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Systematic Review/Meta-analysis

Sex Differences in Cardiovascular Adaptations Following Aerobic Exercise Training Programs: A Systematic Review and Meta-analysis

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ABSTRACT

Background: The influence of aerobic exercise training on cardiovascular adaptations in healthy males vs. females is unclear. This systematic review and meta-analysis summarized sex-based differences in cardiac adaptations following aerobic exercise training interventions in healthy adults.

Methods: Five electronic databases were searched from inception to June 2024. Cardiac adaptation data included peak oxygen uptake, heart rate, arteriovenous oxygen difference, systolic and diastolic blood pressure, stroke volume, cardiac output, left ventricular (LV) mass, LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), and LV ejection fraction (LVEF). Meta-analyses were conducted in RevMan 5.4.

Results: Meta-analyses were conducted on 4 outcomes: LV mass, LVEDV, LVESV, and LVEF. The meta-analysis revealed no sex differences in LV mass (standardized mean difference = −0.01, 95% confidence interval [CI]: −0.29, 0.27, $P = 0.97$), LVESV (mean difference

RÉSUMÉ

Contexte : L'influence de l'entraînement à l'exercice aérobique sur les adaptations cardiovasculaires chez les hommes et les femmes en bonne santé n'est pas claire. Cette revue systématique et méta-analyse résume les différences entre les sexes en ce qui concerne les adaptations cardiaques à la suite d'un entraînement à l'exercice aérobique chez des adultes en bonne santé.

Méthodes : Cinq bases de données électroniques ont été consultées depuis leur création jusqu'à juin 2024. Les données sur l'adaptation cardiaque comprenaient le pic de consommation d'oxygène, la fréquence cardiaque, la différence artérioveineuse en oxygène, la pression artérielle systolique et diastolique, le volume d'éjection, le débit cardiaque, la masse du ventricule gauche (VG), le volume télédiastolique du VG (VTDGV), le volume télésystolique du VG (VTSVG) et la fraction d'éjection du VG (FEVG). Les méta-analyses ont été réalisées avec l'outil RevMan 5.4.

Regular physical activity and exercise are associated with dose-response benefits in reducing cardiovascular (CV) morbidity and all-cause mortality.[1-3] Aerobic exercise training (eg, walking, jogging, cycling, swimming) has been associated with cardiac adaptations within normal physiological range, including atrial and ventricular enlargement.[4] These responses may result from hemodynamic changes that occur during exercise.[5] For example, elevated heart rates due to altered autonomic state, increased

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[MD] = 1.85, 95% CI: −3.45, 7.10, $P = 0.5$), or LVEF (MD = −0.9, 95% CI: −3.26, 1.46, $P = 0.45$) following aerobic exercise interventions. Meta-analyses revealed a sex difference in LVEDV: males show a greater improvement in LVEDV (MD = 7.67, 95% CI: 2.75, 12.59, $P = 0.002$) than females after aerobic exercise training. No other sex differences were observed in any of the other outcomes. The overall risk of bias was low, and the quality of evidence was moderate.
Conclusions: Aerobic exercise interventions were associated with a larger increase in LVEDV in men relative to women, yet no sex differences were found in cardiac morphology (LV mass) or functional indices (LVEF).

Résultats : Les méta-analyses ont porté sur 4 résultats : la masse du VG, VTDVG, VTSVG et FEVG. La méta-analyse n'a révélé aucune différence entre les sexes en ce qui concerne la masse du VG (différence moyenne standardisée = -0,01, intervalle de confiance [IC] à 95 % : -0,29, 0,27, $p = 0,97$), le VTSVG (différence moyenne [DM] = 1,85, IC à 95 % : -3,45, 7,10, $p = 0,5$) ou la FEVG (DM = -0,9, IC à 95 % : -3,26, 1,46, $p = 0,45$) à la suite des interventions d'exercices de type aérobique. Les méta-analyses ont révélé une différence entre les sexes en ce qui concerne le VTDVG : les hommes présentent une amélioration plus importante du VTDVG (DM = 7,67, IC à 95 % : 2,75, 12,59, $p = 0,002$) que les femmes après un entraînement à l'exercice aérobique. Aucune autre différence entre les sexes n'a été observée pour les autres critères d'évaluation. Le risque global de biais était faible et la qualité des preuves était modérée.
Conclusions : Les interventions d'exercice aérobique ont été associées à une augmentation plus importante du VTDVG chez les hommes que chez les femmes, mais aucune différence entre les sexes n'a été observée dans la morphologie cardiaque (masse du VG) ou les indices fonctionnels (FEVG).

myocardial contractility, and changes in loading conditions contribute to increased cardiac output (CO).[6] Repeated exposure to significant increases in CO during exercise lead to increased myocyte contractility, left ventricular (LV) mass, and end diastolic volume (EDV).[4,7] This ultimately contributes to improvements in cardiorespiratory fitness ($\dot{V}O_{2max}$),[8-10] a strong predictor of morbidity and mortality.[11]

Although the influence of long-term exercise training on cardiac adaptations in healthy adults has been reported, there are current knowledge gaps concerning sex-based differences in these adaptations. There is a persistent under-representation of females in sport and exercise research,[12] which may explain this knowledge gap. Nonetheless, cross-sectional analyses and reviews have reported on the effects of aerobic exercise on CV outcomes (eg, peak oxygen uptake [$\dot{V}O_{2peak}$], cardiac remodeling, and cardiac function) in males and females. Such factors as fluctuations in sex steroid hormones, aging, baseline CV fitness, and exercise dose confound our knowledge on sex differences in CV adaptations to aerobic exercise training.[13] A recent review by Petek et al.[14] has summarized the impact of sex on CV adaptations to exercise in athletes. Specifically, $\dot{V}O_{2peak}$ is lower in females, independent of body size, and appears to be related to females' lower exercise stroke volume (SV), blood volume, hemoglobin, and muscle mass.[14,15] Yet, sex-based differences are relevant along the continuum of health and disease.[16] Further data are needed to understand the influence of aerobic exercise training on cardiac remodeling, function, and cardiorespiratory fitness.

There has been no systematic evaluation of the literature focusing on randomized controlled trials (RCTs) and longitudinal studies on sex-based differences in cardiac adaptations after exercise interventions in healthy populations. Therefore, this systematic review and meta-analysis sought to summarize sex-based differences in cardiac adaptation outcomes, related to cardiac remodeling, function, and fitness, following well-controlled and described aerobic exercise training interventions in healthy adults. This review examined absolute (L/min) and relative (mL/kg/min) $\dot{V}O_{2peak}$, heart rate (HR) at rest and maximum (bpm), arteriovenous oxygen difference ($a\text{-}vO_{2diff}$; mL/100 mL), systolic and diastolic blood pressure (SBP and DBP, respectively; mm Hg), SV (mL), CO (L/min), LV mass (g), LVEDV (mL), LV end systolic volume (ESV; mL), and LV ejection fraction (EF; percentage). A clear understanding on the relationship among aerobic exercise training, physiological cardiac adaptation, and sex may help us to define normal physiological cardiac morphologic and functional adaptations following exercise training in each sex, as well as inform aerobic exercise prescription in the primary prevention of CV disease and sex-specific treatment options in the secondary prevention of CV disease.

Methods

The methods of this study are registered in the Open Science Framework (https://doi.org/10.17605/OSF.IO/SYPQV). This review followed **P**referred **R**eporting **I**tems **S**ystematic reviews and **M**eta-**A**nalyses (PRISMA) guidelines[17] and addressed the items outlined in the **A** **M**eas**u**rement **T**ool to **A**ssess Systematic **R**eviews (AMSTAR) checklist.[18] The authors confirm that patient consent is not applicable to this article.

