

BMJ Open Indicators of response to exercise training: a systematic review and meta-analysis

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ABSTRACT

Background Means-based analysis of maximal rate of oxygen consumption (VO_{2max}) has traditionally been used as the exercise response indicator to assess the efficacy of endurance (END), high intensity interval (HIIT) and resistance exercise training (RET) for improving cardiorespiratory fitness and whole-body health. However, considerable heterogeneity exists in the interindividual variability response to the same or different training modalities.

Objectives We performed a systematic review and meta-analysis to investigate exercise response rates in the context of VO_{2max} : (1) in each training modality (END, HIIT and RET) versus controls, (2) in END versus either HIIT or RET and (3) exercise response rates as measured by VO_{2max} versus other indicators of positive exercise response in each exercise modality.

Methods Three databases (EMBASE, MEDLINE, CENTRAL) and additional sources were searched. Both individual response rate and population average data were incorporated through continuous data, respectively. Of 3268 identified manuscripts, a total of 29 studies were suitable for qualitative synthesis and a further 22 for quantitative. Stratification based on intervention duration (less than 12 weeks; more than or equal to 12 weeks) was undertaken.

Results A total of 62 data points were procured. Both END and HIIT training exhibited differential improvements in VO_{2max} based on intervention duration. VO_{2max} did not adequately differentiate between END and HIIT, irrespective of intervention length. Although none of the other exercise response indicators achieved statistical significance, LT and HR_{rest} demonstrated common trajectories in pooled and separate analyses between modalities. RET data were highly limited. Heterogeneity was ubiquitous across all analyses.

Conclusions The potential for LT and HR_{rest} as indicators of exercise response requires further elucidation, in addition to the exploration of interventional and intrinsic sources of heterogeneity.

INTRODUCTION

Physical activity in humans has been recognised to confer a beneficial effect on health since the time of Hippocrates and Galen.^{1 2} WHO defines physical activity as ‘any bodily movement produced by skeletal

Strengths and limitations of this study

- Robust analysis and synthesis of available evidence (randomised-controlled trial, case-control and cohort).
- For continuous data, we used the generic inverse variance statistical method with the random effects model and established the outcome measure as the standardised mean difference.
- Stratification of results dependent on intervention duration was performed.
- Significant heterogeneity of studies (exercise response indicators, training modalities, assessment protocols, population being studied and analytical methods) limits the ability to undertake more extensive meta-analysis of available data, resulting in the majority of outputs demonstrating statistical non-significance.
- Analysis was substantially restricted due to currently insufficient data for several alternative markers, requiring further characterisation through qualitative assessment.

muscles that requires energy expenditure’.³ Physical activity has been shown to not only be cardioprotective,⁴ but prospective data have demonstrated an inverse correlation between increased physical activity and all-cause mortality.^{3 5 6} Over the years, regular physical activity has been implicated in the prevention or management of a considerable number of chronic diseases, including cancer.^{7 8} Physical activity has also been actively implemented as an intervention for age-associated frailty, resulting in a marked improvement in the quality of life of older individuals,^{9–11} as well as improvements in the constellation of age-associated metabolic abnormalities which include dyslipidaemia, hyperglycaemia, hypertension and obesity.^{12–16}

Within the literature concerning structured exercise training as a form of physical activity, and away from specialist athletic training regimes, three broad variants of exercise training modalities are commonly



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described: (1) endurance exercise training (END), (2) high-intensity interval training (HIIT) and (3) resistance exercise training (RET).^{17,18} Each of these training modalities is associated with a multitude of differing components, including content, volume, intensity, duration (training and recovery periods) and frequency.^{19–22} As such, each modality is associated with distinct improvements in musculoskeletal, metabolic and/or cardio/vascular parameters.^{6–8} Guidelines published by the UK Department of Health and Social Care in September 2019 advise that healthy adults should perform at least two instances of RET and a total of 150 min of moderate END on a weekly basis.²³ There is also some recognition of HIIT, as a reduced volume vigorous exercise can replace moderate END as long as this is accumulated in bouts of 10 min or more.

In terms of determining the efficacy of an exercise training programme, despite the aforementioned differences which will likely occur with different training regimes, an assessment of cardiorespiratory fitness (CRF) is often undertaken. In humans, this is most commonly undertaken through assessment of the maximal rate of oxygen consumption ($\text{VO}_{2\text{max}}$), defined as the peak utilisation of oxygen by metabolically active tissue.^{24,25} Subsequently, the $\text{VO}_{2\text{max}}$ plateau has become the gold standard for determining the maximal CRF of an individual, in addition to serving as a comparative marker of response following an exercise intervention.^{26–30}

Although it is well established that improvements in multiple health parameters are generally observed in humans following a period of exercise training,^{27,31} the observance of individuals who do not demonstrate an improvement for a particular indicator above measurement error has emerged in multiple studies (often defined as ‘non-responders’).^{31,32} Estimated to constitute up to ~20% of any given population for the primary expected physiological adaptation (eg, hypertrophy for RET and $\text{VO}_{2\text{max}}$ or insulin sensitivity for END),³² numerous explanations have emerged to try and describe this phenomenon, ranging from innate factors to poor compliance.^{32,33} However, simple explanations based on baseline characteristics or training compliance/intensity do not appear to be able to fully explain the marked heterogeneity in exercise adaptation.²⁷ Furthermore, a subset of individuals demonstrate a worsening of a given indicator below measurement error, with some describing these individuals as ‘adverse responders’.^{31,34} If using this nomenclature, one study reported that an estimated 7% of people are described as being adverse responders in at least two parameters,³³ with commonly assessed variables (in addition to $\text{VO}_{2\text{max}}$) including heart rate (HR), lactate threshold (LT) and power output (PO).^{34,35}

It must however be acknowledged that the concept of non-responders, and certainly that of adverse responders, is not universally accepted with ongoing debate in the scientific community concerning the epistemological validity of this concept.^{27,31} Some of this debate is centred on the definitions of these concepts, with the work of

Mitchell *et al* claiming there are no non-responders to RET as all individuals demonstrated at least one positive adaptive response of the many that were measured.³⁶ This definition of a non-responder is however strikingly different to that used by Phillips *et al* in their work looking at molecular networks of exercise adaptation. In this study, non-responders were classed as those who did not demonstrate significant hypertrophy during 20 weeks RET, but may have displayed other improvements such as strength or vascular conductance. As such, a number of these individuals would have been non-responders in one study but not in another. This apparent uncertainty has been further exacerbated by the observation of a dissociation between $\text{VO}_{2\text{max}}$ and other exercise response indicators (including blood lactate and maximum HR (HR_{max})) with END.³⁷ Furthermore, evidence of a disparity in indicator-based responses has been demonstrated in analyses of outcomes following RET exercise³⁸ with hypertrophic gains not necessarily representing changes in muscle function, for example.

Of the three aforementioned exercise modalities and with respect to improvements in CRF, END and HIIT are each recognised as having a significant and positive effect overall.^{18,39} In contrast, the benefits of RET are distinct from this and are traditionally considered to be improvements in strength and skeletal muscle hypertrophy.¹⁸ Although early evidence determined that RET did not confer any improvement in $\text{VO}_{2\text{max}}$,⁴⁰ a more recent comprehensive assessment through a narrative systematic review comprising 17 studies, concluded that improvements in $\text{VO}_{2\text{max}}$ may be observed with RET in previously untrained individuals irrespective of age.³⁸ As such, sedentary individuals would conceivably benefit from a concurrent improvement in both CRF and the acknowledged skeletal muscle-based improvements associated with RET.³⁸

As a result of the current paradigm within the literature, there exists an uncertainty concerning the suitability of different interventions to elicit an exercise response. In addition to the academic consideration of what may constitute as a ‘response’ to any particular intervention, a determination of whether alternative markers of response to $\text{VO}_{2\text{max}}$ exist in each of the three modalities has not yet been undertaken through a systematic approach.

