Effectiveness of HIIE versus MICT in Improving Cardiometabolic Risk Factors in Health and Disease: A Meta-analysis

FELIPE MATTIONI MATURANA[1], PETER MARTUS[2], STEPHAN ZIPFEL[3], and ANDREAS M. NIEß[1]

[1]Sports Medicine Department, University Hospital of Tübingen, Tübingen, GERMANY; [2]Clinical Epidemiology and Applied Biometrics Department, University Hospital of Tübingen, Tübingen, GERMANY; [3]Psychosomatic Medicine and Psychotherapy Department, University Hospital of Tübingen, Tübingen, GERMANY

ABSTRACT

MATTIONI MATURANA, F., P. MARTUS, S. ZIPFEL, and A. M. NIEß. Effectiveness of HIIE versus MICT in Improving Cardiometabolic Risk Factors in Health and Disease: A Meta-analysis. *Med. Sci. Sports Exerc.*, Vol. 53, No. 3, pp. 559–573, 2021. **Purpose:** We aimed to investigate differences between high-intensity interval exercise (HIIE, including high-intensity interval training and sprint interval training) and moderate-intensity continuous training (MICT) on physical fitness, body composition, blood pressure, blood lipids, insulin and glucose metabolism, inflammation, and endothelial function. **Methods:** Differences between HIIE and MICT were summarized using a random-effects meta-analysis on the effect size (Cohen's *d*). A meta-regression was conducted using the following subgroups: population, age, training duration, men ratio, exercise type, baseline values (clinical relevant ranges), and type of HIIE. Studies were included if at least one of the following outcomes were reported: maximal oxygen uptake ($\dot{V}O_{2max}$), flow-mediated dilation (FMD), body mass index (BMI), body mass, percent body fat, systolic and diastolic blood pressure, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, total cholesterol, C-reactive protein (CRP), fasting glucose and insulin, glycated hemoglobin (HbA1c), and insulin resistance (HOMA-IR). A total of 55 studies were included. **Results:** Overall, HIIE was superior to MICT in improving $\dot{V}O_{2max}$ (d = 0.40, $P < 0.001$) and FMD ($d = 0.54$, $P < 0.05$). Oppositely, MICT was superior to HIIE in improving HbA1c ($d = -0.27$, $P < 0.05$). No differences were observed in BMI ($d = -0.02$), body mass ($d = -0.05$), percent body fat ($d = 0.04$), systolic blood pressure ($d = -0.04$), diastolic blood pressure ($d = 0.03$), HDL ($d = -0.05$), LDL ($d = 0.08$), triglycerides ($d = 0.03$), total cholesterol ($d = 0.14$), CRP ($d = -0.11$), fasting insulin ($d = 0.02$), fasting glucose ($d = 0.02$), and HOMA-IR ($d = -0.04$). Moderator analyses indicated that the difference between HIIE and MICT was affected by different subgroups. **Conclusion:** Overall, HIIE showed to be more effective in improving cardiovascular health and cardiorespiratory fitness, whereas MICT was superior in improving long-term glucose metabolism. In the process of personalized training counseling, health-enhancing effects of exercise training may be improved by considering the individual risk profiles. **Key Words:** EXERCISE, META-ANALYSIS, CARDIORESPIRATORY, CARDIOVASCULAR, METABOLIC RISK FACTORS

A healthy lifestyle is constituted primarily of regular structured physical activity (i.e., exercise) (1). As a result, there is vast research into the clinical benefits of exercise, in most cases showing an overcoming of the effects of drug interventions (2). This extensive body of research in the health-enhancing exercise training has shown relevant benefits on cardiovascular end points and longevity in both healthy and diseased populations (3). Ultimately, the aerobic exercise-induced release of myokines into the circulation plays an important role in cardiometabolic health, improving glucose homeostasis and protection against cardiovascular disease (4).

Address for correspondence: Felipe Mattioni Maturana, M.Sc., Abteilung Sportmedizin, Medizinische Klinik Universitätsklinikum Tübingen Hoppe-Seyler-Str. 6, 72076 Tübingen, Germany; E-mail: felipe.mattioni@med.uni-tuebingen.de.

Submitted for publication April 2020.
Accepted for publication August 2020.

0195-9131/20/5303-0559/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®

DOI: 10.1249/MSS.0000000000002506

Current physical activity guidelines recommend a minimum of 150 min of moderate-intensity exercise, or 75 min of high-intensity exercise per week (i.e., 7.5–15 $MET \cdot h \cdot wk^{-1}$), to maintain and/or improve cardiorespiratory fitness (CRF) and cardiovascular health, as well as to reduce the risk of noncommunicable diseases (e.g., type 2 diabetes [T2D], cancer, osteoporosis, stroke, and others) (5–9). In exercise training prescription, moderate-intensity exercise is commonly classified as endurance training—also defined as moderate-intensity continuous training (MICT)—which is performed for a prolonged time within the moderate-intensity domain (10–12). High-intensity exercise, on the other hand, is often performed as high-intensity interval exercise (HIIE)—which may be divided as follows: (a) high-intensity interval training (HIIT), performed alternating bursts of higher intensity (>80% of maximal oxygen uptake [$\dot{V}O_{2max}$] or >85% of maximal heart rate [HR_{max}]) and lower intensity for active recovery; and (b) sprint interval training (SIT), similar design as HIIT, but the high-intensity bouts of exercise are performed in an all-out manner and very short in time (<30 s) (13).

Different levels of exercise dose are required to induce a relevant clinical benefit in key outcomes in clinical practice (e.g.,

physical fitness, vascular health, etc.) (14). In this context, such variability suggests that the optimal exercise prescription may be best achieved by identifying a specific clinical end point target for each individual. As such, it is crucial for the health-enhancing exercise prescription that the effects associated with the two common exercise modalities (i.e., HIIE and MICT) are known based on an individual basis, thus optimizing the decision-making process. On this basis, the Exercise Prescription in Everyday Practice and Rehabilitative Training tool has been developed, which is a digital system that aids tailored exercise training prescription based on cardiovascular disease risk profiles (15). Moreover, results of Wen et al. (16) led to the conclusion that the total volume of physical activity, necessary to reduce the mortality risk, is much smaller if exercise intensity is higher. Furthermore, studies showed that compared with moderate exercise intensities, more intensive training (e.g., HIIE) leads to a higher improvement in CRF (17–19). On the other hand, studies with coronary artery disease patients showed that HIIE does not seem to be superior with regard to influencing health-relevant variables such as body weight, blood pressure, or resting heart rate (20,21).

Given the increasing interest for intermittent intense exercise (22), we sought to investigate the clinical benefits distinguishing each exercise modality in health and disease. Therefore, this meta-analysis aimed to address the comparison of the effects between HIIE and MICT on seven key clinical end point domains: (i) physical fitness ($\dot{V}O_{2max}$), (ii) endothelial function (flow-mediated dilation [FMD]), (iii) body composition (body mass index [BMI], body mass, and body fat), (iv) blood pressure (systolic and diastolic blood pressure), (v) blood lipids (HDL, LDL, triglycerides, and total cholesterol), (vi) inflammation (C-reactive protein [CRP]), and (vii) insulin and glucose metabolism (fasting glucose, fasting insulin, glycated hemoglobin [HbA1c], and insulin resistance [HOMA-IR]). Furthermore, these differences were explored in subgroup analyses (secondary outcomes): (i) population, (ii) age, (iii) training duration, (iv) men ratio (i.e., number of male participants divided by the sample size), (v) type of exercise (cycling vs running/walking), (vi) baseline values of the clinical end point of interest, and (vii) type of HIIE (HIIT vs SIT). We hypothesized that HIIE would be more effective than MICT in improving physical fitness, but heterogenic results would be found in the other clinical end points.

METHODS

Search strategy. A systematic search of randomized controlled trials was initiated in January 2018 and completed in July 2020, based on the PRISMA guidelines (23). The meta-analysis protocol was preregistered in PROSPERO under the ID CRD42018088023. The search was conducted in PubMed, and the search criteria are available in Supplemental Digital Content 1 (see Document, Supplemental Digital Content 1, PubMed search strategy, http://links.lww.com/MSS/C120).

The titles and abstracts (N = 2056) were individually screened by two independent reviewers (FMM and AMN), which subsequently reviewed the full text of the potential eligible articles (N = 453). In addition, more articles were freely searched in Google Scholar as well as in the reference list of relevant review articles previously published (N = 19), forming the final studies selection (N = 55). Figure 1 displays the flow diagram of studies selection. Our eligible criteria included the following: (i) the study examined at least one of these clinical end points—$\dot{V}O_{2max}$, FMD, BMI, body mass, percent body fat, systolic blood pressure, diastolic blood pressure, HDL, LDL, triglycerides, total cholesterol, CRP, fasting insulin, fasting glucose, HbA1c, or HOMA-IR; (ii) the study was a randomized controlled trial with training programs lasting a minimum of 2 wk, with participants randomly assigned to either HIIE (HIIT/SIT) or MICT; (iii) the study involved only exercise training intervention—studies, or groups within the study, that involved any nutritional, resistance training, or any other kind of intervention were not considered; and (iv) the study was conducted in humans and published in English.

Exercise training classification. HIIE was considered as two exercise training modalities: HIIT, characterized by near-maximal efforts interspersed with active or passive recovery periods, and SIT, characterized by maximal or supramaximal efforts, performed as an "all-out" exercise, interspersed with active or passive recovery periods. Previous research has shown that the different characteristics of HIIT and SIT likely lead to different physiological adaptations (13,24). Therefore, we also aimed to analyze the effectiveness of HIIE protocols compared with MICT (i.e., HIIT vs MICT and SIT vs MICT) in a subgroup analysis for each clinical end point. According to the aforementioned criteria, although studies reported their exercise training interventions as being HIIT, but were performed in an all-out manner, we classified them as being SIT (25–30). In addition, the nomenclature used to identify HIIE in the original studies presented a considerable variability. Classifications included "aerobic interval training," "interval training," "transitory stimulation interval exercise," "maximal intensity interval training," "4 × 4 min," "15/15," "maximal volitional intensity training," and "interval endurance training." Research on exercise training interventions lacks consistent nomenclature based on the characteristics of the training protocols, and there is an increasing need for a consensus, as already suggested elsewhere (31). MICT was considered as a continuous exercise intensity program, performed at lower intensities than HIIE. By definition, MICT should be performed within the moderate-intensity domain (below lactate threshold); however, some studies prescribed the exercise intensity as a percentage of $\dot{V}O_{2max}$ or HR_{max}, limiting the ability to classify as a true moderate exercise. Because conflicting nomenclature exists, all types of MICT were considered. It is important to note that we considered studies that did not explicitly reported that HIIE and MICT interventions were matched. Most of the studies justify their exercise training protocols simply based on previous clinical trials and identify their interventions as being matched. We believe that it is not enough to simply state that

