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High-intensity interval training for reducing cardiometabolic syndrome in healthy but sedentary populations (Protocol)

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[Intervention Protocol]

High-intensity interval training for reducing cardiometabolic syndrome in healthy but sedentary populations

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of high-intensity interval training on cardiometabolic health in healthy, sedentary adults.

BACKGROUND

Description of the condition

Advances in technology have dramatically changed our physical activity. More disposable income, more reliance on personal vehicles, fewer manual jobs reduced day to day activity, and now television, mobile devices, and the Internet all contribute to less physical activity and exercise. This inactivity appears to be contributing to the global epidemic of cardiometabolic syndrome (CMS (Misra 2008)). There are multiple risk factors for CMS: systemic arterial hypertension, hyperlipidaemia, central obesity, and insulin resistance or type 2 diabetes, which are related to developing and dying from cardiovascular disease (CVD (GBD 2017 Risk Factor Collaborators)). CVD is the leading cause of adult deaths globally; an estimated 18 million people die from CVD each year, with hypertension and diabetes being the major risk factors (GBD 2017 Causes of Death Collaborators).

The World Health Organization (WHO) use the presence of type 2 diabetes or insulin resistance as diagnostic of CMS when two other of these risk factors are present: obesity, hypertension, high triglycerides, reduced HDL-C, or micro-albuminuria (Grundy 2008). Thus, CMS causes millions of deaths through the associated downstream effects (impact on cardiovascular system, cerebrovascular system, immune system, and cancer diagnoses), all of which could be minimised (Irace 2005). Public health policies often emphasise preventative and therapeutic clinical interventions that address modifiable risk factors, such as obesity, physical inactivity, systolic arterial hypertension, type 2 diabetes, and dyslipidaemia (Grundy 2005; Guthold 2018); but all of these could by improved by increased exercise (Sato 2007; He 2009; Ding 2016).

Description of the intervention

The WHO recommends 150 minutes of moderate-intensity aerobic exercise (planned, structured physical activity) per week, or 75 minutes of vigorous-intensity exercise per week to promote health in people aged 18 years to 64 years (WHO 2010). However, one third of the global population do not achieve this target, so it is not surprising that conditions, such as obesity, type 2 diabetes, and cardiovascular disease are increasing globally (Sallis 2016).

Traditionally, there have been two main types of exercise training; aerobic (endurance) training and resistance training. High-intensity interval training (HIIT) has recently emerged as a third type of exercise training, which alternates short bouts of high-intensity aerobic exercise with periods of rest and recovery. This novel approach has the potential to be an alternative to the current WHO guidelines for physical activity, as it offers a time-efficient exercise strategy compared to moderate-intensity aerobic exercise (Gibala 2012). It is increasingly popular in some countries; for example, according to the American College of Sports Medicine, HIIT is one of the top two fitness trends for 2020 (Thompson 2019).

The time efficiency with HIIT could be extremely important, as one of the most commonly cited barrier to physical activity and exercise is a lack of time (Arzu 2006; Gibala 2010). With approximately 20 minutes of HIIT, compared to 30 minutes to 45 minutes per session for moderate-intensity endurance exercise, this is an important potential option to traditional, moderate-intensity endurance exercise. Therefore, it is important to be clear that HIIT offers the same benefits as moderate-intensity endurance exercise before any more substantive public health promotion and other active strategies to promote the approach are implemented.

How the intervention might work

Regular physical activity is associated with lower risk of cardiovascular morbidity and mortality (Paffenbarger 1986; Manson 1999; Ekelund 2019). Prospective studies have demonstrated that lifelong physical activity reduces the risk for cardiovascular mortality by 42% to 44% when compared to lifelong sedentary behaviour (Blair 1995; Lee 2011). Regular exercise has been shown to modify cardiovascular risk factors, such as blood pressure, poor blood lipid profile, and insulin resistance (Thompson 2003; Cornelissen 2013). Most research to date explores the beneficial effects of endurance exercise, so we need to understand whether these benefits also occur as a result of HIIT. Adaptations to training are complex and multifaceted. HIIT influences multiple body systems and consequently, multiple risk factors (blood lipid profile (including high density lipoprotein-cholesterol (HDL-C) to low density lipoprotein-cholesterol (LDL-C) ratio), systolic blood pressure, obesity, and insulin resistance), leading to improved CVD risk.