Eligibility criteria

This review included all studies reporting on cardiac adaptations following aerobic exercise training interventions among healthy adult male and female participants.

Population. Studies were included in which both male and female participant data were reported separately and compared for sex differences. Single-sex data, prepubertal human participants, and nonhuman subjects were excluded from analyses.

Intervention. Aerobic physical activity and exercise training interventions were included for sports and physical activities with a moderate to high dynamic component (eg, running, cycling, swimming, walking).[19] Search terms included variations of *endurance*, *exercise training*, *sport*, and *aerobic*

(Supplemental Table S1). Resistance exercise and/or sports with a moderate to high static component (eg, gymnastics) were excluded from the review. There were no restrictions placed on the length or frequency of the interventions.

Outcomes. This review was interested in summarizing differences observed in cardiac adaptations with respect to biological sex (sex assigned at birth). Gender was not captured or discussed in this review. Although some studies included in this review may report sex and gender inconsistently (ie, male and female vs. woman and man), study reporting on differences in biological sex were deemed eligible for inclusion in this review. Cardiac adaptation outcomes included cardiorespiratory fitness, hemodynamic variables, cardiac morphology, and function.

Study design, publication status, and language. Published (peer-reviewed) literature, indexed conference abstracts, and dissertations/theses were deemed eligible for inclusion for this review. RCTs, longitudinal studies, and nonrandomized trials were considered eligible. Cross-sectional study designs (eg, no intervention with pre-post measures) were excluded to control for variations in exercise training dose. The initial search did not have language restrictions; however, at the full-text stage of screening, only English, French, or Portuguese articles were considered because reviewers were proficient in these languages.

Information sources

Search strategy. A comprehensive search strategy was developed, validated, and PRESS peer-reviewed in collaboration with an information specialist (E.M.) using the PICOS (**P**opulation, **I**ntervention, **C**omparison, and **O**utcomes) framework. The search strategy can be found in Supplemental Table S1. The search was performed from inception to June 7, 2024, in 5 databases: Cochrane Central Register of Controlled Trials, CINAHL (Cumulative Index to Nursing & Allied Health Literature), Embase, EMCare, and MEDLINE (Ovid).

Data collection and data extraction. Search results were downloaded to Endnote 21 (Clarivate Analytics, Philadelphia, PA) and imported to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) where duplicate studies were removed. Two of a possible 7 (L.M.C., I.R.M., K.L.W., M.Pa., L.S.L., M.Pe., L.B.) reviewers independently screened each of the titles, abstracts, and full-text publications for study eligibility. Article conflicts in the reviewing and extraction stages were resolved by consensus with a third reviewer (L.M.C., L.B.). The rationale for excluding articles during the full-text screening was recorded. Several strategies were put in place to maintain inter-rater reliability with respect to the screening. All screeners were provided with a screening guidance document that included a summary of the PICOS framework, and a team meeting was conducted to describe and discuss the screening criteria. The first (L.M.C.; full-text screening) and senior (L.B.; title and abstract screening) authors were one of the 2 independent screeners on all articles. Finally, one person was responsible for resolving all screening conflicts, thus ensuring consistency when a conflict arose (L.M.C.).

Data extraction was performed by the first author (L.M.C.) and verified by coauthors (L.L., M.Pa., M.Pe.) in a standardized data sheet (Microsoft Excel). Corresponding authors of included studies were contacted to provide sex-specific data (including 3 reminder emails) when needed. Data extraction included study, population, and intervention characteristics and cardiac adaptation outcomes from all studies that met inclusion criteria. Specifically, study characteristics included authors, title, journal, year of publication, and study design. Extracted participant characteristics included total sample size, number of male vs. female participants, age, and physical activity status at the time of the study. Exercise intervention data were extracted using the FITT principle: frequency of exercise (sessions per week), intensity (ie, percentage of $\dot{V}O_{2peak}$, percentage of maximal HR [HRmax], and rating of perceived exertion), duration of sessions (minutes/session), time or length of intervention (weeks), and type of activity (ie, cycling, walking, running). Cardiac adaptation data extracted included absolute (L/min) and relative (mL/kg/min) $\dot{V}O_{2peak}$, HR at rest and maximum (bpm), a-vO_{2diff} (mL/100 mL), SBP and DBP (mm Hg), S (mL), CO (L/min), LV mass (g), LVEDV (mL), LVESV (mL), and LVEF (%).

Meta-analyses. Meta-analyses were completed using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to compare mean differences (MDs) and standardized mean differences (SMDs) between males and females in LV mass, LVEDV, LVESV, and LVEF after an aerobic exercise intervention. If ≥3 studies reported data on an outcome of interest, a meta-analysis was performed.[20] When the mean and SD of the change from pre to post were not reported in the manuscript, an attempt to contact corresponding authors was made (including 3 follow-up reminders). When these data were not received, the mean was calculated (change mean = mean post − mean pre). As per Cochrane guidelines, the SD was calculated by averaging the SDs of the other studies included in the meta-analyses.[21]

Random effects meta-analyses were performed to determine effect size (MDs / SMDs and 95% confidence intervals [CIs]) for each outcome (ie, LV mass, LVEDV, LVESV, and LVEF). SMDs were used for LV mass to account for the heterogeneity in the methods of measurement (ie, ultrasonography, magnetic resonance imaging, and CV magnetic resonance imaging). MDs were used for all other outcomes.

Subgroup analyses. A priori—determined sub-analyses were described in the registered protocol, including age and exercise intervention intensity. However, no sub-group analyses were included in this review because of the small number of studies eligible for the meta-analysis and insufficient reporting of data, which deviates from the registered protocol.

Risk of bias and GRADE assessment. Two reviewers (L.M.C. and I.R.M.) conducted an independent assessment on the risk of bias in duplicate for included studies using the **R**isk **O**f **B**ias **I**n **N**on-randomized **S**tudies—of **I**nterventions (ROBINS-I)[22] and the **T**ool for the ass**E**ssment of **S**tudy quali**T**y and reporting in **EX**ercise (TESTEX).[23] Overall quality of the evidence was also assessed independently in

duplicate by 2 reviewers (L.M.C. and I.R.M.) with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool.[24] For both risk of bias and quality of evidence, differences in scoring between the reviewers were resolved through consensus. When consensus was not reached, a third reviewer (L.B.) was consulted. The overall quality of evidence in the included studies was categorized as either very low, low, moderate, or high. RCTs started with a high quality of evidence and were rated downward in the presence of study limitations.[24] Studies were assigned a lower GRADE category for limitations such as risk of bias, indirectness of evidence, heterogeneity, imprecision, or publication bias.[24] Inconsistency was assessed by considering the heterogeneity of the studies; an I^2 >75% and P value <0.10 are considered cut-offs for high heterogeneity.[20] Publication bias was assessed using Egger test and visual inspection of funnel plots.

Results

Study selection

The initial literature search resulted in 15,104 records. After duplicate record removal (n = 6265), 8850 articles were screened by title and abstract, from which 153 studies were assessed for eligibility at the full-text level. Twelve studies[25-36] were deemed eligible for data extraction (Figure 1). Of those 12 studies, 4 were eligible for meta-analyses[26,27,30,34] whereas the other 8 were included only in the systematic review.[25,28,29,31-33,35,36] The search results from 4 databases included CINAHL (Cumulative Index to Nursing & Allied Health Literature) (n = 1451), Embase (n = 7029), EMCare (n = 1461), and MEDLINE (Ovid) (n = 3936).

