

# **The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis**

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## **Running Title**

The effects of HIIT on metabolic health

## **Declaration of interests**

The authors declare that there is no conflict of interest associated with this manuscript.

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## Abstract

The aim of this meta-analysis was to quantify the effects of high-intensity interval training (HIIT) on markers of glucose regulation and insulin resistance compared to control conditions (CON) or continuous training (CT). Databases were searched for HIIT interventions based on the inclusion criteria: training  $\geq 2$  weeks, adult participants, and outcome measurements that included insulin resistance, fasting glucose, HbA1c or fasting insulin. Dual interventions and participants with type 1 diabetes were excluded. Fifty studies were included. There was a reduction in insulin resistance following HIIT compared to both CON & CT, (HIIT vs. CON: standardised mean difference (SMD)=-0.49, confidence intervals (CI) -0.87 to -0.12,  $p=0.009$ ; CT: SMD=-0.35, -0.68 to -0.02,  $p=0.036$ ). Compared to CON, HbA1c decreased by 0.19% (-0.36 to -0.03,  $p=0.021$ ) and body weight decreased by 1.3kg (-1.9 to -0.7,  $p<0.001$ ). There were no statistically significant differences between groups in other outcomes overall. However, participants with or at risk of Type 2 diabetes experienced reductions in fasting glucose ( $-0.92\text{mmol.L}^{-1}$ , -1.22 to -0.62,  $p<0.001$ ) compared to CON. HIIT appears effective at improving metabolic health, particularly in those at risk of or with Type 2 diabetes. Larger randomised controlled trials of longer duration than those included in this meta-analysis are required to confirm these results.

## Introduction

Obesity and Type 2 diabetes are inextricably linked with over 80% of people with Type 2 diabetes classed as overweight or obese based on BMI thresholds.<sup>1</sup> Diet and physical activity interventions are the cornerstones for management of both conditions. However, whilst effects of exercise on Type 2 diabetes and insulin sensitivity are well established,<sup>2-4</sup> the effects on weight regulation are more controversial.<sup>5,6</sup> The prevailing recommendation for meaningful improvements in cardiorespiratory fitness and metabolic health to occur in adults is engaging in a minimum of 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity per week, accumulated in bouts of 10 minutes or more.<sup>7-9</sup> The guidelines for weight loss are greater; suggesting that 200-300 minutes per week is required for long term reductions.<sup>10</sup> Given that less than 50% of the population in industrialised societies,<sup>11</sup> with estimates falling to as low as 5% when objective measures of physical activity are employed,<sup>12,13</sup> meet the shorter physical activity recommendations for health, it is becoming more important to elucidate what is the minimum amount of physical activity required to promote health benefits. This notion is supported by findings from surveys investigating perceived barriers to participation in physical activity which consistently highlight “lack of time” as a common barrier for not being more active, a finding applicable to the general population<sup>14,15</sup> as well as those with Type 2 diabetes.<sup>16</sup>

High-intensity interval training (HIIT) has been proposed as a time-efficient exercise intervention that may bring about similar benefits as moderate-intensity aerobic exercise.<sup>17,18</sup> Sprint interval training (SIT) using the Wingate protocol is a well-defined form of HIIT involving just three minutes of activity per session not including warm-up or cool-down.<sup>19</sup> Although this version of HIIT has been shown to improve fitness in a variety of populations,<sup>20-22</sup> the repeated maximal efforts this protocol requires may limit practicality for sedentary individuals.<sup>23</sup> As such, protocols using longer, submaximal intervals have been developed, a form of HIIT described as “aerobic interval training”.<sup>24,25</sup> For the purpose of this review, any form of interval training that incorporates high-intensity exercise within or above the range categorised as vigorous (64-90%  $VO_{2max}$  or 77-95%  $HR_{max}$ ) in the American College of Sports Medicine guidelines<sup>26</sup> shall be collectively referred to as HIIT (i.e. sprint interval training, aerobic interval training).

While HIIT tends to have a potent effect on cardiorespiratory fitness in a variety of populations<sup>27-29</sup>, benefits to obesity and markers of metabolic health, such as glucose regulation and insulin sensitivity are less well defined. One narrative review concluded that despite a reduction in total work volume, HIIT has positive effects on blood glucose control and insulin sensitivity compared to continuous exercise.<sup>30</sup> This literature review was limited as it did not provide quantification of the effect of HIIT on metabolic health outcomes. Nor did it assess the impact of varying HIIT characteristics. The aim of this systematic review was therefore to quantify the impact of HIIT on glucose and insulin regulation, body weight and cardiorespiratory fitness compared to control conditions (CON) or continuous exercise training (CT) using meta-analysis. A secondary aim was to assess whether observed metabolic changes were mediated by characteristics of the training protocol (i.e. interval intensity, training volume) or concurrent changes in participant physiology (e.g. cardiorespiratory fitness, body weight).

## Methods

This meta-analysis has been reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.<sup>31</sup> See *Supplement 1* for the checklist.

