International Journal of EXERCISE SCIENCE

Original Research

Do Surrogate Markers of Cardiorespiratory Fitness Predict Individual Changes in VO_{2peak}? A Randomized Controlled Trial

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ABSTRACT

International Journal of Exercise Science 17(4): 1134-1154, 2024. The purpose of the current study was to test the hypothesis that individual response classification for surrogate markers of cardiorespiratory fitness (CRF) will agree with response classification for VO_{2peak}. Surrogate markers of CRF were time to fatigue on treadmill test (TTF), time trial performance (3kTT), resting heart rate (RHR), submaximal heart rate (SubmaxHR), and submaximal ratings of perceived exertion (SubmaxRPE). Twenty-five participants were randomized into a high-intensity interval training (HIIT: n = 14) group or non-exercise control group (CTL: n = 11). Training consisted of four weeks of high-intensity interval training (HIIT) – 4x4 minute intervals at 90–95% HR_{max} 3 times per week. We observed poor agreement between response classification for VO_{2peak} and surrogate markers (agreement < 60% for all outcomes). Although surrogate markers and VO_{2peak} correlated at the pre- and post-intervention time points, change scores for VO_{2peak} were not correlated with changes in surrogate markers of CRF. Interestingly, a significant relationship (r^2 = 0.36, p = 0.02) was observed when comparing improvements in estimated training performance (VO_2) and change in VO_{2peak}. Contrary to our hypothesis, we observed poor classification agreement and non-significant correlations for changes scores of VO_{2peak} and surrogate markers of CRF. Our results suggest that individuals concerned with their VO_{2peak} response seek direct measurements of VO_2.

KEY WORDS: Responders, measurement error, patterns of response

INTRODUCTION

Improvements in cardiorespiratory fitness (CRF) resulting from exercise training have garnered significant interest from populations concerned with exercise performance and health (21, 25, 35). Importantly, a training-induced increase of 1 MET (3.5 mL/kg/min) reduces the risk of all-cause mortality and cardiovascular disease by 13% and 15%, respectively (22). VO_{2peak} testing is the gold-standard method used to assess CRF, but its widespread use is limited by requisite expertise, high cost, and availability of metabolic equipment (24). While extensive research has been conducted to estimate VO_{2peak} using submaximal exercise tests, heart rate monitoring, or predictive equations based on age, sex, and body composition (studies reviewed in (42)), the

existence of an accessible surrogate measure to monitor individual changes in VO_{2peak} remains underexplored.

In addition to the well-documented physiological and perceptual changes that arise from chronic exercise (resting heart rate [RHR], submaximal heart rate [SubmaxHR] and submaximal ratings of perceived exertion [SubmaxRPE] (13, 15)), there are other accessible metrics that hold potential as surrogates for an individual's VO_{2peak} response. For instance, data from cross-sectional samples suggest the duration of a treadmill stress test (time to fatigue [TTF]) is positively and strongly correlated with VO_{2peak} (4, 30). Similarly, time trial performance over varying distances, is moderately to strongly (24, 27, 39) correlated with VO_{2peak} in cross-sectional studies. While it is tempting to speculate that the physiological mechanisms responsible for increases in VO_{2peak} equally contribute to improvements in TTF and time trial performance, current evidence refutes this speculation (15). Further, although various submaximal (i.e., SubmaxHR, SubmaxRPE, RHR, time trial performance) and maximal (TTF) surrogate markers of CRF can correlate with VO_{2peak} (27, 30, 39), individual changes in these markers do not correlate with individual changes in VO_{2peak} (3, 15). This observation questions the utility of surrogate markers of CRF as accessible proxies for VO_{2peak} training responses.

The absence of a correlation between individual changes in surrogate markers of CRF and changes in VO_{2peak} response may arise from the influence of measurement error and within-subject variability (5, 40). Although individuals can evaluate whether they are experiencing meaningful benefit using classification methods that consider biological and technical error (7, 20, 40), the application of these methods to VO_{2peak} response continues to be limited by access to direct measurement of VO_2. Thus – because an individual demonstrating a meaningful improvement in VO_{2peak} (i.e., be confidently classified as a responder) may also exhibit similarly large improvements in surrogate markers of CRF – classification agreement between VO_{2peak} and surrogate markers of CRF is of interest to anyone interested in facilitating practical and personalized aerobic exercise prescriptions.

Although a limited number of studies have explored agreement of individual response classifications in a small number of outcomes (1, 13, 15, 19, 38), the existence of a relationship between the classification agreement for VO_{2peak} and surrogate markers of CRF following high-intensity interval training (HIIT) remains largely unexplored. HIIT describes a style of exercise characterized by brief, intermittent bouts at an absolute workload requiring near-maximal efforts interspersed with recovery periods (16). While much evidence supports the efficacy of HIIT to induce CRF-related improvements in health and performance (25, 30, 39), the demonstration of accessible measures that both accurately classify VO_{2peak} response and eliminate and/or minimize barriers to access would provide a convenient means to accurately assess the health of individuals seeking to improve VO_{2peak}. Accordingly, the purpose of this study was to test the hypothesis that individual response classification for surrogate markers of CRF will agree with response classification for VO_{2peak}.

METHODS

Participants

A portion of the data presented in this manuscript was included in a previous manuscript (38). Specifically, participant characteristics and VO_{2peak} values for a subset of the participants in the current study (CTL n = 9; "3-Day" HIIT n = 12) were previously published (38). The current dataset includes 4 participants (CTL: n = 2, HIIT: n = 2) who were excluded from our previous publication (38) due to missing data for 1 of 8 VO_{2peak} testing sessions (data from all 8 session were required for inclusion in our previous publication) . None of the data for surrogate markers of CRF, nor any of the results exploring the relationships between surrogate markers of CRF and VO_{2peak} presented in the current manuscript, have been published previously.

A sample size calculation was performed for the relationship between the change in VO_{2peak} and the change in other outcomes. We determined that a sample size of 13 was needed (Z_α = 1.96, Z_β = 0.84, C = 0.89, r = 0.71) to detect significance for a correlation with an expected coefficient of r = 0.71 (i.e., an r^2 value of 0.5) with 80% power.

Participant recruitment and data collection took place in Kingston, Ontario, Canada between June 2017 and November 2017. Forty-two healthy recreationally active (self-reported < 3 hours of physical activity per week) volunteered to participate in the study. From this initial sample, twenty-five participants were enrolled and randomized (men = 9, women = 16). Participants were only enrolled in the study if they met the following inclusion criteria: between 18 and 30 years of age, non-smokers, not taking any prescription medication, free of cardiometabolic disease, self-reported less than three hours of physical activity per week, and not involved in a systematic training program at the time of enrollment. Each participant attended a preliminary screening session where they were briefed on the study and provided informed consent. Participants were not previously trained in running and were not involved in a training program at the start of the study. Participants were instructed to maintain their regular physical activity and nutritional habits throughout the duration of the study.