Study characteristics

Table 1 shows the characteristics of the 12 included studies, published between 1993[33] and 2021.[30] One of the 12 included studies was a PhD dissertation[25] and one a master's thesis.[29] The dissertation separated the chapters by age (older adults: 55-65 years, and younger adults: 18-24 years).[25] The number of participants ranged from 12 in 2 studies[26,32] to 631 in one.[36] Nine studies[25-29,32,33,35,36] were uncontrolled pre-post study design, 2 RCTs,[31,34] and 1 uncontrolled randomized crossover washout design.[30] For the 2 RCTs and the uncontrolled randomized crossover design, we used the aerobic exercise intervention group only, as the other intervention groups did not meet our inclusion criteria. All included studies were published in English.

Participant characteristics

A total of 1230 participants, of which 696 (57%) were female, across 12 studies were included in this review. The mean age ranged from 18.6±0.4 years[35] to 70±5 years.[32] Although the search strategy did not exclude postpubertal adolescent studies, no studies including adolescents were eligible to be included in the review. Seven studies[25,26,29,31,32,34,36] included individuals who were classified as sedentary, whereas 2 studies[28,35] included athletes and 2 other studies[27,30] included healthy individuals. One study[33] did not specify the activity status of the participants.

Intervention details

The frequency (sessions/week), time per session, and intensity of the interventions are described in Table 1. There was large heterogeneity in the physical activity and exercise interventions. Six studies[25,26,28,32,33,36] had interventions lasting longer than 16 weeks. The Holloway dissertation[25] presented data in 2 separate studies (young [18-24 years] vs. older adults [55-65 years]). The older adults study included a 30-week intervention, whereas the younger adults study included 6 weeks of each program (interval training vs. endurance) with a 6-week detraining between interventions. In addition to the Holloway dissertation, 6 other studies[27,29-31,34,35] had interventions that were of 16 weeks or shorter. One study[36] was a cycling-only intervention, 3 studies[25,27,28] running, 1 study[34] walking, and 1 study[35] swimming. Six studies[25,26,29-32] were multimodal, including combinations of walking, running, cycling, stair climbing, swimming, and rowing. Two studies[28,35] did not describe the exercise intensity of the intervention.

Outcome measures

All extracted data are presented in Table 2.

$\dot{V}O_{2peak}$ and a-vO_{2diff}. Seven studies[25-27,29,31-33] reported $\dot{V}O_{2peak}$ (relative and/or absolute) before and following the exercise interventions. In all 7 studies, $\dot{V}O_{2peak}$ increased following the exercise intervention, ranging from 6%[29] to 22%.[26] Six of the studies reported no sex differences in the magnitude of increase with exercise; however, most studies[25,29,31,32] noted that females had lower absolute values than males both prior to and following the exercise interventions. One study,[26] conducted in young previously sedentary males and females, reported relative $\dot{V}O_{2peak}$ values after every 3 months of intensive endurance training up to 12 months. The authors noted a progressive increase in $\dot{V}O_{2peak}$ over 9 months in males, followed by a plateau to 12 months, but interestingly observed a blunted response in females, with the majority of the relative $\dot{V}O_{2peak}$ increases occurring in the first 3 months with an observed plateau after 6-12 months despite progressive increases in intervention intensity approximately every 3 months for the 12-month intervention.[26] Of interest, the increase in males was markedly greater compared with that of the females.[26] One study[25] noted that although increases were observed in $\dot{V}O_{2peak}$, the lower intensity of the intervention in an older sedentary population (55-65 years) may have affected the timeline of improvement, independent of sex, as it took 18 weeks for these changes to become significant in both males and females. As expected, the a-vO_{2diff} increased following the exercise interventions in both men and women, with no notable difference between sexes.[25,26,33]

Cardiovascular outcomes by sex—hemodynamics (HR, CO, SV, SBP, DBP). Eight studies[25,27-29,32-35] reported resting HR and 4 studies[25,26,33,36] HRmax before and after the exercise interventions. Five of these studies[25,28,29,32,34] reported no changes in resting HR after the training intervention in either males or females, 3 studies[27,33,35] observed decreases in resting HR in both males and females but did not

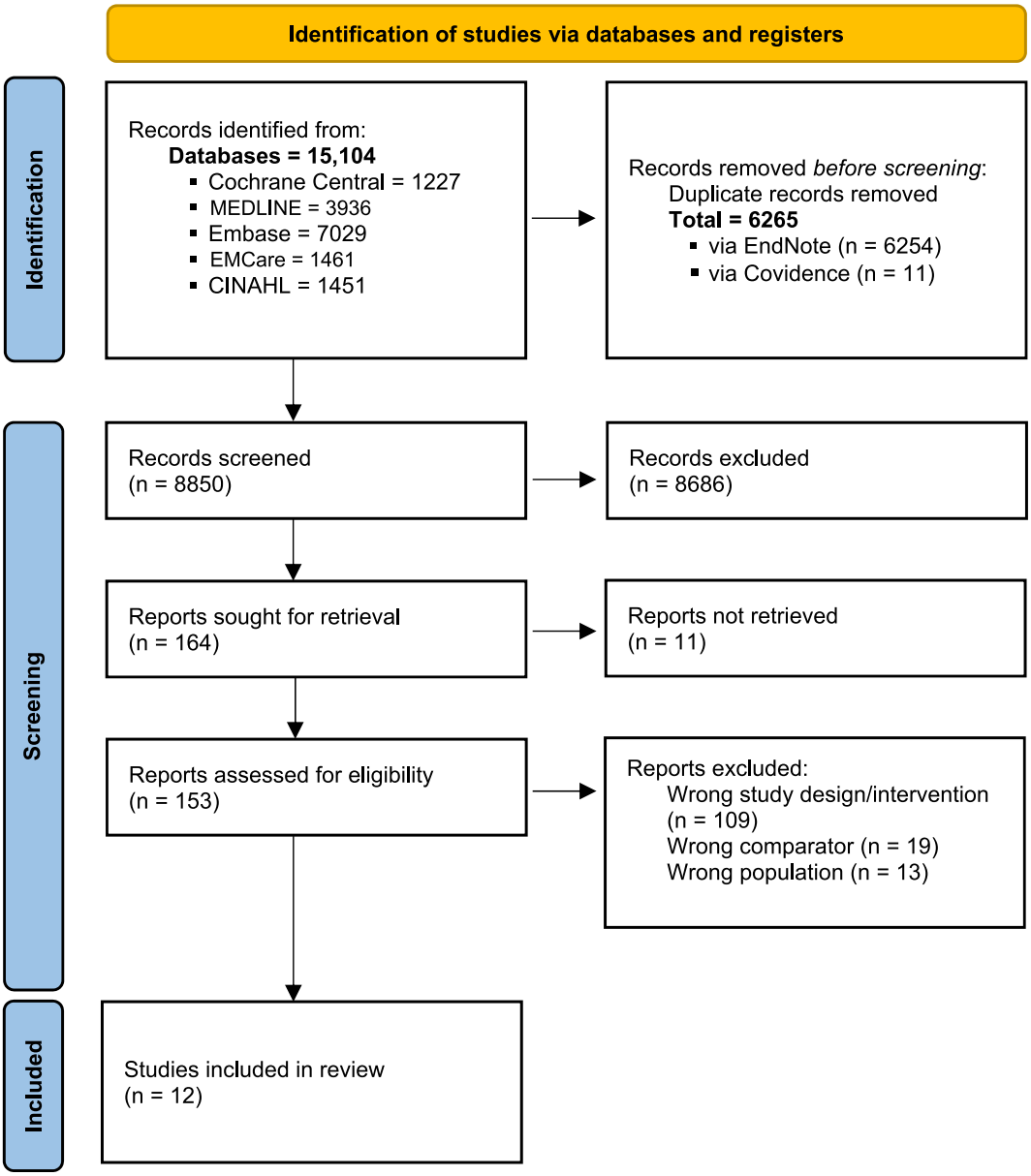


Figure 1. Study flow diagram (PRISMA). PRISMA, **P**referred **R**eporting **I**tems **S**ystematic reviews and **M**eta-**A**nalyses.

