Examining interindividual differences in select muscle and whole-body adaptations to continuous endurance training

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Running Title: Interindividlual variability in muscle responses to exercise training

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References: 30
New Findings

*What is the central question of the study?*

- Do interindivudual differences in trainability exist for morphological and molecular skeletal muscle responses to aerobic exercise training?

*What is the main finding and its importance?*

- Interindivudual differences in trainability were present for some, but not all, morphological and molecular outcomes included in our study.
- Our findings suggest that is inappropriate, and perhaps erroneous, to assume that variability in observed responses reflects interindividual differences in trainability in skeletal muscle responses to aerobic exercise training.
Inter-individual variability in muscle responses to exercise training

Abstract

Studies have interpreted a wide range of morphological and molecular changes in human skeletal muscle as evidence of interindividual differences in trainability. However, these interpretations fail to account for the influence of random measurement error and within-subject variability. The purpose of the present study was to use the standard deviation of individual response (SD_{IR}) statistic to test the hypothesis that interindividual differences in trainability are present for some but not all skeletal muscle outcomes. Twenty-nine recreationally-active males (age: 21±2 years; BMI: 24±3; VO_2 peak: 45±7 mL/kg/min) completed four weeks of continuous training (REL; n=14) or control (CTRL; n=15). Maximal enzyme activities (citrate synthase and β-HAD), capillary density, fibre type composition, fibre-specific SDH activity and substrate storage (IMTG and glycogen), and markers of mitophagy (BNIP3, NIX, PRKN, and PINK1) were measured in vastus lateralis samples collected before and after the intervention. We also calculated SD_{IR} values for VO_2 peak, peak work rate, and the onset of blood lactate accumulation for REL and a separate group that exercised at the negative talk test (TT) stage. Although positive SD_{IR} values – indicating interindividual differences in trainability – were obtained for aerobic capacity outcomes, maximal enzyme activities, capillary density, all fibre-specific outcomes, and BNIP3 protein content, the remaining outcomes produced negative SD_{IR} values indicating a large degree of random measurement error and/or within-subject variability. Our findings question the interpretation of heterogeneity in observed responses as evidence of interindividual differences in trainability and highlight the importance of including control groups when analyzing individual skeletal muscle response to exercise training.

Keywords: SD_{IR}, individual responses, aerobic exercise training, interindividual variability
Introduction

Several studies have reported a wide range of individual molecular and morphological changes following aerobic exercise training in human skeletal muscle (Simoneau et al., 1986; Vollaard et al., 2009; McPhee et al., 2011; Yan et al., 2017; Raleigh et al., 2018). For example, McPhee et al. (2011) presented observed responses in skeletal muscle enzyme content that ranged from a ~3-fold decrease to a ~6-fold increase following six weeks of training. These studies have interpreted a wide range of observed responses (i.e. pre-post training changes) as evidence of interindividual variability in the responses to aerobic exercise training (i.e. interindividual differences in trainability). However, because observed responses contain random measurement error and within-subject variability (Bonafiglia et al., 2019), it is unclear whether observed variability reflects interindividual differences in trainability in skeletal muscle adaptations to exercise training.

The standard deviation of individual response (SD_{IR}) statistic can estimate interindividual differences in trainability in exercise training responses using the following equation (Atkinson & Batterham, 2015):

\[ SD_{IR} = \sqrt{(SD_{EX})^2 - (SD_{CTRL})^2} \]  

(1)

where SD_{EX} and SD_{CTRL} represent the standard deviation of observed variability in an exercise (EX) and a no-exercise control group (CTRL), respectively. Assuming measurement error and within-subject variability equally contribute to observed variability in EX and CTRL, a positive SD_{IR} (i.e. SD_{EX} > SD_{CTRL}) indicates interindividual differences in trainability (Atkinson & Batterham, 2015). Conversely, a negative SD_{IR} value (i.e. SD_{EX} < SD_{CTRL}) suggests interindividual differences in trainability may not exist and that observed variability reflects a large degree of random measurement error and/or within-subject variability (Atkinson & Batterham, 2015). Recent studies using the SD_{IR} approach have
reported a mixture of positive and negative $SD_{IR}$ values for cardiorespiratory fitness and body composition responses to aerobic exercise training (Williamson et al., 2018; Hecksteden et al., 2018; Hammond et al., 2019; Walsh et al., 2020). However, no study has adopted the $SD_{IR}$ statistic to analyze skeletal muscle responses to aerobic exercise training. We speculate that morphological and molecular skeletal muscle changes will also reveal a mixture of positive and negative $SD_{IR}$ values indicating the presence and absence of interindividual differences in trainability, respectively.