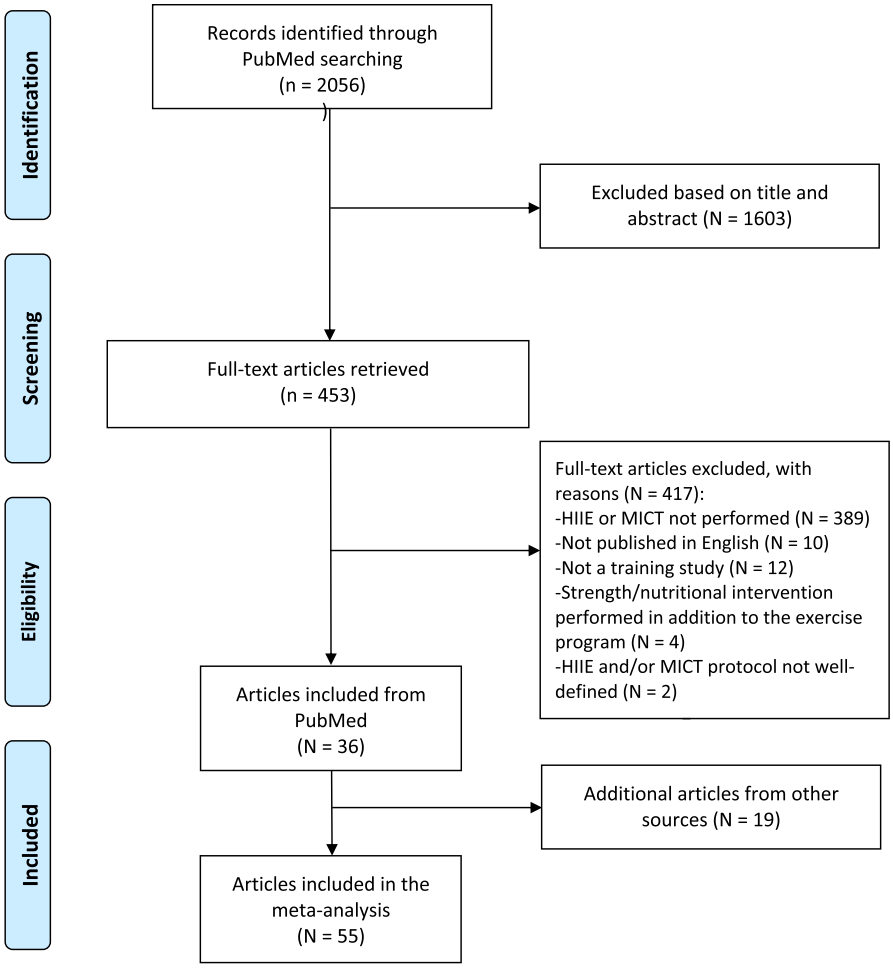

FIGURE 1—Flow diagram displaying the studies selection process following the PRISMA guidelines.

because a certain protocol was shown to be equalized between the two training modes in previous studies, this protocol is also going to be equalized in another study. Researchers conducting randomized controlled trials should justify their statements with actual training data, and this is rarely seen.

Bias assessment. The included studies were assessed for risk of bias according to the Cochrane risk of bias for randomized trials using the most up-to-date guidelines (32). Specifically, bias was assessed in five different domains: bias arising from the randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Judgment was made according to three categories within each domain: "low," "some concerns," and "high."

Small-study effect—the phenomenon in which smaller studies may present different (often larger) treatment effects than bigger sample studies—was assessed for publication bias control. First, the publication bias was analyzed graphically through contour-enhanced funnel plots (33). Contour lines representing well-established levels of statistical significance are added to a funnel plot to indicate regions where a test of treatment effect is significant. The treatment effect (i.e., mean difference) is shown on the x-axis against a measure of precision—the SE. Second, a statistical test for small-study effects was performed. A linear regression test called Egger's test was used to quantify the evidence for funnel plot asymmetry. In addition, this linear regression can be visualized together with a radial plot. If there are no small-study effects, individual studies are expected to scatter randomly around the linear regression line. Altogether, we can note that if the regression line differs markedly from the line through the origin, it is an indication of asymmetry in the funnel plot.

Meta-analysis. In the present meta-analysis, we extracted the mean, SD, and sample size reported for each group (HIIE and MICT) pre- and postintervention. The standardized mean difference (Cohen's d) was the outcome used, which was calculated with the random-effects model, applying the DerSimonian–Laird estimator (34) for the estimation of the between-study variance τ^2. Effect sizes were classified as trivial ($d < 0.2$), small ($d = 0.2$–0.5), medium ($d = 0.5$–0.8), and large ($d > 0.8$). Thereafter, a sensitivity analysis was performed for each meta-analysis to determine the robustness of the observed outcomes to the assumptions made in performing the analysis. The method applied here was the leave-one-out cross-validation (LOOCV), which consists of performing the

meta-analysis on each subset of the included studies by leaving out one study at a time (35). This shows how each individual study affects the overall estimate of the rest of the studies. In case the LOOCV showed that the mean effect was relying on a single study (outlier), the study was then removed from the overall analysis (no subgroups), and the meta-analysis was run again. Importantly, if the single study was identified through the sensitivity analysis, it was excluded from the overall results only, and it was kept in subgroup analyses (meta-regression). The results after the LOOCV analysis (if any outlier) are presented in our meta-analysis. For a comprehensive overview, all the results may be accessed in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/). The significance level was set at $\alpha = 0.05$ (two-sided).

Missing data and data conversion. Whenever relevant measures were not reported in the original study, the respective authors were contacted to provide the missing data (see Document, Supplemental Digital Content 2, Additional data provided by authors, http://links.lww.com/MSS/C121). For instance, if a clinical end point of interest was reported only graphically, we contacted the research group to request the values pre- and posttraining (i.e., mean and SD). In case the study reported the SEM, it was then converted to SD using the formula:

$$\mathrm{SD} = \mathrm{SEM}\sqrt{N}$$

where SD is the standard deviation, SEM is the standard error of the mean, and N is the group sample size (36). In case the study reported confidence intervals, it was then converted to SD using the formula:

$$\mathrm{SD} = \sqrt{N}\,\frac{\mathrm{CI}_{\mathrm{high}} - \mathrm{CI}_{\mathrm{low}}}{2t}$$

where SD is standard deviation, N is the group sample size, $\mathrm{CI}_{\mathrm{high}}$ is the upper limit of the confidence interval, $\mathrm{CI}_{\mathrm{low}}$ is the lower limit of the confidence interval, and t is the t distribution with $N-1$ degrees of freedom the respective level of confidence (e.g., 0.95) (36).

When performing a meta-analysis on the difference in means between two interventions, it is necessary to have (i) the difference in means (raw mean difference between post- and preintervention for each intervention group) and (ii) the SD of the difference between pre- and postintervention. Calculating the raw mean difference is straightforward:

$$M_{\mathrm{diff}} = M_{\mathrm{post}} - M_{\mathrm{pre}}$$

where M_{diff} is the raw mean difference, M_{post} is the reported mean postintervention, and M_{pre} is the reported mean preintervention.

However, calculating the SD of the difference between pre- and postintervention requires additional steps. For this purpose, it is necessary to have the Pearson correlation coefficient (r) between the raw values of pre- and postintervention for each study (37,38). Such measure is rarely seen in exercise training studies. In fact, from the studies included in this meta-analysis, none of them reported it. Therefore, an r value of 0.85 was chosen, and a sensitivity analysis was performed with $r = 0.8$, $r = 0.85$, and $r = 0.9$ (Fig. 2). Once the r coefficient is defined, then the SD of the difference in means is calculated as follows:

$$\mathrm{SD}_{\mathrm{diff}} = \sqrt{\mathrm{SD}_{\mathrm{pre}}{}^2 + \mathrm{SD}_{\mathrm{post}}{}^2 - 2r \times \mathrm{SD}_{\mathrm{pre}} \times \mathrm{SD}_{\mathrm{post}}}$$

where $\mathrm{SD}_{\mathrm{diff}}$ is the standard deviation of the difference in means, SD_{pre} is the standard deviation from preintervention, and $\mathrm{SD}_{\mathrm{post}}$ is the standard deviation from postintervention.

When performing the subgroup analyses (secondary outcomes), categorical groups were used. However, for performing the meta-regression, the number associated with the subgroup was analyzed. For example, the age subgroup was divided into the following categories: (i) <30 yr-{age}, (ii) 30–50 yr-{age}, and (iii) >50 yr-{age}; however, when conducting the meta-regression, the median age between HIIE and MICT was used. For this reason, we converted the end point values that were reported in different units across the studies for performing the meta-regression of the initial values subgroups. If the end point had at least one study reporting its values in different units, it was then converted to common units according to the *AMA Manual of Style: A Guide for Authors and Editors* (39) (see Document, Supplemental Digital Content 3, Conversion of values for performing the meta-regression, http://links.lww.com/MSS/C122).

Meta-regression. Subgroup analyses were performed using the following categories (subgroups were mentioned in the text as *category-{major category}*):

- Population: healthy (*healthy-{population}*), overweight/obese (*overweight/obese-{population}*), cardiac rehabilitation (*cardiac-rehab-{population}*), metabolic syndrome (*MetS-{population}*), and T2D (*T2D-{population}*)
- Age (defined as terciles from the included studies data): <30 yr old (*<30 yr-{age}*), between 30 and 50 yr old (*30–50 yr-{age}*), and >50 yr old (*>50 yr-{age}*)
- Training duration (defined as terciles from the included studies data): <5 wk (*<5 wk-{training duration}*), between 5 and 10 wk (*5–10 wk-{training duration}*), and >10 wk (*>10 wk-{training duration}*)
- Men ratio (number of male participants divided by the sample size): <0.5 (*<0.5-{men ratio}*) and >0.5 (*>0.5-{men ratio}*)
- Type of exercise: cycling (*cycling-{exercise}*) and running/walking (*running/walking-{exercise}*)
- Baseline values—clinically relevant cutoff points in each end point were defined as follows:
  - $\dot{V}O_{2max}$ (age- and sex-adjusted percentile ranks were specified [5]): <30% (*<30%-{bsln-$\dot{V}O_{2max}$}*), between 30% and 60% (*30–60%-{bsln-$\dot{V}O_{2max}$}*), and >60% (*>60%-{bsln-$\dot{V}O_{2max}$}*)
  - FMD (age-related cutting points were defined, as previously described [40]): <6% (*<6%-{bsln-FMD}*) and >6% (*>6%-{bsln-FMD}*)
  - BMI, body mass, and body fat (body composition measures were all normalized by baseline BMI): <25 $\mathrm{kg \cdot m^{-2}}$

