*	-0.09	±	*1.18*	Trivial		*unclear*	0.898
	+ 7.0 h	1.02	±	*2.30*	0.02	±	*1.25*	Trivial		*unclear*	0.973
RES-END	+ 0.5 h	1.65	±	*3.48*	0.59	±	*1.41*	Small		*unclear*	0.480
	+ 3.5 h	1.52	±	*3.79*	0.50	±	*1.61*	Small		*unclear*	0.599
	+ 4.0 h	1.33	±	*2.71*	0.33	±	*1.26*	Small		*unclear*	0.656
	+ 7.0 h	1.33	±	*2.55*	0.33	±	*1.17*	Small		*unclear*	0.629

p-AMPKα^{Thr172}		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	1.94	±	*2.25*	0.90	±	*0.83*	Moderate	*likely* ↑	*@90%*	0.073
	+ 3.5 h	3.27	±	*2.82*	1.62	±	*0.73*	Large	***most likely*** ↑	***@99%***	0.000
	+ 4.0 h	1.66	±	*2.22*	0.69	±	*0.93*	Moderate		*unclear*	0.218
	+ 7.0 h	1.49	±	*2.05*	0.54	±	*0.90*	Small		*unclear*	0.309
END-RES	+ 0.5 h	1.22	±	*1.65*	0.27	±	*0.70*	Small		*unclear*	0.524
	+ 3.5 h	1.36	±	*1.72*	0.42	±	*0.69*	Small		*unclear*	0.310
	+ 4.0 h	0.92	±	*1.48*	-0.12	±	*0.68*	Trivial		*unclear*	0.772
	+ 7.0 h	1.27	±	*1.80*	0.32	±	*0.81*	Small		*unclear*	0.506
RES-END	+ 0.5 h	1.10	±	*1.61*	0.13	±	*0.73*	Trivial		*unclear*	0.766
	+ 3.5 h	2.31	±	*2.29*	1.14	±	*0.73*	Moderate	***very likely*** ↑	***@99%***	0.011
	+ 4.0 h	1.59	±	*1.89*	0.64	±	*0.73*	Moderate	*likely* ↑	*@90%*	0.149
	+ 7.0 h	1.08	±	*1.60*	0.10	±	*0.73*	Trivial		*unclear*	0.820

p-p53^{Ser15}		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	1.88	±	*2.21*	0.55	±	*0.52*	Small	*likely* ↑	*@90%*	0.085
	+ 3.5 h	3.33	±	*3.14*	1.04	±	*0.52*	Moderate	***most likely*** ↑	***@99%***	0.001
	+ 4.0 h	2.14	±	*2.44*	0.66	±	*0.55*	Moderate	*likely* ↑	*@90%*	0.050
	+ 7.0 h	2.22	±	*2.43*	0.69	±	*0.52*	Moderate	***likely*** ↑	***@99%***	0.031
END-RES	+ 0.5 h	1.38	±	*1.83*	0.28	±	*0.49*	Small		*unclear*	0.346
	+ 3.5 h	1.20	±	*1.72*	0.16	±	*0.49*	Trivial		*unclear*	0.591
	+ 4.0 h	0.74	±	*1.45*	-0.26	±	*0.49*	Small		*unclear*	0.387
	+ 7.0 h	1.08	±	*1.67*	0.07	±	*0.50*	Trivial		*unclear*	0.827
RES-END	+ 0.5 h	0.97	±	*1.62*	-0.03	±	*0.52*	Trivial		*unclear*	0.936
	+ 3.5 h	2.13	±	*2.37*	0.65	±	*0.52*	Moderate	***likely*** ↑	***@99%***	0.040
	+ 4.0 h	1.26	±	*1.81*	0.20	±	*0.52*	Small		*unclear*	0.524
	+ 7.0 h	0.85	±	*1.55*	-0.14	±	*0.52*	Trivial		*unclear*	0.655

p-TSC2^{Thr1462}		**Difference from Week 1 (fold)**			**Standardised Effect Size (ES)**				**Likelihood true effect is substantially ↑/↓**	**Threshold for clear effect**	***P* value**
Group	**Time**	mean	±	*90%CI*	ES (*d*)	±	*90%CI*	Magnitude			
RES-Only	+ 0.5 h	0.95	±	*6.06*	-0.10	±	*4.46*	Trivial		*unclear*	0.912
	+ 3.5 h	1.00	±	*1.29*	0.01	±	*0.53*	Trivial		*unclear*	0.986
	+ 4.0 h	1.20	±	*537.53*	0.34	±	*12.75*	Small		*unclear*	0.895
	+ 7.0 h	1.80	±	*3.28*	1.10	±	*1.98*	Moderate		*unclear*	0.249
END-RES	+ 0.5 h	0.49	±	*1.23*	-1.35	±	*0.86*	Large	***very likely*** ↓	***@99%***	0.014
	+ 3.5 h	0.95	±	*1.44*	-0.09	±	*0.84*	Trivial		*unclear*	0.858
	+ 4.0 h	1.16	±	*2.26*	0.28	±	*1.76*	Small		*unclear*	0.782
	+ 7.0 h	0.52	±	*2.41*	-1.22	±	*3.22*	Large		*unclear*	0.518
RES-END	+ 0.5 h	0.74	±	*1.32*	-0.56	±	*0.78*	Small		*unclear*	0.225
	+ 3.5 h	0.90	±	*1.38*	-0.21	±	*0.77*	Small		*unclear*	0.646
	+ 4.0 h	1.05	±	*1.90*	0.10	±	*1.45*	Trivial		*unclear*	0.909
	+ 7.0 h	2.88	±	*6.99*	1.99	±	*2.77*	Large		*unclear*	0.228

Individual responses

Muscle Glycogen

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	**ES**	*90%CI*	**Magnitude**				
Changes to PRE (Week 1 vs Week 10)									
RO	**7.3**	*11*	**0.34**	*0.51*	Moderate			unclear	0.245
ER									
RE	**12**	*15*	**0.56**	*0.70*	Moderate			unclear	0.170
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO	**19**	*21*	**0.84**	*0.91*	Large			unclear	0.116
ER	**18**	*19*	**0.79**	*0.84*	Large			unclear	0.112
RE	**27**	*17*	**1.13**	*0.66*	Very large	*very likely*	↑	@90%	0.041
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO									
ER									
RE	**5.4**	*16*	**0.25**	*0.74*	Small			unclear	0.425
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**26**	*18*	**1.12**	*0.73*	Very large	*very likely*	↑	@90%	0.048
ER	**33**	*19*	**1.38**	*0.71*	Very large	*very likely*	↑	@90%	0.031
RE	**39**	*19*	**1.58**	*0.67*	Very large	*very likely*	↑	@90%	0.016
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO	**4.8**	*16*	**0.22**	*0.75*	Small			unclear	0.441
ER	**23**	*20*	**1.01**	*0.86*	Very large			unclear	0.062
RE	**13**	*17*	**0.60**	*0.79*	Large			unclear	0.189

PGC-1α

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	**ES**	*90%CI*	**Magnitude**				
Changes to PRE (Week 1 vs Week 10)									
RO	**53**	*46*	**0.66**	*0.53*	Large			unclear	0.057
ER	**30**	*43*	**0.40**	*0.58*	Moderate			unclear	0.235
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO									
ER									
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO	**62**	*69*	**0.74**	*0.81*	Large			unclear	0.120
ER	**78**	*65*	**0.89**	*0.66*	Large	*likely*	↑	@90%	0.051
RE	**59**	*60*	**0.71**	*0.70*	Large			unclear	0.090
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**63**	*71*	**0.75**	*0.83*	Large			unclear	0.126
ER									
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO	**74**	*75*	**0.85**	*0.82*	Large			unclear	0.085
ER	**68**	*71*	**0.80**	*0.80*	Large			unclear	0.097
RE	**29**	*61*	**0.39**	*0.84*	Moderate			unclear	0.367

MuRF1

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	**ES**	*90%CI*	**Magnitude**				
Changes to PRE (Week 1 vs Week 10)									
RO									
ER	**25**	*29*	**0.30**	*0.35*	Moderate			unclear	0.151
RE	**17**	*27*	**0.21**	*0.34*	Small			unclear	0.273
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO	**49**	*53*	**0.54**	*0.57*	Moderate			unclear	0.111
ER	**7.5**	*37*	**0.10**	*0.48*	Small			unclear	0.473
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO	**35**	*47*	**0.40**	*0.55*	Moderate			unclear	0.210
ER	**87**	*52*	**0.85**	*0.39*	Large	*very likely*	↑	@90%	0.023
RE	**30**	*44*	**0.35**	*0.53*	Moderate			unclear	0.247
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**61**	*59*	**0.64**	*0.59*	Large			unclear	0.074
ER									
RE	**13**	*37*	**0.16**	*0.48*	Small			unclear	0.427
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO	**79**	*55*	**0.79**	*0.45*	Large	*very likely*	↑	@90%	0.040
ER									
RE	**40**	*50*	**0.46**	*0.57*	Moderate			unclear	0.169

MuRF1

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	**ES**	*90%CI*	**Magnitude**				
Changes to PRE (Week 1 vs Week 10)									
RO									
ER	**7.6**	*15*	**0.09**	*0.18*	Trivial			unclear	0.345
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO	**37**	*48*	**0.38**	*0.49*	Moderate			unclear	0.189
ER									
RE	**38**	*48*	**0.38**	*0.49*	Moderate			unclear	0.180
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO	**89**	*64*	**0.76**	*0.44*	Large	*very likely*	↑	@90%	0.042
ER	**41**	*50*	**0.41**	*0.51*	Moderate			unclear	0.164
RE	**92**	*60*	**0.78**	*0.40*	Large	*very likely*	↑	@90%	0.031
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**64**	*61*	**0.59**	*0.53*	Moderate			unclear	0.073
ER									
RE	**73**	*52*	**0.65**	*0.39*	Large	*very likely*	↑	@90%	0.044
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO	**124**	*76*	**0.96**	*0.43*	Large	*very likely*	↑	@90%	0.020
ER	**77**	*53*	**0.68**	*0.39*	Large	*very likely*	↑	@90%	0.039
RE	**69**	*53*	**0.62**	*0.41*	Large	*likely*	↑	@90%	0.049

Myostatin

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	**ES**	*90%CI*	**Magnitude**				
Changes to PRE (Week 1 vs Week 10)									
RO	**43**	*53*	**0.36**	*0.44*	Moderate			unclear	0.163
ER									
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO	**113**	*110*	**0.75**	*0.67*	Large			unclear	0.068
ER									
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO									
ER	**26**	*58*	**0.23**	*0.53*	Small			unclear	0.381
RE	**16**	*48*	**0.15**	*0.45*	Small			unclear	0.430
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO									
ER	**49**	*71*	**0.40**	*0.59*	Moderate			unclear	0.238
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO	**76**	*89*	**0.56**	*0.65*	Moderate			unclear	0.141
ER									
RE	**41**	*68*	**0.34**	*0.58*	Moderate			unclear	0.289

p-Akt^{Ser473}

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓	Effect clear at:	*P*-value
	%	*90%CI*	ES	*90%CI*	Magnitude			
Changes to PRE (Week 1 vs Week 10)								
RO	**57**	*59*	**0.44**	*0.44*	Moderate		unclear	0.094
ER	**63**	*87*	**0.48**	*0.66*	Moderate		unclear	0.210
RE	**40**	*28*	**0.33**	*0.21*	Moderate	*likely* ↑	@90%	0.047
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h								
RO	**90**	*86*	**0.63**	*0.55*	Large		unclear	0.068
ER	**20**	*55*	**0.18**	*0.50*	Small		unclear	0.418
RE								
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h								
RO								
ER								
RE								
Individual responses in both Weeks 1 and 10, between PRE vs +4 h								
RO	**47**	*64*	**0.37**	*0.52*	Moderate		unclear	0.209
ER	**5.4**	*52*	**0.05**	*0.49*	Trivial		unclear	0.493
RE								
Individual responses in both Weeks 1 and 10, between PRE vs +7 h								
RO								
ER	**102**	*88*	**0.68**	*0.52*	Large	*likely* ↑	@90%	0.051
RE								

p-mTOR^{Ser2448}

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓	Effect clear at:	*P*-value
	%	*90%CI*	ES	*90%CI*	Magnitude			
Changes to PRE (Week 1 vs Week 10)								
RO	**59**	*15*	**0.73**	*0.15*	Large	***most likely*** ↑	**@99%**	0.000
ER	**40**	*43*	**0.53**	*0.57*	Moderate		unclear	0.116
RE	**21**	*28*	**0.29**	*0.41*	Small		unclear	0.209
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h								
RO								
ER	**34**	*52*	**0.45**	*0.72*	Moderate		unclear	0.267
RE	**15**	*38*	**0.22**	*0.57*	Small		unclear	0.406
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h								
RO	**66**	*71*	**0.79**	*0.84*	Large		unclear	0.109
ER								
RE	**43**	*53*	**0.56**	*0.69*	Moderate		unclear	0.169
Individual responses in both Weeks 1 and 10, between PRE vs +4 h								
RO								
ER	**68**	*65*	**0.82**	*0.73*	Large		unclear	0.071
RE								
Individual responses in both Weeks 1 and 10, between PRE vs +7 h								
RO	**164**	*119*	**1.52**	*0.78*	Very large	*very likely* ↑	@90%	0.031
ER	**133**	*87*	**1.33**	*0.63*	Very large	*very likely* ↑	@90%	0.025
RE	**231**	*139*	**1.88**	*0.69*	Very large	*very likely* ↑	@90%	0.008

p-4EBP1$^{Thr37/46}$

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	ES	*90%CI*	Magnitude				
Changes to PRE (Week 1 vs Week 10)									
RO	**14**	*24*	**0.23**	*0.41*	Small			unclear	0.307
ER									
RE	**60**	*44*	**0.83**	*0.54*	Large	*likely*	↑	@90%	0.048
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO	**69**	*39*	**0.92**	*0.42*	Large	*very likely*	↑	@90%	0.022
ER	**27**	*32*	**0.42**	*0.50*	Moderate			unclear	0.151
RE	**38**	*36*	**0.56**	*0.54*	Moderate			unclear	0.081
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO	**62**	*36*	**0.85**	*0.42*	Large	*very likely*	↑	@90%	0.028
ER	**59**	*36*	**0.82**	*0.42*	Large	*very likely*	↑	@90%	0.031
RE	**22**	*30*	**0.34**	*0.48*	Moderate			unclear	0.215
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**9.5**	*24*	**0.16**	*0.42*	Small			unclear	0.406
ER	**59**	*34*	**0.82**	*0.39*	Large	*very likely*	↑	@90%	0.025
RE	**40**	*36*	**0.59**	*0.52*	Moderate			unclear	0.066
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO									
ER	**32**	*34*	**0.50**	*0.52*	Moderate			unclear	0.110
RE	**32**	*36*	**0.49**	*0.55*	Moderate			unclear	0.126

p-rpS6$^{Ser235/236}$

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	ES	*90%CI*	Magnitude				
Changes to PRE (Week 1 vs Week 10)									
RO	**95**	*102*	**0.81**	*0.83*	Large			unclear	0.099
ER	**14**	*60*	**0.16**	*0.68*	Small			unclear	0.464
RE	**110**	*113*	**0.90**	*0.86*	Large			unclear	0.081
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO									
ER	**171**	*161*	**1.21**	*0.93*	Very large			unclear	0.052
RE	**69**	*95*	**0.64**	*0.88*	Large			unclear	0.211
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO	**112**	*122*	**0.91**	*0.93*	Large			unclear	0.098
ER	**249**	*195*	**1.52**	*0.75*	Very large	*very likely*	↑	@90%	0.028
RE	**77**	*101*	**0.70**	*0.90*	Large			unclear	0.184
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**117**	*131*	**0.94**	*0.99*	Large			unclear	0.108
ER	**124**	*125*	**0.98**	*0.89*	Large			unclear	0.072
RE	**120**	*118*	**0.96**	*0.85*	Large			unclear	0.068
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO									
ER	**92**	*109*	**0.79**	*0.91*	Large			unclear	0.139
RE	**145**	*143*	**1.09**	*0.93*	Very large			unclear	0.063

p-eEF2^{Thr56}

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	ES	*90%CI*	Magnitude				
Changes to PRE (Week 1 vs Week 10)									
RO	**74**	*73*	**0.82**	*0.77*	Large			unclear	0.078
ER	**57**	*55*	**0.67**	*0.62*	Large			unclear	0.077
RE	**144**	*152*	**1.32**	*1.26*	Very large			unclear	0.082
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO									
ER									
RE	**68**	*69*	**0.77**	*0.75*	Large			unclear	0.088
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO	**91**	*60*	**0.96**	*0.50*	Large	*very likely*	↑	@90%	0.032
ER									
RE	**121**	*81*	**1.18**	*0.59*	Very large	*very likely*	↑	@90%	0.029
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**29**	*40*	**0.38**	*0.53*	Moderate			unclear	0.214
ER	**82**	*71*	**0.89**	*0.69*	Large			unclear	0.052
RE	**119**	*79*	**1.17**	*0.58*	Very large	*very likely*	↑	@90%	0.028
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO	**159**	*104*	**1.41**	*0.64*	Very large	*very likely*	↑	@90%	0.021
ER	**156**	*97*	**1.40**	*0.60*	Very large	*very likely*	↑	@90%	0.017
RE	**270**	*180*	**1.94**	*0.77*	Very large	*very likely*	↑	@90%	0.012

p-AMPKα^{Thr172}

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	ES	*90%CI*	Magnitude				
Changes to PRE (Week 1 vs Week 10)									
RO	**14**	*37*	**0.18**	*0.50*	Small			unclear	0.413
ER	**10**	*26*	**0.14**	*0.36*	Small			unclear	0.403
RE	**9.4**	*29*	**0.13**	*0.40*	Small			unclear	0.435
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO	**37**	*53*	**0.44**	*0.65*	Moderate			unclear	0.238
ER									
RE	**4.6**	*41*	**0.06**	*0.56*	Trivial			unclear	0.492
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO									
ER									
RE	**1.5**	*39*	**0.02**	*0.53*	Trivial			unclear	0.499
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**59**	*68*	**0.66**	*0.74*	Large			unclear	0.132
ER									
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO	**50**	*64*	**0.57**	*0.73*	Moderate			unclear	0.181
ER									
RE	**47**	*55*	**0.54**	*0.64*	Moderate			unclear	0.146

