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CALLUM, K., SWINTON, P., GORELY, T., CRABTREE, D. and LESLIE, S.

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Physiological and psychological outcomes of high intensity interval training in patients with heart failure compared to moderate continuous training and usual care: A systematic review with meta analysis

Kara Callum, Cardiac Physiologist [a,c,*], Paul Swinton [b], Trish Gorely [c], Daniel Crabtree [f], Stephen Leslie [e,d]

[a] NHS Highland, Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ, United Kingdom
[b] School of Health Sciences, Robert Gordon University, Aberdeen, United Kingdom
[c] Department of Nursing and Midwifery, University of the Highlands and Islands, Inverness, United Kingdom
[d] Division of Biomedical Sciences, University of the Highlands and Islands, Inverness, United Kingdom
[e] Cardiologist NHS Highland, Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ, United Kingdom
[f] Rowett Institute, University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom

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ABSTRACT

Background: An important component of secondary prevention of CVD (including HF) is comprehensive cardiac rehab, including exercise. Novel, individualised approaches are needed to increase uptake and adherence to exercise programmes, one area offering potential is HIIT. HIIT has been shown to be both safe and effective for improving cardiovascular fitness in both coronary artery disease and HF patients.
Objectives: To provide a current and up to date evaluation of the physiological and psychological outcomes of HIIT in patients with HF compared to MCT and UC. Secondly to perform sub-group analyses comparing short and long HIIT protocols.
Methods: A systematic review and meta-analysis of randomised controlled trials was undertaken. Medline, Embase, Scopus, CINAHL and SportDISCUS were searched up to July 2022. Trials were included if they carried out a HIIT intervention (defined at intensity $\geq$ 80% peak HR or $\geq$ 80% $VO2_{peak}$) in HF patients (HFpEF or HFrEF) for at least 6 weeks. Comparator group was UC or MCT.
Results: HIIT was shown to be superior to MCT and UC for improving VO_{2peak} (HIIT mean improvement 3.1 mL. $kg^{-1}min^{-1}$). HITT was superior to MCT and UC for improving LVEF (HIIT mean improvement 5.7%). HIIT was superior to MCT and UC for improving HRQoL, using the MLHFQ (HIIT mean point change of -12.8). Subgroup analysis showed no difference between long and short HIIT.
Conclusion: HIIT improves VO_{2peak}, LVEF and HRQoL in patients with HF, the improvements seen in VO_{2peak} and LVEF are superior in HIIT compared to MCT and UC.

Lay summary

This systematic review with meta-analysis synthesised evidence of outcomes in heart failure patients who undertook high intensity interval training, and assessed potential benefits compared to moderate continuous training and usual care.

High intensity interval training improves oxygen consumption, ejection fraction and quality of life in patients with heart failure. The improvements with high intensity interval training are on the whole superior to those with moderate continuous training and usual care

Introduction

Cardiovascular disease, including coronary artery disease and heart failure (HF) is the leading cause of death worldwide.[1] In the United Kingdom, around 920,000 people are affected by HF. Patients with HF

* Corresponding author at: NHS Highland, Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ, United Kingdom.
E-mail address: Kara.callum@nhs.scot (K. Callum).

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experience many symptoms including breathlessness, fluid retention, fatigue and marked reductions in exercise capacity.[2] Reduced exercise tolerance has been shown to be a relevant predictor of hospital readmission and mortality.[3]

An important intervention in the secondary prevention of cardiovascular disease is comprehensive cardiac rehabilitation (CR), which involves education, lifestyle behaviour modification, psychological support, and exercise.[4] Exercise training has been shown to be a safe and low cost intervention to improve HF symptoms and survival.[5] Most cardiac rehabilitation services in the National Health Service, however, do not feature specific HF programmes. In a national survey conducted in 2011/2012, it was found that only 16% of centres in the United Kingdom provided a specific rehabilitation programme for those with HF.[6] Clearly, novel approaches and new ways of thinking are required to increase participation and completion of cardiac rehabilitation programmes for patients with HF.

One area of growing interest is around the use of high intensity interval training (HIIT) which has been shown to be both safe and effective for improving cardiovascular fitness in both coronary artery disease and HF patients.[5,7] HIIT is defined as repeated short (<45 s) to long (2–4 min) bouts of high (not maximal) intensity exercise interspersed with recovery periods.[8] With such a broad definition, HIIT protocols vary widely, with physiological adaptations likely to be determined by intensity, duration and number of intervals performed, as well as the duration and intensity of recovery. Studies have shown that HIIT may be equal or superior to MCT in improving physiological parameters and health related markers in both coronary artery disease and HF.[9–12] HIIT also has the additional benefit of being relatively time efficient compared to MCT, with some preliminary data suggesting that many individuals report equal or greater enjoyment with HIIT compared to MCT.[13]

Despite increasing evidence supporting the use of HIIT for HF patients, there are few comprehensive systematic reviews assessing potential benefits in both physiological and psychological domains. Although there are previous systematic reviews concluding that HIIT is more effective than MCT for improving VO_{2peak},[10,14,15] none of these included usual care (UC) as an important comparator for greater understanding. There are also discrepancies with the inclusion criteria of these systematic reviews, for example Smart et al.[15] included comparator groups exposed to strength training as well as HIIT, and no clear definition of HIIT was provided. A systematic review conducted by Haykowsy et al.[10] included studies using 70% VO_{2peak} for HIIT interventions, which is below the widely accepted cut off of 80% VO_{2peak} for HIIT. Additionally, few systematic reviews have investigated the effects of HIIT on health-related quality of life (HRQoL) which is important information for health care providers supporting patients living with HF and a predictor of re-hospitalisation of patients with HF.

The aims of this systematic review with meta-analyses were firstly, to provide a current evaluation of the physiological and psychological outcomes of HIIT in patient with HF compared to MCT and UC, using clear and recognised HIIT parameters. Unlike previous systematic reviews and meta-analyses, both MCT and UC will be included as comparators, allowing the data from more HIIT studies to be reviewed. Secondly, to perform sub-group analyses comparing short and long HIIT protocols, which has not been conducted in HF patients. Meta-analyses were also conducted to relate any changes following HIIT with clinical minimally important differences (MID's) to place findings in a more clinically relevant context, which to our knowledge has not been included in previous meta-analyses. The use of MID's allows physiological improvements due to HIIT to be placed in a clinical context.

Methods

This systematic review was completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] The protocol was published in the Prospero database (https://www.crd.york.ac.uk/prospero) with registration number CRD42019138743. In a deviation to the original protocol, assessments of the confidence in cumulative evidence were made using the Grading of Recommendations Assessment Development and Evaluation (GRADE) framework.

Search strategy

The systematic literature search was performed using five online bibliographic databases (Medline, Embase, Scopus, CINAHL and SportDISCUS) for studies published up to July 2020. This search was then updated to include studies published up to July 2022. The search strategy was developed in collaboration with an information specialist (RP) and involved a combination of MeSH terms and free text terms with synonyms. The full electronic search strategy for the Medline database can be found in Appendix A. Reference lists of included studies were cross-checked to identify other studies that were not identified from the database searches.

Eligibility criteria

The studies included were restricted to randomised controlled trials with English full text articles available. Studies were included if they satisfied the following population, intervention, comparator, and outcome (PICO) criteria:

Population: Participants of any age diagnosed with HF, including both HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF).