All experimental procedures performed on human participants were approved by the Health Sciences Human Research Ethics Board at Queen's University. Verbal and written explanation of the experimental protocol and associated risks was provided to all participants prior to obtaining written informed consent. This research was carried out fully in accordance to the ethical standards of the *International Journal of Exercise Science* (33).

Protocol

The experimental design, as stated below, has been previously described in (38). Methods describing the collection and analysis of resting heart rate, 3000m time trial performance, submaximal RPE, submaximal heart rate, and estimated VO_2 were not included in our previous publication. All participants were recruited from the same undergraduate population and met the same inclusion/exclusion criteria. All participants completed a week of familiarization testing, as well as a week of physiological testing prior to and following the four-week intervention. Following baseline testing, participants were randomly allocated using random

computer-generated numbers on Microsoft Excel to a 3-day high-intensity interval training (HIIT) group (n = 14) or a no-exercise control (n = 11), where the participants were instructed to return to their regular daily habits. Allocation was not concealed. All participants were asked to refrain from alcohol and caffeine (12 hours before), nutritional supplements, and strenuous exercise (24 hours before) for all physiological testing.

During a familiarization week, participants reported to the lab on two separate occasions to perform a VO_{2peak} test and a 3000m time trial performance test (3kTT). In the weeks preceding and following the intervention, participants reported to the lab on three separate occasions, separated by 24–48 hours. During the first visit of PRE and POST testing, participants completed a VO_{2peak} test with a supramaximal verification phase (SupraV) (day 1), and 24–48h later participants returned to complete a second VO_{2peak} test with another SupraV (day 2). Briefly, a SupraV involves exercising at a power output greater than the highest power output achieved during a VO_{2peak} test to validate VO_{2max} (34). VO_{2peak} values were not statistically verified in this study. Instead, VO_2 values from SupraV were used as repeated measures (described below) given previous work (17) suggesting that VO_2 values obtained from incremental tests are not statistically different than those obtained from SupraV. On the third visit (24–48 hours after visit 2) a 3kTT was completed (day 3). Following training, the order of the three visits was identical to PRE. The first POST-training visit occurred 72–96h after the final training session (see Figure 1).

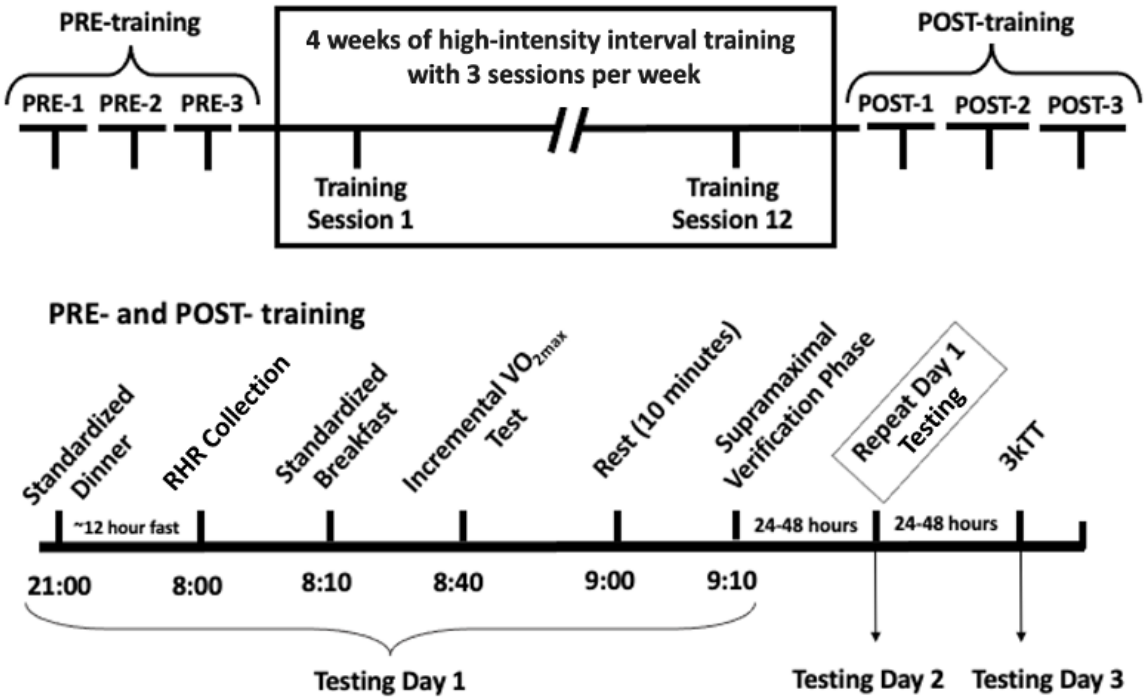

Figure 1. Overview of study protocol. RHR = resting heart rate; VO_{2max} = maximal aerobic capacity; 3kTT = 3000m time trial.

To further standardize experimental testing caloric/macronutrient intake, participants consumed a standardized dinner the night before each VO_{2peak} test (Stouffer's Sauté Sensations [520 kcal; 74 g carbohydrate, 10 g fat, 32 g protein]) and arrived at the laboratory in the morning following a 12-h overnight fast. Upon arrival in a fasted and caffeine-free state, participants began by resting in the supine position for ten minutes, while resting heart rate (RHR) data was collected. Following RHR collection, participants were fed a standardized breakfast consisting of a toasted plain bagel (190 kcal; 1 g fat, 36 g carbohydrate, 7 g protein) with 15 g of cream cheese (45 kcal; 4 g fat, 1 g carbohydrate, 1 g protein). Thirty minutes after breakfast, participants completed a VO_{2peak} test on a motorized treadmill followed by a SupraV phase. The incremental test protocol consisted of three minutes of resting data collection (participants were asked to stand on the treadmill and breathe normally) followed by a five-minute warm-up with the treadmill set to 2.5 mph at an incline of 2 and subsequent increases of either incline or speed every two minutes until volitional fatigue (for details on the incremental protocol, please see Supplemental Table 1 in (1, 18)). Following the incremental test protocol, participants were provided with a minimum of 10 min of rest prior to commencing a supramaximal verification phase. The metabolic cart was not re-calibrated between phases. During the supramaximal verification phase, participants ran until volitional fatigue at a speed that was 0.5 mph faster than the final stage attempted during the incremental test protocol.