report any significant sex differences in these training-induced changes, and 1 study[25] reported an observed decrease in males but no change in females. Maximal HR decreased in both males and females in 1 study,[26] decreased in males only in 2 studies,[33,36] and did not change in either sex in the older or younger adult populations in another study.[25]

Two studies[25,28] reported resting CO, and 3 studies[25,33,36] reported maximal CO. One study[28] observed an increase in resting CO in both male and female elite runners after 3 years of training, whereas another[25] reported no changes in resting CO in either male or female sedentary younger (18-24 years) and older (55-65 years) individuals. Most notably, neither study reported sex differences in resting CO, regardless of the population characteristics or intervention intensity. Maximal CO increased in both sexes in one study,[36] with a greater absolute increase in males and a greater relative increase in females after a low to moderate intensity intervention in sedentary young adults. In contrast, other studies observed an increase in maximal CO in males only,[33] or no change in either sex following exercise training.[25]

Six studies reported SV before and after exercise interventions: 4 studies[28,30,34,35] resting SV, 1 study[33] maximal SV, and 1 study[25] reported both. Three studies[25,30,34] reported no changes in resting SV in males or females, and 2 studies[28,35] reported an increase in resting SV in both sexes after exercise training. One study[25] reported no changes in maximal SV in males or females, and 1 study[33] observed increases in males only.

Resting[25,27-29,32-35] and maximal[25,33] SBP and DBP were reported in 8 and 2 studies, respectively. Five studies[25,28,32,34,35] reported no changes in resting SBP or DBP in males or females after an exercise intervention, 2

Table 1. Study characteristics

Study characteristics			Participant characteristics			Intervention details				
Author (year)	Study type and design	Sample size, N	No. of female participants	Age, y, mean ± SD	Sedentary/ athlete	Duration	Frequency	Intensity	Time/session	Type
Holloway (2008):[25] older	Dissertation, uncontrolled pre-post	19	8	60 ± 1	Sedentary	30 wk	• 3 times a week for the first 6 wks to allow familiarization with exercise equipment • 5 times per week for the remainder of the program	• Exercise intensity started at individually determined 30% heart rate reserve (HRR), with stepwise increments every 6 wk to 45%, 60%, and 75% HRR	30 min/session	Endurance based (10-min walk/run on a motorized treadmill, 10-min cycling, followed by a further 10-min walk/run)
Holloway (2008):[25] younger	Dissertation, uncontrolled pre-post	21	8	20 ± 2	Sedentary	6 wk	• 3 times/wk	• The interval training consisted of a 1-min bout at 90%-100% $\dot{V}o_{2max}$, then 4 min at 50% $\dot{V}o_{2max}$ on a treadmill; this interval set was repeated 6 times over 30 min. • Continuous training consisted of a work rate of 70% $\dot{V}o_{2max}$ on a treadmill covering the same distance as when interval training.	30-min interval; 28-34 min continuous	Treadmill: interval and continuous training; 6-week detraining between 6 wk per program
Howden et al. (2015)[26]	Journal article, uncontrolled pre-post	12	5	26 ± 7	Previously sedentary	52 wk	• Early phase: 3-4 times/wk • Second and third quarters of the training program: sessions of increased intensity (maximal steady-state and interval sessions) were added first 1 time and then 2 times per week • Interval sessions were followed the next day by a recovery session to maximize performance gains.	• HR at maximal steady state and maximum HR were used to calculate training zones for each subject; 5 training zones were determined for individualized training prescription as follows: • Zone 1, recovery; zone 2, base pace; zone 3, maximal steady state or "threshold"; zone 4, race pace/critical power; and zone 5, intervals.	Early phase: 30-45 min/session, as subjects became fitter, the duration of the base training sessions was prolonged, including the addition of 1 long run per week (performed at the lower end of base pace HR range.) By the end of the yearlong training program, subjects were exercising for 7-9 h/wk, including long runs up to 3 h, plus regular interval sessions on the track and races.	Early phase: brisk walking, slow jogging, swimming, or cycling. By the end of the yearlong training program, subjects were exercising for 7-9 h/wk, including long runs of up to 3 h, plus regular interval sessions on the track and races.

Hulke et al. (2012)[27]	Journal article, uncontrolled pre-post	85	42	20.11 ± 1.137	Healthy	16 wk	• 8 sessions/wk	• RPE: somewhat hard, • warmup for 5 min (fairly light), • running somewhat hard intensity (25 min), • rest for 5 min, • running somewhat hard intensity for 25 min.	60 min	Running
Legaz-Arrese et al. (2006)[28]	Journal article, uncontrolled pre-post	41	18	22.7 ± 4.2	Active	1-3 y	• 6-7 d/wk	• Intense athletic conditioning	Not specifically described	Sprint-trained runners (100 and 400 m) and endurance-trained runners (800, 1500, 3000, 5000, 10,000 m and marathon)
Liu (2010)[29]	Thesis, uncontrolled pre-post	17	9	51 ± 2 (SE)	Sedentary	8 wk	• 4 times/wk	• 65% $\dot{V}o_{2max}$	30 min/session	Walking/jogging
Marsh et al. (2021)[30]	Journal article, uncontrolled randomized crossover washout design	72	46	27.5 ± 5.97	Untrained	12 wk	• 2 times/wk running • 1 time/wk cycling	• The "general preparatory" phase (weeks 1-4), consisted of low training intensity/volume (walking/jogging at 60% HR, 1-2.5 km running and/or 15-25 min cycling/running). • The high-intensity phase (weeks 5-8), consisted of higher-intensity work with higher HR (up to 90%) and distance/duration (2.5-5 km running and/or 25-40 min cycling/running). • The "maintenance and distance" phase (weeks 9-12), consisted mostly of maintaining sub-threshold HR (70%-85%) for longer distance/duration (5-7 km running and/or 40 min in week 9 to 60 min by week 12 cycling/running).	15-60 min: duration and intensity progressively increased over the course of the 3-mo exercise intervention from 15 to 60 min of exercise.	Running and cycling

Continued

Table 1. Continued.

Study characteristics			Participant characteristics			Intervention details				
Author (year)	Study type and design	Sample size, N	No. of female participants	Age, y, mean ± SD	Sedentary/ athlete	Duration	Frequency	Intensity	Time/session	Type
Sloan et al. (2009)[31]	Journal article, RCT (only the aerobic training arm was used)	149	91		Sedentary	12 wk	• 3-4 times/wk	• 70% of maximum HR. • A trainer helped participants choose a starting workload setting for each machine, and participants were instructed to increase the workload over time when they felt able, all the while maintaining their HR at 70% of maximum throughout the session.	They were given an initial goal of at least 20 min of aerobic exercise per session, and they increased the duration gradually over 2-3 wk, up to 45-60 min.	Aerobic conditioning: participants chose from cycling on a stationary ergometer, running on a treadmill, or using a stair-climber machine.
Soto et al. (2008)[32]	Journal article, uncontrolled pre-post	12	6	70 ± 5	Sedentary	48 wk	• 4-5 d/wk	• Initial intensity: 60%-70% $\dot{V}o_{2max}$ for the first 3 mo. • Intensity was increased progressively to 70%-80% of $\dot{V}o_{2max}$. • Supplemented by additional brief intervals of intense exercise requiring 90%-100% of $\dot{V}o_{2max}$ 2 or 3 times per week. • $\dot{V}o_{2max}$ was measured at 3-mo intervals to maintain training intensity relative to the current $\dot{V}o_{2max}$.	60 min/session	Walking, running, cycling
Spina et al. (1993)[33]	Journal article, uncontrolled pre-post	40	16	63 ± 3 (SE)		36-52 wk	• 5 d/wk	• Initial exercise intensity was 60%-80% of maximal HR and was gradually increased to 75%-85% of HRmax.	45 min/d	Walking (including uphill treadmill walking) and running on an indoor track and cycling and rowing on ergometers.
Suboc et al. (2014)[34]	Journal article, RCT (we only used pedometer group)	114	85	62 ± 6	Sedentary	12 wk	• 7 d/wk	• 10,000 steps each day • Increasing step count by 10% each week	Not specified	Walking