The primary purpose of the present study was to use the $SD_{IR}$ statistic to test the hypothesis that interindividual differences in trainability are present for some but not all morphological and molecular skeletal muscle responses to aerobic exercise training. To test this hypothesis, we examined changes in a wide range of morphological and molecular skeletal muscle outcomes including: enzyme activities (whole-muscle citrate synthase [CS], beta-hydroxyacyl-CoA dehydrogenase [$\beta$-HAD], and fibre-specific succinate dehydrogenase [SDH]), type I fibre composition, capillary density, fibre-specific substrate storage (glycogen and intramuscular triglycerides [IMTG]), and markers of mitophagy (BCL2-interacting protein 3 [BNIP3], BNIP3-like protein [NIX], Parkin (PRKN), and PTEN-induced kinase 1 [PINK1]). We also examined three whole-body aerobic outcomes including peak oxygen consumption (VO$_2$peak), peak work rate (WRpeak), and work rate at the onset of blood lactate accumulation (OBLA) following continuous training at relative intensity (REL) or an intensity that produced a negative response to the talk test (TT). Confirming our hypothesis would provide evidence supporting the assertion that it is inappropriate, and perhaps erroneous, to assume that observed variability reflects interindividual differences in trainability (Atkinson & Batterham, 2015).

Methods
Ethical Approval

Each participant attended a preliminary screening session where they were provided a verbal and written explanation of the experimental protocol and its associated risks prior to obtaining informed consent. All experimental procedures performed on human participants were approved by the Human Health Sciences Human Research Ethics Board at Queen’s University (reference number: 6003260) and confirmed to the Declaration of Helsinki, except for registration in a database.

Experimental design

Figure 1 provides a schematic of our study design. The current study followed a parallel-arm design in which 29 recreationally-active males (age: 21±2 years; BMI: 24±3; peak oxygen uptake [VO_{2peak}]: 45±7 mL/kg/min) were assigned to either four weeks of supervised continuous training at a relative intensity of 65% WRpeak (REL; n = 14) or a no-exercise control period (CTRL; n = 15). Participants were assigned to REL or CTRL via minimization (Treasure & MacRae, 1998) whereby the first participant was randomly allocated to REL or CTRL and every subsequent participant was allocated in a manner that minimized the imbalance of baseline VO_{2peak} between groups. We also analyzed whole-body aerobic adaptations from a separate group that exercised at an intensity that produced a negative response to the talk test (TT). The TT group was part of a separate study (Preobrazenski et al., 2019), and thus participants were separately recruited and enrolled into this group. Data collection for all three groups occurred concurrently (September-March, 2016), used the same inclusion/exclusion criteria to recruit participants from the same population, and took place in the same location. All participants were recruited through social media advertisements and posters distributed across the Queen’s University’s campus.
Participants were asked to maintain their regular dietary and physical activity habits throughout the 4-week intervention.

