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Changes in aerobic capacity and glycaemic control in response to reduced-exertion high-intensity interval training (REHIT) are not different between sedentary men and women

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ABSTRACT

Purpose: Previously it has been reported that reduced-exertion high-intensity interval training (REHIT; total training time of 3x10 min per week) improves aerobic capacity ($\dot{V}O_2$max) in both sedentary men and women, but improves insulin sensitivity in men only. The aim of the present study was to determine whether there is a true sex difference in response to REHIT, or that these findings can be explained by the large interindividual variability in response inherent to all exercise training.

Methods: Thirty-five sedentary participants (18 women; mean±SD age for men and women respectively: 33±9 and 36±9 y, BMI: 25.1±2.1 and 24.1±3.5 $kg \cdot m^{-2}$, $\dot{V}O_2$max: 38.6±8.3 and 31.6±4.6 $ml \cdot kg^{-1} \cdot min^{-1}$) completed a 6-week REHIT programme consisting of eighteen 10-min unloaded cycling sessions with one (first session) or two (all other sessions) 'all-out' 10-20-s sprints against a resistance of 5% of body mass. $\dot{V}O_2$max and oral glucose tolerance test (OGTT)-derived insulin sensitivity were determined before and after training.

Results: REHIT was associated with an increase in $\dot{V}O_2$max (2.54±0.65 vs. 2.78±0.68 $L \cdot min^{-1}$, main effect of time: $p<0.01$), a trend toward reduced plasma insulin area-under-the-curve (AUC; 6.7±4.8 vs. 6.1±4.0 $iU \cdot min^{-1} \cdot ml^{-1}$, $p=0.096$), but no significant change in plasma glucose AUC or the Cederholm index of insulin sensitivity. Substantial interindividual variability in response to REHIT was observed for all variables, but there was no significant effect of sex.

Conclusions: REHIT improves the key health marker of aerobic capacity within a minimal total training time-commitment. There is large interindividual variability in responses to REHIT, but sex differences in the responses are not apparent.

Key words:

HIT; $\dot{V}O_2$max; insulin sensitivity**;** sex differences

Abbreviations:

AUC: area under the curve; BMI: body mass index; GLUT4; glucose transporter type 4; HIT: high-intensity interval training; IPAQ: international physical activity questionnaire; OGTT: oral glucose tolerance test; PAR-Q: physical activity readiness questionnaire; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; REHIT: reduced-exertion high-intensity interval training; RER: respiratory exchange ratio; RPE: rating of perceived exertion; SIT: sprint interval training; $\dot{V}O_2max$: maximal aerobic capacity

INTRODUCTION

High-volume aerobic exercise is currently the strategy recommended by public health guidelines for improving the key cardiometabolic health markers of $\dot{V}O_2$max and insulin sensitivity (Garber et al. 2011). However, these parameters can also be modified to a similar extent with very short bouts of high-intensity exercise (high-intensity interval training (HIT)) or sprint interval training (SIT; in this article we will refer to both as HIT in order to be consistent with our previous publications on this topic) (Babraj et al. 2009; Cocks et al. 2013; Shepherd et al. 2013; Richards et al. 2010; Weston et al. 2014). As lack of time has been identified as a major barrier to performing regular exercise (Korkiakangas et al. 2009), HIT has been proposed as an alternative/adjunct time-efficient exercise strategy for the general population. However, due to the need for recovery periods in between sprints the majority of HIT protocols studied to date do not save much time compared with aerobic exercise-based recommendations (Gillen and Gibala 2014), and the associated high levels of exertion may present an additional barrier for the target sedentary population.

The mechanisms by which HIT protocols exert their beneficial effects on $\dot{V}O_2$max and insulin sensitivity remain poorly understood. We have recently proposed that the adaptations associated with supramaximal HIT protocols may be explained, at least in part, by the rapid glycogen utilisation and subsequent release and activation of glycogen-bound protein kinases during initial sprints (Metcalfe et al. 2015). As glycogen depletion during supramaximal HIT is limited to the first ~15 s of the initial sprints (Parolin et al. 1999), this would mean that HIT protocols could be effective with fewer and shorter sprints than generally used (Metcalfe et al. 2015; Metcalfe et al. 2012). In support of this hypothesis, we have demonstrated that performing two 20-s Wingate sprints within a 10-min exercise session (reduced-exertion HIT; REHIT) depletes muscle glycogen stores by ~20% (Metcalfe et al. 2015), and as a training stimulus is sufficient to improve $\dot{V}O_2$max in sedentary men and women following 6 weeks of thrice-weekly training sessions (Metcalfe et al. 2012). However,

77 REHIT has been observed to only significantly enhance insulin sensitivity and glycaemic
78 control in men (Metcalfe et al. 2012; Gillen et al. 2014).