### Search strategy and inclusion criteria

Medline (1946-13/03/2015), Embase (1970-13/03/2015) and SportDiscuss (1953-30/03/2015) were searched for HIIT intervention studies that reported a measure of glycaemic control. There is no universal definition of HIIT, therefore, based on a brief overview of the literature, we applied the following criteria to our search: at least two bouts of vigorous- or higher intensity exercise<sup>26</sup> interspersed with periods of lower intensity exercise or complete rest. “High-intensity interval training” is not a MeSH term therefore words and phrases commonly used to describe HIIT were searched in titles and abstracts using the following search terms: “high-intensity interval”, “aerobic interval” and “sprint interval”. These were then combined with the following terms using Boolean commands: intermittent, Wingate, supramaximal, exercise, training, programme, glucose, insulin, glycaemic, and HbA1c. Wildcards: \*, ? and \$ were used so that both English and American spellings would be returned. *Supplement 2* gives a detailed description of the search strategy. Titles and abstracts of returned articles were evaluated based on the following inclusion criteria: human participants aged 18 years or over, participants receiving a HIIT intervention, and at least one measure of glycaemic control defined as: HbA1c, fasting glucose, fasting insulin, postprandial or post-challenge glucose response, or any measure of insulin resistance assessed pre- and post-intervention. HIIT had to be prescribed at least three times per week for two weeks. Two weeks was deemed the minimum period needed to show training adaptations; defined as a temporary or extended change in structure or function that results from performing repeated bouts of exercise and that is independent of the immediate or short-term effects produced by a single bout of exercise.<sup>32</sup> Both controlled and uncontrolled studies were included. Articles were excluded if HIIT was prescribed in combination with another intervention e.g. diet restriction; resistance training, if participants had diagnosed Type 1 Diabetes (studies of people with Type 2 diabetes were included), or if medication had been altered throughout the intervention. Abstracts, case reports, observational studies and studies not published in English were also excluded.

### Risk of bias and study quality

Risk of bias was evaluated based on the PRISMA recommendations<sup>31</sup> which suggest assessing randomised control trial quality using the Cochrane risk of bias tool.<sup>33</sup> This tool consists of five items that have been shown to have an effect on biasing the results of an intervention. Studies with control groups were checked for random sequence generation, allocation concealment, blinding, participants lost to follow-up, and whether an intention-to-treat analysis had been performed. A score of one point was given for each item fulfilled such that studies could score a maximum of five points. Studies without clear descriptions of these processes were considered not to have satisfied these criteria. Uncontrolled trials were not assessed.

### Data extraction and synthesis

Reviewers were not blinded to study authors, institutions, or manuscript journals. If the abstract was considered to be relevant to the review, or did not contain enough information regarding the inclusion or exclusion criteria, full-texts were retrieved for further evaluation. References included in identified studies and previous reviews or commentaries were also hand searched. Where there was uncertainty by the first reviewer regarding appropriate studies, the full text was obtained and a second reviewer (TY) approached for discussion. If evidence of participant repetition was evident participants were only included once, however if necessary, multiple articles were used to obtain all required data.

If, according to the methodology relevant measurements had been taken but the results not reported, or values had been presented in figures, authors were contacted and asked to provide the missing data. When no reply was received the study/outcome was either omitted from the analysis<sup>34</sup> or values estimated from figures.<sup>35-37</sup> Where only pre and post-intervention data were presented, change data were imputed based on guidelines from the Cochrane Handbook for Systematic Reviews of Interventions.<sup>38</sup>

A data extraction form was created and data regarding participant characteristics and disease status, protocol specifics, CT interventions, markers of glucose regulation, insulin resistance,  $VO_{2max}$ , body composition and compliance, attrition, and adverse events were entered independently by two reviewers (CJ and GO). Discrepancies were resolved by consensus or by a third reviewer (TY). A number of studies reported results from both acute (up to 48h) and longer term (72h) blood samples. If this was the case, the 72h reading was included in the analysis. Since the study by Lunt et al.<sup>39</sup> had two HIIT groups and a CT group, as per the Cochrane guidelines, the number of participants in the CT group was halved so that pairwise comparisons between HIIT and continuous exercise could be made for each HIIT protocol. One study compared two HIIT groups and these were entered as separate, uncontrolled trials.<sup>40</sup>

All models of insulin sensitivity were expressed as insulin resistance to account for the directional effect of exercise since a beneficial effect would increase sensitivity and decrease resistance. HOMA-IS% values were inverted ( $100/HOMA-IS\%$ )<sup>41</sup>, and change scores for other models of insulin sensitivity (n=9, 20%) were multiplied by -1.

### **Statistical analysis**

Stata v.13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX, USA) was used to conduct the meta-analyses. Pairwise comparisons comparing the effect of HIIT on glucose/insulin parameters and  $VO_{2max}$ , to that of either CT or CON were carried out on studies that had two or more groups. In keeping with other exercise-related meta-analyses of continuous outcomes,<sup>3, 42</sup> and following best practice,<sup>38</sup> weighted mean differences were calculated in the pairwise comparisons for glucose/insulin parameters and  $VO_{2max}$ . Standardised mean differences were used to account for the different measures of insulin resistance.

When studies had a HIIT group only, within group intervention effect sizes were calculated to estimate the change from baseline. All studies with a control group were included in both the between and within group

comparisons. Since this within group comparison is based on unstandardised data, only HOMA-derived insulin resistance measures could be assessed in this analysis.

Participants were stratified by health characteristics based on the descriptions given by each included study as follows: healthy (well-trained/recreationally active/sedentary); overweight/obese; metabolic syndrome (MetS)/Type 2 diabetes; with another chronic disease. Data were presented according to disease status.

We also performed two sensitivity analyses for insulin resistance: 1) using HOMA scores only to determine whether results were attenuated when more sensitive measures of peripheral insulin resistance were removed and 2) by the length of time elapsed before blood was sampled following the last training session i.e. <24h,  $\geq$ 24h and <72h or  $\geq$ 72h; the latter analysis was undertaken on the within group analysis only due to lack of data for the between group comparisons.

