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High intensity interval training and cardiometabolic health in the general population: A systematic review and meta-analysis of randomised controlled trials

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Running Title: HIIT and cardiometabolic health

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Key Points:

- This large-scale systematic review and meta-analysis of 97 randomised controlled trials provides support for high intensity interval training (HIIT) in the clinical management of cardiometabolic health with implications regarding physical activity guideline recommendations.
- HIIT produced significant improvements in 14 clinically relevant parameters, including peak aerobic capacity, systolic and diastolic blood pressure, resting heart rate, stroke volume and left ventricular ejection fraction.
- Improvements were also observed in parameters of body composition, lipids, fasting insulin, and anti-inflammatory changes via reductions in high sensitivity C-reactive protein.

Abstract

Background: High intensity interval training (HIIT) remains a promising exercise mode in managing cardiometabolic health. Large-scale analyses are necessary to understand its magnitude of effect on important cardiometabolic risk factors and inform guideline recommendations.

Objective: We aimed to perform a novel large-scale meta-analysis on the effects of HIIT on cardiometabolic health in the general population.

Methods: PubMed (MEDLINE), the Cochrane library and Web of Science were systematically searched. Randomised controlled trials (RCT's) published between 1990 and March 2023 were eligible. Research trials reporting the effects of a HIIT intervention on at least 1 cardiometabolic health parameter with a non-intervention control group were considered.

Results: This meta-analysis included 97 RCT's with a pooled sample size of 3399 participants. HIIT produced significant improvements in 14 clinically relevant cardiometabolic health parameters, including peak aerobic capacity (VO_2) (Weighted mean difference [WMD]: 3.895 $ml \cdot min^{-1} \cdot kg^{-1}$, P<0.001), left ventricular ejection fraction (WMD: 3.505%, P<0.001), systolic (WMD: -3.203 mmHg, P<0.001) and diastolic (WMD: -2.409 mmHg, P<0.001) blood pressure, resting heart rate (WMD: -3.902bpm, P<0.001) and stroke volume (WMD: 9.516 mL, P<0.001). Body composition also significantly improved through reductions in body mass index (WMD: -0.565 $kg \cdot m^2$, P<0.001), waist circumference (WMD: -2.843cm, P<0.001) and percentage body fat (WMD: -0.972%, P<0.001). Furthermore, there were significant reductions in fasting insulin (WMD: -13.684 $pmol \cdot L^{-1}$, P=0.004), high sensitivity C-reactive protein (WMD: -0.445 $mg \cdot dL^{-1}$, P=0.043), triglycerides (WMD: -0.090 $mmol \cdot L^{-1}$, P=0.011) and low-density lipoprotein (WMD: -0.063 $mmol \cdot L^{-1}$, P=0.050), concurrent to a significant increase in high-density lipoprotein (WMD: 0.036 $mmol \cdot L^{-1}$, P=0.046)

Conclusion: These results provide further support for HIIT in the clinical management of important cardiometabolic health risk factors, which may have implications regarding physical activity guideline recommendations.

1. Introduction

Physical activity and structured exercise training are well-recognised as primary means to managing cardiometabolic health, independent of other lifestyle factors. Indeed, decades of sustained empirical investigations have consistently reported significant improvements in a wide array of cardiometabolic fitness and health markers following exercise training, including peak aerobic capacity (VO_2) [1], blood pressure [2] and body composition [3], ultimately contributing to a reduction in the risk of all-cause mortality in the general population [4–6].

Traditionally, exercise research and prescription has been primarily focused on moderate intensity continuous training (MICT), which has subsequently directed the current global exercise guidelines [7]. However, despite the unequivocal benefits of exercise training, adoption and adherence to these current guidelines remains poor, with adherence estimates of 27.5% [8], and as low as 5% when measured via objective accelerometer means [9]. Therefore, exploration of novel approaches to exercise training that may better promote adoption and adherence in the general population appears pragmatic.