HIIT has been shown to elicit similar, or even greater, improvements in cardiorespiratory fitness than that from traditional moderate-intensity endurance training, despite the lower time commitment, in a variety of populations (Gibala 2012; Bacon 2013; Weston 2014; Milanovic 2015). The improvement in cardio-respiratory fitness is important, despite it not being a CVD risk factor, because lower cardiorespiratory fitness has been associated with higher risk of all-cause mortality (Myers 2004; Kodama 2009). Indeed, a low cardiorespiratory fitness correlates more closely with mortality than other risk factors, including smoking, obesity, type 2 diabetes, and hypertension (Artero 2012); each 1mL/kg/min increase in cardiorespiratory fitness is associated with a 45-day increase in lifespan (Clausen 2018). A number of recent systematic reviews have also demonstrated that HIIT can lead to improvements in VO2 max in lean, overweight, and obese populations (Batacan 2017; Vollaard 2017; Wen 2019), and to greater improvements in VO2 max when compared to moderate intensity continuous training (Sultana 2019).

HIIT appears to exert a cardioprotective effect on the vasculature by inducing functional and structural adaptations to the vascular wall, which can lead to improved blood flow (assessed via flow mediated dilation (FMD); a surrogate for cardiovascular health and disease risk (Inaba 2010; Green 2011; Thijssen 2011; Ras 2013)). HIIT can also reduce the stiffness of the arteries. Arterial stiffness (measured by pulse wave velocity (PWV)) relates closely with cardiovascular events, with an increased cardiovascular risk of 30% for every one standard deviation change in PWV (Ben-Shlomo 2014). HIIT has been demonstrated to result in reductions in arterial stiffness in previously sedentary lean and obese populations (Rakobowchuk 2008; Cocks 2013; Cocks 2016).

An inactive lifestyle can lead to a poor circulating lipid profile (elevated LDL-C, a marker of risk for stroke). A study of 90 inactive volunteers, who took part in 10-week, instructor-led, group-based stationary cycling class, demonstrated that HIIT led to improvements in a number of cardiovascular risk factors: VO2 peak, insulin sensitivity, and abdominal fat mass, and induced favourable changes in circulating lipid profile (decreased

cholesterol, improved LDL-C:HDL-C ratio (Shepherd 2015; Campbell 2019)). The improvement in risk factors (systolic blood pressure, insulin sensitivity, blood lipid profile, and vascular function) in response to HIIT is not isolated; it is reported in some existing meta-analyses (Jelleyman 2015; Ramos 2015; Batacan 2017).

A key risk factor associated with CMS is obesity. Because of the short duration of HIIT, and therefore, the limited energy expenditure for a single training session compared to endurance training, the benefits of HIIT on body composition are currently equivocal (Skelly 2014). This relationship has been explored in a number of systematic reviews and meta-analyses to date; some showed similar improvements in body composition (reduction in body fat percentage) between HIIT and moderate intensity continuous training (MICT (Keating 2017; Wewege 2017)), some showed improvements only in response to HIIT (Viana 2019), and some showed improvements only in response to MICT (Sultana 2019).

Why it is important to do this review

The global cost of inactivity is estimated to be $53.8 billion (Ding 2016). Exercise has the potential to be a low cost, effective, and accessible intervention, which can improve cardiovascular disease risk in a sedentary population. However, it is well understood that the current WHO exercise guidelines are not met, and do not currently include advise for people who wish to undertake HIIT (WHO 2010; Sallis 2016). The 75 minutes of vigorous exercise outlined in the WHO guidelines still exceeds the time commitment of a true HIIT or sprint interval training (SIT) programme (resulting in a heart rate of at least 80% of your maximum heart rate (> 80% HR max)).

