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Sex-Based Differences in Metabolic Equivalents (METs) After Cardiac Rehabilitation: A Systematic Review

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Abstract

Purpose: The purpose of this systematic review is to investigate the differences in peak Metabolic Equivalents (METs) between men and women post myocardial infarction after participating in a Cardiac Rehabilitation (CR) program.

Methods: Four databases were systematically searched through August 2020. Search terms related to cardiac rehabilitation, treatment outcomes, and gender differences were used. Papers were considered relevant if they compared outcomes in cardiac rehabilitation between men and women. Information from the studies was extracted by two independent authors. Risk of bias was assessed using the Downs and Black instrument.

Results: A total of 12,786 records were identified from the search and 8 observational studies were included in the final review. Improvements in absolute METs during CR ranged from 1.1 to 2.0 for women and 0.8 to 2.5 for men. Seven studies reported a statistically significant increase in peak METs for both men and for women after outpatient CR. Three of these studies showed a greater increase in absolute METs in men compared to women that were statistically significant. Four studies showed no sex-based differences before and after. Several of these studies reported significant improvements in both men and women in other outcomes including cholesterol, blood glucose, and BMI.

Conclusion: Both men and women improve functional capacity from CR. The majority of studies reported that there were more men participating in CR programs than women. Given the underrepresentation of women in these studies, it is difficult to speculate if any differences in MET levels reported in these studies are a true representation of sex differences with respect to peak MET levels. Nonetheless, the statistically significant improvement in METs in both sexes suggests that women experience clinical benefit from CR and that efforts should be made for greater referral of women to CR programs.

Keywords: Sex; Cardiac Rehabilitation; Cardiovascular Disease; METs

Background

Worldwide, cardiovascular disease is the leading cause of morbidity for both women and men [1]. In the United States, over 720,000 people experience Myocardial Infarctions (MI) annually [2]. Cardiac Rehabilitation (CR), an evidenced-based multidisciplinary intervention that incorporates health behavior adjustment, patient education, biopsychosocial counseling, and exercise training, has become a standard of care following a MI [3-6]

An increasing body of research demonstrates the broad health outcome benefits of CR. A meta-analysis estimated a 21% to 34% reduction in mortality rate in older coronary patients who underwent CR [7]. Another study noted that CR coupled with medical management is more effective in improving health-related quality of life and reducing future hospitalizations when compared to medical management alone [6]. These benefits are consistent across different adult age groups [8]. Research demonstrates that CR, whether in an inpatient or outpatient setting, is more cost-effective than no CR [9].

While robust evidence favors the use of CR for the medical management of patients after an MI, a significant sex disparity exists for CR participation where women are at a significant disadvantage [10-13]. While this sex disparity is likely complex and multifactorial, differences in CR outcomes between men and women has not been explored in a systematic review. As exercise capacity has been shown to play a significant role in prognosis after an MI, we sought to synthesize the nature of possible differences in post-CR peak exercise capacities between women and men [14-17].

Literature Review

We performed a systematic review examining changes in peak exercise capacity as measured in Metabolic Equivalents (METs). This review was conducted using the criteria established by the PRISMA guidelines [18]. Search strategies were developed in conjunction with a research librarian to answer the following PICO question: In adults that have experienced ischemic heart disease, is there a difference in METs between men and women after phase II CR? Searches of PubMed, SCOPUS, CINAHL, and Cochrane Central Registry of Controlled Trials from inception through August 21, 2020 were performed. In order to maximize search results, we used MeSH headings and free-text terms that included sex, cardiac rehabilitation, cardiovascular disease, and treatment outcomes. Two authors screened titles and abstracts to identify potential articles. Full-text articles were then reviewed by two coauthors to determine eligibility. Co-authors also scanned reference lists of eligible articles and reviews. A third author was used to resolve any discrepancies.

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Papers were included if they met the following criteria: (1) Men and women engaged in outpatient, phase II CR after ischemic heart disease (i.e. after sustaining an MI or angina); (2) utilized exercise testing to measure Metabolic Equivalents (METs) as an outcome of CR in both men and women; and (3) peer-review publication in the English language A single MET is defined as the metabolic cost of resting and is understood to be approximately equal to 3.5 ml of oxygen consumed per kilogram body weight. Since METs are measured in ml of oxygen consumed, it is a surrogate measure of the ability of the cardiorespiratory and metabolic systems to support physical activity. Quantifying peak exercise capacity using METs therefore describes the individual's maximal level of cardiorespiratory and metabolic capacity in terms multiples of the resting metabolic rate [19-21].

