Women Have Lower Mortality Than Men After Attending a Long-Term Medically Supervised Exercise Program

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Purpose: Medically supervised exercise programs (MSEPs) are equally recommended for men and women with cardiovascular disease (CVD). Aware of the lower CVD mortality in women, we hypothesized that among patients attending a MSEP, women would also have better survival.

Methods: Data from men and women, who were enrolled in a MSEP between 1994 and 2018, were retrospectively analyzed. Sessions included aerobic, resistance, flexibility and balance exercises, and cardiopulmonary exercise test was performed. Date and underlying cause of death were obtained. Kaplan-Meier methods and Cox proportional hazards regression were used for survival analysis.

Results: A total of 2236 participants (66% men, age range 33-85 yr) attended a median of 52 (18, 172) exercise sessions, and 23% died during 11 (6, 16) yr of follow-up. In both sexes, CVD was the leading cause of death (39%). Overall, women had a more favorable clinical profile and a longer survival compared to men (HR = 0.71: 95% CI, 0.58-0.85; $P < .01$). When considering those with coronary artery disease and similar clinical profile, although women had a lower percentage of sex- and age-predicted maximal oxygen uptake at baseline than men (58 vs 78%; $P < .01$), after adjusting for age, women still had a better long-term survival (HR = 0.68: 95% CI, 0.49-0.93; $P = .02$).

Conclusion: Survival after attendance to a long-term MSEP was better among women, despite lower baseline cardiorespiratory fitness. Future studies should address whether men and women would similarly benefit when participating in an MSEP.

Key Words: cardiac rehabilitation • exercise • mortality • physical activity • survival

Although cardiovascular disease (CVD) mortality has declined progressively over the past three decades, CVD remains the leading cause of morbidity and mortality globally among both adult men and women. According to the World Health Organization, >17 million people die each year from CVD, which accounts for an estimated 31% of all deaths worldwide.[1] In addition to its effect on morbidity and mortality, CVD has a major impact on health care costs, disability, and reduction in quality of life.[2] Therefore, additional strategies are needed to reduce the societal and economic burden of CVD.

Physical inactivity has been associated with CVD and all-cause mortality in both healthy and unhealthy middle-aged and older individuals. It is considered the fourth-leading risk factor for global health, and it is estimated that physical inactivity is independently responsible for 8% of deaths that occur globally.[3,4] Conversely, regular exercise is associated with a number of health benefits.[5-7] Considerable evidence supports the protective and therapeutic effects of regular exercise, including improvement in insulin sensitivity, blood glucose control, lipid profile, resting blood pressure, attenuation of autonomic nervous system sympathetic activity, and upregulation of antioxidant defense mechanisms.[8] Medically supervised exercise programs (MSEPs) have been shown to be effective in reducing recurrent cardiac events while improving survival, functional status, and psychosocial well-being. Moreover, its safety and effectiveness have been well established, and MSEPs have been equally recommended for men and women for primary and secondary CVD prevention in several clinical practice guidelines.[9-12]

However, sex inequalities have been reported in terms of the pathophysiology of CVD, the burden of risk factors, the access to and impact of specific cardiovascular therapies, and it is also known that women are less likely to adhere to structured exercise programs when they have access to them.[13-16] Most clinical outcome improvements after participation in an exercise-based rehabilitation program, including modification in cardiac risk factors, functional exercise testing parameters, and quality of life, appear to be similar among men and women.[17,18] However, there remains a lack of studies addressing sex differences in terms of the so-called hard outcomes of morbidity and mortality among those who have attended structured exercise programs.[19] Therefore, given the lower CVD mortality in women, we hypothesized that among patients, attending a MSEP, women would also demonstrate better survival.

METHODS

Prospectively collected data from an open cohort of men and women who were evaluated at a privately owned exercise clinic (Exercise Medicine Clinic—CLINIMEX—Rio de Janeiro) and enrolled in a MSEP between March 1994 and November 2018 were retrospectively analyzed. Individuals were referred to the MSEP by their attending physicians or self-enrolled in the program mainly due to diagnosed coronary artery disease (CAD), but the sample also included participants at high risk for developing and/or presenting CVD and with other clinical conditions such as cancer, metabolic and neurodegenerative diseases.

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Before entering the MSEP, all individuals underwent a pre-participation comprehensive assessment, which included exercise habits, a clinical history and physical examination, as well as several anthropometric measurements, a battery of musculoskeletal (MUSK) fitness tests (including a sitting-rising test[20] and Flexitest[21]) for evaluation of muscle strength/power, flexibility, and balance, resting 12-lead electrocardiogram, lung spirometry, and assessment of cardiac vagal tone by the 4-sec exercise test.[22]

As part of the pre-participation evaluation and to develop an aerobic prescription, a maximal cardiopulmonary exercise test (CPX) was performed on a CG-04 leg cycle ergometer (Inbramed) using individualized ramp protocols[23] in a temperature humidity controlled room equipped for providing medical emergency support if needed. All CPX were conducted by four specialized physicians with extensive experience in exercise medicine, following a well-defined routine, particularly regarding the verbal stimulus to achieve a true maximal exertion. The CPX was considered maximal based on a combination of physician subjective assessment and other objective variables, such as surpassing the ventilatory threshold, existence of a clear U-pattern of ventilatory equivalents, and a score of 10 on the 0-10 Borg perceived exertion scale.