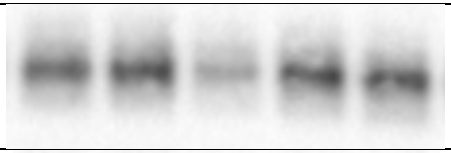
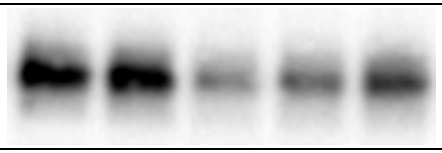
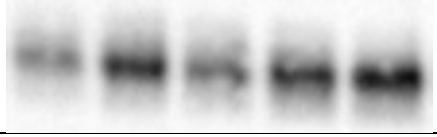
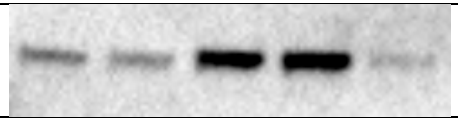
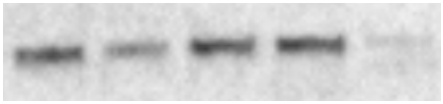
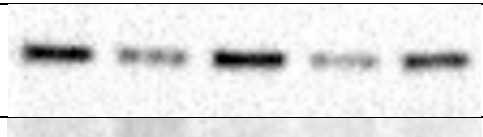
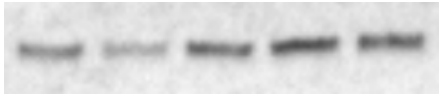
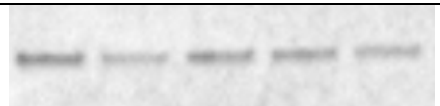
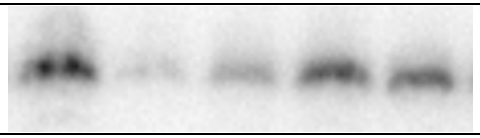
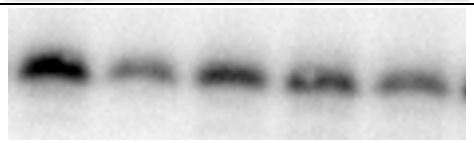
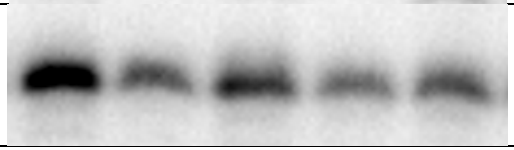
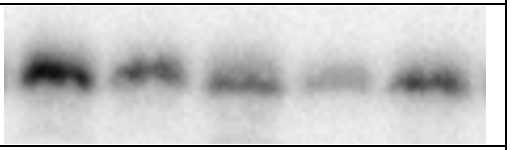
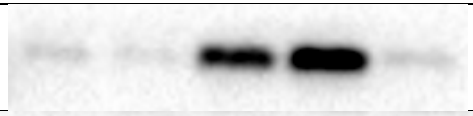
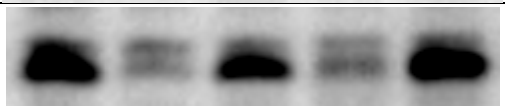
p-p53^{Ser15}

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	ES	*90%CI*	Magnitude				
Changes to PRE (Week 1 vs Week 10)									
RO	**52**	*57*	**0.37**	*0.40*	Moderate			unclear	0.118
ER									
RE	**36**	*31*	**0.28**	*0.23*	Small	*likely*	↑	@90%	0.059
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO									
ER									
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO									
ER									
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**15**	*54*	**0.12**	*0.45*	Small			unclear	0.450
ER									
RE									
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO									
ER									
RE	**9.8**	*49*	**0.08**	*0.42*	Trivial			unclear	0.474

p-TSC2^{Thr1462}

	Mean variation		Standardised Effect Sie (ES)			Likelihood true effect is substantially ↑/↓		Effect clear at:	*P*-value
	%	*90%CI*	ES	*90%CI*	Magnitude				
Changes to PRE (Week 1 vs Week 10)									
RO	**19**	*31*	**0.33**	*0.56*	Moderate			unclear	0.285
ER	**43**	*45*	**0.69**	*0.72*	Large			unclear	0.109
RE	**25**	*35*	**0.44**	*0.62*	Moderate			unclear	0.223
Individual responses in both Weeks 1 and 10, between PRE vs +0.5 h									
RO	**33**	*33*	**0.56**	*0.55*	Moderate			unclear	0.091
ER	**41**	*41*	**0.66**	*0.66*	Large			unclear	0.093
RE	**58**	*38*	**0.88**	*0.50*	Large	*very likely*	↑	@90%	0.040
Individual responses in both Weeks 1 and 10, between PRE vs +3.5 h									
RO									
ER	**40**	*40*	**0.65**	*0.65*	Large			unclear	0.095
RE	**55**	*46*	**0.84**	*0.65*	Large			unclear	0.053
Individual responses in both Weeks 1 and 10, between PRE vs +4 h									
RO	**56**	*36*	**0.86**	*0.48*	Large	*very likely*	↑	@90%	0.037
ER	**126**	*67*	**1.58**	*0.61*	Very large	*very likely*	↑	@90%	0.010
RE	**199**	*104*	**2.12**	*0.70*	Extremely large	*most likely*	↑	@99%	0.004
Individual responses in both Weeks 1 and 10, between PRE vs +7 h									
RO	**468**	*320*	**3.37**	*1.14*	Extremely large	*very likely*	↑	@90%	0.005
ER	**420**	*280*	**3.19**	*1.09*	Extremely large	*very likely*	↑	@90%	0.005
RE	**685**	*488*	**3.99**	*1.25*	Extremely large	*most likely*	↑	@99%	0.003

Representative Blots

Protein	Week	Resistance-Only	Endurance-Resistance	Resistance-Endurance
Akt^{Ser473}	1			
	10			
mTOR^{Ser2448}	1			
	10			
4EBP1$^{Thr37/46}$	1			
	10			
rpS6$^{Ser235/236}$	1			
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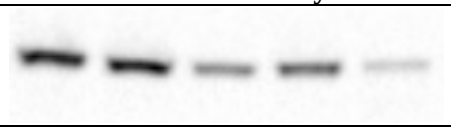
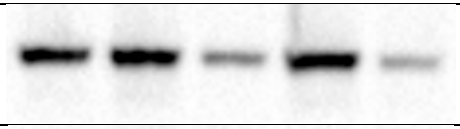
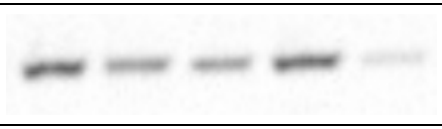
Protein	Week	Resistance-Only	Endurance-Resistance	Resistance-Endurance
eEF2^{Thr56}	1			
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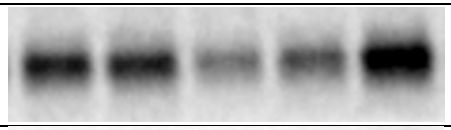
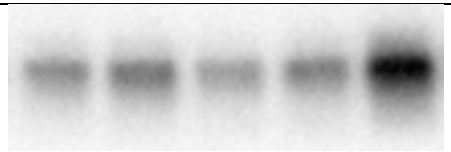
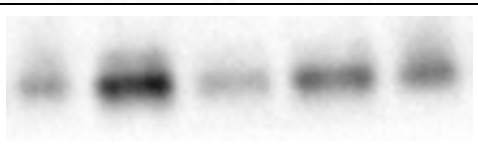
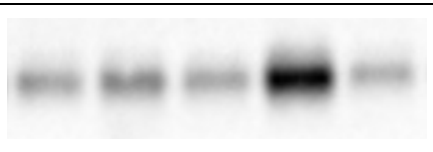
AMPKα^{Thr172}	1			
	10			
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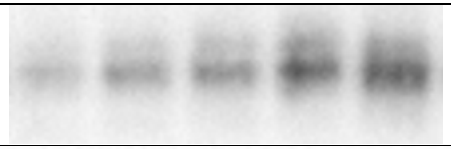
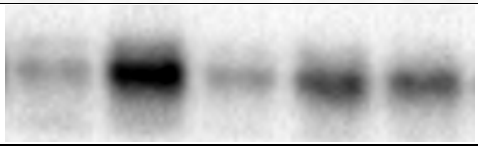
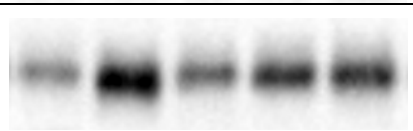
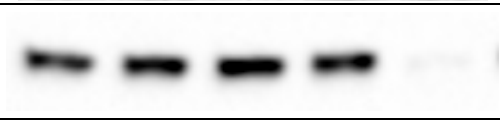
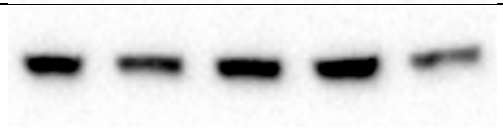
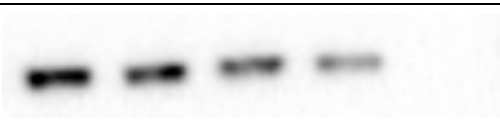
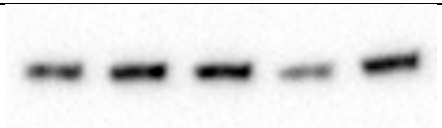
	10			
TSC2^{Thr1462}	1			
	10			

Appendix C – Chapter 5 Resources & Data

3-day food diary

INSTRUCTIONS FOR THE 3-DAY DIETARY RECORD

For the research project entitled: "*The effect of concurrent endurance and resistance exercise order on genotypic and phenotypic adaptations in previously-untrained males, following a single bout, one week, and 10-week training period*".

Please read carefully the following instructions to be followed when completing the 3-day dietary record form:

- You are required to record a detailed food diary (see next 3 pages) for the entire period specified by the student investigator.
- You will need to complete 3x 3-day food diaries during the training study: (1) at the beginning of the study; (2) 3 randomly selected days during the first 4 weeks; (3) and during the last 4 weeks. This is to monitor your normal food intake.
- As accurately as possible, please record ALL food and drink that is consumed during the specified 3-day period.
- Be as specific as possible: include brands of foods (e.g., Helga's bread), amounts (e.g., 2 slices, 20 grams, weigh where possible, estimate when weighing not possible), and types (e.g., mixed grain).

If you have any questions whatsoever, please do not hesitate to contact me either by phone or email:

Matt Lee
Mobile: 0432 043 596
Email: matthew.lee10@live.vu.edu.au

Participant ID: _____ Date: _____

Training Day		Rest/Non-exercise Day		*(Please tick)*

Meal	Time	Food/Drink (incl. type/brands/flavour/cooking method etc.)	Portion Size (g/mL)	Training/Exercise (if applicable)

In general, how did you feel today?

1-RM Prediction Table

Reference: *(Baechle and Earle, 2008)*

Max Reps (RM)	1	2	3	4	5	6	7	8	9	10	12	15
%1RM	100	95	93	90	87	85	83	80	77	75	67	65
Load (lbs or kg)	10	10	9	9	9	9	8	8	8	8	7	7
	20	19	19	18	17	17	17	16	15	15	13	13
	30	29	28	27	26	26	25	24	23	23	20	20
	40	38	37	36	35	34	33	32	31	30	27	26
	50	48	47	45	44	43	42	40	39	38	34	33
	60	57	56	54	52	51	50	48	46	45	40	39
	70	67	65	63	61	60	58	56	54	53	47	46
	80	76	74	72	70	68	66	64	62	60	54	52
	90	86	84	81	78	77	75	72	69	68	60	59
	100	95	93	90	87	85	83	80	77	75	67	65
	110	105	102	99	96	94	91	88	85	83	74	72
	120	114	112	108	104	102	100	96	92	90	80	78
	130	124	121	117	113	111	108	104	100	98	87	85
	140	133	130	126	122	119	116	112	108	105	94	91
	150	143	140	135	131	128	125	120	116	113	101	98
	160	152	149	144	139	136	133	128	123	120	107	104
	170	162	158	153	148	145	141	136	131	128	114	111
	180	171	167	162	157	153	150	144	139	135	121	117
	190	181	177	171	165	162	158	152	146	143	127	124
	200	190	186	180	174	170	166	160	154	150	134	130
	210	200	195	189	183	179	174	168	162	158	141	137
	220	209	205	198	192	187	183	176	170	165	148	143
	230	219	214	207	200	196	191	184	177	173	154	150
	240	228	223	216	209	204	199	192	185	180	161	156
	250	238	233	225	218	213	208	200	193	188	168	163
	260	247	242	234	226	221	216	208	200	195	174	169
	270	257	251	243	235	230	224	216	208	203	181	176
	280	266	260	252	244	238	233	224	216	210	188	182
	290	276	270	261	253	247	241	232	224	218	195	189
	300	285	279	270	261	255	249	240	231	225	201	195
	310	295	288	279	270	264	258	248	239	233	208	202
	320	304	298	288	279	272	266	256	247	240	215	208
	330	314	307	297	287	281	274	264	254	248	221	215
	340	323	316	306	296	289	282	272	262	255	228	221
	350	333	325	315	305	298	291	280	270	263	235	228
	360	342	335	324	313	306	299	288	277	270	241	234
	370	352	344	333	322	315	307	296	285	278	248	241
	380	361	353	342	331	323	316	304	293	285	255	247
	390	371	363	351	340	332	324	312	301	293	262	254
	400	380	372	360	348	340	332	320	308	300	268	260

	410	390	381	369	357	349	341	328	316	308	275	267
	420	399	391	378	366	357	349	336	324	315	282	273
	430	409	400	387	374	366	357	344	331	323	288	280
	440	418	409	396	383	374	366	352	339	330	295	286
	450	428	418	405	392	383	374	360	347	338	302	293
	460	437	428	414	401	391	382	368	355	345	309	299
	470	447	437	423	409	400	390	376	362	353	315	306
	480	456	446	432	418	408	399	384	370	360	322	312
	490	466	456	441	427	417	407	392	378	368	329	319
	500	475	465	450	435	425	415	400	385	375	335	325
	510	485	474	459	444	434	424	408	393	383	342	332
	520	494	484	468	453	442	432	416	401	390	349	338
	530	504	493	477	461	451	440	424	408	398	355	345
	540	513	502	486	470	459	449	432	416	405	362	351
	550	523	511	495	479	468	457	440	424	413	369	358
	560	532	521	504	488	476	465	448	432	420	376	364
	570	542	530	513	496	485	474	456	439	428	382	371
	580	551	539	522	505	493	482	464	447	435	389	377
	590	561	549	531	514	502	490	472	455	443	396	384
	600	570	558	540	522	510	498	480	462	450	402	390

Subjective Wellbeing and Fatigue Responses

Repetitions in Reserve (RIR) Scale

Resistance exercise-specific RPE – Reps. in Reserve

[Zourdos et al. 2016]

Rating	Description of Perceived Exertion
10	*Maximum effort – no further reps*
9.5	*No further reps, but could increase load*
9	*1 rep remaining*
8.5	*1-2 reps remaining*
8	*2 reps remaining*
7.5	*2-3 reps remaining*
7	*3 reps remaining*
5-6	*4-6 reps remaining*
3-4	*Light effort*
1-2	*Little to no effort*

Reference: *(Zourdos et al., 2016)*

Wellness/Readiness to train questionnaire

Reference: *(McLean et al., 2010)*

	5	4	3	2	1	TOTAL
Fatigue	Very fresh	Fresh	Normal	More tired than normal	Always tired	
Sleep Quality	Very restful	Good	Difficulty falling asleep	Restless sleep	Insomnia	
General muscle soreness	Feeling great	Feeling good	Normal	Increase in soreness/tightness	Very sore	
Stress Levels	Very relaxed	Relaxed	Normal	Feeling stressed	Highly stressed	
Mood	Very positive mood	A generally good mood	Less interested than usual in others and/or activities	Snappiness at teammates, family, and/or co-workers	Highly annoyed/ irritable/ down	

Session rating of perceived exertion (sRPE)

Reference: *(Foster et al., 2001)*

Session Rate of Perceived Exertion (sRPE)

