# Sex Differences in Cardiometabolic Health Indicators after HIIT in Patients with Coronary Artery Disease

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## ABSTRACT

WAY, K. L., S. VIDAL-ALMELA, T. MOHOLDT, K. D. CURRIE, I.-L. A. AKSETØY, M. BOIDIN, V. A. CORNELISSEN, K.-L. JOA, A. KEECH, J. A. JAYO-MONTOYA, J. L. TAYLOR, K. FOURINER, and J. L. REED. Sex Differences in Cardiometabolic Health Indicators after HIIT in Patients with Coronary Artery Disease. *Med. Sci. Sports Exerc.*, Vol. 53, No. 7, pp. 1345–1355, 2021. **Purpose:** Cardiorespiratory fitness (CRF) is an independent predictor of mortality, and females typically achieve smaller improvements in CRF than males after exercise-based cardiac rehabilitation. High-intensity interval training (HIIT) has been shown to produce superior improvements in CRF than traditional cardiac rehabilitation, but the sex differences are unknown. The purpose of this systematic review and meta-analysis was to evaluate sex differences for changes in CRF and cardiometabolic health indicators after HIIT in adults with coronary artery disease (CAD). **Methods and Results:** A systemic search of five electronic databases for studies examining the effect of HIIT on measured CRF and cardiometabolic health indicators in adults with CAD was performed. Data (published and unpublished) from 14 studies were included in the meta-analyses with approximately eightfold greater male than female participation ($n = 836$ vs $n = 103$). Males with CAD achieved a near-significant absolute improvement in CRF (mean difference [MD] = 1.07, 95% confidence interval [CI] = −0.08 to 2.23 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P = 0.07$) after HIIT when compared with control; there were insufficient data to conduct such an analysis in females. Significantly smaller improvements in CRF were experienced by females than males (MD = −1.10, 95% CI = −2.08 to −0.12 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P = 0.03$); there was no sex difference for the relative (percentage) change in CRF after HIIT. Females achieved significantly smaller reductions in body mass index (MD = −0.25, 95% CI = −0.03 to −0.47 $\text{kg}\cdot\text{m}^{-2}$, $P = 0.02$) and fasting blood glucose (MD = −0.38, 95% CI = −0.05 to −0.72, $P = 0.03$); no sex differences were observed for other cardiometabolic health indicators. **Conclusion:** There are no sex differences for relative improvements in CRF after HIIT; however, females are greatly underrepresented in trials. Future studies should increase female participation and perform sex-based

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analyses to determine sex-specific outcomes following HIIT. **Key Words:** FEMALES, MALES, HIIT, CARDIORESPIRATORY FITNESS, CARDIOMETABOLIC HEALTH

Cardiovascular disease (CVD) is the leading cause of mortality worldwide (1), with coronary artery disease (CAD) accounting for 43.2% of these deaths (2). Relative cardiorespiratory fitness (CRF), a strong predictor of prognosis (3) and future cardiovascular events (4), is lower in females with CVD than males (5). Strong observational evidence demonstrates that females with CVD present with more cardiovascular risk factors, including hypertension, type 2 diabetes, dyslipidemia, obesity, anxiety, and depression, than males (6). Females are also more likely to die within 1 yr of a cardiac procedure than males (6.2% vs 4.1%, $P < 0.001$) (7). Given the sex disparities in prognosis and treatment strategies for CVD (8,9), greater efforts are needed to optimize CVD management based on sex (10).

The current cardiac rehabilitation (CR) guidelines recommend moderate- to vigorous-intensity continuous training (MICT) (11); the benefits from such programming in managing cardiovascular conditions are well documented (12,13). Sex-specific analyses on the effects of traditional CR are sparse and have shown that females may not achieve the same improvements in CRF and cardiometabolic health indicators as males (14,15). High-intensity interval training (HIIT) may be a suitable alternative exercise paradigm for females with CVD and has received heightened attention as a safe and superior exercise paradigm for improving CRF (16,17). HIIT consists of repeated short bouts of high-intensity aerobic exercise, interspersed with either passive or low- to moderate-intensity active recovery periods (16). Meta-analyses have revealed that HIIT leads to significantly greater increases in CRF in patients with CAD when compared with traditional MICT (range, +1.15 to +1.60 $mL \cdot kg^{-1} \cdot min^{-1}$) (16,18). These greater improvements in CRF suggest that HIIT programming may be a more effective exercise approach for females with CAD. However, none of the previous meta-analyses examining the effect of HIIT in patients with CAD have conducted sex-specific analyses.

Our recent perspective article identified that females with CAD are severely underrepresented in HIIT clinical trials; there are approximately fivefold more males participating in such studies (19). Findings from previous clinical trials may not be generalizable for females with CAD as females suffer a greater cardiovascular burden with worse cardiometabolic health indicators and experience sex-specific risk factors such as gestational diabetes, preterm delivery, and menopause (20). The first female-only study by Reed et al. (21) comparing HIIT ($n = 30$) with MICT ($n = 30$) in patients with CVD demonstrated that only HIIT led to clinically meaningful reductions in waist circumference (−4.4 ± 7.4 cm). Lee et al. (22) also conducted a female-only HIIT study in CAD patients and found in their per-protocol analyses that the combination of HIIT and MICT resulted in significantly greater improvements in CRF than MICT alone after 24 wk (+0.95 $mL \cdot kg^{-1} \cdot min^{-1}$, $P < 0.001$). These findings suggest that HIIT may be a more appropriate exercise modality than MICT for females with CAD to improve their poor cardiometabolic health profile. A systematic collection and analysis of the available data will facilitate a greater understanding of the effects of HIIT on CRF and cardiometabolic health indicators in females and males.