During CPX, individuals were continuously monitored using a digital ErgoPC Elite electrocardiogram (Micromed), and measurements of heart rate (HR) were obtained from the electrocardiographic tracing in the CC5 or CM5 leads before, during, and for ≥5 min after the end of CPX. Individuals used a nose clip and breathed through a mouthpiece to collect expired gas. Determination of airflow and O_2 and CO_2 expired fractions were carried out using a $\dot{V}O_{2000}$ metabolic analyzer (Medical Graphics) that was regularly calibrated using known syringe volumes and two different gas concentrations. Expired gases were read every 10 sec and averaged every 60 sec. The highest oxygen uptake ($\dot{V}O_2$) value obtained at a given minute was considered the maximal $\dot{V}O_2$ ($\dot{V}O_{2max}$). For comparison purposes, sex- and age-predicted $\dot{V}O_{2max}$ (p$\dot{V}O_{2max}$) related to body weight in cycling CPX was determined using the following equations: men = 60 – 0.55 × age (yr); women = 48 – 0.37 × age (yr).[24]

EXERCISE SESSIONS

The participants were free to attend the exercise sessions anytime from 6:00 to 21:30 (weekdays) and from 7:00 to 16:00 (Saturdays). Before each exercise session, the participant was briefly assessed by a physician who remained continuously present in the exercise room during the MSEP. Aerobic exercise was individually prescribed by the physician, prioritizing moderate- to high-intensity exercise, regardless of the underlying clinical condition, based on the CPX and pre-participation evaluation/previous session data. Using this approach, individual exercise prescription was optimized regularly by adjusting the intensity and volume.

A typical exercise session lasted lasted 60-75 min and included aerobic exercises such as treadmill, arm/leg cycling, rowing, and skiing ergometers (continuous and interval training regimens). In an effort to improve nonaerobic or MUSK fitness, individually prescribed resistance, flexibility, and balance exercises were regularly performed. Additionally, according to clinical conditions and individual objectives, isometric handgrip, inspiratory muscular training, and gross and fine motor coordination exercises were conducted. All exercise sessions were carried out under direct supervision of a multiprofessional team. Most of the participants performed a 3-d/wk regimen but some attended up to 6 d/wk.

DATA COLLECTION

Data were reviewed for clinical conditions, regular medications, basic anthropometry (height, weight, and body mass index), resting HR/blood pressure, and directly measured $\dot{V}O_{2max}$ relative to body weight (r$\dot{V}O_{2max}$), obtained from CPX, as well as the percent of sex- and age-predicted $\dot{V}O_{2max}$ (%p$\dot{V}O_{2max}$).

MORTALITY OUTCOMES

Date of death and underlying cause of death were obtained from official death records from the State of Rio de Janeiro from March 1, 1994, to November 30, 2018. Complementary data checking was obtained from medical records, web searching, and direct information provided by attending physicians, relatives, and friends of participants. Underlying cause of death when available was categorized according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

STATISTICAL ANALYSIS

Descriptive statistics for continuous variables were presented as median and interquartile range. Frequency distribution was used for nominal variables. Differences between men and women or between participants according to vital status were analyzed with the Wilcoxon rank sum test for continuous variables, and with the χ^2 test for categorical variables.

Probabilities of survival rates were estimated with the Kaplan-Meier survival method. Baseline date was considered the date of pre-participation assessment before entering the MSEP, and for the endpoint death, participants were censored as dead or alive on November 30, 2018. Survival models were estimated with Cox proportional hazards regression to compare risks between sex; 95% CIs were calculated to express the degree of uncertainty. The Stata14 software package (Stata) was used for all analyses. Statistical significance was set at 5% probability.

RESULTS

Data from 2236 participants (66% men; 33-85 yr) were analyzed. Participant survival status was followed up for 11 (6, 16) yr (minimum of 16 d). There was no specific time limit for MSEP attendance; participants attended 52 (18, 172) exercise sessions and >700 of the subjects completed >100 sessions. Overall, 60% of the participants attended ≥36 sessions, with no differences between men and women (61 vs 57%, respectively; $P = .05$).

As shown in Table 1, although men and women had similar age, men had a more unfavorable clinical profile as compared with women, including a higher prevalence of CAD. Nevertheless, when considering only participants who had already been diagnosed with CAD before entering the MSEP, men and women had similar risk factors, including history of myocardial infarction and use of prescribed medications, with the exception of angiotensin-converting enzyme inhibitors and psychoactive drugs. Women with CAD were slightly older and had undergone coronary artery bypass grafting less frequently than men. Regardless of the presence of CAD, women achieved a lower %p$\dot{V}O_{2max}$ than men.

During the 24-yr follow-up, 525 participants (23%) died. Table 2 depicts the main characteristics of participants in the MSEP according to sex and vital status at the end of follow-up. As expected, both men and women who died were older and had a worse clinical profile when starting the MSEP. Women who died were less frequently diagnosed with CAD or diabetes before enrollment compared with men and had less frequently undergone an invasive coronary therapeutic strategy. Once again, regardless of the vital status at the end of censoring, women achieved a lower %p$\dot{V}O_{2max}$ as compared with men.