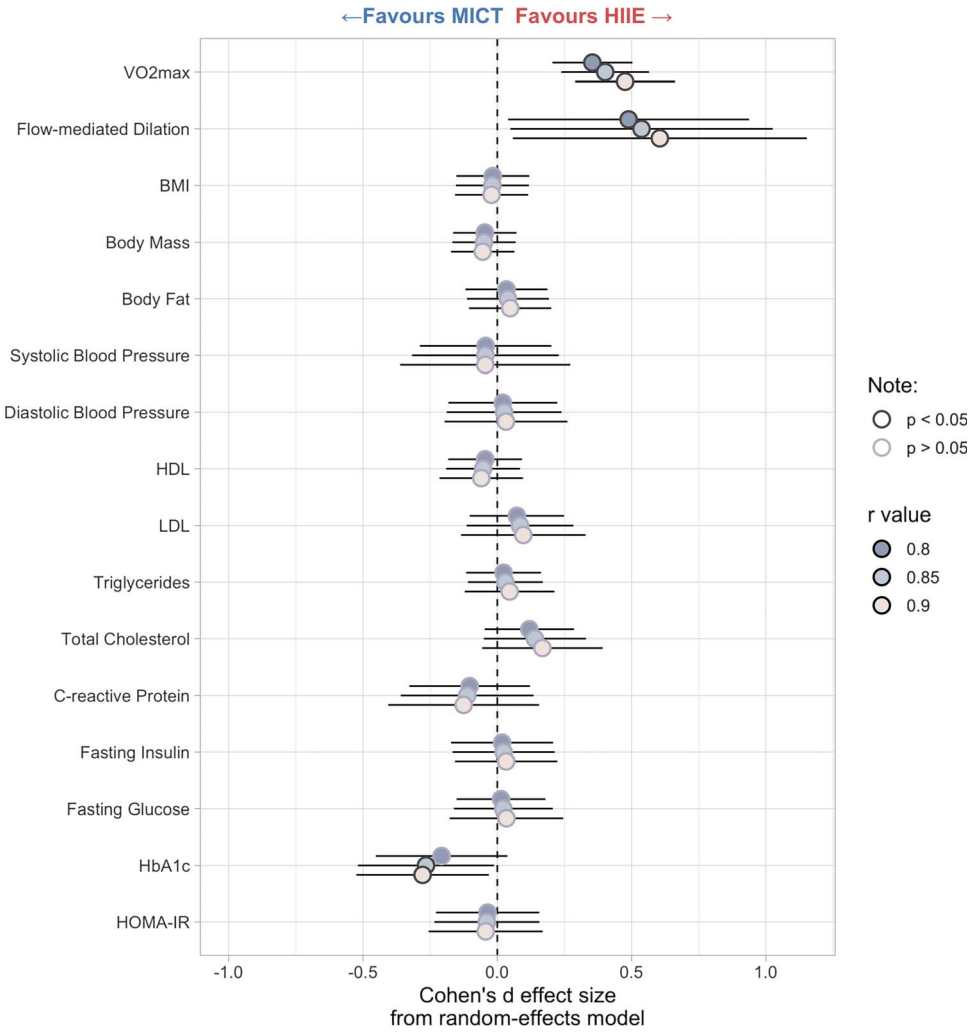

FIGURE 2—Summary of the Cohen's *d* effect sizes in the random-effects model of each overall meta-analysis from the sensitivity analysis performed on the Pearson correlation (*r*) used for calculating the SD of the difference in means. A sensitivity analysis was performed using $r = 0.8$, $r = 0.85$, and $r = 0.95$. The *r* value chosen in our meta-analysis was $r = 0.85$.

(*<25 kg·m^{-2}-{bsln-BMI}*), between 25 and 30 kg·m^{-2} (*25–30 kg·m^{-2}-{bsln-BMI}*), and >30 kg·m^{-2} (*>30 kg·m^{-2}-{bsln-BMI}*)
- Systolic blood pressure: <120 mm Hg (*<120 mm Hg-{bsln-SBP}*), between 120 and 140 mm Hg (*120–140 mm Hg-{bsln-SBP}*), and >140 mm Hg (*>140 mm Hg-{bsln-SBP}*)
- Diastolic blood pressure: <80 mm Hg (*<80 mm Hg-{bsln-DBP}*), between 80 and 90 mm Hg (*80–90 mm Hg-{bsln-DBP}*), and >90 mm Hg (*>90 mm Hg-{bsln-DBP}*)
- HDL: <1.3 mmol·L^{-1} (*<1.3 mmol·L^{-1}-{bsln-HDL}*) and >1.3 mmol·L^{-1} (*>1.3 mmol·L^{-1}-{bsln-HDL}*)
- LDL: <3 mmol·L^{-1} (*<3 mmol·L^{-1}-{bsln-LDL}*) and >3 mmol·L^{-1} (*>3 mmol·L^{-1}-{bsln-LDL}*)
- Triglycerides: <1.7 mmol·L^{-1} (*<1.7 mmol·L^{-1}-{bsln-TG}*), and >1.7 mmol·L^{-1} (*>1.7 mmol·L^{-1}-{bsln-TG}*)
- Total cholesterol: <5.2 mmol·L^{-1} (*<5.2 mmol·L^{-1}-{bsln-TC}*) and >5.2 mmol·L^{-1} (*>5.2 mmol·L^{-1}-{bsln-TC}*)
- CRP: <2 mg·L^{-1} (*<2 mg·L^{-1}-{bsln-CRP}*) and >2 mg·L^{-1} (*>2 mg·L^{-1}-{bsln-CRP}*)
- Fasting insulin (cutting points were defined according to previous research [41]): <40 pmol·L^{-1} (*<40 pmol·L^{-1}-{bsln-fINS}*) and >40 pmol·L^{-1} (*>40 pmol·L^{-1}-{bsln-fINS}*)
- Fasting glucose: <5.6 mmol·L^{-1} (*<5.6 mmol·L^{-1}-{bsln-fGLU}*) and >5.6 mmol·L^{-1} (*>5.6 mmol·L^{-1}-{bsln-fGLU}*)
- HbA1c: <40 mmol·mol^{-1} (*<40 mmol·mol^{-1}-{bsln-HbA1c}*) and >40 mmol·mol^{-1} (*>40 mmol·mol^{-1}-{bsln-HbA1c}*)
- HOMA-IR: <3 (*<3-{bsln-HOMA}*) and >3 (*>3-{bsln-HOMA}*)
- Type of HIIE: HIIT (HIIT-{type of HIIE}) and SIT (SIT-{type of HIIE}).

To test for subgroup differences, a meta-regression (i.e., mixed-effects model) was performed, at which subgroups within the study were tested if their effects differ (42,43). Information on heterogeneity and residual heterogeneity as well as a test of moderators was reported for each analysis in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/).

All data analyses and visualizations were performed in R version 4.0.2 (44) with the packages *tidyverse* (45), *meta* (46), *metafor* (47), *robvis* (48), and *patchwork* (49). For improving transparency in the data analysis performed in this manuscript, as well as to make all the data collected available, the *metabolic* R package was developed. It may be accessed in GitHub (https://github.com/fmmattioni/metabolic). The package is also a collection of tools to reproduce the meta-analysis presented here in the manuscript.

RESULTS

Figure 3 displays the overall results (primary outcomes) across the clinical end points. Figure 4 summarizes the effect sizes obtained from each subgroup meta-analysis (secondary outcomes), individually reported in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/).

Study characteristics. Figure 1 in Supplemental Digital Content 4 shows the study characteristics (see Figure, Supplemental Digital Content 4, Summary of all the included studies and their respective designs, http://links.lww.com/MSS/C123). Fifty-five studies were included, which were published between 1976 and 2020. In total, HIIE had 775 participants (476 males, 222 females, and 77 not reported) and MICT had 754 participants (468 males, 242 females, and 44 not reported). Thirty-seven studies performed the HIIE intervention using HIIT (50–86), and 21 studies performed SIT (25–30,56,58,64,87–98). The mean ± SD sample size for both HIIE and MICT was 13 ± 11 participants. The men ratio was 0.64 ± 0.33 for HIIE and 0.64 ± 0.34 for MICT. The session duration (excluding warm-up and cooldown) was 25.1 ± 9.5 min for HIIE and 42.3 ± 13.2 min for MICT. The duration of exercise training per week was 72.1 ± 37.3 min for HIIE and 123 ± 44.7 for MICT. The exercise training

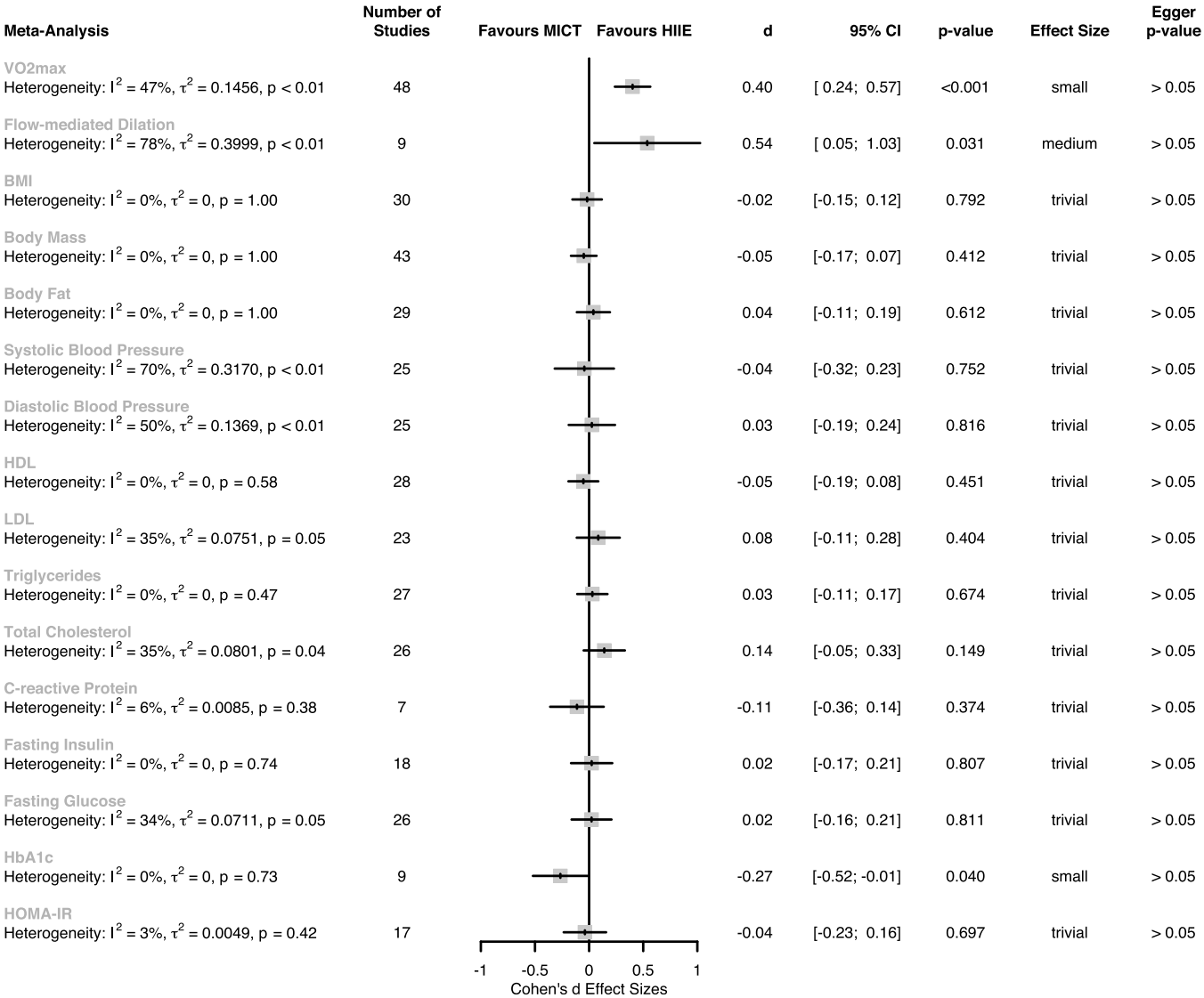

FIGURE 3—Overall meta-analyses results for each end point. The results of each analysis are displayed in the right-hand side of the graph as the effect size (Cohen's *d*), the 95% confidence interval of *d*, the *P* value of the overall pooled estimate, the classification of the effect size, two measures of heterogeneity —τ^2 and I^2, and the *P* value from the Egger test.