Therefore, through a combined systematic review and meta-analysis strategy, this study appraises the available evidence of studies in order to answer the following research questions:

1. In untrained human adults, is each exercise modality (END, HIIT and RET) more effective than controls in eliciting an improvement in CRF based on $\text{VO}_{2\text{max}}$?
2. In untrained human adults, is END more effective than either HIIT and RET in eliciting an improvement in CRF based on $\text{VO}_{2\text{max}}$?
3. In untrained human adults and per each exercise modality, do other measures of exercise response (HR_{rest} , HR_{max} , LT and PO) elicit a similar rate of exercise response when compared with $\text{VO}_{2\text{max}}$?

METHOD

The population assessed in this study was human adults between the ages of 18–80 years. As the extent of exercise response is noted to be similar between both males and females,²⁶ both sexes were included in all analyses. The investigated intervention training modalities were END, HIIT and RET. To permit the investigation of the three research questions, the comparisons and outcome measures used were (1) intervention (END, HIIT or RET) vs control using VO_{2max} as the response indicator, (2) END versus HIIT or RET using VO_{2max} as the response indicator and (3) VO_{2max} vs HR_{rest} , HR_{max} , LT or PO in each of END, HIIT and RET. The outcome measures included in this study were continuous data (ie, numerical values defined by a defined scale and range, such as HR or watts) represented by mean±SD values. A complete Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist is provided in online supplemental file 1.

The inclusion criteria are all published clinical trials with an intervention component (randomised controlled trial (RCT), case–control and cohort), as the investigated phenomenon (indicators of exercise response) require an actioned stimulus. In previously untrained healthy or obese individuals or individuals with type two diabetes mellitus without physical impediment, and the utilisation of VO_{2max} as an endpoint. The exclusion criteria are limited to qualitative studies, non-human studies, studies where participants are younger than 18 or older than 80 years of age, physically impaired individuals, pregnant volunteers or participants with any established cardiovascular, renal, musculoskeletal, neurological, malignant or pulmonary disease.

Three electronic online literature databases (EMBASE, MEDLINE, CENTRAL) were used as primary data sources. Search strategies for EMBASE and MEDLINE were undertaken (online supplemental file 2). The search strategy for CENTRAL was ‘VO2 exercise response’. To screen for clinical trials not captured in the above search strategies, and to definitively address the anticipated deficiency in RET intervention studies, two further search procedures were performed through PubMed. The search terms in each were ‘VO2 exercise response’ and ‘resistance exercise response variability’. Only clinical trials were selected. Furthermore, grey literature sources were sought in addition to the above (Google and ClinicalTrials.Gov). The search phrase ‘exercise response VO2’ was submitted to the Google search engine (147 results, seven relevant studies). An additional search was made through ClinicalTrials.Gov (completed studies, adult, all sex, ‘exercise response’ search string, only studies with preliminary or final results selected, 1308 results, six relevant studies). A further search through the reference lists of studies selected for synthesis was implemented to further address any undetected primary sources.

The MeSH terms undertaken in this study are provided (online supplemental file 2). Two of the primary database sources (EMBASE, MEDLINE) were searched by two

independent researchers (AA and HA), with CENTRAL, PubMed, Google, ClinicalTrials.Gov and reference list review searches and further selection stages being undertaken by one researcher (AA).

In the first screening procedure, all studies were initially assessed on their implementation of END, HIIT and/or RET as a primary intervention and their utilisation of at least one response indicator, where VO_{2max} was mandatory. In accordance with the findings of a meta-analysis published by Bacon *et al* that determined VO_{2max} trainability is increased with prolonged intervention periods,⁴¹ studies with a duration of less than 2 weeks were excluded from the analysis. Following the completion and compilation of the studies obtained from the preliminary data source searches, duplicates were highlighted and the novel studies were spliced into a new list. Thereafter, any new studies obtained from the other search strategies were added to a continuously updated version of this list. The extracted summary data for all studies that were deemed suitable for synthesis included the study title, primary author, year of publication, association with any other studies or trials, study design type, target population characterisation, assessed interventions, duration of intervention, intervention detail (including means of exercise, frequency, volume parameters and/or intensity), primary and secondary endpoints, criteria for exercise response (if applicable), data type (categorical vs continuous) and suitability for any combination of the intended analyses specific for each research question (I–III).

The values incorporated in our synthesis were absolute units of postintervention values in the pertinent data fields per exercise modality or assessed group (either interventional or control). The data specific to response rate included exercise modality (END, HIIT and/or RET), the parameters utilised (VO_{2max} , HR_{rest} , HR_{max} , LT and/or PO) and the data type (continuous data). With the incorporated data type, the postintervention mean and SD for intervention and control (or other intervention) groups were entered for comparison. The information per study was separately recorded in three tables, each pertaining to one of the three research questions established (online supplemental file 3A–C). One study (Gurd *et al*), containing pooled unweighted sample complete or subset data from five studies,⁴² was incorporated as a single datapoint.

The Cochrane Risk of Bias (RoB) 2 template was implemented for randomised studies.⁴³ Qualitative assessment of the studies was undertaken by three researchers. Both study and outcome level outputs were produced. The resulting outputs were generated through Review Manager (RevMan) V.5.3.5. Additionally, case–control studies were assessed using the CLARITY McMaster University Risk of Bias assessment framework. These were independently undertaken by three researchers (AA, BM and IR).

One principal summary measure was produced in this meta-analysis. The generic inverse variance (IV) statistical method was selected with the random effects model and

established the outcome measure as a standardised mean difference (SMD) with an SE calculation for the assessed groups based on Cochrane recommendations.⁴⁴ Further, a simplified pooled SD for the generation of the SMD was utilised in all instances.⁴⁵ All data were reported as IV values and 95% CI for all individual studies, where individual datapoints that were not eligible for pooled analyses having CI values derived through SE values as advocated by Cochrane.⁴⁶ With pooled data reported with the addition of Z data and p values.

Forest plots were generated for all datasets which contained at least three data points. All statistics and forest plots were produced with RevMan V.5.3.5. Data per study were manually entered into each of the variable listed. No *post hoc* data merging between studies was undertaken. Measures of statistical heterogeneity were calculated using the I^2 statistic through RevMan V.5.3.5 and are reported within the produced forest plots. In order to address anticipated heterogeneity within our dataset, a stratified approach based on age, intervention duration and/or weekly modality frequency will be considered. Further, subgrouping within forest plots based on the above was undertaken if at least two data points were present. Certain studies permitted the inclusion of multiple groups separately for comparative purposes (table 1, online supplemental file 3A–C).

In order to assess for publication bias, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach⁴⁷ was adopted on a study-specific level and was assessed by two independent researchers (AA and IR). Due to the limited number of studies per area of analysis, statistical assessment of publication bias, meta-regression and trial sequential analysis was infeasible.

Patient and public involvement

Patients and/or the general public were not involved in undertaking and devising this systematic review and meta-analysis. No external groups, stakeholders or members of the public were involved in any element of the study's inception, planning, implementation or analysis.

RESULTS

A total of 3268 studies were generated from the identification stage. A total of 29 studies—20 RCTs and 9 case-control or cohort studies—were deemed suitable for inclusion in our qualitative and quantitative appraisal (figure 1).^{18 26–30 42 48–79} The publication dates ranged from 1991 to 2018, where the majority of the assessed studies were not associated with any other trials. A total sample size of 1937 individuals was assessed.