Wasfy et al. (2019)[35]	Journal article, uncontrolled pre-post	17	8	18.6 ± 0.4	Athletes	12 wk	• 7 d/wk in pool • 1-2 weekly dryland training	• Not described	1-3 h in pool training per day	Swimming and dry land training
Wilmore et al. (2001)[36]	Journal article, uncontrolled pre-post	631	354	35.7 ± 14.1	Sedentary	20 wk	• 3 d/wk	• Started at 55% of $\dot{V}o_{2max}$ for 30 min/session, • gradually increased to 75% of $\dot{V}o_{2max}$ for 50 min/session (maintained during last 6 wk).	30 min gradually increasing to 50 min	Cycle ergometer

HR, heart rate; RCT, randomized controlled trial; RPE, rating of perceived exertion; SE, standard error; $\dot{V}o_{2max}$, maximum oxygen uptake.

studies[27,29] reported decreases in SBP and DBP at rest in both males and females, 1 study[25] reported a decrease in resting SBP in both sexes but found a reduction in DBP in males only, whereas 1 study[33] observed no change in SBP in either sex at rest but observed a decrease in DBP in females. Finally, there were no changes in maximal SBP in males or females, with 1 study[25] showing a decrease in maximal DBP in males and the other[33] reporting no change in maximal DBP in either males or females.

Cardiovascular outcomes by sex—LV mass. Six studies reported on changes in LV mass in males and females after an aerobic exercise intervention. Although statistical analyses were not reported in all studies, LV mass was lower at baseline and after the exercise interventions in females compared with males. Three studies[27,28,32] reported no changes in LV mass in males or females, and 3 studies[26,30,35] reported increases with exercise training, with 2 studies[30,35] reporting no sex differences in these changes but 1 study[26] reporting a difference in the pattern of increase over the intervention. Specifically, males saw significant increases from baseline to 3 months (11%) and an additional significant increase from 3 to 6 months (9%) of exercise training, whereas females experienced a significant, but notably smaller than the males, increase after 3 months (13%) of exercise training with, no further increases during the 12-month intervention.[26]

Cardiovascular outcomes by sex—systolic and diastolic function (LVEDV, LVESV, LVEF). Four studies reported LVEDV and LVESV before and after exercise interventions.[26,30,34,35] One study[34] found no change in either LVEDV or LVESV in males or females following a low-intensity walking intervention, 2 studies[26,35] reported increases in both males and females in LVEDV and LVESV following high-intensity training programs, and 1 study[30] observed a novel finding of an increase in LVEDV in males (4.5%) but not females (1.2%) and no change in LVESV in either males or females. Six studies reported LVEF, 5 of which saw no changes in either males or females[27,28,32,34,35] and 1 observed an increase in both males (5.5%) and females (1.5%), with no reported significance between the sexes.[26]

Meta-analysis: Synthesis of results

Meta-analyses were conducted on 4 outcomes: LV mass, LVEDV, LVESV, and LVEF (Figure 2). The results of the meta-analysis demonstrated that there were no sex differences in LV mass (SMD = −0.01, 95% CI: −0.29, 0.27, P = 0.97), LVESV (MD = 1.85, 95% CI: −3.45, 7.10, P = 0.5), or LVEF (MD = −0.9, 95% CI: −3.26, 1.46, P = 0.45) following exercise intervention, regardless of intervention characteristics. Results of the meta-analysis for LVEDV demonstrated a sex difference in the effect of aerobic exercise interventions, such that males show a greater improvement in LVEDV (MD = 7.67, 95% CI: 2.75, 12.59, P = 0.002) than females.

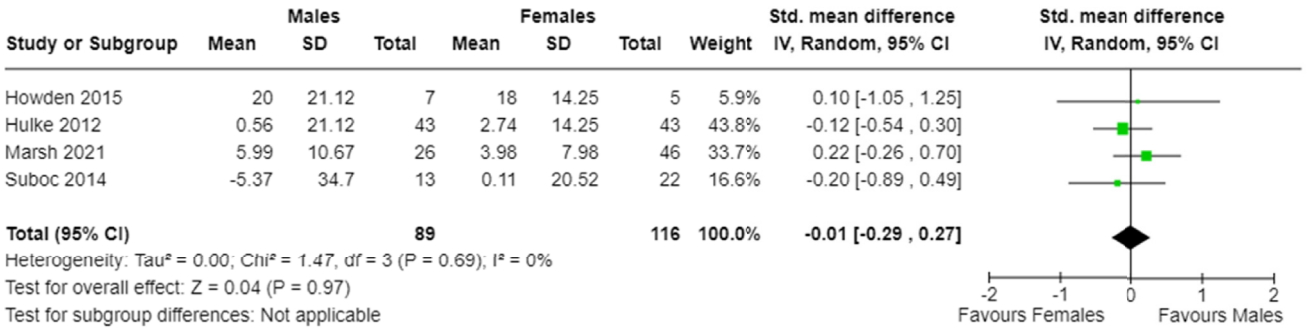
Risk of bias within studies. Table 3 shows the summary of risk of bias for each individual study using the ROBINS-I. Table 4 shows the results of the risk of bias evaluation

