Functional Capacity in Men and Women
Following Cardiac Rehabilitation

By
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Date

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Date
Abstract

Nearly one in three Americans suffers from cardiovascular disease (CVD), which is responsible for over 850,000 U.S. deaths each year. Cardiac rehabilitation (CR) is an effective treatment for CVD; CR involves multifaceted interventions of supervised exercise, dietary modifications, and counseling. Based on previous research, which is confirmed by this paper’s systematic review, CR is effective at improving patients’ functional capacity. Although women represent over half of CVD patients, there is surprisingly little known about the comparative effectiveness of CR in men and women. This master’s paper seeks to determine whether CR is equally effective at improving functional capacity, as determined by maximal metabolic equivalents (METs) achieved in men and women. The research is based upon data between 2001 to 2011 from the University of North Carolina health Care Cardiac Rehabilitation Program at Meadowmont. Based on de-identified records from 680 CR participants (189 women; 491 men), CR does seem to be somewhat more effective in men than in women. Specifically, adjusting for potential confounders, men achieved an average improvement of 2.15 METs after CR and women achieved an average improvement of 1.61 METs. It is unclear why men benefit more from CR than do women; these results, however, imply that tailoring cardiac rehabilitation programs to women may yield further improvement in functional capacity for female participants.
Acknowledgements

I would like to thank my advisor, Dr Tolleson-Rinehart, for patiently guiding and mentoring me throughout this process. I would also like to thank my second reader, Dr Paula Miller, for generously offering her time and expertise. I appreciate the support of all the faculty in the UNC Health Care and Prevention program. And I am very grateful to Betty Matteson, Rebecca Rodriguez, and all of the staff at UNC Meadowmont for making this research possible.
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Introduction

Nearly one in three Americans suffers from cardiovascular disease (CVD), which is responsible for over 850,000 American deaths each year.\(^1\) In fact, fully 35% of American deaths each year are due to CVD.\(^2\) Although cardiovascular disease is often considered a disease of men, over half of CVD patients in the U.S. are women, and over half of CVD-related deaths in the U.S. occur in women.\(^3\)

Cardiac rehabilitation (CR) is an effective CVD treatment.\(^4\) CR involves multifaceted interventions of supervised exercise, diet modification, and counseling, as well as education on the cardiovascular disease process, medications, and returning to a normal life. Cardiac rehabilitation has been endorsed by a wide array of medical organizations, including the American College of Cardiology Foundation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the American Heart Association.\(^5\) Still, according to the Agency for Healthcare Research and Quality (AHRQ), fewer than 30% of eligible patients participate in CR after a CVD event,\(^6\) and AHRQ reports that the rate of CR referral for female patients is particularly low.\(^6\)

Despite the general effectiveness of CR and the prevalence of CVD in women, surprisingly few studies examine the effectiveness of CR in women. Only five studies have been published on the effectiveness of CR in women over the last twenty years. The authors of these studies are Cannistra et al., Ades et al., Lavie et al., O’Farrell et al., and Gupta et al. These authors show that cardiac rehabilitation does provide benefit to women.\(^7\)\(^-\)\(^11\) The degree of benefit,
however, is largely unclear. Of the five studies above, three did not assess intergroup p values, so it is impossible to determine whether differences between men and women are statistically significant in these studies.\textsuperscript{7,9} O’Farrell, Murray, Huston, et al.’s and Gupta, Sanderson, and Bittner’s are the only two studies examining intergroup p values; both showed greater improvement in post-CR functional capacity for men than for women. However, while Gupta, Sanderson, and Bittner found statistically significant differences between men and women, O’Farrell, Murray, Huston et al did not.\textsuperscript{10,11} Given the lack of clarity on this point, our research seeks to address the question of whether CR is actually more effective in men than in women.