The study protocol, eligibility criteria, and training and mean VO$_2$peak, WRpeak, and OBLA data are provided elsewhere (Preobrazenski et al., 2019). In brief, REL involved 30 minutes of cycling at 65% WRpeak, whereas TT involved 30 minutes of cycling at an intensity that caused uncomfortable speech production. Both groups exercised for 4 days per week for 4 weeks (15 sessions total; 3d/wk in one week). All three whole-body aerobic outcomes were assessed during incremental step tests to exhaustion before and after training: VO$_2$peak was calculated as the highest 30 second average oxygen consumption (collected via gas exchange using a metabolic cart), WRpeak was calculated as the highest 30 second average work rate, and OBLA was determined as the work rate during when blood lactate levels exceeded 4.0 mmol/L. Using the Bergström skeletal muscle biopsy technique as previously described (Bonafiglia et al., 2020), vastus lateralis biopsies were collected from the REL and CTRL groups only. Biopsies were collected after an overnight fast (~12 hours) before (pre) and ~72 hours (post) following the final REL session or the end of the no-exercise control intervention. All participants were asked to refrain from exercising 24 hours before their biopsy and physiological testing visits, and to arrive to our laboratory in an overnight fasted state. Upon arrival, we provided participants with a standardized breakfast (12 grain bagel with ~1.5oz of cream cheese and 300mL of orange juice [total ~510 kcals; ~20g fat, ~71g carbohydrate, and ~14g protein]). A small portion of skeletal muscle samples were embedded in optimal cutting temperature (O.C.T.) compound (Tissue-Tek, Sakura Finetek, USA) for immunofluorescent and histochemical analysis, and the remaining sample was immediately snap-frozen in liquid nitrogen.

Tissue Analysis

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~10-20 mg of muscle was homogenized to determine maximal CS and \( \beta \)-HAD activities as previously described (Raleigh et al., 2018).

Immunofluorescent analysis of myosin heavy chain isoforms was performed as previously described (Bloemberg & Quadrilatero, 2012). MHCIIa/x or MHCIIx fibres were not examined given our previous observation of a low abundance of these fibres in samples collected from recreational active males (Islam et al., 2020b). This observation is also consistent with recent estimates that type IIIX fibres represent <1% of the total muscle fibre pool (Murach et al., 2019). All fibres were counted in each cross-section, and type I composition was expressed as a percentage of type I fibres relative to the total sum of type I and IIa fibres. Additionally, we used immunofluorescence to count capillaries, and capillary density was expressed as the average number of capillaries per millimetre squared (cap/mm\(^2\)) as previously described (Scribbans et al., 2014). Lastly, SDH activity, glycogen content, and IMTG content were quantified via histochemical analysis as previously described (Bloemberg & Quadrilatero, 2012), and were matched to fibre-type to quantify these outcomes in a fibre-specific manner.

Western blotting was performed on whole-muscle homogenates to quantify the content of mitophagy regulators as previously described (Carter et al., 2018). We used commercially available antibodies against BNIP3 (1:1000 dilution; antibody gifted from Dr. Kirshenbaum), NIX (1:200; Santa Cruz, sc-166332 lot #D0114), PRKN (1:1000; Cell Signalling, 4211 lot #4), and PINK1 (1:1500; Santa Cruz, sc-33796 lot #C2107). Ponceau staining was used as a loading control, and there were no differences in protein between conditions or time (all \( p > 0.05 \)). All protein data were expressed relative to total protein loaded.

**Statistical analysis**

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Observed responses for all outcomes were calculated by subtracting post-intervention values from pre-intervention values. Two-way repeated measures ANOVAs were used to assess main effects of time, group, and time x group interactions for skeletal muscle outcomes only (results for mean changes in VO$_2$peak, WRpeak, and OBLA reported elsewhere (Preobrazenski et al., 2019)). Three-way repeated measures ANOVAs were used for fibre-specific outcomes (factors: time, group, and fibre type). SD$_{IR}$ values were calculated for each outcome using equation 1, and were calculated separately for REL and TT groups. Because participants in TT group were not randomized (Figure 1), analysis on the TT group violates the assumptions of independence required for the SD$_{IR}$ (Atkinson & Batterham, 2015). The TT analysis was therefore exploratory and the associated results should be interpreted with caution. For VO$_2$peak, SD$_{IR}$ values were appraised against a minimum clinically important difference (MCID) of 1.75mL/kg/min – a value associated with reduced risk of all-cause morbidity and mortality (Ross et al., 2016). Because the other variables examined do not have similar evidence-informed MCIDs, we appraised the other SD$_{IR}$ values against smallest worthwhile changes (SWC) calculated as 0.2 times SD of pre-training CTRL group values (thresholds that approximate small effect sizes (Hecksteden et al., 2018)). 95% confidence intervals CI were calculated for each SD$_{IR}$ using the following equation (Hopkins, 2015):

$$95\% \text{ CI: } SD_{IR}^2 \pm 1.96 \times \sqrt{\frac{2 \times \left( \frac{SD_{EX}^4}{n_{EX} - 1} + \frac{SD_{CTRL}^4}{n_{CTRL} - 1} \right)}{n_{EX} \times n_{CTRL}}}$$