The purpose of this systematic review was to evaluate the impact of sex on changes in CRF after HIIT in patients with CAD. Our secondary aim was to examine the impact of sex on other cardiometabolic health indicators after HIIT. We hypothesized that females with CAD would experience a smaller improvement in CRF and cardiometabolic health indicators with HIIT when compared with their male counterparts.

## METHODS

The review methodology was prospectively registered with PROSPERO (registration no. 160255) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting items for systematic reviews and meta-analyses (23).

### Study Inclusion Criteria

**Population.** Studies were included if the sample comprised adults with CAD, with a mean age ≥18 yr.

**Interventions.** Eligible studies conducted HIIT for at least 3 wk. HIIT was considered as repeated short bouts of high-intensity aerobic exercise, interspersed with either passive or low- to moderate-intensity active recovery periods. Studies that reported high-intensity bouts at a vigorous or near maximal intensity (>64% maximum rate of oxygen consumption [$\dot{V}O_{2max}$], >76% heart rate maximum [$HR_{max}$], >60% $\dot{V}O_2$ reserve/heart rate reserve [HRR], >6 METs, or >14 Borg RPE) in accordance with the American College of Sports Medicine guidelines were deemed eligible (24). Studies that combined HIIT with other exercise training interventions were excluded.

**Primary outcome: CRF.** Eligible studies reported the measurement of CRF with gold standard methodology through indirect calorimetry to obtain maximum or peak aerobic power ($\dot{V}O_{2max}$/$\dot{V}O_{2peak}$). Studies were required to report pre- and postintervention CRF values separated by sex. In instances where males and females were included but did not report sex-based analyses, corresponding authors were contacted to seek permission to obtain sex-specific data for pre- and postintervention data for all eligible studies.

**Secondary outcomes: cardiometabolic health indicators.** Cardiometabolic health indicators included body composition (body mass index [BMI], waist circumference, waist-to-hip ratio, and body fat percentage), blood pressure, blood lipids, fasting plasma glucose, glycosylated hemoglobin A1c, fasting plasma insulin, functional capacity, and physical activity levels.

**Study designs.** Prospective cohort and experimental designs (randomized controlled trials, randomized trials, quasi-experimental investigations, and pre- and postdesign) were eligible. Control or MICT groups were used, when available, to compare effects;

there were no restrictions placed on the nature of the control groups (e.g., no exercise intervention and standard care advice).

**Publication status and language.** Published (peer-reviewed and conference abstracts) literature was examined; no language restrictions were imposed on the search.

**Search strategy.** A comprehensive search strategy was designed by a research librarian ([SV] and reviewed and conducted by a second [KF]) to identify relevant studies. The strategy is illustrated using the MEDLINE search as an example (see Table, Supplemental Digital Content 1, Example of search strategy—MEDLINE, http://links.lww.com/MSS/C255); it was modified according to the indexing systems of other databases. Five electronic bibliographic databases were searched: MEDLINE (OvidSP), Embase (OvidSP), CINAHL (EBSCOhost), AMED (OvidSP), and SPORTDiscus (EBSCOhost). An original search was conducted in all the databases from inception to March 8, 2019. The search included gray literature (i.e., conference abstracts) and published peer-reviewed journal articles. An update was completed that included articles that were published as of January 31, 2020.

**Selection of studies.** Citations were imported into Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia), and duplicates were removed using the “duplicate” function. Two independent reviewers (KLW and SVA) screened the titles and abstracts of all studies to identify potentially relevant articles. The full texts of all studies that met the inclusion criteria were obtained and reviewed independently by two reviewers (KLW and SVA). Disagreements were resolved through discussion with a third reviewer (JLR). Reviewers were not blinded to the authors or journals screened.

**Data extraction.** Standardized data abstraction tables were completed by KLW and SVA. Information extracted included the following: publication details (authors and publication year); participant characteristics (mean age, sex distribution, cardiac diagnosis, and medications); study design; sample size; HIIT and MICT length and description; control group description; cardiorespiratory outcomes; and cardiometabolic health indicators. When corresponding authors were contacted for outcome data, authors were provided the option to provide (i) the within-group pre- and postintervention mean, SD, and change scores or (ii) the data set of all participants. In instances where the data set was provided, the mean, SD, and change scores were calculated. When several publications reported results from the same primary data source, the seminal publication was retained. In instances where there were multiple HIIT interventions implemented in a trial, the exercise prescription that was the most homogenous to the other included studies was used for the analysis.

**Assessment of methodological quality.** Three researchers (KLW, SVA, and JLR) assessed the methodological quality of the included studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and the Cochrane Risk of Bias tool recommended by the Cochrane Handbook for Systematic Reviews of Interventions (25). The GRADE approach assesses the quality of the evidence as high, moderate, low, or very low; randomized controlled trials are deemed as high-quality evidence, and observational studies are seen as low-quality evidence. The quality of evidence was determined after risk of bias, imprecision, heterogeneity, indirectness, and suspicion of publication bias. The Cochrane Risk of Bias Tool consists of seven items: (i) random sequence generation, (ii) allocation concealment, (iii) selective reporting, (iv) blinding (participants and personnel), (v) blinding (outcome assessment), (vi) incomplete outcome data, and (vii) other sources of bias. Each criterion was rated as either “high risk,” “low risk,” or “unclear risk” of bias by KLW, SVA, and JLR. Disagreements were resolved by discussion.