Briefly, our findings suggest that men benefit more from cardiac rehabilitation than do women; we will discuss this at greater length in the Results Section of this paper. A secondary question is why men benefit more from CR: is the difference a result of innate biological differences between the sexes, a consequence of learned, behavioral, and perhaps societal differences, or simply a result of cardiac rehabilitation programs that have been preferentially designed for male participants? We will review this question at greater length in the Discussion Section as we examine ways to tailor cardiac rehabilitation to better meet women’s needs.
Methods

Population

Our research uses University of North Carolina (UNC) Health Care System Cardiac Rehabilitation Program participant data, from 2001 through 2011. The UNC Program receives referrals from unaffiliated private providers as well as from providers within the UNC system. Program participants come from five different counties, with the majority (over 56%) of participants from Orange County, where the University and Program are located. Approval for this research was obtained from the UNC IRB.

We only included CR participants with both baseline and completion data for the outcome of maximal metabolic equivalents (METs) achieved. This yielded exactly 900 participant records. We excluded 133 records of patients referred to CR for nonischemic diagnoses, and we eliminated another 77 records for which independent variable data were missing. This yielded a total of 680 participants’ data for analysis.

Cardiac Rehabilitation Program

The UNC Health Care Cardiac Rehabilitation Program is an outpatient-based cardiac rehabilitation program. In line with CR standards, the program includes supervised exercise, dietary education, and counseling. Cardiac rehabilitation participants are encouraged to attend three CR sessions per week for a period of three months, which amounts to thirty-six total sessions. This is consistent with the number of total sessions (typically between 24 and 36) in most other cardiac rehabilitation programs.
Statistical Analysis

This retrospective observational analysis uses de-identified participant data. The outcome measure is absolute change in maximal metabolic equivalents (METs) achieved. This measure is assessed at baseline (with the initial measurement taken 1 to 2 weeks before initiation of exercise in the cardiac rehabilitation program) and upon Program completion (with the final measurement actually taken between 2 and 10 days prior to the end of CR training). METs are expressed in the units of mL O$_2$/kg/min.$^{14}$ METs achieved “is considered the best measure of cardiovascular fitness and exercise capacity,” according to the American Heart Association.$^{15}$ (p1695)

The main independent variable is the sex of each participant. Other independent variables include age, race, body mass index (BMI), zip code prosperity, total cholesterol at baseline, and primary referral diagnosis. “Zip code prosperity” is a proxy measure of respondents’ relative affluence; we identified each participant’s residential zip code and then calculated each zip code’s average income by dividing the zip code’s total adjusted gross income by its total number of returns, based on 2008 IRS data.$^{16}$ We assessed the relationship of each of these independent variables (measured at program initiation) to both the primary independent variable (sex) as well as the outcome of interest (absolute change in METs). We ran an analysis of covariance model to show the relationship between sex and absolute change in METs, adjusting for all appropriate covariates listed above. All statistical analyses were performed using STATA 12.0 Reported p-values are two-sided; a p-value of <0.05 is considered to indicate statistical significance.
Results

Sample Characteristics and Sex-Based Subgroup Analysis

A total of 680 participants were included. Women were 27.8% of all participants (189 women) and men made up the remaining 72.2% (491 men) of the sample (Table 1). Given the research question, we closely assessed demographic/baseline differences between male and female participants (Table 1). The covariates of race, CR referral indication, and baseline cholesterol were significantly different in male and female participants. Fully 15.9% of female participants were black while only 5.5% of male participants were black (p< 0.001). Cardiac rehabilitation referral indications also showed a significant difference between men and women. Medicare and most private insurances will cover CR for just six diagnoses. The covered ischemic heart disease (IHD) diagnoses include stable angina, myocardial infarction (MI), percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG). The two covered non-ischemic diagnoses are valve replacement and heart transplant. A higher percentage of women (36.5%) compared with men (21.8%) were enrolled in CR because of a previous cardiac intervention (either PCI or CABG). In contrast, a higher percentage of men (31.4%) than women (19.1%) were enrolled in CR due only to anginal symptoms. It is unclear why this difference should exist; the difference itself implies that women in CR may suffer from more severe cardiac disease than do men. Women also had higher average cholesterol levels at baseline (178 mg/dL) than did men (160 mg/dL). In our model, we adjusted for all significant covariate differences. We found no statistically significant difference by sex for other variables such as age, body mass index (BMI), and zip code prosperity level.
Table 1