Meaningful interindividual differences in trainability were considered present for a given variable when the SD$_{IR}$ exceeded the SWC (Atkinson & Batterham, 2015). For outcomes where SD$_{CTRL}$ exceeded SD$_{EX}$, we reversed the SD$_{IR}$ formula and reported these instance as negative SD$_{IR}$ values. Outliers were identified as z-scores that exceeded ± 2.54, and these data were removed prior to any statistical analysis. Shapiro-Wilk tests revealed
that all data were normal ($p>0.05$) except for observed changes in OBLA ($p=0.03$) and fibre-type composition ($p=0.02$). Although the SD_{IR} statistic relies on the assumption of normality, we used the SD_{IR} on OBLA and fibre-type data as we are unaware of a non-parametric alternative for estimating interindividual differences in trainability. Significance was accepted as $p<0.05$ and all data presented as mean ± SD.

Results

As reported elsewhere (Preobrazenski et al., 2019), VO_{2peak} increased significantly following REL (+ 3.67 ± 3.1 mL/kg/min) and TT (+ 5.43 ± 3.0 mL/kg/min) but not CTRL (+ 0.17 ± 2.8 mL/kg/min; group˟time interaction: $p < 0.01$) indicating that the training stimuli were sufficient to induce aerobic adaptations. Representative images for all immunofluorescent, histochemical, and western blotting analyses are provided in Figure 2.

Table 1 presents mean and SD of observed responses, as well as SD_{IR} and SWC values for all skeletal muscle outcomes. CS activity increased over time (significant main effect of time) and trended to increase more in EX (near-significant group˟time interaction [$p = 0.07$]). β-HAD activity and capillary density also increased over time (significant main effects of time) but changes across time were not different between groups (group˟time interactions: $p = 0.4$ for both outcomes). A significant main effect of time and group˟time interaction was observed for glycogen content in both fibre types, whereby REL increased glycogen content more than CTRL. Significant main effects of fibre type were observed for all fibre specific outcomes: SDH activity and IMTG content higher in type I fibres whereas glycogen content was higher in type IIA fibres. No other significant main or interaction effects were observed (Table 1).
We observed positive SDIR values (value [95% CI]) for VO\(_2\)peak (1.42 mL/kg/min [-2.72 – 3.38]) and WRpeak (3.80 W [-20.48 – 21.17]) that did not exceed the MCID of 1.75 mL/kg/min or SWC of 10.02 W, respectively. OBLA also revealed a positive SDIR value (26.10 W [-11.57 – 38.68]), and this value exceeded the SWC of 8.25 W.

Interestingly, similar SDIR results were observed in the TT group (VO\(_2\)peak: 1.12 mL/kg/min [-2.30 – 3.04]; WRpeak: 6.83 W [-18.99 – 21.31]; OBLA: 28.24 W [-9.63 – 41.09]); however, these results should be interpreted with caution given the lack of randomization for the TT group.

For skeletal muscle outcomes, Figure 3 presents individual observed responses and SDCTRL/SDEX values. SDEX was greater than SDCTRL for most, but not all outcomes. Our SDIR analysis revealed three main results (Table 1): 1) some outcomes revealed meaningful interindividual variability whereby positive SDIR values exceeded the SWC (CS activity, capillary density, type I and IIA glycogen and IMTG content, and BNIP3 protein content); 2) some outcomes revealed interindividual variability that was not meaningful whereby positive SDIR values did not exceed the SWC (β-HAD activity and type I and IIA SDH activity); and 3) some outcomes revealed negative SDIR values indicating a lack of interindividual differences in trainability (type I composition, and NIX, Parkin, and PINK1 protein content).