Intervention: HIIT interventions were required to be at least 6 weeks in duration. HIIT programmes were limited to interval durations between 30 s and 4 min and interval intensities classified as ≥80% peak heart rate (HR) or a surrogate physiological measure (e.g., ≥80% VO_{2peak} or a rating of perceived exertion ≥15 on the Borg scale). No discrimination was made between active or passive recovery, but this was noted as part of the data extraction. Subgrouping of HIIT protocols were made with short HIIT ($HIIT_{short}$) categorised as exercise intervals of less than 2 min and long HIIT ($HIIT_{long}$) being categorised as intervals 2–4minutes.

Comparator: Usual care or MCT.

Outcomes: VO_{2peak}, left ventricular ejection fraction (LVEF) and HRQoL Not all outcome categories were required from each study.

Study selection and data extraction

Duplicates were removed following the electronic searches, and eligibility criteria applied to all title and abstracts. This process was carried out by two researchers (KC, SJL) independently, with a third researcher (TG) resolving any discrepancies. Full texts were then retrieved and independently assess for eligibility and adjudicated by the same researchers. Data from the screened texts were extracted using a form agreed by KC, SJL and TG describing baseline and study characteristics, details of the intervention and the control / comparator group, study methodology, study completion rates, outcome measurements and risk of bias assessments.

Quality assessment and confidence in cumulative evidence

The quality of the studies included was independently assessed by two assessors (KC, SJL) using the Cochrane Risk of Bias (RoB2) tool.[17] The two assessors independently assessed the risk of bias by using signalling questions to consider trial design, conduct and reporting. Disagreements were resolved by discussion, with involvements of a third reviewer (TG) where necessary. Overall assessments regarding the confidence in cumulative evidence were made using the GRADE guidelines.[18] Confidence in evidence was assessed at the outcome level with: (1) overall risk of bias ranked as high, low or some concerns, as

identified by the mode rating across all data in the specific analysis; (2) inconsistency assessed based on meta-analysis results and comparisons of location and variance parameter estimates; (3) imprecision judged by the number of available data points and the magnitude of uncertainty in the location parameter; (4) indirectness based on evaluation of the population, the HIIT intervention, the protocol for measuring the outcome, and indirectness of any comparisons; and (5) small study effects assessed by visual inspection of effect size distribution and sampling variance (downgraded when substantive number of points outside bounds). Overall confidence in evidence for each analysis was recorded as either high, moderate, low, or very low. Categorisations began with high confidence in cumulative evidence and were downgraded a level for each domain not judged as low risk.

Statistical analysis

Extracted data were transformed into both non-controlled mean difference effect sizes (for HIIT only) and pairwise-controlled effect sizes comparing mean differences between UC or MCT and HIIT. Non-controlled effect sizes were presented for HIIT only as this was the intervention of interest, with MCT and UC serving as comparators. Absolute value mean differences (post-intervention – pre-intervention) were selected to facilitate clinical interpretations and adapted for VO_{2peak}, LVEF and QoL outcomes assessed by the Minnesota living with heart failure questionnaire (MLHFQ). Analyses were also performed with standardised mean difference effect sizes. This was achieved by subtracting the mean difference from UC or MCT from the mean difference from the HIIT group and dividing by the pooled baseline standard deviation. Standard distributional assumptions were used to calculate effect size standard errors.[19] For QoL outcomes, the use of standardised mean difference effect sizes enabled pooling of data on results obtained by tools other than the MLHFQ. All results from standardised mean difference effect sizes are presented in Appendix B.

Most previous meta-analyses have been conducted within a frequentist framework where parameters such as the pooled mean effect size are estimated and uncertainty expressed with a 95% confidence interval (i.e. the values that would not be rejected by $p<0.05$).[20] However, confidence intervals contain no distributional information, such that there is no direct sense by which parameter values in the middle of the interval are more probable than the ends.[20] In contrast, Bayesian frameworks combine prior beliefs regarding the most plausible values with data to provide estimates that can be directly interpreted as probabilities. Results can therefore be interpreted intuitively, and more clinically relevant contexts can be addressed including calculating the probability that pooled estimates exceed thresholds such as established MID's. In the present meta-analysis, a Bayesian framework was implemented through two or three-level hierarchical models with random effects to account for variation in study mean effect and three-level models included where covariance of multiple outcomes (e.g. a single study comparing both UC and MCT with HIIT) were reported in the same study.[21]

Standard distributional assumptions for effect size standard errors including pre and post-intervention data require an estimate of their correlation which is rarely reported in studies.[19] To account for this uncertainty, a standard value of 0.7 was used to generate an informative prior for the correlation with variance included to account for correlations ranging from 0.5 to 0.9.[22] Weakly informative Student-t and Half-Student-t priors with 3 degrees of freedom and scale parameter equal to max(2.5, Median Absolute deviation) were used for location and all other variance parameters, respectively.[23] Inferences were performed on posterior samples generated by Hamiltonian Markov Chain Monte Carlo with Bayesian 95% and 75% credible intervals (CrI's) used for location and variance parameters, respectively. Interpretations were initially based on visual inspection of the posterior sample, the median value ($ES_{0.5}$: 0.5-quantile) and CrI's. MID values of 3.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$,[24] 5%[25] and −5[26] were used to interpret non-controlled mean differences for VO_{2peak}, LVEF and QoL, respectively, with the probability that the pooled effect size exceeded the MID calculated and interpreted. For non-controlled effect sizes, a regression covariate was also added to the meta-analysis model to estimate the pooled value for short and long HIIT protocols and assess the probability that these values were different. Analyses were performed using the R wrapper package brms, which interfaced with Stan to perform sampling.[27] Convergence of parameter estimates was obtained for all models with Gelman-Rubin R-hat values below 1.1. Where outliers were present, sensitivity analyses were conducted by repeating the analysis with the outlier removed and both sets of estimates presented.

Results

Search results

Fig. 1 illustrates the flow of studies through the systematic review, including the search and screening process. Thirty-six studies were screened at full text with 21 excluded based primarily on exercise protocols failing to meet inclusion criteria (reasons for exclusion are presented in Fig. 1. A total of 15 studies were included from the initial search and following the updated search one additional study was added, making a total of 16 included studies.

Study characteristics

Across the 16 studies[9,28–42] 1094 (482 for HIIT, 266 for MCT and 346 for UC) patients were included. There was a slight male dominance, with 65% of participants reported as male. In contrast, two individual studies compromised a majority of females[33,36] and interestingly these two studies were solely for those patients with HFpEF. Patient characteristics across individual studies are presented in Table 1.

Protocols for HIIT and MCT programs were reported in all studies and are summarised in Table 2. Training intensity was determined by percentage VO_{2peak} in five studies, by percentage HR_{peak} in five studies, by percentage max workload / rate and percentage peak power output (PPO) in three studies, by Borg scale in two studies, and by percentage of heart rate reserve (HRR) in one study. The median program length for both HIIT and MCT programs was 12 weeks across all studies and median sessions per week was 3 for both HIIT and MCT. Twelve studies were classified as comprising $HIIT_{long}$ protocols and 4 studies as comprising $HIIT_{short}$ protocols. Seven studies compared HIIT to UC and nine studies compared HIIT to MCT. MCT protocols intensities ranged from 35% to 75%, 1 study, by Mueller was a lower intensity of 35–40%, with one other study reporting intensities of 40–60% and all other studies reporting intensities between 50 and 75%.

There was a range in modalities for training used, the HIIT studies were made up of 9 x bike, 2 x treadmill, 1 x bike or treadmill, 3 x aerobics and 1 not reported. In the MCT studies 6 were using bikes, 2 treadmills and 1 bike or treadmill.