The study characteristic data for all studies are presented (table 1). The assessed populations were found to be heterogeneous with respect to biological sex, degree of physical fitness, body mass index and age. The majority of studies featured a comparison between END and HIIT and included either END or HIIT

within their analysis, with only three studies assessing the response rates for RET. One study⁴⁸ was found to employ a parallel assessment of exercise intensity and volume. The implemented exercise protocols exhibited substantial heterogeneity, with only two studies^{49 50} displaying a congruent basis for their assessment due to their common derivation from the Dose-Response to Exercise in Women (DREW) study. The intervention period varied between 3 and 52 weeks. In accordance with our inclusion criteria, the majority of studies utilised VO_{2max} as a primary endpoint, with most studies also incorporating data pertaining to body composition. Twelve of the 29 studies defined exercise responsiveness through differing thresholds of VO_{2max} change, where 3 of these 12 defined any improvement from VO_{2max} baseline ($\Delta > 0\%$) as evidence of a positive adaptation in their cohorts.^{49–51}

The RoB summaries are provided (online supplemental files 4–6), which demonstrate varied degrees of bias across the assessed domains. Furthermore, GRADE score appraisal of each study was undertaken (online supplemental file 4). A total of 62 data points were obtained from these studies for inclusion in the forest plots (figures 1–5). Sufficient overlap and representation in characteristics permitted a stratification based on intervention duration, with 12 weeks selected as the criteria for group formation.

Exercise responsiveness versus controls using VO_{2max} (analysis 1)

END versus CON

Nine data points from eight studies were observed (online supplemental file 3A). Within the <12 week subgroup, the response through END as an intervention did not result in an intervention favouring (IV=0.06, 95% CI -1.01 to 1.13) or statistically significant (p=0.64) outcome (figure 2). However, the ≥ 12 weeks subgroup demonstrated an unequivocal and statistically significant improvement in VO_{2max} (IV=2.0, 95% CI 0.68 to 3.32, p<0.05).

HIIT versus CON

Nine data points from eight studies were incorporated in this analysis (figure 2). Although the effect size trends observed in both the <12 and ≥ 12 weeks subgroups demonstrated congruence with the duration-based observation in the END assessment (figure 2), the results did not reach statistical significance (p=0.18–0.66) (figure 2).

RET versus CON

Only two studies (Nybo *et al*, Hautala *et al*) contained data indicating VO_{2max} improvements using RET (online supplemental file 3A).^{18 52} Neither data points demonstrated an improvement in VO_{2max} through RET interventions lasting two and 12 weeks (IV=-0.35, 95% CI -1.64 to 0.94; IV=0, 95% CI -1.43 to 1.43, respectively) (online supplemental file 3A).

Table 1 Study characteristics of the studies that achieved synthesis

Study	Year	Design	Sample size	Patient characteristics	Intervention	Exercise protocol (modality, intensity, volume, frequency)	Intervention period	Comparison type	Primary endpoint	Secondary endpoint	Response criteria
Weatherwax ^{56,58}	2018	RCT	39	Male and female. Less than 30 min activity in 3 days per week. 30–75 years old.	HIIT	Stationary bike, elliptical machine or treadmill. Stepwise progression in intensity depending on exercise group.	12 weeks	Standardised vs Individualised	VO _{2max}	Physical activity, sitting time, HRrest, HRmax, body measurement parameters, dietary intake	VO _{2max} Δ>ME (4.7%)
Sisson ⁴⁹	2009	RCT	310	Female only (postmenopausal). Sedentary. 45–75 years old. Multiple ethnicities.	END	Recumbent cycle ergometer or treadmill (alternating); 50% baseline VO _{2max} * 3–4 sessions/week	24 weeks	4 vs 8 vs 12 kcal/kg/week	VO _{2max}	N/A	VO _{2max} Δ>0%
Earnest ⁵⁰	2011	RCT	251	Female only (postmenopausal). Sedentary. 45–75 years old. Caucasian only.	END	Recumbent cycle ergometer or treadmill (alternating); 50% baseline VO _{2max} * 3–4 sessions/week	24 weeks	Control vs 4 vs 8 vs 12 kcal/kg/week	VO _{2max}	N/A	VO _{2max} Δ>0%
Pandley ³⁰	2015	RCT	202	Male and female. T2DM. 30–75 years old.	END RET	Treadmill; 50%–80% VO _{2max} * 3 session/week Full body training, compound movements (upper, lower, abdominal); 10–12 repetition range, 3 sessions/week	36 weeks	Control vs END vs RET vs both	VO _{2max}	HbA1c, body measurement parameters, systolic and diastolic blood pressure (at rest), systolic blood pressure (peak), HRrest, RER, insulin use	VO _{2max} = Δ>5%
Montero ²⁸	2017	RCT	78	Male only. Sedentary. Healthy. 18–35 years old.	END, HIIT, mixed	Recumbent cycle ergometer; average of 65% of Wmax (between four intensity profiles), range from 1 to 5 sessions/week	6 weeks	Exercise frequency (1 vs 2 vs 3 vs 4 vs 5 sessions/week)	VO _{2max} , W _{max}	Haemoglobin mass, plasma volume, red blood cell volume, blood volume, body measurement parameters, mitochondrial volume density	VO _{2max} & W _{max} =>1 T.E.
Bonafiglia ²⁷	2016	RCT (cross-over)	21	Male and female. Recreationally active only. Age range not stated.	END HIIT	30 min cycling at 65% of VO _{2max} * 4 sessions/week Eight blocks of 170% of VO _{2max} (20 s activity, 10 s rest), 4 sessions/week	3 weeks x 2	END vs HIIT	VO _{2max}	Lactate threshold, all HR _{submax} * W _{max} parameters =>2 S.E.	
Ross ⁴⁸	2015	RCT	121	Male and female. Sedentary. Average age 53.2.	LALI HALI HAHI	180–300kcal at 50% of VO _{2max} per session, 5 sessions/week 360–600kcal at 50% of VO _{2max} per session, 5 sessions/week 360–600 kcal at 75% of VO _{2max} per session, 5 sessions/week	24 weeks	LALI vs HALI vs HAHl at 4, 8, 16 and 24 week intervals	VO _{2max}	N/A	VO _{2max} =>1 T.E.

Continued

Table 1 Continued

Study	Year	Design	Sample size	Patient characteristics	Intervention	Exercise protocol (modality, intensity, volume, frequency)	Intervention period	Comparison type	Primary endpoint	Secondary endpoint	Response criteria
Gurd ⁴²	2016	RCT	63	Healthy males who had previously attended prior, similar studies.	HIIT	Synthesis of five HIIT studies, each with differing methods.	4–6 weeks	HIIT vs control	VO _{2max}	Lactate threshold, time to completion	VO _{2max} =>2 T.E.
Yan ⁵¹	2017	Cohort	39	Male only. Moderately-trained. 18–45 years old. Caucasian only. BMI <30 kg/m ² .	HIIT	Variable intensity tailored to individual's preintervention measures. 3 HIIT sessions/week	4 weeks	N/A (no control/comparison)	VO _{2max}	Lactate threshold, power output, distance	VO _{2max} Δ>0%
Scharhag-Rosenberger ⁵⁷	2012	Cohort	18	Male and female. 32–50 years old. BMI 19–28 kg/m ² .	END	Jogging or walking. 45 min duration at intensity of 60% hour or HR at lactate threshold, 3 sessions/week	50 weeks	N/A (no control/comparison)	VO _{2max}	Lactate threshold, resting heart rate, submaximal heart rate	Variable; VO _{2max} = Δ>5.6%
Higgins ^{58 67}	2015	Cohort	23	No population data provided in detail.	HIIT	Cycling. 3 sessions/week	6 weeks	N/A (no control/comparison)	VO _{2max}	Glucose, systolic blood pressure, diastolic blood pressure, lipid profile	VO _{2max} =>2 s.I.E.
Astorino ²⁹	2018	Cohort	14	Male and female. Healthy, previously active (150 minute/week). 20–49 years old.	HIIT	Eight to 10 1 min rounds of HIIT, 130% of power output based on volunteer ventilatory threshold, 3 session/week	3 weeks	control vs HIIT	VO _{2max}	Time trial performance, ventilatory threshold	VO _{2max} ≥2 s.I.E.
Kohrt ²⁵	1991	Cohort	320	Male and female. Healthy. Untrained. 60–71 years old.	END	Up to 50 minutes/day. 85% of HR _{max} graded increase in volume and intensity up to third month, daily exercise	36–52 weeks	Control vs END	VO _{2max}	RER _{max} , VE _{max} , HR _{max} , HR _{rest}	None
Nybo ¹⁸	2010	Cohort	36	Male only. Untrained. No training in prior 2 years. 20–43 years old.	HIIT	Running. 20 min total exercise duration. Five sets of 2 min at above 95% of calculated HR _{max} two sessions/week	12 weeks	HIIT vs END vs RET vs control	VO _{2max}	HR _{rest} , BP _{rest} , HR _{max}	None
Osei-Tutu & Campagna ³⁹	2004	RCT	40	Male and female. Healthy. Sedentary. 20–40 years old.	END	Treadmill. 60 min at 80% of HR _{max} 2.5 sessions/week Lower body compound and isolation exercises, 3–4 sets per exercise, 1 min rest interval, average duration 60 min, 2 sessions/week	8 weeks	'Long bout' (END) vs 'short bout' vs control	VO _{2max}	N/A	None