Discussion

Four weeks of REL resulted in positive and negative SDIR values for the morphological and molecular outcomes included in the present study. Although we obtained positive SDIR values for VO\(_2\)peak, WRpeak, and OBLA, all three outcomes had large CIs that overlapped zero, and only OBLA had an SDIR value that exceeded the SWC. Because previous studies failed to account for the influence of random measurement error and/or
within-subject variability (Simoneau et al., 1986; Vollaard et al., 2009; McPhee et al., 2011; Yan et al., 2017; Raleigh et al., 2018), our study is the first to demonstrate that exercise training results in meaningful interindividual variability in certain morphological and molecular adaptations in human skeletal muscle (Table 1; i.e. positive $SD_{IR}$ values exceeding SWC). However, our results also revealed non-meaningful interindividual variability (i.e. positive $SD_{IR}$ values not exceeding the SWC; Table 1) or no evidence of interindividual differences in trainability (i.e. a negative $SD_{IR}$ value; Table 1) for roughly half of our outcomes (Table 1). These latter findings add to the growing body of evidence indicating that observed responses contain a large degree of random measurement error and/or within-subject variability (Williamson et al., 2018; Islam et al., 2020a); observations that raise concerns for whether researchers, clinicians, or coaches can accurately quantify an individual’s true response to exercise training (Islam & Gurd, 2020). Accordingly, our findings suggest that it is inappropriate, and perhaps erroneous, to assume that variability in observed skeletal muscle responses to continuous exercise training reflects interindividual differences in trainability.

Our study also adds to the limited body of work examining changes in markers of mitophagy following aerobic exercise training in human skeletal muscle (Brinkmann et al., 2017; Brandt et al., 2018; Arribat et al., 2019). Rodent studies demonstrate that exercise training increases mitochondrial turnover to maintain or improve mitochondrial quality and function (Hood et al., 2019). In support of these animal findings, two human studies (Brandt et al., 2018; Arribat et al., 2019) reported elevated mitochondrial content and markers of mitophagy after exercise training. In contrast, we (Table 1) and others (Brinkmann et al., 2017) found no changes in markers of mitophagy, and these discrepant findings may be explained by differences in exercise training protocols. It is important to note that measuring changes in markers of mitophagy does not sufficiently quantify mitochondrial turnover.
dynamics and current techniques for quantifying mitophagy-flux are currently limited to animal models (Hood et al., 2019). Collectively, these discrepant findings and methodological limitations highlight important areas for future work.

The present study has some limitations that are important to consider. First, the lack of randomization for the TT group violates the assumptions of independence and thus violates assumptions required for the $\text{SD}_{\text{IR}}$ (Bonafiglia et al., 2019). The results of the TT group should therefore be interpreted with caution and within the context of this limitation. Further, the inability to blind participants to CTRL or REL risked introducing participant preference bias: a bias that occurs when participants alter their behaviour based on knowing their assigned group (Halpern, 2003). Participant preference bias may lead to differences in variability of behavioural changes between CTRL and REL, and such changes could violate the $\text{SD}_{\text{IR}}$ assumption that within-subject variability is equal between groups (Bonafiglia et al., 2019). In the current study, although we attempted to mitigate changes in within-subject variability by asking all participants to maintain their dietary and physical activity habits throughout the intervention, we did not objectively measure these behavioural factors. Direct assessment of the factors contributing to within-subject variability remains a major challenge for future studies because it requires collecting objective measurements of diet, physical activity, and other potential behavioural/environmental factors (e.g. exercise recovery habits, psychological stress, or major life events (Mann et al., 2014)). However, confirming or refuting the assumption of equal between-group within-subject variability is paramount if the individual response field is to move forward in a meaningful way. Future work also needs to establish statistical approaches that incorporate objective measurements of behavioural/environmental factors when estimating interindividual differences in trainability. Additionally, because the sample size of the present study was based on changes in VO$_2$peak (Preobrazenski et al., 2019), poor statistical power may explain the lack of group*time
inter-individual variability in muscle responses to exercise training (e.g. CS activity: \( p = 0.07 \)). Indeed, large-scale, rigorous, and well-controlled training studies remain an important direction for future exercise physiology research (Bonafiglia et al., 2021).