Risk of bias summary /GRADE ASSEMENT

Using the ROB2 tool agreement between researchers was 87%, this rose to 100% after discussion. Using the ROB2 tool, all but one study[30] were scored as having a low risk of bias. Benda et al. [37] was scored as having some concerns, due to limitations in the randomisation process. Confidence in evidence as established by the GRADE assessment is presented in Appendix C. For non-controlled effects sizes, confidence was generally low or very low due to imprecision, inconsistency, and evidence of small-study effects. Confidence was higher for assessments with controlled studies due to improvements in all three areas.

Non-Controlled effect sizes

An initial assessment of the effectiveness of HIIT interventions was

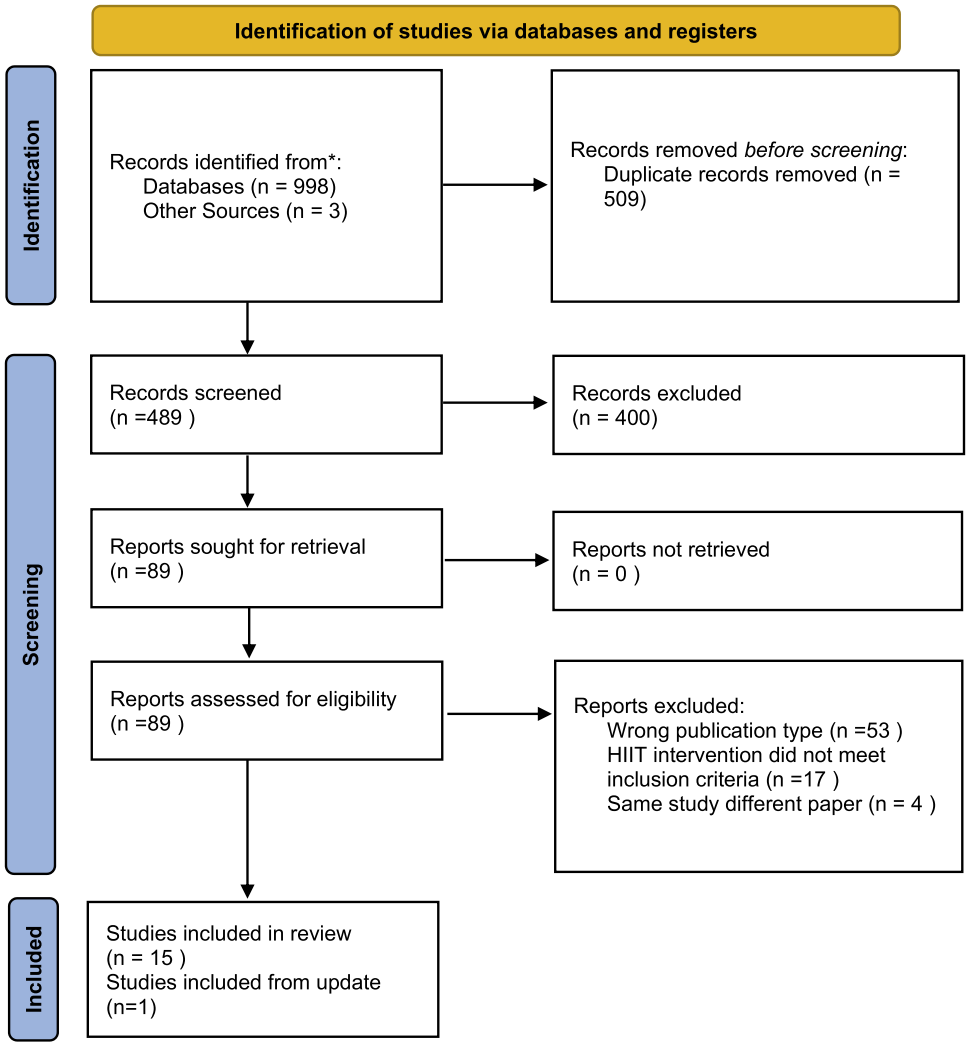

Fig. 1. PRISMA flow diagram of systematic review screening process.
Abbreviations: PRISMA, preferred Reporting Items for Systematic Reviews and Meta-analysis; HIIT, High Intensity Interval Training. Total number of studies included in review after screening = 16.

conducted through non-controlled mean difference effect sizes, enabling comparisons of pooled estimates with MCID values.

- VO_{2Peak}

Data from 13 studies and 381 participants were included in the meta-analysis generating a pooled effect size estimate of $ES_{0.5} = 3.1$ [95%Cri: 1.8 to 4.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$] and between study standard deviation of $\tau_{0.5} = 2.2$ [75%Crl: 1.7 to 2.9 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$]. The probability that the pooled effect size exceeded zero and the MID of 3.5 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ was $p>0.999$ and $p = 0.264$, respectively (Fig. 2), with very low confidence in the evidence identified.

- *LVEF*

Data from 10 studies and 244 participants were included in the meta-analysis generating a pooled effect size estimate of $ES_{0.5} = 5.7$ [95%Cri: 2.2 to 9.1%] and between study standard deviation of $\tau_{0.5} = 5.22$ [75% Crl: 3.9 to 7.1%]. The probability that the pooled effect size exceeded zero or the MID of 5% was $p = 0.998$ and $p = 0.666$, respectively (Fig. 2), with very low confidence in the evidence identified.

- *HRQoL assessment*

A total of 12 studies investigated QoL outcomes, with 8 studies and 190 participants completing the MLHFQ. With negative change scores representing an improvement in QoL, the meta-analysis generated a pooled effect size estimate of $ES_{0.5}=-12.8$ [95%Cri: −20.3 to −5.6] and between study standard deviation of $\tau_{0.5} = 13.6$ [75%Crl: 10.6 to 18.2]. The probability that the pooled effect size was less than zero or the MID of −5 was $p>0.999$ and $p = 0.982$, respectively (Fig. 2), with very low confidence in the evidence identified. A single large outlier was identified (mean difference: −48.3, Zaky 2018[30]) and removed to conduct a sensitivity analysis, producing more consistent estimates ($ES_{0.5} = -9.6$ [95%Cri: −13.5 to −5.5 points; $\tau_{0.5} = 4.6$ [75%Crl: 2.7 to 7.3 points]). Meta-analysis results using standardized mean difference effect sizes enabling pooling of QoL results across 12 studies are presented in Appendix B and provided evidence of an improvement beyond zero (p00.994).

- *Long and short HIIT Intervals*

Comparisons between long and short HIIT protocols are presented in Table 3, with limited evidence to show a difference in mean improvement between the conditions (VO_{2peak}: short>long $p = 0.337$; LVEF: short>long $p = 713$; QoL: short<long $p = 0.867$).

Table 1
Baseline and patient characteristics all studies.