Continued

Table 1 Continued

Study	Year	Design	Sample size	Patient characteristics	Intervention	Exercise protocol (modality, intensity, volume, frequency)	Intervention period	Comparison type	Primary endpoint	Secondary endpoint	Response criteria
Trapp ⁶⁰	2008	RCT	45	Female only. Healthy. Inactive. 18–30 years old. Mixed ethnicity.	HIIT	Ergometer. 8s sprinting, 12s recovery. Maximum of 60 bouts per session. Up to 20 min/session, 45 total exercise sessions in intervention period.	15 weeks	HIIT vs END vs control	VO _{2max}	Body fat and muscle comparisons	None
Metcalfe ⁶¹	2012	RCT	29	Male and female. Healthy. Sedentary. Range for intervention and control averages 19–26 years old.	HIIT	Ergometer, maximal pedalling against 7.5% volunteer bodyweight, 10 min duration, 3 sessions/week	6 weeks	HIIT vs control	VO _{2max}	N/A	None
Ziemann ⁶²	2011	RCT	21	Male only. Healthy. Inactive. College age.	HIIT	Six 90s maximal effort and 180s recovery rounds, set to 80% VO _{2max} , 3 sessions/week	6 weeks	HIIT vs control	VO _{2max}	Power output (multiple parameters)	None
Burgomaster ⁶³	2008	Cohort	20	Male and female. Healthy. Sedentary. No intense exercise for at least 1 year prior. Range for intervention and control averages 23–24 years old.	END HIIT	40–60 min cycling, 65% of VO _{2max} , 5 sessions/week 30 s of 4–6 bouts (increasing count), maximum effort (Wingate test), 4.5 min recovery interval, 3 session/week	6 weeks	HIIT vs END	VO _{2max}	HR _{max} , RER	None
Lo ⁶⁵	2011	RCT	34	Male only. Healthy. Inactive. Average age 20.4 years old.	END RET	30 min treadmill, 70%–85% HR _{max} , 3 session/week Ten exercises (full body, compound and isolation), incremental increase in intensity (weight), 3 session/week	24 weeks	END vs RET	HR _{max}	N/A	None
McKay ⁶⁴	2009	RCT	12	Male only. Healthy. Not previously in a formal training programme. Average age 25 years old.	END HIIT	90–120 min of 65% pretraining VO _{2max} . Permitted 60–90s intermittent recovery if required. 8 sessions total. 60s 120% W _{max} followed by 60s recovery for 8–12 bouts, 8 sessions total	3 weeks	END vs HIIT	VO _{2max}	W _{max} , lactate threshold (multiple parameters)	None
Dunham ⁶⁵	2012	RCT	15	Male and female. Healthy. Physically active. Average age range 20.2–21.3 years old.	END HIIT	Ergometer, 45 min of 60%–70% VO _{2max} , 3 sessions/week Ergometer, five bouts of 1 min at 90% VO _{2max} followed by 2 min recovery, 3 sessions/week	4 weeks	END vs HIIT	VO _{2max}	RER _{max} , HR _{max}	None

Continued

Table 1 Continued

Study	Year	Design	Sample size	Participant characteristics	Intervention	Exercise protocol (modality, intensity, volume, frequency)	Intervention period	Comparison type	Primary endpoint	Secondary endpoint	Response criteria
Macpherson ⁶⁶	2010	C	20	Male and female. Recreationally active only. Ages per groups 24.3±3.3 and 22.8±3.1.	END HIIT	Treadmill, continuous running, 30–60 min (progressive increase), at 65% VO_{2max} intensity, 3 sessions/week Treadmill, 30s maximal effort sprinting, 4 min recovery interval, increase in bout count from 4 to 6, 3 sessions/week	6 weeks	END vs HIIT	VO_{2max}	Cardiac output, resting metabolic rate	None
Shepherd ⁶⁷	2013	RCT	16	Male only. Sedentary. Healthy. Average age per groups 21±1 and 22±2.	END HIIT	Ergometer, 40–60 min per session (increasing volume during intervention), 65% VO_{2max} , 5 sessions/week. Ergometer, 30 s maximal effort cycling, 4.5 min recovery interval with 30W resistance at 50 rpm pace, increase in bout count from 4 to 6, 3 sessions/week.	6 weeks	END vs HIIT	Intramuscular triglyceride, perilipin	VO_{2max} , W_{max} , insulin and glucose	None
Warburton ⁶⁴	2004	RCT	20	Male only. Active. Healthy. Average age per total group 29±4.	END HIIT	Ergometer, 30–48 min per session (increasing volume during intervention), 64.3%±3.7% VO_{2max} , 3 sessions/week. Ergometer, 2 min high effort (90% VO_{2max}) followed by 2 min low effort (40% VO_{2max}) for a number of bouts that would match the END equivalent in terms of total work output, 3 sessions/week.	12 weeks	END vs HIIT vs control	Blood volume constituents	VO_{2max} , HR_{max} , W_{max} , systolic and diastolic blood pressure	None
Berger ⁵⁵	2006	C	23	Male and female. No intense exercise in preceding 2 years. Healthy. Average age per total group 24±5.	END HIIT	Ergometer, 30 min per session, intensity 60% VO_{2max} , 3–4 sessions/week Ergometer, 20 1 min bouts of 90% VO_{2max} followed by 1 min rest, 3–4 sessions/week	6 weeks	END vs HIIT vs control	VO_{2max} time delay, primary amplitude, primary time constant	W_{max} , lactate threshold, HR_{max}	None
Matsuo ⁶⁸	2013	RCT	42	Male only. Sedentary. Healthy. Average age in study 26.5±6.2.	END HIIT	Ergometer, 40 min, 60%–65% VO_{2max} , 60 rpm maintained, 5 sessions/week 'sprint'; ergometer, 30 s 120% VO_{2max} >85 rpm followed by 15s rest period for seven rounds; 'HIAT'; alternating between 3 min 80% VO_{2max} at 70–80 rpm against 2 min 50% VO_{2max} at 60 rpm (cooldown at end for both); five sessions/week	8 weeks	END vs HIIT ('sprint') vs HIIT ('HIAT')	VO_{2max} , cardiac parameters (multiple)	Blood constituents	None