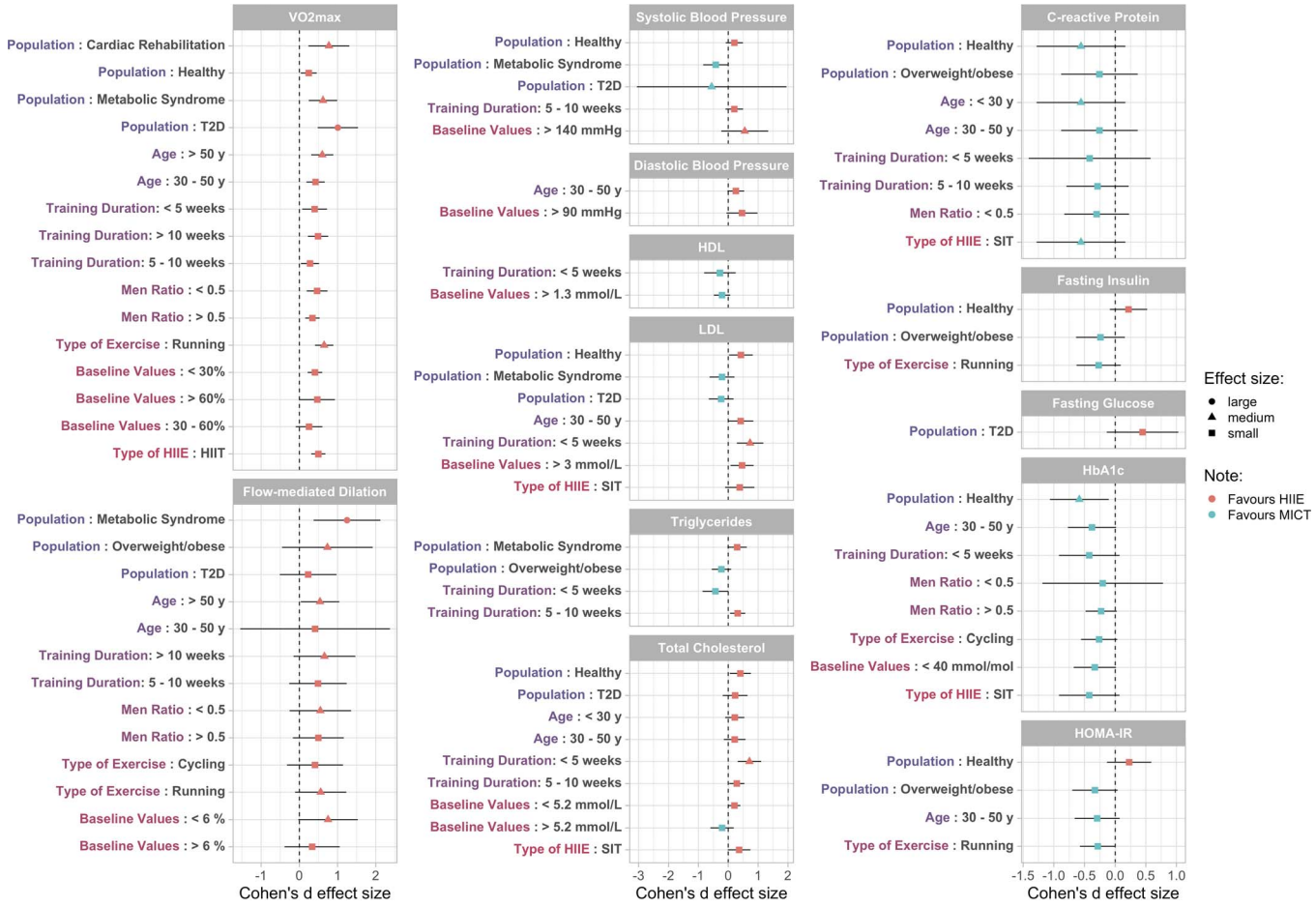

FIGURE 4—Summary of the small, medium, and large effect sizes obtained from subgroups meta-analyses. Data points represent the Cohen's *d* effect size from the random-effects model and its 95% confidence interval (*black lines*). The *dashed line* on each plot ($y = 0$) represents no difference between HIIE and MICT. Positive and negative values represent favorable effects for HIIE and MICT, respectively.

intervention was 9 ± 5 wk for both HIIE and MICT. The ranges of exercise training intensities are summarized in Figure 5. The total sessions during the intervention were 26 ± 14 sessions for HIIE and 28 ± 17 sessions for MICT. The compliance with the exercise training was 93.5% ± 9.0% for HIIE and 94.1% ± 8.5% for MICT. HIIE presented in total 11 participants with adverse effects related to the training intervention, which were described as ankle fracture (77), headache (97), injury (25,64), knee pain (60), muscle pain (27), hip pain (28), hamstring muscle pull (93), and pain (70). MICT presented a total of four participants with adverse effects, which were described as knee injury (77), leg pain (60), knee pain (93), and one syncopal (fainting) episode (92). The Cochrane bias assessment revealed that all the included studies presented a low risk of bias in the bias related to the randomization process (domain 1), missing outcome data (domain 3), measurement of the outcome (domain 4), as well as selection of the reported result (domain 5). A total of 24 studies presented low bias in the bias related to deviations

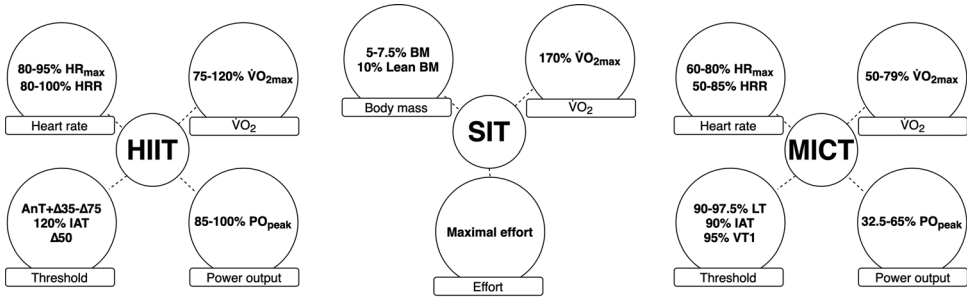

FIGURE 5—Summary of the exercise training prescriptions in HIIT, SIT, and MICT. The prescriptions were divided into heart rate based, oxygen uptake based, threshold based, power output based, and effort based. The numbers provided are the ranges from the reported intensities across the included studies. HRR, heart rate reserve; PO_{peak}, peak power output; AnT, anaerobic threshold; VT1, ventilatory threshold 1; IAT, individual anaerobic threshold; Δ50, 50% of the difference between gas exchange threshold and $\dot{V}O_{2max}$; BM, body mass; LT, lactate threshold.

from intended intervention (domain 2), and 30 studies presented a bias classified as "some concerns." This bias was due to the fact that these studies did not present *a priori* statistical power analysis to justify their sample sizes. Detailed information may be found in Supplemental Digital Content 5 (see Figure, Supplemental Digital Content 5, Figs. 1 and 2 show the summary of the risk of bias judgment and the judgment for each study, respectively, http://links.lww.com/MSS/C124).

Physical fitness. Overall, HIIE was associated with higher benefits over MICT in increasing $\dot{V}O_{2max}$ (d = 0.40, 95% CI = 0.24–0.57, P < 0.001, I^2 = 47%, τ^2 = 0.15), with no single-study influence in the pool estimate during sensitivity analysis. The Egger test revealed no small-study effect (bias = 0.738, P = 0.3). In subsequent subgroup analyses, the level of significance was maintained for the all the population subgroups, except the overweight and obese population. A larger effect size was observed as age increased: <30 yr-{age} (d = 0.14, 95% CI = −0.10 to 0.39, P = 0.3), 30–50 yr-{age} (d = 0.43, 95% CI = 0.19–0.66, P < 0.001), and >50 yr-{age} (d = 0.60, 95% CI = 0.31–0.89, P < 0.001). When baseline values were adjusted by age and sex, *<30%-{bsln-$\dot{V}O_{2max}$}* and *>60%-{bsln-$\dot{V}O_{2max}$}* presented a significant ES favoring HIIE, whereas no significant differences were observed in *30–60%-{bsln-$\dot{V}O_{2max}$}* between HIIE and MICT. An interaction effect (P = 0.05) was observed in type of HIIE: *HIIT-{type of HIIE}* (d = 0.5, P < 0.001) and *SIT-{type of HIIE}* (d = 0.18, P = 0.2). Section 1 in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/) shows the results for each analysis.

Endothelial function. Overall, HIIE was associated with higher benefits over MICT in increasing FMD with a medium ES (d = 0.54, 95% CI = 0.05–1.03, P = 0.031, I^2 = 78%, τ^2 = 0.40), with no single-study influence in the pool estimate during sensitivity analysis. The Egger test revealed no small-study effect (bias = 1.671, P = 0.4). The small number of studies (9 in total) limits the discussion of subgroup analyses; however, noteworthy, *>50 yr-{age}* (d = 0.54, P < 0.05), *>10 wk-{training duration}* (d = 0.66, P = 0.1), and *<6%-{bsln-FMD}* (d = 0.75, P = 0.06) presented an increased ES favoring HIIE. Section 2 in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/) shows the results for each analysis.

Body composition. Overall, no significant differences were observed in BMI (d = −0.02, 95% CI = −0.15 to 0.12, P = 0.8, I^2 = 0%, τ^2 = 0), body mass (d = −0.05, 95% CI = −0.17 to 0.07, P = 0.4, I^2 = 0%, τ^2 = 0), and body fat (d = 0.04, 95% CI = −0.11 to 0.19, P = 0.6, I^2 = 0%, τ^2 = 0) between HIIE and MICT. In addition, no single-study and small-study effects were detected during the sensitivity analysis and the Egger test for all the body composition results. No interaction effects between HIIT and SIT were observed for BMI (P = 0.7), body mass (P = 0.5), and body fat (P = 0.7). Sections 3 to 5 in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/) show the results for each analysis.

Blood pressure. Overall, no significant differences in systolic blood pressure were found when comparing HIIE and MICT, with a trivial ES (d = −0.04, 95% CI = −0.32 to 0.23, P = 0.8, I^2 = 70%, τ^2 = 0.32), and no additional single-study effect during sensitivity analysis. The Egger test revealed no significant small-study effect (P > 0.05). Similarly, there were no overall significant differences in diastolic blood pressure when comparing HIIE and MICT, with a trivial ES (d = 0.03, 95% CI = −0.19 to 0.24, P = 0.8, I^2 = 50%, τ^2 = 0.14), and no single-study effect during sensitivity analysis. The Egger test revealed no small-study effect (P > 0.05). Both systolic and diastolic blood pressure presented an increased ES favoring HIIE as baseline values increased: *>140 mm Hg-{bsln-SBP}* (d = 0.55, P = 0.17) and *>90 mm Hg-{bsln-DBP}* (d = 0.46, P = 0.08). No interaction effects between HIIT and SIT were observed in systolic (P = 0.7) and diastolic blood pressure (P = 0.9). Sections 6 and 7 in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/) show the results for each analysis.

Blood lipids. Overall, no differences between HIIE and MICT in improving HDL were found (d = −0.05, 95% CI = −0.19 to 0.08, P = 0.5, I^2 = 0%, τ^2 = 0). No single-study effect was observed during sensitivity analysis, and the Egger test revealed no significant small-study effect (P > 0.05). Although no interaction effects were observed in subgroup analyses, an increased ES favoring MICT was observed in *<30 yr-{age}* (d = −0.19, P = 0.2) and *>1.3 mmol·L^{-1}-{bsln-HDL}* (d = −0.21, P = 0.1). No interaction effects between HIIT and SIT were observed (P = 0.7).