Importantly though, we still do not known whether HIIT is an efficacious and acceptable alternative for sedentary populations to use to reduce their risk for CMS. Given the large public interest in HIIT at present, and a lack of time being cited as the most common barrier to exercise, the topic is ripe for a high quality, non-bised exploration of the literature (Arzu 2006; Gibala 2010). Physical activity and exercise training are paramount for health promotion, therefore, it is important to make a variety of exercise modes available for people to consider incorporating into their weekly exercise regimens. Public health guidelines should be applicable for all populations, regardless of their culture, or their ability to pay for the programmes. This review has the potential to inform activity guidelines and recommendations for health promotion, should HIIT prove to be of benefit in reducing the risk of CMS risk in healthy, sedentary individuals.

OBJECTIVES

To assess the effects of high-intensity interval training on cardiometabolic health in healthy, sedentary adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include individual and cluster-randomised controlled trials (RCTs), including cross-over trials. We will include studies reported as full-text, those published as abstract only, and unpublished data.

Types of participants

We will include healthy adults, aged 18 years to 64 years, who are sedentary (at baseline). We will define sedentary as activity that does not meet the World Health Organization (WHO) global recommended levels of physical activity for adults aged 18 years to 64 years, described as 150 minutes or more of moderate-intensity physical activity, or at least 75 minutes of vigorous-intensity aerobic physical activity per week (WHO 2010).

We will exclude studies of athletes, as this review is concerned about public health, not high-intensity interval training (HIIT) for performance; studies of overweight (body mass index (BMI) 25 kg/m^2 to 29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) populations recruited as a result of a medical event or diagnosis, as this review is focusing on healthy participants; and studies with co-interventions, as healthy participants would not require preventative treatment strategies or medications.

Types of interventions

Intervention

We will define an exercise training programme as an intervention in which participants undergo an exercise programme. The exercise programme must have been prescribed, and must report details of type of exercise, frequency, intensity, and duration (Colberg 2016).

Programmes that assure high-intensity interval training (HIIT), defined as short periods of intense aerobic exercise (resulting in a heart rate of at least 80% of your maximum heart rate (> 80% HR max)) interspersed with periods of recovery. This will include sprint interval training (SIT; short, up to 30 seconds, of 'all out' bursts of HIIT). The maximum interval duration is four minutes; there is no minimum duration, so we can include various HIIT protocols currently in the literature. We will consider all types of exercise (e.g. treadmill, running, cycling, swimming, cross training, rowing, martial arts, recumbent cycling). We will exclude programmes in which HIIT is combined with resistance training.

The period of training must be at least four weeks. We selected four weeks, as existing studies have shown meaningful increases in cardiorespiratory fitness (VO2 max) within this time. For example, in obese men, four weeks of exercise training resulted in an increase in VO2 max from 2 to 4 mL/kg/min with some individuals demonstrating larger increases (Cocks 2016; Shepherd 2017). Given that each 1 mL/kg/min increase in cardiorespiratory fitness is associated with a 45-day increase in lifespan, even these smaller improvements are clinically relevant (Clausen 2018).

We will include both supervised and unsupervised training schemes, and will consider them in a subgroup analysis.

Control

The controls can be either:

- People who are not in an active training programme
- People training at a constant, moderate intensity (minimum session duration 30 minutes, at an intensity 50% to 70% HR max), with no intervals

There are two comparisons of interest in this review:

1. HIIT versus no active training, and

2. HIIT versus moderate-intensity, continuous training.

Types of outcome measures

Reporting one or more of the outcomes of interest is not an inclusion criterion for the review. If a published report does not appear to report one of these outcomes, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. We will include relevant trials that measured these outcomes, but either did not report the data at all, or did not report them in a usable format, as part of the narrative.

All outcomes will be measured at the end of the defined training period. We will include outcomes followed with * in the 'Summary of findings' table.

Primary outcomes

- Cardiorespiratory fitness, measured by VO2 peak*
- Systolic blood pressure*
- Waist circumference*
- Waist-to-hip ratio*

Secondary outcomes

Clinical

- All cause-mortality*
- Cardiovascular mortality
- Myocardial infarction (number of events during prescribed exercise)
- Stroke (number of events during prescribed exercise)
- Quality of life (assessed with a validated quality of life scale (Flanagan 1978; Flanagan 1982))