Study	NYHA Class	Comparator Group	Sample Size (n)			Male (%)			Age (years)			LVEF (%)			Peak VO2 (mL/min/kg)		
			HIIT	UC	MCT	HIIT	UC	MCT	HIIT	UC	MCT	HIIT	UC	MCT	HIIT	UC	MCT
Benda 2015	II-III	MCT	10		10	90		100	63±8		64±8	37±6		38±6	19.1 ± 4.1		21.0 ± 3.4
Byrkjeland 2011	II-IIIB	UC	40	40		75	83		68.8 ± 7.9	71.5 ± 7.8		30.2 ± 7.6	30.8 ± 9.4				
Chou 2019	II-III	UC	17	17		71	71		60.9 ± 0.5	59.7 ± 5.3		36.1 ± 5.2	34.7 ± 5.1		15.8 ± 4.0	15.9 ± 3.5	
Chrysohoou 2014	I-IV	UC	50	50		88	72		63±9	56±11		31	32		(max) 16±6	(max) 17±6	
Donelli da Silveira 2020	II-III	MCT	12		12	30		44	60±10		60±9	65±5		65±5	16.1 ± 3.3		17.6 ± 3.5
Ellingsen 2017	II-III	MCT and UC	77	60	65	82	81	82	65 (58–68)	60 (55–65)	60 (58–65)	29 (26–31)	30 (28–32)	29 (26–32)	16.8 (15.8–17.8)	18.4 (16.8–19.6)	16.2 (15.5–18.7)
Fu 2013	II-III	MCT and UC	15	15	15	67	67	60	67.5 ± 1.8	67.8 ± 2.5	66.3 ± 2.1	38.3 ± 3.5	38.0 ± 3.8	38.6 ± 4.8	16.0 ± 1.0	17.5 ± 1.5	15.9 ± 0.7
Koufaki 2014	I-III	MCT	16		17	88		76	59.8 ± 7.4		59.7 ± 10.8	41.7 ± 10.3		35.2 ± 6.4	14.6 ± 4.8		14.6 ± 4.8
Mueller 2021	II-III	MCT and UC	58	60	58	29	32	40	70±7	69±10	70±8				18.9 ± 5.4	19.4 ± 5.6	18.2 ± 5.1
Nilsson 2008	II-III	UC	40	40		78	80		69±8	72±8							
Papathanasiou 2020	II-III	MCT	60		60	58		58	63.65 ±6.71		63.82 ±6.71	35.88 ±2.3		36.03±2	13.49±3.7		12.51±3.5
Santa-Clara 2019	III-IV	UC	34	29		77	75		68±2	67±2		27.0 ± 1.4	25.5 ± 1.6		14.0 ± 1.4	17.4 ± 1.7	
Spee 2020	II-III	UC	12	12		100	58		68.9 ± 6.7	68.8 ± 6.5		26.9 ± 7.9	30.2 ± 6.6		19.4 ± 6.7	18.5 ± 6.3	
Spee2016	II-III	UC	12	14		83	93		58±7.8	66.5 ± 8.7		33±9	32±12		20.8 ± 5.4	20.2 ± 6.0	
Wisloff 2007	n/a	MCT and UC	9	9	9	78	67	78	76.5 ± 9	75.5 ± 13	74.4 ± 12	28.0 ± 7.3	26.2 ± 8	32.8 ± 4.8	13.0 ± 1.6	13.2 ± 1.9	13.0 ± 1.1
Zaky 2018	II-III	MCT	20		20	100		100	54±2.72		52.8 ± 11.58	37±1.94		37.45 ±3.05			

Table 2
Summary of HIIT and MCT protocols for all studies.

Study	HIIT PROTOCOL							MCT PROTOCOL				
	Mode of Exercise	Intensity	Exercise Interval	Rest Interval	Repeat	Times per week	Programme Duration (weeks)	Mode of Exercise	Intensity	Exercise Duration	Times per week	Programme Duration (weeks)
Benda 2015	Bike	90% max workload	1 min	2min30sec	10	2	12	Bike	60–75% max workload	30 min	2	12
Byrkjeland 2011	Aerobics	15–18 Borg	5–10 min	not stated	3	2	16	Usual Care				
Chou 2019	Bike	80% peak VO2	3 min	3 min	5	3	12	Usual Care				
Chrysohoou 2014	Bike	80% peak WR	30 secs	30 secs	45	3	12	Usual Care				
Donelli da Silveira 2020	Treadmill	80–90% peak VO2	4 min	3 min	4	3	12	Treadmill	50–60% peak VO2	47min	3	12
Ellingsen 2017	Treadmill / Bike	90–95% max HR	4 min	3 min	4	3	12	Treadmilll / Bike	60–70% max HR	47 min	3	12
Fu 2013	Bike	80% peak VO2	3 min	3 min	5	3	12	Bike	60% peak VO2	30 min	3	12
Koufaki 2014	Bike	100% PPO	30 secs	1 min	2 × 10	3	24	Bike	40–60% peak VO2	40 min	3	24
Mueller 2021	Bike	80–90% HR reserve	4 min	3 min	4	3	12	Bike	35–40% HR reserve	40 min	5	12
Nilsson 2008	Aerobics	15–18 Borg	5–10 min	not stated	3	2	16	Usual Care				
Papathanasiou 2020	Aerobics	15–18 Borg / 90% max HR	5–10 min	not stated	3	2	12	Bike	70% HR max	40 min	2	12
Santa-Clara 2019	not stated	90–95% max HR	4 min	3 min	4	2	24	Usual Care				
Spee 2020	Bike	85–95% peak VO2	4 min	3 min	4	3	12	Usual Care				
Spee2016	Bike	85–95% peak VO2	4 min	3 min	4	3	12	Usual Care				
Wisloff 2007	Treadmill	90–95% peak HR	4 min	3 min	4	3	12	Treadmill	70–75% peak HR	47 min	3	12
Zaky 2018	Bike	90–95% peak HR	1 min	4 min	6	3	12	Bike	60–75% peak HR	30 min	3	12

Controlled effect sizes

To compare the effectiveness of HIIT relative to UC or MCT, pairwise controlled effect sizes were calculated, and forest plots used to illustrate the results (Figs. 3–5).

- VO_{2Peak}

Data from 12 studies were included with 7 pairwise effect sizes comparing HIIT with UC ($n = 399$) and 8 pairwise effect sizes comparing HIIT with MCT ($n = 422$). Consistent evidence (Fig. 3) was obtained showing improvements in VO_{2peak} were superior with HIIT compared with both UC ($ES_{0.5} = 4.0$ [95%Crl: 2.1 to 5.9 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$]; $p>0.999$; high confidence) and MCT ($ES_{0.5} = 1.6$ [95%Crl: 0.4 to 2.7 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$]; $p>0.992$; high confidence). A combined analysis also identified that the superiority of HIIT was likely to be greater relative to UC rather than MCT ($p = 0.998$).

- *LVEF*

Data from 10 studies were included with 5 pairwise effect sizes comparing HIIT with UC ($n = 248$) and 7 pairwise effect sizes comparing HIIT with MCT ($n = 395$). Evidence (Fig. 4) was obtained that improvements in LVEF were superior with HIIT compared with both UC ($ES_{0.5} = 3.9$ [95%Crl: −3.0 to 9.8%]; $p = 0.892$; low confidence) and MCT ($ES_{0.5} = 3.0$ [95%Crl: 0.4 to 6.0%]; $p = 0.985$; low confidence), however, substantive uncertainty was obtained in estimates including UC.

- *HRQoL Assessment*

Data from 8 studies were included with 3 pairwise effect sizes comparing HIIT with UC ($n = 172$) and 5 pairwise effect sizes comparing HIIT with MCT ($n = 216$). Evidence (Fig. 5) was obtained showing absolute improvements in QoL from the MLHFQ were superior with HIIT compared with both UC ($ES_{0.5} = -13.0$ [95%Crl: −16.0 to −10.0]; $p>0.999$; high confidence) and MCT ($ES_{0.5} = -2.7$ [95%Crl: −5.4 to 1.0]; $p = 0.926$; moderate confidence). A combined analysis also identified that the superiority of HIIT was likely to be greater relative to UC rather than MCT ($p = 0.996$). Meta-analysis results using standardized mean difference effect sizes enabling pooling of QoL results across 12 studies are presented in Appendix B and provided some evidence of a superiority of HIIT compared with UC ($p = 0.939$). However, evidence comparing HIIT with MCT was equivocal ($p = 0.317$).