We excluded review articles, other systematic reviews, dissertations, and articles that did not specifically look at phase II outpatient CR or did not report before and after differences in physiological treatment outcomes between men and women. Articles that did not measure METs directly and only estimated METs were excluded in order to minimize inflation of the values [22-24].

Quality assessment

Two authors independently assessed study quality using the Downs and Black criteria [25]. Consensus was reached for each item by discussion and a third reviewer was used when consensus was not reached. The Downs and Black scale was selected as it can be used to assess the quality of both observational and randomized clinical trials. We removed the item on power of the study, leaving a total of 26 items. Most items are scored either a 0 for no or 1 for yes if the item was present in the article; however, one item can receive 2 points, resulting in a maximum score of 27 points. The scores for the items were summed and divided by 27 to obtain the final score for each article.

Data extraction and analysis

For each study, two coauthors collected data using a standardized form. Data included answering if the study related to the PICO question, the study design, the population in the study, the cardiac rehabilitation intervention, any comparison intervention, the time points at which the outcomes were measured, and all primary outcome measures including METs. Results are reported as mean (SD) unless noted otherwise.

A total of 12,786 records were identified from the search and 8 eligible studies were included in the final review [10, 26-32] (Figure 1). The design of all 8 articles was observational in nature. Of the 8 studies included in the review, 7 directly compared differences in absolute METs between men and women before and after CR [10, 26-31]. Three of these studies showed a greater increase in absolute METs in men compared to women that was statistically significant [10, 30, 31]. Four studies showed no sex-based differences before and after CR [26-29]. The study design, quality of the studies, characteristics of the subjects, and the duration of the cardiac rehabilitation interventions were comparable between the studies that did and did not demonstrate sex-based differences in METs after cardiac rehabilitation. One study reported changes in METs by sex after cardiac rehabilitation, but they did not directly compare for sex-based differences [32].

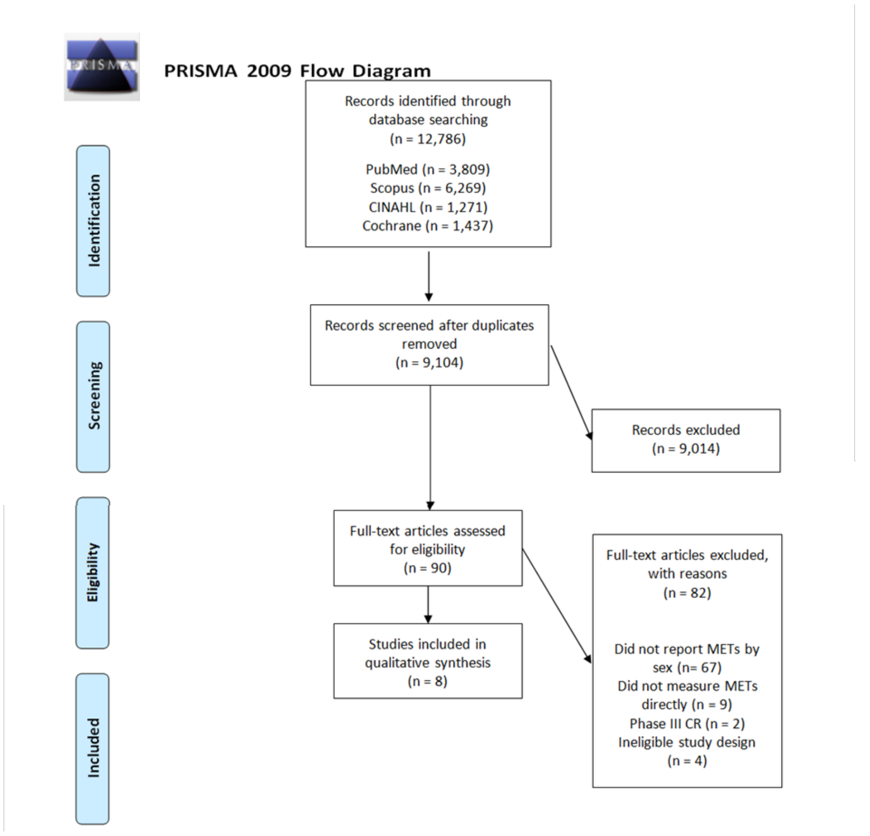

Figure 1: Flow of information through the different phases of a systematic review..