High intensity interval training (HIIT), is a convenient and time efficient exercise modality consisting of short bouts of high intensity work, separated with appropriate recovery periods. Since its emergence, a plethora of HIIT trials have demonstrated substantial effects on various cardiometabolic risk factors, with numerous meta-analyses to support [10–13]. While these analyses have provided important information regarding the efficacy of HIIT, much of this work has been in specialized populations/diseases, only analysed single risk factors, which inevitably limits interpretation regarding wider cardiometabolic health, and/or involved analyses using standardised mean differences (SMD) [14]. Although the benefits of SMD regarding generalisability and statistical heterogeneity are well known in meta-analysis research, the primary consequence of this outcome lies within its inability to provide concise contextualisation as to the magnitude of effect [15]. Indeed, effectively interpretating and contextualising the magnitude of effect is imperative when considering global guideline adjustments and establishing optimal practices in clinical exercise prescription for the management of cardiometabolic health.

As such, we aimed to perform an important and novel large-scale meta-analysis on the precise effects of HIIT on cardiometabolic health in the general population.

2. Methods

2.1 Information sources and search strategy

This systematic review and meta-analysis was performed in accordance to the PRISMA guidelines [16], with PROSPERO registration (CRD42022326576). Potential studies were identified via a comprehensive search of PubMed (MEDLINE), the Cochrane library and Web of Science for research trials reporting the effects of a HIIT intervention on cardiometabolic health in the general population. The search strategy included combinations of the relevant medical subject heading (MeSH) terms, text words, and word variants for HIIT, high intensity interval training and cardiometabolic health, as well as each individual parameter of interest (see advanced search details in the supplementary file). Randomised controlled trials (RCT's) published between 1990 and 24th March 2023 were eligible. Reference lists of relevant articles and previous systematic reviews were hand searched for additional reports not identified in the initial search.

2.2 Study eligibility

Two authors (MG and AD) independently screened all papers for eligibility. Studies were firstly screened by title and abstract, and subsequently by full text if they met the relevant inclusion criteria. Following study recruitment, the respective data of all included studies was extracted via Microsoft Excel. Any inconsistencies in data collection or confliction regarding study eligibility were discussed by the researchers and a consensus was reached with the opinion of a third researcher (JE) if necessary. If more than one study is published for the same cohort and respective outcomes, the study containing the most comprehensive information was included to avoid overlapping populations. Studies were considered eligible if they reported the effects of a HIIT intervention on at least 1 of the following cardiometabolic health parameters: Peak VO_2, left ventricular ejection fraction (LVEF), ratio of early to late diastolic peak blood flow velocity (E/a ratio), ratio of early mitral inflow velocity and mitral annular early diastolic velocity (E/e'), systolic and/or diastolic blood pressure (sBP/dBP), resting heart rate (RHR), stroke volume (SV), body mass index (BMI), waist circumference, body fat percentage, glycated haemoglobin (HbA1c), fasting plasma glucose, fasting plasma insulin, triglycerides, high-density and low-density lipoprotein (HDL and LDL), high sensitivity C-reactive protein (hs-CRP), interluikin-6 (IL-6), Tumour necrosis factor alpha (TNF-a) and TNF receptor-1 (TNFR1). Where applicable, the reported units of measurement for each parameter were converted for consistency. Studies that might appear

eligible but were excluded are available on request from the corresponding author (with exclusion reason).

This review strictly recruited RCT's only, including cross-over trials, with adult participants (≥18 years). To effectively represent the general population, there were no predetermined limitations on health or disease state. However, for sub-analysis purposes, study populations in this work were categorised as 'diseased' or 'non-diseased' based on whether the included participants had any clinically relevant diagnoses/history except for overweight/obesity and hypertension. The non-intervention control groups of the included papers were required to minimise confounders, with any dietary, counselling or exercise influence resulting in exclusion. Following the definitions employed by the Physical Activity Guidelines Advisory Committee [10], this review defines HIIT as 'episodic short bouts of high intensity exercise separated by short periods of recovery at a lower intensity'. High intensity exercise was classified in accordance with the EXPERT tool [17], at intensity metrics falling within the categories of 'High intensity, vigorous effort' or 'Very hard effort'. As sub-groups of HIIT, sprint interval training (SIT) was defined as an 'all-out' maximal, low-volume protocol, whereas aerobic interval training (AIT) consisted of entirely 4 x 4-minute protocols of a lower intensity.