Table 1

Demographics and Maximal Cardiopulmonary Exercise Test Results of Participants Who Were Enrolled in a Medically Supervised Exercise Program in a Brazilian Private Clinic From March 1994 to November 2018 According to Sex and Presence of Coronary Artery Disease

	All Participants				Participants With CAD			
Variables[a]	Total n = 2236	Men n = 1484	Women n = 752	*P* Value[b]	Total n = 1086	Men n = 898	Women n = 188	*P* Value[b]
Age, yr	63 (54, 71)	63 (55, 71)	63 (54, 72)	.92	64 (56, 72)	64 (56, 72)	68 (59, 76)	.001
Weight, kg	77 (67, 88)	82 (73, 91)	67 (60, 77)	<.001	77 (69, 87)	80 (72, 88)	66 (60, 73)	<.001
Height, cm	169 (162, 175)	172 (168, 177)	159 (155, 164)	<.001	170 (164, 176)	172 (167, 176)	157 (153, 162)	<.001
BMI, kg·m^{-2}	27 (25, 30)	27 (25, 30)	27 (24, 30)	.001	27 (25, 30)	27 (25, 30)	26 (24, 29)	.05
Comorbidities								
CAD	49	61	25	<.001	…	…	…	…
Acute MI	26	32	14	<.001	52	52	54	.71
Hypertension	50	53	44	<.001	55	56	52	.32
Dyslipidemia	51	55	43	<.001	65	65	64	.82
Obesity	27	27	26	.52	23	24	19	.18
Diabetes	18	21	12	<.001	23	24	19	.12
Medications								
β-blockers	46	52	34	<.001	66	67	64	.45
CaBlock	20	21	18	.11	25	25	29	.18
ACEInh	18	22	11	<.001	22	23	15	.02
ARB	25	27	23	.05	30	29	32	.40
Diuretics	24	23	25	.52	25	24	31	.06
Vasodilators	20	24	13	<.001	35	34	36	.59
Lipidlow	54	61	39	<.001	79	79	78	.84
Antiplat	56	67	35	<.001	91	91	90	.82
Antiarrhyth	13	14	11	.13	15	15	16	.86
Psycho	41	39	41	.01	44	42	54	.003
Intervention								
PCI	28	35	15	<.001	56	56	59	.53
CABG	17	22	7	<.001	35	36	28	.03
Resting								
HR, bpm	65 (58, 74)	64 (57, 73)	67 (61, 75)	<.001	63 (56, 71)	63 (56, 71)	62 (57, 70)	.68
SBP, mm Hg	132 (120, 144)	133 (121, 145)	130 (118, 144)	<.001	132 (119, 144)	132 (120, 144)	131 (118, 142)	.36
DBP, mm Hg	76 (70, 83)	76 (70, 84)	76 (70, 82)	.07	74 (68, 80)	74 (68, 82)	72 (67, 78)	.003
Maximal CPX								
r$\dot{V}O_{2max}$	18 (14, 23)	20 (15, 25)	16 (12, 19)	<.001	18 (14, 23)	19 (15, 24)	13 (11, 17)	<.001
p$\dot{V}O_{2max}$	25 (21, 29)	25 (21, 30)	25 (22, 28)	.03	25 (20, 29)	25 (21, 29)	23 (20, 27)	.002
%p $\dot{V}O_{2max}$	73 (58, 88)	78 (64, 95)	62 (51, 75)	<.001	74 (59, 91)	78 (63, 94)	58 (47, 70)	<.001
Sessions, n	52 (18, 172)	55 (19, 182)	46 (16, 151)	.01	66 (23, 245)	68 (23, 255)	60 (25, 213)	.46
≥36 sessions	60	61	57	.05	66	66	65	.92
Follow-up, d	3914 (2209, 5755)	3724 (2063, 5531)	4254 (2417, 6136)	<.001	3341 (1809, 5231)	3362 (1819, 5253)	3211 (1784, 5164)	.69

Abbreviations: ACEInh, angiotensin-converting enzyme inhibitors; Antiarrhyth, antiarrhythmic drugs; Antiplat, antiplatelet drugs; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CaBlock, calcium channel blockers; CAD, coronary artery disease; CPX, cardiopulmonary exercise test; DBP, diastolic blood pressure; HR, heart rate; Lipidlow, lipid-lowering agents; MI, myocardial infarction; PCI, percutaneous coronary intervention; Psycho, psychoactive drugs; p$\dot{V}O_{2max}$, age-predicted maximal oxygen uptake; %p$\dot{V}O_{2max}$, percentage of age, and sex, predicted maximal oxygen uptake achieved; r$\dot{V}O_{2max}$, maximal oxygen uptake relative to body weight (mL/kg·min); SBP, systolic blood pressure.

[a]Data expressed as % or median (IQR).

[b]Between men and women.