**Data analyses.** The within-trial mean difference (MD) effect size and the 95% confidence interval (CI) were calculated. The MD was determined by calculating the difference in the mean outcome between groups and by dividing by the SD of the outcome among the participants. In instances where different units of measurements were reported for a cardiometabolic health indicator, the standardized MD (SMD) was calculated to determine the effect size. Values of 0.2, 0.5, and 0.8 were considered low, moderate, and large SMD, respectively (26). $I^2$ was used to assess heterogeneity. Values of 0% to 40%, 40% to 60%, 60% to 90%, and 90% to 100% were considered to indicate low, moderate, substantial, and considerable heterogeneity, respectively (25). Publication bias was assessed through visual inspection of funnel plots. Pooled estimates of the effect of HIIT on CRF (absolute [$\mathrm{mL \cdot kg^{-1} \cdot min^{-1}}$] and relative [percentage change from baseline CRF] change) and cardiometabolic health indicators for females versus males were obtained using a random-effects model. Pooled estimates were calculated for the effect of HIIT versus control on absolute CRF in males separately. As previous research has indicated a low participation of females with CAD in HIIT trials, a minimum of five studies were needed to conduct a meta-analysis (27). This was done in an attempt to reduce the heterogeneity among small sample sizes and increase statistical power (27). All analyses were conducted using Review Manager, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

## RESULTS

**Identification and selection of studies.** The original search conducted in March 2019 yielded 2127 studies. An updated search in January 2020 yielded an additional 402 studies. A total of 2529 records were therefore retrieved (Fig. 1). After removal of duplicates and exclusion of articles based on the eligibility criteria, 62 studies remained (Fig. 1). Of the 62 eligible studies, the corresponding authors of 59 studies were contacted on at least three occasions to discern whether CRF and cardiometabolic health indicator data could be provided as unpublished results, and 2 studies had sufficient sex-specific data within the published manuscript. The corresponding author of 14 studies provided data. Upon contacting authors, 9 authors declined to provide data, 28 authors did not respond to the query, and 8 manuscripts had the incorrect contact information and, thus, could not be contacted. Therefore, a total of 16 studies (published between 1976 and 2020) were included in the systematic review. All the included studies were published in English. Of the 16 studies,

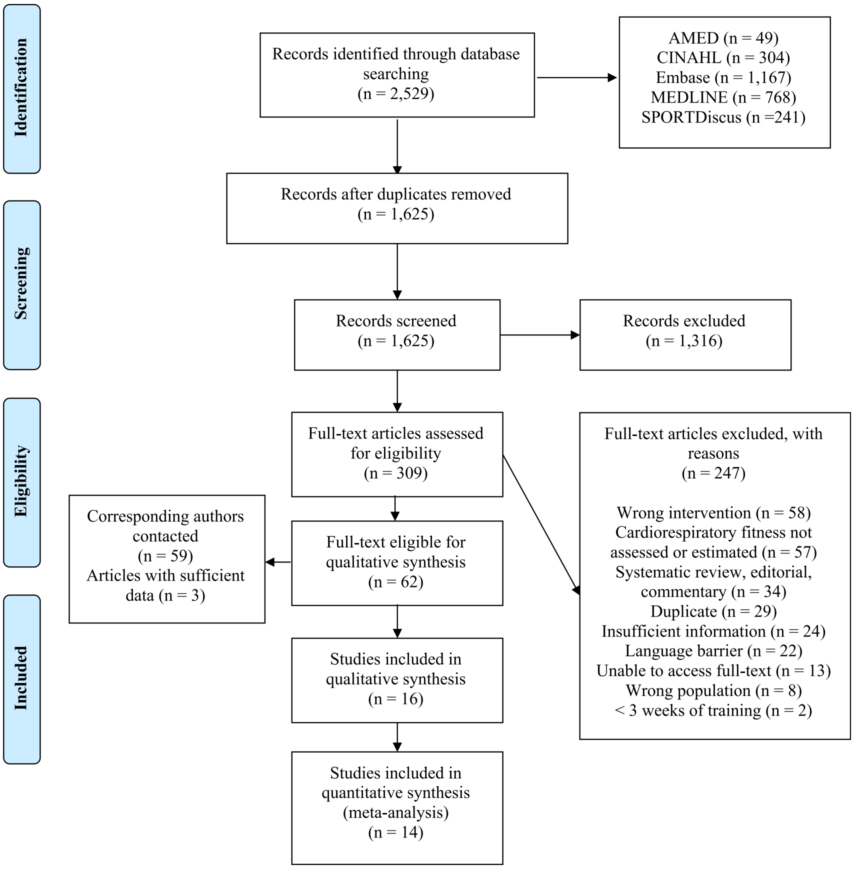

**FIGURE 1—PRISMA flow diagram.**

10 studies were randomized trials (28–36), 4 studies were randomized controlled trials (37–40), and 2 pre- and posttrials (41,42) examined the effect of HIIT on changes in CRF. Studies were conducted in Australia (*n* = 2) (42,43), Belgium (*n* = 1) (39), Canada (*n* = 3) (29,31,32), Korea (*n* = 1) (30), Norway (*n* = 6) (28,34,35–37,39), Poland (*n* = 1) (41), Spain (*n* = 1) (33), and the United States (*n* = 1) (40).