Random effects models using Cohen's *d* were carried out to account for the differences in study protocol and duration. Statistical heterogeneity of the treatment effect among studies was assessed using the chi-squared test. A threshold  $\alpha$  value of <0.05 was considered statistically significant and an  $I^2$  test with values greater than 50% were indicative of high heterogeneity.

### **Publication bias**

Publication bias based on reporting of the main outcomes was assessed using a contour-enhanced funnel plot of each trial's effect size against the standard error.<sup>43</sup> Funnel plot asymmetry was assessed by visual interpretation. If publication bias was apparent, Begg & Egger tests were used as a secondary determinant.<sup>44</sup>  
<sup>45</sup> Significant publication bias was deemed apparent if  $p < 0.1$ .

### **Meta-regression**

Where significant results were found, meta-regression was performed in an attempt to determine whether baseline levels, exercise volume variables and changes to body weight and  $VO_{2max}$  mediated observed changes.

Interval intensity and weekly high-intensity exercise duration and total training period (weeks) were deemed the most relevant components of HIIT protocols. Where possible, using regression equations derived from early work<sup>46, 47</sup> we converted interval intensity to a percentage of  $VO_{2max}$  in order to be able to directly compare exercise prescriptions. High-intensity exercise duration was estimated by multiplying the number of high-intensity intervals x interval length x the number of sessions per week and controlled for intensity and the number of weeks the study was run.

Change in body weight and cardiorespiratory fitness were also entered into the regression given their association with the primary outcomes.<sup>48, 49</sup>

For within group regression, change summary data were used as the dependent variable and were weighted by the standard error. In studies with a control group, the dependent variable was the mean difference calculated from the pairwise comparison, with each study weighted by the standard error of its effect size.

## Results

### Studies retrieved

Study selection flow is presented in *Figure 1*. The initial searches returned a total of 6209 articles (Medline n=3569, Embase n=1933, SportsDiscuss n=707), of which 4523 were original articles. Titles and abstracts of returned articles were searched for suitability leading to the retrieval of 317 full-texts. Of these, 263 did not fulfil the inclusion criteria and four were excluded due to the nature of the methods used. The total number of papers included in the analysis was 50, described in *Table 1*. Fourteen (28%) studies did not have a control group and were therefore only included in the within group analyses. Of the 36 (72%) controlled trials 14 (30%) had a CT group, 9 (18%) a CON group, 11 (22%) had both, one (2%) had two HIIT groups and a CT group and one (2%) compared two HIIT groups.

### Study quality and risk of bias

The 36 controlled trials were assessed for risk of bias. The median quality score was 1/5 (see *Table S1*). Of the included studies 13/36 (36%) presented adequate sequence generation, nine (25%) reported allocation concealment and 11 (31%) blinded where possible. It was unclear in three (8%) studies how many participants were lost to follow-up and five (14%) used the intention-to-treat principle for statistical analysis.

### Publication bias

Visual interpretation of funnel plots suggested limited publication bias and as such no statistical adjustment was made. See *Supplement 3* for figures.

### Heterogeneity

Heterogeneity statistics are presented in *Table 1*.  $I^2$  values were generally high, with all the within group comparisons indicative of wide heterogeneity (mean score = 89.1%). Controlled trials scored lower, with some showing homogenous statistics (mean CON = 49.2%; CT =31.3%).

### Participants

There were a total of 2033 participants included in the analysis, of which 1383 (68%) underwent a HIIT intervention. Participants were aged 21-68 years and spanned a wide range of health and disease characteristics; from well-trained individuals (n=61, 3%) through recreationally active (n=895, 44%), sedentary but otherwise healthy (n=86, 4%), overweight/obese (n=230, 11%), with metabolic syndrome (n=157, 8%), Type 2 diabetes (n=143, 7%) or with another chronic disease (e.g. cancer, heart failure; n=461, 23%). For subgroup analysis we stratified participants by disease status; healthy, n=1042 (51%), overweight/obese n=230 (11%), metabolic syndrome (MetS)/Type 2 diabetes n=300 (15%) and other chronic disease n=461 (23%).

### Overview of exercise interventions

Exercise interventions are described briefly in *Table S2*. Study protocols varied widely between both HIIT and CT interventions. HIIT interventions included aerobic interval training (e.g.<sup>39, 50, 51</sup>), sprint interval training (e.g.<sup>52-54</sup>), and high-intensity interval training (e.g.<sup>25, 40, 55</sup>). The number (range 2 - >60), duration (range 4s-5min) and intensity (range 65%  $VO_{2max}$  – Wingate effort) of “high-intensity” intervals, as well as duration (range 12s-5min) and intensity (range from complete rest- 70%  $HR_{max}$ ) of recovery intervals varied widely between studies. Exercise session duration (mean 34 mins, range 10-60 mins) total training volume (range 8-5040 mins) and total length of intervention (range 2- 16 weeks) also varied widely between studies. Not all studies reported how the continuous training intervention had been selected, although some were energy matched to HIIT (e.g.<sup>56-58</sup>) or based on the global recommendations for moderate intensity exercise (e.g.<sup>59, 60</sup>). Continuous training ranged from 30-120min per session at intensities between 55%  $VO_{2max}/HR_{max}$  to 80%  $HR_{max}$ .