Table 2

Demographics and Maximal Cardiopulmonary Exercise Test Results of Participants Who Were Enrolled in a Medically Supervised Exercise Program in a Brazilian Private Clinic From March 1994 to November 2018 According to Sex and Vital Status at the End of the Follow-up Period

		Dead				Alive				
Variables[a]	Total n = 2236	Total n = 525	Men n = 375	Women n = 150	*P* Value[b]	Total n = 1711	Men n = 1109	Women n = 602	*P* Value[b]	*P* Value[c]
Age, yr	63 (54, 71)	71 (63, 77)	71 (63, 77)	73 (64, 79)	.09	60 (53, 68)	60 (53, 68)	60 (52, 69)	.96	<.001
Male	66	71	…	…	…	65	…	…	…	.005
Weight, kg	77 (67, 88)	76 (65, 87)	80 (69, 89)	65 (58, 77)	<.001	77 (68, 88)	82 (73, 92)	68 (60, 76)	<.001	.02
Height, cm	169 (162, 175)	168 (161, 174)	171 (167, 176)	157 (153, 163)	<.001	169 (162, 175)	173 (168, 177)	160 (155, 164)	<.001	.35
BMI, $kg \cdot m^{-2}$	27 (25, 30)	27 (24, 30)	27 (24, 30)	26 (24, 29)	.25	27 (25, 30)	27 (25, 30)	27 (24, 30)	.001	.03
Comorbidities										
CAD	49	56	65	31	<.001	47	60	24	<.001	.001
Acute MI	26	34	39	22	<.001	24	30	12	<.001	<.001
Hypertension	50	55	56	52	.41	48	52	42	<.001	.015
Dyslipidemia	51	49	52	43	.07	52	56	43	<.001	.32
Obesity	27	25	26	23	.53	27	27	26	.66	.43
Diabetes	18	24	29	13	<.001	16	19	12	<.001	<.001
Medications										
β-blockers	46	42	45	35	.05	47	54	34	<.001	.05
CaBlock	20	26	26	26	.95	19	20	16	.10	<.001
ACEInh	18	24	29	11	<.001	16	19	11	<.001	<.001
ARB	25	23	23	23	.96	26	28	23	.02	.19
Diuretics	24	34	35	29	.19	21	19	24	.05	<.001
Vasodilators	20	34	39	22	<.001	16	19	11	<.001	<.001
Lipidlow	54	49	55	34	<.001	55	63	40	<.001	.02
Antiplat	56	60	66	42	<.001	55	67	34	<.001	.10
Antiarrhyth	13	20	23	12	.009	10	10	10	.76	<.001
Psycho	41	45	43	50	.20	40	38	44	.02	.04
Intervention										
PCI	28	28	32	18	.002	28	35	14	<.001	.99
CABG	17	24	30	11	<.001	15	20	6	<.001	<.001
Resting										
HR, bpm	65 (58, 74)	68 (60, 76)	68 (60, 77)	67 (61, 75)	.99	65 (58, 73)	64 (56, 71)	68 (61, 75)	<.001	<.001
SBP, mm Hg	132 (120, 144)	136 (123, 150)	137 (123, 150)	136 (122, 148)	.57	130 (120, 142)	132 (120, 142)	128 (117, 142)	.0006	<.001
DBP, mm Hg	76 (70, 83)	76 (70, 82)	76 (70, 82)	75 (69, 82)	.49	76 (70, 83)	76 (70, 84)	76 (70, 82)	.08	.70
Maximal CPX										
$r\dot{V}o_{2max}$	18 (14, 23)	14 (11, 18)	15 (12, 19)	12 (9, 16)	<.001	19 (15, 24)	21 (17, 26)	16 (13, 20)	<.001	< .001
$p\dot{V}o_{2max}$	25 (21, 29)	21 (18, 25)	22 (18, 26)	21 (19, 25)	.45	26 (23, 30)	27 (23, 31)	26 (22, 29)	.0002	<.001
$\%p\dot{V}o_{2max}$	73 (58, 88)	66 (51, 83)	71 (56, 87)	54 (41, 69)	<.001	74 (60, 90)	81 (67, 97)	64 (53, 77)	<.001	<.001
Sessions, n	52 (18, 172)	55 (19, 178)	64 (19, 210)	46 (19, 163)	.30	50 (18, 171)	53 (20, 182)	46 (16, 150)	.02	.40
≥36 sessions	60	60	62	57	.30	60	61	57	.10	.81
Follow-up, d	3914 (2209, 5755)	2754 (1435, 4120)	2673 (1294, 4055)	2982 (1527, 4191)	.18	4490 2590, 6077)	4340 (2459, 5896)	4797 (2716, 6402)	.0007	<.001

Abbreviations: ACEInh, Angiotensin-converting enzyme inhibitors; Antiarrhyth, antiarrhythmic drugs; Antiplat, antiplatelet drugs; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CaBlock, calcium channel blockers; CAD, coronary artery disease; CPX, cardiopulmonary exercise test; DBP, diastolic blood pressure; HR, heart rate; Lipidlow, lipid-lowering agents; MI, myocardial infarction; PCI, percutaneous coronary intervention; Psycho, psychoactive drugs; $p\dot{V}o_{2max}$, age-predicted maximal oxygen uptake; $\%p\dot{V}o_{2max}$, percentage of age- and sex-predicted maximal oxygen uptake achieved; $r\dot{V}o_{2max}$, maximal oxygen uptake relative to body weight (mL/kg·min); SBP, systolic blood pressure

[a]Data expressed as % or median (IQR).

[b]Between men and women.

[c]Between dead and alive.