79 While factors such as a potential effect of the menstrual cycle (Valdes and Elkind-Hirsch
80 1991) and differences in baseline insulin sensitivity and glycaemic control (Boulé et al. 2005)
81 should be studied in more detail in an attempt to explain this observed sexual dimorphism,
82 another possible explanation is related to the large interindividual variability in response to
83 exercise training in general. Large supervised training studies have demonstrated that
84 although *on average* important risk factors of cardiometabolic disease improve in response
85 to regular exercise, individual responses range from highly positive ('high responders') to
86 little or no change ('low responders') (Bouchard and Rankinen 2001; Bouchard et al. 2012;
87 Leifer et al. 2016). Due to the small sample sizes that are more typically used in most
88 exercise training studies, such studies are highly susceptible to the influence of individual
89 low or high responders on the mean results. Therefore, it is worth noting that the previous
90 two studies which have demonstrated sex differences in the response to REHIT were both
91 small (≤8 participants per group) (Gillen et al. 2014; Metcalfe et al. 2012). Furthermore,
92 acute changes (3 hr post-exercise) in skeletal muscle expression of genes encoding proteins
93 related to glucose metabolism or insulin sensitivity (e.g. PGC-1α, GLUT4, hexokinase,
94 pyruvate dehydrogenase kinase) in response to a single REHIT session were found not to
95 be different between men and women in a study by Skelly et al. (2016), and a study
96 investigating the response to a more strenuous HIT protocol did not demonstrate different
97 training responses for $\dot{V}O_2$max, maximal power output, or substrate oxidation for men and
98 women (Astorino et al. 2011). Thus, the evidence for a sex difference in the response to
99 REHIT is not definitive. Studies with a larger sample size are required to address this issue.

100 Considering the urgent need to identify shorter exercise protocols effective at modifying the
101 key risk factors of cardiometabolic disease, the REHIT protocol presents a promising
102 intervention: to date no other intervention has been shown to improve important risk factors
103 of cardiometabolic disease with such a low time-commitment (30 min per week) combined

104 with manageable ratings of perceived exertion (RPE<15). However, the evidence-base for
105 the effectiveness and safety of this intervention has to be expanded before it can be
106 incorporated into physical activity recommendations for the general public, and there should
107 be no uncertainty about its effectiveness, on average, in specific populations such as
108 women. Therefore, the aim of the present study was to examine the effects of REHIT on
109 $\dot{V}O_2$max and OGTT-derived insulin sensitivity in a larger cohort of men and women. We
110 hypothesised that, similar to other types of training, interindividual variability in the response
111 to REHIT would be high, but that there would be no sex differences in the mean responses.

METHODS

Participants

Fifty participants (27 men / 23 women) gave their written informed consent to take part in this study, which received ethical approval from the NHS South West Research Ethics Committee (Central Bristol REC Reference: 12/SW/0018). Seven participants dropped out prior to completing baseline testing, and eight discontinued the intervention (**Figure 1**), leaving 17 men and 18 women for inclusion in the analysis (**Table 1**). Participants were recruited based on the following inclusion criteria: aged 18-50 y, classified as sedentary according to the IPAQ self-report questionnaire (Craig et al. 2003), no contraindications to strenuous exercise according to a standard PAR-Q (Thomas et al. 1992), body mass-stable and no conscious change in diet or physical activity patterns over the preceding 6 months, no evidence of clinically significant hypertension (≥140/90 mm Hg), resting heart rate <100 bpm, and no personal history of metabolic or cardiovascular disease. The potentially confounding impact of changes in diet and exercise patterns was fully explained to all participants and they were asked to maintain their normal lifestyle outside the intervention for the duration of the study period.

Experimental design

Participants underwent baseline testing for insulin sensitivity and $\dot{V}O_2$max two weeks prior to starting the training intervention. Insulin sensitivity was assessed during an oral glucose tolerance test (OGTT) and $\dot{V}O_2$max was assessed during an incremental cycle test to limit of tolerance. OGTTs were repeated 3 days after the final training bout, at the same time of day as the pre-intervention OGTTs, leaving 8 weeks between the pre- and post-training OGTTs. This was done in order to reduce potential influences of the menstrual cycle in female participants, but the stage of the menstrual cycle was not determined. $\dot{V}O_2$max tests took place 1-2 days after the OGTTs.