Other reported health outcomes

Although out with the scope of this meta analyses some of the studies also reported other physiological health outcomes. Five studies[9,30,33,36,42] reported on measures of diastolic dysfunction, such as E/e' and strain measured by echo. Four[9,30,36,42] also reported on vascular function and structure as determined by flow mediated dilation (FMD). Three[9,31,36] measured NT pro-BNP. Other blood work was also carried out by some studies to allow reporting on TNFα, CRP and other inflammatory markers,[31] platelet mitochondrial oxygen consumption (OCR),[28] cerebral and muscular haemodynamics,[29] skeletal muscle oxygenation[41] and mitochondrial function.[9]

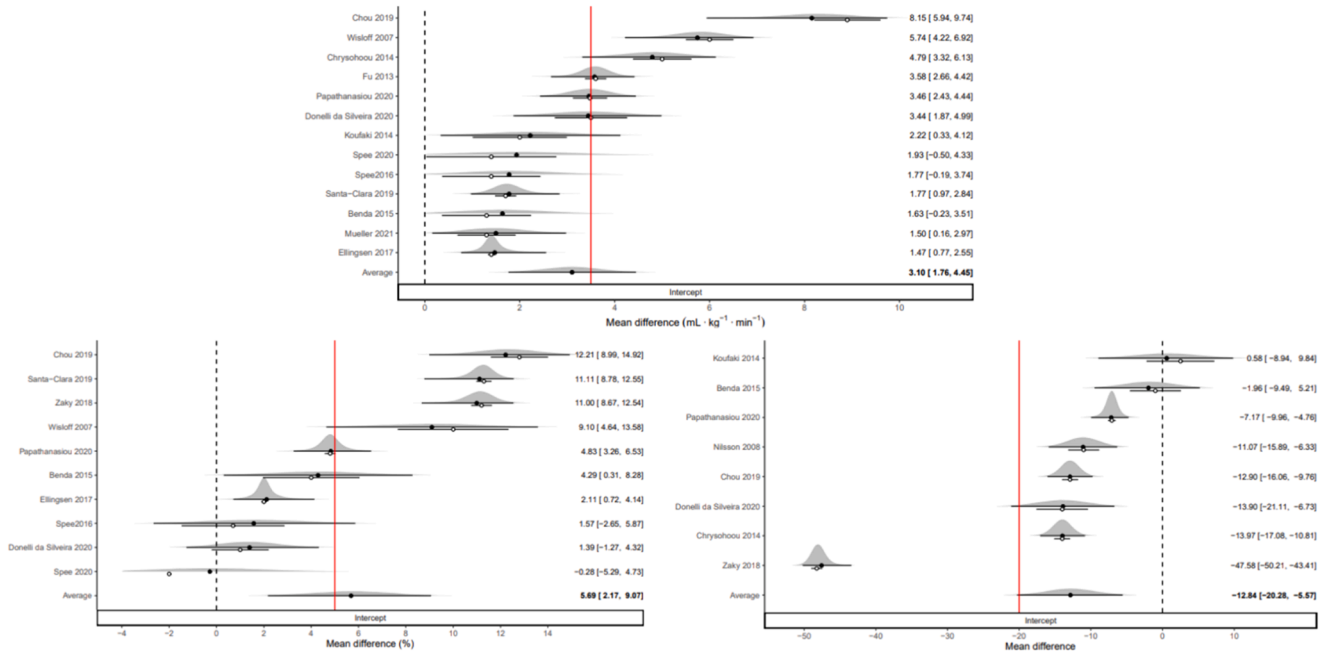

Fig. 2. Forest plots of non-controlled high intensity interval training effect sizes for VO_{2peak} (top), left ventricular ejection fraction (bottom left), and Quality of life (bottom right).
Distributions represent "shrunken estimates" based on all effects sizes included, the random effects model fitted and borrowed information across studies to reduce uncertainty. Black circles and connected intervals represent the median value and 95% credible intervals for the shrunken estimates. White circles and intervals represent the raw estimates and sampling variance calculated directly from study data. Vertical red lines illustrate minimum important differences.

Table 3
Results from meta-regressions comparing short and long high intensity interval training protocols with non-controlled effect sizes and minimal important differences (MIDs).

Moderator		Pooled Estimate [95% CrI]	Probability exceed MID	Between study SD τ [75%CrI]	Confidence in evidence	Probability comparison
VO_{2peak}						
[*Protocol Length*]	Short (η=3)	2.7 [0.0 to 5.1 mL·kg^{-1}·min^{-1}]	0.223	1.9 [0.9 to 3.5 mL·kg^{-1}·min^{-1}]	Moderate	P(Short > Long) = 0.337
	Long (η=9)	3.5 [1.8 to 5.4 mL·kg^{-1}·min^{-1}]	0.514	2.5 [1.8 to 3.5 mL·kg^{-1}·min−1]	Moderate	
Left ventricular ejection fraction (LVEF)						
[*Protocol Length*]	Short (η=2)	8.0 [−1.1 to 14.1%]	0.830	4.6 [2.3 to 8.8%]	Low	P(Short > Long) = 0.713
	Long (η=8)	4.9 [0.92 to 8.6%]	0.483	5.3 [3.9 to 7.6%]	Very low	
Quality of Life (QoL)						
[*Protocol Length*]	Short (η=3)	−18.6 [−46.9 to 9.7]	0.853	25.7 [16.7 to 42.9]	Very low	P(Short < Long) = 0.868
	Long (η=5)	−9.7 [−13.7 to −5.7]	0.989	3.8 [2.1 to 6.3]	High	

η is the number of effect sizes included in the analysis. Positive pooled effect sizes represent improved outcomes for VO_{2peak} and LVEF. Negative effect sizes represent improvement in QOL. CrI: Credible interval.

Discussion

This systematic review with meta-analyses provides clear evidence that HIIT produces improvements in VO_{2peak}, LVEF and HRQoL in patients living with HF (both HFpEF and HFrEF). The data from the meta analyses also allows these improvements to be placed in a clinical context by using MID's. Across all included studies there was clear evidence that HIIT improves $VO2_{peak}$ with a pooled mean improvement of 3.1 mL·kg^{-1}·min^{-1}. Findings show a relatively low probability that mean improvement in $VO2_{peak}$ would exceed the MID of 3.5 mL·kg^{-1}·min^{-1}, however, improvements are expected to be relatively heterogeneous due to factors including the HIIT protocol and patient characteristics. There was a high probability that HIIT was superior to both MCT and UC for improved $VO2_{peak}$. Meta analyses by Smart, Haykowsky, Gomes Neto and Garcia[10,14,15,43] also found that interval training was more effective than MCT for improving $VO2_{peak}$, in patients with stable HFrEF. This systematic review adds additional data demonstrating the improvements in $VO2_{peak}$ also possible for patients living with HFpEF.