**Cohort characteristics.** Participant characteristics of the included studies are shown in Supplemental Digital Content 2 (see Table, Supplemental Digital Content 2, Study and participant characteristics, http://links.lww.com/MSS/C256). Of the studies examined, most included patients who had experienced a myocardial infarction (*n* = 11 studies) (28,30–34,41,42,44). A total of 939 individuals (835 males [range, *n* = 1–161]; 103 females [range, *n* = 0–15]; ~11% female) participated in the trials. When examining the total participants in all eligible full texts, a total of 2280 male (range, *n* = 1–489) and 386 female (range, *n* = 0–68; ~14% of total participants) individuals were involved in the trials. Three studies exclusively recruited male participants (40,41,45), no studies exclusively recruited female participants, and 14 studies recruited both males and females (28–34,36–39,41–44). The majority of individuals participating in the trials were prescribed anticoagulants, antidyslipidemics, antihypertensives, and β-blockers (28,29,31–34,36–39,42–44). Three studies did not report the medications of participants (30,40,41). In six trials, participants had recently undergone revascularization procedures such as percutaneous coronary interventions and coronary artery bypass graft surgery (28,31,32,37,41,42,44). The mean age of participants ranged from 46 to 68 yr, of which female participants appeared to be older than male participants (males, 59 ± 5 yr; females, 61 ± 5 yr). Based on BMI classification (see Table, Supplemental Digital Content 3, Cardiorespiratory fitness and other cardiometabolic health indicators, http://links.lww.com/MSS/C257), 12 studies included participants who were classified, on average, as overweight (28–34,37–39,42,43), and three studies did not report mean BMI (40,41). In four studies, females, on average, had a normal BMI, whereas males were considered overweight (36,42,43) or obese (44).

**Exercise characteristics.** Exercise intervention characteristics are shown in Supplemental Digital Content 3 (see Table, Cardiorespiratory fitness and other cardiometabolic health indicators, http://links.lww.com/MSS/C257). Cycling was the most frequently prescribed exercise modality (29,31,32,38,40–42). Four studies used treadmills (28,34,36,44) and one trial used mixed modalities (cycling and treadmill) for HIIT (33). Two studies examined the effect of home-based HIIT (i.e., the individual chose an exercise they enjoyed using large muscle groups and received oral/written instructions on how to perform HIIT) (37,39). One study allowed participants to choose their preferred type of aerobic exercise to perform HIIT within a gym setting (43). The frequency of HIIT sessions ranged from 1 to 4 sessions per week, with 3 sessions per week being the most commonly prescribed (29,34,36–41,43,44). The duration of the HIIT sessions (excluding warm-up and cooldown) was between 12 and 30 min. The Norwegian 4 × 4 min protocol was the most commonly prescribed HIIT intervention (8 out of the 15 included studies [30,34,36–40,43,44]). The intensity of the high-intensity work bouts ranged from 85% to 95% peak heart rate ($\text{HR}_{\text{peak}}$) (28,36,38), 75%–100% maximal heart rate ($\text{HR}_{\text{max}}$) (30,34,37,39,40,45), 80%–95% heart rate reserve (HRR) (33,41), 75%–100% peak power output (PPO) (29,31,32), or 85%–95% maximum work rate ($W_{\text{max}}$) (42). One study used the RPE scale to prescribe the high-intensity intervals (RPE, 15–18) (43). The duration of the high-intensity work bouts were between 15 s and 4 min, with 2 to 20 repetitions in each exercise session. For active recoveries, the prescribed intensity ranged between 15% and 75% of either $\text{HR}_{\text{peak}}$, $\text{HR}_{\text{max}}$, HRR, or $W_{\text{max}}$ (28,30,33,34,36–39,42,44). RPE was used to prescribe the intensity of active recoveries in one study (RPE, 11–13) (43). Two studies implemented passive recoveries (29,41), and three studies did not report the intensity of the recovery periods (31,32,40). The duration of the recovery periods was between 15 s and 3 min.

One study provided dietary advice for participants (Mediterranean diet) in conjunction with exercise and control (33). The same dietary advice was given to the HIIT and control groups.

**Risk of bias and GRADE approach.** Risk of bias results are summarized in Figure 2. Half of the studies provided a description on randomization sequencing for group allocation with ~30% of studies deemed as unclear risk as there was no description on the randomization strategy used. The majority of studies had a high risk of selection bias because of the lack of reporting of allocation concealment. Approximately 75% had no description of blinding of outcome assessors to group allocation (performance and detection bias). Almost half the studies had a high attrition rate (>10%) or did not report dropouts, and over 50% of studies only reported data on participants who completed the study. Most studies used objective measures of cardiometabolic outcomes. The GRADE Approach results are summarized in Table 1. Five criteria (selection, performance, detection, attrition, and reporting bias) were rated as high risk, resulting in a two-point downgrade from not serious to very serious across all outcomes.

**Meta-analysis—CRF.** Meta-analyses for comparing sex differences were conducted in nine studies (28,29,33,34,37,39,43), and the male-only analysis involved five studies (28,33,37,39,41) to determine the effect of HIIT on relative CRF. Two studies had only one female participant in the HIIT group and, thus, were excluded from the sex comparison meta-analyses (31,42). Two studies were excluded from the sex comparison analyses because they exclusively recruited males (40,41). However, these male-only studies were included in the male-only pooled analysis for changes in CRF with HIIT. For the sex difference analysis, a total of 186 participants ($n = 38$ females; $n = 173$ males) were included (Fig. 3A). Upon pooled analysis, females experienced significantly smaller improvements in absolute CRF after HIIT when compared with males (MD = −1.10, 95% CI = −2.08 to −0.12 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P = 0.03$). Low, nonsignificant heterogeneity among studies was observed ($I^2 = 31\%$, $P = 0.17$). There were no sex differences in relative improvements in CRF after HIIT (MD = 0.49, 95% CI = −2.77 to 3.75%, $P = 0.77$; Fig. 1, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258). Considerable, significant heterogeneity among studies was observed ($I^2 = 90\%$, $P < 0.01$). For the male-only analysis, a total of 321 participants were included (28,33,37,39,41). The pooled analyses revealed a near-significant increase in relative CRF with HIIT in males (MD = 1.07, 95% CI = −0.08 to 2.23 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $P = 0.07$; Fig. 3B). Moderate, nonsignificant heterogeneity among studies was observed ($I^2 = 48\%$, $P = 0.11$). There were insufficient data to conduct a female-only analysis to determine the effect of HIIT on CRF ($n = 3$ studies). Upon visual inspection, all analyses had low publication bias as demonstrated by symmetrical funnel plots (Figs. 2–4, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258).