Study quality

The mean Downs & Black score of the 8 included studies was 13.75 out of 27 (sd 2.66) or 0.509. The range of the scores was from 10 to 17. Items that were frequently scored lower included those related to random assignment, the accessible population, blinding of participants and outcome assessors, and adverse effects of the interventions.

Participant and study characteristics

Sample sizes of the included studies ranged from 51 to 206 for women and 72 to 652 for men. The total number of subjects in the 8 studies was 3,564 (862 women and 2,702 men). All of the studies, except for Ghashghaei, et al. included more men than women [32].

Seven of the studies reported age by sex; in these studies, the mean age of women ranged from 50 to 63 years, while for men it ranged from 54 to 61 years. The other study provided a mean age of 54.5 years for the total sample, but did not report ages of male and female participants separately [10].

All articles provided descriptions of the CR interventions used. Supervised exercise sessions varied by study, but always included forms of aerobic exercise (i.e. walking on a treadmill) and often resistance exercise training. These exercise regimens were supplemented by other CR components focused on risk factor modification, including nutrition and dietary counselling, biopsychosocial counselling, and smoking cessation.

The total number of sessions for each CR program ranged from 24 to 36 sessions. The exercise sessions typically lasted 40 to 60 minutes; however, Sadeghi, et al. described exercise sessions lasting 60 to 90 minutes [31]. The duration of the programs ranged from 8 to 12 weeks.

Exercise capacity

Improvements in absolute METs during CR, as reported by 8 studies, ranged from 1.1 to 2.0 for women and 0.8 to 2.5 for men. Improvements in percent improvement in METs from baseline, as reported by 4 studies, ranged from 6.1% to 33% in women and 10.6% to 40% in men (Tables 1 and 2). Seven studies reported a statistically significant increase in peak METs for both men and for women after outpatient CR. O'Farrell, et al. was the only study in which a statistically significant improvement for either men or women was not reported after CR [29].

Authors	Women			
	n	Baseline	Post-intervention	Change
Anjo et al 2014	85	7.6	8.7	1.2
Cannistra et al 1992	26	3.7	4.8	1.1
Caulin-Glaser et al 2007	71	4.9	6.3	1.4 (20%)
Ghashghaei et al 2012	84	5.9	7.9	2
Lavie et al 1995	83	6.1	8.1	2.0 (33% increase)
O'Farrell et al 2010	70	4.9	5.2	(6.1% increase)
Sadeghi et al 2012	121	7	8.7	1.7
Sarafzadegan et al 2007	147	6.9	8.7	2.0 (30% increase)
Authors	**Men**			
	n	Baseline	Post-intervention	Change
Anjo et al 2014	301	9.1	10.6	1.5
Cannistra et al 1992	107	5.1	5.9	0.8
Caulin-Glaser et al 2007	224	6.7	8.6	1.9 (14%)
Ghashghaei et al 2012	72	8.4	10.9	2.5
Lavie et al 1995	375	6.7	9.4	2.7 (40% increase)
O'Farrell et al 2010	317	6.6	7.3	(10.6% increase)
Sadeghi et al 2012	464	9.4	11.9	2.5
Sarafzadegan et al 2007	400	9.7	12.2	2.5 (21%)

Table 1: Metabolic equivalents before and after cardiac rehabilitation for women and men.

Authors	Type of Study	Quality Rating	Participants	Intervention	Outcomes
Anjo et al, 2014	Retrospective	13 (0.46)	858 patients	Duration: 8-12 weeks	-METs
			206 women, 652 men	Sessions: 2x/week	-Metabolic Profile
			85 women and 301 men were analyzed	Length of session: 60 minutes	-Heart Rate (Resting, recovery, chronotropic index)
			Mean Age	Exercise: Aerobic and strength training with weights	
			Men 59 y with an SD of 10	Consultations in psychiatry, urology, risk factor modification (i.e. smoking cessation and nutrition) depending on clinical indication	