Oral glucose tolerance test (OGTT)

Participants were asked not to perform moderate or vigorous intensity physical activities for the three days prior to OGTTs, to refrain from drinking alcohol and caffeine for one day prior, and to drink half a litre of water on the morning of the test to ensure adequate hydration. Participants reported to the laboratory between 7:30 and 9:30 am following an overnight fast from 22:00 pm the previous evening. Having rested for 15 min, a cannula (BD Venflon Pro, BD, Helsingborg, Sweden) was inserted into an antecubital vein and a fasting venous blood sample was drawn. Participants then consumed 75 g of glucose (Polycal, Nutricia, UK) dissolved in 300 mL of water, and further blood samples were drawn at 30 min intervals for 2 h. All blood samples were collected into pre-cooled plastic tubes containing EDTA, stored on ice for 30 min, and then centrifuged at 5000 rpm and 4°C for 10 min, with plasma stored at -80°C until analysis. Plasma glucose concentrations were determined in duplicate on an automated analyser with a CV for repeated measures of <1% (Randox RX Daytona, Co. Antrim, UK). Plasma insulin concentrations were determined in duplicate using a commercially available ELISA kit with a CV for repeated measures of 3.2% (Mercodia, Uppsala, Sweden). Area under the curve (AUC) for the glucose and insulin responses was calculated using the trapezoid model, and peripheral insulin sensitivity was determined using the Cederholm Index (Cederholm and Wibell 1990). OGTT-derived data are presented for 16 men only due to technical difficulties with blood sampling in one participant.

$\dot{V}O_2$max test

Maximal oxygen uptake capacity ($\dot{V}O_2$max) was determined during an incremental cycling test to the limit of tolerance. For reasons of availability of equipment, two different protocols and sets of equipment were used to determine $\dot{V}O_2$max, with protocols kept identical for individual participants. Fourteen participants (7 men and 7 women) completed the tests on a mechanically-braked cycle ergometer (Ergomedic 874e, Monark, Vansbro, Sweden) with expired air analysed using the Douglas bag method. The test started at 60 W and increased in increments of 30 W every 2 min until volitional exhaustion, with expired air samples collected into pre-evacuated Douglas bags. Expired concentrations of O_2 and CO_2

(Servomex miniMP 5200), volume of expired air (Harvard Apparatus, Kent, UK), and air temperature (Model C, Edale Intruments, Cambridge, UK) were measured for calculation of $\dot{V}O_2$max by indirect calorimetry (Frayn 1983). All values were corrected to reflect standard temperature and pressures, dry (STPD), and during each gas collection, samples of ambient (i.e. inspired) CO_2 and O_2 concentrations were measured within close proximity to the participant (Servomex miniMP 5200) rather than just assuming standard atmospheric concentrations, as has been recommended recently (Betts and Thompson 2012). The remaining 20 participants (10 men and 10 women) completed the test on an electrically braked cycle ergometer (Lode Excalibur Sport, Groningen, the Netherlands) with expired air analysed using an online metabolic cart (ParvoMedics TrueOne 2400, Utah, USA). Participants cycled at 50 W for 5 min followed by a 15 W·min^{-1} continuous ramp protocol to volitional exhaustion. $\dot{V}O_2$max was determined as the highest value for a 15-breath rolling average. In all tests two or more of the following criteria were met: a plateau in $\dot{V}O_2$ despite increasing intensity (<50% of the expected increase for a 5-W increase in workload), RER>1.15, heart rate within 10 beats of age-predicted maximum, and/or volitional exhaustion (Howley et al. 1995). We were unable to perform the post-training $\dot{V}O_2$max test in one female participant due to technical difficulties, so $\dot{V}O_2$max data are presented for 17 men and 17 women. An independent sample t-test revealed no difference in the change in $\dot{V}O_2$max (L·min^{-1}) between the two protocols used, so the data were pooled.

Training protocol

All training sessions were fully supervised and carried out on a mechanically-braked cycle ergometer (Ergomedic 894e, Monark Vansbro, Sweden). Participants completed three exercise sessions per week for 6 weeks with 1-2 days recovery between sessions, completing 18 sessions overall. All exercise sessions lasted 10 min in total (including a 3-min warm-up, 3:20-3:40-min recovery in between sprints, and a 3-min cool-down; **Figure 2**), resulting in a total training time-commitment of 30 min per week. Each training session consisted of unloading pedalling and one (first session) or two (all other sessions) ‘all-out’

cycling sprints. Just before each sprint, participants increased their pedal cadence to their maximal speed, a braking force equivalent to 5% of body mass was then applied to the ergometer, and participants sprinted against the applied braking force for a designated time period. The duration of the sprints increased from 10 s in week 1, to 15 s in weeks 2 and 3, and 20 s in the final 3 weeks. Strong verbal encouragement was given during each sprint. At the end of the third training session of each week an RPE score (6-20 Borg scale) was collected to reflect the session as a whole (i.e. participants were asked to consider the whole training session when giving their ratings, not just the sprints).