Continued

Table 1 Continued

Study	Year	Design	Sample size	Patient characteristics	Intervention	Exercise protocol (modality, intensity, volume, frequency)	Intervention period	Comparison type	Primary endpoint	Secondary endpoint	Response criteria
O'Donovan ⁶⁹	2005	RCT	42	Male only. Sedentary. Healthy. Age range 30–45 years old.	END (lo intensity) END (hi intensity)	Ergometer, 400 kcal at 60% $\dot{V}O_{2max}$, 3 sessions/week Ergometer, 400kcal at 80% $\dot{V}O_{2max}$, 3 sessions/week	24 weeks	END (lower intensity) vs END (higher intensity) vs control	$\dot{V}O_{2max}$	Lipid profile, fibrinogen	None
Sandvei ⁷⁰	2012	RCT	23	Male and female. Sedentary to moderately trained. Healthy. Age range 18–35 years old.	END HIIT	Outdoor running, 30–60 weeks (5 min incremental increase per week), 70%–80% HRmax, 3 sessions/week Sprinting, 30 s maximal effort followed by 3 min recovery, 5–10 sprints (one incremental increase per week), 3 sessions/week	8 weeks	HIIT (sprint) vs END	Glucose, insulin	Lipid profile, HR _{max} , $\dot{V}O_{2max}$	None
Hautala ⁵²	2005	RCT (crossover)	91	Male and female. Sedentary. Healthy. Average age in study 42±5.	RET	15 exercises including major muscle groups, 1 set of 8–12 repetitions to near fatigue. Resistance training every 2 days with a focus on arm or leg strength. 5 consecutive sessions/week 40 min cycle ergometer, 5 consecutive sessions/week	2 weeks	END vs RET vs control	BMI	$\dot{V}O_{2max}$, HR _{max} , RER _{max} , maximum quadriceps strength	$\dot{V}O_{2max}$, $\Delta > 0\%$

BMI, body mass index; END, endurance exercise training; HAHI, high amount, high intensity exercise; HALLI, high amount, low intensity exercise; HIIT, high intensity interval training; HR_{max}, maximum heart rate; LAL1, low amount, low intensity exercise; ME, measurement error; N/A, not available; RCT, randomised controlled trial; RER, respiratory exchange ratio; RET, resistance exercise training; T2DM, type 2 diabetes mellitus; $\dot{V}O_{2max}$, maximal rate of oxygen consumption.



PRISMA 2009 Flow Diagram

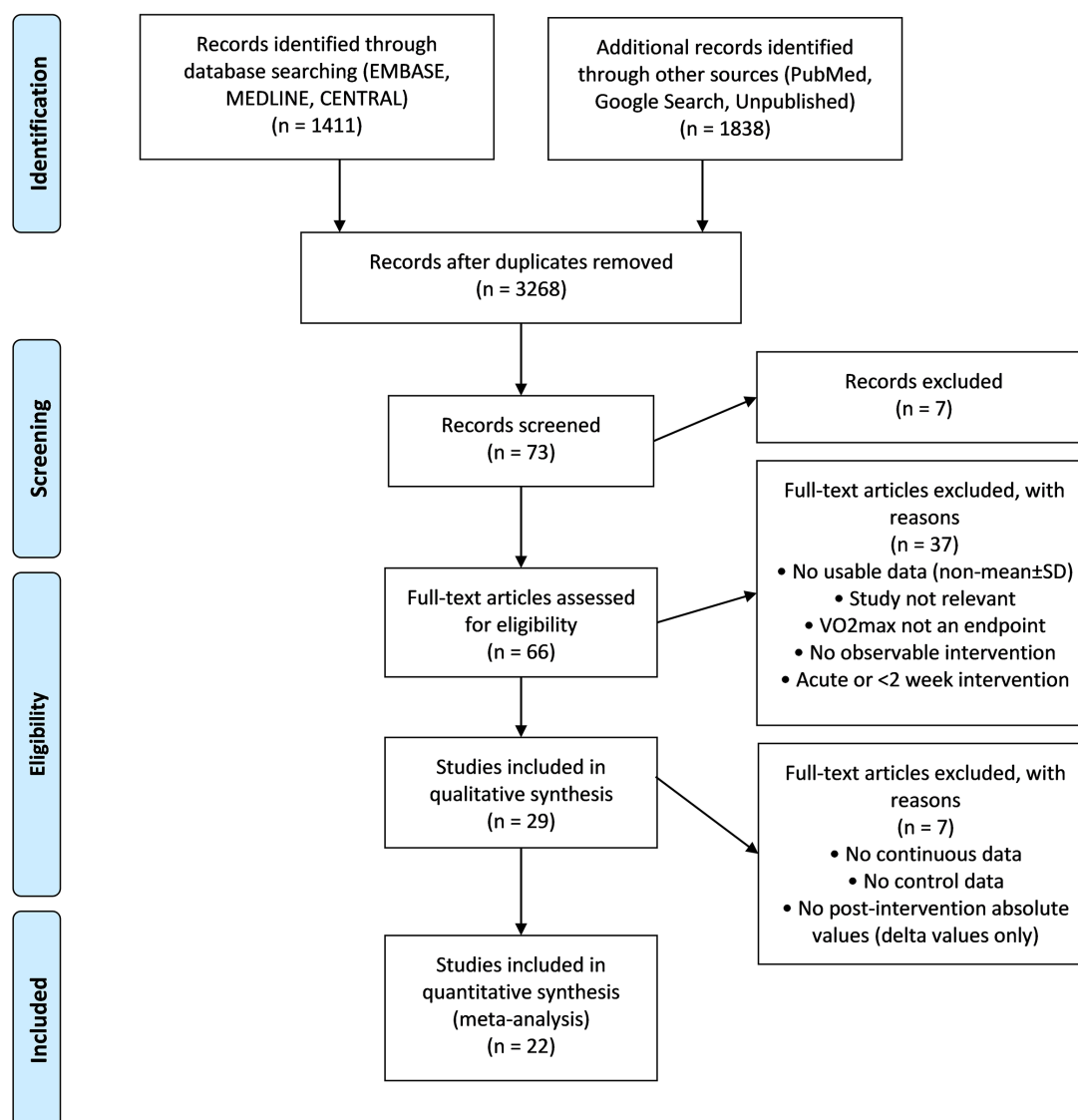


Figure 1 PRISMA flow diagram of the study selection and identification process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; VO_{2max} , maximal rate of oxygen consumption.

End versus HIIT and RET responsiveness using VO_{2max} (analysis 2)

END versus HIIT

Twelve studies provided data permitting a postintervention comparison between END and HIIT intervention groups (figure 3). The overall effect size in both the <12 and ≥ 12 weeks subgroups were found to be residual ($IV = -0.29$, 95% CI -1.38 to 0.81 ; $IV = 0.35$, 95% CI -0.12 to 0.81 , respectively) and did not achieve statistical significance (figure 3).

END versus RET

Two studies (Nybo *et al*, Hautala *et al*) permitted a comparison between END and RET (online supplemental file

3B).^{18 52} Both studies demonstrated an improvement in END when compared with RET ($IV = 1.62$, 95% CI 0.37 to 2.87 ; $IV = 0.14$, 95% CI -1 to 1.28 , respectively) (online supplemental file 3B).