2.3 Study quality

Risk of bias and methodological quality of all recruited studies was evaluated using the TESTEX scale [18]. TESTEX is a 15-point (12 item) tool designed for the assessment of exercise science studies. Two reviewers (MG and AD) independently scored all eligible articles (see Table S1). Any disputes in quality analyses were resolved via consensus, or a third reviewer was consulted (JE).

2.4 Statistical analysis

A pooled analysis was performed on all included studies separately for each outlined parameter. The weighted mean difference (WMD) between the HIIT group and the non-intervention control group was measured. Comprehensive Meta-Analysis (Comprehensive Meta-Analysis Version 3, Biostat, Englewood, NJ, USA) was utilised as the data synthesis software. Statistical heterogeneity was measured for each individual pooled outcome and subsequently reported as the I^2 statistic. A 40% threshold was determined a priori, with heterogeneity above this point considered significant. Fixed effects analysis was preferred

unless the I^2 statistic was beyond this threshold, in which a random-effects analysis was selected as suggested when interstudy variability is confirmed through significant heterogeneity. Furthermore, a post-hoc Egger's regression test (1997) was systematically planned to assess the presence of funnel plot asymmetry with consideration of potential publication bias. Sub-group and meta-regression analyses were also employed to measure the effects of differing study-level variables on peak VO_2, of which included HIIT sub-mode (AIT versus SIT), intervention duration, weekly HIIT frequency and mode of HIIT application (walking/running versus cycling protocols). Separate parallel pooled analyses were also performed in only those studies free from any cardiovascular or other disease. The results of the pooled analyses was considered significant with a P value of ≤ 0.05 and a Z-value of >2.

3. Results

Figure 1 details the PRISMA flowchart. 4459 studies were initially identified through database searching and 27 through other sources, which reduced to 359 for full-text screening following the removal of duplicates and initial screening. This meta-analysis ultimately included 97 studies (112 analysed effect sizes) with a pooled sample size of 3399 participants. The full TESTEX risk of bias assessment scoring can be found in Table S1. There were several consistent limitations throughout the HIIT literature. Most frequently, trials failed to monitor control group activity or perform intention-to-treat analysis when appropriate. Study and HIIT intervention characteristics (Table S2) are provided in the supplementary file. For sensitivity and study heterogeneity purposes, we also ran parallel analyses on all outcomes excluding cardiovascular or other disease (See Table S3).

3.1 Peak aerobic capacity (VO_2)

Figure 2 displays the changes in peak VO_2 following HIIT compared to the control group. Analysis of 65 effect sizes (ES) demonstrated a statistically significant increase in peak VO_2 following HIIT by 3.895 $ml \cdot min^{-1} \cdot kg^{-1}$ (95% CI = 3.34-4.45, $P_{random}<0.001$) compared to the control group. There was statistically significant heterogeneity ($I^2 = 77.42\%$), but no evidence of publication bias. Subgroup analyses demonstrated significant reductions following both AIT (3.77$ml \cdot min^{-1} \cdot kg^{-1}$, 95% CI = 2.56-5.00, $P_{random}<0.001$) and SIT (3.25$ml \cdot min^{-1} \cdot kg^{-1}$, 95% CI = 1.62-4.88, $P_{random}<0.001$) with no significant difference between the sub-modes. However, there was a significantly greater improvement in peak VO_2 in walking/running HIIT protocols compared to cycling HIIT protocols (5.10 vs 3.52$ml \cdot min^{-1} \cdot kg^{-1}$, P=0.008). Moderator analyses determined no significant effect of intervention duration (B=-0.0364, P=0.337) or number of HIIT session per week (B=0.6774, P=0.1343).