### **Training modalities**

In most cases HIIT was carried out in an exercise laboratory supervised by an investigator or trained exercise physiologist. Three studies investigated the practicality of home-based HIIT interventions.<sup>61-63</sup> An exercise bike was used in 26 (52%) studies, 15 (30%) used a treadmill, one (2%) an athletics track<sup>64</sup> and six (12%) a free-living walking environment.<sup>39, 50, 61, 62, 65</sup> Two (4%) studies allowed participants to choose between treadmill and exercise bike throughout the intervention.<sup>55, 66</sup>

### **Compliance, attrition and adverse events**

Adherence to the intervention was reported by 20 (40%) studies and was  $90\pm 11\%$  of exercise sessions. Minimum adherence to be included in analysis was specified by 12 (24%) studies and ranged from 66-90% attendance of exercise training sessions. Mean dropout from follow-up measurement was  $10\pm 10\%$  in the 36 (72%) studies in which attrition was clear. Adverse events were reported in 17 (34%) studies. There were 18 musculoskeletal injuries attributable to the exercise interventions; 14/18 (72%) occurred in the HIIT group. Injuries did not necessarily result in the affected participant having to drop out from the study or discontinue the intervention. No serious adverse events were reported (see *Table S1*).



## 1 **Meta-analysis**

2 Data for fasting glucose, fasting insulin, HbA1c, insulin resistance,  $VO_{2max}$  and body weight were included in  
3 the meta-analysis. Effect sizes for within groups and comparisons with CON and CT are presented in *Table*  
4 *1*. Postprandial or post-challenge glucose levels were extracted but not analysed as there were not enough  
5 data to perform meaningful comparisons.

### 6 *Insulin resistance*

7 Insulin resistance was estimated in 29 (58%) studies. Of these, 20/29 (69%) had at least one control group.  
8 The HOMA model was employed by 21/29 (72%) studies. Other models of IR used were the QUICKI  
9 method (n=1, 3%<sup>67</sup>), Matsuda index (n=4, 14%<sup>37, 52, 68, 69</sup>), Cederholm index (n=2, 7%<sup>70, 71</sup>) and the  
10 euglycaemic hyperinsulinaemic clamp (n=1, 3%<sup>53</sup>). There was a significant reduction in HOMA score of  
11 0.33 (95% CI -0.47 to -0.18,  $p < 0.001$ ) with HIIT compared to baseline (*Fig. S1*). With all models of insulin  
12 resistance standardised for between group comparisons there was a significant reduction in insulin resistance  
13 compared to both CON and CT groups; *Figure 2a & 2b*.

### 14 Sensitivity analyses

15 When only studies using HOMA were included in pairwise comparisons, the standardised mean differences  
16 between HIIT and CT as well as HIIT and CON were somewhat attenuated; however, effects for HIIT versus  
17 CT remained significant (data not shown).

18 When studies were categorised by the time between final exercise session and post-test blood sample, we  
19 found that the improvement in insulin sensitivity diminished as the time after exercise increased (*Fig S2*).

### 20 *Fasting glucose*

21 Fasting glucose was reported in 47 (94%) studies. Of these, 30/47 (64%) were compared to at least one  
22 control group. There was a reduction in fasting glucose of  $0.13 \text{mmol.L}^{-1}$  (-0.19 to -0.07,  $p < 0.001$ ) with HIIT  
23 compared to baseline (*Fig. S3*), though this reduction was not different compared to the CON or CT groups  
24 overall (*Figure 3a & 3b*). Conversely, in those with metabolic syndrome or Type 2 diabetes, there was a  
25 reduction in fasting glucose of  $0.92 \text{mmol.L}^{-1}$  (-1.22 to -0.63,  $p < 0.001$ ) following HIIT compared to CON  
26 (five studies; *Figure 3a*).

### 27 *HbA1c*

28 Baseline and post-intervention HbA1c was reported by 13 (26%) studies. Of these, 6/13 (46%) had a CON  
29 group and 7/13 (54%) had a CT group. Compared to baseline, there was no change in HbA1c (*Fig.S4*),  
30 however within the metabolic syndrome/Type 2 diabetes population there was a significant reduction of -  
31 0.25% (-0.27 to -0.23,  $p < 0.001$ ). Similarly, there was no effect of HIIT compared to CON overall, but a  
32 significant reduction of 0.47% (-0.92 to -0.01,  $p = 0.04$ ) was observed in the metabolic syndrome/Type 2  
33 diabetes group (*Figure 4a*). There was no change in HbA1c compared to CT overall, or within any of the  
34 population subgroups (*Figure 4b*).

1 *Fasting insulin*

2 Fasting insulin was reported in 28 (56%) studies. Of these, 19/28 (68%) were compared to at least one  
3 control group. There was a significant reduction in fasting insulin from baseline of  $-0.93\mu\text{U.L}^{-1}$  ( $-1.39$  to  $-$   
4  $0.48$ ,  $p<0.001$ ; *Fig S5.1*) however, this effect was not present when HIIT was compared to a control group  
5 (*Fig S5.2 & 5.3*).