$VO2_{peak}$ is a well-recognised predictor of prognosis in HF patients,[44] the mechanisms by which HIIT elicits greater changes in $VO2_{peak}$ are likely due to intensity-dependant improvements in cardiovascular and skeletal muscle function.[29,45,46]

If cardiac contractility and left ventricular filling is improved because of HIIT interventions, then it would be expected that LVEF would consequently be improved. Previous reviews and individual studies have proved inconclusive.[10,47] Haywcowsky et al.[48] reported that HIIT did improve LVEF but was not more effective that MCT,

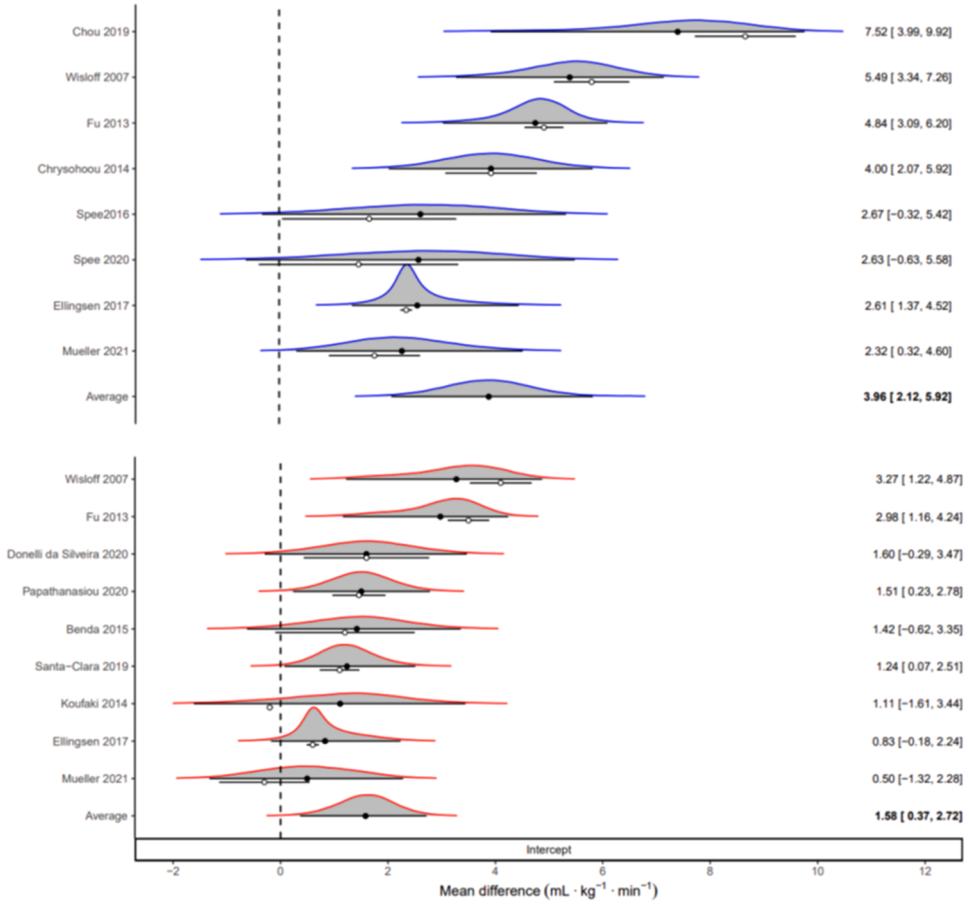

Fig. 3. Forest Plot of VO2peak controlled effect sizes comparing high intensity interval training with usual care (top: blue), and moderate continuous training (bottom: red).
Distributions represent "shrunken estimates" based on all effects sizes included, the random effects model fitted and borrowed information across studies to reduce uncertainty. Black circles and connected intervals represent the median value and 95% credible intervals for the shrunken estimates. White circles and intervals represent the raw estimates and sampling variance calculated directly from study data.

whereas Tucker et al.[47] reported that HIIT was superior to usual care but not to MCT. Contrary to these findings, the results from the present review provide clear evidence that HIIT improves LVEF with a mean improvement of 5.7% across all included studies. Additionally, there was high probability that HIIT was superior to both MCT and UC for improving LVEF, however, confidence in the evidence was limited by imprecision and variability across studies. It is worth noting that measurement of LV function by echo may not be sufficiently precise or repeatable to pick up small changes. Despite this, it is well established that improvement in LVEF can reduce breathlessness and improve quality of life. Additionally, the meta-analyses in the present review included two studies with HFpEF patients which also provided evidence of improvement in LVEF.

The ability of an intervention to improve HRQoL for patients is beneficial not only to the patient but for healthcare providers. Patients clearly feel better with an improved HRQoL but it has also been proven that HRQoL is a predictor of hospital readmission for patients with HF,[49] thereby improving a patient HRQoL can reduce pressure on hospitals and healthcare professionals. This meta-analysis showed that HIIT improves HRQoL with a pooled mean change of −12.8 points for those studies using the MLHFQ. This is far beyond the MID of a difference of 5 points having been shown to represent a clinically important meaningful difference for patients.[50] Improvements in HRQoL presented here are in agreement with previous systematic reviews by Sagar et al.[51]and an updated review by Long et al.[52] Although these systematic reviews investigated all exercise interventions and were not specific to HIIT. To our knowledge this is the first systematic review and meta-analyses that has shown the positive effects on HRQoL as a result of a HIIT intervention. It is also important to recognise that the findings from this systematic review include all patients with HF (i.e., HFrEF and HFpEF), whereas previous reviews have only included those with HFrEF.

The results from this meta-analysis also show that improvements in all three outcome measures are likely to be superior with HIIT compared to UC (VO_{2peak}: $p>0.999$; LVEF: $p = 0.892$; HRQoL: $p>0.999$) and MCT (VO_{2peak}: $p = 0.992$; LVEF: $p = 0.985$; HRQoL: $p = 0.926$). In general, an ordered effect was identified with the greatest improvements obtained with HIIT, followed by MCT then UC. Confidence in the evidence was, however, frequently low and very low, due primarily to imprecision and inconsistency in meta-analysis estimates, and associated evidence of small study-effects. The results show that mean improvements in HRQoL are in general expected to exceed the MID ($p = 0.982$). In contrast, mean improvements in LVEF ($p = 0.666$) and VO_{2peak} ($p = 0.264$) may be unlikely to exceed the MID; however, mean improvements are expected to be relatively heterogeneous due to factors including the HIIT protocol and patient characteristics.

Sub-group analyses of $HIIT_{long}$ and $HIIT_{short}$ did not indicate any difference in outcomes dependant on interval duration. However, there was limited data, with a high degree of uncertainty. To draw conclusions further research is needed with an emphasis on shorter HIIT protocol. Although not significant the biggest difference in outcome was for the measure of HRQoL, with greater improvements seen in $HIIT_{short}$, which could in part be attributed to patients' perception of their abilities. Meyer et al.[53] conducted a study investigating the effects of short duration (30secs) HIIT compared to moderate duration (90secs), with