Rating = Descriptor

0 = Rest

1 = Very, very easy

2 = Easy

3 = Moderate

4 = Somewhat Hard

5 = Hard

6 = *

7 = Very Hard

8 = *

9 = *

10 = Maximal

Participant characteristics for group allocation

		Age (y)	Height (cm)	Body Mass (kg)	Lean Mass (kg)	Fat Mass (kg)	1-RM Leg Press (kg)	$\dot{V}O_{2peak}$ (ml/kg/min)	W_{peak} (W)
END-RES	1	29.8	176	79.5	52.3	24.0	240.50	32.9	154
	2	22.6	179	88.6	55.5	30.1	315.50	31.9	170
	3	25.0	181	83.6	66.8	13.3	481.75	46.0	268
	4	26.4	193	84.0	65.3	14.9	433.00	51.2	280
	5	19.9	182	74.2	59.3	11.3	328.00	52.0	247
	6	18.8	182	58.5	43.6	10.0	193.00	46.9	190
	7	29.0	182	65.6	49.9	12.9	233.00	50.6	231
	8	18.5	179	77.8	58.3	12.1	333.00	46.5	213
	9	26.0	179	83.3	61.9	17.8	395.50	44.6	250
	10	18.4	169	54.1	43.4	8.2	251.75	49.2	162
MEAN		23.4	180.1	74.9	55.6	15.5	320.5	45.2	216.5
SD		4.4	6.0	11.7	8.3	6.8	94.0	7.2	45.5
RES-END	1	22.6	166	58.1	47.9	7.5	253.00	43.6	162
	2	18.8	174	63.1	48.8	11.5	218.00	45.4	189
	3	19.2	168	65.2	50.8	11.7	269.25	46.2	187
	4	23.2	174	74.4	59.0	12.4	423.00	42.0	177
	5	23.7	177	81.0	66.6	11.2	468.00	45.7	228
	6	23.6	182	70.8	53.7	13.8	228.00	43.8	189
	7	22.8	192	88.3	71.7	12.4	378.00	47.4	279
	8	28.9	181	75.4	53.4	18.8	263.00	36.7	172
	9	28.6	190	93.4	62.3	27.7	344.25	32.2	197
	10	18.4	179	74.1	62.5	8.4	381.75	53.9	270
MEAN		23.0	178.2	74.3	57.7	13.5	322.6	43.7	204.9
SD		3.7	8.5	11.0	8.0	5.8	87.8	5.9	40.8
RES-ONLY	1	27.5	177	85.1	63.3	17.8	418.00	51.1	283
	2	22.6	185	70.7	59.8	7.6	206.75	52.6	235
	3	22.4	186	70.2	49.7	17.4	201.75	30.6	140
	4	38.2	176	86.5	59.3	24.1	423.00	36.4	204
	5	27.6	182	80.6	58.6	18.9	398.00	35.0	186
	6	28.9	177	63.6	51.7	9.4	300.50	50.1	205
	7	30.6	188	91.6	71.5	15.9	480.50	50.0	313
	8	21.3	182	71.8	53.3	15.7	275.50	46.4	184
	9	28.0	175	61.1	51.8	6.5	318.00	45.8	187
MEAN		27.5	180.9	75.7	57.7	14.8	335.8	44.2	215.0
SD		5.2	4.6	10.7	6.9	5.8	99.4	8.1	53.6

Performance data & statistical analyses

Leg press 1-RM strength

Absolute 1-RM (kg)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	233.0	233.0	248.0	323.0	373.0	240.5
	2	303.0	313.0	318.0	368.0	395.5	315.5
	3	448.0	473.0	490.5	543.0	600.5	481.8
	4	413.0	433.0	433.0	463.0	483.0	433.0
	5	*	303.0	353.0	465.5	498.0	328.0
	6	153.0	183.0	203.0	240.5	258.0	193.0
	7	213.0	223.0	243.0	298.0	318.0	233.0
	8	318.0	333.0	333.0	403.0	443.0	333.0
	9	378.0	383.0	408.0	463.0	508.0	395.5
	10	223.0	245.5	258.0	283.0	313.0	251.8
	MEAN	298.0	312.3	328.8	385.0	419.0	320.5
	SD	100.4	95.1	93.5	98.3	106.4	94.0
RES-END	1	248.0	250.5	255.5	305.5	335.5	253.0
	2	213.0	223.0	213.0	268.0	330.5	218.0
	3	238.0	265.5	273.0	318.0	345.5	269.3
	4	393.0	423.0	423.0	463.0	473.0	423.0
	5	*	463.0	473.0	545.5	583.0	468.0
	6	223.0	223.0	233.0	283.0	315.5	228.0
	7	*	363.0	393.0	443.0	478.0	378.0
	8	263.0	263.0	263.0	303.0	323.0	263.0
	9	343.0	333.0	355.5	423.0	443.0	344.3
	10	373.0	373.0	390.5	453.0	493.0	381.8
	MEAN	286.8	318.0	327.3	380.5	412.0	322.6
	SD	71.6	85.4	90.5	95.9	93.7	87.8
RES-ONLY	1	383.0	413.0	423.0	458.0	503.0	418.0
	2	208.0	205.5	208.0	258.0	325.5	206.8
	3	173.0	185.5	218.0	273.0	320.5	201.8
	4	403.0	418.0	428.0	488.0	500.5	423.0
	5	358.0	373.0	423.0	455.5	458.0	398.0
	6	293.0	298.0	303.0	358.0	378.0	300.5
	7	453.0	473.0	488.0	560.5	603.0	480.5
	8	253.0	263.0	288.0	313.0	303.0	275.5
	9	273.0	318.0	318.0	363.0	383.0	318.0
	MEAN	310.8	327.4	344.1	391.9	419.4	335.8
	SD	94.1	99.3	100.1	103.9	102.4	99.4

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; ; SD = standard deviation.*

Countermovement jump performance

Peak Displacement (m)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	0.29	0.33	0.32	0.33	0.37	0.32
	2	0.28	0.29	0.30	0.29	0.31	0.29
	3	0.43	0.43	0.41	0.39	0.41	0.42
	4	0.41	0.40	0.39	0.42	0.39	0.40
	5	**	0.33	0.36	0.35	0.37	0.34
	6	0.31	0.34	0.32	0.33	0.31	0.33
	7	0.30	0.30	0.32	0.34	0.36	0.31
	8	**	0.33	0.32	0.34	0.35	0.33
	9	0.38	0.39	0.34	0.40	0.40	0.37
	10	0.37	0.40	0.40	0.41	0.42	0.40
	MEAN	0.35	0.35	0.35	0.36	0.37	0.35
	SD	0.06	0.05	0.04	0.04	0.04	0.04
RES-END	1	0.41	0.37	0.39	0.37	0.38	0.38
	2	0.35	0.33	0.32	0.30	0.32	0.33
	3	0.31	0.33	0.33	0.34	0.37	0.33
	4	0.47	0.45	0.45	0.42	0.40	0.45
	5	**	0.41	0.41	0.40	0.40	0.41
	6	0.30	0.32	0.32	0.31	0.32	0.32
	7	**	0.41	0.41	0.39	0.42	0.41
	8	0.30	0.28	0.29	0.31	0.29	0.28
	9	0.26	0.26	0.28	0.28	0.29	0.27
	10	0.37	0.41	0.38	0.37	0.39	0.39
	MEAN	0.35	0.36	0.36	0.35	0.36	0.36
	SD	0.07	0.06	0.06	0.05	0.05	0.06
RES-ONLY	1	**	0.33	0.40	0.42	0.39	0.36
	2	0.37	0.37	0.37	0.41	0.41	0.37
	3	0.28	0.30	0.28	0.33	0.34	0.29
	4	0.28	0.28	0.27	0.29	0.31	0.28
	5	0.37	0.40	0.41	0.40	0.40	0.41
	6	0.39	0.37	0.37	0.36	0.34	0.37
	7	0.33	0.34	0.34	0.36	0.36	0.34
	8	0.27	0.28	0.29	0.36	0.35	0.28
	9	0.47	0.52	0.48	0.49	0.44	0.50
	MEAN	0.35	0.35	0.36	0.38	0.37	0.36
	SD	0.07	0.07	0.07	0.06	0.04	0.07

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; ** Force plate error, trial data unavailable; SD = standard deviation.*

Peak Velocity (m/s)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	2.50	2.64	2.59	2.65	2.75	2.62
	2	2.43	2.47	2.54	2.54	2.58	2.50
	3	2.95	2.94	2.89	2.83	2.88	2.92
	4	2.92	2.89	2.86	2.95	2.85	2.88
	5	*	2.66	2.73	2.72	2.78	2.70
	6	2.56	2.68	2.57	2.63	2.57	2.62
	7	2.53	2.53	2.62	2.67	2.76	2.57
	8	*	2.65	2.60	2.69	2.74	2.63
	9	2.83	2.86	2.71	2.90	2.89	2.78
	10	2.77	2.87	2.89	2.89	2.93	2.88
	MEAN	2.69	2.72	2.70	2.75	2.77	2.71
	SD	0.21	0.16	0.14	0.14	0.12	0.15
RES-END	1	2.92	2.78	2.82	2.78	2.78	2.80
	2	2.69	2.65	2.59	2.50	2.59	2.62
	3	2.55	2.63	2.69	2.68	2.76	2.66
	4	3.13	3.07	3.07	2.98	2.94	3.07
	5	*	2.94	2.93	2.90	2.93	2.94
	6	2.51	2.59	2.60	2.54	2.58	2.60
	7	*	2.93	2.93	2.87	2.95	2.93
	8	2.55	2.45	2.51	2.55	2.50	2.48
	9	2.49	2.46	2.57	2.56	2.59	2.51
	10	2.78	2.89	2.81	2.75	2.83	2.85
	MEAN	2.70	2.74	2.75	2.71	2.75	2.75
	SD	0.23	0.22	0.19	0.17	0.17	0.20
RES-ONLY	1	**	2.62	2.88	2.94	2.86	2.75
	2	2.78	2.78	2.80	2.91	2.90	2.79
	3	2.52	2.57	2.48	2.67	2.73	2.52
	4	2.43	2.43	2.41	2.46	2.55	2.42
	5	2.77	2.87	2.92	2.87	2.87	2.90
	6	2.84	2.79	2.78	2.76	2.69	2.79
	7	2.64	2.66	2.67	2.72	2.73	2.66
	8	2.49	2.45	2.49	2.73	2.70	2.47
	9	3.09	3.24	3.13	3.17	3.00	3.19
	MEAN	2.69	2.71	2.73	2.80	2.78	2.72
	SD	0.22	0.25	0.24	0.20	0.14	0.24

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; ** Force plate error, trial data unavailable; SD = standard deviation.*

Peak Force (N)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	753	914	1007	1101	1104	961
	2	1202	1105	1089	998	990	1097
	3	1405	1413	1444	1216	1349	1429
	4	1286	1333	1421	1197	1156	1377
	5	*	884	1049	949	995	967
	6	732	863	938	829	868	901
	7	792	790	644	747	896	717
	8	*	977	995	1142	1060	986
	9	1232	1339	1190	1365	1382	1265
	10	674	670	681	691	771	675
	MEAN	1010	1029	1046	1023	1057	1037
	SD	298	257	265	220	199	256
RES-END	1	1025	1042	1045	1277	1271	1044
	2	825	921	1053	895	1004	987
	3	725	872	954	927	843	913
	4	1178	1169	1221	1136	1169	1195
	5	*	1320	1122	1198	1111	1221
	6	928	925	861	744	833	893
	7	*	1249	1304	1289	1308	1277
	8	770	718	790	771	780	754
	9	987	1032	1015	1073	1054	1023
	10	857	831	833	925	890	832
	MEAN	912	1008	1020	1023	1026	1014
	SD	149	192	167	199	188	174
RES-ONLY	1	**	1144	1331	1557	1233	1237
	2	1139	1103	1140	1148	1186	1122
	3	703	720	684	864	1045	702
	4	766	739	730	794	813	734
	5	1178	1148	1230	1271	1262	1189
	6	734	816	821	941	941	818
	7	1155	1303	1143	1233	1258	1223
	8	817	754	861	818	870	807
	9	783	779	824	857	884	801
	MEAN	909	945	974	1054	1054	959
	SD	208	226	237	263	183	227

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; ** Force plate error, trial data unavailable; SD = standard deviation.*

Peak Power (W)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	3341	3736	3501	3787	4216	3618
	2	3948	3941	3949	3949	3971	3945
	3	5171	5090	4783	4736	4812	4937
	4	4587	4450	4377	4496	4292	4414
	5	*	3547	3852	3763	3975	3699
	6	2796	3070	2969	2941	2987	3020
	7	2737	2688	2917	3006	3094	2803
	8	*	3943	3827	4178	4210	3885
	9	4694	4674	4461	4572	4769	4568
	10	2828	2879	3001	3031	3228	2940
	MEAN	3763	3802	3764	3846	3956	3783
	SD	971	787	662	672	654	720
RES-END	1	3564	3293	3341	3552	3722	3317
	2	3025	3113	3203	3135	3376	3158
	3	2949	3043	3022	3067	3352	3032
	4	5038	4997	4908	4651	4539	4952
	5	*	4284	4524	4242	4413	4404
	6	3249	3450	3329	3227	3427	3389
	7	*	4858	4861	4657	4952	4860
	8	3276	3112	3327	3392	3265	3219
	9	3752	3653	3834	3933	4032	3744
	10	3737	3856	3719	3627	3803	3788
	MEAN	3574	3766	3807	3748	3888	3786
	SD	664	723	707	597	581	712
RES-ONLY	1	**	3956	4472	4919	4688	4214
	2	4309	4227	4380	4666	4712	4304
	3	2915	3070	2834	3550	3938	2952
	4	3330	3382	3316	3581	3723	3349
	5	4324	4552	4711	4652	4720	4632
	6	3381	3407	3425	3590	3478	3416
	7	4575	4734	4590	4856	4950	4662
	8	2907	2812	2937	3465	3311	2875
	9	3810	3951	3903	4118	3914	3927
	MEAN	3694	3788	3841	4155	4159	3814
	SD	657	662	732	620	613	689

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; ** Force plate error, trial data unavailable; SD = standard deviation.*

Body composition

Total Body Mass (kg)

		BASE1	BASE2	MID	POST	PRE
END-RES	1	79.4	79.5	80.5	80.6	79.5
	2	88.3	88.9	87.9	87.6	88.6
	3	*	83.6	86.2	87.3	83.6
	4	83.8	84.2	84.6	83.3	84.0
	5	73.5	74.9	75.7	75.8	74.2
	6	58.2	58.8	60.2	62.2	58.5
	7	65.8	65.3	67.1	65.3	65.6
	8	78.5	77.1	76.1	77.1	77.8
	9	83.8	82.8	83.2	85.0	83.3
	10	54.0	54.2	56.3	56.5	54.1
	MEAN	73.9	74.9	75.8	76.1	74.9
	SD	12.1	11.7	11.1	11.1	11.7
RES-END	1	58.2	57.9	58.6	59.9	58.1
	2	62.5	63.6	66.5	66.0	63.1
	3	64.9	65.5	65.0	66.0	65.2
	4	74.8	74.0	73.8	73.6	74.4
	5	80.9	81.0	78.3	78.5	81.0
	6	70.6	70.9	73.5	73.8	70.8
	7	88.3	88.2	88.2	87.8	88.3
	8	75.6	75.1	74.4	74.0	75.4
	9	92.8	93.9	91.8	91.4	93.4
	10	74.1	74.2	75.5	75.0	74.1
	MEAN	74.3	74.4	74.6	74.6	74.3
	SD	11.0	11.0	10.1	9.6	11.0
RES-ONLY	1	85.8	84.3	85.8	84.9	85.1
	2	70.9	70.4	73.3	72.5	70.7
	3	69.6	70.8	72.3	73.2	70.2
	4	86.9	86.1	87.8	87.7	86.5
	5	80.8	80.4	81.2	83.2	80.6
	6	64.0	63.2	65.7	65.5	63.6
	7	91.6	91.5	92.8	94.0	91.6
	8	71.9	71.6	71.9	73.3	71.8
	9	60.7	61.4	62.5	62.3	61.1
	MEAN	75.8	75.5	77.0	77.4	75.7
	SD	10.9	10.5	10.4	10.6	10.7

*BASE1 = baseline scan 1; BASE2 = baseline scan 2; MID = mid-training scan; POST = post-training scan; PRE = average of BASE1 & BASE2, used for analysis; * participant was unable to complete two baseline scans; SD = standard deviation.*

Total Lean Mass (kg)

		BASE1	BASE2	MID	POST	PRE
END-RES	1	52.0	52.6	54.2	54.1	52.3
	2	55.3	55.7	56.2	56.6	55.5
	3	*	66.8	68.5	68.8	66.8
	4	65.4	65.2	66.2	65.2	65.3
	5	58.7	59.8	60.5	61.6	59.3
	6	41.7	45.6	46.6	47.6	43.6
	7	50.2	49.6	50.5	51.4	49.9
	8	58.8	57.9	62.1	63.2	58.3
	9	61.6	62.2	62.4	63.4	61.9
	10	43.4	43.3	46.1	45.6	43.4
	MEAN	54.1	55.9	57.3	57.7	55.6
	SD	8.0	8.0	7.9	7.9	8.3
RES-END	1	47.8	48.0	49.0	50.8	47.9
	2	48.3	49.4	52.6	52.6	48.8
	3	50.8	50.7	51.4	52.4	50.8
	4	59.0	59.1	59.8	60.2	59.0
	5	66.5	66.6	65.6	66.2	66.6
	6	53.6	53.7	56.3	55.9	53.7
	7	72.0	71.4	72.4	72.9	71.7
	8	53.5	53.3	55.4	56.4	53.4
	9	62.1	62.5	61.9	63.1	62.3
	10	62.6	62.4	63.4	63.8	62.5
	MEAN	57.6	57.7	58.8	59.4	57.7
	SD	8.1	7.9	7.2	7.1	8.0
RES-ONLY	1	63.8	62.9	63.5	64.0	63.3
	2	60.2	59.4	61.7	60.5	59.8
	3	49.4	50.0	51.8	52.5	49.7
	4	59.4	59.3	61.9	60.9	59.3
	5	58.8	58.4	59.7	61.3	58.6
	6	52.0	51.4	53.4	53.1	51.7
	7	71.3	71.7	72.8	74.8	71.5
	8	53.9	52.6	52.7	53.3	53.3
	9	51.5	52.0	53.0	53.0	51.8
	MEAN	57.8	57.5	58.9	59.3	57.7
	SD	6.9	6.9	6.9	7.3	6.9