For each VO_{2peak} test, VO_2 was collected breath-by-breath, sampled from a mixing chamber, and averaged into 10-s bins (Moxus AEI Technologies, Pittsburgh, PA). HR was collected continuously using a heart rate monitor (Polar Team2 Pro, Kempele, Finland). Rating of perceived exertion (RPE) was collected in the final thirty seconds of each interval using a 6–20 BORG scale (11). As previously done (38), VO_{2peak} was calculated as the highest 30-s average during each part of the protocol (incremental test and supramaximal verification) resulting in four values (two incremental test values and two supramaximal verification values) for each participant at each time point (PRE and POST). The four values at each time point were averaged together to provide each participant with single PRE and POST VO_{2peak} values. TTF was recorded as the duration (seconds) of the incremental test. SubmaxRPE and submaxHR were collected in the final thirty seconds of the fourth stage of the incremental test (speed: 5.5 mph, incline: 6).

The 3kTT was performed on an outdoor rubber track, where participants were given a five-minute warm up at a self-selected intensity, and then were instructed to complete the 3000m as quickly as possible. The 3kTT was recorded as the duration (seconds) to complete the 3000m distance.

Participants trained on the same motorized treadmill three times per week for four weeks and were trained by the same group of trainer(s) throughout. The 4-week HIIT period consisted of 12 total sessions each including a ten-minute warm up at 70–75% maximal heart rate (HRmax), followed by 4x4-minute intervals at 90–95% HRmax, separated by 3 minutes of active recovery at 70–75% HRmax, and a 5-minute cooldown after the final interval at 70–75% HRmax (a total of 40 minutes per session). If the target HR was not attained by the two-minute mark during each four-minute interval, speed or incline (based on participant preference) were adjusted by

a trained volunteer during training sessions to ensure appropriate training intensity. Heart rate (training HR) was collected in the final thirty seconds of each interval using Polar HR monitors (Polar Team2 Pro, Kempele, Finland). Average exercise VO_2 was estimated using an online calculator derived from an ACSM predictive equation (18) that considers the speed (miles per hour; [mph]) and incline of the treadmill (14, 18). Participants nor trainers were blinded to treadmill speed or incline.

Statistical Analysis

Training responses for all outcomes were calculated by subtracting post-intervention values from pre-intervention values (POST-PRE). Two-way mixed ANOVAs (time x group) were used to examine group-level changes in relative VO_{2peak}, 3kTT, RHR, submaxHR, submaxRPE, TTF. Significant interaction or main effects were subsequently analyzed using Bonferroni post-hoc analyses. Corresponding effect sizes were calculated using the equation for partial eta squared (η_p^2) (η_p^2 = SS_{effect} ÷ [SS_{effect} + SS_{error}]) (23). SS_{error} is reported as $SS_{residual}$ in GraphPad Prism. Resulting effect sizes were interpreted using partial η^2 values (small = 0.0099; medium = 0.0588; large = 0.1379) (23). A one-way ANOVA was used to examine changes in training performance (i.e., estimated VO_2) across training sessions in the exercising group (HIIT).

Simple linear regressions were used to determine i) cross-sectional (using all data collected at both time points [pre- and post- training] and from both groups [CTL and HIIT]) correlations, and ii) the relationship between changes in VO_{2peak} and changes in surrogate measures of CRF. Pearson correlation coefficients were classified as very weak (< 0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79) or very strong (> 0.80).

Individual response classification was calculated using typical errors (TE) calculated using the standard deviations (SD) of change from the no-exercise control group (n = 11):

$$(1)\ TE = \frac{SD_{CTL}}{\sqrt{2}}$$

As our group has done previously (20), we determined response classification using typical error (TE) thresholds for each outcomes and individual change (POST-PRE). Additionally, we ran individual linear regressions between time (independent variable) and change in training performance ([Estimated VO_2], independent variable). The slope of the linear regressions represented each individual's response estimate and the TE of the slope was used to calculate 95% CIs (10) (Supplemental Figure 1 provides examples of response classification determined by individual linear regressions).

Consistent with previous work (7-9, 28, 40), we have opted against labelling individuals as 'non-responders' when classifying individual response. Instead, we use the term 'uncertain' to reflect individuals who are less likely to have experienced benefit beyond what would have been expected had they been allocated to the control/non-exercise condition. Similarly, we use the term 'responder' to represent an individual that has experienced benefit beyond what would be expected had they been allocated to the control condition. For VO_{2peak}, TTF, 3kTT, RHR, submaxHR, and submaxRPE individuals were classified as "responders", "uncertain" or

"adverse" if their observed changes lay above a 1xTE threshold, lay below a 1xTE threshold, or diminish beyond a 1xTE threshold (in the opposite direction of intended change), respectively. For changes in training performance (Estimated VO_2) individuals were classified as "responders", "uncertain", or "adverse-responders" if their 95% CI lay above, crossed, or fell below a zero-based threshold. VO_2 classification agreement (%) was calculated as the percentage of participants whose surrogate measure classification matched their VO_{2peak} classification.

The SD of individual response (SD_{IR}) and the standard error (SE) for each SD_{IR} value were calculated to construct 90% CI's in Microsoft Excel using the methods forwarded by (2), as we have done previously (5, 6, 8, 34) (see Table 4). Negative SD_{IR} values were interpreted as zero variability attributable to the exercise intervention. We estimated the proportion of response by calculating the area of the normal distribution that lies beyond zero (45).

Correlation analyses, ANOVAs and corresponding effect sizes were performed in GraphPad Prism Version 9.5.1. Outcome assessors were not blinded. Statistical significance was set at $p < 0.05$, and all data are presented as mean ± SD.

RESULTS

Of the 42 participants screened, 25 met inclusion criteria for randomization into the exercise training (HIIT) or non-exercise control (CTL) arm (Figure 2). Four participants (CTL: $n = 2$; HIIT: $n = 2$) completed three of four VO_{2peak} testing procedures, whereas the other 21 participants (CTL: $n = 12$; HIIT: $n = 9$) completed all PRE and POST physiological testing. TE thresholds were determined for the following measures: relative VO_{2peak} = 1.77 mL/kg/min, TTF = 35.47 s, 3kTT = −22.35 s, RHR = −1.90 bpm, submaxHR = −5.12 bpm, and submaxRPE = −1.06; CVs: 5.49%, 4.24%, 3.08%, 3.96%, 4.32%, 11.15%, respectively). Table 1 presents baseline participant characteristics for both groups. As per our study design, target HR were achieved for all participants across all training sessions and no significant ($p > 0.05$, $\eta_p^2 = 0.05$) changes in training heart rate were observed across the duration of our study (see Figure 3A). Although training HR was unchanged, we observed significant ($p < 0.001$, $\eta_p^2 = 0.28$) improvements in training performance (estimated VO_2) across training sessions (Figure 3B).