Statistical analysis

All data are presented as mean±SD unless stated otherwise. Statistical analysis was performed using the commercially available software Statistics Package for Social Sciences (SPSS). We calculated that to detect a difference in insulin sensitivity response between men and women of 1 SD, a sample size of 16 participants in each group would be sufficient to achieve a power of 0.80 with $\alpha=0.05$. In order to determine the effects of the intervention and potential sex differences in these responses, $\dot{V}O_2max$ and OGTT summary statistics were analysed using two-way mixed model analysis of variance (sex [male / female] x time [pre-training / post-training]) with Greenhouse-Geisser corrections applied for contrasts where $\varepsilon<0.75$ and the Huynh-Feldt corrections applied for less severe asphericity. Correlations between variables were determined using Pearson's product-moment correlation coefficient. Statistical significance was accepted at $p<0.05$.

RESULTS

Thirty participants completed all 18 training sessions (i.e. 100% adherence), three participants missed 1 session, and two participants missed a total of 3 non-consecutive sessions, resulting in a mean adherence to the training programme of 98.5%. The training sessions were well tolerated by all participants and rated at 14±2 on the Borg 6-20 scale (i.e. between 'somewhat hard' and 'hard'), with no significant differences in the ratings given at the end of each of the six training weeks or in the ratings given by male and female participants. A small but significant increase in body mass was observed following REHIT (80.3±15.7 vs. 80.9±15.6 kg; main effect of time: $p<0.05$), with no significant interaction effect of sex x time.

REHIT increased mean absolute $\dot{V}O_2$max by 9.6% (main effect of time: $p<0.001$), with no significant interaction effect of sex x time (women: +10.1%, men: +9.3%; **Table 2**), and these results were similar when $\dot{V}O_2$max was expressed in $L \cdot min^{-1}$ or $ml \cdot kg^{-1} \cdot min^{-1}$. We observed considerable interindividual variability in the response to REHIT for $\dot{V}O_2$max (range: -4 to +34%; **Figure 3**). There was no significant correlation between baseline $\dot{V}O_2$max and the subsequent training response ($R^2=0.08$), and the likelihood of showing a low/average/high response for $\dot{V}O_2$max did not appear to be influenced by sex (**Figure 3**).

The effect of REHIT on the plasma glucose and insulin responses to the OGTTs is shown in **Figure 4**. REHIT was associated with a trend toward reduced plasma insulin AUC (-8.3%, main effect of time: $p=0.096$), but there was no significant sex x time interaction (women: -9.5%, men: -7.4%; **Table 2**). Plasma glucose AUC and insulin sensitivity as determined using the Cederholm Index did not significantly change following training (**Table 2**). Similar to the $\dot{V}O_2$max responses there was considerable variability associated with the training-induced change in insulin AUC (range: -54 to +70%), glucose AUC (-24 to +62%) and Cederholm index (-48% to +55%; **Figure 3**). There were significant negative correlations between the pre-training value and the change score (%) for insulin AUC ($R^2=0.14$, $p<0.05$), glucose AUC ($R^2=0.18$, $p<0.05$), and for the Cederholm index ($R^2=0.19$, $p<0.01$).

DISCUSSION

The aim of the present study was to determine whether there is a true sex difference in response to REHIT, or that previously observed sex differences may be explained by the large interindividual variability inherent to the response to all exercise training. We demonstrate that interindividual variability in response to REHIT is substantial for all measured parameters, and that no sex differences are evident in response to REHIT, with similar mean changes for men and women. This suggests that previously observed sex difference for changes in insulin sensitivity in the small training studies by Metcalfe et al (2012) and Gillen et al. (2014) may be explained by the inclusion of different proportions of low and high responders within the male and female training groups. We demonstrate that on average REHIT is effective at substantially improving the important cardiometabolic risk factor of $\dot{V}O_2$max in sedentary individuals, with manageable ratings of perceived exertion and a total training time commitment of just 30 min per week (and a total volume of high-intensity exercise of less than 10 min over the 6-week training period). Previously observed improvements in insulin sensitivity could not be reproduced in the present study.

Following 6 weeks of REHIT we observed a trend toward a mean improvement of 8% in the plasma insulin AUC in response to an oral glucose load, but this value masks the fact that the individual change scores ranged from -54% to +70%, and that 14 out of 34 participants (41%) experienced a numerical increase rather than a decrease. Likewise, 38% of participants failed to numerically improve plasma glucose AUC or the Cederholm index of insulin sensitivity. This is strikingly similar to the variation in response to 20 weeks of high-volume aerobic exercise training as observed in the >700 participants of the Heritage Family Study (Boulé et al. 2005). Although various modes of exercise may be effective at improving measures of glycaemic control and insulin sensitivity on average, it is clear that many individuals do not get this benefit. In this light it is important to note the significant negative correlation between baseline and response for measures of insulin sensitivity: those individuals with poorer insulin sensitivity pre-training tend to have a greater improvement.