*BASE1 = baseline scan 1; BASE2 = baseline scan 2; MID = mid-training scan; POST = post-training scan; PRE = average of BASE1 & BASE2, used for analysis; * participant was unable to complete two baseline scans; SD = standard deviation.*

Upper-body Lean Mass (kg)

		BASE1	BASE2	MID	POST	PRE
END-RES	1	29.5	30.2	30.5	30.3	29.9
	2	30.2	30.6	30.7	31.1	30.4
	3	*	39.3	40.5	40.5	39.3
	4	40.4	39.6	40.4	38.9	40.0
	5	35.2	36.1	36.4	37.4	35.6
	6	25.7	26.6	27.1	28.2	26.1
	7	30.2	29.5	30.0	30.3	29.9
	8	37.4	36.8	37.6	38.1	37.1
	9	36.2	37.3	37.4	37.5	36.8
	10	26.2	26.2	27.6	27.8	26.2
	MEAN	32.3	33.2	33.8	34.0	33.1
	SD	5.1	5.1	5.1	4.9	5.2
RES-END	1	28.8	29.2	29.6	31.0	29.0
	2	29.0	31.0	31.4	32.2	30.0
	3	30.7	30.6	31.1	31.9	30.6
	4	35.3	35.9	35.4	36.4	35.6
	5	40.4	40.4	39.6	40.3	40.4
	6	32.7	32.7	34.6	34.1	32.7
	7	44.0	43.2	44.1	41.3	43.6
	8	31.6	31.6	32.9	34.1	31.6
	9	35.9	35.9	35.9	36.9	35.9
	10	37.7	37.3	37.9	37.9	37.5
	MEAN	34.6	34.8	35.3	35.6	34.7
	SD	5.0	4.6	4.4	3.6	4.8
RES-ONLY	1	38.3	37.7	39.1	38.7	38.0
	2	36.8	36.1	37.9	37.1	36.4
	3	29.1	29.9	30.4	31.0	29.5
	4	36.0	36.2	37.3	36.8	36.1
	5	34.3	34.1	34.5	35.5	34.2
	6	31.9	31.5	32.8	32.3	31.7
	7	41.8	41.9	42.4	44.2	41.9
	8	32.1	31.1	30.8	31.3	31.6
	9	31.1	31.6	31.6	31.6	31.4
	MEAN	34.6	34.5	35.2	35.4	34.5
	SD	4.0	3.9	4.2	4.4	3.9

*BASE1 = baseline scan 1; BASE2 = baseline scan 2; MID = mid-training scan; POST = post-training scan; PRE = average of BASE1 & BASE2, used for analysis; * participant was unable to complete two baseline scans; SD = standard deviation.*

Lower-body Lean Mass (kg)

		BASE1	BASE2	MID	POST	PRE
END-RES	1	18.8	18.7	19.9	20.1	18.8
	2	21.6	21.5	22.0	22.1	21.6
	3	*	24.1	24.7	25.0	24.1
	4	22.6	22.8	22.7	22.7	22.7
	5	19.8	20.1	20.3	20.3	20.0
	6	16.0	15.8	16.3	16.3	15.9
	7	16.6	16.7	17.2	17.9	16.7
	8	21.4	21.1	21.2	21.8	21.2
	9	21.8	21.3	21.5	22.3	21.6
	10	14.2	14.1	15.4	14.8	14.2
	MEAN	19.2	19.6	20.1	20.3	19.7
	SD	3.0	3.2	3.0	3.2	3.2
RES-END	1	16.2	16.0	16.6	17.0	16.1
	2	16.1	15.2	17.9	17.1	15.6
	3	17.2	17.1	17.3	17.5	17.1
	4	20.1	19.7	20.9	20.3	19.9
	5	22.9	22.9	22.7	22.7	22.9
	6	17.4	17.5	18.3	18.5	17.5
	7	25.5	25.9	25.9	26.2	25.7
	8	17.8	18.1	18.8	18.6	17.9
	9	23.5	23.1	22.9	23.2	23.3
	10	21.4	21.6	21.8	22.4	21.5
	MEAN	19.8	19.7	20.3	20.4	19.8
	SD	3.3	3.5	3.0	3.1	3.4
RES-ONLY	1	21.6	21.4	20.8	21.4	21.5
	2	19.9	19.8	20.2	19.8	19.8
	3	16.9	16.7	18.0	19.2	16.8
	4	19.7	19.6	20.9	20.6	19.7
	5	20.8	20.6	21.4	22.1	20.7
	6	16.5	16.4	17.0	17.2	16.5
	7	26.0	26.2	26.8	27.1	26.1
	8	18.8	18.2	18.6	18.5	18.5
	9	17.3	17.2	18.3	18.1	17.2
	MEAN	19.7	19.6	20.2	20.4	19.6
	SD	2.9	3.0	2.9	2.9	3.0

*BASE1 = baseline scan 1; BASE2 = baseline scan 2; MID = mid-training scan; POST = post-training scan; PRE = average of BASE1 & BASE2, used for analysis; * participant was unable to complete two baseline scans; SD = standard deviation.*

Total Fat Mass (kg)

		BASE1	BASE2	MID	POST	PRE
END-RES	1	24.3	23.8	23.3	23.4	24.0
	2	30.0	30.3	28.7	28.0	30.1
	3	*	13.3	14.2	14.9	13.3
	4	14.6	15.1	14.5	14.1	14.9
	5	11.1	11.4	11.5	10.6	11.3
	6	9.7	10.3	10.8	11.6	10.0
	7	13.0	12.8	13.7	11.0	12.9
	8	12.3	11.8	10.9	10.8	12.1
	9	18.5	17.1	17.2	17.9	17.8
	10	8.1	8.4	7.7	8.4	8.2
	MEAN	15.7	15.4	15.3	15.1	15.5
	SD	7.3	6.7	6.4	6.3	6.8
RES-END	1	7.8	7.3	7.0	6.4	7.5
	2	11.5	11.5	11.2	10.7	11.5
	3	11.4	12.1	10.9	10.9	11.7
	4	12.8	12.0	11.1	10.4	12.4
	5	11.1	11.2	9.5	9.0	11.2
	6	13.7	13.9	14.0	14.6	13.8
	7	12.2	12.7	11.5	10.8	12.4
	8	19.0	18.7	16.4	14.6	18.8
	9	27.4	28.0	26.5	25.0	27.7
	10	8.2	8.6	8.9	8.8	8.4
	MEAN	13.5	13.6	12.7	12.1	13.5
	SD	5.8	5.9	5.5	5.2	5.8
RES-ONLY	1	18.1	17.5	18.3	17.0	17.8
	2	7.4	7.8	8.4	8.7	7.6
	3	17.1	17.7	17.2	17.6	17.4
	4	24.4	23.8	22.8	23.6	24.1
	5	18.9	18.9	18.4	18.8	18.9
	6	9.5	9.3	9.8	9.8	9.4
	7	16.1	15.7	15.8	14.9	15.9
	8	16.2	15.3	16.4	17.3	15.7
	9	6.3	6.6	6.6	6.5	6.5
	MEAN	14.9	14.7	14.9	14.9	14.8
	SD	5.9	5.7	5.4	5.5	5.8

*BASE1 = baseline scan 1; BASE2 = baseline scan 2; MID = mid-training scan; POST = post-training scan; PRE = average of BASE1 & BASE2, used for analysis; * participant was unable to complete two baseline scans; SD = standard deviation.*

Aerobic fitness

Absolute $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	**	2.54	2.66	2.89	3.00	2.60
	2	2.58	2.77	2.87	3.07	3.17	2.82
	3	3.88	3.85	3.87	4.02	4.06	3.86
	4	4.41	4.45	4.26	**	4.60	4.36
	5	*	3.78	3.87	**	4.16	3.82
	6	2.94	2.72	2.76	2.68	3.02	2.74
	7	*	3.25	3.42	3.58	3.74	3.33
	8	3.41	3.78	3.47	3.98	3.91	3.63
	9	3.63	3.73	3.81	3.87	4.02	3.77
	10	2.81	2.64	2.64	2.93	3.09	2.64
	MEAN	3.38	3.35	3.36	3.38	3.68	3.36
	SD	0.65	0.66	0.59	0.55	0.57	0.62
RES-END	1	2.41	2.45	2.58	2.81	2.72	2.51
	2	**	2.84	2.89	2.72	3.32	2.86
	3	3.01	3.03	3.14	3.09	3.07	3.09
	4	**	3.11	3.18	3.46	3.48	3.15
	5	*	3.73	3.52	3.81	3.88	3.63
	6	3.04	2.98	3.16	3.35	3.40	3.07
	7	*	4.35	4.11	4.52	4.31	4.23
	8	2.82	2.82	2.81	3.31	3.31	2.81
	9	2.92	3.09	3.06	3.30	3.52	3.07
	10	*	3.87	4.13	**	4.13	4.00
	MEAN	2.84	3.23	3.26	3.38	3.51	3.24
	SD	0.26	0.58	0.52	0.54	0.48	0.54
RES-ONLY	1	**	4.26	4.37	4.21	3.85	4.31
	2	3.96	3.69	3.63	3.70	3.81	3.66
	3	2.33	2.18	2.12	2.40	2.27	2.15
	4	3.11	3.17	3.13	3.18	3.52	3.15
	5	2.86	2.74	2.91	2.96	2.95	2.83
	6	3.57	3.15	3.25	3.09	3.09	3.20
	7	4.82	4.62	4.57	4.61	4.50	4.60
	8	3.06	3.30	3.34	3.07	3.17	3.32
	9	2.62	2.83	2.75	2.84	2.82	2.79
	MEAN	3.29	3.33	3.34	3.34	3.33	3.33
	SD	0.80	0.76	0.77	0.70	0.66	0.76

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; ** Moxus system error, trial data unavailable; SD = standard deviation.*

Relative $\dot{V}O_{2peak}$ ($mL \cdot kg \cdot min^{-1}$)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	**	32.4	33.4	36.5	36.8	32.9
	2	29.0	31.2	32.5	34.5	36.0	31.9
	3	46.1	46.1	45.9	47.3	47.0	46.0
	4	52.4	52.0	50.3	**	54.3	51.2
	5	*	52.2	51.8	**	55.5	52.0
	6	50.5	46.6	47.2	44.9	49.0	46.9
	7	*	49.1	52.1	53.5	57.3	50.6
	8	43.7	47.9	45.2	52.2	50.6	46.5
	9	42.6	44.1	45.2	45.8	47.5	44.6
	10	51.4	49.8	48.6	53.0	54.7	49.2
	MEAN	45.1	45.1	45.2	45.9	48.9	45.2
	SD	8.1	7.5	6.9	7.3	7.4	7.2
RES-END	1	41.9	42.3	44.9	48.2	46.2	43.6
	2	**	44.9	46.0	41.2	50.7	45.4
	3	46.0	44.8	47.6	46.8	46.6	46.2
	4	**	41.3	42.6	47.1	46.9	42.0
	5	*	47.6	43.9	49.2	49.0	45.7
	6	43.3	43.2	44.5	45.8	45.5	43.8
	7	*	48.4	46.4	50.0	47.7	47.4
	8	36.4	36.8	36.6	43.8	44.5	36.7
	9	30.8	32.2	32.1	34.8	36.8	32.2
	10	*	52.1	55.6	**	54.6	53.9
	MEAN	39.7	43.4	44.0	45.2	46.9	43.7
	SD	6.1	5.7	6.3	4.8	4.6	5.9
RES-ONLY	1	**	50.9	51.3	48.1	45.3	51.1
	2	55.7	53.1	52.1	49.8	51.9	52.6
	3	33.7	30.9	30.3	33.5	31.4	30.6
	4	36.2	36.6	36.3	36.2	39.4	36.4
	5	35.9	34.1	36.0	36.3	35.1	35.0
	6	56.3	49.6	50.7	47.2	47.1	50.1
	7	51.8	50.2	49.7	49.3	48.0	50.0
	8	47.7	46.1	46.8	40.4	43.4	46.4
	9	43.0	46.3	45.3	45.5	45.6	45.8
	MEAN	45.0	44.2	44.3	42.9	43.0	44.2
	SD	9.2	8.2	8.0	6.4	6.5	8.1

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; ** Moxus system error, trial data unavailable; SD = standard deviation.*

Power at the Lactate Threshold (W)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	133	114	117	131	137	116
	2	130	127	133	157	152	130
	3	164	182	205	216	230	193
	4	206	205	207	236	254	206
	5	*	203	209	217	227	206
	6	146	114	123	141	156	119
	7	*	168	170	183	184	169
	8	147	173	173	215	214	173
	9	190	187	201	221	226	194
	10	129	113	119	135	147	116
	MEAN	156	159	166	185	193	162
	SD	29	38	39	41	42	38
RES-END	1	109	123	124	141	124	123
	2	130	148	140	134	153	144
	3	152	141	134	146	136	138
	4	115	130	131	146	168	130
	5	*	166	159	189	199	163
	6	128	138	141	158	173	139
	7	*	212	227	227	231	220
	8	119	130	127	157	176	128
	9	148	146	153	167	198	150
	10	*	190	203	217	227	196
	MEAN	128	152	154	168	179	153
	SD	16	29	34	32	36	31
RES-ONLY	1	190	230	220	177	179	225
	2	210	160	143	184	183	152
	3	96	111	109	109	111	110
	4	149	153	146	159	178	150
	5	136	130	129	129	143	129
	6	127	134	120	**	120	127
	7	254	246	240	244	239	243
	8	136	143	136	137	109	139
	9	150	139	140	143	127	139
	MEAN	161	161	154	160	154	157
	SD	49	46	45	42	44	45

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; ** YSI system error, trial data unavailable; SD = standard deviation.*

Peak Aerobic Power (W)

		FAM1	FAM2	BASE	MID	POST	PRE
END-RES	1	165	152	156	172	180	154
	2	155	171	169	199	199	170
	3	256	260	276	282	298	268
	4	272	281	279	288	312	280
	5	*	251	243	243	262	247
	6	165	195	185	191	201	190
	7	*	228	233	237	247	231
	8	230	223	204	268	281	213
	9	239	241	259	277	284	250
	10	178	159	166	184	200	162
	MEAN	207	216	217	234	246	217
	SD	47	45	47	44	48	46
RES-END	1	151	158	165	176	175	162
	2	189	190	188	189	205	189
	3	200	186	187	203	199	187
	4	175	169	185	203	220	177
	5	*	226	230	244	249	228
	6	185	190	188	206	228	189
	7	*	264	294	281	303	279
	8	170	170	174	209	230	172
	9	183	199	196	220	239	197
	10	*	265	276	279	293	270
	MEAN	179	202	208	221	234	205
	SD	16	38	44	36	40	41
RES-ONLY	1	286	282	283	248	245	283
	2	223	233	237	244	231	235
	3	133	145	135	148	148	140
	4	201	203	205	209	226	204
	5	189	181	190	180	178	186
	6	205	202	207	190	193	205
	7	320	306	319	319	311	313
	8	175	179	188	169	186	184
	9	190	186	188	185	186	187
	MEAN	214	213	217	210	211	215
	SD	57	52	55	52	48	54

*FAM1 = familiarisation trial 1; FAM2 = familiarisation trial 2; BASE = baseline trial; MID = mid-training trial; POST = post-training trial; PRE = average of FAM2 & BASE, used for analysis; * participant was unable to complete two familiarisation trials; SD = standard deviation.*