**Subanalysis: cardiometabolic health indicators.** Ten studies reported BMI (Fig. 5, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258) (28,29,33,34,36–39,43,44). The pooled analysis revealed females experienced significantly smaller improvements in BMI after HIIT than males (MD = −0.25, 95% CI = −0.03 to −0.47 $\text{kg}\cdot\text{m}^{-2}$, $P = 0.02$); low, nonsignificant heterogeneity was observed ($I^2 = 9\%$, $P = 0.36$). Six trials reported systolic blood

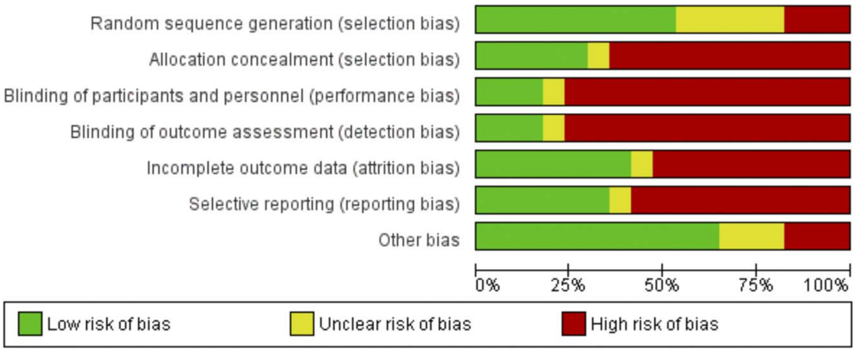

FIGURE 2—Risk of bias.

TABLE 1. GRADE approach.

| Certainty Assessment | | | | | | | No. of Patients | | Effect | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of Studies | Study Design | Risk of Bias | Inconsistency | Indirectness | Imprecision | Other Considerations | Females | Males | Relative (95% CI) | Absolute (95% CI) | Certainty | Importance |
| CRF (follow-up: range, 4 to 52 wk; assessed with $\dot{V}O_{2peak}$) | | | | | | | | | | | | |
| 9 | Randomized trials | Very serious [a] | Not serious | Serious [b] | Not serious | None | 38 | 173 | – | MD, 1.1 $mL\cdot kg^{-1}\cdot min^{-1}$ more (0.12 more to 2.08 more) | ⊕◯◯◯<br>VERY LOW | Important |
| BMI (follow-up: range 4 to 52 wk) | | | | | | | | | | | | |
| 10 | Randomized trials | Very serious [a] | Not serious | Serious [b] | Not serious | None | 43 | 255 | – | MD, 0.25 $kg\cdot m^{-2}$ lower (0.47 lower to 0.03 lower) | ⊕◯◯◯<br>VERY LOW | Important |
| Fasting blood glucose | | | | | | | | | | | | |
| 7 | Randomized trials | Very serious [a] | Not serious | Serious [b] | Not serious | None | 26 | 120 | – | MD, 0.38 $mmol\cdot L^{-1}$ lower (0.72 lower to 0.05 lower) | ⊕◯◯◯<br>VERY LOW | Important |
| Systolic blood pressure (follow-up: range, 4 to 52 wk) | | | | | | | | | | | | |
| 6 | Randomized trials | Very serious [a] | Not serious | Serious [b] | Serious [c] | None | 31 | 199 | – | MD, 2.51 mm Hg lower (6.57 lower to 1.55 higher) | ⊕◯◯◯<br>VERY LOW | Important |
| Diastolic blood pressure (follow-up: range, 4 to 52 wk) | | | | | | | | | | | | |
| 6 | Randomized trials | Very serious [a] | Very serious [d] | Serious [b] | Serious [c] | None | 31 | 197 | – | MD, 0.91 mm Hg lower (4.98 lower to 3.15 higher) | ⊕◯◯◯<br>VERY LOW | Important |
| HDL cholesterol (follow-up: range, 4 to 52 wk) | | | | | | | | | | | | |
| 7 | Randomized trials | Very serious [a] | Not serious | Serious [b] | Not serious | None | 40 | 191 | – | SMD, 0.06 SD higher (0.42 lower to 0.52 higher) | ⊕◯◯◯<br>VERY LOW | Important |
| LDL cholesterol (follow-up: range, 4 to 52 wk) | | | | | | | | | | | | |
| 7 | Randomized trials | Very serious [a] | Not serious | Serious [b] | Not serious | None | 34 | 213 | – | SMD, 0.07 SD lower (0.45 lower to 0.3 higher) | ⊕◯◯◯<br>VERY LOW | Important |
| Triglycerides (follow-up: range, 4 to 52 wk) | | | | | | | | | | | | |
| 7 | Randomized trials | Very serious [a] | Not serious | Serious [b] | Not serious | None | 32 | 200 | – | SMD, 0.12 SD lower (0.27 lower to 0.51 higher) | ⊕◯◯◯<br>VERY LOW | Important |
| Total Cholesterol (follow-up: range, 4 to 26 wk) | | | | | | | | | | | | |
| 6 | Randomized trials | Very serious [a] | Not serious | Serious [b] | Not serious | None | 25 | 182 | – | SMD, 0.23 SD lower (0.21 lower to 0.66 higher) | ⊕◯◯◯<br>VERY LOW | Important |

[a] Five criteria in the Risk of Bias assessment were rated a high risk of bias (selection, performance, detection, attrition, and reporting biases).