This may provide an explanation for the discrepancies between the present study and our previous study concerning changes in insulin sensitivity and potential sex differences in the response to REHIT (Metcalfe et al. 2012), as the male participants in our original study appear to have had poorer insulin sensitivity at baseline. However, regardless of the reason for these discrepancies, in our present, larger study we provide strong support against a sex difference in the response to REHIT; interindividual variability in response is evidently of a greater magnitude than any potential sex differences.

The relevance of the trend toward a reduced insulin AUC remains unclear. Although the majority of the participants improved OGTT-derived parameters, several participants had effects in the opposite direction. Whereas some authors suggest that adverse responses to training may occur (Bouchard et al. 2012), others have pointed out that responses of a similar magnitude in control participants demonstrate that it is not the intervention *per se* that causes adverse effects (Leifer et al. 2016; Yates et al. 2014). As we did not include a control group in the present study it remains unclear whether the negative responses in some participants can be attributed to day-to-day biological variation or technical error. Apart from the influence of the negative correlation between baseline values and response, another potential explanation for the lack of a significant improvement in OGTT-derived measures could be that we reduced the sprint resistance from 7.5% of body mass in our previous study (Metcalfe et al. 2012) to 5% in the present study, in order to make the exercise more manageable for the female participants. Future studies should examine whether a greater sprint resistance may lead to superior improvements.

Maximal aerobic capacity following REHIT improved on average by ~10%, with similar mean increases in men and women. This confirms our previous observations (Metcalfe et al. 2012) and those by Gillen et al. (2014). Whilst improved aerobic capacity is now a well-established finding with HIT (Weston et al. 2014), our data are important as REHIT still represents the smallest volume of high-intensity exercise which has been shown to improve this key health parameter. The fact that $\dot{V}O_2$max appears to improve so consistently following such a small

volume of exercise provides support for exercise intensity as a crucial variable underpinning adaptations in $\dot{V}O_2$max following exercise training in humans. Given that aerobic capacity is a powerful predictor of cardiovascular and metabolic disease (Blair et al. 1996; Blair et al. 1989; Blair et al. 1995; Myers et al. 2002), this has implications for exercise prescription. Based upon the results of Lee et al. (2011) the mean increase of ~3-4 $ml \cdot kg^{-1} \cdot min^{-1}$ in $\dot{V}O_2$max (i.e. ~1 metabolic equivalent) following REHIT would be expected to reduce the risk of all-cause mortality by 15% and cardiovascular mortality by 19%.

Although aerobic capacity improved *on average* following REHIT it should be noted that this improvement too was associated with substantial interindividual variation. Indeed, similar to large-scale aerobic training studies (Bouchard et al. 1999; Sisson et al. 2009) change in $\dot{V}O_2$max ranged from no measurable response to particularly large improvements (>30% increase from baseline). Previous studies have also demonstrated substantial interindividual variability in response to more strenuous HIT interventions (Astorino and Schubert 2014; Bacon et al. 2013; Gurd et al. 2016), which suggests that the variability in response to REHIT observed in the present study was not caused by an insufficient training stimulus. In light of this consistent finding of substantial interindividual variability in the response to training, it seems of increasing importance to move away from studying the mean effect of various HIT protocols and start focussing more on establishing 1) what causes the large interindividual differences in response to training, 2) what clinical relevance this has, 3) what can be done to improve the response in low responders, and 4) how low responders can be identified prior to prescribing exercise interventions. At least part of the interindividual variability can be explained by genetic factors (Bouchard et al. 1999), and a set of predictor genes has been validated that can establish the magnitude of change in aerobic capacity *prior* to the initiation of aerobic training (Timmons et al. 2010). It now needs to be established whether the same predictor can be used to explain/predict the variability in $\dot{V}O_2$max responses to different modes of training, for example HIT/REHIT. In combination with the development of similar biomarkers for adaptability of insulin sensitivity and other

cardiometabolic risk factors this would greatly enhance our ability to prescribe the most appropriate intervention to individuals.

A number of limitations to the present study should be noted. Firstly, male and female participants were not matched for the included parameters at baseline, and a number of significant sex differences were apparent prior to the start of the intervention. Furthermore, we did not control for the female participants' menstrual cycle phase. Lack of control for these potentially confounding factors is common in this area of research, but their potential influence on training responses will need to be examined in further studies. Secondly, although our use of a 75-g glucose load in the OGTT is consistent with standard practice, the significant sex difference in body mass will have resulted in a different *relative* glucose load. It remains unknown whether this may have affected the results and/or may explain some of the observed variability in response. Therefore, a suggestion for further research is to investigate sex differences in the effects of REHIT using different methods for measuring insulin sensitivity, such as for example the euglycemic hyperinsulinemic clamp technique.