Differences at baseline

Variable	Group	Mean	*SD*	Between-group comparison	Standardised Effect Size Cohen's d	Magnitude
Lower Body Maximal Dynamic Strength						
Leg Press 1-RM (kg)	RES-Only	344	*100*	RES-Only vs END-RES	-0.15	Trivial
	END-RES	329	*94*	RES-Only vs RES-END	-0.17	Trivial
	RES-END	327	*90*	END-RES vs RES-END	0.01	Trivial
Lower Body Maximal Power						
Peak Displacement (cm)	RES-Only	35.6	*7.0*	RES-Only vs END-RES	-0.08	Trivial
	END-RES	35.2	*4.2*	RES-Only vs RES-END	0.04	Trivial
	RES-END	35.8	*5.9*	END-RES vs RES-END	-0.12	Trivial
Peak Velocity (m/s)	RES-Only	2.72	*0.24*	RES-Only vs END-RES	-0.06	Trivial
	END-RES	2.71	*0.15*	RES-Only vs RES-END	0.15	Trivial
	RES-END	2.75	*0.20*	END-RES vs RES-END	-0.21	Small
Peak Force (N)	RES-Only	959	*227*	RES-Only vs END-RES	0.38	Small
	END-RES	1037	*256*	RES-Only vs RES-END	0.26	Small
	RES-END	1014	*174*	END-RES vs RES-END	0.11	Trivial
Peak Power (W)	RES-Only	3814	*689*	RES-Only vs END-RES	-0.05	Trivial
	END-RES	3783	*720*	RES-Only vs RES-END	-0.04	Trivial
	RES-END	3786	*712*	END-RES vs RES-END	-0.01	Trivial
Body Composition						
Total Lean Mass (kg)	RES-Only	57.7	*6.9*	RES-Only vs END-RES	-0.28	Small
	END-RES	55.6	*8.3*	RES-Only vs RES-END	0.00	Trivial
	RES-END	57.7	*8.0*	END-RES vs RES-END	-0.28	Small
Upper Body Lean Mass (kg)	RES-Only	34.5	*3.9*	RES-Only vs END-RES	-0.32	Small
	END-RES	33.1	*5.2*	RES-Only vs RES-END	0.04	Trivial
	RES-END	34.7	*4.8*	END-RES vs RES-END	-0.35	Small
Lower Body Lean Mass (kg)	RES-Only	19.6	*3.0*	RES-Only vs END-RES	0.00	Trivial
	END-RES	19.7	*3.2*	RES-Only vs RES-END	0.04	Trivial
	RES-END	19.8	*3.4*	END-RES vs RES-END	-0.03	Trivial
Total Fat Mass (kg)	RES-Only	14.8	*5.8*	RES-Only vs END-RES	0.11	Trivial
	END-RES	15.5	*6.8*	RES-Only vs RES-END	-0.22	Small
	RES-END	13.5	*5.8*	END-RES vs RES-END	0.33	Small
Maximal Aerobic Fitness						
Absolute $\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	RES-Only	3.33	*0.76*	RES-Only vs END-RES	0.04	Trivial
	END-RES	3.36	*0.62*	RES-Only vs RES-END	-0.15	Trivial
	RES-END	3.24	*0.54*	END-RES vs RES-END	0.19	Trivial
Relative $\dot{V}O_{2peak}$ ($mL \cdot kg \cdot min^{-1}$)	RES-Only	44.2	*8.1*	RES-Only vs END-RES	0.14	Trivial
	END-RES	45.2	*7.2*	RES-Only vs RES-END	-0.08	Trivial
	RES-END	43.7	*5.9*	END-RES vs RES-END	0.23	Small
Lactate Threshold, W_{LT} (W)	RES-Only	157	*45*	RES-Only vs END-RES	0.12	Trivial
	END-RES	162	*38*	RES-Only vs RES-END	-0.10	Trivial
	RES-END	153	*31*	END-RES vs RES-END	0.22	Small
Peak Aerobic Power, W_{peak} (W)	RES-Only	215	*54*	RES-Only vs END-RES	0.03	Trivial
	END-RES	217	*46*	RES-Only vs RES-END	-0.22	Small
	RES-END	205	*41*	END-RES vs RES-END	0.25	Small

kg = kilogram; cm = centimetre; m/s = meters per second; N = Newtons; W = Watts; L.min-1 = litres per minute; $mL \cdot kg \cdot min^{-1}$ = millilitres per kilogram of body mass per minute; SD = standard deviation.

Within-group changes (PRE to MID-training)

		Percent Change			Standardised Effect Size (ES)				Likelihood true effect		Threshold for	
Variable	**Group**	*mean %*	±	*SD*	ES	±	*90%CI*	Magnitude	**is substantially ↑ ↔ ↓**		**clear effect:**	***P* value**
Leg Press 1-RM	Resistance-Only	*15.1*	±	*4.6*	0.49	±	*0.10*	**Small**	***most likely***	↑	**@5/.1%**	0.000
	Endurance-Resistance	*17.7*	±	*7.0*	0.56	±	*0.14*	**Small**	***most likely***	↑	**@5/.1%**	0.000
	Resistance-Endurance	*16.9*	±	*3.1*	0.54	±	*0.07*	**Small**	***most likely***	↑	**@5/.1%**	0.000
Peak Displacement	Resistance-Only	*6.9*	±	*9.8*	0.41	±	*0.40*	Small	*likely*	↑	OR>66.3	0.089
	Endurance-Resistance	*2.4*	±	*4.8*	0.15	±	*0.17*	Trivial	*possibly*	↑	@25/.5%	0.150
	Resistance-Endurance	*-2.2*	±	*4.6*	-0.14	±	*0.16*	**Trivial**	***likely***	↔	**@5/.1%**	0.157
Peak Velocity	Resistance-Only	*3.0*	±	*4.2*	0.42	±	*0.40*	Small	*likely*	↑	OR>66.3	0.087
	Endurance-Resistance	*1.3*	±	*2.1*	0.18	±	*0.17*	Trivial	*possibly*	↑	@25/.5%	0.081
	Resistance-Endurance	*-1.0*	±	*2.0*	-0.15	±	*0.17*	**Trivial**	***possibly***	↓	**@5/.1%**	0.135
Peak Force	Resistance-Only	*8.7*	±	*9.6*	0.37	±	*0.27*	Small	*likely*	↑	@25/.5%	0.035
	Endurance-Resistance	*0.1*	±	*11.2*	0.00	±	*0.28*	Trivial	*likely*	↔	@25/.5%	0.985
	Resistance-Endurance	*0.6*	±	*11.6*	0.03	±	*0.29*	Trivial	*likely*	↔	@25/.5%	0.866
Peak Power	Resistance-Only	*9.7*	±	*5.5*	0.50	±	*0.18*	**Small**	***very likely***	↑	**@5/.1%**	0.001
	Endurance-Resistance	*1.9*	±	*3.7*	0.10	±	*0.11*	**Trivial**	***unlikely***	↑	**@5/.1%**	0.142
	Resistance-Endurance	*-0.6*	±	*4.2*	-0.03	±	*0.13*	**Trivial**	***very likely***	↔	**@5/.1%**	0.632
Total Lean Mass	Resistance-Only	*2.3*	±	*1.9*	0.16	±	*0.08*	**Trivial**	***unlikely***	↑	**@5/.1%**	0.008
	Endurance-Resistance	*3.0*	±	*1.9*	0.21	±	*0.08*	**Small**	***possibly***	↑	**@5/.1%**	0.001
	Resistance-Endurance	*2.3*	±	*2.1*	0.16	±	*0.09*	**Trivial**	***unlikely***	↑	**@5/.1%**	0.008
Upper Body Lean Mass	Resistance-Only	*1.8*	±	*2.1*	0.13	±	*0.09*	**Trivial**	***unlikely***	↑	**@5/.1%**	0.034
	Endurance-Resistance	*2.0*	±	*1.3*	0.15	±	*0.06*	**Trivial**	***unlikely***	↑	**@5/.1%**	0.001
	Resistance-Endurance	*2.2*	±	*2.5*	0.15	±	*0.11*	**Trivial**	***unlikely***	↑	**@5/.1%**	0.029
Lower Body Lean Mass	Resistance-Only	*3.0*	±	*3.2*	0.19	±	*0.12*	**Trivial**	***possibly***	↑	**@5/.1%**	0.023
	Endurance-Resistance	*2.6*	±	*2.1*	0.16	±	*0.08*	**Trivial**	***unlikely***	↑	**@5/.1%**	0.006
	Resistance-Endurance	*3.2*	±	*3.5*	0.20	±	*0.12*	**Small**	***possibly***	↑	**@5/.1%**	0.017
Total Fat Mass	Resistance-Only	*1.6*	±	*3.1*	0.04	±	*0.05*	**Trivial**	***most likely***	↔	**@5/.1%**	0.175
	Endurance-Resistance	*-0.5*	±	*6.5*	-0.01	±	*0.09*	Trivial	*most likely*	↔	@25/.5%	0.798
	Resistance-Endurance	*-6.2*	±	*7.2*	-0.16	±	*0.10*	**Trivial**	***likely***	↔	**@5/.1%**	0.019

(continued)

Variable	Group	Percent Change mean % ± *SD*	Standardised Effect Size (ES) ES ± *90%CI* Magnitude	Likelihood true effect is substantially ↑ ↔ ↓	Threshold for clear effect:	*P* value
Absolute $\dot{V}O_{2peak}$	Resistance-Only	0.8 ± *4.5*	0.04 ± *0.14* **Trivial**	***very likely*** ↔	**@5/.1%**	0.597
	Endurance-Resistance	6.7 ± *5.0*	0.33 ± *0.16* **Small**	***likely*** ↑	**@5/.1%**	0.006
	Resistance-Endurance	6.3 ± *6.7*	0.32 ± *0.21* **Small**	***likely*** ↑	**@5/.1%**	0.023
Relative $\dot{V}O_{2peak}$	Resistance-Only	-2.3 ± *4.5*	-0.14 ± *0.16* **Trivial**	***likely*** ↔	**@5/.1%**	0.158
	Endurance-Resistance	5.4 ± *4.8*	0.31 ± *0.17* **Small**	***likely*** ↑	**@5/.1%**	0.011
	Resistance-Endurance	5.5 ± *7.0*	0.31 ± *0.25* Small	*likely* ↑	@25/.5%	0.045
Lactate Threshold	Resistance-Only	-0.2 ± *12.1*	-0.01 ± *0.32* Trivial	*possibly* ↔	@25/.5%	0.971
	Endurance-Resistance	15.0 ± *4.7*	0.60 ± *0.12* **Moderate**	***most likely*** ↑	**@5/.1%**	0.000
	Resistance-Endurance	9.7 ± *7.9*	0.40 ± *0.19* **Small**	***very likely*** ↑	**@5/.1%**	0.005
Peak Aerobic Power	Resistance-Only	-1.9 ± *6.7*	-0.09 ± *0.19* **Trivial**	***likely*** ↔	**@5/.1%**	0.401
	Endurance-Resistance	8.8 ± *7.6*	0.39 ± *0.20* **Small**	***likely*** ↑	**@5/.1%**	0.006
	Resistance-Endurance	7.7 ± *5.0*	0.35 ± *0.13* **Small**	***very likely*** ↑	**@5/.1%**	0.001

mean % = mean percent change; SD = standard deviation; ES = standardised effect size (Cohen's d); 90%CI = 90% confidence interval;
↑ = improved; ↔ = trivial; ↓ = interfered;
Clinical thresholds: @25/.5% = >25% chance of improvement, <0.5 % risk of interference; @5/.1% = >5% chance of improvement, <0.1% risk of interference;
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1%) after adjusting for multiple inferences.*

Within-group changes (MID to POST-training)

		Percent Change			Standardised Effect Size (ES)				Likelihood true effect		Threshold for	
Variable	**Group**	mean %	±	*SD*	ES	±	90%CI	Magnitude	**is substantially ↑ ↔ ↓**		**clear effect:**	***P* value**
Leg Press 1-RM	Resistance-Only	7.7	±	*8.4*	0.26	±	0.17	**Small**	***possibly***	↑	**@5/.1%**	0.025
	Endurance-Resistance	8.9	±	*2.8*	0.29	±	0.06	**Small**	***very likely***	↑	**@5/.1%**	0.000
	Resistance-Endurance	8.9	±	*5.1*	0.30	±	0.10	**Small**	***likely***	↑	**@5/.1%**	0.000
Peak Displacement	Resistance-Only	-1.4	±	*5.4*	-0.09	±	0.20	**Trivial**	***likely***	↔	**@5/.1%**	0.432
	Endurance-Resistance	2.0	±	*5.5*	0.13	±	0.20	Trivial	*possibly*	↔	@25/.5%	0.270
	Resistance-Endurance	2.1	±	*5.1*	0.13	±	0.18	Trivial	*possibly*	↑	@25/.5%	0.209
Peak Velocity	Resistance-Only	-0.8	±	*2.7*	-0.11	±	0.23	**Trivial**	***possibly***	↔	**@5/.1%**	0.411
	Endurance-Resistance	0.9	±	*2.4*	0.13	±	0.19	Trivial			unclear	0.256
	Resistance-Endurance	1.3	±	*1.8*	0.18	±	0.15	**Trivial**	***possibly***	↑	**@5/.1%**	0.054
Peak Force	Resistance-Only	1.3	±	*11.6*	0.06	±	0.30	Trivial	*possibly*	↔	@25/.5%	0.730
	Endurance-Resistance	3.9	±	*7.9*	0.17	±	0.20	Trivial	*possibly*	↑	@25/.5%	0.143
	Resistance-Endurance	0.5	±	*7.2*	0.02	±	0.18	Trivial	*likely*	↔	@25/.5%	0.811
Peak Power	Resistance-Only	0.1	±	*5.2*	0.01	±	0.17	**Trivial**	***likely***	↔	**@5/.1%**	0.950
	Endurance-Resistance	3.0	±	*4.2*	0.16	±	0.13	**Trivial**	***possibly***	↑	**@5/.1%**	0.049
	Resistance-Endurance	3.9	±	*4.2*	0.21	±	0.13	**Small**	***possibly***	↑	**@5/.1%**	0.016
Total Lean Mass	Resistance-Only	0.5	±	*1.7*	0.04	±	0.07	**Trivial**	***most likely***	↔	**@5/.1%**	0.408
	Endurance-Resistance	0.7	±	*1.3*	0.05	±	0.05	**Trivial**	***most likely***	↔	**@5/.1%**	0.101
	Resistance-Endurance	1.2	±	*1.2*	0.08	±	0.05	**Trivial**	***most likely***	↔	**@5/.1%**	0.014
Upper Body Lean Mass	Resistance-Only	0.5	±	*2.2*	0.04	±	0.10	**Trivial**	***very likely***	↔	**@5/.1%**	0.485
	Endurance-Resistance	0.6	±	*2.0*	0.04	±	0.08	**Trivial**	***most likely***	↔	**@5/.1%**	0.356
	Resistance-Endurance	1.3	±	*3.3*	0.09	±	0.14	Trivial	*likely*	↔	@25/.5%	0.249
Lower Body Lean Mass	Resistance-Only	1.1	±	*2.7*	0.07	±	0.10	**Trivial**	***very likely***	↔	**@5/.1%**	0.243
	Endurance-Resistance	0.9	±	*2.3*	0.06	±	0.08	**Trivial**	***very likely***	↔	**@5/.1%**	0.251
	Resistance-Endurance	0.2	±	*2.3*	0.01	±	0.08	**Trivial**	***most likely***	↔	**@5/.1%**	0.772
Total Fat Mass	Resistance-Only	0.2	±	*4.4*	0.01	±	0.07	**Trivial**	***most likely***	↔	**@5/.1%**	0.882
	Endurance-Resistance	-1.3	±	*9.1*	-0.03	±	0.12	**Trivial**	***very likely***	↔	**@5/.1%**	0.654
	Resistance-Endurance	-4.5	±	*4.7*	-0.11	±	0.06	**Trivial**	***very likely***	↔	**@5/.1%**	0.011

(continued)

Variable	Group	Percent Change mean % ± *SD*	Standardised Effect Size (ES) ES ± *90%CI* Magnitude	Likelihood true effect is substantially ↑ ↔ ↓	Threshold for clear effect:	*P* value
Absolute $\dot{V}O_{2peak}$	Resistance-Only	-0.2 ± *5.6*	-0.01 ± *0.17* **Trivial**	***likely*** ↔	**@5/.1%**	0.930
	Endurance-Resistance	3.8 ± *4.0*	0.19 ± *0.13* **Trivial**	***possibly*** ↑	**@5/.1%**	0.030
	Resistance-Endurance	2.3 ± *7.4*	0.12 ± *0.23* Trivial		unclear	0.370
Relative $\dot{V}O_{2peak}$	Resistance-Only	0.2 ± *5.5*	0.01 ± *0.20* Trivial	*likely* ↔	@25/.5%	0.930
	Endurance-Resistance	3.0 ± *4.0*	0.17 ± *0.15* Trivial	*possibly* ↑	@25/.5%	0.068
	Resistance-Endurance	2.0 ± *7.9*	0.12 ± *0.27* Trivial		unclear	0.452
Lactate Threshold	Resistance-Only	-2.1 ± *11.8*	-0.09 ± *0.31* Trivial	*possibly* ↓	@25/.5%	0.600
	Endurance-Resistance	4.0 ± *4.3*	0.17 ± *0.10* **Trivial**	***possibly*** ↑	**@5/.1%**	0.016
	Resistance-Endurance	5.8 ± *10.1*	0.24 ± *0.24* Small	*possibly* ↑	@25/.5%	0.097
Peak Aerobic Power	Resistance-Only	0.9 ± *4.8*	0.04 ± *0.14* **Trivial**	***very likely*** ↔	**@5/.1%**	0.591
	Endurance-Resistance	5.2 ± *2.5*	0.24 ± *0.07* **Small**	***likely*** ↑	**@5/.1%**	0.000
	Resistance-Endurance	5.7 ± *4.5*	0.26 ± *0.12* **Small**	***likely*** ↑	**@5/.1%**	0.003

mean % = mean percent change; SD = standard deviation; ES = standardised effect size (Cohen's d); 90%CI = 90% confidence interval;
↑ = improved; ↔ = trivial; ↓ = interfered;
Clinical thresholds: @25/.5% = >25% chance of improvement, <0.5 % risk of interference; @5/.1% = >5% chance of improvement, <0.1% risk of interference;
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1%) after adjusting for multiple inferences.*