Table 2. Study outcomes

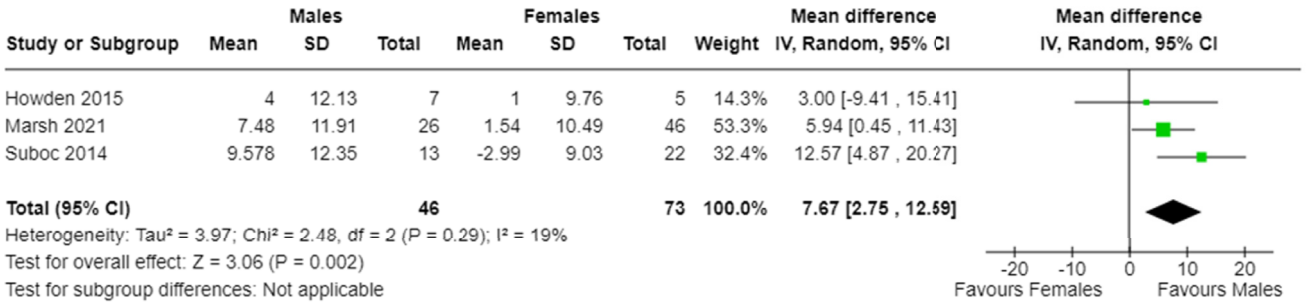
Author (year)	Intervention length, wk	$\dot{V}O_{2peak}$		a-$\dot{V}O_{2diff}$		Resting HR		Maximal HR		Cardiac output		Stroke volume		Systolic blood pressure		Diastolic blood pressure		LV mass, g		LVEDV, mL		LVESV, mL		LVEF, %	
		F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M
Holloway (2008)[25]	30 (O) and 6 (Y)	↑ (O), ↑ (Y)	↑ (O), ↑ (Y)	↑ (O), ↑ (Y)	↔ (O), ↑ (Y)	↔ (O), ↔ (Y)	↔ (O), ↓ (Y)	↔ (Y)	↔ (Y)	↔ (O & Y) resting and max	↔ (O & Y) resting and max	↔ (O & Y) resting and max	↔ (O & Y) resting and max	↔ (O & Y) max, ↓ (O) resting, ↔ (Y) resting	↔ (O & Y) max, ↓ (O) resting, ↔ (Y) resting	↔ (O & Y) resting and max	↓ (O & Y) max, ↓ (O) resting, ↔ (Y) resting								
Howden et al. (2015)[26]	12 and 52	↑	↑	↑	↑			↓	↓									↑	↑	↑	↑	↑	↑	↑	↑
Hulke et al. (2012)[27]	16	↑↑	↑↑			↓	↓							↓	↓	↓	↓	↔	↔					↔	↔
Legaz-Arrese et al. (2006)[28]	52, 104, 156					↔	↔			↑ (after 3 y)	↑ (after 3 y)	↑ (after 1, 2, and 3 y)	↑ (after 1, 2, and 3 y)	↔	↔	↔	↔	↔	↔					↔	↔
Liu (2010)[29]	8	↑	↑	n/a	n/a	↔	↔	n/a	n/a	n/a	n/a	n/a	n/a	↓	↓	↓	↓	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Marsh et al. (2021)[30]	12	↑	↑									↔	↔							↔	↑	↔	↔		
Sloan et al. (2009)[31]	12	↑	↑																						
Soto et al. (2008)[32]	48	↑	↑	n/a	n/a	↔	↔	n/a	n/a	n/a	n/a	n/a	n/a	↔	↔	↔	↔	↔	↔	n/a	n/a	n/a	n/a	↔	↔
Spina et al. (1993)[33]	36-52	↑	↑	↑	↑	↓	↓	↔	↓	↔ max CO	↑ max CO	↔ max SV	↑ max SV	↔ resting and max	↔ resting and max	↓ resting ↔ max	↔ resting and max								
Suboc et al. (2014)[34]	12				↔	↔								↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Wasfy et al. (2019)[35]	12					↓	↓					↑	↑	↔	↔	↔	↔	↑	↑	↑	↑	↑	↑	↔	↔
Wilmore et al. (2001)[36]	20							↓	↔	Max CO ↑ (greater relative)	Max CO ↑ (greater absolute)														

CO, cardiac output; F, female; HR, heart rate; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; M, male; n/a, not applicable; O, older adults (55-65 years); SV, stroke volume; $\dot{V}O_{2peak}$, peak oxygen uptake; Y, younger adults (18-24 years).

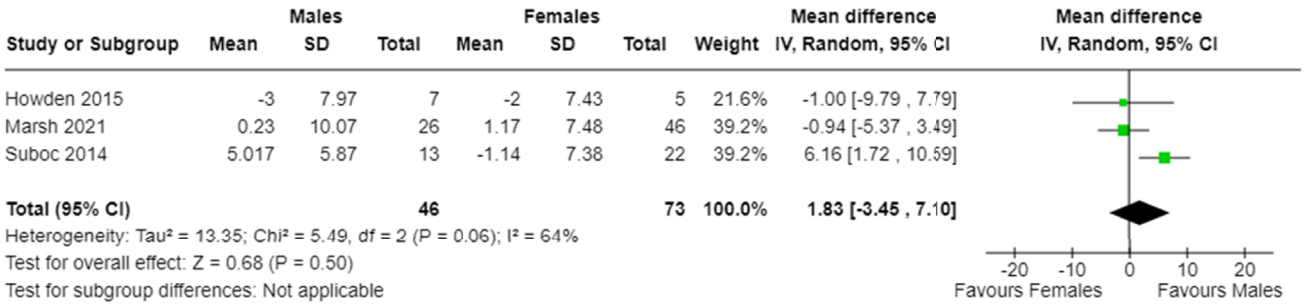
A LV mass



B LV EDV



C LV ESV



D LVEF

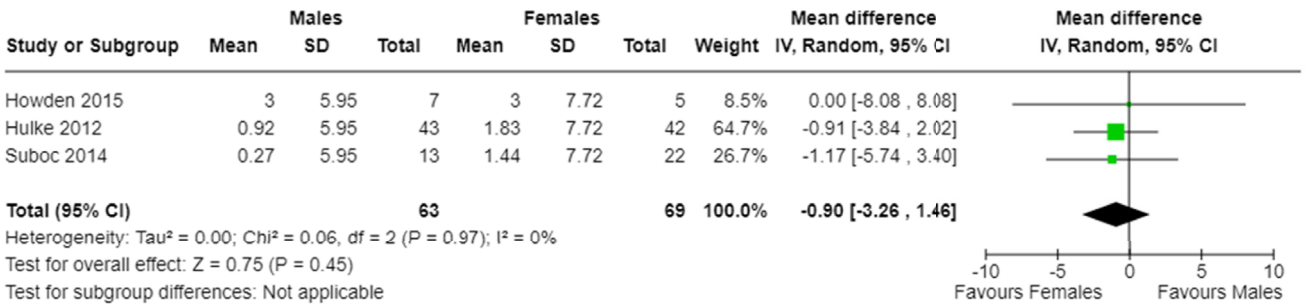


Figure 2. Meta-analysis forest plots: (**A**) LV mass, (**B**) LVEDV, (**C**) LVESV, (**D**) LVEF. LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume.

Table 3. Risk of bias evaluation: ROBINS-I

Author (year)	Domain 1: Confounding	Domain 2: Selection of participants	Domain 3: Classification of intervention	Domain 4: Deviation from intended interventions	Domain 5: Missing data	Domain 6: Measurement of outcomes	Domain 7: Selection of the reported results	Overall risk of bias
Holloway (2008)[25]	Low	Low	Low	Low	High	Moderate	Low	Moderate
Howden et al. (2015)[26]	Low	Low	Low	Low	Moderate	Moderate	Low	Low
Hulke et al. (2012)[27]	Moderate	Low	Low	Low	Low	Moderate	Low	Low
Legaz-Arrese et al. (2006)[28]	Low	Low	Low	Low	High	Moderate	Low	Moderate
Liu (2010)[29]	Low	Low	Low	Low	Moderate	Moderate	Low	Low
Marsh et al. (2021)[30]	Low	Low	Low	Low	High	Moderate	Low	Moderate
Sloan et al. (2009)[31]	Low	Low	Low	Low	Low	Low	Low	Low
Soto et al. (2008)[32]	Low	Low	Low	Low	Low	Moderate	Low	Low
Spina et al. (1993)[33]	Low	Low	Low	Low	Low	Moderate	Low	Low
Suboc et al. (2014)[34]	Low	Low	Low	Low	Low	Moderate	Low	Low
Wasfy et al. (2019)[35]	Low	Low	Low	Low	Low	Moderate	Low	Low
Wilmore et al. (2001)[36]	Low	Moderate	Low	No information	Moderate	Low	Low	Low

ROBINS-I, **R**isk **O**f **B**ias **I**n **N**on-randomized **S**tudies—of **I**nterventions.

using the TESTEX tool. The greatest risk of bias resulted from missing data and the measurement of outcomes by nonmasked personnel. Although it is not possible to mask the participants in an exercise study, assessors could be masked. The overall rating of risk of bias was low from both the ROBINS-I and TESTEX tools.