In conclusion, we demonstrate that performing 6 weeks of REHIT involving a maximum of 2 min of intermittent high-intensity exercise within a total training time-commitment of 30 min per week is sufficient, on average, to increase maximal aerobic capacity, but did not significantly improve OGTT-derived parameters. In contrast to previous smaller studies (Metcalfe et al. 2012; Gillen et al. 2014) we did not observe different responses in sedentary men and women, suggesting that low response to REHIT in some individuals is not explained by a sexual dimorphism.

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Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

Astorino TA, Allen RP, Roberson DW, Jurancich M, Lewis R, McCarthy K, Trost E (2011) Adaptations to high-intensity training are independent of gender. European journal of applied physiology 111 (7):1279-1286. doi:10.1007/s00421-010-1741-y

Astorino TA, Schubert MM (2014) Individual responses to completion of short-term and chronic interval training: a retrospective study. PloS one 9 (5):e97638. doi:10.1371/journal.pone.0097638

Babraj J, Vollaard N, Keast C, Guppy F, Cottrell G, Timmons J (2009) Extremely short duration high intensity interval training substantially improves insulin action in young healthy males. BMC Endocr Disord 9:3

Bacon AP, Carter RE, Ogle EA, Joyner MJ (2013) VO2max trainability and high intensity interval training in humans: a meta-analysis. PloS one 8 (9):e73182. doi:10.1371/journal.pone.0073182

Betts JA, Thompson D (2012) Thinking outside the bag (not necessarily outside the lab). Med Sci Sports Exerc 44 (10):2040; author reply 2041. doi:10.1249/MSS.0b013e318264526f

Blair SN, Kampert JB, Kohl HW, 3rd, Barlow CE, Macera CA, Paffenbarger RS, Jr., Gibbons LW (1996) Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. JAMA : the journal of the American Medical Association 276 (3):205-210

Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA (1995) Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. JAMA : the journal of the American Medical Association 273 (14):1093-1098

Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW (1989) Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA : the journal of the American Medical Association 262 (17):2395-2401

Bouchard C, An P, Rice T, Skinner JS, Wilmore JH, Gagnon J, Perusse L, Leon AS, Rao DC (1999) Familial aggregation of VO(2max) response to exercise training: results from the HERITAGE Family Study. J Appl Physiol (1985) 87 (3):1003-1008

Bouchard C, Blair SN, Church TS, Earnest CP, Hagberg JM, Hakkinen K, Jenkins NT, Karavirta L, Kraus WE, Leon AS, Rao DC, Sarzynski MA, Skinner JS, Slentz CA, Rankinen T (2012) Adverse metabolic response to regular exercise: is it a rare or common occurrence? PloS one 7 (5):e37887. doi:10.1371/journal.pone.0037887

Bouchard C, Rankinen T (2001) Individual differences in response to regular physical activity. Med Sci Sports Exerc 33 (6 Suppl):S446-451; discussion S452-443

Boulé NG, Weisnagel SJ, Lakka TA, Tremblay A, Bergman RN, Rankinen T, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C, Study HF (2005) Effects of exercise training on glucose homeostasis: the HERITAGE Family Study. Diabetes Care 28 (1):108-114

Cederholm J, Wibell L (1990) Insulin release and peripheral sensitivity at the oral glucose tolerance test. Diabetes research and clinical practice 10 (2):167-175

Cocks M, Shaw CS, Shepherd SO, Fisher JP, Ranasinghe AM, Barker TA, Tipton KD, Wagenmakers AJ (2013) Sprint interval and endurance training are equally effective in increasing muscle microvascular density and eNOS content in sedentary males. The Journal of physiology 591 (Pt 3):641-656. doi:10.1113/jphysiol.2012.239566

Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF, Oja P (2003) International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 35 (8):1381-1395. doi:10.1249/01.MSS.0000078924.61453.FB

Frayn KN (1983) Calculation of substrate oxidation rates in vivo from gaseous exchange. J Appl Physiol 55 (2):628-634

Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, Nieman DC, Swain DP, Medicine ACoS (2011) American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 43 (7):1334-1359. doi:10.1249/MSS.0b013e318213fefb

Gillen JB, Gibala MJ (2014) Is high-intensity interval training a time-efficient exercise strategy to improve health and fitness? Appl Physiol Nutr Metab 39 (3):409-412. doi:10.1139/apnm-2013-0187

Gillen JB, Percival ME, Skelly LE, Martin BJ, Tan RB, Tarnopolsky MA, Gibala MJ (2014) Three minutes of all-out intermittent exercise per week increases skeletal muscle oxidative capacity and improves cardiometabolic health. PloS one 9 (11):e111489. doi:10.1371/journal.pone.0111489