Table 3

Survival Probability and 95% CI of Participants Who Were Enrolled in a Medically Supervised Exercise Program in a Brazilian Private Clinic From March 1994 to November 2018 According to Sex and Presence of Coronary Artery Disease

		All Participants		Participants With CAD	
	Total (n = 2236)	Men (n = 1484)	Women (n = 752)	Men (n = 898)	Women (n = 188)
Follow-up	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
1 yr	98.4 (97.8-98.9)	98.0 (97.1-98.6)	99.2 (98.2-99.6)	98.1 (97.0-98.8)	98.4 (95.1-99.5)
5 yr	91.5 (90.2-92.6)	90.7 (89.0-92.1)	92.9 (90.8-94.6)	90.1 (87.9-92.0)	88.8 (83.0-92.7)
10 yr	81.2 (79.4-82.9)	79.3 (76.9-81.5)	85.0 (81.9-87.5)	75.9 (72.6-79.0)	77.9 (69.9-84.0)
15 yr	72.1 (69.7-74.3)	69.3 (66.3-72.0)	77.3 (73.6-80.7)	64.8 (60.6-68.6)	65.2 (55.4-73.4)
20 yr	65.1 (62.1-68.0)	62.2 (58.2-65.9)	70.7 (65.9-74.9)	56.3 (50.6-61.7)	62.9 (52.3-71.8)
24 yr	56.0 (50.2-61.4)	50.2 (41.9-58.0)	64.9 (56.4-72.1)	49.4 (42.0-56.3)	50.3 (25.9-70.5)

Abbreviation: CAD, coronary artery disease.

Table 3 and Figure 1 show the survival probabilities of men and women over the 24 yr of follow-up. Overall, women had better long-term survival than men (HR = 0.70: 95% CI, 0.58-0.85; $P < .001$). When considering only participants with a previous diagnosis of CAD, women and men had similar survival probabilities (HR = 0.90: 95% CI, 0.66-1.24; $P = .53$). However, since women with CAD were slightly older than men with CAD (68 vs 64 yr, respectively; $P < .001$), when adjusting for age, women had a higher survival probability than men (HR = 0.68: 95% CI, 0.49-0.93; $P = .02$) (Figure 2).

Overall, CVD was the leading cause of death (39%), followed by neoplasm (26%) and diseases of the respiratory system (13%). External and ill-defined causes accounted for 3% and 1% of all-cause mortality, respectively (Table 4). With the exception of diseases of the respiratory system, all other causes of death had similar frequencies in men and women. Similar findings were observed when considering only participants with a previous diagnosis of CAD. However, as expected, CVD was more frequently the underlying cause of death in this latter population ($P = .006$).

DISCUSSION

Despite robust evidence of clinical and cost-effectiveness, formal cardiac rehabilitation or clinical exercise-based programs tend to be underutilized worldwide, with participation rates typically ranging from 20 to 50%.[25] Unfortunately, although being a class I recommendation for several heart diseases and/or conditions, due to relevant logistic and economic constrains, globally the vast majority of MSEPs are limited to only 12 wk, strikingly different from our MSEP in which the participants pay a modest fee directly and there is no time limit on length of participation.

In the related literature, participation rates vary greatly according to sex, and unique barriers for women are associated with reduced referral, enrollment, and adherence.[26,27] Accordantly, only a third of the population were women in our study, most likely due to disparities in referral of women to MSEPs. Moreover, as shown by Oosenbrug et al,[14] not only does adherence to exercise programs favors men, but even higher differences in adherence rates between men and women have been reported in the few programs that last >12 wk. This leads to a dearth of morbidity and mortality data available comparing men and women who participate in an exercise program for primary and secondary prevention of CVD. Therefore, given that the present population had a reasonable and similar percentage of adherence to ≥36 sessions between men and women (~60%), including >700 participants with >100 sessions and a long follow-up period (up to 24 yr), it provided an ideal opportunity to evaluate and compare hard outcomes according to sex.

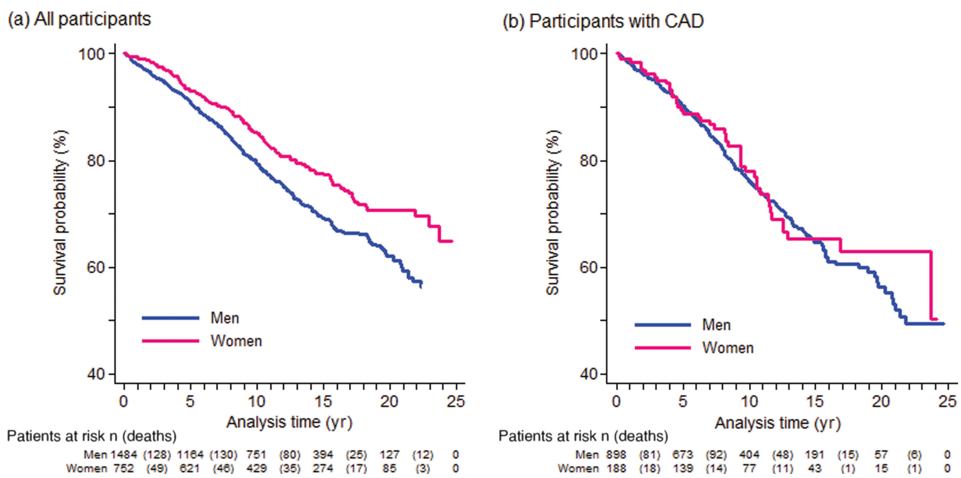

Figure 1. Kaplan-Meier survival probabilities according to sex of (a) all participants ($P < .001$) and (b) participants with coronary artery disease (CAD) ($P = .53$) who were enrolled in a medically supervised exercise program in a Brazilian private clinic from March 1994 to November 2018. This figure is available in color online (www.jcrpjournal.com).