**Conclusions**

We found that four weeks of continuous endurance training did not result in meaningful interindividual differences in trainability across all molecular, morphological, and whole-body aerobic outcomes included in our study. Our findings highlight the need to include no-exercise control groups and adopt statistical approaches (e.g. the SDIR; (Atkinson & Batterham, 2015) that account for random measurement error/within-subject variability when analyzing interindividual variability. Although we measured several morphological and molecular outcomes in human skeletal muscle, future work should explore additional outcomes and different training protocols.

**References**


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*Sports Exerc* 51, 315–322.


Murach KA, Dungan CM, Kosmac K, Voigt TB, Tourville TW, Miller MS, Bamman MM,
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Figure Captions

Figure 1. Schematic of study design. Participants in study 1 were assigned to control (CTRL) or continuous training at relative intensity (REL) via minimization based on pre-training peak oxygen consumption (VO_{2peak}) measures – see (Preobrazenski et al., 2019) for details. A separate cohort of participants were recruited to complete four weeks of continuous training at the negative talk test (TT) stage. Incremental step tests were completed to measure VO_{2peak}, peak work rate (WRpeak), and the onset of blood lactate accumulation (OBLA). NEG refers to the negative talk test stage – an intensity where participants cannot maintain comfortable speech (see (Preobrazenski et al., 2019) for details).
Figure 2. Representative images for immunofluorescent and histochemical analysis (A) and western blotting analysis (B). White scale bars represent 100 µm (A). REL, relative intensity continuous training; CTRL, control group; PRE, pre-training; POST, post-training; CAP. DENS., Capillary density; SDH, succinate dehydrogenase; IMTG, intramuscular triglyceride; BNIP3, BCL2 interacting protein 3; NIX, BNIP3-like protein; PRKN, Parkin; and PINK1, PTEN-induced kinase 1.
Figure 3. Individual changes in citrate synthase (CS) activity (A), beta-hydroxyacyl-CoA dehydrogenase (β-HAD) activity (B), capillary density (C), type I fibre composition (D), fibre-specific succinate dehydrogenase (SDH) activity and glycogen and IMTG content (E), and protein content of mitophagy markers (F) following four weeks of continuous exercise training at a relative intensity (REL) or a control group (CTRL). Upper and lower 95% confidence interval limits are provided in square brackets below each SD_{IR} value. SD, standard deviation; SD_{IR}, standard deviation of individual responses (calculated using equation 1; see text); BNIP3, BCL2 interacting protein 3; NIX, BNIP3-like protein; PRKN, parkin; and PINK1, PTEN-induced kinase 1.
### Table 1. Mean changes and interindividual differences in trainability in molecular and morphological skeletal muscle.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Δ REL Mean (SD)</th>
<th>Δ CTRL Mean (SD)</th>
<th>SD\textsubscript{IR} [95% CI limits]</th>
<th>SWC</th>
<th>SD\textsubscript{IR} &gt; SWC?</th>
</tr>
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<td><strong>Whole muscle outcomes</strong></td>
<td></td>
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<tr>
<td>CS Max Activity (AU)</td>
<td>0.78 (0.91)*</td>
<td>0.07 (0.57)</td>
<td>0.71</td>
<td>0.35</td>
<td>Yes</td>
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<td></td>
<td></td>
<td></td>
<td>[-0.42 – 1.42]</td>
<td></td>
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<tr>
<td>β-HAD Max Activity (AU)</td>
<td>0.51 (0.86)</td>
<td>0.23 (0.86)</td>
<td>0.02</td>
<td>0.16</td>
<td>No</td>
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<td></td>
<td></td>
<td></td>
<td>[-0.93 – 0.93]</td>
<td></td>
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<tr>
<td>Capillary Density (cap/mm\textsuperscript{2})</td>
<td>56.77 (110.45)</td>
<td>23.13 (87.31)</td>
<td>67.65</td>
<td>35.56</td>
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<td></td>
<td></td>
<td>[-81.31 – 125.56]</td>
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<tr>
<td>Type I Composition (%)</td>
<td>-0.16 (12.77)</td>
<td>-5.08 (17.25)</td>
<td>-11.60</td>
<td>2.24</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>[-19.70 – 10.92]</td>
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<td><strong>Fibre-specific outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>SDH Activity Type I (AU) †</td>
<td>1.67 (6.51)</td>
<td>1.82 (4.78)</td>
<td>4.41</td>
<td>1.67</td>
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<td>[-4.77 – 7.85]</td>
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<td>SDH Activity Type IIA (AU)</td>
<td>2.19 (4.39)</td>
<td>0.88 (3.40)</td>
<td>2.77</td>
<td>0.89</td>
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<td></td>
<td>[-3.47 – 5.23]</td>
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<tr>
<td>Glycogen Content Type I (AU)</td>
<td>3.38 (2.92)**</td>
<td>-0.55 (2.37)</td>
<td>1.71</td>
<td>0.64</td>
<td>Yes</td>
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<td></td>
<td>[-2.49 – 3.47]</td>
<td></td>
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<td>Glycogen Content Type IIA (AU) †</td>
<td>5.26 (3.82)**</td>
<td>-0.80 (3.00)</td>
<td>2.37</td>
<td>0.74</td>
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<td></td>
<td></td>
<td>[-3.11 – 4.57]</td>
<td></td>
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<tr>
<td>IMTG Content Type I (AU) †</td>
<td>0.63 (2.51)</td>
<td>0.45 (1.40)</td>
<td>2.08</td>
<td>0.30</td>
<td>Yes</td>
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<td>[-1.07 – 3.13]</td>
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<td>IMTG Content</td>
<td>0.29 (1.69)</td>
<td>-0.22 (1.15)</td>
<td>1.24</td>
<td>0.22</td>
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<table>
<thead>
<tr>
<th>Type IIA (AU)</th>
<th>[-1.04 – 2.03]</th>
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**Markers of mitophagy**