Gurd BJ, Giles MD, Bonafiglia JT, Raleigh JP, Boyd JC, Ma JK, Zelt JG, Scribbans TD (2016) Incidence of nonresponse and individual patterns of response following sprint interval training. Appl Physiol Nutr Metab 41 (3):229-234. doi:10.1139/apnm-2015-0449

Howley ET, Bassett DR, Welch HG (1995) Criteria for maximal oxygen uptake: review and commentary. Med Sci Sports Exerc 27 (9):1292-1301

Korkiakangas E, Alahuhta M, Laitinen J (2009) Barriers to regular exercise among adults at high risk or diagnosed with type 2 diabetes: a systematic review. Health Promot Int

Lee DC, Sui X, Artero EG, Lee IM, Church TS, McAuley PA, Stanford FC, Kohl HW, Blair SN (2011) Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. Circulation 124 (23):2483-2490. doi:10.1161/CIRCULATIONAHA.111.038422

Leifer ES, Mikus CR, Karavirta L, Resnick BD, Kraus WE, Hakkinen K, Earnest CP, Fleg JL (2016) Adverse Cardiovascular Response to Aerobic Exercise Training: Is This a Concern? Med Sci Sports Exerc 48 (1):20-25. doi:10.1249/MSS.0000000000000752

Metcalfe RS, Babraj JA, Fawkner SG, Vollaard NB (2012) Towards the minimal amount of exercise for improving metabolic health: beneficial effects of reduced-exertion high-intensity interval training. European journal of applied physiology 112 (7):2767-2775. doi:10.1007/s00421-011-2254-z

Metcalfe RS, Koumanov F, Ruffino J, Stokes KA, Holman GD, Thompson D, Vollaard NBV (2015) Physiological and molecular responses to an acute bout of reduced-exertion high-intensity interval training (REHIT). European journal of applied physiology 115 (11):2321-2334

Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE (2002) Exercise capacity and mortality among men referred for exercise testing. The New England journal of medicine 346 (11):793-801. doi:10.1056/NEJMoa011858

Parolin ML, Chesley A, Matsos MP, Spriet LL, Jones NL, Heigenhauser GJ (1999) Regulation of skeletal muscle glycogen phosphorylase and PDH during maximal intermittent exercise. The American journal of physiology 277 (5 Pt 1):E890-900

Richards JC, Johnson TK, Kuzma JN, Lonac MC, Schweder MM, Voyles WF, Bell C (2010) Short-term sprint interval training increases insulin sensitivity in healthy adults but does not affect the thermogenic response to beta-adrenergic stimulation. The Journal of physiology 588 (Pt 15):2961-2972. doi:10.1113/jphysiol.2010.189886

Shepherd SO, Cocks M, Tipton KD, Ranasinghe AM, Barker TA, Burniston JG, Wagenmakers AJ, Shaw CS (2013) Sprint interval and traditional endurance training increase net intramuscular triglyceride breakdown and expression of perilipin 2 and 5. The Journal of physiology 591 (Pt 3):657-675. doi:10.1113/jphysiol.2012.240952

Sisson SB, Katzmarzyk PT, Earnest CP, Bouchard C, Blair SN, Church TS (2009) Volume of exercise and fitness nonresponse in sedentary, postmenopausal women. Med Sci Sports Exerc 41 (3):539-545. doi:10.1249/MSS.0b013e3181896c4e

Skelly L, MacInnis M, Safdar A, Akhtar M, Tarnopolsky M, Gibala M (2016) The influence of sex on the skeletal muscle gene expression response to sprint interval exercise. Proceedings of the Physiological Society 35:C06

Thomas S, Reading J, Shephard RJ (1992) Revision of the Physical Activity Readiness Questionnaire (PAR-Q). Can J Sport Sci 17 (4):338-345

Timmons JA, Knudsen S, Rankinen T, Koch LG, Sarzynski M, Jensen T, Keller P, Scheele C, Vollaard NB, Nielsen S, Akerstrom T, MacDougald OA, Jansson E, Greenhaff PL, Tarnopolsky MA, van Loon LJ, Pedersen BK, Sundberg CJ, Wahlestedt C, Britton SL, Bouchard C (2010) Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. J Appl Physiol (1985) 108 (6):1487-1496. doi:10.1152/japplphysiol.01295.2009

Valdes CT, Elkind-Hirsch KE (1991) Intravenous glucose tolerance test-derived insulin sensitivity changes during the menstrual cycle. The Journal of clinical endocrinology and metabolism 72 (3):642-646. doi:10.1210/jcem-72-3-642