No differences between HIIE and MICT were found in the overall effect in improving LDL (d = 0.08, 95% CI = −0.11 to 0.28, P = 0.4, I^2 = 35%, τ^2 = 0.08) and triglycerides (d = 0.03, 95% CI = −0.11 to 0.17, P = 0.7, I^2 = 0%, τ^2 = 0). In addition, no single- and small-study effects were observed for both LDL (bias = 0.462, P = 0.5) and triglycerides (bias = 0.035, P = 0.9). In LDL, there was a significant interaction effect in the training duration (P < 0.01) and baseline values (P = 0.01) subgroups. An interaction effect of P = 0.13 was observed in type of HIIE: *HIIT-{type of HIIE}* (d = −0.02, P = 0.8) and *SIT-{type of HIIE}* (d = 0.38, P = 0.1). Noteworthy, there was a significant effect of HIIE over MICT in *healthy-{population}* (d = 0.42, P = 0.036), *30–50 yr-{age}* (d = 0.42, P = 0.05), and *>3 mmol·L^{-1}-{bsln-LDL}* (d = 0.46, P < 0.05). In triglycerides, there was a significant interaction effect in the training duration (P < 0.01) subgroup. No differences between HIIT and SIT were observed (P = 0.3).

No significant differences between HIIE and MICT in improving total cholesterol were found (d = 0.14, 95% CI = −0.05 to 0.33, P = 0.15, I^2 = 35%, τ^2 = 0.08). No single-study effect was observed in the sensitivity analysis, and the Egger test revealed no significant small-study effect (bias = 0.359, P = 0.6). There was a significant interaction effect in the training duration (P < 0.01) subgroup. An interaction effect of P = 0.17 was observed in type of HIIE: *HIIT-{type of HIIE}* (d = 0.06, P = 0.5) and *SIT-{type of HIIE}* (d = 0.36, P = 0.06). In addition, HIIE had a significant effect over MICT in *healthy-{population}* (d = 0.40, P < 0.05).

Sections 8 to 11 in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/) show the results for each analysis.

Inflammation. Overall, there were no significant effects between MICT and HIIE in CRP ($d = -0.11$, 95% CI = −0.36 to 0.14, $P = 0.4$, $I^2 = 0\%$, $\tau^2 = 0$). No small-study and single-study effects were observed ($P > 0.05$). Although not statistically significant, an increased ES favoring MICT was observed in *healthy-{population}* ($d = -0.56$, $P = 0.1$), *<30 yr-{age}* ($d = -0.56$, $P = 0.1$), and *SIT-{type of HIIE}* ($d = -0.56$, $P = 0.1$). An interaction effect of $P = 0.2$ was observed in the type of HIIE subgroup analysis. Section 12 in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/) shows the results for each analysis.

Insulin and glucose metabolism. No significant differences were found in fasting insulin ($d = 0.02$, 95% CI = −0.17 to 0.21, $P = 0.8$, $I^2 = 0\%$, $\tau^2 = 0$) and fasting glucose ($d = 0.02$, 95% CI = −0.16 to 0.21, $P = 0.8$, $I^2 = 34\%$, $\tau^2 = 0.07$) when comparing the effects of HIIE and MICT. No single- and small-study effects were observed for both end points (fasting insulin: bias = −1.5, $P = 0.3$; fasting glucose: bias = 0.65, $P = 0.4$). Albeit not statistically significant, increased ES favoring MICT were observed in *overweight/obese-{population}* ($d = -0.24$, $P = 0.2$) and *running-{exercise}* ($d = -0.27$, $P = 0.1$) for fasting insulin. For fasting glucose, an increased ES favoring HIIE was observed in *T2D-{population}* ($d = 0.45$, $P = 0.1$). No interaction effects between HIIT and SIT were observed for fasting insulin ($P = 0.3$) and fasting glucose ($P = 0.6$).

Significant differences were observed in HbA1c, with a small ES favoring MICT over HIIE ($d = -0.27$, 95% CI = −0.52 to −0.01, $P = 0.04$, $I^2 = 0\%$, $\tau^2 = 0$). A single-study influence was observed during sensitivity analysis, but small-study effects were not found (bias = −9.0, $P = 0.7$). An increased ES favoring MICT was observed in *healthy-{population}* ($d = -0.58$, $P = 0.02$), *30–50 yr-{age}* ($d = -0.38$, $P = 0.06$), *<5 wk-{training duration}* ($d = -0.42$, $P = 0.09$), *<40 mmol·mol^{-1}-{bsln-HbA1c}* ($d = -0.33$, $P = 0.06$), and *SIT-{type of HIIE}* ($d = -0.42$, $P = 0.09$). No interaction effects between HIIT and SIT were observed ($P = 0.3$).

Overall, no differences between MICT and HIIE were observed in HOMA-IR ($d = -0.04$, 95% CI = −0.23 to 0.16, $P = 0.7$, $I^2 = 0\%$, $\tau^2 = 0$). No single-study effect was observed in the sensitivity analysis, and the Egger test revealed no significant small-study effect (bias = −0.283, $P = 0.9$). Albeit not statistically significant, *overweight/obese-{population}* presented an increased ES favoring MICT ($d = -0.33$, $P = 0.08$), whereas *healthy-{population}* presented an increased ES favoring HIIE ($d = 0.23$, $P = 0.2$). The type of exercise subgroup presented a significant interaction effect ($P < 0.05$), with an increased ES favoring MICT in *running/walking-{exercise}* ($d = -0.28$, $P = 0.06$). No interaction effects between HIIT and SIT were observed ($P = 0.5$).

Sections 13 to 16 in the Appendix (https://www.medizin.uni-tuebingen.de/sportmedizin/hiiemict/) show the results for each analysis.

DISCUSSION

The present meta-analysis is the first to comprehensively combine and analyze the effectiveness in the effects associated with HIIE and MICT on seven clinical end point domains related to cardiometabolic health: physical fitness, endothelial function, body composition, blood pressure, blood lipids, inflammation, and insulin and glucose metabolism. Overall, HIIE showed to be more effective in improving CRF ($\dot{V}O_{2max}$) and cardiovascular health (FMD), whereas MICT was superior in improving long-term glucose metabolism (HbA1c).

Regardless of training modality, epidemiological evidence shows that the general practice of PA is associated with extended life expectancy (99–101). However, when examining the effects of exercise training in cardiovascular health, a comprehensive view of the entire body system is essential. Despite the well-known HIIE benefits on CRF, these improvements do not necessarily happen cooperatively with other risk factors (e.g., blood pressure, blood lipids, fasting glucose, body composition, etc.) (4,102), such that the underlying mechanisms controlling the modification of clinical end points differ widely. As posed by a fundamental review (1), exercise may be the real polypill. Although, the efficacy of each dose of exercise on a specific cardiometabolic factor in a particular individual is yet not well understood. In this context, the present review investigated the efficacy of HIIE and MICT on essential subgroups: population, age, training duration, sex, exercise modality, baseline values, and HIIE mode (HIIT and SIT).

Physical fitness. A wide body of research has previously shown a significantly higher effect of HIIE over MICT on $\dot{V}O_{2max}$ in health and disease (17–21,31,103–105). In general, our results indeed go in line with these findings. However, our analysis provided a few more insights and new outcomes into what was previously known. For example, an increase in the ES favoring HIIE as the sample age increased was observed. In other words, HIIE showed a higher effect over MICT for older participants in improving $\dot{V}O_{2max}$. The age-related decline in aerobic fitness may be mainly attributed to (i) reduction in cardiac output (106), (ii) aging-associated loss in vasodilation (4,107), and (iii) reduction in physical activity levels (108). In this context, it has already been shown that age does not affect the improvements in $\dot{V}O_{2max}$ when young and old individuals perform HIIE (106) or MICT (109). Our analysis, however, showed that indeed aging plays a role in the response when the effects of HIIE and MICT are compared. These adaptations are mainly ascribed by exercise-induced central adaptations, such as increased HR_{max} and maximal stroke volume (improving oxygen delivery to the active tissues) (106,110,111). In addition, when baseline $\dot{V}O_{2max}$ values were adjusted by age and sex, a significant effect of HIIE over MICT was observed for the participants in the $\dot{V}O_{2max} < 30\%$ and in the $\dot{V}O_{2max} > 60\%$ percentile ranks, indicating not a clear effect of initial physical fitness on the exercise training response.

Endothelial function. Similar to aerobic fitness, FMD adaptations to exercise training showed, in general, higher effects with HIIE than with MICT. Such finding is partially

explained by the ability of interval-like exercise training programs to induce a higher shear stress, promoting an increased nitric oxide release (through activation of endothelial nitric oxide synthase), and the aging-associated loss in vasodilation (4,107). With regular exercise training, chronic (structural) adaptations start to occur. These adaptations include (but are not limited to) the increase in the luminal diameter, the decrease of the wall thickness of conduit arteries, and the increased atherosclerotic plaque collagen and elastin content (which may also be impaired with aging) (4,112,113). In summary, exercise training-induced adaptations in endothelial function, especially in aging, play a major role in improving vasodilation, which ensures an adequate oxygen delivery to the active tissues at the microvascular level. Such improvement explains the fact that HIIE presented a higher effect size in improving FMD in the older subgroup, and also when baseline FMD values were below 6% before engaging in the exercise training program.

Body composition. In general, markers of anthropometrics —BMI, body mass, and percent body fat—did not present any significant difference between HIIE and MICT, with trivial effect sizes. Despite the potential ability of exercise intensity to increase basal energy expenditure, changes in body composition may not occur unless accompanied by a controlled diet, ensuring a disturbance in the energy balance (114–116). A meta-analysis on the effects of HIIE on cardiometabolic health in the overweight/obese population showed that only long-term HIIE (i.e., more than 12 wk) significantly improved body composition markers (i.e., waist circumference and percent body fat), whereas short-term HIIE did not present effects (19). However, our subgroup analyses revealed no effectiveness of HIIE over MICT in any training duration or initial BMI levels. Despite that the effects of HIIE on reducing body fat are known (19,117), our results show that HIIE may be as effective as MICT in reducing body fat both in longer exercise training interventions and in individuals with high BMI. In addition, a recent meta-analysis showed that low-volume HIIE was not more efficient than MICT in reducing body mass and body fat in normal-weight and overweight/obese individuals (118). Altogether, our results highlight that, in general, HIIE and MICT likely induce similar effects on body composition, and a nutritional intervention should be accompanied.

Blood pressure. A recent meta-analysis of 391 randomized controlled trials showed that, in a hypertensive population, exercise interventions may be as effective as antihypertensive medications in lowering systolic blood pressure (119). These promising results, instead of abdicating medications for patients, should aid in the physical activity promotion. It should be noted that in the aforementioned meta-analysis, all sorts of aerobic exercise were included, such that HIIE and MICT were considered into one category of exercise intervention. In our review, we had the possibility to meta-analyze whether HIIE and MICT would induce different effects overall and between subgroups in systolic and diastolic blood pressure. Out of all these comparisons, HIIE showed greater effect sizes in the middle-age subgroup (*30–50 yr-{age}*) in reducing diastolic blood pressure, as well as in participants with a higher initial baseline (i.e., >140 and >90 mm Hg for systolic and diastolic blood pressure, respectively). Otherwise, no evidence for different effects between training interventions was found, as already indicated in another meta-analysis (120).