Within-group changes (PRE to POST-training)

		Percent Change			Standardised Effect Size (ES)				Likelihood true effect is substantially ↑ ↔ ↓		Threshold for clear effect:	*P* value
Variable	**Group**	mean %	±	*SD*	ES	±	*90%CI*	Magnitude				
Leg Press 1-RM	Resistance-Only	23.9	±	*12.4*	0.74	±	*0.25*	**Moderate**	***most likely***	↑	**@5/.1%**	0.001
	Endurance-Resistance	28.1	±	*8.3*	0.86	±	*0.16*	**Moderate**	***most likely***	↑	**@5/.1%**	0.000
	Resistance-Endurance	27.4	±	*7.9*	0.84	±	*0.15*	**Moderate**	***most likely***	↑	**@5/.1%**	0.000
Peak Displacement	Resistance-Only	5.3	±	*6.3*	0.32	±	*0.25*	Small	*likely*	↑	@25/.5%	0.046
	Endurance-Resistance	4.5	±	*6.3*	0.27	±	*0.23*	Small	*possibly*	↑	@25/.5%	0.056
	Resistance-Endurance	-0.1	±	*4.8*	0.00	±	*0.17*	**Trivial**	***likely***	↔	**@5/.1%**	0.959
Peak Velocity	Resistance-Only	2.2	±	*2.7*	0.31	±	*0.24*	Small	*likely*	↑	@25/.5%	0.046
	Endurance-Resistance	2.2	±	*2.7*	0.31	±	*0.22*	Small	*likely*	↑	@25/.5%	0.031
	Resistance-Endurance	0.2	±	*1.9*	0.03	±	*0.16*	**Trivial**	***likely***	↔	**@5/.1%**	0.761
Peak Force	Resistance-Only	10.1	±	*10.1*	0.43	±	*0.28*	Small	*likely*	↑	@25/.5%	0.025
	Endurance-Resistance	4.0	±	*9.7*	0.18	±	*0.25*	Trivial	*possibly*	↑	OR>66.3	0.220
	Resistance-Endurance	1.2	±	*9.4*	0.05	±	*0.24*	Trivial	*likely*	↔	@25/.5%	0.699
Peak Power	Resistance-Only	9.8	±	*7.6*	0.50	±	*0.25*	**Small**	***very likely***	↑	**@5/.1%**	0.006
	Endurance-Resistance	4.9	±	*5.8*	0.26	±	*0.18*	**Small**	***possibly***	↑	**@5/.1%**	0.027
	Resistance-Endurance	3.2	±	*4.5*	0.17	±	*0.14*	**Trivial**	***possibly***	↑	**@5/.1%**	0.053
Total Lean Mass	Resistance-Only	2.8	±	*2.0*	0.20	±	*0.09*	**Small**	***possibly***	↑	**@5/.1%**	0.004
	Endurance-Resistance	3.7	±	*2.4*	0.27	±	*0.10*	**Small**	***likely***	↑	**@5/.1%**	0.001
	Resistance-Endurance	3.5	±	*1.4*	0.25	±	*0.06*	**Small**	***likely***	↑	**@5/.1%**	0.000
Upper Body Lean Mass	Resistance-Only	2.3	±	*2.0*	0.17	±	*0.09*	**Trivial**	***possibly***	↑	**@5/.1%**	0.010
	Endurance-Resistance	2.7	±	*2.5*	0.19	±	*0.11*	**Trivial**	***possibly***	↑	**@5/.1%**	0.010
	Resistance-Endurance	3.5	±	*1.6*	0.24	±	*0.07*	**Small**	***likely***	↑	**@5/.1%**	0.001
Lower Body Lean Mass	Resistance-Only	4.2	±	*4.2*	0.25	±	*0.16*	**Small**	***possibly***	↑	**@5/.1%**	0.017
	Endurance-Resistance	3.5	±	*2.1*	0.21	±	*0.08*	**Small**	***possibly***	↑	**@5/.1%**	0.001
	Resistance-Endurance	3.4	±	*2.2*	0.21	±	*0.08*	**Small**	***possibly***	↑	**@5/.1%**	0.001
Total Fat Mass	Resistance-Only	1.8	±	*5.6*	0.04	±	*0.08*	**Trivial**	***most likely***	↔	**@5/.1%**	0.359
	Endurance-Resistance	-1.8	±	*9.8*	-0.04	±	*0.13*	**Trivial**	***very likely***	↔	**@5/.1%**	0.558
	Resistance-Endurance	-10.5	±	*11.0*	-0.27	±	*0.15*	**Small**	***likely***	↑	**@5/.1%**	0.009

(continued)

Variable	Group	Percent Change mean % ± *SD*	Standardised Effect Size (ES) ES ± *90%CI* Magnitude	Likelihood true effect is substantially ↑ ↔ ↓	Threshold for clear effect:	*P* value
Absolute $\dot{V}O_{2peak}$	Resistance-Only	0.7 ± *5.9*	0.03 ± *0.19* Trivial	*likely* ↔	@25/.5%	0.745
	Endurance-Resistance	10.7 ± *1.9*	0.53 ± *0.06* **Small**	***most likely*** ↑	**@5/.1%**	0.000
	Resistance-Endurance	8.7 ± *5.0*	0.43 ± *0.15* **Small**	***very likely*** ↑	**@5/.1%**	0.001
Relative $\dot{V}O_{2peak}$	Resistance-Only	-2.1 ± *4.4*	-0.13 ± *0.16* **Trivial**	***likely*** ↔	**@5/.1%**	0.170
	Endurance-Resistance	8.6 ± *3.4*	0.48 ± *0.12* **Small**	***most likely*** ↑	**@5/.1%**	0.000
	Resistance-Endurance	7.6 ± *4.2*	0.43 ± *0.14* **Small**	***very likely*** ↑	**@5/.1%**	0.000
Lactate Threshold	Resistance-Only	-2.2 ± *17.1*	-0.10 ± *0.42* Trivial	*possibly* ↓	@25/.5%	0.681
	Endurance-Resistance	19.6 ± *5.5*	0.77 ± *0.14* **Moderate**	***most likely*** ↑	**@5/.1%**	0.000
	Resistance-Endurance	16.1 ± *12.8*	0.64 ± *0.30* **Moderate**	***very likely*** ↑	**@5/.1%**	0.004
Peak Aerobic Power	Resistance-Only	-1.1 ± *6.7*	-0.05 ± *0.19* **Trivial**	***likely*** ↔	**@5/.1%**	0.638
	Endurance-Resistance	14.5 ± *7.1*	0.63 ± *0.19* **Moderate**	***most likely*** ↑	**@5/.1%**	0.000
	Resistance-Endurance	13.9 ± *7.5*	0.61 ± *0.20* **Moderate**	***most likely*** ↑	**@5/.1%**	0.000

mean % = mean percent change; SD = standard deviation; ES = standardised effect size (Cohen's d); 90%CI = 90% confidence interval;
↑ = improved; ↔ = trivial; ↓ = interfered;
Clinical thresholds: @25/.5% = >25% chance of improvement, <0.5 % risk of interference; @5/.1% = >5% chance of improvement, <0.1% risk of interference;
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1%) after adjusting for multiple inferences.*

Between-group differences (PRE to MID-training)

		Percent Difference			Standardised Effect Size (ES)				Likelihood true effect			Threshold for	
Variable	**Comparison**	mean %	±	*90%CI*	ES	±	*90%CI*	Magnitude	**is substantially ↑ ↔ ↓**			**clear effect:**	***P* value**
Leg Press 1-RM	RES-Only vs END-RES	2.2	±	*4.7*	0.08	±	*0.16*	Trivial	*likely*	↔		@25/.5%	0.411
	RES-Only vs RES-END	1.6	±	*3.3*	0.06	±	*0.11*	**Trivial**	***very likely***	↔		**@5/.1%**	0.391
	END-RES vs RES-END	-0.6	±	*4.2*	-0.02	±	*0.15*	Trivial	*very likely*	↔		@90%	0.796
Peak Displacement	RES-Only vs END-RES	-4.2	±	*6.3*	-0.27	±	*0.41*	**Small**	***possibly***	↓		**@5/.1%**	0.255
	RES-Only vs RES-END	-8.4	±	*6.0*	-0.55	±	*0.41*	**Small**	***likely***	↓		**@5/.1%**	0.037
	END-RES vs RES-END	-4.4	±	*3.4*	-0.28	±	*0.22*	**Small**	***possibly***	↓		**@99%**	0.040
Peak Velocity	RES-Only vs END-RES	-1.7	±	*2.8*	-0.24	±	*0.41*	**Small**	***possibly***	↓		**@5/.1%**	0.302
	RES-Only vs RES-END	-3.9	±	*2.8*	-0.57	±	*0.41*	**Small**	***likely***	↓		**@5/.1%**	0.034
	END-RES vs RES-END	-2.3	±	*1.5*	-0.33	±	*0.22*	**Small**	***likely***	↓		**@99%**	0.020
Peak Force	RES-Only vs END-RES	-8.0	±	*7.4*	-0.37	±	*0.36*	**Small**	***likely***	↓		**@5/.1%**	0.092
	RES-Only vs RES-END	-7.4	±	*7.6*	-0.35	±	*0.37*	**Small**	***likely***	↓		**@5/.1%**	0.118
	END-RES vs RES-END	0.5	±	*8.5*	0.02	±	*0.38*	Trivial				unclear	0.912
Peak Power	RES-Only vs END-RES	-7.1	±	*3.5*	-0.40	±	*0.20*	**Small**	***likely***	↓		**@5/.1%**	0.005
	RES-Only vs RES-END	-9.4	±	*3.5*	-0.53	±	*0.21*	**Small**	***very likely***	↓		**@5/.1%**	0.001
	END-RES vs RES-END	-2.5	±	*2.9*	-0.13	±	*0.16*	**Trivial**	***likely***	↔		**@99%**	0.166
Total Lean Mass	RES-Only vs END-RES	0.7	±	*1.5*	0.05	±	*0.11*	**Trivial**	***very likely***	↔		**@5/.1%**	0.445
	RES-Only vs RES-END	0.0	±	*1.6*	0.00	±	*0.11*	Trivial	*very likely*	↔		@25/.5%	0.978
	END-RES vs RES-END	-0.7	±	*1.5*	-0.05	±	*0.11*	**Trivial**	***very likely***	↔		**@99%**	0.473
Upper Body Lean Mass	RES-Only vs END-RES	0.2	±	*1.4*	0.02	±	*0.10*	Trivial	*very likely*	↔		@25/.5%	0.774
	RES-Only vs RES-END	0.3	±	*1.8*	0.03	±	*0.13*	Trivial	*very likely*	↔		@25/.5%	0.742
	END-RES vs RES-END	0.1	±	*1.6*	0.01	±	*0.11*	**Trivial**	***very likely***	↔		**@99%**	0.902
Lower Body Lean Mass	RES-Only vs END-RES	-0.4	±	*2.2*	-0.03	±	*0.14*	**Trivial**	***very likely***	↔		**@5/.1%**	0.730
	RES-Only vs RES-END	0.2	±	*2.6*	0.01	±	*0.16*	**Trivial**	***very likely***	↔		**@5/.1%**	0.915
	END-RES vs RES-END	0.6	±	*2.2*	0.04	±	*0.14*	**Trivial**	***very likely***	↔		**@99%**	0.644
Total Fat Mass	RES-Only vs END-RES	-2.1	±	*4.0*	-0.05	±	*0.10*	**Trivial**	***very likely***	↔		**@5/.1%**	0.376
	RES-Only vs RES-END	-7.7	±	*4.1*	-0.20	±	*0.11*	**Small**	***possibly***	↓		**@5/.1%**	0.007
	END-RES vs RES-END	-5.7	±	*5.0*	-0.15	±	*0.13*	**Trivial**	***likely***	↔		**@99%**	0.067

(continued)

Variable	Comparison	Percent Difference mean %	±	*90%CI*	Standardised Effect Size (ES) ES	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑ ↔ ↓	Threshold for clear effect:	*P* value
Absolute $\dot{V}O_{2peak}$	RES-Only vs END-RES	5.8	±	*4.1*	0.29	±	*0.20*	**Small**	***likely*** ↑	**@5/.1%**	0.024
	RES-Only vs RES-END	5.4	±	*4.9*	0.27	±	*0.24*	Small	*possibly* ↑	@25/.5%	0.064
	END-RES vs RES-END	-0.4	±	*4.8*	-0.02	±	*0.25*	Trivial		unclear	0.899
Relative $\dot{V}O_{2peak}$	RES-Only vs END-RES	7.9	±	*4.1*	0.44	±	*0.22*	**Small**	***very likely*** ↑	**@5/.1%**	0.003
	RES-Only vs RES-END	8.0	±	*5.2*	0.45	±	*0.28*	**Small**	***likely*** ↑	**@5/.1%**	0.013
	END-RES vs RES-END	0.1	±	*4.9*	0.00	±	*0.29*	Trivial		unclear	0.977
Lactate Threshold	RES-Only vs END-RES	15.2	±	*8.9*	0.61	±	*0.33*	**Moderate**	***very likely*** ↑	**@5/.1%**	0.008
	RES-Only vs RES-END	9.9	±	*9.1*	0.41	±	*0.35*	Small	*likely* ↑	OR>66.3	0.064
	END-RES vs RES-END	-4.6	±	*4.8*	-0.20	±	*0.22*	**Small**	***possibly*** ↓	**@99%**	0.121
Peak Aerobic Power	RES-Only vs END-RES	11.0	±	*6.2*	0.49	±	*0.26*	**Small**	***very likely*** ↑	**@5/.1%**	0.005
	RES-Only vs RES-END	9.8	±	*5.2*	0.44	±	*0.22*	**Small**	***very likely*** ↑	**@5/.1%**	0.004
	END-RES vs RES-END	-1.0	±	*4.9*	-0.05	±	*0.23*	Trivial	*likely* ↔	@90%	0.716

mean % = mean percent difference between groups; 90%CI = 90% confidence interval; ES = standardised effect size (Cohen's d);
↑ = improved; ↔ = trivial; ↓ = interfered;
Clinical thresholds: @25/.5% = >25% chance of improvement, <0.5 % risk of interference; @5/.1% = >5% chance of improvement, <0.1% risk of interference;
Non-clinical thresholds: @90% = 90% confidence limits; @99% = 99% confidence limits
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1% and @99%), after adjusting for multiple inferences.*

Between-group differences (MID to POST-training)

		Percent Difference			Standardised Effect Size (ES)				Likelihood true effect		Threshold for	
Variable	**Comparison**	mean %	±	*90%CI*	ES	±	*90%CI*	Magnitude	**is substantially ↑ ↔ ↓**		**clear effect:**	***P* value**
Leg Press 1-RM	RES-Only vs END-RES	1.1	±	*5.2*	0.04	±	*0.18*	Trivial	*likely*	↔	@25/.5%	0.707
	RES-Only vs RES-END	1.1	±	*5.6*	0.04	±	*0.19*	Trivial	*likely*	↔	@25/.5%	0.722
	END-RES vs RES-END	0.0	±	*3.2*	0.00	±	*0.11*	**Trivial**	***very likely***	↔	**@99%**	0.984
Peak Displacement	RES-Only vs END-RES	3.5	±	*4.4*	0.22	±	*0.27*	Small	*possibly*	↑	OR>66.3	0.176
	RES-Only vs RES-END	3.6	±	*4.3*	0.22	±	*0.26*	Small	*possibly*	↑	OR>66.3	0.148
	END-RES vs RES-END	0.1	±	*4.0*	0.01	±	*0.25*	Trivial			unclear	0.963
Peak Velocity	RES-Only vs END-RES	1.7	±	*2.0*	0.23	±	*0.28*	Small	*possibly*	↑	OR>66.3	0.167
	RES-Only vs RES-END	2.0	±	*1.9*	0.28	±	*0.26*	Small	*possibly*	↑	@25/.5%	0.075
	END-RES vs RES-END	0.3	±	*1.6*	0.05	±	*0.23*	Trivial	*likely*	↔	@90%	0.715
Peak Force	RES-Only vs END-RES	2.6	±	*7.9*	0.11	±	*0.35*	Trivial			unclear	0.568
	RES-Only vs RES-END	-0.8	±	*7.5*	-0.03	±	*0.34*	Trivial	*possibly*	↔	@25/.5%	0.860
	END-RES vs RES-END	-3.3	±	*5.5*	-0.15	±	*0.25*	Trivial	*possibly*	↓	@90%	0.321
Peak Power	RES-Only vs END-RES	2.9	±	*3.9*	0.15	±	*0.20*	Trivial	*possibly*	↑	@25/.5%	0.205
	RES-Only vs RES-END	3.8	±	*3.9*	0.20	±	*0.20*	Small	*possibly*	↑	@25/.5%	0.104
	END-RES vs RES-END	0.9	±	*3.2*	0.05	±	*0.17*	Trivial	*likely*	↔	@90%	0.645
Total Lean Mass	RES-Only vs END-RES	0.3	±	*1.2*	0.02	±	*0.09*	**Trivial**	***most likely***	↔	**@5/.1%**	0.718
	RES-Only vs RES-END	0.7	±	*1.2*	0.05	±	*0.09*	**Trivial**	***most likely***	↔	**@5/.1%**	0.326
	END-RES vs RES-END	0.4	±	*1.0*	0.03	±	*0.07*	**Trivial**	***most likely***	↔	**@99%**	0.447
Upper Body Lean Mass	RES-Only vs END-RES	0.1	±	*1.7*	0.01	±	*0.12*	Trivial	*very likely*	↔	@25/.5%	0.917
	RES-Only vs RES-END	0.7	±	*2.2*	0.05	±	*0.16*	Trivial	*likely*	↔	@25/.5%	0.560
	END-RES vs RES-END	0.6	±	*2.1*	0.05	±	*0.15*	Trivial	*likely*	↔	@90%	0.603
Lower Body Lean Mass	RES-Only vs END-RES	-0.2	±	*2.0*	-0.01	±	*0.12*	**Trivial**	***very likely***	↔	**@5/.1%**	0.851
	RES-Only vs RES-END	-0.9	±	*2.0*	-0.06	±	*0.12*	**Trivial**	***very likely***	↔	**@5/.1%**	0.446
	END-RES vs RES-END	-0.7	±	*1.8*	-0.04	±	*0.11*	**Trivial**	***very likely***	↔	**@99%**	0.521
Total Fat Mass	RES-Only vs END-RES	-1.5	±	*5.4*	-0.04	±	*0.13*	**Trivial**	***very likely***	↔	**@5/.1%**	0.638
	RES-Only vs RES-END	-4.7	±	*3.4*	-0.12	±	*0.09*	**Trivial**	***likely***	↔	**@5/.1%**	0.030
	END-RES vs RES-END	-3.3	±	*5.3*	-0.08	±	*0.13*	**Trivial**	***likely***	↔	**@99%**	0.302