[b] The majority of the research has been conducted in males (18% females, 82% males).

[c] There is a wide pooled 95% CI for this outcome.

[d] There is substantial, significant heterogeneity ($I^2$ = 62%, $P$ = 0.02) for sex differences in diastolic blood pressure.

CRF, cardiorespiratory fitness; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

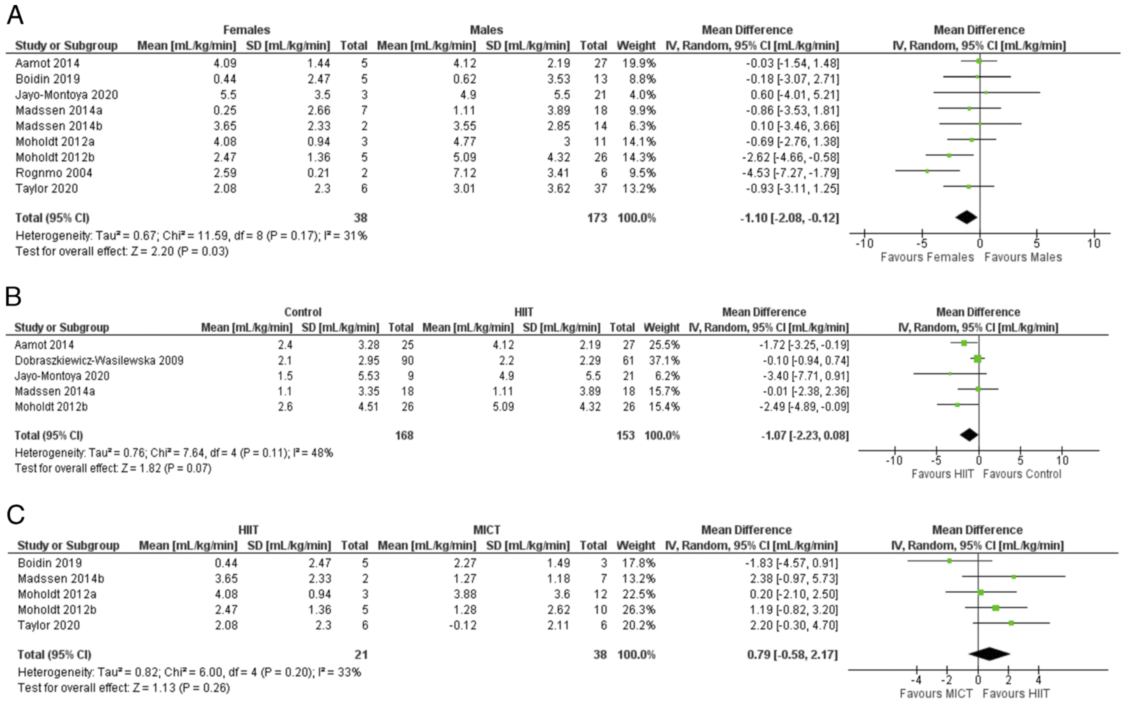

**FIGURE 3—A, Forest plot of the sex differences for absolute changes in CRF with HIIT in females and males with CAD. B, Forest plot of absolute changes in CRF in males with CAD after HIIT. C, Forest plot comparing HIIT vs moderate- to vigorous-intensity continuous training (MICT) in absolute CRF changes in females with CAD.**

pressure (Fig. 6, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258) (28,29,33,38,39,43). The pooled analysis revealed no sex differences for changes in systolic blood pressure with HIIT (MD = −2.51, 95% CI = −6.57 to 1.55 mm Hg, *P* = 0.23); low, nonsignificant heterogeneity was observed ($I^2$ = 0%, *P* = 0.50). Six studies reported diastolic blood pressure (Fig. 7, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258) (28,29,33,38,39,43). The pooled analyses showed no sex differences for changes in diastolic blood pressure with HIIT (MD = −0.91, 95% CI = −4.98 to 3.15 mm Hg, *P* = 0.66); there was significant, substantial heterogeneity across trials ($I^2$ = 62%, *P* = 0.02). Six studies reported fasting blood glucose (Fig. 8, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258). Females experienced significantly smaller reductions in fasting blood glucose values than males after HIIT (MD = −0.38, 95% CI = −0.05 to −0.72, *P* = 0.03); low, nonsignificant heterogeneity was observed between trials ($I^2$ = 0%, *P* = 0.42). Seven studies reported HDL cholesterol (Fig. 9, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258) (29,34,36–39,43). No sex differences were observed for changes in HDL with HIIT (SMD = 0.06, 95% CI = −0.40 to 0.52, *P* = 0.80); low, nonsignificant heterogeneity was observed between trials ($I^2$ = 26%, *P* = 0.23). Seven studies reported LDL cholesterol (Fig. 10, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258). No sex differences were observed for changes in LDL with HIIT (SMD = −0.07, 95% CI = −0.45 to 0.30, *P* = 0.70); low, nonsignificant heterogeneity was observed between trials ($I^2$ = 0%, *P* = 0.43). Seven studies evaluated the effect of HIIT on triglycerides (Fig. 11, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258). The pooled analysis showed no sex differences for changes in triglycerides after HIIT (SMD = 0.12, 95% CI = −0.27 to 0.51, *P* = 0.54); low, nonsignificant heterogeneity was observed between trials ($I^2$ = 0%, *P* = 0.56). Six studies examined changes in total cholesterol after HIIT (Fig. 12, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258) (29,34,36–38,43). The pooled analysis showed no sex differences for changes in total cholesterol with HIIT (SMD = 0.23, 95% CI = −0.21 to 0.66, *P* = 0.31); low, nonsignificant heterogeneity was observed between trials ($I^2$ = 0%, *P* = 0.76). Upon visual inspection, asymmetry is present in the funnel plots for the analyses examining diastolic blood pressure (Fig. 15, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258), HDL (Fig. 17, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258), and total cholesterol (Fig. 20, Supplemental Digital Content 4, Forest and funnel plots of the sex-differences for changes in cardiometabolic health indicators, http://links.lww.com/MSS/C258). For all other analyses, funnel plots appear symmetrical, indicating low publication bias (BMI, systolic blood pressure, fasting blood glucose, LDL, and triglycerides).