Exercise responsiveness using other exercise response indicators (analysis 3)

When assessed with HR_{rest} , END demonstrated a consistent reduction when assessed through two studies (Kohrt *et al*, Nybo *et al*), where the duration was (or exceeded) 12 weeks ($IV = -0.18$, 95% CI -1.92 to 1.56 ; $IV = -3.14$, 95% CI -4.26 to -2.02 , respectively) (online supplemental file 3C).^{18 26} Similarly, a pooled analysis demonstrated that interventions with HIIT exceeding (or lasting) 12 weeks

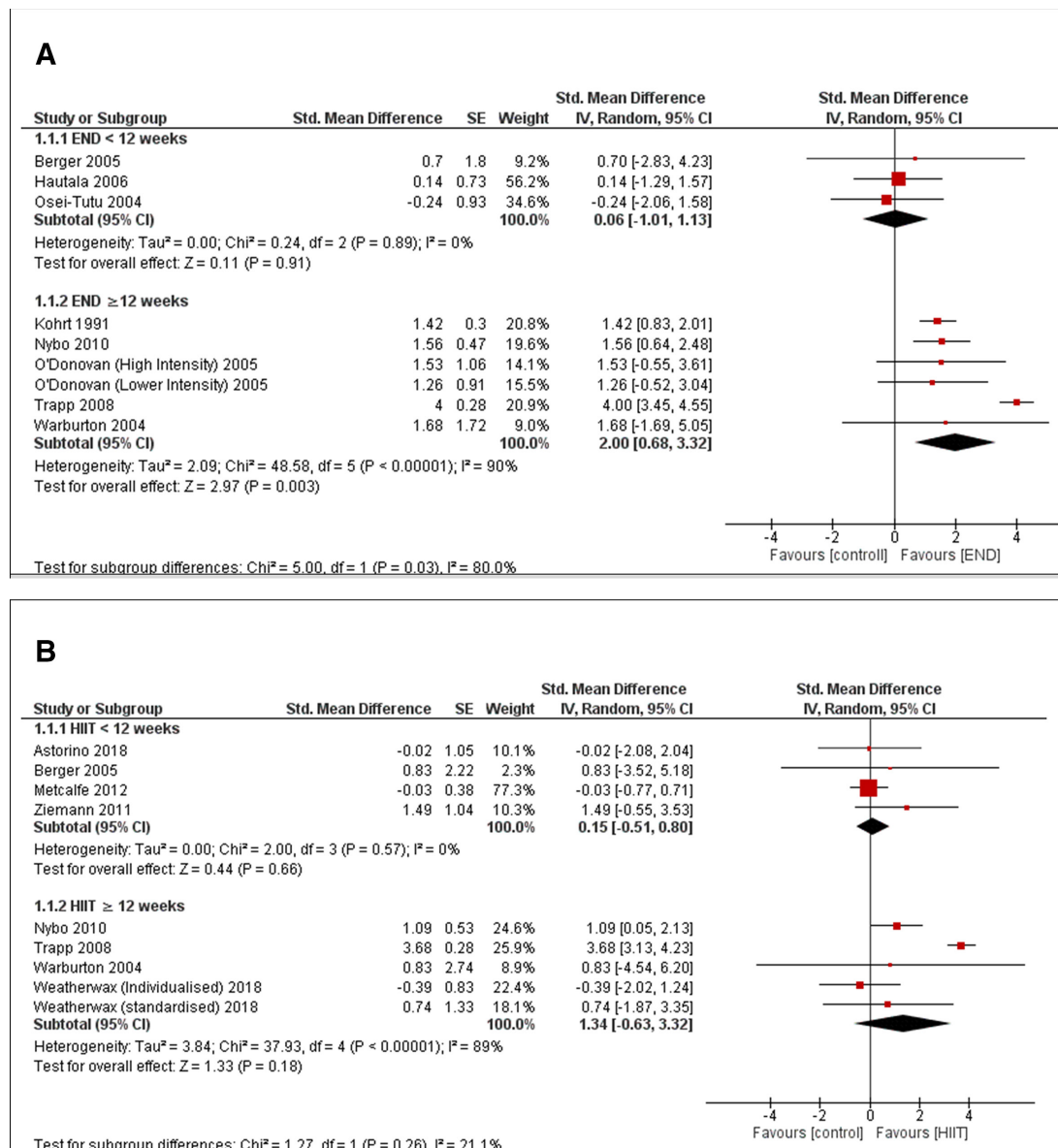


Figure 2 (A) END versus controls using VO_{2max} (<12 or ≥12 week subgrouping), (B) HIIT versus controls using VO_{2max} (<12 or ≥12 weeks subgrouping). END, endurance; HIIT, high intensity interval; VO_{2max} , maximal rate of oxygen consumption.

demonstrated a reduction in following intervention (IV=-0.65, 95% CI -4.29 to 0.99), although this result was not statistically significant ($p=0.66$) (figure 5A). A single data point (Nybo *et al*) was present for RET, which revealed a similar outcome (IV=-1.96, 95% CI -3.1 to -0.82) (online supplemental file 3C).¹⁸

Five studies containing post-interventional data with respect to HR_{max} found no significant change in the effect size following END irrespective of training duration (<12 weeks; IV=0.02, 95% CI -1.92 to 1.96; ≥12 weeks; IV=0.04, 95% CI -1.43 to 1.50) (figure 4A). A similar assessment using HIIT-based data demonstrated aligned outcomes (<12 weeks; IV=0, 95% CI -3.18 to 3.18, ≥12 weeks; IV=-0.23, 95% CI -3.67 to 3.22) (figure 4B). However, neither of these outcomes are statistically significant (figure 4B). With respect to RET, Lo *et al* and Hautala *et al* revealed similar effect sizes, although the findings were

also statistically non-significant (IV=0.42, 95% CI -3.81 to 4.65; IV=0, 95% CI -2.16 to 2.16, respectively) (online supplemental file 3C).^{52 53}

Within our dataset, only one study (Berger *et al*) presented data for END and HIIT pertaining to LT (online supplemental file 3C). The effect sizes in both indicated a comparable improvement in LT following 6 weeks of training with either modality (END; IV=0.68, 95% CI 0.23 to 1.13; HIIT; IV=0.71, 95% CI 0.36 to 1.06) (online supplemental file 3C).

Two studies (Warburton *et al*, Berger *et al*) contained data for PO changes following 6 and 12 weeks of END training, respectively (online supplemental file 3C).^{54 55} Both demonstrated a marginal improvement in PO (IV=1.08, 95% CI -28.93 to 31.09; IV=0.44, 95% CI -22.71 to 23.59, respectively) (online supplemental file 3C). In HIIT, interventions of less than 6 weeks demonstrated an overall

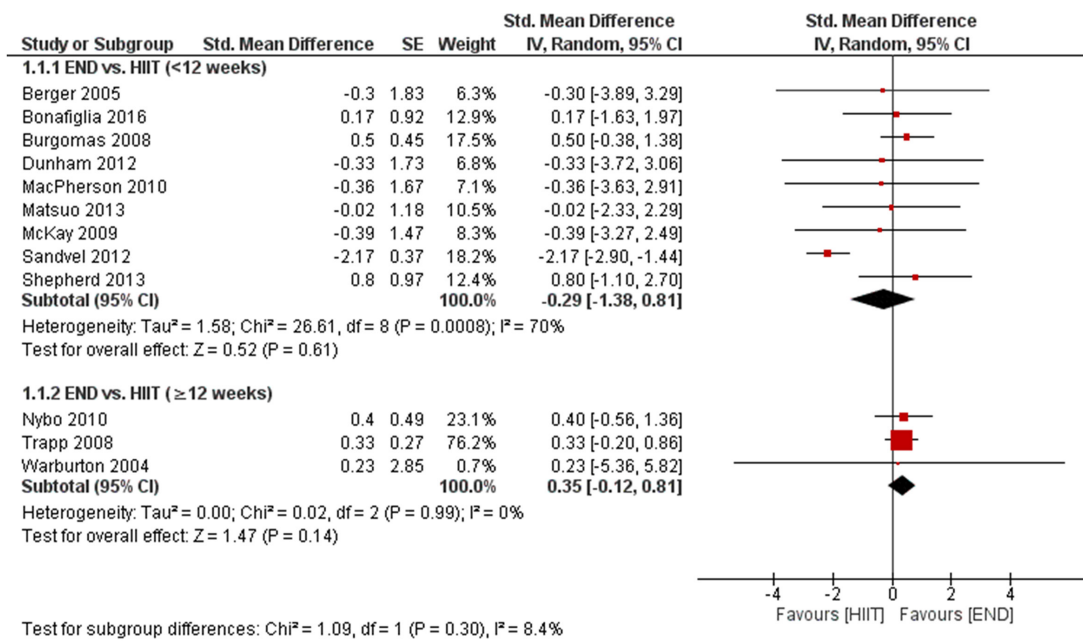


Figure 3 END versus HIIT using VO_{2max} (<12 or ≥12 weeks subgrouping). END, endurance; HIIT, high intensity interval training; IV, inverse variance; VO_{2max} , maximal rate of oxygen consumption.

effect size that suggested an improvement (IV=1.26, 95% CI -9.17 to 11.69), although this result was not statistically significant (figure 5B). No comparable data pertaining to improvements in PO following RET was observed in our dataset (online supplemental file 3C).