(continued)

Variable	Comparison	Percent Difference mean %	±	*90%CI*	Standardised Effect Size (ES) ES	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑ ↔ ↓	Threshold for clear effect:	*P* value
Absolute $\dot{V}O_{2peak}$	RES-Only vs END-RES	3.9	±	4.1	0.20	±	0.21	Small	*possibly* ↑	@25/.5%	0.110
	RES-Only vs RES-END	2.4	±	5.3	0.13	±	0.27	Trivial		unclear	0.431
	END-RES vs RES-END	-1.4	±	4.8	-0.08	±	0.25	Trivial	*likely* ↔	@90%	0.605
Relative $\dot{V}O_{2peak}$	RES-Only vs END-RES	2.8	±	4.1	0.16	±	0.23	Trivial	*possibly* ↑	OR>66.3	0.237
	RES-Only vs RES-END	1.8	±	5.5	0.11	±	0.32	Trivial		unclear	0.565
	END-RES vs RES-END	-1.0	±	5.0	-0.06	±	0.30	Trivial		unclear	0.739
Lactate Threshold	RES-Only vs END-RES	6.2	±	7.8	0.26	±	0.32	Small	*possibly* ↑	OR>66.3	0.169
	RES-Only vs RES-END	8.0	±	9.3	0.33	±	0.37	Small	*possibly* ↑	OR>66.3	0.135
	END-RES vs RES-END	1.7	±	6.0	0.07	±	0.25	Trivial	*likely* ↔	@90%	0.617
Peak Aerobic Power	RES-Only vs END-RES	4.3	±	3.3	0.20	±	0.15	**Small**	***possibly*** ↑	**@5/.1%**	0.035
	RES-Only vs RES-END	4.8	±	3.8	0.22	±	0.17	**Small**	***possibly*** ↑	**@5/.1%**	0.040
	END-RES vs RES-END	0.5	±	2.8	0.02	±	0.13	**Trivial**	***very likely*** ↔	**@99%**	0.761

mean % = mean percent difference between groups; 90%CI = 90% confidence interval; ES = standardised effect size (Cohen's d);
↑ = improved; ↔ = trivial; ↓ = interfered;
Clinical thresholds: @25/.5% = >25% chance of improvement, <0.5 % risk of interference; @5/.1% = >5% chance of improvement, <0.1% risk of interference;
Non-clinical thresholds: @90% = 90% confidence limits; @99% = 99% confidence limits
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1% and @99%), after adjusting for multiple inferences.*

Between-group differences (PRE to POST-training)

		Percent Difference			Standardised Effect Size (ES)				Likelihood true effect		Threshold for	
Variable	**Comparison**	mean %	±	*90%CI*	ES	±	*90%CI*	Magnitude	**is substantially ↑ ↔ ↓**		**clear effect:**	***P* value**
Leg Press 1-RM	RES-Only vs END-RES	3.4	±	*8.5*	0.12	±	*0.28*	Trivial			unclear	0.487
	RES-Only vs RES-END	2.8	±	*8.4*	0.09	±	*0.28*	Trivial			unclear	0.561
	END-RES vs RES-END	-0.6	±	*6.0*	-0.02	±	*0.21*	Trivial	*likely*	↔	@90%	0.868
Peak Displacement	RES-Only vs END-RES	-0.8	±	*5.0*	-0.05	±	*0.31*	Trivial	*possibly*	↔	@25/.5%	0.778
	RES-Only vs RES-END	-5.1	±	*4.3*	-0.33	±	*0.28*	**Small**	***likely***	↓	**@5/.1%**	0.061
	END-RES vs RES-END	-4.3	±	*4.1*	-0.28	±	*0.27*	**Small**	***possibly***	↓	**@99%**	0.089
Peak Velocity	RES-Only vs END-RES	0.0	±	*2.2*	0.00	±	*0.30*	Trivial	*possibly*	↔	@25/.5%	0.989
	RES-Only vs RES-END	-2.0	±	*1.9*	-0.28	±	*0.27*	**Small**	***possibly***	↓	**@5/.1%**	0.088
	END-RES vs RES-END	-2.0	±	*1.8*	-0.28	±	*0.26*	**Small**	***possibly***	↓	**@99%**	0.073
Peak Force	RES-Only vs END-RES	-5.6	±	*7.4*	-0.26	±	*0.35*	**Small**	***possibly***	↓	**@5/.1%**	0.215
	RES-Only vs RES-END	-8.2	±	*7.1*	-0.38	±	*0.35*	**Small**	***likely***	↓	**@5/.1%**	0.072
	END-RES vs RES-END	-2.7	±	*7.0*	-0.12	±	*0.32*	Trivial	*possibly*	↓	@90%	0.509
Peak Power	RES-Only vs END-RES	-4.4	±	*5.1*	-0.24	±	*0.29*	**Small**	***possibly***	↓	**@5/.1%**	0.156
	RES-Only vs RES-END	-6.0	±	*4.7*	-0.33	±	*0.27*	**Small**	***likely***	↓	**@5/.1%**	0.048
	END-RES vs RES-END	-1.6	±	*3.9*	-0.09	±	*0.22*	Trivial	*likely*	↔	@90%	0.482
Total Lean Mass	RES-Only vs END-RES	0.9	±	*1.7*	0.07	±	*0.13*	**Trivial**	***very likely***	↔	**@5/.1%**	0.360
	RES-Only vs RES-END	0.7	±	*1.4*	0.05	±	*0.10*	**Trivial**	***very likely***	↔	**@5/.1%**	0.380
	END-RES vs RES-END	-0.2	±	*1.5*	-0.02	±	*0.11*	**Trivial**	***very likely***	↔	**@99%**	0.800
Upper Body Lean Mass	RES-Only vs END-RES	0.3	±	*1.8*	0.02	±	*0.13*	Trivial	*very likely*	↔	@25/.5%	0.750
	RES-Only vs RES-END	1.1	±	*1.5*	0.08	±	*0.11*	**Trivial**	***very likely***	↔	**@5/.1%**	0.221
	END-RES vs RES-END	0.8	±	*1.7*	0.05	±	*0.12*	**Trivial**	***very likely***	↔	**@99%**	0.443
Lower Body Lean Mass	RES-Only vs END-RES	-0.7	±	*2.7*	-0.04	±	*0.17*	**Trivial**	***likely***	↔	**@5/.1%**	0.674
	RES-Only vs RES-END	-0.7	±	*2.7*	-0.05	±	*0.17*	**Trivial**	***likely***	↔	**@5/.1%**	0.639
	END-RES vs RES-END	-0.1	±	*1.7*	0.00	±	*0.10*	**Trivial**	***most likely***	↔	**@99%**	0.937
Total Fat Mass	RES-Only vs END-RES	-3.5	±	*5.9*	-0.09	±	*0.15*	**Trivial**	***likely***	↔	**@5/.1%**	0.321
	RES-Only vs RES-END	-12.0	±	*5.9*	-0.32	±	*0.16*	**Small**	***likely***	↑	**@5/.1%**	0.004
	END-RES vs RES-END	-8.8	±	*7.0*	-0.23	±	*0.19*	**Small**	***possibly***	↑	**@99%**	0.053

(continued)

Variable	Comparison	Percent Difference			Standardised Effect size (ES)				Likelihood true effect is substantially ↑ ↔ ↓		Threshold for clear effect:	*P* value
		mean %	±	*90%CI*	ES	±	*90%CI*	Magnitude				
Absolute $\dot{V}O_{2peak}$	RES-Only vs END-RES	10.0	±	*4.0*	0.49	±	*0.19*	**Small**	***very likely***	↑	**@5/.1%**	0.001
	RES-Only vs RES-END	8.0	±	*4.7*	0.40	±	*0.22*	**Small**	***likely***	↑	**@5/.1%**	0.007
	END-RES vs RES-END	-1.8	±	*2.9*	-0.09	±	*0.15*	**Trivial**	***likely***	↔	**@99%**	0.297
Relative $\dot{V}O_{2peak}$	RES-Only vs END-RES	11.0	±	*3.5*	0.61	±	*0.18*	**Moderate**	***most likely***	↑	**@5/.1%**	0.000
	RES-Only vs RES-END	10.0	±	*3.7*	0.56	±	*0.20*	**Small**	***most likely***	↑	**@5/.1%**	0.000
	END-RES vs RES-END	-0.9	±	*2.9*	-0.05	±	*0.17*	Trivial	*likely*	↔	@90%	0.605
Lactate Threshold	RES-Only vs END-RES	22.3	±	*12.4*	0.87	±	*0.44*	**Moderate**	***very likely***	↑	**@5/.1%**	0.005
	RES-Only vs RES-END	18.7	±	*13.6*	0.74	±	*0.49*	Moderate	*very likely*	↑	@25/.5%	0.019
	END-RES vs RES-END	-3.0	±	*7.2*	-0.13	±	*0.32*	Trivial	*possibly*	↓	@90%	0.487
Peak Aerobic Power	RES-Only vs END-RES	15.7	±	*6.2*	0.68	±	*0.25*	**Moderate**	***most likely***	↑	**@5/.1%**	0.000
	RES-Only vs RES-END	15.1	±	*6.4*	0.65	±	*0.26*	**Moderate**	***most likely***	↑	**@5/.1%**	0.000
	END-RES vs RES-END	-0.5	±	*5.5*	-0.03	±	*0.26*	Trivial			unclear	0.867

mean % = mean percent difference between groups; 90%CI = 90% confidence interval; ES = standardised effect size (Cohen's d);
↑ = improved; ↔ = trivial; ↓ = interfered;
Clinical thresholds: @25/.5% = >25% chance of improvement, <0.5 % risk of interference; @5/.1% = >5% chance of improvement, <0.1% risk of interference;
Non-clinical thresholds: @90% = 90% confidence limits; @99% = 99% confidence limits
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1% and @99%), after adjusting for multiple inferences.*

Habitual dietary intake

		Energy		Carbohydrates		Protein		Fat	
		kJ/ day	kJ/ kg/d	g/ day	g/kg/ day	g/ day	g/kg/ day	g/ day	g/kg/ day
END-RES	1	1598	20	206	2.6	82	1.0	42	0.5
	2	3370	38	386	4.4	124	1.4	198	2.2
	3	2640	32	279	3.3	184	2.2	122	1.5
	4	2529	30	252	3.0	109	1.3	123	1.5
	5	3008	41	261	3.5	169	2.3	127	1.7
	6	2868	49	306	5.2	154	2.6	107	1.8
	7	1617	25	130	2.0	93	1.4	78	1.2
	8	2535	33	221	2.8	159	2.0	101	1.3
	9	3113	37	334	4.0	156	1.9	115	1.4
	10	3208	59	476	8.8	141	2.6	81	1.5
	MEAN	2649	36	285	4.0	137	1.9	110	1.5
	SD	617	11	97	1.9	34	0.6	41	0.4
RES-END	1	2754	47	302	5.2	138	2.4	103	1.8
	2	2537	40	232	3.7	152	2.4	104	1.6
	3	1527	23	182	2.8	117	1.8	42	0.7
	4	2108	28	206	2.8	120	1.6	76	1.0
	5	1827	23	168	2.1	114	1.4	70	0.9
	6	2978	42	260	3.7	254	3.6	95	1.3
	7	3757	43	357	4.0	208	2.4	149	1.7
	8	2955	39	309	4.1	127	1.7	117	1.6
	9	3016	32	266	2.8	174	1.9	103	1.1
	10	3454	47	379	5.1	152	2.0	139	1.9
	MEAN	2691	36	266	3.6	156	2.1	100	1.4
	SD	703	9	71	1.0	45	0.6	32	0.4
RES-ONLY	1	1732	20	126	1.5	140	1.6	70	0.8
	2	2776	39	277	3.9	182	2.6	86	1.2
	3	2197	31	208	3.0	102	1.5	89	1.3
	4	2890	33	154	1.8	258	3.0	133	1.5
	5	3159	39	398	4.9	207	2.6	50	0.6
	6	2303	36	193	3.0	127	2.0	107	1.7
	7	2545	28	254	2.8	141	1.5	99	1.1
	8	1677	23	179	2.5	69	1.0	68	0.9
	9	2833	46	324	5.3	153	2.5	92	1.5
	MEAN	2457	33	235	3.2	153	2.0	88	1.2
	SD	519	8	87	1.3	56	0.7	24	0.4

kcal/day = kilocalories per day; g/day = grams per day; kcal/kg/day = kilocalories per kilogram of body mass per day; g/kg/day = grams per kilogram of body mass per day; SD = standard deviation.

Differences at baseline

Variable	Group	Mean	±	*SD*	Between-group comparison	Effect Size Cohen's *d*	Effect Size Magnitude
Absolute values							
Energy (kcal/day)	RES-Only	2457	±	*519*	RES-Only vs END-RES	0.32	Small
	END-RES	2649	±	*617*	RES-Only vs RES-END	0.39	Small
	RES-END	2691	±	*703*	END-RES vs RES-END	-0.07	Trivial
Carbohydrates (g/day)	RES-Only	235	±	*87*	RES-Only vs END-RES	0.68	Moderate
	END-RES	285	±	*97*	RES-Only vs RES-END	0.42	Small
	RES-END	266	±	*71*	END-RES vs RES-END	0.26	Small
Protein (g/day)	RES-Only	153	±	*56*	RES-Only vs END-RES	-0.39	Small
	END-RES	137	±	*34*	RES-Only vs RES-END	0.06	Trivial
	RES-END	156	±	*45*	END-RES vs RES-END	-0.45	Small
Fat (g/day)	RES-Only	88	±	*24*	RES-Only vs END-RES	0.64	Moderate
	END-RES	110	±	*41*	RES-Only vs RES-END	0.34	Small
	RES-END	100	±	*32*	END-RES vs RES-END	0.30	Small
Relative values							
Energy (kcal/kg/day)	RES-Only	33	±	*8*	RES-Only vs END-RES	0.34	Small
	END-RES	36	±	*11*	RES-Only vs RES-END	0.35	Small
	RES-END	36	±	*9*	END-RES vs RES-END	-0.01	Trivial
Carbohydrates (g/kg/day)	RES-Only	3.2	±	*1.3*	RES-Only vs END-RES	0.61	Moderate
	END-RES	4.0	±	*1.9*	RES-Only vs RES-END	0.35	Small
	RES-END	3.6	±	*1.0*	END-RES vs RES-END	0.27	Small
Protein (g/kg/day)	RES-Only	2.0	±	*0.7*	RES-Only vs END-RES	-0.26	Small
	END-RES	1.9	±	*0.6*	RES-Only vs RES-END	0.16	Trivial
	RES-END	2.1	±	*0.6*	END-RES vs RES-END	-0.43	Small
Fat (g/kg/day)	RES-Only	1.2	±	*0.4*	RES-Only vs END-RES	0.59	Small
	END-RES	1.5	±	*0.4*	RES-Only vs RES-END	0.35	Small
	RES-END	1.4	±	*0.4*	END-RES vs RES-END	0.24	Small

kcal/day = kilocalories per day; g/day = grams per day; kcal/kg/day = kilocalories per kilogram of body mass per day; g/kg/day = grams per kilogram of body mass per day; SD = standard deviation.