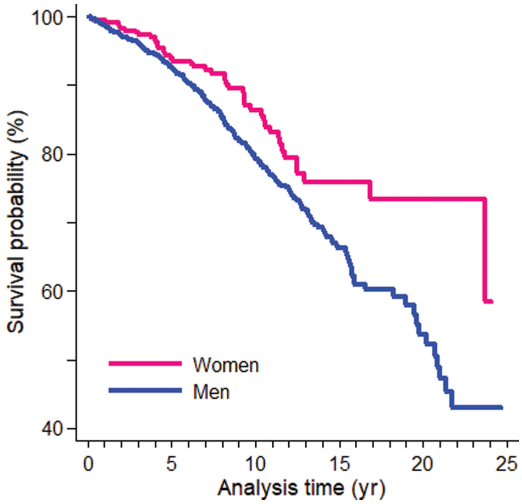

Figure 2. Age-adjusted Kaplan-Meier survival probabilities according to sex of participants with coronary artery disease who were enrolled in a medically supervised exercise program in a Brazilian private clinic from March 1994 to November 2018 ($P = .02$). This figure is available in color online (www.jcrpjournal.com).

Overall, women had higher long-term survival after enrolling in our MSEP compared with men, and there are two potential explanations for this finding. First, women had a better baseline clinical profile than men, particularly a lower prevalence of more serious chronic conditions, such as CAD. Moreover, similar to what is seen globally, in the population of Rio de Janeiro State, women have a longer life expectancy as compared with men.[28] Although the underlying reasons for better survival among women remain incompletely understood, regardless of whether it is due to biological, environmental, social, or behavioral factors, the difference in longevity between sexes is considered one of the more robust features of human biology.[29]

Table 4

Underlying Cause of Death of Participants Who Were Enrolled in a Medically Supervised Exercise Program in a Brazilian Private Clinic From March 1994 to November 2018 According to Sex and Presence of Coronary Artery Disease

Underlying Cause of Death (%)	Total (n = 525)	Men (n = 375)	Women (n = 150)	P Value
All participants				
Cardiovascular disease	39	41	34	.22
Neoplasm	26	28	20	.08
Diseases of the respiratory system	13	11	20	.01
Ill-defined	1	1	2	.40
External causes	3	2	4	.16
Others	18	17	20	.73
	Total (n = 287)	**Men (n = 242)**	**Women (n = 45)**	
Participants with CAD				
Cardiovascular disease	44	45	39	·81
Neoplasm	22	24	12	.11
Diseases of the respiratory system	13	11	21	.04
Ill-defined	2	1	5	.13
External causes	3	3	5	.34
Others	16	16	18	.59

Abbreviation: CAD, coronary artery disease.

Moreover, among participants with a previous diagnosis of CAD and a similar clinical profile, after adjusting for age, women again exhibited better long-term survival than men. Furthermore, it should be underscored that women achieved a lower percentage of sex- and age-predicted $\dot{V}O_{2max}$ at the time of enrollment in the MSEP. Considerable evidence shows that cardiorespiratory fitness (CRF) expressed as $\dot{V}O_{2max}$ or estimated as metabolic equivalents (METs) has a strong and independent association with all-cause mortality in both healthy and unhealthy individuals.[30] Moreover, CRF has been shown to be an even more powerful predictor of mortality risk than traditional risk factors such as hypertension and type 2 diabetes.[31] Therefore, it might be expected that women who were older, had similar clinical profiles, and lower CRF would have a lower long-term survival than men, unless participating in an exercise program provided greater benefits in women compared with men.

Previous studies have addressed outcome differences according to sex in participants of an exercise program with conflicting results. While Cannistra et al[32] observed increases of 20% and 14% in CRF among women and men, respectively, after a 12-wk program of exercise training, and O'Callaghan et al[33] reported 72% and 48% improvements in CRF among women and men with CAD, respectively; after exercise regimens of 3 times/wk for 8 wk, these results did not differ significantly between sex. On the other hand, Sarrafzadegan et al[17] compared pre- and post-clinical profiles of patients with documented CAD who participated in a 24-session exercise program and showed that, while men and women had significant and similar decreases in cholesterol levels, weight, waist and hip circumferences, and an increase in left ventricular ejection fraction, men achieved a higher improvement in estimated METs following training. More recently, using directly measured gas analysis, Rengo et al[34] observed that women experienced a significantly lower improvement in CRF than men (13 vs 17% increase in $\dot{V}O_{2peak}$) after participation in an exercise training program. However, due to a limited number of studies on this topic,[20,35] especially related to mortality outcomes,[19] it remains difficult to draw definitive conclusions in terms of whether the degree of benefit is similar between men and women. Moreover, since a follow-up CPX was not performed in our sample, a definitive conclusion regarding whether the sex differences in mortality observed relates to different responses to exercise training cannot be made. There is a clear need for additional studies designed to clarify this issue, as more extensive information about the benefits of exercise might help providers to better appreciate and promote participation in exercise programs especially among women.[36,37]