Group means at PRE and POST training along with mean change (Δ) scores and all associated statistical outcomes are presented in Table 2. Significant interaction effects (group x time) were observed for VO_{2peak}, TTF and 3kTT. Post-hoc analyses revealed VO_{2peak} increased significantly following HIIT (+1.6 ± 2.2 mL/kg/min; $p = 0.031$, $d_{av} = 0.19$), but not following CTL (−0.6 ± 2.5; $p > 0.05$, $d_{av} = -0.1$). Similarly, post-hoc analyses revealed that TTF (HIIT, +77.7 ± 108.5 s; $p < 0.01$, $d_{av} = 0.37$; CTL, −20.8 ± 50.2 s; $p > 0.05$, $d_{av} = -0.10$) and 3kTT (HIIT, −38.5 ± 31.9 s; $p < 0.001$, $d_{av} = -0.16$; CTL, +2.6 ± 31.6; $p > 0.05$, $d_{av} = 0.01$) improved following HIIT but not CTL.

Individual changes in VO_{2peak}, TTF, 3kTT, RHR, submaxHR, and submaxRPE are presented in Figure 5, and individual changes in training performance (for HIIT participants only) are presented in Figure 3C. Correlations between individual changes in VO_{2peak}, TTF, 3kTT, RHR, submaxHR, submaxRPE, and training performance and VO_{2peak} are presented in Figure 6 and

individual patterns of response, rates of response and classification agreement are presented in Figure 4. Only changes in RHR ($p = 0.02$, $r^2 = 0.39$, Figure 6C) and training performance ($p = 0.02$, $r^2 = 0.36$, Figure 6E) were significant and had strong positive correlations ($r > 0.60$) correlated with changes in VO_{2peak}. The correlation between RHR and VO_{2peak} was significant and surprisingly positive (i.e., decreases in RHR were associated with smaller changes in VO_{2peak}). Consistent with poor and non-statistically significant correlations, we observed rates of agreement for response classification between VO_{2peak} and surrogate markers of CRF that were consistently < 60% (Figure 4). Importantly, no participants in the HIIT group were global non-responders (uncertain or adverse for all 7 outcomes).

Cross-sectional correlation analyses of CRF outcomes with VO_{2peak} are presented in Table 3. Overall, we observed moderate to strong cross-sectional correlations between VO_{2peak},TTF, 3kTT, RHR, submaxHR, and submaxRPE. SD_{IR} and proportion of response analyses are presented in Table 4. These data indicate a lack of evidence for inter-individual differences in trainability.

Table 1. Baseline participant characteristics ($n = 25$).

Participants	All ($n = 25$)	CTL ($n = 11$)	HIIT ($n = 14$)
Age (years)	21.9 ± 2.1	22.7 ± 2.6	21.9 ± 1.8
Sex (M/F)	(5/20)	(2/9)	(3/11)
Height (cm)	172.2 ± 9.5	164.5 ± 9.1	171.1 ± 7.3
Body Weight (kg)	70.9 ± 12.9	65.3 ± 12.2	72.2 ± 15.0

Values are presented as mean ± standard deviation. CTL = non-exercise control group; HIIT = high-intensity interval training.

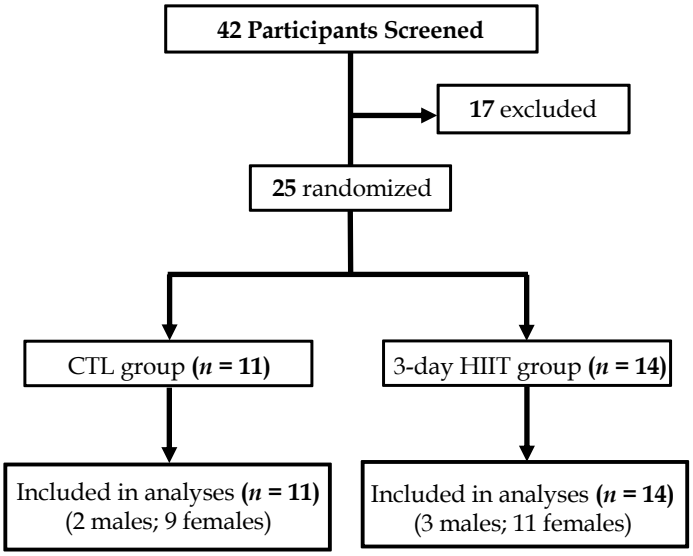

Figure 2. Participant flow diagram. CTL = no-exercise control group; HIIT = high intensity interval training.