Demographic & Baseline Health Characteristics - by Sex

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
<th>Average</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants by Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent (%)</td>
<td>27.8</td>
<td>72.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>189</td>
<td>491</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>65.8</td>
<td>65.1</td>
<td>65.4</td>
<td>0.506</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian (%)</td>
<td>2.1</td>
<td>1.0</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Black (%)</td>
<td>15.9</td>
<td>5.5</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>Hispanic (%)</td>
<td>2.1</td>
<td>1.6</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>79.4</td>
<td>89.2</td>
<td>86.5</td>
<td></td>
</tr>
<tr>
<td>Other (%)</td>
<td>0.5</td>
<td>2.7</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Home Zip Code</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg Income ($/yr)</td>
<td>82,300</td>
<td>86,000</td>
<td>85,000</td>
<td>0.127</td>
</tr>
<tr>
<td>CR Referral Indication</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stable Angina (%)</td>
<td>19.1</td>
<td>31.4</td>
<td>27.9</td>
<td></td>
</tr>
<tr>
<td>*MI (%)</td>
<td>44.4</td>
<td>46.8</td>
<td>46.2</td>
<td></td>
</tr>
<tr>
<td>**PCI (%)</td>
<td>20.1</td>
<td>14.9</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>***CABG (%)</td>
<td>16.4</td>
<td>6.9</td>
<td>9.6</td>
<td></td>
</tr>
<tr>
<td>****BMI (kg/m^2)</td>
<td>29.1</td>
<td>28.4</td>
<td>28.5</td>
<td>0.128</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>prior to CR</td>
<td>178</td>
<td>160</td>
<td>165</td>
<td></td>
</tr>
</tbody>
</table>

* MI = myocardial infarction
**PCI = percutaneous coronary intervention
***CABG = coronary artery bypass grafting
****BMI=body mass index

SOURCE: Data collected by first author from UNC Health Care System Meadowmont Cardiac Rehabilitation Program
Relationship Between the Outcome of MET Change and the Analyzed Covariates

The primary research outcome, as discussed previously, is absolute change in METs, the AHA standard indicator for CR success. This measure was used to evaluate participants’ functional capacity. Apart from the main independent variable of sex, several other independent variables showed a statistically significant relationship to the outcome variable of MET change. CR referral indication and baseline BMI showed statistically significant associations with change in METs. Age and race also appeared to be associated with MET change, although these associations did not reach statistical significance. Those participants with a history of stable angina tended to show the greatest absolute improvement in METs (2.37 mL O$_2$/kg/min increase) while those post-CABG tended to show the least (1.79 mL O$_2$/kg/min increase). Participants referred for the other two ischemic CR indications (of MI and PCI), meanwhile, showed a degree of improvement somewhere in between (Table 2). Those with a higher BMI tended to show less improvement in METs compared to those with a lower BMI. Specifically, for every increase of 5 kg/m$^2$ in BMI, participants showed an average 0.23 ml O$_2$/kg/min less improvement in METs. Although age and race did not reach statistical significance, younger patients and Caucasians (compared to Blacks) did tend to show greater improvement in METs after CR. The small numbers of Asians and Hispanics present in the data made it difficult to assess the effect of CR in these groups.
### Table 2

**Relationship of Demographic/Baseline Variables To Absolute Change in METs**

<table>
<thead>
<tr>
<th>ABSOLUTE Met Change</th>
<th>Beta Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.010</td>
<td>0.060</td>
</tr>
<tr>
<td>Home Zip Code</td>
<td>0.00314</td>
<td>0.151</td>
</tr>
<tr>
<td>Avg Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.045</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total Chol</td>
<td>0.0025</td>
<td>0.086</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Average ABSOLUTE Met Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2.08</td>
</tr>
<tr>
<td>Black</td>
<td>1.73</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.98</td>
</tr>
<tr>
<td>Caucasian</td>
<td>2.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CR Referral Indication</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Angina</td>
<td>2.37</td>
</tr>
<tr>
<td>* MI</td>
<td>1.81</td>
</tr>
<tr>
<td>**PCI</td>
<td>2.05</td>
</tr>
<tr>
<td>***CABG</td>
<td>1.79</td>
</tr>
</tbody>
</table>