## DISCUSSION

This study systematically reviewed and analyzed the available data regarding sex differences after HIIT in adults with CAD. The results from our review highlight a striking disparity in female participation when compared with males (approximately eightfold greater number of male participants) in studies evaluating the effects of HIIT; this disparity is still present when examining participation between sexes across all eligible studies (approximately sixfold greater number of male participants). None of the included studies performed sex-based analyses. Our pooled analyses of published and unpublished data revealed that males with CAD experienced a near-significant improvement in absolute CRF after HIIT (males, +1.07 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$); there was insufficient data to determine the efficacy of HIIT in females only. The average $\dot{V}O_{2\text{peak}}$ of the male cohort in our meta-analysis was 22.56 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; this is above the average $\dot{V}O_{2\text{peak}}$ of males with CVD (19.3 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) (3). Individuals with a higher CRF may not experience large increases in CRF with aerobic training; this may explain our results. It should be noted that for every 1 $\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ increase in CRF in adults with CVD, there is ~17% and ~15% reduction in all-cause and cardiovascular mortality, indicating a small change in CRF has large patient benefits (3).

Consistent with our primary hypothesis, our results showed females with CAD achieve smaller absolute improvements in CRF after HIIT when compared with males. However, there was no sex difference when examining relative (percentage) improvements in CRF. Our secondary analyses of cardiometabolic health indicators further demonstrated that females achieved smaller improvements in BMI and fasting blood glucose after HIIT; no sex differences were found for changes in blood pressure and lipid profile in patients with CAD. Our systematic review and meta-analysis highlight the continued severe underrepresentation of female patients with CAD in HIIT trials (38 females vs 173 males). As the majority of the available literature does not include sex-based analyses, it is difficult to determine what is the most appropriate exercise prescription for each sex. Future studies examining the effect of exercise on CRF and cardiovascular health indicators in patients with CAD must increase female representation and report sex-stratified analyses to increase the evidence-base in this area.

Only one meta-analysis has performed a subanalysis of the sex differences after traditional CR; both females and males improved CRF, yet males achieved significantly greater increases in CRF than females after CR (SMD females, 0.92, vs males, 1.44, $P < 0.01$) (46). Similarly, we observed that males improved absolute CRF to a greater extent than females after HIIT. To determine whether there was a difference between HIIT and traditional CR (MICT) for changes in absolute CRF in females with CAD, we conducted a meta-analysis comparing HIIT and MICT in females only; there were no significant differences between the interventions. It should be noted that there were only 21 females pooled in the HIIT group and 38 females in the MICT group. To increase the likelihood of achieving clinically meaningful improvements in CRF for females, sex differences in physiological adaptations warrant consideration. There are several sex differences in cardiac function that may explain the lower absolute CRF change observed in females when compared with males after HIIT. During exercise, females have an attenuated ejection fraction, cardiac index, lower hemodynamic responses (systolic blood pressure and mean arterial pressure), and stroke volume (relative to body mass) when compared with males (10). To compensate for these differences, females increase heart rate to achieve the required cardiac output needed to meet the metabolic demands of exercise. In contrast, males increase cardiac output predominately through greater cardiac preload and the Frank Starling mechanism (10). Given that males increase cardiac output through changes in cardiac mechanics, they are more likely to experience cardiac adaptations after exercise than females. There is a lack of research examining the sex differences in cardiac function during and after HIIT in patients with CAD. Such knowledge will provide further insight into possible cardiac sex-specific responses to exercise in patients with heart disease.

Sex differences in peripheral (skeletal muscle) changes with aerobic exercise should also be considered. Females have a higher capillary density per muscle area, when compared with males, to increase oxygen extraction (10); the greater oxygen extraction capacity is thought to compensate for the higher cardiac demands females experience for the same exercise workload (10). After isometric contractions, males have been shown to experience muscle fatigue at a faster rate than females (10). This suggests that females may need to exercise at higher intensities for longer durations to experience the same aerobic adaptions as males. This is supported by studies showing that females have an oxidative muscle phenotype (a greater proportion of Type I muscle fibers) and males have a greater proportion of glycolytic muscle fibers (Type II) (10). As the high-intensity work bouts in HIIT rely on a greater contribution of glycolytic metabolism, this leads to greater use of glycogen stores within Type II muscle fibers. This may explain why males experience greater reductions in fasting blood glucose and BMI after HIIT. Females are more likely to achieve peripheral adaptations to improve CRF with exercise as females have a higher vasodilatory response and eNOS expression in the skeletal muscle than males (10). Previous work has highlighted that HIIT significantly increases vascular function and eNOS bioavailability (10); these adaptations are likely to lead to the improvement in CRF after HIIT in both sexes. Most females who present with CAD are postmenopausal; a decrease in estrogen concentrations can reduce mitochondrial biogenesis and exercise-induced vasodilation in females (47). This could explain why females with CAD may not experience the same absolute degree of improvement as males. Given these physiological sex differences, HIIT appears to be an appropriate strategy to improve CRF in both females and males.