Weekly training loads

Variable	Group	Week 1 Mean	Week 1 *SD*	Week 2 Mean	Week 2 *SD*	Week 3 Mean	Week 3 *SD*	Week 4 Mean	Week 4 *SD*	Week 5 Mean	Week 5 *SD*	Week 6 Mean	Week 6 *SD*	Week 7 Mean	Week 7 *SD*	Week 8 Mean	Week 8 *SD*	Week 9 Mean	Week 9 *SD*
Internal Load																			
Resistance Sessions (AU)	RO	113	*48*	262	*90*	262	*65*	271	*76*	267	*73*	417	*120*	355	*99*	372	*110*	365	*100*
	ER	137	*28*	338	*93*	342	*90*	350	*75*	338	*90*	474	*85*	438	*82*	427	*71*	414	*84*
	RE	104	*37*	265	*61*	265	*62*	258	*61*	282	*76*	417	*94*	370	*70*	392	*80*	384	*79*
Endurance Sessions (AU)	ER	212	*59*	193	*52*	215	*52*	242	*75*	192	*59*	235	*59*	261	*66*	297	*80*	210	*74*
	RE	179	*36*	171	*41*	226	*48*	238	*48*	188	*44*	256	*50*	271	*52*	306	*65*	212	*51*
External Load																			
Resistance Sessions (kg)	RO	14,300	*4,100*	14,100	*3,500*	14,300	*3,000*	12,900	*2,600*	11,400	*2,800*	20,800	*5,400*	19,700	*4,700*	16,900	*4,400*	15,200	*3,100*
	ER	13,800	*3,800*	13,600	*4,100*	13,500	*3,700*	12,500	*3,200*	11,700	*3,500*	20,100	*6,100*	19,900	*5,300*	16,700	*4,600*	14,700	*3,100*
	RE	13,800	*3,700*	13,800	*3,300*	14,000	*3,000*	12,700	*2,600*	11,200	*2,700*	20,100	*4,700*	19,600	*4,000*	16,200	*3,100*	13,900	*2,100*
Endurance Sessions (kJ)	ER	913	*180*	838	*190*	954	*200*	1,100	*220*	891	*190*	1,050	*220*	1,180	*240*	1,290	*250*	1,020	*240*
	RE	846	*180*	786	*180*	884	*200*	1,020	*210*	813	*180*	984	*190*	1,100	*210*	1,220	*240*	962	*220*

AU = arbitrary units; kg = kilograms; kJ = kilojoules; SD = standard deviation.

Between-group comparisons

Variable	Group	Weekly Average mean ± *SD*	Between-group comparison	Percent Difference mean % ± *90%CI*	Standardised Effect Size (ES) ES ± *90%CI* Magnitude	Likelihood true effect is substantially ↑↔↓	Threshold for clear effect:	*P* value
Resistance Sessions (AU)	RES-Only	269 ± *100*	RES-Only vs END-RES	25 ± *20*	0.84 ± *0.59* **Moderate**	***very likely*** ↓	***@99%***	0.022
	END-RES	337 ± *84*	RES-Only vs RES-END	2.4 ± *16*	0.09 ± *0.57* Trivial		*unclear*	0.792
	RES-END	275 ± *76*	END-RES vs RES-END	-18 ± *9.3*	-0.76 ± *0.43* **Moderate**	***very likely*** ↓	***@99%***	0.006
Endurance Sessions (AU)	END-RES	218 ± *71*						
	RES-END	217 ± *49*	END-RES vs RES-END	-0.6 ± *13*	-0.02 ± *0.54* Trivial		*unclear*	0.942
Resistance Sessions (kg)	RES-Only	14,800 ± *3,900*	RES-Only vs END-RES	-4.3 ± *19*	-0.18 ± *0.79* Trivial		*unclear*	0.706
	END-RES	14,200 ± *4,500*	RES-Only vs RES-END	-1.5 ± *17*	-0.06 ± *0.67* Trivial		*unclear*	0.880
	RES-END	14,600 ± *3,400*	END-RES vs RES-END	2.9 ± *19*	0.11 ± *0.74* Trivial		*unclear*	0.792
Endurance Sessions (kJ)	END-RES	993 ± *230*						
	RES-END	929 ± *190*	END-RES vs RES-END	-6.4 ± *14*	-0.33 ± *0.74* Small		*unclear*	0.453

SD = standard deviation; mean % = mean percent difference between groups; 90%CI = 90% confidence interval; ES = standardised effect size (Cohen's d);
↑ = improved; ↔ = trivial; ↓ = interfered;
Non-clinical thresholds: @90% = 90% confidence limits; @99% = 99% confidence limits
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1% and @99%), after adjusting for multiple inferences*

Weekly wellbeing & 'readiness-to-train' data

Resistance training sessions

		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8		Week 9	
Variable	**Group**	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Total Score (/25)	RES-Only	18.0	*3.2*	18.6	*2.2*	18.1	*2.9*	18.8	*2.5*	18.1	*2.9*	17.6	*2.4*	18.2	*2.5*	17.4	*2.8*	18.3	*2.3*
	END-RES	17.0	*2.8*	16.6	*2.9*	15.8	*3.5*	16.5	*3.1*	16.4	*2.6*	15.9	*2.6*	16.6	*2.3*	16.2	*2.4*	15.7	*2.8*
	RES-END	17.9	*2.8*	17.3	*3.6*	18.4	*3.3*	17.7	*3.2*	17.8	*3.7*	17.1	*3.3*	17.2	*3.3*	17.1	*3.6*	17.7	*3.2*
Fatigue (/5)	RES-Only	3.3	*1.0*	3.3	*0.7*	3.3	*0.8*	3.5	*0.8*	3.2	*0.9*	3.2	*0.8*	3.5	*0.6*	3.2	*0.9*	3.3	*0.7*
	END-RES	3.1	*0.9*	3.0	*0.9*	2.9	*0.9*	3.0	*0.8*	3.2	*0.6*	2.9	*0.8*	2.9	*0.7*	3.1	*0.8*	2.9	*0.8*
	RES-END	3.5	*0.9*	3.3	*0.9*	3.3	*1.0*	3.3	*0.8*	3.3	*1.0*	3.1	*0.9*	3.1	*1.0*	3.0	*1.0*	3.1	*0.9*
Sleep Quality (/5)	RES-Only	3.5	*0.8*	3.7	*0.7*	3.6	*0.8*	3.7	*0.7*	3.7	*0.7*	3.7	*0.8*	3.6	*0.7*	3.4	*0.8*	3.6	*0.8*
	END-RES	3.5	*0.8*	3.4	*0.9*	3.2	*0.8*	3.5	*0.9*	3.3	*0.8*	3.5	*0.8*	3.6	*0.9*	3.6	*0.7*	3.3	*0.7*
	RES-END	3.7	*0.8*	3.6	*0.9*	3.8	*0.7*	3.5	*0.9*	3.6	*1.0*	3.4	*0.9*	3.4	*0.9*	3.5	*0.9*	3.5	*1.0*
General Muscle Soreness (/5)	RES-Only	3.1	*1.3*	3.4	*1.0*	3.6	*0.8*	3.7	*0.8*	3.5	*1.0*	3.1	*0.8*	3.4	*0.8*	3.4	*1.0*	3.7	*0.6*
	END-RES	2.7	*1.1*	3.1	*0.9*	3.1	*0.8*	2.9	*0.9*	3.1	*0.7*	2.7	*0.9*	3.0	*0.7*	2.6	*0.7*	2.7	*0.8*
	RES-END	2.9	*0.9*	2.9	*0.9*	3.4	*1.0*	3.1	*0.9*	3.3	*1.0*	3.2	*0.8*	3.0	*1.0*	3.1	*1.1*	3.1	*1.1*
Stress (/5)	RES-Only	3.9	*0.7*	4.0	*0.6*	3.8	*0.6*	3.8	*0.5*	3.8	*0.7*	3.7	*0.4*	3.7	*0.6*	3.5	*0.7*	3.7	*0.6*
	END-RES	3.7	*0.7*	3.4	*0.8*	3.2	*0.9*	3.5	*0.7*	3.3	*0.8*	3.3	*0.8*	3.5	*0.7*	3.4	*0.7*	3.3	*0.8*
	RES-END	3.8	*0.6*	3.6	*0.8*	3.8	*0.7*	3.8	*0.7*	3.7	*0.7*	3.5	*0.7*	3.6	*0.7*	3.5	*0.8*	3.8	*0.6*
Mood (/5)	RES-Only	4.1	*0.6*	4.3	*0.5*	3.9	*0.6*	4.0	*0.5*	4.0	*0.5*	3.9	*0.6*	4.0	*0.5*	3.9	*0.4*	4.0	*0.3*
	END-RES	3.9	*0.6*	3.7	*0.6*	3.4	*1.1*	3.7	*0.7*	3.5	*0.7*	3.6	*0.7*	3.6	*0.6*	3.5	*0.5*	3.5	*0.8*
	RES-END	4.2	*0.4*	4.0	*0.7*	4.1	*0.5*	4.0	*0.5*	4.0	*0.7*	3.8	*0.7*	4.0	*0.5*	4.0	*0.5*	4.1	*0.5*

Endurance training sessions

		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8		Week 9	
Variable	**Group**	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*	Mean	*SD*
Total Score (/25)	END-RES	17.8	*2.9*	16.7	*3.2*	16.3	*3.3*	17.6	*2.8*	16.7	*2.9*	17.3	*2.8*	18.7	*3.1*	17.2	*3.2*	16.2	*2.4*
	RES-END	17.6	*2.6*	17.1	*3.2*	17.9	*3.1*	17.5	*3.2*	17.7	*3.6*	16.9	*3.3*	17.0	*3.4*	17.2	*3.6*	17.7	*3.1*
Fatigue (/5)	END-RES	3.2	*0.9*	3.1	*1.0*	3.1	*1.0*	3.4	*0.7*	3.2	*0.9*	3.2	*0.9*	3.6	*0.9*	3.2	*1.1*	3.0	*0.8*
	RES-END	3.2	*0.9*	3.2	*0.9*	3.3	*1.0*	3.2	*0.9*	3.3	*1.0*	3.1	*1.0*	3.2	*1.0*	3.2	*0.9*	3.2	*0.8*
Sleep Quality (/5)	END-RES	3.6	*0.8*	3.4	*0.9*	3.2	*0.8*	3.5	*0.8*	3.3	*0.9*	3.5	*0.8*	3.7	*0.9*	3.5	*0.9*	3.2	*0.6*
	RES-END	3.7	*0.9*	3.5	*0.9*	3.7	*0.7*	3.5	*0.8*	3.6	*0.9*	3.5	*0.8*	3.5	*0.9*	3.5	*1.0*	3.5	*0.9*
General Muscle Soreness (/5)	END-RES	3.2	*1.2*	3.2	*1.0*	3.3	*0.8*	3.4	*0.9*	3.3	*0.8*	3.1	*1.1*	3.7	*0.9*	3.3	*0.9*	3.0	*0.8*
	RES-END	2.8	*0.8*	2.8	*0.7*	3.3	*0.8*	3.1	*0.8*	3.1	*1.0*	2.9	*0.9*	3.0	*0.9*	3.0	*1.2*	3.0	*0.9*
Stress (/5)	END-RES	3.7	*0.7*	3.4	*0.8*	3.2	*1.0*	3.4	*0.8*	3.3	*0.8*	3.6	*0.7*	3.8	*0.6*	3.6	*0.9*	3.5	*0.8*
	RES-END	3.8	*0.6*	3.6	*0.8*	3.6	*0.7*	3.7	*0.7*	3.7	*0.8*	3.6	*0.7*	3.5	*0.7*	3.7	*0.7*	3.9	*0.6*
Mood (/5)	END-RES	4.1	*0.6*	3.7	*0.7*	3.4	*1.0*	3.9	*0.6*	3.6	*0.7*	3.8	*0.6*	4.0	*0.6*	3.5	*0.9*	3.6	*0.6*
	RES-END	4.1	*0.3*	4.0	*0.6*	3.9	*0.5*	4.0	*0.6*	4.0	*0.7*	3.8	*0.7*	3.8	*0.6*	3.9	*0.6*	4.0	*0.6*

Between-group comparisons

Resistance training sessions

Variable	Group	Weekly Average mean	±	*SD*	Between-group comparison	Difference (raw) mean	±	*90%CI*	Standardised Effect Size (ES) ES	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑↔↓	Threshold for clear effect:	*P* value
Total Score	RES-Only	18.1	±	*2.7*	RES-Only vs END-RES	-1.8	±	*1.4*	-0.60	±	*0.45*	**Moderate**	***likely*** ↓	**@99%**	0.031
	END-RES	16.3	±	*2.9*	RES-Only vs RES-END	-0.6	±	*1.8*	-0.20	±	*0.60*	Small		unclear	0.569
	RES-END	17.5	±	*3.4*	END-RES vs RES-END	1.2	±	*1.9*	0.40	±	*0.62*	Small		unclear	0.277
Fatigue	RES-Only	3.3	±	*0.8*	RES-Only vs END-RES	-0.3	±	*0.4*	-0.36	±	*0.43*	Small	*possibly* ↓	@90%	0.168
	END-RES	3.0	±	*0.8*	RES-Only vs RES-END	-0.1	±	*0.5*	-0.10	±	*0.55*	Trivial		unclear	0.760
	RES-END	3.2	±	*1.0*	END-RES vs RES-END	0.2	±	*0.5*	0.26	±	*0.56*	Small		unclear	0.441
Sleep Quality	RES-Only	3.6	±	*0.8*	RES-Only vs END-RES	-0.2	±	*0.3*	-0.21	±	*0.32*	Small	*possibly* ↓	@90%	0.280
	END-RES	3.4	±	*0.8*	RES-Only vs RES-END	-0.1	±	*0.4*	-0.08	±	*0.44*	Trivial		unclear	0.747
	RES-END	3.5	±	*0.9*	END-RES vs RES-END	0.1	±	*0.4*	0.12	±	*0.46*	Trivial		unclear	0.654
General muscle soreness	RES-Only	3.4	±	*0.9*	RES-Only vs END-RES	-0.6	±	*0.4*	-0.62	±	*0.46*	**Small**	***likely*** ↓	**@99%**	0.030
	END-RES	2.9	±	*0.8*	RES-Only vs RES-END	-0.3	±	*0.5*	-0.37	±	*0.55*	Small	*possibly* ↓	@90%	0.267
	RES-END	3.1	±	*1.0*	END-RES vs RES-END	0.2	±	*0.5*	0.25	±	*0.53*	Small		unclear	0.430
Stress	RES-Only	3.8	±	*0.6*	RES-Only vs END-RES	-0.4	±	*0.3*	-0.51	±	*0.39*	**Small**	***likely*** ↓	**@99%**	0.036
	END-RES	3.4	±	*0.8*	RES-Only vs RES-END	-0.1	±	*0.3*	-0.14	±	*0.46*	Trivial		unclear	0.607
	RES-END	3.7	±	*0.7*	END-RES vs RES-END	0.3	±	*0.4*	0.37	±	*0.57*	Small		unclear	0.281
Mood	RES-Only	4.0	±	*0.5*	RES-Only vs END-RES	-0.4	±	*0.2*	-0.68	±	*0.39*	**Moderate**	***very likely*** ↓	**@99%**	0.006
	END-RES	3.6	±	*0.7*	RES-Only vs RES-END	0.0	±	*0.3*	-0.03	±	*0.42*	Trivial		unclear	0.905
	RES-END	4.0	±	*0.6*	END-RES vs RES-END	0.4	±	*0.3*	0.65	±	*0.47*	**Moderate**	***likely*** ↑	**@99%**	0.026

SD = standard deviation; mean % = mean percent difference between groups; 90%CI = 90% confidence interval; ES = standardised effect size (Cohen's d);
↑ = improved; ↔ = trivial; ↓ = interfered;
Non-clinical thresholds: @90% = 90% confidence limits; @99% = 99% confidence limits
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1% and @99%), after adjusting for multiple inferences*

Endurance training sessions

Variable	Group	Weekly AVG mean	±	*SD*	Between-group comparisons	Difference (raw) mean	±	*90%CI*	Standardised Effect Size (ES) ES	±	*90%CI*	Magnitude	Likelihood true effect is substantially ↑↔↓		Threshold for clear effect:	P-value
Total Score	END-RES	17.1	±	*3.0*												
	RES-END	17.3	±	*3.3*	END-RES vs RES-END	0.2	±	*1.9*	0.06	±	*0.57*	Trivial			unclear	0.863
Fatigue	END-RES	3.2	±	*0.9*												
	RES-END	3.2	±	*0.9*	END-RES vs RES-END	0.0	±	*0.5*	-0.01	±	*0.54*	Trivial			unclear	0.977
Sleep Quality	END-RES	3.4	±	*0.8*												
	RES-END	3.5	±	*0.9*	END-RES vs RES-END	0.1	±	*0.4*	0.11	±	*0.44*	Trivial			unclear	0.682
General Muscle Soreness	END-RES	3.3	±	*0.9*												
	RES-END	3.0	±	*0.9*	END-RES vs RES-END	-0.3	±	*0.5*	-0.32	±	*0.51*	Small	*possibly*	↓	@90%	0.300
Stress	END-RES	3.5	±	*0.8*												
	RES-END	3.7	±	*0.7*	END-RES vs RES-END	0.2	±	*0.4*	0.21	±	*0.51*	Small			unclear	0.484
Mood	END-RES	3.7	±	*0.7*												
	RES-END	3.9	±	*0.6*	END-RES vs RES-END	0.2	±	*0.3*	0.34	±	*0.45*	Small	*possibly*	↑	@90%	0.203

SD = standard deviation; mean % = mean percent difference between groups; 90%CI = 90% confidence interval; ES = standardised effect size (Cohen's d);
↑ = improved; ↔ = trivial; ↓ = interfered;
Non-clinical thresholds: @90% = 90% confidence limits; @99% = 99% confidence limits
***Bold** text indicates effects which remained clear at more conservative thresholds (i.e., @5/.1% and @99%), after adjusting for multiple inferences*