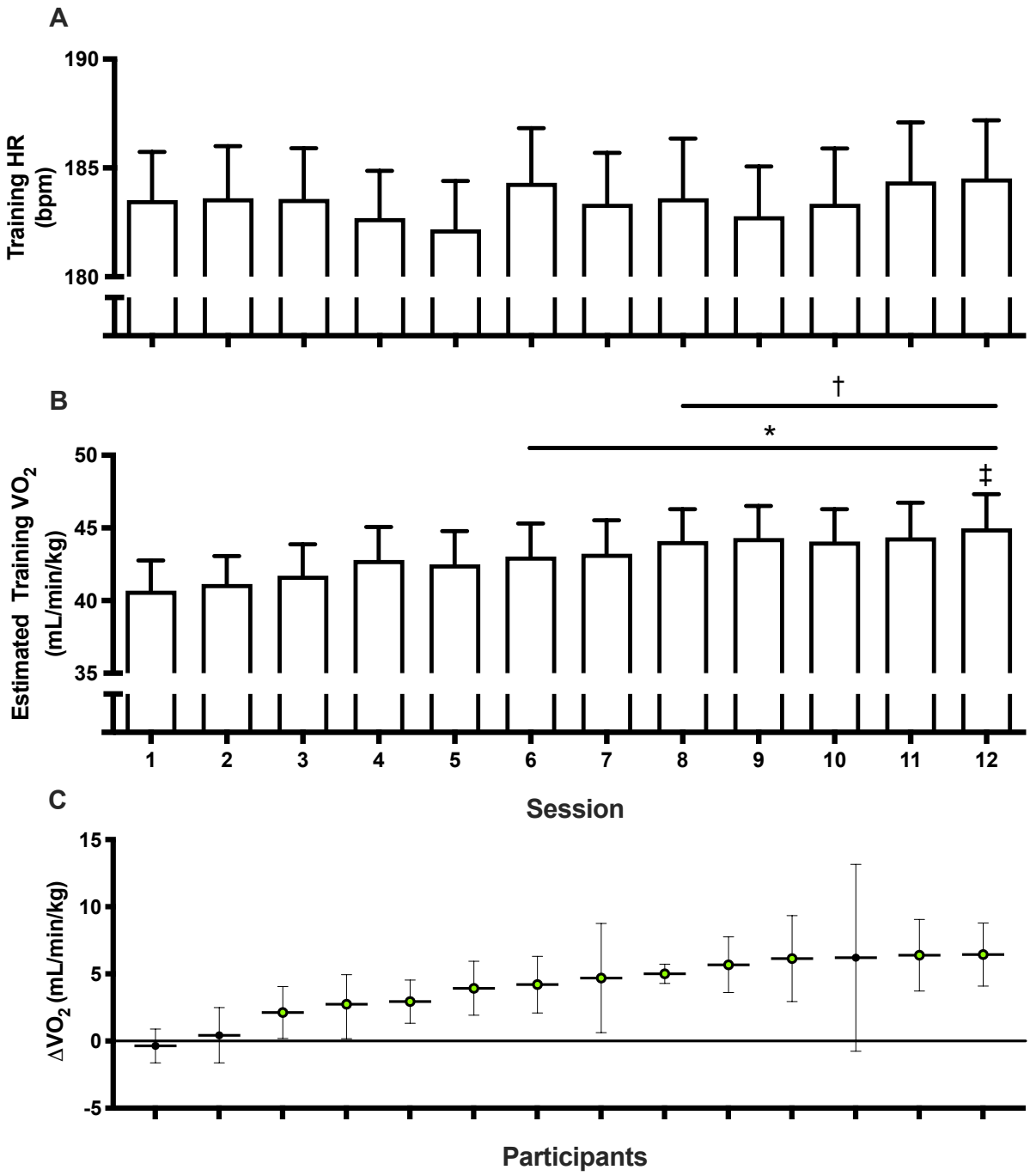

Figure 3. A) Mean training heart rate and **B)** mean estimated training VO_2 are presented across 12 high-intensity interval training sessions (n = 14).* Significantly (p < 0.05) different from Session 1; † Significantly (p < 0.05) different from Sessions 1 and 2; ‡ Significantly (p < 0.05) different from Session 4. **C)** Individual changes in training performances (estimated VO_2) are presented following 4 weeks of HIIT (n = 14). Mean response estimate (ΔVO_2) following training was 4.04 ± 2.21 mL/kg/min. The proportion of responders was 79% (11/14). Changes in training performances are arranged by magnitude of smallest individual response estimate to largest. Green dots represent individuals who are classified as "responders"; black dots represent "uncertain" responses. Data presented as mean ± SD. CTL = no-exercise control group; HIIT = high intensity interval training; VO_2 = oxygen uptake; HR = heart rate.

Table 2. Means and changes of surrogate measures of cardiorespiratory fitness (CRF) following short-term HIIT (n = 25).

Participants	CTL (n = 11)			HIIT (n = 14)			Effect Sizes
Measure	Pre	Post	Δ	Pre	Post	Δ	
VO_{2peak} (mL/kg/min)	45.6 ± 8.6	45.0 ± 10.1	−0.6 ± 2.5	45.5 ± 8.4	47.1 ± 8.9	1.6 ± 2.2*	Time (p > 0.05, η_p^2 = 0.05) Group (p > 0.05, η_p^2 < 0.01) Interaction (p < 0.03, η_p^2 = 0.19)
TTF (sec)	1182.6 ± 184.5	1161.8 ± 213.7	−20.8 ± 50.2	1210.7 ± 178.2	1282.4 ± 210.1	77.7 ± 108.5*‡	Time (p > 0.05, η_p^2 = 0.08) Group (p > 0.05, η_p^2 = 0.04) Interaction (p < 0.01, η_p^2 = 0.23)
3KTT (sec)	1027.8 ± 194.4	1030.4 ± 205.3	2.6 ± 31.6	1005.6 ± 229.6	967.1 ± 240.9	−38.5 ± 31.9*	Time (p < 0.01, η_p^2 = 0.26) Group (p > 0.05, η_p^2 = 0.01) Interaction (p < 0.01, η_p^2 = 0.31)
SubmaxHR (bpm)	167.7 ± 16.7	165.3 ± 18.7	−2.4 ± 7.2	168.4 ± 13.6	161.8 ± 12.8	−6.5 ± 6.7‡	Time (p < 0.01, η_p^2 = 0.31) Group (p > 0.05, η_p^2 < 0.01) Interaction (p > 0.05, η_p^2 = 0.10)
SubmaxRPE	13.5 ± 3.0	13.3 ± 3.1	−0.1 ± 1.5	13.2 ± 2.0	13.0 ± 1.7	−0.2 ± 1.3	Time (p > 0.05, η_p^2 < 0.01) Group (p > 0.05, η_p^2 < 0.01) Interaction (p > 0.05, η_p^2 = 0.01)
RHR (bpm)	67.7 ± 12.8	66.3 ± 11.6	−1.4 ± 2.7	63.4 ± 7.5	59.5 ± 6.3	−3.9 ± 3.5‡	Time (p < 0.01, η_p^2 = 0.44) Group (p > 0.05, η_p^2 = 0.09) Interaction (p = 0.06, η_p^2 = 0.14)

Data are presented as mean ± SD; CTL = no exercise control group; HIIT = high-intensity interval training; VO_{2peak}; peak oxygen uptake; 3kTT = 3000m time trial performance; TTF = VO_{2peak} test time; SubmaxHR = submaximal heart rate achieved immediately following the fourth stage of an incremental test; SubmaxRPE = submaximal rating of perceived exertion following the fourth stage of an incremental test; Correlations incorporate all data collected from CTL and HIIT groups at pre- and post-testing. * Significant interaction effect observed (p < 0.01); ‡ Significant effect of time observed p < 0.05).

HIIT	Individual Responses														Resp %	VO_2 Agreement %
	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
VO_{2peak} (mL/kg/min)															43%	
TTF (sec)															71%	57%
Submax HR (bpm)															57%	57%
Submax RPE															14%	43%
Resting HR (bpm)															71%	29%
3kTT (sec)															64%	50%
Estimated Training VO_2															79%	50%
Overall	5	6	5	4	2	2	6	2	4	3	5	5	5	2		

Control	Individual Responses											Resp %	VO_2 Agreement %
	1	2	3	4	5	6	7	8	9	10	11		
VO_{2peak} (mL/kg/min)												36%	
TTF (sec)												9%	27%
Submax HR (bpm)												18%	18%
Submax RPE			X									20%	10%
Resting HR (bpm)												36%	27%
3kTT (sec)												27%	18%
Overall	1	1	0	0	2	4	4	2	0	1	1		

Figure 4. Individual responses, total response (%) and agreement (%) with VO_{2peak} response following short-term HIIT in both the HIIT group (n = 14) and CTL group (n = 11) of HIIT (n = 14). VO_{2peak} = maximal aerobic capacity; TTF = time to fatigue; Submax HR = submaximal heart rate achieved immediately following the fourth stage of an incremental test; Submax RPE = submaximal rating of perceived exertion following the fourth stage of an incremental test; RHR = resting heart rate; 3kTT = 3000m time trial. White tiles denote individuals classified as a "responder", black tiles denote "uncertain" response, grey tiles denote "adverse" response and tiles with an "x" represent data was unable to be collected. "Resp%": Percentage of individuals who have demonstrated meaningful improvement beyond 1xTE. "VO_2 agreement %": Indicates the percentage of participants whose surrogate measure classification matched their VO_{2peak} classification.