* MI = myocardial infarction  
**PCI = percutaneous coronary intervention  
***CABG = coronary artery bypass grafting

**SOURCE:** Data collected by first author from UNC Health Care System Meadowmont Cardiac Rehabilitation Program
**Relationship Between the Outcome of MET Change and Sex**

Men achieved a greater improvement in absolute METs than did women (Table 3). We evaluated other variables including age, race, BMI, baseline cholesterol, baseline METs, CR indication, and zip code prosperity on the relationship between sex and MET improvement and eliminated variables showing no effect at the simple bivariate level. Our final model adjusted only for baseline METs and CR indication. The adjusted absolute MET improvement for women was 1.59 METs; the improvement for men was 2.16 METs, a 36% difference between men and women that is significant at the $p < 0.0001$ level, even with the relatively smaller number of women in the data set (Table 3).
## Table 3

### Absolute Change in METs after Cardiac Rehabilitation - by Sex

<table>
<thead>
<tr>
<th>Maximal METs Achieved Before CR Initiation</th>
<th>Maximal METs Achieved - After Completion of CR (3 Months)</th>
<th>Absolute Change in METS (95% CI)</th>
<th>Intergroup P Value</th>
<th>Absolute Change in METS (95% CI)</th>
<th>Intergroup P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td>UNADJUSTED</td>
<td></td>
<td>UNADJUSTED</td>
<td>ADJUSTED*</td>
</tr>
<tr>
<td>7.02</td>
<td>8.63</td>
<td>1.61 (1.38 to 1.85)</td>
<td>0.0001</td>
<td>1.59 (1.35 to 1.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td>2.15 (2.01 to 2.29)</td>
<td></td>
<td>2.16 (2.02 to 2.30)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for appropriate Table 1 covariates; CR Referral Dx and Maximal METs Achieved Prior to CR

**SOURCE:** Data collected by first author from UNC Health Care System Meadowmont Cardiac Rehabilitation Program
Discussion

Our findings support previous research\textsuperscript{7-9} showing that cardiac rehabilitation enhances functional capacity for both men and women. Our research’s important contribution is its additional clarification of CR’s differential effects in men and women. The uncertainty of sex effects has arisen from the divergent findings of Gupta, Sanderson and Bittner on one hand and O’Farell, Murray, Huston, et al. on the other.\textsuperscript{10,11} Again, Gupta et al. found a statistically significant difference between men and women while O’Farell et al. did not. Part of the reason for their different findings and conclusions may be the different confounders considered by each as well as the different outcomes each group measured. Gupta et al. adjust for participant age, race, and baseline functional capacity; O’Farrell et al. do not adjust for any potential confounders. Gupta et al. use 6 Minute Walk Test (6 MWT) to assess functional capacity while O’Farrell et al. use METs achieved during maximal exertion. As discussed earlier, METs achieved is the preferred measure, according to the AHA.\textsuperscript{15} While Gupta et al’s study more effectively adjusts for confounders, O’Farrell et al’s uses the better measure of functional capacity. Given these differences between Gupta et al.’s and O’Farrell et al.’s studies, one could not conclude that cardiac rehabilitation provided greater benefits to men than to women. We found that, after adjusting for confounders and using the preferred measure of METs achieved, men still experience a greater improvement in functional capacity following CR than do women (Table 3). In addition to being statistically significant, this difference of 0.57 METs or 36\% is likely to be clinically significant as well.

Our analysis has several limitations. First, our research was specifically designed to assess functional capacity. We used the measure of absolute change in METs achieved (Of note, although this measure of absolute change in METs is very common, some other studies have
instead reported percent change in METs achieved. It is unclear which measure is more accurate for measuring sex differences in functional capacity.\textsuperscript{7-9} Besides functional capacity, other patient-oriented outcomes are quality of life, recurrent cardiac events, and cardiac mortality. All of these important outcome measures are beyond the scope of this analysis.