6 *Body Weight*

7 Studies reported body weight (9/50; 18%), body mass index (5/50; 10%) or both (25/50; 48%). Of these,  
8 23/34 (68%; body weight) and 23/31 (74%; body mass index) compared HIIT to at least one control group.  
9 Compared to baseline, there was a 0.7kg reduction in weight following HIIT ( $-1.19$ ,  $-0.25$ ,  $p=0.002$ ; *Fig.*  
10 *S6.1*). Compared to CON, the reduction was 1.3kg ( $-1.90$ ,  $-0.68$ ,  $p<0.001$ ; *Fig S6.2*). A greater effect of  
11 2.3kg ( $-3.27$  to  $-1.22$ ,  $p<0.001$ ) was observed in the metabolic syndrome/ Type 2 diabetes subgroup. In  
12 contrast, there was no difference in weight loss following HIIT compared to CT overall (WMD= $0.32$ ,  $-0.17$ ,  
13  $0.81$ ,  $p=0.20$ ; *Fig S6.3*). As expected, a similar pattern of changes were observed for BMI (data not shown).

14 *Cardiorespiratory fitness*

15 Cardiorespiratory fitness, expressed as  $\text{VO}_{2\text{max}}$ , was reported in 42 (84%) studies. Of these, 31/42 (74%)  
16 compared change in  $\text{VO}_{2\text{max}}$  to a control group. Compared to baseline, there was a  $0.30\text{L}\cdot\text{min}^{-1}$  increase in  
17  $\text{VO}_{2\text{max}}$  with HIIT ( $0.25$  to  $0.35$ ,  $p<0.001$ ; *Fig. S7.1*). This increase was similar in comparison to CON  
18 (WMD= $0.28$ ,  $0.12$  to  $0.44$ ,  $p=0.001$ ; *Fig S7.2*) and attenuated but still significant when compared to CT  
19 (WMD= $0.16$ ,  $0.07$  to  $0.25$ ,  $p=0.001$ ; *Fig S7.3*).

**Table 1 Effect sizes of comparisons of HIIT after training, compared to control and continuous training**

		Within groups <sup>†</sup>	Compared to CON	Compared to CT
Insulin Resistance	N	23	11	17
	ES (95% CI)	-0.33 (-0.47, -0.18)	-0.49 (-0.87, -0.12)	-0.35 (-0.68, -0.02)
	I <sup>2</sup> (%)	89.0	56.4	58.7
	p	<0.001	0.009	0.036
Fasting Glucose	N	47	18	23
	ES (95% CI)	-0.13 (-0.19, -0.07)	-0.17 (-0.34, 0.01)	-0.07 (-0.17, 0.03)
	I <sup>2</sup> (%)	74.4	67.8	4.9
	p	<0.001	0.067	0.178
HbA1c	N	13	6	7
	ES (95% CI)	-0.13 (-0.27, 0.01)	-0.19 (-0.36, -0.03)	0.02 (-0.07, 0.11)
	I <sup>2</sup> (%)	99.0	0.0	18.5
	p	0.068	0.021	0.678
Fasting Insulin	N	28	11	16
	ES (95% CI)	-0.93 (-1.39, -0.48)	-1.0 (-2.32, 0.32)	-0.34 (-1.42, 0.73)
	I <sup>2</sup> (%)	81.4	57.5	0.0
	p	<0.001	0.138	0.531
Body weight	N	34	14	18
	ES (95% CI)	-0.72 (-1.19, -0.25)	-1.29 (-1.90, -0.68)	0.32 (-0.17, 0.81)
	I <sup>2</sup> (%)	93.0	21.4	33.2
	p	0.002	<0.001	0.201
VO2max	N	44	18	23
	ES (95% CI)	0.30 (0.25, 0.35)	0.28 (0.12, 0.44)	0.16 (0.07, 0.25)
	I <sup>2</sup> (%)	97.9	91.8	76.3
	p	<0.001	0.001	0.001

<sup>†</sup>Within groups effect sizes reflect the pooled difference before and after the intervention in the HIIT arm of each study including both controlled and non-controlled trials.

CON: non-exercising control; CT: continuous training; CI: confidence interval; N: number of studies included in analysis; ES: effect size; I<sup>2</sup>: study heterogeneity statistic; WMD: weighted mean difference; SMD: standardised mean difference

## 1 **Meta-regression**

2 *Table 2* shows the  $\beta$  coefficients and confidence intervals for the regression analyses. HIIT characteristics;  
3 interval intensity and weekly high-intensity exercise did not predict the improvements observed in insulin  
4 resistance, fasting glucose, fasting insulin or HbA1c. Baseline levels of insulin resistance, fasting glucose  
5 and fasting insulin predicted changes in these outcomes overall. Using the regression equation, we calculated  
6 baseline insulin resistance would have to be  $\geq 3.18$  to experience a reduction in HOMA-IR of -0.5 or greater.  
7 Similarly, for a  $0.1\text{mmol.L}^{-1}$  or greater reduction in fasting glucose, baseline glucose would have to be  
8  $\geq 4.92\text{mmol.L}^{-1}$ . When compared to non-exercising control groups, there was an inverse association between  
9 baseline level and change in fasting glucose. Changes in body weight did not predict changes in insulin  
10 resistance or glucose regulation.  $\text{VO}_{2\text{max}}$  was associated with a reduction in fasting glucose in studies that  
11 included a non-exercising control group, however  $\text{VO}_{2\text{max}}$  did not predict other outcomes.