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<td><strong>BNIP3 Content</strong></td>
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<tr>
<td>(AU)</td>
<td>-0.10 (0.47)</td>
<td>0.04 (0.42)</td>
<td>0.21</td>
<td>0.09</td>
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<td><strong>NIX Content</strong></td>
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<tr>
<td>(AU)</td>
<td>0.10 (0.62)</td>
<td>0.16 (0.78)</td>
<td>-0.48</td>
<td>0.15</td>
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<td><strong>PRKN Content</strong></td>
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<td></td>
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<tr>
<td>(AU)</td>
<td>-0.11 (0.53)</td>
<td>0.10 (0.55)</td>
<td>-0.16</td>
<td>0.12</td>
<td>-</td>
</tr>
<tr>
<td><strong>PINK1 Content</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(AU)</td>
<td>-0.08 (0.54)</td>
<td>0.03 (0.61)</td>
<td>-0.28</td>
<td>0.15</td>
<td>-</td>
</tr>
</tbody>
</table>

SD_{IR} > SWC interpretations only provided for outcomes with positive SD_{IR} values. REL, continuous training at a relative intensity; CTRL, control group; SD_{IR}, standard deviation of individual responses; SWC, smallest worthwhile change; CI, confidence intervals; CS, citrate synthase; β-HAD, beta-hydroxyacyl-CoA dehydrogenase; SDH, succinate dehydrogenase; IMTG, intramuscular triglyceride; BNIP3, BCL2 interacting protein 3; NIX, BNIP3-like protein; PRKN, parkin; and PINK1, PTEN-induced kinase 1. * near-significant interaction effect (p = 0.07); ** significant interaction effect (p < 0.05); † main effect of fibre type.
Additional Information

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Competing interests

The authors declare no competing interests.

Author contributions

All authors contributed to the conception and design of the study, analyzed and interpreted data, edited and approved of the final manuscript for submission. J.T.B. wrote the initial draft of the manuscript. All authors are also agreeable to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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