Cannistra et al, 1992	Prospective	16 (0.57)	225 total patients	Duration: 12 weeks	-METs
			51 women, 174 men	Sessions: 3x/week	-Exercise time in minutes
			Mean age		-Heart Rate: Percent max heart rate, Peak rate-pressure product
			Total sample: 54.4 y (SD=9.9)	Length of sessions: 30 minutes (Participants exercised while maintaining a heart rate between 75% and 85% of their maximal heart rate during 30 minutes of exercise)	-Exercise induced ischemia
			Women: 56 y (SD=10)		-Metabolic Profile
			Men: 54 y (SD=10)		
			Race: White (84%)		
			348 patients	Duration: 12 weeks	-METs
			100 women, 248 men	Sessions: Frequency not reported	-BMI
				Length of sessions: not reported	-Metabolic Profile
			Mean age		-Biopsychosocial (Depression)
			Completers 63.9 y (SD=10.6)	Components: Sessions included exercise training, education and extensive behavior modification therapy which included management of diet, cholesterol, blood pressure, stress, and glucose as well as smoking cessation)	
			Non-completers 55.5 y (SD=13.3)		
				Participants must have completed at least 7 weeks.	
Ghashghaei et al, 2012	Prospective	17 (0.61)	156 total of obese patients	Duration: 2 months long (8 weeks)	-METS
			84 women, 72 men	Sessions: 24 sessions, 3x/week	-Weight (body weight, BMI)
			Mean age		-Metabolic profile
			Women: 57.7 y	Length of Sessions: 90 minutes (10 minutes of warm-up, 60 minutes of aerobic/resistance training, 20 minutes of cooldown)	-Fasting blood sugar
			Men: 54.5 y		
				Components: Included exercise training sessions, nutritional and psychologic consultation, and risk factor management. Each patient had individual dietary instruction by a visiting dietitian during the program.	
Lavie et al, 1995	Retrospective Cohort	10 (0.36)	458 total	Duration: 12 weeks	-METs
			-83 women, 375 men	Sessions: 3x/week, total of 36 exercise and educational sessions	-Metabolic Profile
			Mean age	Length of Session: 50-60 minutes (included a 10-minute warm up, 30-40 minutes of upright dynamic exercise, and a 10-min cool down)	-BioPsychosocial outcomes
			Women: 63 y (SD=10)	Type of Exercise: Intensity individualized at 70-85% HRmax	
O'Farrell et al, 2010	Retrospective	16 (0.57)	387 total	Duration of program: Three-month program	-METs
			-70 women, 317 men	Sessions: 2 exercise sessions per week	-Metabolic Risk Factors
				Length of sessions: Exercise sessions included warm-up and 30 minutes of exercise at prescribed HR	-Physical Function (energy expenditure/ week)
			Mean Age	Exercise: Consisted of walking, stationary cycling, rowing, biking	-Biopsychosocial (Mental Health)
			- Men 59 y (SD=10)	Supplement: Varied by individual patient goals (i.e. stress management, smoking cessation, dietary); all had physician-guided risk factor management	
Sadeghi et al, 2012	Retrospective cohort	14 (0.50)	585 total patients	Duration: Two months	-METs
			-121 women, 464 men	Sessions: 24 exercise training sessions	-Metabolic profile
			Mean age	Frequency: 3 x/week	
			Women 58.1 y (SD=8.95)	Length of Sessions: 90 minutes (20 minute warm up and 10 minute cool down, with 60 minutes of aerobic and resistance training between.) Training intensity was 60-85% of HR max.	
			Men 56.2 y (SD=9.94)	Exercise: Using a treadmill, stationary cycles, stationary steppers, stair climbing, rowing, jogging, and some resistance devices.	
			Mean BMI	Data collected from 2000 to 2011	
			Women 26.29 kg/m2 (SD=2.66)		

Sarafzadegan et al, 2008	Retrospective	10 (0.36)	All patients had documented heart disease	Duration: 8 weeks	-METs
			547 patients	Sessions: 24 exercise sessions over 8 weeks	-Weight (BMI, Body weight)
			147 women, 400 men	Length of Sessions: 60-90 minutes each session	-Metabolic Profile
			Mean Age	Exercise: Intensity of the exercise was calculated according to the determined risk, between 60 and 85% of the maximum HR achieved on the exercise test.	-HR
			147 women 57.3 y (SD=0.67)	Supplement: All patients received psychological, nutritional and smoking cessation consultations. There were also weekly educational sessions for patients and their families.	-Blood pressure (systolic)
					-Cardiac variables (LV EF)

Table 2: Summary of characteristics of included studies.