3.2 Cardiac function

HIIT produced a statistically significant increase in LVEF by 3.505% (95% CI = 1.81-5.20, 8 ES, $P_{random}<0.001$) compared to the control group. Conversely, there was no significant change in E/a ratio following HIIT (WMD=-0.024, [95% CI] = -0.16-0.11, 5 ES, $P_{random}=0.737$) compared to the control group. Both LVEF and E/a ratio analyses contained high heterogeneity ($I^2 = 69.20\%$ and 64.85% respectively), but no evidence of publication bias. There was insufficient data to perform rigorous E/e' analyses.

3.3 Haemodynamics

HIIT significantly reduced resting sBP and dBP by 3.203 mmHg (95% CI = 1.86-4.55, 54 ES, $P_{random}<0.001$) and 2.409 mmHg (95% CI = 1.25-3.56, 52 ES, $P_{random}<0.001$) compared to the control group. There was significant heterogeneity for both sBP and dBP (I^2 = 82.11% and 90.12% respectively), with no evidence of publication bias.

RHR also significantly decreased following HIIT by a magnitude of 3.902 bpm (95% CI = 2.88-4.93, 40 ES, $P_{random}<0.001$) compared to the control group. There was significant heterogeneity (I^2 = 79.96%) and funnel plot asymmetry for RHR, indicating potential publication bias (Figure S1, P=0.020). Separately, SV significantly increased following HIIT by 9.516 mL (95% CI = 4.69-14.34, 12 ES, $P_{random}<0.001$) with significant heterogeneity (I^2 = 91.50%) and no publication bias.

3.4 Body composition

HIIT significantly reduced BMI by 0.565 $kg \cdot m^2$ (95% CI = 0.40- 0.73, 58 ES, $P_{fixed}<0.001$), compared to the control group with no significant heterogeneity (I^2 = 23.67%), but evidence of publication bias (Figure S2, P= 0.016). HIIT also significantly decreased waist circumference by 2.843cm (95% CI = 2.31-3.38, 31 ES, $P_{fixed}<0.001$) and body fat by 0.972% (95% CI = 0.46-1.48, 36 ES, $P_{random}<0.001$) compared to the control group. There was no significant heterogeneity or evidence of publication bias for waist circumference analyses. Oppositely, body fat analyses demonstrated significant heterogeneity (I^2 = 57.46%).

3.5 Lipids, insulin and glucose

Triglycerides significantly decreased by 0.090 $mmol \cdot L^{-1}$ following HIIT (95% CI = 0.02-0.16, 40 ES, $P_{random}=0.011$) compared to the control group. HIIT also produced a statistically significant increase in HDL (WMD= 0.036, [95% CI] = 0.00-0.07, 38 ES, $P_{random}=0.046$) concurrent to a significant reduction in LDL (WMD= -0.063, [95% CI] = 0.00--0.013, 32 ES, $P_{random}=0.050$) compared to the control group. Triglycerides, HDL and LDL analyses were all significant for heterogeneity (I^2 = 44.01%, 81.61% and 64.21% respectively). There was no evidence of publication bias for HDL, LDL or triglycerides.

HIIT produced a statistically significant reduction in fasting insulin by 13.684 $pmol \cdot L^{-1}$ (95% CI = 4.29-23.08, 19 ES, $P_{random}=0.004$). Differently, although borderline, there was no significant change in fasting plasma glucose (WMD= 0.120 $mmol \cdot L^{-1}$, 95% CI = -0.00-0.24,

30 ES, P_{random}=0.053) compared to the control group. There was also no change in HbA1c (WMD= 1.583 mmol, 95% CI = -1.18-4.34, 7 ES, P_{random}=0.261); however, when the analysis was limited to those with abnormal baseline HbA1c values, this value became statistically significant (Table S3). Fasting insulin, fasting plasma glucose and HbA1c analyses all demonstrated significant heterogeneity (I^2 = 88.52%, 80.99%, 86.08%, respectively). Fasting plasma glucose analyses were significant for publication bias (Figure S3, p<0.001), whereas insulin and HbA1c were not.