**Table 2. Meta-regression coefficients**

		Interval Intensity♣	Time at high-intensity/week♦	Weeks•	Change in body weight	Baseline level	Change in VO <sub>2max</sub>
B (95% CI)							
Insulin Resistance	WG	1.46 (-12.97, 15.88) <sup>‡</sup>	2.64 (-10.63, 15.92) <sup>‡</sup>	-27.71 (-71.43, 16.00) <sup>‡</sup>	0.10 (-0.09, 0.29)	-0.22 (-0.37, -0.06) <sup>*</sup>	0.00 (-0.31, 0.32)
	CON	8.19 (-33.34, 12.90) <sup>‡</sup>	-0.01 (-0.02, 0.03)	-0.07 (-0.17, 0.03)	0.35 (-0.39, 1.10)	-0.24 (-0.90, 0.43)	-0.09 (-1.37, 1.19)
	CT	2.73 (-33.84, 28.38) <sup>‡</sup>	8.00 (-38.33, 22.34) <sup>‡</sup>	-0.02 (-0.13, 0.09)	0.27 (-1.19, 1.73)	-0.10 (-0.50, 0.31)	-0.72 (-1.66, 0.65)
Fasting Glucose	WG	2.30 (-3.90, 0.54) <sup>‡</sup>	-1.65 (-5.45, 2.15) <sup>‡</sup>	-1.15 (-15.02, 12.72) <sup>‡</sup>	0.02 (-0.07, 0.10)	-0.12 (-0.22, -0.02) <sup>*</sup>	0.08 (-0.20, 0.36)
	CON	1.59 (-12.50, 15.68) <sup>‡</sup>	0.33 (-13.71, 14.38)	-0.01 (-0.03, 0.02)	0.09 (-0.12, 0.30)	-0.29 (-0.45, -0.12) <sup>*</sup>	-1.03 (-1.89, -0.17) <sup>*</sup>
	CT	-1.93 (-4.86, 8.72) <sup>‡</sup>	-0.54 (-10.74, 9.66) <sup>‡</sup>	-0.02 (-0.07, 0.03)	-0.01 (-0.13, 0.12)	-0.10 (-0.24, 0.03)	-0.25 (-0.58, 0.07)
HbA1c	WG	1.53 (-12.31, 15.37) <sup>‡</sup>	0.56 (-11.31, 12.43) <sup>‡</sup>	-0.54 (-13.57, 12.83) <sup>‡</sup>	-0.01 (-0.08, 0.06)	-0.14 (-0.31, 0.03)	0.25 (-0.56, 1.05)
	CON	-0.10 (-1.21, 1.01)	0.02 (-0.25, 0.29)	0.002 (-1.12, 0.12)	0.02 (-0.10, 0.14)	-0.13 (-0.56, 0.30)	-1.01 (-4.40, 2.38)
	CT	-	-	-	0.01 (-0.21, 0.22)	-0.14 (-0.38, 0.10)	0.42 (-1.14, 1.97)
Fasting Insulin	WG	-0.01 (-0.07, 0.04)	-0.01 (-0.05, 0.04)	-0.15 (-0.33, 0.03)	0.29 (-0.41, 1.00)	-0.26 (-0.42, -0.10) <sup>*</sup>	-0.36 (-2.74, 2.02)
	CON	-0.003 (-0.11, 0.10)	0.02 (-0.07, 0.12)	-0.21 (-0.60, 0.18)	1.56 (-0.06, 3.17)	-0.40 (-0.87, 0.08)	8.34 (-7.90, 24.59)
	CT	0.003 (-0.12, 0.12)	-0.05 (-0.18, 0.08)	0.05 (-0.37, 0.46)	0.71 (-0.62, 2.04)	-0.29 (-0.63, 0.04)	-0.77 (-4.20, 2.66)

WG: within groups; CON: non-exercising control; CT: continuous training; CI: confidence intervals

♣: controlled for weekly high intensity duration and study length; ♦: controlled for interval intensity and study length; •: controlled for interval intensity and weekly high-intensity duration; ‡: these values have been multiplied by 1000 and therefore represent a per 1000 unit change in the independent variable; \*: p<0.05; -: not enough data to perform this analysis

## 1 **Discussion**

2 The results of this meta-analysis suggest that HIIT is effective at improving measures of insulin resistance  
3 compared to continuous exercise and a non-exercising control group. Importantly, the largest effects were  
4 seen in those with Type 2 diabetes or metabolic syndrome. Furthermore, in those with Type 2 diabetes or the  
5 metabolic syndrome there was a 0.92mmol.L<sup>-1</sup> reduction in fasting glucose and a 0.47% (5mmol.L<sup>-1</sup>)  
6 reduction in HbA1c when compared to studies with a non-exercising control group. Results for these  
7 measures and fasting insulin were less conclusive amongst the cohort as a whole and when compared to  
8 continuous exercise. There was a significant reduction of 1.3kg in body weight compared to the non-  
9 exercising control group, an effect largely observed in those described as overweight, obese, with, or at risk  
10 of Type 2 diabetes. In addition, cardiorespiratory fitness improved compared to both controls, to an extent  
11 comparable with previous meta-analyses of HIIT interventions.<sup>22, 27</sup>

12 The primary modifiable elements of HIIT protocols, defined here as interval intensity and weekly time spent  
13 at high-intensity, did not significantly alter intervention effectiveness in terms of insulin resistance, fasting  
14 glucose, HbA1c or fasting insulin. Consistent with the results observed in the meta-analysis, those with the  
15 highest baseline values experienced the greatest benefits in insulin resistance and glucose regulation,  
16 although these associations were, largely, not present in controlled studies. Body weight and  
17 cardiorespiratory fitness both improved following HIIT, but changes in these outcomes did not tend to  
18 predict improvements in insulin resistance or glucose regulation. There was however, an inverse relationship  
19 between change in VO<sub>2max</sub> and fasting glucose in controlled studies.