Quality of the evidence. The quality of evidence was assessed using the GRADE approach.[24] The rating of evidence began as moderate because most of the included studies were not RCTs. Few studies reported a high rate of attrition (≥25%). This was unexpected as attrition rates in exercise interventions are often as high as 30%.[37] Risk of bias for most of the studies included was classified as low or moderate, and therefore the quality of evidence was not downgraded. No studies reported masking participants to the exercise intervention they were engaging in; this is typically not possible in physical activity interventions because of their nature and, therefore, we did not downgrade the quality of evidence based on these criteria. Inconsistency was assessed by considering the heterogeneity of the studies. Results of our meta-analyses (Figure 2) revealed low heterogeneity across all 4 meta-analyses, and therefore our quality of evidence, was not downgraded further (LV mass: $I^2 = 0\%$, LVEDV: $I^2 = 19\%$, LVESV: $I^2 = 64\%$, LVEF: $I^2 = 0\%$). The evidence was not downgraded for indirectness or imprecision, as the pooled sample is moderately large and the 95% CIs are not wide. No publication bias was detected with the funnel plots and Egger test for any of the outcomes. The quality of the evidence used in our meta-analysis was determined to be moderate.

Discussion

This study investigated sex differences in cardiac adaptations following aerobic exercise training in healthy adults. In our meta-analysis, aerobic exercise interventions were associated with a larger increase in LVEDV in men relative to women, yet no sex differences were found in cardiac morphology (LV mass) or functional indices (LVEF) following these aerobic exercise interventions. The small number of studies eligible or containing usable data for the meta-analysis may have affected our ability to see further sex differences in other outcomes. Additionally, no other remarkable sex differences were observed in any of the other described cardiac outcomes ($\dot{V}O_{2peak}$, a-vO_{2diff}, resting HR, HRmax, CO, SV, SBP, or DBP). Notably, this systematic review and meta-analysis used a rigorous approach as it included longitudinal aerobic exercise training intervention studies only, and excluded cross-sectional studies where exercise training may have unknown heterogeneity because training intervention details may not be well reported and understood. Finally, this systematic review illustrates a persistent under-representation and/or under-reporting of study data by sex among clinical exercise research studies.

Sex differences in CV outcomes following aerobic exercise training

Across all studies, despite females having lower absolute values, males and females had comparably significant improvements in cardiorespiratory fitness following aerobic exercise training interventions. These data are not surprising and highlight the increase in maximal oxygen consumption with aerobic training and further demonstrate that included studies prescribed effective exercise doses to observe possible cardiac adaptations. There are no apparent sex differences in the overall observed increase in $\dot{V}O_{2peak}$; however, if we look more granularly at the responses to exercise, we start to observe some nuanced differences across sex, age, and dose of intervention. For instance, Howden et al[26] reported a progressive increase in $\dot{V}O_{2peak}$ over 9 months for males, followed by a plateau, but a blunted response in females, with most $\dot{V}O_{2peak}$ increases occurring in the first 3 months of the 12-month intervention followed by a plateau, despite progressive increases in intervention intensity every 3 months. Notably, the males and females in this study received identical training stimuli.[26] The study authors were unable to explain the mechanisms behind these observed sex differences; however, they suggested factors such as suboptimal exergy intake, inappropriate recovery time, or other life stressors may have contributed.[26] Some of the possible explanations for observed sex differences in $\dot{V}O_{2peak}$ include differences in hemoglobin, O_2-carrying capacity, O_2 transport, a-vO_{2diff}, CO (albeit not observed in this review), SV_{max}, and blood volume. Overall,

Table 4. Risk of bias evaluation: TESTEX

Author (year)	Eligibility criteria specific	Randomization specified	Allocation concealment	Groups similar at baseline	Masking of assessors	Outcome measures assessed in 85% of patients	Intention-to-treat analysis	Between-group statistical comparisons reported	Point measures and measures of variability for all reported outcome measures	Activity monitoring in control groups	Relative exercise intensity remained constant	Exercise volume and energy expenditure	Total
Holloway (2008)[25]	1	n/a	n/a	n/a	n/a	0	n/a	2	1	n/a	0 (O), 1 (Y)	1	5/9 (O), 6/9 (Y)
Howden et al. (2015)[26]	1	n/a	n/a	n/a	n/a	1	n/a	2	1	n/a	1	1	7/9
Hulke et al. (2012)[27]	1	n/a	n/a	n/a	n/a	1	n/a	2	1	n/a	0	1	6/9
Legaz-Arrese et al. (2006)[28]	1	n/a	n/a	n/a	n/a	1	n/a	2	1	n/a	0	0	5/9
Liu (2010)[29]	1	n/a	n/a	n/a	n/a	2	n/a	2	1	n/a	0	1	7/9
Marsh et al. (2021)[30]	1	1	1	0	1	3	0	2	1	1	1	1	13/15
Sloan et al. (2009)[31]	1	0	0	0	0	0	1	2	1	1	1	0	7/9
Soto et al. (2008)[32]	1	n/a	n/a	n/a	n/a	1	n/a	2	1	n/a	1	1	7/9
Spina et al. (1993)[33]	1	n/a	n/a	n/a	n/a	1	n/a	0	1	0	1	1	5/9
Suboc et al. (2014)[34]	1	1	1	1	0	1	0	2	1	0	1	1	10/15
Wasfy et al. (2019)[35]	1	n/a	n/a	n/a	n/a	1	n/a	2	1	n/a	1	1	7/9
Wilmore et al. (2001)[36]	1	n/a	n/a	n/a	n/a	1	n/a	2	1	n/a	1	1	7/9

n/a, not applicable; O, older adults (55-65 years); SV, stroke volume; TESTEX, **T**ool for the ass**E**ssment of **S**tudy quali**T**y and reporting in **EX**ercise; Y, younger adults (18-24 years).

aerobic exercise capacity is improved with exercise training but the underlying mechanisms responsible for these changes may differ between sexes and across the life span.

There were mixed findings for hemodynamic outcomes between sexes and across intervention dose. On closer investigation, it appears that a larger intervention dose (eg, greater intensity, longer durations) may have been associated with more hemodynamic improvements. Some sex differences were observed across all hemodynamic outcomes. These observations suggest that hemodynamic measures are highly sensitive to the nature and dose of the exercise intervention (eg, duration and intensity) and the characteristics of the population (eg, sex and age).

Differences exist in the mechanisms through which males and females meet the metabolic demands of exercise. Despite the 3- to 4-fold increase in HR with exercise, likely acting as the predominant mechanism by which CO is augmented in both males and females, other mechanisms are likely to contribute to the observed differences in sex. Studies have shown that females experience lower ejection fraction, cardiac index, lower hemodynamic responses (SBP and MAP), and SV (relative to body mass) when compared to males.[38] Previous work[39] has shown that, regardless of training status, women present with an absolute and relatively smaller heart volume, likely because of their smaller body mass. A recent study by Kontro et al.[40] suggests that sex differences exist in relative blood volume, plasma volume, and red blood cell volume (relative to lean body mass) after matching for aerobic fitness in males and females, thereby suggesting that there may be sex-specific mechanisms for oxygen delivery and/or extraction. Future studies are needed to further elucidate these sex-specific mechanisms underlying aerobic exercise performance.