Sex differences in CR participation and experience should be considered when interpreting our findings. Despite a large male presence, CR is underutilized by females with 36% lower enrolment (48). Females also present with more comorbidities than males entering CR, including dyslipidemia, hypertension, obesity, diabetes, depression, and anxiety (20); this may lower participation and adherence and influence the physiological response to CR. Barriers to CR reported by females include lack of time, being more likely to fulfill caregiving roles, feeling uncomfortable in CR with the predominately male presence, and lack of enjoyment from the program offered (49). We recently evaluated the feasibility of HIIT within a CR setting and showed that there were no sex differences with compliance to the intensity and duration of the HIIT protocol, and all participants found participating in the program to be satisfying and challenging (50). It should be noted that participants had the option to partake in HIIT through the use of aerobic exercise equipment or dance/movement-based routines (50). A study examining females involved in community-based exercise programs has shown that alternative exercise modes such as dancing or aerobic-based classes are well received and have high attendance (up to 100%) (49). This may explain why our feasibility study showed high compliance to HIIT.

Although there was a small proportion of female participants involved in the HIIT trials included in our review, a low level of participation is also observed in traditional CR (11%–14% vs ~28%) (51). Low rates of participation may be due to barriers or lower proportion of females who enroll or get referred into CR after a cardiac event. For instance, Lee et al. (22) described the challenges of the recruitment for their HIIT female-only study; it was not anticipated that females were predominately referred for primary prevention or they presented with other conditions, which excluded them from the trial (22). It is important that the inclusion criteria for future HIIT studies reflect the complex health considerations of females in CR to facilitate recruitment. Further, studies included in our review did not report on the reasons for low recruitment rates in females; researchers should report such challenges to inform future trial designs.

It has been suggested that sex-specific HIIT protocols should be developed to address the sex differences in adaptations to aerobic exercise (52). Schmitz et al. (52) examined the effect of two different HIIT protocols in moderately trained females ($n = 30$) and males ($n = 20$). One group performed 4 × 30 s “all out” runs with 180 s of active recovery, and the second group completed the 4 × 30-s efforts with 30-s active recovery, twice weekly for 4 wk (52). They found that females significantly improved running speed and lowered speed decrement only after the protocol which had 30-s recovery periods (52). Schmitz’s findings suggest that longer recoveries, which reduce the time spent at a high intensity, may mitigate aerobic adaptations and performance in females. HIIT is an appealing exercise strategy for people with CAD as the recovery periods serve to reduce the fatigue and discomfort during exercise (19). Such an exercise training strategy allows for exercising at high intensities for a longer duration. Given that females have greater oxidative muscle fibers, which are more fatigue resistant, exercising at high intensities may provide a more specific physiological stimulus for females to elicit superior improvements in CRF. Most trials included in the female-only CRF analysis used the 4 × 4 Norwegian protocol, in which patients exercise at a high intensity for 16 min (28,34,36,37,39,43,44). All of these studies comprised active recoveries that were shorter or of the same duration as the high-intensity work bouts, which may serve females well and target sex-specific needs to improve CRF. However, more research on sex-specific HIIT protocols are needed.

Our systematic review has several strengths. We pooled published and unpublished data from trials across the world to conduct sex-based analyses. Only studies using gold standard indirect calorimetry to assess CRF were included in our analysis. Further, the search strategy was developed by a research librarian (KF), and we used the Cochrane Risk of Bias tool and GRADE approach to assess the quality of evidence. There are some limitations that should be considered when interpreting the results. Although 62 studies met the inclusion criteria and were eligible, we received data for only 14 studies from the corresponding authors. Many authors failed to reply or did not have data available by sex; such difficulties in accessing data from previous trials have been discussed elsewhere (53). Differences in HIIT exercise prescription (i.e., intensity, duration, frequency, and intervention length) contributed to the heterogeneity in the available research. We also excluded studies that performed HIIT in combination with resistance training. Although combined exercise training (aerobic and resistance training) is advised for CR settings, by excluding such trials, heterogeneity between studies was reduced. The potential confounding impact of resistance training on CRF was removed, allowing us to examine our primary aim of comparing the effects of HIIT between sexes. The evaluation of the quality of studies using the GRADE approach identified there was a high risk of selection, performance, detection, attrition, and reporting bias among the included studies. This led to downgrading the risk of bias to “very serious” using the GRADE approach. Further, the results from the GRADE assessment indicate that the certainty of the results for CRF and cardiometabolic health indicators is very low. This is predominately due to a high risk of bias and the indirectness (underrepresentation of females, only 11%) of the included studies.

## CONCLUSION

This is the first systematic review and meta-analysis pooling unpublished and published data to assess the sex differences in CRF and cardiometabolic indicators in patients with CAD after HIIT. Our study highlights that there are no sex differences for relative changes in CRF; however males experience a larger absolute improvement after HIIT. Further, there continues to be a striking underrepresentation of females. Our study emphasizes the need for more research to investigate the effect of HIIT in females with CAD and sex-specific mechanisms of exercise-related adaptations with HIIT to tailor the exercise prescription to best meet the needs of each sex.

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