Blood lipids. In general, the blood lipid profile often seen in physically active individuals reflects a reduced CVD risk when compared with their inactive counterparts (121). Our analysis presented distinct results on the influence of HIIE and MICT on blood lipids. The overall analyses revealed similar effects of HIIE and MICT. In this regard, exercise endurance training (as characterized by MICT here) has already been associated with significant increases in HDL in both men and women (122,123). HIIE has also been shown as an effective strategy in increasing HDL levels, but such changes do not seem to occur before approximately 8 wk of training (79,124,125). Overall, no difference between HIIE and MICT on LDL was observed. However, there was an increased effect size favoring HIIE, albeit not significant, when SIT was performed. Coincidently, however, most of these studies also had participants with elevated LDL levels, which also showed an increased effect size favoring HIIE in our baseline values subgroup. Our results suggest that HIIE may be more effective than MICT for improving LDL levels depending on the characteristics of the sample and the exercise training program, contradicting previous studies (51,126–128). After all, the exercise training program that can trigger a higher fat oxidation on a specific individual will induce a higher reduction in LDL, either by increased clearance of blood lipids or by reduced lipid secretion by the liver (129). However, such improvement is challenging if not accompanied by a controlled diet. In addition, the HIIE modality had an increased effect size on the total cholesterol response when SIT (as opposed to HIIT) was performed. Such finding suggests that SIT might be an important exercise mode in lowering LDL levels, which is one of the measures in the total cholesterol score.

Inflammation. Our analysis indicated increased effect sizes favoring MICT in the healthy and young population, as well as when SIT (as opposed to HIIT) was performed. Although previous research has indicated that reductions in CRP only occur with reductions in body composition markers (i.e., body fat and BMI) (130–132), only one study (52) in our analysis presented significant reductions in BMI and body mass. It suggests that reductions in CRP after exercise training may occur regardless of improvements in anthropometrics, as indicated in a previous meta-analysis with 84 studies (133). As for the difference between HIIE and MICT in improving CRP, there is clear evidence showing the higher effectiveness of MICT (131,134–136); contrarily, for HIIE, despite the potential of high-intensity training to elicit greater improvements in insulin sensitivity, and the role of systemic inflammation to develop insulin resistance, there is conflicting evidence that HIIE can effectively reduce CRP levels (a marker for systemic inflammation) (137).

Insulin and glucose metabolism. Structured exercise training programs have already been shown to improve insulin and glucose metabolism (138,139). Overall, not many differences

between HIIE and MICT were observed in the improvements in fasting insulin and fasting glucose. On the other side, MICT showed superior improvements in long-term glycemic control (HbA1c), a precursor of type 2 diabetes (140). In addition, MICT showed an increased effect size in improving HbA1c in the healthy population, as well as in improving HOMA-IR in overweight and obese individuals. Despite evidence on the mechanisms that HIIE and MICT induce improvements in insulin and glucose metabolism, conflicting findings exist regarding which one of these pathways might be more efficient (141). Debate exist regarding the intramuscular calcium increase promoted by the calcium–calmodulin kinase activation, mainly induced by moderate endurance exercise training (141–143), and the activation of the adenosine monophosphate-activated protein kinase (AMPK), induced by high-intensity exercise training (144,145). The activation of calcium–calmodulin kinase and/or AMPK is associated with an increase in the PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) expression in mRNA, which is key for the increase in mitochondrial biogenesis and the overall fat metabolism, providing large improvements in insulin sensitivity in individuals with obesity, metabolic syndrome, and T2D (89,146,147). Worth noting, the increased effect of MICT in improving HOMA-IR was mainly seen in studies that performed the exercise training in running. Such exercise modality might promote the downregulation of the transforming growth factor-beta, which has shown to impair mitochondrial biogenesis (148), and key signals in the skeletal muscle: increased muscle tension, increased reactive oxygen species (up to nonharmful levels), and increased muscle calcium concentration (141).

Limitations. Studies comparing the effects of HIIE versus MICT often equalize their training interventions by work performed or energy expenditure. However, actual training data to justify the matching of exercise intensities are rarely seen. Future exercise training interventions should consider collecting and presenting the training data and discuss how the possible distinct training stimulus might lead to different results. In addition, it should be noted that insulin resistance in the present manuscript was analyzed as the homeostasis model assessment (HOMA), which is not a direct measurement of insulin resistance but a surrogate. HOMA is calculated from fasting glucose and fasting insulin, and other methods such as glucose clamp, insulin suppression test, and intravenous glucose tolerance test offer a more direct and accurate measure.

Finally, it seems that individualized exercise training programs with the goal of health promoting might take an advantage in combining HIIE and MICT. A recent study investigated the improvements and rate of responders in individuals that performed a mix of HIIE and MICT in their exercise training for 13 wk (149). The authors found all the participants in that group to be responders to the increase in $\dot{V}O_{2max}$ as well as to improve cardiometabolic health.

In conclusion, our results suggest that HIIE and MICT exhibit an inhomogeneous effectiveness, improving different clinical end point domains related to cardiometabolic health. Although HIIE seems to be a powerful training program for improving CRF and cardiovascular health, MICT showed to be more efficient in improving long-term glucose metabolism. In the process of personalized training counseling, health-enhancing effects of exercise training may be improved by considering the individual risk profiles. Further research is warranted to assess the effectiveness of these training regimens in the long term and of combined programs addressing both HIIE and MICT.

The authors acknowledge the help of the contacted authors in providing the requested data. This work was not supported by external funding. All authors had no conflict of interest, including financial interests, relationships, and affiliations to declare in the present manuscript. The results of the study are presented clearly, honestly, without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

REFERENCES

1. Fiuza-Luces C, Garatachea N, Berger NA, Lucia A. Exercise is the real Polypill. *Phys Ther*. 2013;28(5):330–58.
2. Green DJ, Smith KJ. Effects of Exercise on vascular function, structure, and health in humans. *Cold Spring Harb Perspect Med*. 2018; 8(4):a029819.
3. Gabriel BM, Zierath JR. The limits of Exercise physiology: from performance to health. *Cell Metab*. 2017;25(5):1000–11.
4. Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. *Nat Rev Cardiol*. 2018;15(12):731–43.
5. American College of Sports Medicine, Riebe D, Ehrman JK, Liguori G, Magal M, editors. In: *ACSM's Guidelines for Exercise Testing and Prescription*. 10th ed. Philadelphia: Wolters Kluwer; 2018. p. 472.
6. Global Recommendations on Physical Activity for HealthGeneva: World Health Organization; 2010. [cited 2018 Sep 17] Available from: http://www.ncbi.nlm.nih.gov/books/NBK305057/.
7. Piepoli MF, Hoes AW, Agewall S, et al. European guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR). *Eur Heart J*. 2016;37(29):2315–81.
8. Piercy KL, Troiano RP, Ballard RM, et al. The Physical Activity Guidelines for Americans. *JAMA*. 2018;320(19):2020–8.
9. Ambrosetti M, Abreu A, Corrà U, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiolog*. 2020;204748732091337.
10. Binder RK, Wonisch M, Corra U, et al. Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. *Eur J Cardiovasc Prev Rehabil*. 2008; 15(6):726–34.
11. Hofmann P, Tschakert G. Intensity- and duration-based options to regulate endurance training. *Front Physiol*. 2017;8:337.
12. Iannetta D, Inglis EC, Mattu AT, et al. A critical evaluation of current methods for exercise prescription in women and men. *Med Sci Sports Exerc*. 2020;52(2):466–73.
13. MacInnis MJ, Gibala MJ. Physiological adaptations to interval training and the role of exercise intensity: training adaptations and the nature of the stimulus. *J Physiol*. 2017;595(9):2915–30.

14. Wasfy MM, Baggish AL. Exercise dose in clinical practice. *Circulation*. 2016;133(23):2297–313.
15. Hansen D, Niebauer J, Cornelissen V, et al. Exercise prescription in patients with different combinations of cardiovascular disease risk factors: a consensus statement from the EXPERT working group. *Sports Med*. 2018;48(8):1781–97.
16. Wen CP, Wai JPM, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet*. 2011;378(9798):1244–53.
17. Seiler S, Jøranson K, Olesen BV, Hetlelid KJ. Adaptations to aerobic interval training: interactive effects of exercise intensity and total work duration: effort-matched interval training. *Scand J Med Sci Sports*. 2013;23(1):74–83.
18. Milanović Z, Sporiš G, Weston M. Effectiveness of high-intensity interval training (HIT) and continuous endurance training for VO_{2max} improvements: a systematic review and meta-analysis of controlled trials. *Sports Med*. 2015;45(10):1469–81.
19. Batacan RB, Duncan MJ, Dalbo VJ, Tucker PS, Fenning AS. Effects of high-intensity interval training on cardiometabolic health: a systematic review and meta-analysis of intervention studies. *Br J Sports Med*. 2017;51(6):494–503.
20. Elliott AD, Rajopadhyaya K, Bentley DJ, Beltrame JF, Aromataris EC. Interval training versus continuous exercise in patients with coronary artery disease: a meta-analysis. *Heart Lung Circ*. 2015;24(2):149–57.
21. Liou K, Ho S, Fildes J, Ooi S-Y. High intensity interval versus moderate intensity continuous training in patients with coronary artery disease: a meta-analysis of physiological and clinical parameters. *Heart Lung Circ*. 2016;25(2):166–74.
22. Gibala MJ, Heisz JJ, Nelseon AJ. Interval training for cardiometabolic and brain health. *ACSMs Health Fit J*. 2018;22(6):30–4.
23. Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):1–6.
24. Viana RB, de Lira CAB, Naves JPA, et al. Can we draw general conclusions from interval training studies? *Sports Med*. 2018;48(9):2001–9.
25. Fisher G, Brown AW, Bohan Brown MM, et al. High intensity interval- vs moderate intensity-training for improving cardiometabolic health in overweight or obese males: a randomized controlled trial. *PLoS One*. 2015;10(10):e0138853.
26. Honkala SM, Motiani KK, Eskelinen J-J, et al. Exercise training reduces intrathoracic fat regardless of defective glucose tolerance. *Med Sci Sports Exerc*. 2017;49(7):1313–22.
27. Martins C, Kazakova I, Ludviksen M, et al. High-intensity interval training and isocaloric moderate-intensity continuous training result in similar improvements in body composition and fitness in obese individuals. *Int J Sport Nutr Exerc Metab*. 2016;26(3):197–204.
28. Motiani KK, Savolainen AM, Eskelinen J-J, et al. Two weeks of moderate-intensity continuous training, but not high-intensity interval training, increases insulin-stimulated intestinal glucose uptake. *J Appl Physiol*. 2017;122(5):1188–97.
29. Scribbans TD, Edgett BA, Vorobej K, et al. Fibre-specific responses to endurance and low volume high intensity interval training: striking similarities in acute and chronic adaptation. *PLoS One*. 2014;9(6):e98119.
30. Trapp EG, Chisholm DJ, Freund J, Boutcher SH. The effects of high-intensity intermittent exercise training on fat loss and fasting insulin levels of young women. *Int J Obes (Lond)*. 2008;32(4):684–91.
31. Weston KS, Wisløff U, Coombes JS. High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med*. 2014;48(16):1227–34.
32. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;l4898.
33. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
34. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–88.
35. Viechtbauer W, Cheung MW-L. Outlier and influence diagnostics for meta-analysis. *Res Synth Methods*. 2010;1:112–25.
36. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. Repr. Chichester: Wiley-Blackwell; 2012. 649 p.
37. Borenstein M. Effect sizes for continuous data. In: *The Handbook of Research Synthesis and Meta-analysis, 2nd ed*. New York (NY): Russell Sage Foundation; 2009. pp. 221–35.
38. Borenstein M, Higgins JPT, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods*. 2017;8(1):5–18.
39. Editors JN, Alink M, Iverson C, et al. *AMA Manual of Style: A Guide for Authors and Editors*. Oxford University Press; 2007. Available from: https://books.google.de/books?id=kJ0t15dCL10C.
40. Maruhashi T, Kajikawa M, Kishimoto S, et al. Diagnostic criteria of flow-mediated vasodilation for normal endothelial function and nitroglycerin-induced vasodilation for normal vascular smooth muscle function of the brachial artery. *JAHA*. 2020;9(2):e013915.
41. Ghasemi A, Tohidi M, Derakhshan A, Hasheminia M, Azizi F, Hadaegh F. Cut-off points of homeostasis model assessment of insulin resistance, beta-cell function, and fasting serum insulin to identify future type 2 diabetes: Tehran Lipid and Glucose Study. *Acta Diabetol*. 2015;52(5):905–15.
42. Higgins JPT, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med*. 2004;23(11):1663–82.
43. Borenstein M, Higgins JPT. Meta-analysis and subgroups. *Prev Sci*. 2013;14(2):134–43.
44. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna (Austria); 2020. Available from: https://www.R-project.org/.
45. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *JOSS*. 2019;4(43):1686.
46. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Mental Health*. 2019;22(4):153–60.
47. Viechtbauer W. Conducting meta-analyses in *R* with the metafor package [Internet]. *J Stat Soft*. 2010; [cited 2019 Dec 3];36(3) available from: http://www.jstatsoft.org/v36/i03/.
48. McGuinness LA, Higgins JPT. Risk-of-bias visualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments. *Res Syn Meth*. 2020; jrsm.1411.
49. Pedersen TL. *Patchwork: The Composer of Plots*. 2019.
50. BæKkerud FH, Solberg F, Leinan IM, WisløFf U, Karlsen T, Rognmo Ø. Comparison of three popular exercise modalities on $\dot{V}O_{2max}$ in overweight and obese. *Med Sci Sports Exerc*. 2016;48(3):491–8.
51. Ciolac EG, Bocchi EA, Bortolotto LA, Carvalho VO, Greve JM, Guimarães GV. Effects of high-intensity aerobic interval training vs. moderate exercise on hemodynamic, metabolic and neuro-humoral abnormalities of young normotensive women at high familial risk for hypertension. *Hypertens Res*. 2010;33(8):836–43.
52. Conraads VM, Pattyn N, De Maeyer C, et al. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: the SAINTEX-CAD study. *Int J Cardiol*. 2015;179:203–10.
53. Currie KD, Bailey KJ, Jung ME, McKelvie RS, MacDonald MJ. Effects of resistance training combined with moderate-intensity endurance or low-volume high-intensity interval exercise on cardiovascular risk factors in patients with coronary artery disease. *J Sci Med Sport*. 2015;18(6):637–42.
54. Earnest C, Lupo M, Thibodaux J, et al. Interval training in men at risk for insulin resistance. *Int J Sports Med*. 2012;34(4):355–63.
55. Eguchi Y, Ohta M, Inoue T, et al. Effects of transitory stimulation interval exercise on physical function: a randomized controlled pilot study among Japanese subjects. *J UOEH*. 2012;34(4):297–308.