Laboratory measurements

- Body mass
- Body mass index
- Lean mass and fat mass, measured by magnetic resonance imaging (MRI) and dual-x-ray absorptiometry (DXA), bioelectrical impedance, and skinfold
- Visceral fat measured by MRI or DXA only
- Insulin sensitivity, measured by hyperinsulinaemic euglycaemic clamp (gold standard) or an oral glucose tolerance test (OGTT); OGTT may be reported as area under the curve, Matsuda index, or Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index
- Fasting insulin levels
- Glycated haemoglobin (HBA1c) (commonly used clinical marker of glucose control over the previous three months)
- Diastolic blood pressure
- Vascular function (often measured with flow mediated dilation or pulse wave velocity to give an indication of arterial stiffness)
- Circulating triglycerides (TG)*
- Low density lipoprotein cholesterol (LDL-C)
- High density lipoprotein cholesterol (HDL-C)

Programme measurements

- Duration of exercise (minutes/week) in HIIT versus traditional, moderate-intensity continuous training
- Participant dropout or adherence, as a surrogate for adverse events

Adverse Events

- Injuries occurring during a prescribed training session
- Other adverse events occurring during a prescribed training session*
- Any adverse event not attributed to, and unrelated to the exercise programme

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library
- MEDLINE Ovid (1946 onwards)
- Embase Ovid (1980 onwards)
- Web of Science Core Collection Clarivate Analytics – SCI-Expanded, SSCi, CPCI-S

We will adapt the preliminary search strategy for MEDLINE Ovid for use in the other databases (Appendix 1). We will apply the Cochrane sensitivity and precision maximising RCT filter MEDLINE Ovid and the adaptations of it to the other databases, except CENTRAL (Higgins 2019).

We will search the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.ClinicalTrials.gov), and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/) for ongoing or unpublished trials.

We will search all databases from their inception to the present, and we will impose no restriction on language of publication or publication status.

We will consider adverse effects described in included studies only.

Searching other resources

We will check reference lists of all included studies and any relevant systematic reviews identified for additional references to trials. We will also examine any relevant retraction statements and errata for included studies. We will contact study authors for missing, unclear, or contradictory data.

Data collection and analysis

Selection of studies

Two or more review authors (JS, CR, EC, SS, LS) will independently screen titles and abstracts to include all the potential studies we identify as a result of the search, and code them as 'retrieve' (eligible, potentially eligible, or unclear) or 'do not retrieve'. If there are any disagreements, they will ask another review author to arbitrate (PG). We will retrieve the full-text study reports and publications, and two or more review authors (JS, CR, EC, SS, LS) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for excluding the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult another author (PG). We

will identify and exclude duplicates and collate multiple reports of the same study, so that each study, rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009). We will log studies awaiting classification if the full text is unavailable (e.g. conference abstracts), unclear, or missing information (cannot be obtained from study authors).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least two studies in the review. Study characteristics will be extracted independently by two review authors (JS, CR). For any missing data, we will contact the study authors. We will extract the following study characteristics.

1. Methods: authors' contact details, type of record (e.g. journal article, thesis), study design, study population, study dates, total duration of the intervention, and follow-up duration after the intervention where relevant, details of 'run in' periods where relevant, number of study centres and location, study setting, method of recruitment, number of study arms, description of eligible study arms, outcome used for sample size calculation, other relevant notes on the methods.
2. Participants: N randomised, N lost to follow-up or withdrawn, N analysed, mean age, age range, sex (number of males and females per group), inclusion criteria, exclusion criteria, baseline body weight status, other baseline cardiovascular disease risk factors and potential confounders, any group differences.
3. Interventions: description of the exercise programme (e.g. high intensity interval training, resistance training, endurance training), intervention type (e.g. cycle ergometer, treadmill), dose (e.g. number of intervals, prescribed intensity, work:rest or recovery ratio), mode of control training intervention (e.g. no training or endurance exercise training), supervision (e.g. supervised or unsupervised), concomitant interventions.
4. Outcomes: primary and secondary outcomes specified and collected at relevant time points, data on adherence to the interventions.
5. Notes: funding for trial, notable conflicts of interest of trial authors, and other relevant notes.

We will assess outcomes via change data (change from baseline for each outcome variable per group) and include data on variance for treatment and control arms and 'n' at the time point. If no change data are available, we will extract data from the end of the study, or other appropriate time points, and include data on variance and 'n' at the time point. Where possible, we will convert variables to comparable units to allow pooling of data as appropriate.