20 As far as we are aware this is the first systematic review and meta-analysis of the effects of HIIT on  
21 outcomes related to metabolic health. The findings extend the conclusions made by Adams<sup>30</sup> who inferred  
22 that HIIT resulted in similar acute physiological adaptations as continuous training despite a lower energy  
23 expenditure. Here, we provide a quantified estimation of the training effects of HIIT on insulin resistance,  
24 HbA1c, fasting glucose, fasting insulin and body weight.

## 25 **Clinical application**

26 Our study suggests that HIIT may reduce insulin resistance compared to both continuous exercise training  
27 and control conditions. Insulin resistance is a recognised precursor to Type 2 diabetes<sup>72</sup> and has been  
28 identified as an independent risk factor for cardiovascular disease.<sup>73-75</sup> We have shown that under supervised,  
29 laboratory conditions HIIT is effective in improving insulin sensitivity and potentially therefore improving  
30 glycaemic control and diabetes-related outcomes. Indeed, while data on HbA1c in this area are limited, the  
31 reduction following HIIT in those with or at risk of Type 2 diabetes in this study was 0.47% which is  
32 consistent with previous observations that report clinically significant reductions of up to 0.6% in HbA1c  
33 after a minimum of eight weeks of exercise training.<sup>2-4</sup>

34 Meta-regression results suggest that to achieve the observed reduction in HOMA-IR of 0.5 units, baseline  
35 HOMA needs to be at least 3.18, a value that has been consistently associated with the 50% most insulin

1 resistant individuals within a population<sup>73, 74</sup> and indicating that HIIT may improve insulin sensitivity only in  
2 those who are insulin resistant. HIIT therefore has the potential to be used as an alternative therapeutic  
3 strategy to traditional physical activity interventions for those with or at risk of Type 2 diabetes.

#### 4 **Potential mechanisms**

5 Improvement in peripheral insulin sensitivity is one of the main mechanisms that has been used to explain  
6 the enhancement in glycaemia following exercise training and has been widely demonstrated following both  
7 acute and chronic exercise training.<sup>76</sup>

8 Improvements in insulin sensitivity have often been associated with a reduction in body weight<sup>77</sup>. We found  
9 that HIIT reduced both insulin resistance and body weight, although meta-regression did not reveal an  
10 association between these two factors. This is congruous with the findings of Karstoft et al.<sup>78</sup> who found that  
11 changes in body composition following HIIT explained less than 25% of improvements in insulin sensitivity  
12 in patients with Type 2 diabetes. However, we were unable to determine whether body composition or fat  
13 distribution were affected by HIIT. A reduction in abdominal adiposity – often achieved with exercise  
14 training<sup>79</sup> – may cause an improvement in hepatic insulin sensitivity,<sup>80</sup> and it may be this that resulted in an  
15 improvement in HOMA-IR scores, rather than overall weight loss.

16 Furthermore, given the protective effect of cardiorespiratory fitness on HbA1c<sup>81</sup>, morbidity<sup>82</sup> and mortality<sup>83</sup>  
17 in Type 2 diabetes, it is notable that change in VO<sub>2max</sub> also did not predict changes in insulin resistance or  
18 glycaemic control in this study. It therefore appears that some adaptations associated with increased muscle  
19 oxidative capacity may be independent of those that promote metabolic health. Nonetheless, by providing  
20 evidence that HIIT may lead to greater reductions in insulin resistance than continuous exercise training, our  
21 study suggests that either the interval modality, or the greater exercise intensity facilitate benefits observed  
22 with continuous moderate-intensity exercise training. There are a number of established metabolic pathways  
23 that are likely to be enhanced by HIIT, with some support from recent investigations. These include skeletal  
24 muscle glucose uptake,<sup>84</sup> GLUT-4 content<sup>85, 86</sup> and muscle glycogen depletion induced insulin sensitivity.<sup>71, 87</sup>

25 Training adaptations have been associated with changes in body composition, muscle physiology<sup>84-86, 88, 89</sup>  
26 and glucose metabolism<sup>90</sup>. There is some evidence that while muscle glycogen content is not greatly affected  
27 following moderate-intensity continuous activity lasting less than one hour,<sup>91</sup> glycogen depletion is observed  
28 following vigorous-intensity exercise<sup>92</sup> and is one way HIIT may enhance acute insulin sensitivity superior to  
29 moderate-intensity continuous exercise.<sup>71</sup> It is unclear whether this acute response promotes chronic  
30 adaptations that enhance insulin sensitivity, although it is possible that repeated acute improvements may be  
31 as beneficial.<sup>93</sup>

32 The mechanisms that may be enhanced following HIIT compared to continuous exercise training need  
33 further elucidation as there is disagreement as to the optimum volume and intensity of exercise that  
34 stimulates the greatest benefits<sup>94, 95</sup> and which of these factors is more important in metabolic health. We  
35 found no relationship between exercise intensity or time spent at high-intensity and changes in

1 glucose/insulin parameters meaning that we are unable to determine which characteristics of HIIT protocols  
2 induce the observed improvements in these outcomes. HIIT presents a unique challenge to optimising  
3 exercise prescription given the range of variables that can be manipulated. Some,<sup>42</sup> but not all,<sup>95</sup> studies  
4 suggest that exercise intensity is the primary factor determining the degree of metabolic adaptations, though  
5 these investigations have not assessed HIIT programmes specifically which, as discussed, introduces more  
6 nuanced exercise variables.