Three studies showed a greater increase in absolute METs in men compared to women that was statistically significant [10, 30, 31]. Caulin-Glaser, et al., calculated a percentage change from baseline in METs that was relatively similar for both sexes (20% for men, 14% for women). Sarafzadegan, et al., an increase of 2.5 METs in men compared to 1.8 METs in women was noted, which represented a 30% increase from baseline in METs for women and a 21% increase in men [30]. Sadeghi et. al a 2.43 increase in METs in men compared to 1.74 in women [31].

Four studies that compared differences in METs before and after CR found no statistically significant difference between men and women. Two of these studies examined the change in METs as a percentage change from baseline. One, by Lavie et. al, noted a 33% increase from baseline in women and a 40% increase from baseline in men [28]. Cannistra, et al., noted a greater change in women compared to men in terms of METs, but this difference was not statistically significant (P=0.08) [27].

Ghashghaei, et al did not report a direct comparison between men and women [32]. However, this study described similar improvements in METs for both men and women (2.5 in men vs. 2.0 in women) [32].

Other outcomes

AAll studies included in this review reported outcomes in addition to METs. Seven reported outcomes related to lipid profile [10, 26, 28-32]. Other common outcomes reported included body mass index (BMI) (n=6), blood glucose levels (n=4), and various psychosocial incomes (i.e. depression, tobacco cessation) (n=4).

In the studies which compared lipid profiles, five showed a statistically significant improvement for both men and women before and after cardiac rehabilitation with no statistically significant difference between the two groups [26, 29-32]. Two of these studies, by Cannistra, et al. and Lavie, et al. showed no statistically significant change in total cholesterol in both men and women [27, 28].

Six studies investigated BMI changes before and after CR. Three studies noted statistically significant decreases in BMI after CR [10, 26, 32]. When the changes in BMI between sexes were compared, they were not statistically significant. Sarrafzadegan, et al., noted statistically significant decreases in BMI in both men and women after CR; when these differences were compared, women had a statistically significant greater decrease in BMI compared to men [30]. In contrast, Lavie, et al. noted a statistically significant decrease in BMI in men but not women after CR; these differences were not directly compared [28]. Finally, O'Farrell, et al. noted no statistically significant differences in BMI in both men and women after CR [29].

Discussion

While studies have reported that women specifically benefit from cardiac rehabilitation programs, no systematic review has compared differences in CR outcomes between men and women [33, 34]. In this systematic review, we analyzed 8 studies examining typical CR programs conducted in North America, Europe, and the Middle East that reported changes in peak METs in men and women who completed outpatient CR programs. Three of these studies reported statistically greater differences in peak absolute METs following CR completion between men and women, favoring men; four studies reported global improvements in peak METs for both sexes following CR completion, but noted no significant differences in peak MET improvements between men and women [10, 26-31]. The other study included did not directly compare changes in METs before and after CR between men and women, though the improvement in METs in both sexes was relatively similar [32]. Strength of the current systematic review was the inclusion of articles which reported MET values as determined from exercise testing. In comparison, MET values as calculated from exercise workloads may be misleading [22, 23].

Although our findings suggest that women sometimes experience a smaller magnitude of improvement in peak exercise capacity when compared to men, the majority of the studies in our analysis suggest that women still benefit from CR. While CR may be underutilized post myocardial infarction, it is particularly underutilized in women [8, 12]. A recent meta-analysis indicated that women were significantly less likely than men to be referred to CR (39.6% vs. 49.4%, odds ratio 0.68, 95% confidence interval 0.62-0.74) [13].

Women are typically referred to CR only when they present with greater cardiovascular risk than men [26]. Even after referral, women tend to participate at lower rates than men [35, 36]. They are also less likely to successfully complete CR programs compared to men [10].

Barriers to CR participation among women are diverse and complex. A recent systemic review identified non modifiable barriers, such as age and diagnosis, and difficult to modify barriers, such as financial constraints and level of education that may be more prevalent among women [37]. Ades, et al. noted that women were significantly more likely than men to encounter transportation problems (32% vs. 16%; P=.01) [38]. Other barriers such as low awareness of CR and lack/lower physician advisement and referral of women to CR are prevalent but modifiable [39]. Research demonstrates that both sets of barriers among women can be addressed with a variety of interventions [37]. Notwithstanding, additional research is still needed to better understand how to close this sex disparity in CR participation. These disparities in referral are compounded by research that suggests that women experience improvements in a wide variety of clinical outcomes [37, 40-42].