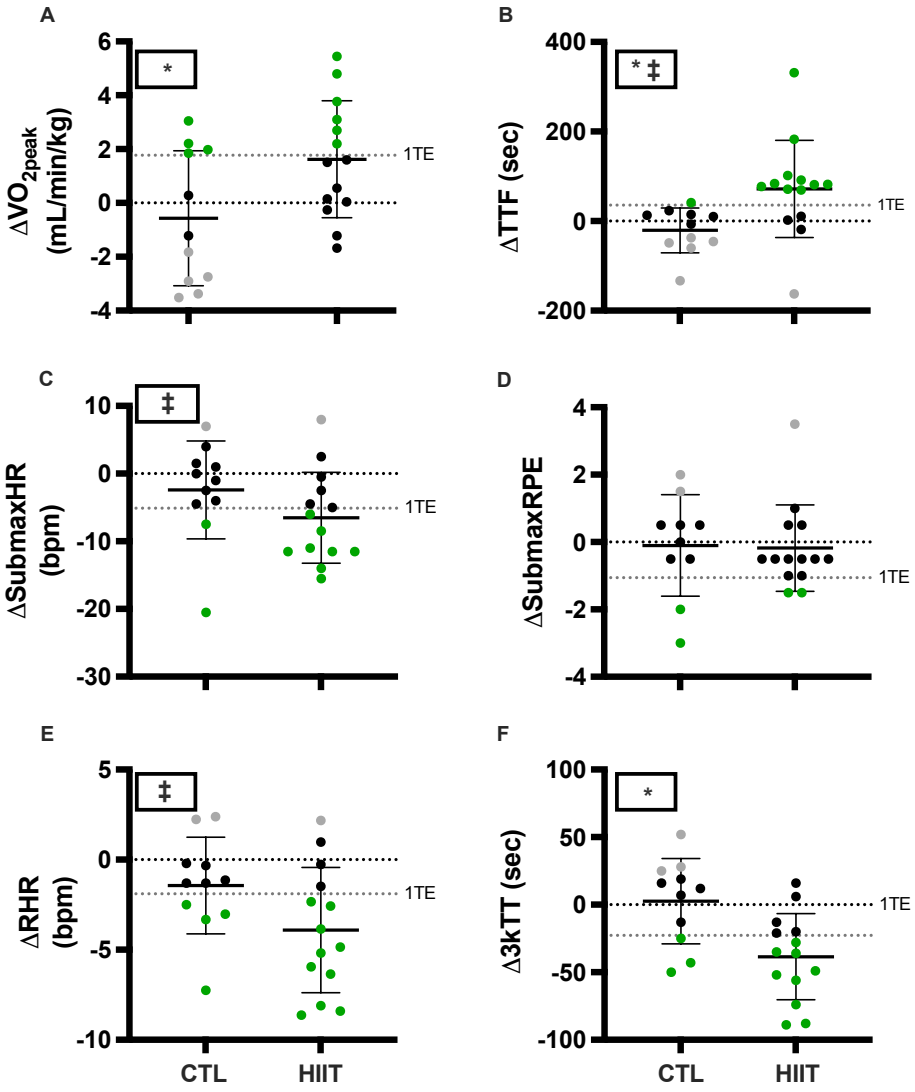

Figure 5. Individual response classification following four-week training period in non-exercise CTL group (n = 11) and in HIIT group (n = 14). Coloured data points reflect response classification for each individual; green data points represent a 1TE responder; black data points represent an "uncertain" response; grey data points represent an "adverse-responder". See Table 2 for p-values and effect sizes; * Significant interaction effect observed ($p < 0.01$); † Significant effect of group observed ($p < 0.05$); ‡ = Significant effect of time observed $p < 0.05$). Data presented as mean ± SD. CTL = no-exercise control group; HIIT = high intensity interval training; VO_{2peak} = peak oxygen uptake; TTF = time to fatigue; SubmaxHR = submaximal heart rate; SubmaxRPE = submaximal rating of perceived exertion; RHR = resting heart rate; 3kTT = 3000m time trial performance.