DISCUSSION

This systematic review and meta-analysis investigated the variability in reported responses to END, HIIT and RET. We found that various factors such as training modality, training duration and response indicators may affect the reported exercise training responses. HIIT demonstrated a significant effect size using VO_{2max} versus controls. Overall, END resulted in a significant improvement in CRF vs controls using VO_{2max} , but this was only statistically significant within our dataset examining training periods of 12 weeks or longer (figure 2A,B). Although HIIT demonstrated a similar pattern, the results were not found to be statistically significant (figure 2B). This finding contradicts an earlier meta-analysis performed in 2015, which assessed the responsiveness of END and HIIT in healthy adults between the ages of 18–45 years.³⁹ This difference may be due to our inclusion of studies including older cohorts, potentially reflecting an age-determined effect differential between exercise modalities. Age has previously been identified as a source of attenuation in exercise response—Earnest *et al* conducted an RCT study assessing 251 postmenopausal women over a 6 month period, where the intervention was exercise on a cycle ergometer at 4, 8 or 12 kcal/kg/week versus control (no exercise).⁵⁰ They were stratified into three groups based by age ≤55 years, 55–59 years and >60 years. The results indicated that the control group had

a reduction in maximal aerobic capacity by 1.6% (95% CI -4.8 to 1.0). Moreover, there was a reduced training response attributed to age and a correlation between age group and intervention ($p < 0.0002$).⁵⁰

Likely a consequence of the historically-attested reduced effect afforded by RET in improving CRF, a deficiency in data concerning RET and exercise response indicators of CRF was observed which limits our ability to form comparisons with END and HIIT data. As a consequence of this, the currently-available data cannot elucidate the potential for an improvement in VO_{2max} in untrained individuals through RET.³⁸ However, additional studies suggest a similar responsiveness to exercise when RET is compared with END. Pandey *et al* conducted a RCT with 202 diabetics for 9 months, where the interventions were aerobic training, resistance training or a combination of both.³⁰ The control group was a non-exercise group. The participants involved in exercise training were classified according to their ΔVO_{2max} , where fitness responders had a $\Delta VO_{2max} \geq 5\%$ and non-responders had a $\Delta VO_{2max} < 5\%$. There were a similar proportion of fitness responders in the aerobic training-only (31.3%) and resistance training-only (33.9%) groups. Fitness non-responders had a $\Delta VO_{2max} -0.07$ (95% CI -0.1 to 0.04) and fitness responders had a $\Delta VO_{2max} 0.24$ (95% CI 0.20 to 0.28), $p < 0.0010$.³⁰

Our findings concerning LT are partially in accordance with a recent cohort study in eleven moderately trained cyclists which determined that PO exhibited a more pronounced relationship with athletic performance than VO_{2max} .⁷¹ Our inconclusive outcome concerning LT appears to contradict earlier work, where a moderate positive correlation ($r^2 = 0.39$, $p < 0.05$) was inferred from a

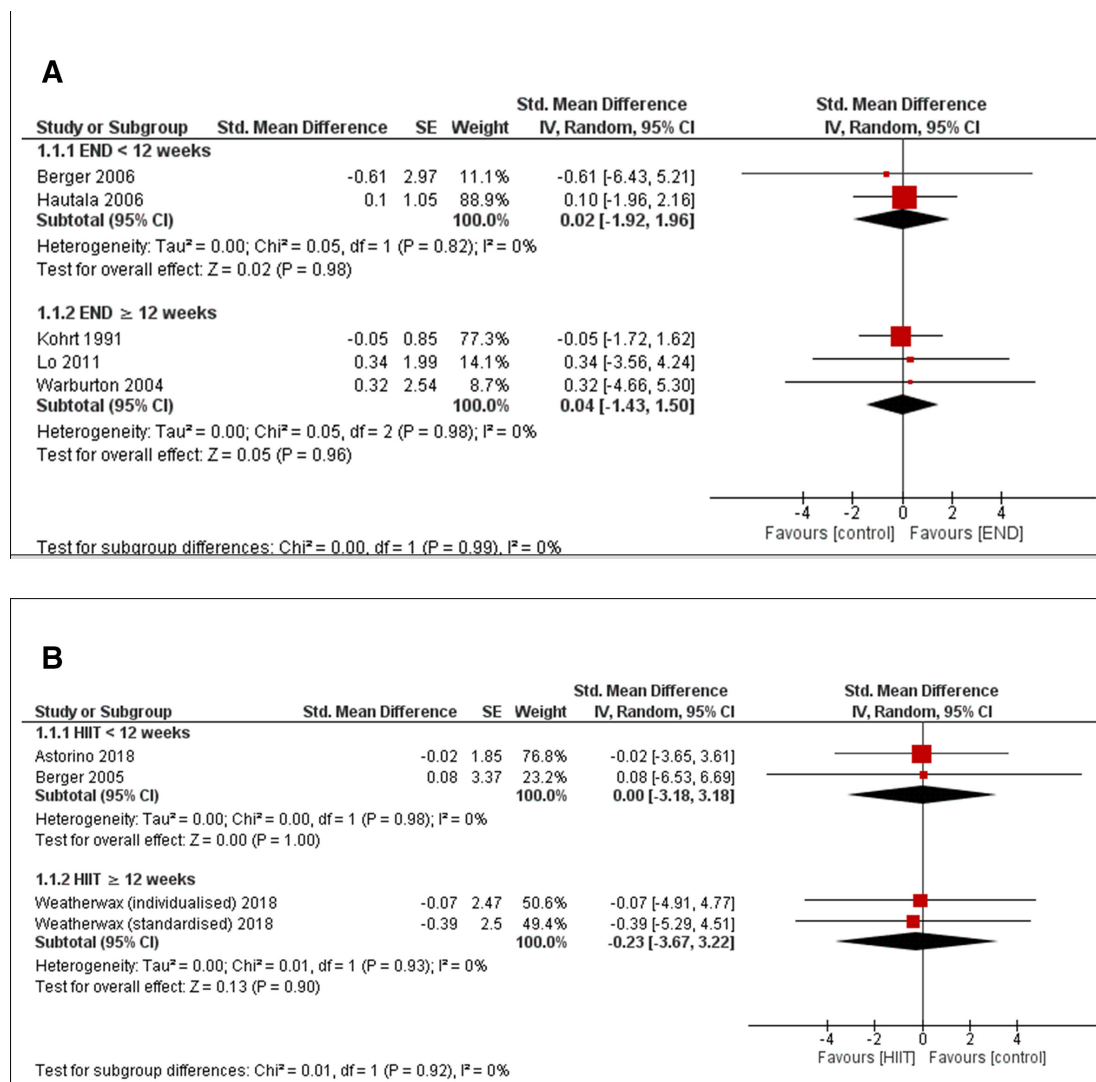


Figure 4 (A) END versus controls using HR_{max} (<12 or ≥12 weeks subgrouping), (B) HIIT versus controls using HR_{max} (<12 or ≥12 weeks subgrouping). END, endurance; HIIT, high intensity interval training; HR_{max}, maximum heart rate; IV, inverse variance.

prior cohort study assessing the effect of END in sedentary males.⁷²

Additional studies demonstrated similar outcomes—Yan *et al* conducted a multicentre study where they sought to recruit 200 individuals, to determine the response to one session of HIIT and 4 weeks of HIIT.⁵¹ In retrospect, they stated 39 individuals had done HIIT and found there was an average improvement in VO_{2max} of 3.85% (p<0.001) and an increase in LT of 9.01%±6.66% (p<0.001). Further, Gurd *et al* used data from five previously published studies that included 63 adults, to ascertain the response to sprint interval training protocols. Responders for VO_{2max} was 41% and for LT was 50%.⁴²