3.6 Inflammatory markers

hs-CRP significantly decreased following HIIT by a magnitude of 0.445 $mg \cdot dL^{-1}$ (95% CI = 0.01-0.88, 9 ES, P_{random}=0.043) compared to the control group, with significant heterogeneity (I^2 = 42.150) and publication bias (Figure S4, P=0.01). IL-6, TNF-a and TNFR1 were not analysed due to limited data (<5 available effect sizes).

4. Discussion

This meta-analysis aimed to determine the effects of HIIT on cardiometabolic health in the general population through the analysis of 17 clinically relevant parameters. As presented in Figure 3, the findings of this work highlight the broad efficacy of HIIT, with significant improvements in peak VO_2, blood pressure, heart rate, stroke volume, LVEF, body composition, triglycerides, HDL, LDL, plasma insulin and systemic inflammation via hs-CRP. These findings further support the role of HIIT in the management of cardiometabolic health, with clear potential for guideline and clinical implementation.

Peak VO_2 remains a primary measure of cardiorespiratory fitness and health, with conclusive prognostic implications [19]. Following the analysis of 65 effect sizes, the findings of this work demonstrate a statistically significant increase in peak VO_2 by 3.895 $ml \cdot min^{-1} \cdot kg^{-1}$, representing a greater than 1 metabolic equivalent (MET) improvement. Importantly, previous predictive research has reported a 1-MET increase to be associated with a 13% and 15% reduction in the risk of all-cause mortality and cardiovascular events respectively [19]. Furthermore, changes of this magnitude are similar to that typically reported from previous MICT analyses [20]. Of interest, our novel analysis showed significantly greater peak VO_2 improvements in walking/running HIIT protocols when compared to cycling HIIT protocols. These results are supported by Mallol et al. [21] who found significant improvements in VO_2 in running HIIT, but not in cycling HIIT despite identical training protocols. While this finding certainly requires further independent exploration, one may postulate the importance of bodyweight bearing in achieving maximal cardiometabolic adaptations following exercise training. To further clarify optimal HIIT prescription practices, we also analysed the role of intervention duration and weekly HIIT frequency, finding no significant effects. Considering the overwhelming majority of HIIT protocols tend to employ 3 weekly sessions for 4-16 weeks (See Table S2), deviations away from this standard does not appear to provide obvious advantages towards cardiometabolic fitness.

The blood pressure findings of this research are supported by a recent HIIT analysis from our group [12], and are similar to that seen following MICT [22]. With hypertension remaining the leading modifiable risk factor for cardiovascular disease and all-cause mortality [23], these reductions following HIIT carry important independent clinical implications. Although HIIT does not produce blood pressure reductions to the magnitude of that seen following the likes of isometric exercise training, the wider cardiometabolic adaptations observed in this

work confirm previous hypothesis that HIIT is the more effective mode in the general maintenance of optimal health [12]. Similar to isometric exercise training [24], the improvements in cardiac function evidenced through the present changes in LVEF and SV following HIIT are likely to be somewhat mediated through a reduction in blood pressure as load-dependant parameters. In turn, these cardiac functional adaptations may have contributed towards enhanced exercise oxygen delivery and thus peak VO_2 after HIIT [25]. Unfortunately, there is very limited RCT evidence regarding the effects of HIIT on more advanced measures of systolic cardiac performance such as global longitudinal strain as a more sensitive parameter, or myocardial work as a less load-dependant measure; resulting in the omission from the present meta-analysis.

Body composition is often considered central to cardiometabolic health, with BMI, body fat percentage and waist circumference all closely associated with other key risk factors such as hypertension and elevated HbA1c [26]. Although caution in interpretation should be applied given the wide error ranges often reported with body composition assessment [27,28], these findings further support HIIT in risk factor and general health management, especially given the well documented associations between BMI, fat mass and waist circumference as independent predictors of cardiovascular and all-cause mortality [29,30]. Naturally, a recent meta-analysis also determined similar improvements in body composition between HIIT and MICT [31]. Although this evidence was acknowledged, a recent International Atherosclerosis Society (IAS) and International Chair on Cardiometabolic Risk (ICCR) consensus statement for waist circumference in clinical practice supports moderate intensity training interventions [32]. Therefore, this work further echoes Wewege's [31] support and encouragement of equal representation for HIIT as an effective intervention for body composition management.