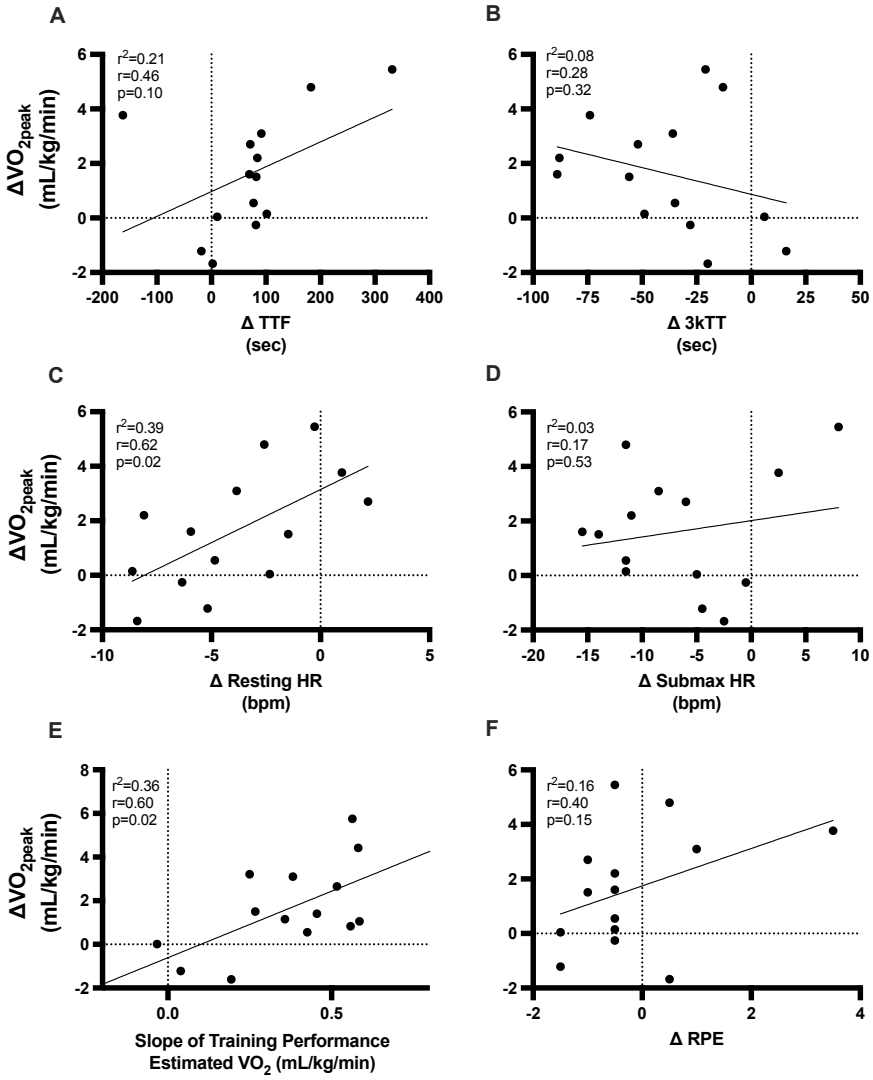

Figure 6. Change scores of all surrogate markers of CRF and their correlations with changes in VO_{2peak} following 4 weeks of HIIT (n = 14). Effect size (r^2), Pearson correlation value (r) and p-values are presented on the figure for each surrogate marker of CRF. CRF = cardiorespiratory fitness; VO_{2peak} = peak oxygen update; TTF = time to fatigue; SubmaxHR = submaximal heart rate; SubmaxRPE = submaximal rating of perceived exertion; RHR = resting heart rate; 3kTT = 3000m time trial performance.

Table 3. Cross-sectional correlation strength of surrogate measures of CRF (n = 25).

Measure	VO_{2peak}	3kTT	TTF	SubmaxHR	SubmaxRPE
VO_{2peak} (mL/kg/min)		-	-	-	-
3kTT (sec)	0.772†		-	-	-
TTF (sec)	0.888†	0.725†		-	-
SubmaxHR (bpm)	0.519†	0.310†	0.464†		-
SubmaxRPE	0.492†	0.451†	0.478†	0.451†	
RHR (bpm)	0.341†	0.276†	0.380†	0.356†	0.09*

Data are presented as r^2; VO_{2peak} = peak oxygen uptake; 3kTT = time trial performance; TTF = VO_{2peak} test time to fatigue; SubmaxHR = submaximal heart rate achieved immediately following the fourth stage of an incremental test; SubmaxRPE = submaximal rating of perceived exertion following the fourth stage of an incremental test. 50 data points were used for each correlation, with the exception of SubmaxRPE, where one data point was missing. * Significant relationship observed ($p < 0.05$), † Significant relationship observed ($p < 0.001$).

Table 4. SD_{IR} with 90% confidence limits and the proportion of response for each surrogate marker of CRF.

Measure	VO_{2peak}	3kTT	TTF	SubmaxHR	SubmaxRPE	RER (bpm)
SD_{IR}	−1.34	4.37	96.21	−2.69	−0.80	2.22
90% CIs	(−2.79–2.05)	(−32.76–33.33)	(26.79– 133.4)	(−7.73–6.72)	(−1.66– 1.22)	(−2.33–3.91)
Proportion of Response	100%*	100%*	77.2%*	100%	100%	96.2%

VO_{2peak} = peak oxygen uptake; 3kTT = time trial performance; TTF = VO_{2peak} test time to fatigue; SubmaxHR = submaximal heart rate achieved immediately following the fourth stage of an incremental test; SubmaxRPE = submaximal rating of perceived exertion following the fourth stage of an incremental test; proportion of response describes the proportion of individuals that have likely experienced benefit from the intervention per se. * Significant interaction effect observed ($p < 0.01$).

DISCUSSION

This study investigated the potential for accessible surrogate markers of CRF to accurately predict classification of VO_{2peak} response following short-term HIIT. Our hypothesis was that the response classification between surrogate markers of CRF and VO_{2peak} would agree, and thus relatively accessible surrogate markers of CRF would provide a convenient and accurate approach for assessing individual changes in VO_{2peak}. Contrary to our hypothesis, we observed poor agreement between the response classification of VO_{2peak} and surrogate markers of CRF (agreement less than 60% for all outcomes). Similarly, no relevant correlations were observed between the change scores of surrogate markers of CRF and changes in VO_{2peak}. Notably, although classification agreement between training performance and VO_{2peak} was poor, we found a positive correlation between improvements in training performance (estimated VO_2) and improvements in VO_{2peak}. This latter finding suggests that individuals could consider using training performance as an accessible and potentially reliable proxy for assessing changes in their VO_{2peak} following the commencement of training program.

We classified individual responses using a time-matched control group-derived typical error (TE) – a robust and conservative means of classifying individual response that considers measurement error (i.e., instrumentation error and day-to-day biological variability), and within subject variability (12, 40). Consistent with previous studies that have utilized a similar classification approach (12, 15, 19), we observed a lack of agreement between individual responses classifications of VO_{2peak} and surrogate markers of CRF following 4 weeks of HIIT training. Unfortunately, this suggests that direct measurements of VO_2 are necessary for individuals seeking to accurately determine their VO_{2peak} response classification.

Importantly, all HIIT participants demonstrated meaningful improvement in one or more surrogate markers of CRF, regardless of their VO_{2peak} classification. Further, we observed instances where participants improved their VO_{2peak} in the absence of submaximal CRF improvements, and vice versa. This demonstration of individual patterns of response is consistent with the results of others (1, 15, 19, 38), and supports the contention that individuals who have failed to demonstrate an increase in VO_{2peak} are likely to have improved other CRF-related outcomes. The existence of individual patterns of response argues against the notion of exercise non-responders (28, 36), a contention strengthened by our demonstration that all individuals who completed short-term HIIT experienced benefit in one or more outcomes. Individual patterns of response following HIIT may also support the existence of a dissociation between underlying mechanisms and adaptive potential for maximal CRF (mCRF) and submaximal performance (sCRF) (15).

Short-term HIIT has been previously shown to elicit central (e.g., increased stroke volume and cardiac output) and peripheral adaptations (e.g., increased muscle mitochondrial biogenesis and capillarization) (27). However, previous work suggests that individuals may experience peripheral adaptations more readily captured by a sCRF test (i.e., 3kTT), and thus may exhibit improvements in sCRF in the absence of changes in mCRF (15). Our data support this notion as we observed that 75% (6 of 8) of the HIIT participants classified as uncertain for changes in mCRF (VO_{2peak}) showed improvements in sCRF, as indicated by improved 3kTT performance and/or higher estimated training VO_2.