Regarding causes of death, several results were notable. First, the percentage of deaths attributable to CVD was higher in our sample than what has been observed in the Brazilian general population and in other countries, regardless of sex and history of CAD. While 39% of the participants in our MSEP died of CVD, approximately 30% and 25% of the Brazilian and US populations have CVD as their underlying cause of death, respectively.[38] This might be explained by the fact that CVD and/or cardiac risk factors are still the main reasons to referral to an MSEP,[25] and thus our sample was biased. In addition, we found a low rate of ill-defined causes of death (1.5%), similar to that seen in the United States (1.2%) but lower than that reported in Brazil (5.8%).[39] Our MSEP is carried out in a privately owned clinic that has a monthly fee, which is higher than the average minimum wage in Brazil. This undoubtedly reflects a higher socioeconomic status and educational level in our MSEP participants in comparison to the general population of Brazil, and therefore they had better access to health care.

Finally, it is important to highlight some peculiarities of this study. First, as stated earlier, more than half of our sample participated in the MSEP for a longer time than what is usually observed in similar North American and European rehabilitation programs. According to the National Heart, Lung, and Blood Institute,[40] Medicare and most insurance plans only cover a standard MSEP that includes 36 sessions over 12 wk. As the patients from the present study made payments out-of-pocket, there is not a maximal number of sessions or time one could participate in this particular MSEP. In practical terms, the majority of the study sample attended a higher number of exercise sessions that are usually prescribed in North American and European programs, including a few participants with > 1000 sessions over > 20 yr.

Some limitations of this study should also be pointed out. Inherent to observational studies, potential selection bias might have influenced some of our findings, especially regarding differences in baseline clinical profiles. Therefore, as discussed earlier, a subanalysis with men and women with CAD that had similar baseline characteristics was performed, diminishing the possibility that these features might have contributed to our survival results particularly in CAD participants. Moreover, since the MSEP was conducted in a privately owned clinic, this undoubtedly influenced socioeconomic and ethnic status, which might limit the generalizability of the results to other MSEP populations. Lastly, smoking status was not included in the analysis of our study. However, since only 1-2% of the participants from our MSEP reported being current smokers during their baseline assessment, it is unlikely that this risk factor might have influenced the study results.

CONCLUSION

In summary, underlying causes of death were similar between sexes, but long-term survival among MSEP participants was better among middle-aged/older women compared with men, even though women had lower sex- and age-predicted CRF at baseline. Future studies should address further the extent to which men and women differ in response to participation in a long-term MSEP.