56. Granata C, Oliveira RSF, Little JP, Renner K, Bishop DJ. Training intensity modulates changes in PGC-1α and p53 protein content and mitochondrial respiration, but not markers of mitochondrial content in human skeletal muscle. *FASEB J*. 2016;30(2):959–70.
57. Grieco CR, Swain DP, Colberg SR, et al. Effect of intensity of aerobic training on insulin sensitivity/resistance in recreationally active adults. *J Strength Cond Res*. 2013;27(8):2270–6.
58. Helgerud J, Høydal K, Wang E, et al. Aerobic high-intensity intervals improve $\dot{V}O_{2max}$ more than moderate training. *Med Sci Sports Exerc*. 2007;39(4):665–71.
59. Henriksson J, Reitman JS. Quantitative measures of enzyme activities in type I and type II muscle fibres of man after training. *Acta Physiol Scand*. 1976;97(3):392–7.
60. Keteyian SJ, Hibner BA, Bronsteen K, et al. Greater improvement in cardiorespiratory fitness using higher-intensity interval training in the standard cardiac rehabilitation setting. *J Cardiopulm Rehabil Prev*. 2014;34(2):98–105.
61. Kim C, Choi HE, Lim MH. Effect of high interval training in acute myocardial infarction patients with drug-eluting stent. *Am J Phys Med Rehabil*. 2015;94:879–86.
62. Klonizakis M, Moss J, Gilbert S, Broom D, Foster J, Tew GA. Low-volume high-intensity interval training rapidly improves cardiopulmonary function in postmenopausal women. *Menopause*. 2014; 21(10):1099–105.
63. Lira FS, dos Santos T, Caldeira RS, et al. Short-term high- and moderate-intensity training modifies inflammatory and metabolic factors in response to acute exercise. *Front Physiol*. 2017;8:856.
64. Lunt H, Draper N, Marshall HC, et al. High intensity interval training in a real world setting: a randomized controlled feasibility study in overweight inactive adults, measuring change in maximal oxygen uptake. *PLoS One*. 2014;9(1):e83256.
65. Madssen E, Moholdt T, Videm V, Wisløff U, Hegbom K, Wiseth R. Coronary atheroma regression and plaque characteristics assessed by grayscale and radiofrequency intravascular ultrasound after aerobic Exercise. *Am J Cardiol*. 2014;114(10):1504–11.
66. Maillard F, Rousset S, Pereira B, et al. High-intensity interval training reduces abdominal fat mass in postmenopausal women with type 2 diabetes. *Diabetes Metab*. 2016;42(6):433–41.
67. Matsuo T, Saotome K, Seino S, et al. Low-volume, high-intensity, aerobic interval exercise for sedentary adults: $\dot{V}O_{2max}$, cardiac mass, and heart rate recovery. *Eur J Appl Physiol*. 2014;114(9):1963–72.
68. Matsuo T, So R, Shimojo N, Tanaka K. Effect of aerobic exercise training followed by a low-calorie diet on metabolic syndrome risk factors in men. *Nutr Metab Cardiovasc Dis*. 2015;25(9):832–8.
69. Mitranun W, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients: continuous vs interval training. *Scand J Med Sci Sports*. 2014;24(2):e69–76.
70. Molmen-Hansen HE, Stolen T, Tjonna AE, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prev Cardiol*. 2012;19(2):151–60.
71. Moreira MM, Carozo de Souza HP, Schwingel PA, Couto de Sá CK, Zoppi CC. Effects of aerobic and anaerobic exercise on cardiac risk variables in overweight adults. *Arq Bras Cardiol*. 2008; 91(4):200–6.
72. Nie J, Zhang H, Kong Z, et al. Impact of high-intensity interval training and moderate-intensity continuous training on resting and postexercise cardiac troponin T concentration. *Exp Physiol*. 2018; 103(3):370–80.
73. O'Leary TJ, Collett J, Howells K, Morris MG. Endurance capacity and neuromuscular fatigue following high- vs moderate-intensity endurance training: a randomized trial. *Scand J Med Sci Sports*. 2017;27(12):1648–61.
74. Ramos JS, Dalleck LC, Borrani F, et al. The effect of different volumes of high-intensity interval training on proinsulin in participants with the metabolic syndrome: a randomised trial. *Diabetologia*. 2016;59(11):2308–20.
75. Ramos JS, Dalleck LC, Ramos MV, et al. 12 min/week of high-intensity interval training reduces aortic reservoir pressure in individuals with metabolic syndrome: a randomized trial. *J Hypertens*. 2016;34(10):1977–87.
76. Robinson E, Durrer C, Simtchouk S, et al. Short-term high-intensity interval and moderate-intensity continuous training reduce leukocyte TLR4 in inactive adults at elevated risk of type 2 diabetes. *J Appl Physiol*. 2015;119(5):508–16.
77. Rognmo Ø, Hetland E, Helgerud J, Hoff J, Slørdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil*. 2004;11(3):216–22.
78. Sawyer BJ, Tucker WJ, Bhammar DM, Ryder JR, Sweazea KL, Gaesser GA. Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults. *J Appl Physiol*. 2016;121(1):279–88.
79. Tjonna AE, Lee SJ, Rognmo O, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation*. 2008;118(4):346–54.
80. Wegmann M, Hecksteden A, Poppendieck W, et al. Postexercise hypotension as a predictor for long-term training-induced blood pressure reduction: a large-scale randomized controlled trial. *Clin J Sport Med*. 2018;28(6):509–15.
81. Winn NC, Liu Y, Rector RS, Parks EJ, Ibdah JA, Kanaley JA. Energy-matched moderate and high intensity exercise training improves nonalcoholic fatty liver disease risk independent of changes in body mass or abdominal adiposity—a randomized trial. *Metabolism*. 2018;78:128–40.
82. Zapata-Lamana R, Henríquez-Olguín C, Burgos C, et al. Effects of polarized training on cardiometabolic risk factors in young overweight and obese women: a randomized-controlled trial [Internet]. *Front Physiol*. 2018;9:1287.
83. Wisløff U, Støylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007; 115(24):3086–94.
84. Abdelbasset WK, Tantawy SA, Kamel DM, et al. Effects of high-intensity interval and moderate-intensity continuous aerobic exercise on diabetic obese patients with nonalcoholic fatty liver disease: a comparative randomized controlled trial. *Medicine*. 2020; 99(10):e19471.
85. Jo E-A, Cho K-I, Park J-J, Im D-S, Choi J-H, Kim B-J. Effects of high-intensity interval training versus moderate-intensity continuous training on epicardial fat thickness and endothelial function in hypertensive metabolic syndrome. *Metab Syndr Relat Disord*. 2020;18(2):96–102.
86. Beetham KS, Howden EJ, Fassett RG, et al. High-intensity interval training in chronic kidney disease: a randomized pilot study. *Scand J Med Sci Sports*. 2019; sms.13436.
87. Burgomaster KA, Howarth KR, Phillips SM, et al. Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans: metabolic adaptations to sprint or endurance training in humans. *J Physiol*. 2008;586(1): 151–60.
88. Cocks M, Shaw CS, Shepherd SO, et al. Sprint interval and endurance training are equally effective in increasing muscle microvascular density and eNOS content in sedentary males: microvascular adaptations to training in sedentary males. *J Physiol*. 2013;591(3):641–56.
89. Gillen JB, Martin BJ, MacInnis MJ, Skelly LE, Tarnopolsky MA, Gibala MJ. Twelve weeks of sprint interval training improves indices of cardiometabolic health similar to traditional endurance training despite a five-fold lower exercise volume and time commitment. *PLoS One*. 2016;11(4):e0154075.
90. Gorostiaga EM, Walter CB, Foster C, Hickson RC. Uniqueness of interval and continuous training at the same maintained exercise intensity. *Eur J Appl Physiol Occup Physiol*. 1991;63(2):101–7.