## 7 **Strengths and Limitations**

8 The strengths of this review include the comprehensive search strategy employed, the use of random effects  
9 meta-analysis and the focus on metabolic outcomes. Of note, none of the individual studies of metabolic  
10 syndrome or Type 2 diabetes patients reported a significant reduction in HbA1c compared to control,  
11 whereas the pooled effect showed one may occur following HIIT training. This demonstrates the advantages  
12 of meta-analysis and highlights the importance of conducting adequately powered trials.

13 However, this meta-analysis is not without limitation. Firstly, study quality was poor with only 4/36 (11%)  
14 controlled studies deemed to have low risk of bias. Secondly, there was wide heterogeneity between  
15 participants, HIIT protocol, and intervention length as well as CT interventions making it difficult to  
16 generalise conclusions and make direct comparisons between HIIT and CT. This issue was addressed to the  
17 best of our ability by stratifying results by participant disease status and using meta-regression. Nonetheless,  
18 we highlight the need for more robust randomised controlled trials to be carried out in the future using  
19 standardised continuous training protocols. Thirdly, the length of time between the last bout of exercise and  
20 post-test blood samples was not reported by many of the studies measuring insulin resistance. This is  
21 important since we demonstrated that the improvement in HOMA-IR score diminished with increasing time  
22 to assessment. In addition it is possible that the use of HOMA-IR may underestimate the impact of HIIT on  
23 insulin sensitivity given that HOMA is more representative of hepatic insulin resistance<sup>41</sup> and exercise is  
24 more likely to affect peripheral insulin resistance.<sup>96</sup> Indeed, our sensitivity analysis indicated that this may  
25 have been the case in the included studies. It is also difficult to apply the reduction in HOMA-IR score found  
26 in this meta-analysis in a wider context and the clinical relevance of a change of -0.33 units is unclear.

27 The number of participants who underwent a HIIT intervention and who were likely to be insulin resistant  
28 represented just 23% of the study population. This could mean that the potential of HIIT to reduce insulin  
29 resistance is not fully illustrated by this study; as demonstrated by our meta-regression, and emphasises the  
30 need for more trials to be carried out in those at risk of or with Type 2 diabetes.

31 Despite the safety concerns associated with HIIT, few studies reported pre-screening results or adverse  
32 events. There were more exercise-related injuries reported in the HIIT interventions than control conditions,  
33 but it is difficult to draw conclusions from the limited data available.

34 Finally, HIIT has been promoted as being a time-efficient exercise modality. This review provides some  
35 support that exercise induced health benefits can be achieved with as little as  $21 \pm 16$  minutes of vigorous-



1 intensity physical activity performed three times per week. However, it is worth noting that in total, exercise  
2 sessions took  $34 \pm 13$  minutes to complete (including warm-up, recovery intervals and cool down). It is  
3 important to elucidate whether the requirement to set aside 35 minutes three times per week to perform HIIT  
4 addresses the perceived barrier to physical activity of “lack of time”.

## 5 **Suggestions for future research**

6 Our results suggest that HIIT *per se* has the potential to improve health outcomes, regardless of the precise  
7 protocol employed. However, it is clear that more studies should be conducted that compare the effects of  
8 HIIT to those of continuous training, particularly in people at risk of or with type 2 diabetes given these were  
9 where the strongest effects were observed. To this end studies should be of long enough duration and  
10 adequately powered to detect any potential changes in clinically relevant outcomes such as HbA1c. A greater  
11 understanding of the potential mechanisms stimulating the more potent effects of HIIT compared to  
12 continuous training should be elucidated so they can be maximised through exercise training.

13 Just six studies included in this review were conducted in either a “free-living” or “real world” context.<sup>39, 50,</sup>  
14 <sup>61-63, 65</sup> If HIIT is to be recommended to the general population it must be made practical and accessible.  
15 Interventions in community settings, requiring minimal specialist equipment and supervision should be  
16 conducted to assess uptake, adherence and compliance to the protocol. Few studies have measured effort and  
17 enjoyment of completing HIIT, with some positive responses,<sup>97-99</sup> including in sedentary populations.<sup>100</sup> The  
18 results should be extended to populations averse to exercise in order to determine whether HIIT would be  
19 taken up as a health promoting form of physical activity.

## 20 **Conclusions**

21 In conclusion, we have demonstrated that HIIT conveys benefits to metabolic health which in the instance of  
22 insulin resistance and  $VO_{2max}$  may be superior to the effect of traditional continuous training. HIIT may  
23 therefore be suitable as an alternative to continuous exercise training in the promotion of metabolic health  
24 and weight loss, particularly in those with Type 2 diabetes or the metabolic syndrome. However, given the  
25 identified limitations, more research is needed to determine both behavioural responses and clinical benefits  
26 over the longer term.

## 27 **Figure legends**

28 **Figure 1** Study selection

29 **Figure 2** Change in insulin resistance after HIIT compared to (a) control and (b) continuous training

30 **Figure 3** Change in fasting glucose after HIT compared to (a) control and (b) continuous training

31 **Figure 4** Change in HbA1c after HIT compared to (a) control and (b) continuous training

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1 **Contribution statement**

2 CJ and TY had the original idea for the review. CJ developed and revised the protocol with input from all  
3 authors. CJ developed the search strategy, performed the searches and statistical analyses and wrote the first  
4 draft of the article. CJ & GO reviewed and extracted data. All authors contributed to the writing of the paper,  
5 provided input throughout the study and approved the final manuscript.

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