This review found a sex difference in LVEDV, such that males have a larger response to aerobic exercise than females. This blunted response in females is consistent with previous findings.[41] Diaz et al.[41] reported a 67% reduction in LVEDV improvements in women than men following endurance training. Potential mechanisms have been described explaining the sex differences observed in cardiac adaptations.[41-44] It is possible this sex-specific response may be a result of the effect of training on blood volume. Studies have suggested that blood and plasma volumes contribute to LVEDV after endurance training in both sexes, albeit to a lesser degree in females.[42-44] Interestingly, one of the included studies in this review reported total blood and plasma volumes before and after a 12-month high-intensity intervention and found no sex differences in either.[25] In the early (days and weeks) stages of training, the mechanisms of LVEDV differences are likely based on loading conditions. An increase in LVEDV increases the preload on the heart and, through the Frank-Starling mechanisms of the heart, increases the amount of blood ejected from the ventricle during systole. Females have a reduced training-induced enhancement of the Frank-Starling mechanism compared with males.[26] This likely shifts to a structural remodeling in the longer-term (months and years) stages of training.[45] Animal studies have reported an increased LV hypertrophy with endurance training in female vs. male mice. This is mediated by the estrogen receptor—dependent protein kinase B/mitogen-activated protein kinase pathway. Further research should focus on the role of cardiac structure

and blood volume phenotypic responses to the blunted LV adaptations to aerobic exercise training in females. These findings further suggest the existence of sex dimorphism in cardiac adaptations in response to aerobic exercise training in healthy adults and therefore a potential downstream effect on sex differences in overall cardiorespiratory fitness and performance.

Six studies included in this review reported on cardiac morphology, specifically LV mass. Four of these were included in the meta-analysis.[26,27,30,34] Some studies[26,30,35] reported small changes in LV mass, whereas others[27,28,32] reported no changes. Interestingly, no sex differences were observed in any of the studies, and the meta-analysis confirmed these findings. We expected to observe a difference in LV mass between males and females. For instance, studies suggest that females' hearts may remodel differently in response to exercise by mechanisms not fully understood.[14] Decreased peak exercise SBP in female athletes (albeit not observed in this review) may result in a diminished pressure load on the heart and therefore lead to less hypertrophy relative to chamber enlargement.[46,47] Additionally, sex hormones such as higher testosterone levels in males may lead to more LV mass and hypertrophy.[48,49] Our meta-analysis was limited by the inclusion of only 4 studies, and therefore a small sample size. The included studies also did not control for the physical activity history of participants in a robust way. For these reasons, it is possible that anticipated sex differences were not detected. Although plenty of cross-sectional work exists in this area, further longitudinal work focused on specific mechanisms is needed to further refine sex-based determinants of exercise-induced cardiac morphology.

Although cardiac adaptation may seem similar across males and females, females tend to be smaller, have lower lean body mass, and a different hormone profile than males, which likely have a significant impact on absolute cardiac adaptations, specifically cardiac dimensions, which are often eliminated when indexed for body size.[50] Mechanisms such as sex hormones, sex-specificity of acute responses to exercise, and differing dose-response relationships to CV outcomes in men and women may contribute to the observed differences regarding the influence of cardiorespiratory fitness on the CV system, disease risk, and aging.[13] Additional research may elucidate mechanisms and therapeutic benefits associated with observed CV adaptations to short- and long-term exercise training programs in men and women.

Clinical implications and future considerations

Aerobic exercise should be recommended for all healthy adults independent of sex. At this time, our data do not support sex-specific aerobic exercise prescription as we largely failed to observe significant sex differences in cardiac adaptations. Yet, it is still possible that sex differences in cardiac adaptations following aerobic exercise training may exist. Further research is required for the reasons discussed here within. This systematic review illustrates a persistent underrepresentation and/or under-reporting of study data by sex among clinical research studies. During full-text screening, many studies were excluded as they failed to include both male and female participants (Figure 1). Additionally, studies included in this systematic review often failed to adequately report data by sex, often citing the limited participation of females to enable statistical analyses. A recent review article has highlighted the barriers and facilitators linked to clinical trial enrollment, trends, and the rationale for representativeness specific to CV medicine.[51] Challenges at the trial stage then leads to obstacles for conducting systematic reviews to address sex differences.[52] Systemic changes in study inclusion and reporting are needed to further our understanding of sex differences in CV medicine.[53] There are growing numbers of calls from government and international agencies for the inclusion of both male and female participants in clinical research. As an example, the Canadian Institutes of Health Research "expects that all research applicants will integrate sex and gender into their research designs, methods and analyses and interpretation and/or dissemination of findings when appropriate." Recommendations to improve sex-specific reporting in clinical research publications should consider the SAGER guidelines,[54] including (1) identifying the sex of participants in the title and abstract; (2) reporting whether sex difference may be expected; (3) describing inclusion of sex in study design and analysis; (4) reporting of sex-specific differences in participants approached, eligible, consented, or who dropped out, in addition to sex-specific results; and (5) discussing the implications of sex on study results.

Consequently, systemic changes may enable an intersectional lens to evaluate other important demographic variables, such as race and age. Intersectionality may challenge the CV research that has focused on male sex and White race demographics while largely failing to encompass equity, diversity, and inclusion in CV medicine.[42] It is undeniable that multiple factors including cultural connectedness may interact and summate to influence CV outcomes.

Future reviews should explore the cellular mechanisms underlying pathologic hypertrophy and elaborate on the sex differences underlying CV regulation.

Strengths and limitations

This systematic review has methodologic strengths. The research protocol was registered in the Open Science Framework, describing the inclusion and exclusion criteria and the approach to analysis to be used. All deviations from the registered protocol were reported throughout the methods and results. Additionally, the robust nature of our search strategy created in partnership with a research information specialist (E.M.) and the thorough assessment of the literature synthesized contribute to the strength of our findings.

This review is not without limitations. The effect size of cardiac outcomes in this study must be evaluated with caution given the small number of included studies with adequately reported outcomes data. Not all studies reported full patient demographics or clinical outcomes based on sex. We contest that all studies involving male and female participants should report publication data by sex, regardless of whether the study is powered for sex-based analyses. This approach may enable meta-analyses to be conducted in a field where underrepresentation of females in clinical research is still prevalent and problematic. Subsequent research should investigate the interactions of sex, race, and age and their impact on main cardiorespiratory fitness, cardiac morphology, and functional indices. Corresponding authors should have an obligation to

share data for use in meta-analyses.[55] This was a barrier and ultimately limitation of this study. Systematic reviews and meta-analyses are the strongest form of evidence when presented using well-controlled and designed studies; however, if researchers are unable to access the data necessary to summarize the existing literature on a given topic, their ability to advance knowledge and clinical guidelines in these key areas becomes limited.

A determination of long-term aerobic exercise training history from these studies was not possible, and is quite challenging, as retrospective physical activity histories may be subject to recall bias. Cardiac morphology heterogeneity within and between the study cohorts indicates that genotypic factors influence aerobic exercise—induced cardiac adaptations independent of aerobic exercise interventions.[56] Large prospective, long-term aerobic exercise training studies are required to evaluate the predictive factors contributing to the exercise dose-response relationship in cardiac remodeling among healthy individuals across the life span.

Although studies reported left ventricular outcomes, data were lacking with respect to right ventricular and atrial responses to aerobic exercise. A more comprehensive understanding of the sex-specific responses to aerobic exercise training in the entire heart would lead to abetter sex-specific options for prevention and rehabilitation from CV diseases. It has been well established that right ventricular function is a strong predictor of mortality.[57] Studies have begun to explain the sex differences observed in the right ventricle;[58] however, this work warrants greater focus.

Conclusions

In conclusion, our meta-analysis revealed that aerobic exercise interventions were associated with a larger increase in LVEDV in males relative to females, yet no sex differences were found in cardiac morphology (LV mass) or functional indices (LVEF) following these aerobic exercise interventions. Moreover, this review illustrates and addresses the importance of transparency in data reporting to enable sex-based analyses in clinical exercise research. This study identified considerable knowledge gaps in the reported literature with respect to sex-specific reporting of outcomes, independent of statistical power. As a result, this systematic review serves as a call to action that future clinical research studies need to integrate sex into their research designs, methods, and analyses, as well as knowledge dissemination efforts, to advance our understanding of sex differences in CV medicine and exercise science.

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Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a systematic review and meta-analysis using aggregated data from previously published studies.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2024.12.005.