No data were assessed concerning the relationship between PO and RET, although this will ostensibly demonstrate an improvement due to the recognised development of skeletal muscle through type II fibre cross-sectional area increases, sarcoplasmic hypertrophy and neuromuscular efficiency.⁷³

A major limitation to our investigation is the ubiquitous heterogeneity in study design, intervention(s) and population characteristics were a recurrent feature in the assessed literature. A paucity in congruent measures restricted our ability to perform the appropriate multi-study subanalysis. Indeed, exercise intensity is an established variable in the determination of exercise response, as defined by group-wide changes to VO_{2max}. This was demonstrated by Ross *et al*, who conducted a RCT with 121 individuals that completed a minimum 90% of 5 weekly exercise sessions over a 24-week period. Although there was an increase in CRF in all three groups at 24 weeks (p<0.001), An increase in the intensity of exercise (when matched for volume) resulted in a decrease in the number of cardiorespiratory non-responders.⁴⁸

Similarly, the majority of comparisons incorporated data from studies that implemented differing exercise training protocols. This heterogeneity is reflected in the statistical data, where statistical heterogeneity is demonstrated (I² >50%) in the majority of the incorporated

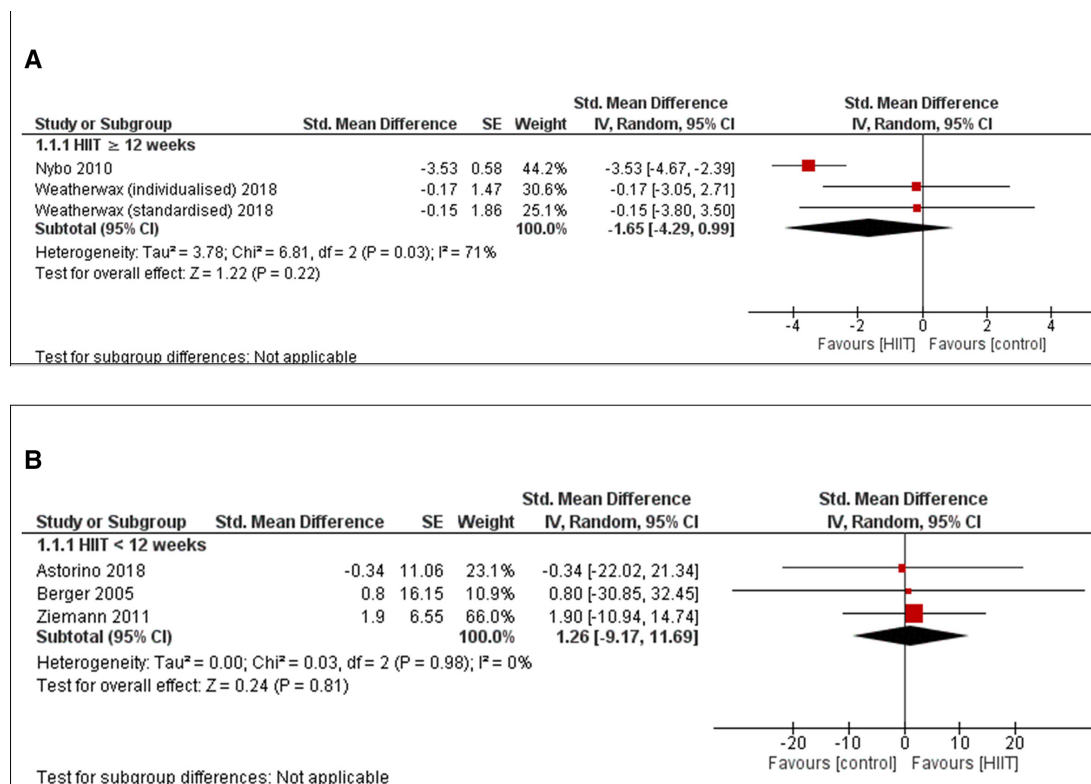


Figure 5 (A) HIIT versus controls using HR_{rest} (≥ 12 weeks subgrouping), (B) HIIT versus controls using PO (< 12 weeks subgrouping). HIIT, high intensity interval training; IV, inverse variance; PO, high intensity interval training.

forest plots. Furthermore, exercise response is a complex trait, with multiple innate and environmental factors implicated.⁷⁴ As such, the absence of further participant differentiation due to the paucity in data, in combination with an enumeration of the known variables in exercise responsiveness ('trainability'), represents a source of confounding.⁷⁵

The apparent heterogeneity described above likely contributes to the inability for all of the potential exercise response alternative indicators to achieve statistical significance (figures 2–5). However, some consistency in outcomes were nonetheless observed in our analyses. HR_{max} did not demonstrate any clear direction in effect size in either END or HIIT (figure 4A,B). Further to this, HR_{rest} was reliably reduced in END, HIIT and RET (figure 4). The potential for PO to serve as an alternative to VO_{2max} remains inconclusive based on the presented data (figure 5B), although our findings are not aligned with Montero and Lundby, who carried out an RCT with 78 individuals over a 6-week period, where they performed 60 min sessions per week of endurance training on a cycle ergometer.²⁸ The results from this study indicated that the more often exercise was performed, an improvement in both ΔVO_{2max} ($p < 0.001$) and in ΔW_{max} ($p < 0.001$) was observed.²⁸ As such, differing volume strategies and patient demographics between this study and those which achieved synthesis in our study are anticipated sources of confounding between these disparate results.

Differing criteria for exercise non-responsiveness in studies utilising VO_{2max} was observed, resulting in added

variability. This limitation was also present with other indicators. Lastly, cardiovascular-dependent indicators of exercise response typically require longer to elicit a change in comparison to VO_{2max} .⁷⁶ As such, we speculate that HR_{rest} may serve as a reliable alternative for all exercise modalities, particularly over longer time frames of intervention.

The lack of consistency with respect to the definition of exercise non-response³¹ using VO_{2max} requires addressing.⁷⁷ The utilisation of $\Delta > 0\%$, which was implemented in three studies, in our opinion is inappropriate given the acknowledged issue of measurement error.⁶² Bonafiglia *et al* derived an alternative approach, using response CI and the smallest worthwhile change.⁷⁸ Further elucidation on the relationship between VO_{2max} and PO across the different exercise modalities in the general population may indicate differing patterns of responsiveness. Similarly, the relationship between extrinsic factors and exercise indicators may yield differing effects on chronic adaptation in each exercise modality. Additionally, the relationship between the role of exercise indicators beyond VO_{2max} and the interference effect (the frequently observed diminishment of RET-specific adaptations to muscle size and function in a concurrent training setting)⁷⁹ may reveal novel or anticipatory patterns, which may predict this outcome. As such, future work investigating the potential relationship(s) and degrees of collinearity between intrinsic patient characteristics, intervention characteristics and the potential alternative exercise indicators of interest, preferentially through multivariate or meta-regression analyses, is advocated.

In addition to demonstrating current areas of uncertainty within the literature, the feasibility of alternatives to VO_{2max} for exercise response are tentatively substantiated through this work. Although safe, cardiopulmonary testing in physiological studies serves as an additional logistical consideration which is mitigated through the consideration of less-intensive measures, such as HR_{rest} .

In conclusion, our findings highlight the potential role of alternative indicators of exercise response in differing exercise modalities. Additionally, the constraints presented by extensive differences in study design, intervention type and duration, measurement variation and population characteristics require addressing in the literature. Our results suggest, dependent on the addressing of confounders, for HR_{rest} and LT to be explored further as viable alternatives to VO_{2max} .

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