Alternatively, individual patterns of response may result from measurement variability obscuring our ability to accurately classify individual response. Importantly, instrumentation error (e.g., error associated with a metabolic cart), day-to-day biological variations (e.g., variations in external physical activity prior to an experimental trial) and within-subject variability (e.g., chronic changes to participant diet) can impact an individual's observed response (reviewed in (29)). Although within-subject variability may influence different outcomes equally (e.g., VO_{2peak} and TTF) – it is possible that some outcomes may be differentially impacted (e.g., mCRF vs sCRF). Further, each outcome's measurement will be independently influenced by the measurement error associated with that outcome. This interpretation is supported by our observation that there is little to no inter-individual variability attributable to an effect of exercise training, per se, across all outcomes (see SD_{IR} values in Table 4) (5). Taken together, these issues raise the potential that different response

classification across outcomes within an individual reflect variability in measurement error and/or within-subject variability rather than true individual differences in training responsiveness.

Surprisingly, rates of agreement for response classification between VO_{2peak} and surrogate markers of CRF that were consistently less than 60% (Figure 4). We observed that the HIIT group exhibited greater rates of VO_2 agreement for all surrogate measures than the control group. This is attributable to the increased (TTF) or decreased (3kTT, SubmaxHR, RHR) mean responses for most outcomes following HIIT. As such, many individuals exhibited "responder/responder" agreement following HIIT. On the contrary, no mean changes were observed following training in the control group. Thus, many participants demonstrated "responder/uncertain" or "uncertain/adverse" disagreement.

Our observations of poor agreement between individual classification of VO_{2peak} and surrogate markers of CRF (i.e., individual patterns of response) are likely attributable to i) dissociations between mCRF and sCRF adaptations and/or ii) a large influence of measurement error and/or within-subject variability obscuring our ability to accurately classify individual response. Regardless, our findings refute the existence of non-response to exercise.

In addition to classification agreement, we also used cross-sectional and change score correlation analyses to assess the relationship between surrogate markers of CRF and VO_{2peak}. Consistent with previous findings (13, 15, 27, 30, 39), we observed moderate to strong cross-sectional correlations between VO_{2peak} and all surrogate markers of CRF (see Table 3). Although these observations suggest potential for surrogate markers of CRF like TTF or 3kTT (both exhibit strong correlations with VO_{2peak}) as proxy measures for improvements in VO_{2peak}, change scores for these outcomes did not significantly correlate with individual changes in VO_{2peak} following 4 weeks of HIIT (see Figure 6). Similar to the lack of classification agreement discussed above, the weak to moderate change score correlations across all surrogate markers of CRF and VO_{2peak} suggest that individual changes within surrogate markers of CRF (i.e., TTF or 3kTT) may have limited value for predicting individual changes in VO_{2peak}. Of note, we unexpectedly observed a significant and strong positive correlation between increases in RHR and changes in VO_{2peak}. Given the well-established association between reductions in RHR and increased VO_{2peak} following exercise training, we suggest that the observed positive correlation between RHR and VO_{2peak} may be spurious.

Interestingly, although response classification between training performance (estimated training VO_2) and VO_{2peak} did not agree, we observed a positive correlation between individual improvements in training performance and changes in VO_{2peak} (Figure 6E). This correlation is consistent with the long established relationship between VO_{2peak} and performance (19) and the moderate to strong relationship between time trial performance and VO_{2peak} in cross-sectional samples (24, 27, 39). Although the strong (r = 0.60) relationship between training performance and VO_{2peak} does not mean an individual can assume direct agreement between training performance and VO_{2peak}, it does mean that training performance can provide insight into changes in CRF in the absence of direct measures of VO_2.

Our work adds to a growing body of research attempting to identify practical solutions to potentially expensive prescription/diagnostic tools (i.e., direct testing of VO_2) (35–37). Although our results support the use of training performance as a useful proxy for changes in VO_{2peak}, we acknowledge that improvements in training performance were determined using a predictive equation using training speed and treadmill incline. Future studies are needed to directly assess changes in training performance and to further examine the relationship between training performance and VO_{2peak} in larger samples.

While our findings suggest there may be value in monitoring changes in training speed, they also suggest surrogate markers of CRF have limited utility as predictors of individual changes of VO_{2peak}. However, this interpretation is limited by our sample size, participant characteristics, and study design, which was not preregistered nor included any sample size calculations. Of particular interest is the disproportionately high number of females in the current sample. Although we are unaware of data that support the notion that physiological or perceptual responses following HIIT are influenced by sex, future investigations examining the impact of sex on individual patterns of response are warranted.

Our low sample size (n = 14) provided limited statistical power to detect significance ($p < 0.05$) in several potentially meaningful weak (3kTT) and moderate (TTF, submaxRPE) correlations ($r < 0.71$) (Figure 6). If weaker, but true correlations existed for these outcomes, studies with larger sample sizes are required to statistically detect them. Thus, our conclusion that surrogate markers of CRF do not predict changes in VO_{2peak} should be interpreted with caution as future studies with larger sample sizes may support the opposite interpretation. Further, our study design limited the collection of surrogate markers of CRF to pre- and post- testing only. Incorporating repeat measurements throughout the intervention period (i.e., measure RHR every training session) may have reduced the influence of measurement error on our observed responses (5, 20). Thus, future work with a larger sample size and more frequent measurements markers of CRF is needed before the predictive utility of surrogate markers of CRF is fully understood.

To avoid recruiting individuals previously engaged in aerobic exercise training, prospective participants were required to self-report engaging in fewer than three hours of exercise per week. However, we did not record or monitor external physical activity in the current study. Consequently, accumulation of external physical activity may have influenced individual responses within both control and exercise groups. Future studies should record and/or directly measure external physical activity to provide additional context when classifying individual response.

The length of our training protocol may have also influenced our confidence when classifying individual response (9). We observed relatively small mean changes across all outcomes, which are likely attributable to the short training duration utilized in the current study (4-weeks). In many instances, the value of the observed mean change was similar to the value of our response threshold (1xTE), leading to high rates of uncertain response and increasing the probability of

incorrectly classifying a true responder as uncertain or vice-versa. We suggest future studies report external physical activity performed throughout the duration of a study period when classifying individual responses.

This study examined response classification agreement between VO_{2peak} and surrogate markers of CRF, individual patterns of response, and correlation of change scores following short-term HIIT. We found poor agreement between individual classification of VO_{2peak} and surrogate markers of CRF and weak change score correlations, suggesting that obtaining direct measurements of VO_2 are required for individuals interested in accurately quantifying their VO_{2peak} response to training. The observation of individual patterns of response – potentially refuting the existence of exercise non-response – is likely attributable to dissociations between maximal and submaximal adaptations in CRF and/or a large influence of measurement error and/or within-subject variability. Notably, we observed a strong, significant correlation between the change in training performance and VO_{2peak} suggesting that individuals can evaluate changes in VO_{2peak} using changes in their training performance. We therefore recommend that individuals concerned with their VO_{2peak} response seek direct measurements of VO_2, but in the absence of direct measurements, changes in training performance may provide an alternative means of estimating changes in VO_{2peak}.

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