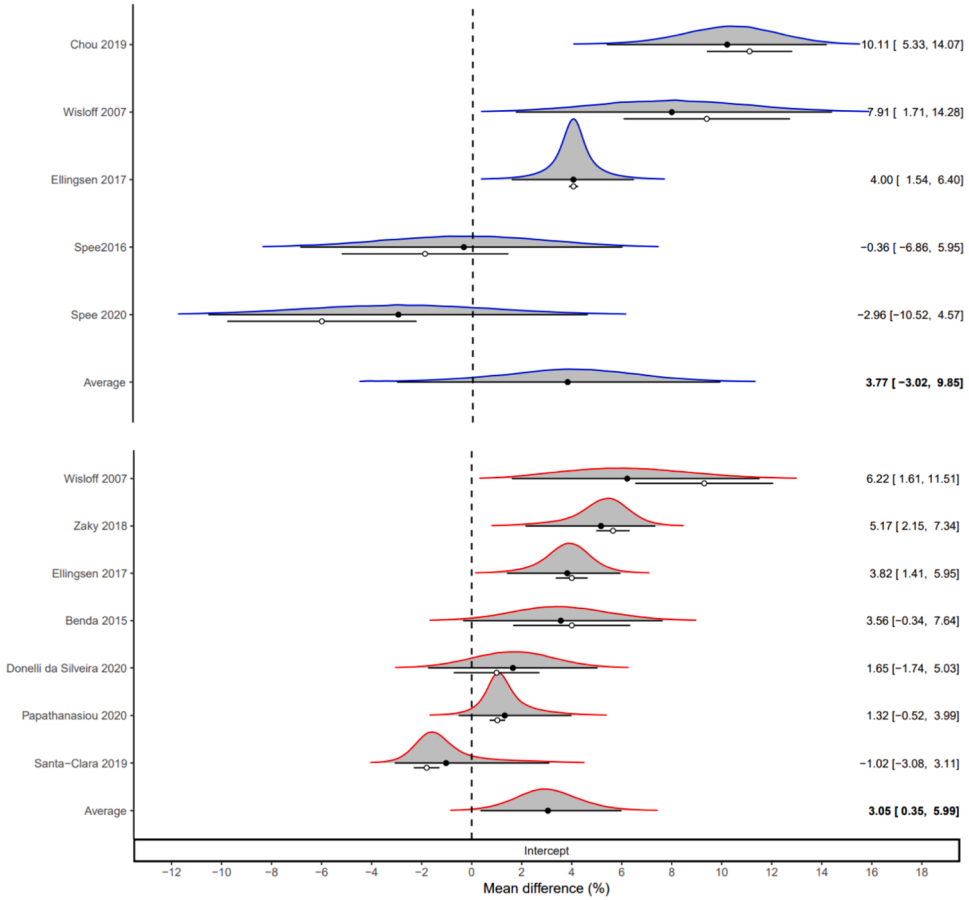

Fig. 4. Forest Plot of left ventricular ejection fraction controlled effect sizes comparing high intensity interval training with usual care (top: blue), and moderate continuous training (bottom: red).
Distributions represent "shrunken estimates" based on all effects sizes included, the random effects model fitted and borrowed information across studies to reduce uncertainty. Black circles and connected intervals represent the median value and 95% credible intervals for the shrunken estimates. White circles and intervals represent the raw estimates and sampling variance calculated directly from study data.

the main finding being that patients were more likely to complete the prescribed exercise and had a lower rate of perceived exertion despite a similar time spent at VO_{2peak} for short duration HIIT. These findings are consistent with those of Garcia et al.[54] who also found no significant differences between HIIT interval durations. Although studies investigating the optimal protocol are limited, the findings here support the assumption that HIIT should not be viewed as a 'one size fits all approach' and that a degree of variation in protocol can still elicit positive outcomes.

Previous meta-analyses have shown that HIIT is safe for patients with HF[5] and that it is effective in improving VO_{2peak},[54] however, it is worth noting these studies have only included HFrEF patients. This systematic review and associated meta-analyses have added to these data showing that HIIT in all HF patients is effective in improving VO_{2peak}, LVEF and HRQoL. Demonstrating that HIIT is an effective exercise modality for patients with HF, the nature of HIIT and the intensities / exercises involved may not be suitable for all patient with HF and programs should be tailored towards patients' needs and preferences. Presenting a more individualised approach to CR for HF patients, as described in current guidelines.[55–58] In order to fully individualise CR care for HF patients it is also important to understand barriers to interventions in order to deliver CR and HIIT in a way which is feasible and accessible to patients.

Limitations

Following the GRADE assessment confidence in evidence was generally low, and this was primarily due to imprecision caused by pooling of results from heterogeneous studies and small study effects. A limitation of this work is the lack of investigator blinding in outcomes assessments. There were also differences between protocols of included studies, and not all studies reported actual intensities achieved, only the prescribed intensity. Although HIIT protocols had a strict inclusion criteria this systematic review did not have a strict inclusion criteria for MCT protocols which did lead to a variation in intensities prescribed. Several studies did not report if there were any adverse events, it is unknown if this is because there were in fact no adverse events, or simply not reported. Although the search strategy was designed to not exclude HFpEF, this group of patients are possibly sub-represented in this meta analysis, with only two studies included investigating those patients with HFpEF.

Conclusion

HIIT improves VO_{2peak}, LVEF and HRQoL in patient with HF, the improvements seen in VO_{2peak} and LVEF are superior in HIIT compared to MCT and UC. Although it is recognised that larger and longer-term studies are needed to address deficiencies in current evidence, HIIT has the potential to offer an effective method of CR for patients living with HF.

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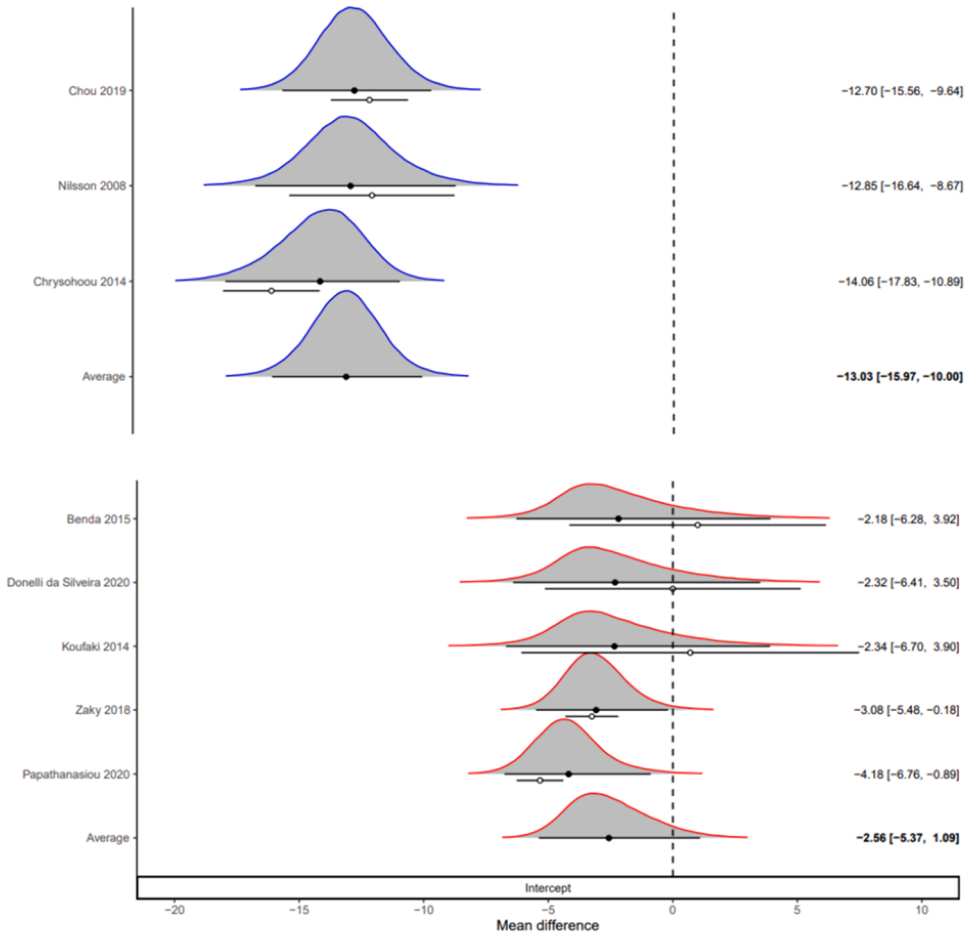

Fig. 5. Forest Plot of quality of life controlled effect sizes comparing high intensity interval training with usual care (top: blue), and moderate continuous training (bottom: red).
Distributions represent "shrunken estimates" based on all effects sizes included, the random effects model fitted and borrowed information across studies to reduce uncertainty. Black circles and connected intervals represent the median value and 95% credible intervals for the shrunken estimates. White circles and intervals represent the raw estimates and sampling variance calculated directly from study data.