Where data are included in eligible studies, we will measure adherence as the percentage of training sessions completed of the overall prescribed programme. We will also examine studies for measure of compliance to the training prescription, such as whether the heart rate target is achieved. This is likely to be an important effect modifier, but may well be poorly described.

At least two review authors (JS, CR, EC, SS, LS) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving another review author (PG). One review author (JS) will transfer data into the Review Manager 5 file (Review Manager 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (SS) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

At least two review authors (JS, CR, EC, SS, LS) will independently assess risk of bias for each study, using version two of the Cochrane 'Risk of bias' tool (RoB2), outlined in the *Cochrane Handbook for Systematic Reviews of Interventions, Chapter 8* (Higgins 2019). We will resolve any disagreements by discussion or by involving another review author (PG). We will assess the risk of bias of trials that measure the outcomes that will be included in our 'Summary of findings' table according to the following domains:

1. bias arising from the randomisation process;
2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome; and
5. bias in selection of the reported result.

We will use the signalling questions in the RoB2 tool, and rate each domain as 'low risk of bias', 'some concerns' or 'high risk of bias'. We will summarise the risk of bias judgements across different studies for each of the domains listed for each outcome. The overall risk of bias for the result is the least favourable assessment across the domains of bias.

We will assess the risk of bias of cross-over trials using the ROB2 tool, which specifically addresses carry-over effects and period effects, and takes into account the possibility of selective reporting in the first period of results (Higgins 2019).

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol, and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios with 95% confidence intervals. We will enter data presented as a scale with a consistent direction of effect. For continuous outcomes collected with different scales (e.g. quality of life), we will measure the effect using standardised mean differences with 95% confidence intervals. for continuous outcomes collected on the same scale, we will measure the effect using mean differences with corresponding standard deviation and 95% confidence intervals.

We will use the latest Review Manager version to conduct meta-analyses for each outcome, where appropriate, to determine a pooled effect of high-intensity interval training compared to endurance-type exercise training, or no training.

We will narratively describe skewed data reported as medians and interquartile ranges.

Unit of analysis issues

In the case of multiple intervention groups, we will include all eligible intervention arms. If we encounter a case where multiple

intervention arms contribute data to the same meta-analysis, we will split the control group so that participants are not double-counted in any meta-analysis.

We will include RCTs, whether randomised at the level of the participant or as a cluster-randomised design. If we do find cluster-RCTs that did not perform adjustments for clustering, we will re-analyse, where possible, following the method of adjusting for clustering, taking into account the correlated nature of within-cluster data, as described in the *Handbook* (Higgins 2019).

We will analyse cluster-randomised trials in accordance with guidance in the *Handbook, Chapter 23* (Higgins 2019). Cluster-randomised trials trials should account for clustering in the data, e.g. based on a multilevel model or generalised estimating equation. If the study authors have not properly accounted for clustering, we will use effective sample size methods where the following information can be extracted:

- The number of clusters (or groups) randomised to each intervention group, and the total number of participants in the study; or the average (mean) size of each cluster;
- The outcome data ignoring the cluster design for the total number of individuals (e.g. the number or proportion of individuals with events, or means and standard deviations for continuous data);
- An estimate of the intracluster (or intraclass) correlation coefficient (ICC).

If ICC estimates are not available in published reports. we will use external estimates obtained from similar studies, or use an estimate based on known patterns in ICCs for particular types of cluster or outcome. If we estimate the ICC, we will conduct sensitivity analyses to investigate the robustness of our conclusions.

We will analyse cross-over trials in accordance with guidance in the *Handbook, Chapter 23* (Higgins 2019). If we judge that period effects and carry-over effects are unlikely to be a problem in a cross-over trial, we will use a paired analysis. If the required data for a paired analysis are not available, or we consider period effects, carry-over effects, or both to be a problem, we will include data from the first cross-over period, treating this period as a randomised parallel trial.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data, where possible (e.g. when a study is identified as abstract only). Where possible, we will use the RevMan calculator to impute missing standard deviations, using other data from the trial, such as confidence intervals, based on methods outlined in the *Handbook* (Higgins 2019). If we cannot calculate these with reasonable confidence, we will contact the study authors directly, via email, to obtain the missing standard deviations, or impute standard deviations by borrowing values from similar studies. If any imputations are performed, we will explore the impact of changing the assumptions made in sensitivity analyses. In the event of missing outcome data from participants, we may perform imputations using methods outlined in section 10.12.2 of the *Handbook*, and perform sensitivity analyses to investigate the potential impact of reasonable changes in the assumptions made.

Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between confidence intervals. We will use the I^2 statistic to measure heterogeneity among the trials in each analysis, but acknowledge that there is substantial uncertainty in the value of I^2 when there is only a small number of studies, We will also consider the P value from the Chi^2 test. If we identify substantial heterogeneity (I^2 > 50%), we will report it and explore possible causes by prespecified subgroup analysis (see below).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases for the primary outcomes.

Data synthesis

We will undertake meta-analyses only where this is meaningful, that is, if the intervention, participants, and the underlying question are similar enough for pooling to make sense.

We will use a fixed-effect model in the absence of substantial heterogeneity, defined above. With substantial quantitative heterogeneity not explained by subgroup analysis, we will consider meta-analysis using a random-effects model, if the combination of participants and the intervention make sense.

Summary of findings table

We will create a 'Summary of findings' table for each comparison using the following outcomes cardiorespiratory fitness, systolic blood pressure, waist circumference, waist-to-hip ratio, all-cause mortality, circulating triglycerides, adverse events occurring during a prescribed training session.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Chapter 12 of the *Handbook* and GRADEpro GDT software for the two comparisons anticipated (HIIT versus no training, and HIIT versus moderate-intensity continuous training (Higgins 2019; GRADEpro GDT)). We will justify all decisions to downgrade the certainty of evidence using footnotes, and we will make comments to aid reader's understanding of the review where necessary.

Two review authors (JS and CR) will independently judge the certainty of the evidence, with disagreements resolved by discussion or by involving a third review author (PG). They will justify, document, and incorporate the judgements into the result reports for each outcome.

Subgroup analysis and investigation of heterogeneity

We plan to carry out these subgroup analyses.

1. extent of supervision provided during the training (supervised versus unsupervised)
2. duration of the work interval (stratify HIIT- versus SIT-based protocols)

3. programme duration, to identify short-term versus long-term changes (less than 12 weeks; more than 12 weeks)
4. protocol adherence to identify the effect of adhereing to the prescibed trial interventions (the 'per-protocol effect') (Hernan 2017)
5. sex (males versus females)

We will use the formal test for subgroup differences in Review Manager 5, and base our interpretation on this.

Sensitivity analysis

Our primary analysis will include all studies. We will carry out a sensitivity analysis in which we only include studies with overall low risk of bias or some concerns, excluding studies at high risk of bias.

Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice; our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.

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APPENDICES

Appendix 1. Preliminary MEDLINE Ovid search strategy

1 High-Intensity Interval Training/ (862)

2 HIIT.tw. (921)

3 (high intensity adj3 (exercise* or training*)).tw. (6766)

4 ((intermittent or interval*) adj3 (exercise* or training*)).tw. (6359)

5 1 or 2 or 3 or 4 (10871)

6 randomized controlled trial.pt. (499754)

7 controlled clinical trial.pt. (93551)

8 randomized.ab. (468539)

9 placebo.ab. (204834)

10 clinical trials as topic.sh. (190007)

11 randomly.ab. (326338)

12 trial.ti. (212295)

13 6 or 7 or 8 or 9 or 10 or 11 or 12 (1266315)

14 exp animals/ not humans.sh. (4669549)

15 13 not 14 (1164784)

16 5 and 15 (3524)

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CONTRIBUTIONS OF AUTHORS

JS contributed to, read, and approved the final protocol

CR contributed to, read, and approved the final protocol

LS contributed to, read, and approved the final protocol

SS contributed to, read, and approved the final protocol

MC contributed to, read, and approved the final protocol

PG contributed to, read, and approved the final protocol

DECLARATIONS OF INTEREST

JS has no conflicts of interest to declare

CR has no conflicts of interest to declare

LS has no conflicts of interest to declare

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