Based on these data and the relatively smaller sample sizes of women in the majority of studies, it is difficult to make any definitive conclusion that women or men benefit more from CR than the other in terms of improvements in exercise capacity. Regardless, it is important to note that 7 of the 8 studies in this review found a clinically and statistically significant improvement in exercise capacity in both men and women after CR, underscoring the benefits of CR participation for eligible candidates regardless of sex.

We specifically examined changes in peak METs as a key outcome after completing a CR program because peak exercise capacity has been linked to several important clinical outcomes. From a disability standpoint, both the peak level of exercise capacity and the level of physical activity that can be sustained for a given period of time will determine the types of physical activities one can participate in. According to the work compiled by Ainsworth, et al. the metabolic cost of engaging in general kitchen activities like cooking or washing dishes requires an absolute energy expenditure of approximately 3.3 METs [19-21]. A hypothetical person with a peak exercise capacity of 3.0 METs may find that they are unable to participate in such kitchen activities, and might be considered "disabled," necessitating assistance from family members or aides to perform such activities. For this person, a seemingly small improvement of 1.0 MET from participating in a CR program would be enough to theoretically enable this person to now perform their own kitchen activities and no longer require the same level of external assistance. Viewed in this light, the seemingly small changes in peak MET levels reported by several of the authors reviewed in this paper may translate to meaningful differences in the participation of daily activities or other meaningful pursuits.

A possible reason why men showed greater improvements in peak METs in some of the studies we examined may be due to underrepresentation of women as men appear to have higher CR completion rates when referred [43, 44]. Caulin-Glaser, et al. determined via logistic regression that women had a non-completion odds ratio of 2.52 (p=0.024) compared to men [10]. Factors, such as increased family responsibilities (on average) by women compared to men, may contribute to this disparity [27]. Women referred to CR programs may also start with an average greater baseline cardiovascular risk, an observation highlighted Anjo, et al. O'Farrell et al., and Sadeghi et al. [26, 29, 31]. This could limit the improvement women have in CR, resulting in selection bias that is reflected by poorer outcomes in METs.

The structure of CR programs may explain some of our findings as they appear to be better tailored towards men than women [40, 45]. Other research has suggested that CR programs with flexible, personalized treatment options may be "even more ideally suited for women than for men," which may provide improved clinical outcomes [37].

Most of the studies included in the review except for one assessed the effect of CR on lipid profile. Five out of these seven studies showed a statistically significant improvement without any statistically significant difference between men and women after CR, suggesting that both experience clinical benefit in terms of risk factor modification due to CR [26, 29-32]. Anjo, et al. concluded that women benefitted from CRP and showed significant improvements in modification of cardiovascular risk factors and other prognostic indiactors, thus increasing the need for increased utilization in women [26]. Similarly, Sadeghi et al., who found a greater improvement in METs in men compared to women after CR, still noted the role that CR plays in improving lipid profile in both sexes [31]. Six studies additionally looked at BMI, with half of them noting statistically significant decreases in BMI after CR in both sexes with no differences between sexes when statistically compared.

Six studies additionally looked at BMI, with half of them noting statistically significant decreases in BMI after CR in both sexes with no differences between sexes when statistically compared [10, 26, 32]. Two of the other studies noted decreases in BMI in at least one sex [28, 30].

Ghashghaei et al., who included obese subjects for their CR intervention, concluded that CR, is an effective tool for modifying both BMI and lipid profiles [32]. Thus, in addition to improvements in metabolic profile, both men and women may experience a reduction in BMI, another clinical benefit of CR for both sexes.

Conclusion

The majority of studies confirm that more men participate in cardiac rehabilitation programs than women. Given the underrepresentation of women in these studies, it is difficult to speculate if any differences in peak MET levels reported in these studies are a true representation of sex differences with respect to peak MET levels. Nonetheless, the statistically significant improvement in METs in both sexes suggests that women experience clinical benefit from CR and that efforts should be made for greater referral of women to CR programs.

Limitations

The majority of the observational studies included were retrospective, which are of lower quality than prospective studies and more prone to selection bias. The studies may have also been prone to selection bias through the inclusion of more men than women. Finally, studies did not specify if they included cis-gendered, trans-gendered, or gender non-binary individuals.

Future Research

Researches with larger, ethnically diverse sample sizes of women are needed to further evaluate different responses to CR between men and women. Future systematic reviews examining other outcomes, such as long-term mortality, would be helpful in evaluating other possible sex-based responses to CR.

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