Declaration of Competing Interest

None of the authors have any conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2023.12.002.

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Search history sorted by search number ascending

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8	1 or 2 or 3 or 4 or 5 or 6 or 7	527687
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23	21 and 22	5667
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25	8 and 24	402
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☐	29	exp consumer health information/	3608
☐	30	patient participation/	25310
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☐	43	preferenc*.af.	189350
☐	44	(client* opinion* or opinion*client* or client* attitud* or attitud* client* or client* satisfaction* or satisfaction* client* or client* preferenc* or preferenc* client).af.	1855
☐	45	(customer* opinion* or opinion* customer* or customer* attitud* or attitud* customer* or customer* satisfaction* or satisfaction* customer* or customer* particpat* or participat* customer* or customer* preferenc* or preferenc* customer*).af.	1368
☐	46	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45	3064503
☐	47	25 and 46	48

Appendix B: Meta-analysis results for mean difference standardized effect sizes

In text results are presented for the three outcome variables in the actual measurement scale. Here we present meta-analyses of standardised mean difference effect sizes. First we present non-controlled effect sizes for the HIIT groups only. Controlled effect sizes are then presented relative to both usual care and moderate continuous training.

Non-Controlled effect sizes

VO_{2Peak}

Data from 13 studies and 381 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=1.2 [95%Cri: 0.49 to 1.9] and between study standard deviation of $\tau_{0.5}$=0.73 [75%CrI: 0.21 to 1.2]. The probability that the pooled effect size exceeded zero was p>0.999.

LVEF

Data from 10 studies and 244 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=1.8 [95%Cri: 0.35 to 3.4] and between study standard deviation of $\tau_{0.5}$=1.5 [75%CrI: 0.43 to 2.6]. The probability that the pooled effect size exceeded zero was p=0.990.

QoL

Data from 12 studies and 349 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=1.2 [95%Cri: 0.40 to 2.5] and between study standard deviation of $\tau_{0.5}$=1.3 [75%CrI: 0.70 to 2.2]. The probability that the pooled effect size exceeded zero was p=0.994.

Controlled effect sizes

VO_{2Peak}

For comparison with usual care, data from 8 studies and 504 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=1.8 [95%Cri: 0.36 to 3.2] and between study standard deviation of $\tau_{0.5}$=1.2 [75%CrI: 0.34 to 2.1]. The probability that the pooled effect size exceeded zero was *p*=0.990

For comparison with moderate continuous training, data from 9 studies and 529 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=0.98 [95%Cri: 0.02 to 2.1] and between study standard deviation of $\tau_{0.5}$=0.90 [75%CrI: 0.26 to 1.6]. The probability that the pooled effect size exceeded zero was *p*=0.979.

LVEF

For comparison with usual care, data from 5 studies and 248 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=1.3 [95%Cri: -0.67 to 3.1] and between study standard deviation of $\tau_{0.5}$=1.3 [75%CrI: 0.38 to 2.4]. The probability that the pooled effect size exceeded zero was *p*=0.918

For comparison with moderate continuous training, data from 7 studies and 395 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=0.95 [95%Cri: -0.21 to 2.4] and between study standard deviation of $\tau_{0.5}$=0.98 [75%CrI: 0.29 to 1.7]. The probability that the pooled effect size exceeded zero was *p*=0.958.

QoL

For comparison with usual care, data from 6 studies and 445 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=1.2 [95%Cri: -0.41 to 2.8] and between study

standard deviation of $\tau_{0.5}$=1.7 [75%CrI: 0.92 to 2.7]. The probability that the pooled effect size exceeded zero was *p*=0.941

For comparison with moderate continuous training, data from 9 studies and 519 participants were included in the meta-analysis and returned a pooled value of $ES_{Standardised0.5}$=-0.31 [95%Cri: -1.5 to 1.0] and between study standard deviation of $\tau_{0.5}$=1.7 [75%CrI: 1.1 to 2.4]. The probability that the pooled effect size exceeded zero was *p*=0.317.

Table X: GRADE Summary of findings table

High Intensity Interval Training vs. Usual Care

Outcomes	Certainty assessment							№ of patients		Effect		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Intensity Interval Training	Moderate Continuous Training	Relative (95% CrI)	Absolute (95% CI)	
VO_{2peak}	8	randomised trials	not serious	not serious	not serious	not serious	none	257	247	-	MD **4** mL.kg^{-1}min^{-1} **higher** (2.1 higher to 5.9 higher)	⨁⨁⨁⨁ High
left ventricular ejection fraction	5	randomised trials	not serious	serious[a]	not serious	serious[b]	none	125	123	-	MD **3.9 % higher** (3 lower to 9.8 higher)	⨁⨁◯◯ Low
Quality of life Minnesota living with heart failure questionnaire	6	randomised trials	not serious	not serious	not serious	not serious	none	266	253	-	MD **13 more** (10 more to 16 more)[c]	⨁⨁⨁⨁ High

High Intensity Interval Training vs. Moderate Continuous Training

Outcomes	Certainty assessment							№ of patients		Effect		Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High Intensity Interval Training	Moderate Continuous Training	Relative (95% CrI)	Absolute (95% CI)	
VO_{2peak}	9	randomised trials	not serious	not serious	not serious	not serious	none	283	246	-	MD **1.6** mL.kg^{-1}min^{-1} **higher** (0.4 higher to 2.7 higher)	⨁⨁⨁⨁ High
left ventricular ejection fraction	7	randomised trials	not serious	serious[d]	not serious	serious[e]	none	205	190	-	MD **3 % higher** (0.4 higher to 6 higher)	⨁⨁◯◯ Low
Quality of life Minnesota living with heart failure questionnaire	9	randomised trials	not serious	not serious	not serious	serious[b]	none	266	253	-	MD **2.7 more** (1 fewer to 5.4 more)[f]	⨁⨁⨁◯ Moderate

CrI: Credible interval; **MD:** Mean difference

Explanations

a. Substantial heterogeneity ($\tau_{0.5}$=6.1 [75%CrI: 1.9 to 12.2]).

b. Substantial range that stretches across zero.

c. Represents an estimated 13 unit greater improvement in Quality of life for HIIT (which equates to a score that is 13 units lower on the Minnesota living with heart failure questionnaire).

d. Substantial heterogeneity ($\tau_{0.5}$=2.3 [75%CrI: 0.66 to 4.3]).

e. Substantial range in pooled estimate.

f. Represents an estimated 2.7 unit greater improvement in Quality of life for HIIT (which equates to a score that is 2.7 units lower on the Minnesota living with heart failure questionnaire).