Weston M, Taylor KL, Batterham AM, Hopkins WG (2014) Effects of low-volume high-intensity interval training (HIT) on fitness in adults: a meta-analysis of controlled and non-controlled trials. Sports Med 44 (7):1005-1017. doi:10.1007/s40279-014-0180-z

Yates T, Davies MJ, Edwardson C, Bodicoat DH, Biddle SJ, Khunti K (2014) Adverse responses and physical activity: secondary analysis of the PREPARE trial. Med Sci Sports Exerc 46 (8):1617-1623. doi:10.1249/MSS.0000000000000260

Table 1 Participant characteristics

	Men (n=17)	**Women (n=18)**
Age (y)	33±9 (*21-43*)	36±9 (*18-50*)
Height (m)	1.75±0.08 (*1.59-1.87*)	1.67±0.07 (*1.54-1.84*) **
Body mass (kg)	76.9±7.2 (*66.6-88.9*)	66.7±9.6 (*56.4-85.9*)**
BMI ($kg \cdot m^{-2}$)	25.1±2.1 (*21.0-28.9*)	24.1±3.5 (*18.4-29.1*)
$\dot{V}O_2max$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	38.6±8.3 (*24.7-57.0*)	31.6±4.6 (*25.8-39.0*) **

*Data shown are mean ± SD (range); BMI: body mass index; $\dot{V}O_2max$: maximal aerobic capacity; Sex differences: ** $p<0.01$*

Table 2 The impact of REHIT on $\dot{V}O_2$max and OGTT-derived variables

	Men (n=17)		Women (n=18)		Combined (n=35)		Statistics		
	Pre	Post	Pre	Post	Pre	Post	Time	Sex	Time*Sex
$\dot{V}O_2$max ($L \cdot min^{-1}$)	3.01±0.57	3.28±0.53	2.08±0.29	2.29±0.37	2.54±0.65	2.78±0.68	<0.001	<0.001	0.402
$\dot{V}O_2$max ($mL \cdot kg^{-1} \cdot min^{-1}$)	38.3±9.1	41.4±8.9	31.7±4.6	34.7±5.2	35.0±7.8	38.1±7.9	<0.001	0.010	0.926
Fasting plasma glucose ($mmol \cdot l^{-1}$)	5.29±0.47	5.25±0.51	4.96±0.46	4.91±0.40	5.09±0.49	5.05±0.49	0.534	0.014	0.909
Fasting plasma insulin ($\mu IU \cdot ml^{-1}$)	5.7±3.2	6.6±3.3	5.6±3.2	5.7±4.2	5.7±3.6	6.0±3.8	0.356	0.643	0.337
HOMA-IR	1.39±0.86	1.56±0.86	1.28±1.02	1.23±0.93	1.33±0.93	1.38±0.90	0.589	0.455	0.323
Peak plasma glucose ($mmol \cdot l^{-1}$)	9.26±1.68	8.91±2.17	7.29±1.69	7.15±1.23	8.22±1.94	7.98±1.93	0.296	0.002	0.624
Peak plasma insulin ($\mu IU \cdot ml^{-1}$)	111.3±82.0	97.9±51.5	63.1±43.2	61.5±39.5	85.8±67.9	61.5±39.5	0.158	0.029	0.265
Plasma glucose AUC ($mmol \cdot 120\ min \cdot l^{-1}$)	898±185	853±185	721±160	699±126	804±192	771±172	0.119	0.004	0.581
Plasma insulin AUC ($iU \cdot 120\ min \cdot ml^{-1}$)	8.37±5.75	7.74±4.54	5.21±3.37	4.72±2.94	6.69±4.84	6.14±4.02	0.096	0.036	0.844
Cederholm index ($mg \cdot l^{2} \cdot mmol^{-1} \cdot mU^{-1} \cdot min^{-1}$)	55.5±19.3	56.7±18.2	78.6±27.2	80.7±23.4	67.8±26.2	69.4±24.1	0.607	0.002	0.882

Data shown are mean ± SD.

Figure 1 Flow of participants through the study

Figure 2 Schematic of the REHIT training protocol. Grey boxes represent 'all-out' sprints against a fixed resistance of 5% of body mass. Training sessions 1-3 were in training week 1, sessions 4-9 were in training weeks 2 and 3, and sessions 10-18 were in training weeks 4-6.

Figure 3 Variability in training responses following REHIT. Dots represent the training adaptation for individual female (white dots) and male (black dots) participants compared to their individual baseline. Note that for $\dot{V}O_2$max and insulin sensitivity (Cederholm) an 'improvement' is represented by a % increase, whilst for glucose AUC and insulin AUC an 'improvement' is represented by a % decrease.

Figure 4 Plasma glucose and insulin responses to the pre- and post-training OGTTs in men and women. Results are presented as mean±SEM for clarity. N=16 for men and n=18 for women.