Significant improvements were also observed in triglycerides, HDL, LDL, plasma insulin and hs-CRP. Interestingly, many of these findings contrast that observed in Batacan et al. [14], which may be due to the large number of recently published trials included in this work, as well as our exclusion of non-randomised trials and differing analysis approaches. Regardless, improvements in insulin, lipids and inflammatory regulation are of importance, again carrying independent and collective implications for cardiometabolic health and risk of adverse outcomes [33–36]. Although follow-up outcomes were not available for analysis in the present study, these observed cardiometabolic risk factor adaptations may be conservatively extrapolated to the wider literature, with the recent 'Generation 100' study demonstrating a 37% and 49% lower all-cause mortality risk following HIIT compared both

to the current physical activity guidelines and MICT programmes respectively; however, it should be noted that these findings were not statistically significant [37]. As such, our work may provide some underlying contextualisation as to the physiology level changes responsible for the potential benefits of HIIT regarding all-cause mortality outcomes in the general population.

4.1 Limitations

Likely attributable to a wide array of methodological and population differences, we found significant heterogeneity for the majority of analyses. However, given our predetermined decision not to exclude specific populations in a bid to represent the wider general population, such heterogeneity was anticipated. We therefore performed random-effects models and meta-regression analyses to account for such heterogeneity, as well as exploring the Eggers plots for publication bias. We did indeed find evidence of publication bias for several analyses which should be considered when interpreting the present findings. The inclusion of a separate parallel disease-free analysis for all parameters was also provided to support a clearer interpretation of this analysis. The overall HIIT effect sizes also included varying HIIT protocols, including that of SIT and AIT, which were also independently analysed as sub-groups. Therefore, the direct applicability of these wider results to specific HIIT protocols is limited. While our application of the EXPERT tool was credible for standardising intensity eligibility, other definitions have suggested that HIIT should target higher intensity thresholds than the minimum recommendations of the EXPERT tool [38].

5. Conclusion

This large-scale meta-analysis demonstrates the widespread efficacy of HIIT in the management of cardiometabolic health, with significant improvements in peak VO_2, blood pressure, heart rate, stroke volume, systolic cardiac function, body composition, lipids, plasma insulin and systemic inflammation. These results provide further support for HIIT in the clinical management of cardiometabolic health, with implications regarding physical activity guidelines.

Declarations

Ethics approval and consent to participate: Not applicable.

Contributorship: JE and JO'D contributed to the conception and design of the study. JE and JO'D contributed to the development of the search strategy. JE and JO'D conducted the systematic review. JE, MG, AD and JO'D completed the acquisition of data. JE, MG, AD and JO'D performed the data analysis. All authors assisted with the interpretation. JE and JO'D were the principal writers of the manuscript. All authors contributed to the drafting and revision of the final article. All authors approved the final submitted version of the manuscript.

Consent for publication: Not applicable.

Availability of data and materials: Data may be available on request to the corresponding author.

Competing interests: The authors declare that they have no conflicts of interest relevant to the content of this review.

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Figure Legends

Figure 1: PRISMA systematic review and meta-analysis flowchart.

Figure 2: Random-effects meta-analysis demonstrating the effects of HIIT on peak VO2. HIIT: High intensity interval training., SIT: Sprint Interval Training., HV-HIIT: High Volume-HIIT., LV-HIIT: Low Volume-HIIT., F: Female., M: Male., p/w: Per week., A/B: Used to separate different studies of the same year and first author.

Figure 3: Central Illustration. Asterisks signify statistical significance. VO_2: Volume of oxygen uptake., LV: Left ventricle., hs-CRP: High sensitivity C-reactive protein., LDL: Low-density lipoprotein., HDL: High-density lipoprotein., BMI: Body mass index., BF: Body fat., WC: Waist circumference., RCT: Randomised controlled trial.