91. Hovanloo F, Arefirad T, Ahmadizad S. Effects of sprint interval and continuous endurance training on serum levels of inflammatory biomarkers. *J Diabetes Metab Disord*. 2013;12(1):22.
92. Keating SE, Machan EA, O'Connor HT, et al. Continuous exercise but not high intensity interval training improves fat distribution in overweight adults. *J Obes*. 2014;2014:1–12.
93. Macpherson REK, Hazell TJ, Olver TD, Paterson DH, Lemon PWR. Run sprint interval training improves aerobic performance but not maximal cardiac output. *Med Sci Sports Exerc*. 2011;43(1):115–22.
94. Nalcakan GR. The effects of sprint interval vs. continuous endurance training on physiological and metabolic adaptations in young healthy adults. *J Hum Kinet*. 2014;44(1):97–109.
95. Sandvei M, Jeppesen PB, Støen L, et al. Sprint interval running increases insulin sensitivity in young healthy subjects. *Arch Physiol Biochem*. 2012;118(3):139–47.
96. Shepherd SO, Cocks M, Tipton KD, et al. Sprint interval and traditional endurance training increase net intramuscular triglyceride breakdown and expression of perilipin 2 and 5: perilipin expression and IMTG metabolism. *J Physiol*. 2013;591(3):657–75.
97. Sjöros TJ, Heiskanen MA, Motiani KK, et al. Increased insulin-stimulated glucose uptake in both leg and arm muscles after sprint interval and moderate-intensity training in subjects with type 2 diabetes or prediabetes. *Scand J Med Sci Sports*. 2018; 28(1):77–87.
98. Skleryk JR, Karagounis LG, Hawley JA, Sharman MJ, Laursen PB, Watson G. Two weeks of reduced-volume sprint interval or traditional exercise training does not improve metabolic functioning in sedentary obese men. *Diabetes Obes Metab*. 2013;15(12):1146–53.
99. Lee I-M, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet*. 2012;380(9838):219–29.
100. Moore SC, Patel AV, Matthews CE, et al. Leisure time physical activity of moderate to vigorous intensity and mortality: a large pooled cohort analysis. *PLoS Med*. 2012;9(11):e1001335.
101. Ruiz JR, Moran M, Arenas J, Lucia A. Strenuous endurance exercise improves life expectancy: it's in our genes. *Br J Sports Med*. 2011;45(3):159–61.
102. Green DJ, O'Driscoll G, Joyner MJ, Cable NT. Exercise and cardiovascular risk reduction: time to update the rationale for exercise? *J Appl Physiol*. 2008;105(2):766–8.
103. Türk Y, Theel W, Kasteleyn MJ, et al. High intensity training in obesity: a meta-analysis: high intensity training in obesity. *Obes Sci Pract*. 2017;3(3):258–71.
104. De Nardi AT, Tolves T, Lenzi TL, Signori LU, Silva AMVda. High-intensity interval training versus continuous training on physiological and metabolic variables in prediabetes and type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract*. 2018;137:149–59.
105. Gomes-Neto M, Durães AR, dos Reis HFC, Neves VR, Martinez BP, Carvalho VO. High-intensity interval training versus moderate-intensity continuous training on exercise capacity and quality of life in patients with coronary artery disease: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2017;24(16):1696–707.
106. Støren Ø, Helgerud J, Sæbø M, et al. The effect of age on the $\dot{V}O_{2max}$ response to high-intensity interval training. *Med Sci Sports Exerc*. 2017;49(1):78–85.
107. DeSouza CA, Shapiro LF, Clevenger CM, et al. Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation*. 2000;102(12):1351–7.
108. Buchman AS, Wilson RS, Yu L, James BD, Boyle PA, Bennett DA. Total daily activity declines more rapidly with increasing age in older adults. *Arch Gerontol Geriatr*. 2014;58(1):74–9.
109. Kohrt WM, Malley MT, Coggan AR, et al. Effects of gender, age, and fitness level on response of $\dot{V}O_{2max}$ to training in 60-71 yr olds. *J Appl Physiol*. 1991;71(5):2004–11.
110. Howden EJ, Sarma S, Lawley JS, et al. Reversing the cardiac effects of sedentary aging in middle age—a randomized controlled trial: implications for heart failure prevention. *Circulation*. 2018;137(15): 1549–60.
111. Lundby C, Montero D, Joyner M. Biology of $\dot{V}O_{2max}$: looking under the physiology lamp. *Acta Physiol*. 2017;220(2):218–28.
112. Hosoda Y, Kawano K, Yamasawa F, Ishii T, Shibata T, Inayama S. Age-dependent changes of collagen and elastin content in human aorta and pulmonary artery. *Angiology*. 1984;35(10):615–21.
113. Spence AL, Carter HH, Naylor LH, Green DJ. A prospective randomized longitudinal study involving 6 months of endurance or resistance exercise. Conduit artery adaptation in humans. *J Physiol*. 2013;591(5):1265–75.
114. Trapp EG, Chisholm DJ, Boutcher SH. Metabolic response of trained and untrained women during high-intensity intermittent cycle exercise. *Am J Physiol Regul Integr Comp Physiol*. 2007;293(6): R2370–5.
115. Burguera B, Proctor D, Dietz N, Guo Z, Joyner M, Jensen MD. Leg free fatty acid kinetics during exercise in men and women. *Am J Physiol Endocrinol Metab*. 2000;278(1):E113–7.
116. Schubert MM, Clarke HE, Seay RF, Spain KK. Impact of 4 weeks of interval training on resting metabolic rate, fitness, and health-related outcomes. *Appl Physiol Nutr Metab*. 2017;42(10): 1073–81.
117. Viana RB, Naves JPA, Coswig VS, et al. Is interval training the magic bullet for fat loss? A systematic review and meta-analysis comparing moderate-intensity continuous training with high-intensity interval training (HIIT). *Br J Sports Med*. 2019;53(10):655–64.
118. Sultana RN, Sabag A, Keating SE, Johnson NA. The effect of low-volume high-intensity interval training on body composition and cardiorespiratory fitness: a systematic review and meta-analysis. *Sports Med*. 2019;49(11):1687–721.
119. Naci H, Salcher-Konrad M, Dias S, et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomised controlled trials assessing exercise and medication effects on systolic blood pressure. *Br J Sports Med*. 2018; bjsports-2018-099921.
120. Kessler HS, Sisson SB, Short KR. The potential for high-intensity interval training to reduce cardiometabolic disease risk. *Sports Med*. 2012;42(6):489–509.
121. Durstine JL, Grandjean PW, Davis PG, Ferguson MA, Alderson NL, DuBose KD. Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis. *Sports Med*. 2001;31(15):1033–62.
122. Durstine JL, Haskell WL. Effects of exercise training on plasma lipids and lipoproteins. *Exerc Sport Sci Rev*. 1994;22:477–521.
123. Leon AS, Rice T, Mandel S, et al. Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the HERITAGE family study. *Metabolism*. 2000;49(4):513–20.
124. Tjønna AE, Stølen TO, Bye A, et al. Aerobic interval training reduces cardiovascular risk factors more than a multitreatment approach in overweight adolescents. *Clin Sci*. 2009;116(4):317–26.
125. Musa DI, Adeniran SA, Dikko AU, Sayers SP. The effect of a high-intensity interval training program on high-density lipoprotein cholesterol in young men. *J Strength Cond Res*. 2009;23(2): 587–92.
126. Nybo L, Sundstrup E, Jakobsen MD, et al. High-intensity training versus traditional exercise interventions for promoting health. *Med Sci Sports Exerc*. 2010;42(10):1951–8.
127. Moholdt TT, Amundsen BH, Rustad LA, et al. Aerobic interval training versus continuous moderate exercise after coronary artery bypass surgery: a randomized study of cardiovascular effects and quality of life. *Am Heart J*. 2009;158(6):1031–7.
128. Wallman K, Plant LA, Rakimov B, Maiorana AJ. The effects of two modes of exercise on aerobic fitness and fat mass in an overweight population. *Res Sports Med*. 2009;17(3):156–70.
129. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med*. 2015;45(5):679–92.

130. Arikawa AY, Thomas W, Schmitz KH, Kurzer MS. Sixteen weeks of exercise reduces C-reactive protein levels in young women. *Med Sci Sports Exerc*. 2011;43(6):1002–9.
131. Martins RA, Neves AP, Coelho-Silva MJ, Veríssimo MT, Teixeira AM. The effect of aerobic versus strength-based training on high-sensitivity C-reactive protein in older adults. *Eur J Appl Physiol*. 2010;110(1):161–9.
132. Church TS, Earnest CP, Thompson AM, et al. Exercise without weight loss does not reduce C-reactive protein: the INFLAME study. *Med Sci Sports Exerc*. 2010;42(4):708–16.
133. Fedewa MV, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. *Br J Sports Med*. 2017;51(8):670–6.
134. Daray LA, Henagan TM, Zanovec M, et al. Endurance and resistance training lowers C-reactive protein in young, healthy females. *Appl Physiol Nutr Metab*. 2011;36(5):660–70.
135. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers. *J Am Coll Cardiol*. 2005;45(10):1563–9.
136. Kohut ML, McCann DA, Russell DW, et al. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun*. 2006;20(3):201–9.
137. Allen NG, Higham SM, Mendham AE, Kastelein TE, Larsen PS, Duffield R. The effect of high-intensity aerobic interval training on markers of systemic inflammation in sedentary populations. *Eur J Appl Physiol*. 2017;117(6):1249–56.
138. Avery L, Flynn D, van Wersch A, Sniehotta FF, Trenell MI. Changing physical activity behavior in type 2 diabetes: a systematic review and meta-analysis of behavioral interventions. *Diabetes Care*. 2012; 35(12):2681–9.
139. Umpierre D, Ribeiro PAB, Schaan BD, Ribeiro JP. Volume of supervised exercise training impacts glycaemic control in patients with type 2 diabetes: a systematic review with meta-regression analysis. *Diabetologia*. 2013;56(2):242–51.
140. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539–53.
141. Laursen PB. Training for intense exercise performance: high-intensity or high-volume training? *Scand J Med Sci Sports*. 2010;20(2 Suppl): 1–10.
142. Cho Y, Tachibana S, Hazen BC, et al. Perm1 regulates CaMKII activation and shapes skeletal muscle responses to endurance exercise training. *Mol Metab*. 2019;23:88–97.
143. Eilers W, Jaspers RT, de Haan A, Ferrié C, Valdivieso P, Flück M. CaMKII content affects contractile, but not mitochondrial, characteristics in regenerating skeletal muscle. *BMC Physiol*. 2014; 14(1):7.
144. Ruderman NB, Carling D, Prentki M, Cacicedo JM. AMPK, insulin resistance, and the metabolic syndrome. *J Clin Investig*. 2013; 123(7):2764–72.
145. Gibala MJ, McGee SL, Garnham AP, Howlett KF, Snow RJ, Hargreaves M. Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1α in human skeletal muscle. *J Appl Physiol*. 2009;106(3):929–34.
146. Widmann M, Nieß AM, Munz B. Physical exercise and epigenetic modifications in skeletal muscle [Internet]. *Sports Med*. 2019; [cited 2019 Mar 7]; available from: http://link.springer.com/10.1007/s40279-019-01070-4.
147. McConell GK, Wadley GD, Le plastrier K, Linden KC. Skeletal muscle AMPK is not activated during 2 hours of moderate intensity exercise at ~65% VO_2 peak in endurance trained men. *J Physiol*. 2020;JP277619.
148. Böhm A, Hoffmann C, Irmler M, et al. TGF-β contributes to impaired exercise response by suppression of mitochondrial key regulators in skeletal muscle. *Diabetes*. 2016;65(10):2849–61.
149. Byrd BR, Keith J, Keeling SM, et al. Personalized moderate-intensity exercise training combined with high-intensity interval training enhances training responsiveness. *Int J Environ Res Public Health*. 2019;16(12):2088.