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REFERENCES

1. World Health Organization. *World Health Statistics Overview 2019: Monitoring Health for the SDGs, Sustainable Development Goals*. Geneva, Switzerland: World Health Organization; 2019
2. Carter HE, Schofield D, Shrestha R. Productivity costs of cardiovascular disease mortality across disease types and socioeconomic groups. *Open Heart*. 2019;6(1):e000939.
3. Benjamin EJ, Muntner P, Alonso A, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56-528.
4. Goertzen L, Halas G, Rothney J, et al. Mapping a decade of physical activity interventions for primary prevention: a protocol for a scoping review of reviews. *JMIR Res Protoc*. 2015;4(3):e91.
5. Franklin BA, Brubaker P, Harber MP, Lavie CJ, Myers J, Kaminsky LA. The *Journal of Cardiopulmonary Rehabilitation and Prevention* at 40 yr and its role in promoting preventive cardiology: part 2. *J Cardiopulm Rehabil Prev*. 2020;40(4):209-214.
6. Franklin BA, Thompson PD, Al-Zaiti SS, et al. Exercise-related acute cardiovascular events and potential deleterious adaptations following long-term exercise training: placing the risks into perspective-an update: a scientific statement from the American Heart Association. *Circulation*. 2020;141(13):e705-e736.
7. MacDonald CS, Johansen MY, Nielsen SM, et al. Dose-response effects of exercise on glucose-lowering medications for type 2 diabetes: a secondary analysis of a randomized clinical trial. *Mayo Clin Proc*. 2020;95(3):488-503.
8. Tian D, Meng J. Exercise for prevention and relief of cardiovascular disease: prognoses, mechanisms, and approaches. *Oxid Med Cell Longev*. 2019;2019:3756750.
9. Jeong SW, Kim SH, Kang SH, et al. Mortality reduction with physical activity in patients with and without cardiovascular disease. *Eur Heart J*. 2019;40(43):3547-3555.
10. Groot C, Hooghiemstra AM, Raijmakers PG, et al. The effect of physical activity on cognitive function in patients with dementia: a meta-analysis of randomized control trials. *Ageing Res Rev*. 2016;25:13-23.
11. Edwards S. Physical exercise and psychological well-being. *S Afr J Psychol*. 2006;36(2):357-373.
12. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477.
13. Sanghavi M, Gulati M. Sex differences in pathophysiology, treatment and outcomes in IHD. *Curr Atheroscler Rep*. 2015;17(6):511.
14. Oosenbrug E, Marinho RP, Zhang J, et al. Sex differences in cardiac rehabilitation adherence: a meta-analysis. *Can J Cardiol*. 2016;32(11):1316-1324.
15. Marzolini S, Colella TJF. Factors that predispose women to greater depressive symptoms a sex- age- and diagnosis matched cardiac rehabilitation cohort. *Can J Cardiol*. 2021;37(3):382-390.
16. Hyun K, Negrone A, Redfern J, et al. Gender difference in secondary prevention of cardiovascular disease and outcomes following the survival of acute coronary syndrome. *Heart Lung Circ*. 2021;30(1):121-127.
17. Sarrafzadegan N, Rabiei K, Kabir A, et al. Gender differences in risk factors and outcomes after cardiac rehabilitation. *Acta Cardiol*. 2008;63(6):763-770.
18. Vilela EM, Ladeiras-Lopes R, Joao A, et al. Differential impact of a cardiac rehabilitation program in functional parameters according to patient gender. *Am J Cardiovasc Dis*. 2020;10(4):367-375.
19. Ghisi GLM, Chaves GSDS, Bennett A, Lavie CJ, Grace SL. The effects of cardiac rehabilitation on mortality and morbidity in women: a meta-analysis attempt. *J Cardiopulm Rehabil Prev*. 2019;39(1):39-42.
20. Araújo CG, Castro CL, Franca JF, Araujo DS. Sitting-rising test: sex- and age-reference scores derived from 6141 adults. *Eur J Prev Cardiol*. 2020;27(8):888-890.
21. Araújo CG. Flexibility assessment: normative values for Flexitest from 5 to 91 years of age. *Arq Bras Cardiol*. 2008;90(4):257-263.
22. Araújo CG, Castro CLB, Franca JF, Ramos PS. 4-second exercise test: reference values for ages 18-81 years. *Arq Bras Cardiol*. 2015;104(5):366-374.
23. Araújo CG, Castro CL, Franca JF, de Souza e Silva CG. CLINIMEX aerobic fitness questionnaire: proposal and validation. *Int J Cardiovasc Sci*. 2019;32(4):331-342.
24. Jones NL, Campbell EK, Edwards RH, Robertson DG. *Clinical Exercise Testing*. Philadelphia, PA: WB Saunders; 1975.
25. Supervia M, Turk-Adawi K, Lopez-Jimenez F, et al. Nature of cardiac rehabilitation around the globe. *EClinicalMedicine*. 2019;13:46-56.
26. Supervía M, Medina-Inojosa JR, Yeung C, et al. Cardiac rehabilitation for women: a systematic review of barriers and solutions. *Mayo Clin Proc*. 2017;S0025-6196(17)30026-5.
27. Gaalema DE, Savage PD, Leadholm K, et al. Clinical and demographic trends in cardiac rehabilitation: 1996-2015. *J Cardiopulm Rehabil Prev*. 2019;39(4):266-273.
28. Instituto Brasileiro de Geografia e Estatítica (IBGE). Tábua completa de mortalidade para o Brasil—2015: Breve análise da evolução da mortalidade no Brasil. www.ibge.gov.br. Accessed May 23, 2017.

29. Austad SN, Fischer KE. Sex differences in lifespan. *Cell Metab*. 2016;23(6):1022-1033.
30. Ross R, Blair SN, Arena R, et al. Importance of assessing cardiorespiratory fitness in clinical practice: a case for fitness as a clinical vital sign: a scientific statement from the American Heart Association. *Circulation*. 2016;134(24):e653-e699.
31. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis*. 2015;57(4):306-314.
32. Cannistra LB, Balady GJ, O'Malley CJ, Weiner DA, Ryan TJ. Comparison of the clinical profile and outcome of women and men in cardiac rehabilitation. *Am J Cardiol*. 1992;69(16):1274-1279.
33. O'Callaghan WG, Teo KK, O'Riordan J, Webb H, Dolphin T, Horgan JH. Comparative response of male and female patients with coronary artery disease to exercise rehabilitation. *Eur Heart J*. 1984;5(8):649-651.
34. Rengo JL, Khadanga S, Savage PD, Ades PA. Response to exercise training during cardiac rehabilitation differs by sex. *J Cardiopulm Rehabil Prev*. 2020;40(5):319-324.
35. Eijsvogels TMH, Maessen MFH, Bakker EA, et al. Association of cardiac rehabilitation with all-cause mortality among patients with cardiovascular disease in the netherlands. *JAMA Netw Open*. 2020;3(7):e2011686.
36. Yoo BW, Wenger NK. Gender disparities in cardiac rehabilitation among older women: key opportunities to improve care. *Clin Geriatr Med*. 2019;35(4):587-594.
37. Galati A, Piccoli M, Tourkmani N, et al. Cardiac rehabilitation in women: state of the art and strategies to overcome the current barriers. *J Cardiovasc Med (Hagerstown)*. 2018;19(12):689-697.
38. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet*. 2017;390(10100):1151-1210.
39. Pan American Health Organization. Ill-defined and unknown causes of death. www.paho.org. Accessed December 4, 2019.
40. US Department of Health & Human Services. National Heart, Lung and Blood Institute. www.nhlbi.nih.gov. Accessed November 2, 2019.