A second limitation is that we assessed the measure of METs achieved at only two time points, program initiation and program completion. Using these time points demonstrates the short-term effect of CR; however, extending measurement beyond program completion could help demonstrate whether improvement persists. In addition, we limited participants to those with MET measurements at both program initiation and completion. Those who failed to complete the Program, for example, were excluded from analysis, and it is unclear whether excluded patients differed in some ways from included patients.

A third limitation is that this analysis uses retrospective observational data from a single outpatient-based CR program. Thus, the participant population in this program may not be entirely reflective of the cardiac rehabilitation population at large. Also, the specific UNC CR Program protocol may differ slightly from those of other CR programs. It is unlikely, however, that the UNC Program protocol is significantly different from other programs’ protocols, as the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) requires that all CR programs use standard guidelines to receive accreditation.

Our analysis has several strengths. First, our data set includes 680 program participants; this is more than the number of participants in any other similar study. Second, our assessment of the relationship between sex and post-CR functional improvement considers a wide array of possible confounders. Prior studies have evaluated confounders such as age, race, BMI, and
baseline METs. To our knowledge, however, our research is unique in evaluating CR referral diagnosis and zip code prosperity; these indicators of cardiovascular disease and socioeconomic advantage are important contributors to overall health status. A third strength of our research is that it uses the standard measure of “METs achieved”\(^{15}\) to evaluate functional capacity.

Our finding that men benefit more from CR than do women do raises the question of whether tailoring CR programs to women may result in their greater functional improvement. It is not immediately clear, however, how best to tailor CR and its various components (supervised exercise, dietary instruction, and counseling) to female participants. One component of CR is supervised exercise; researchers have noted that women experience unique barriers to exercise, including social stigma against over-exertion and a high prevalence of co-morbidities (such as arthritis, osteoporosis, and exercise-induced urinary incontinence) that can complicate engaging in exercise programs.\(^{17}\) It is important to take these issues into account when tailoring CR exercise programs; as a first step, studies have shown that female-only CR cohorts may be more effective than are co-ed groups.\(^{18}\) The second component of CR is dietary modification; research has shown that women are better at making heart healthy dietary changes following CR.\(^{11}\) It is thus unlikely that tailoring the dietary component of CR to women would yield significant gains, although this might be an area in which CR programs could be improved for men. The third component of CR is counseling; studies have shown that women typically experience higher levels of depression and lower self-efficacy for positive change following a cardiac event.\(^{18,19}\) Beckie and Beckstead’s research has shown that tailoring CR counseling to women may prove quite effective.\(^{18}\) Thus, based on the results of previous studies by various researchers, modifying both the exercise and counseling components of CR appears to hold great promise. Our findings, moreover, show a real difference in functional improvement following CR between men and
women. Our research thus demonstrates genuine potential for further studies on how to tailor CR to better meet female participants’ needs.

The first question related to improving CR practice and policy is how to encourage more and better research on tailoring CR programs to women; the second question is how to translate that research into practice. Consistent with the National Institutes of Health (NIH) Revitalization Act of 1993, the NIH has adopted some measures to encourage research on women’s health. However, enforcement of the Act has often been inconsistent. According to Institute of Medicine recommendations, the NIH needs to be more strict in enforcing rules governing women’s health research. To spur research in the area, the NIH might even consider offering grants specifically dedicated to female-centered CR research.

The next challenge is to translate the results of this research into practice. The NIH could help bridge this gap between research and practice by providing cardiac rehabilitation programs with the results of successful women-centered research studies. The Centers for Medicare and Medicaid Services (CMS) and other public and private payers could further encourage the implementation of evidence-based women-tailored cardiac rehabilitation programs by offering financial incentives to those Centers that adopt and implement these programs. This process of encouraging women-tailored research and translating this research to application carries considerable challenges. At the same time, given the significant potential benefits, the process of tailoring CR programs to women also carries great promise.
Appendix 1: History of Women’s Health Research

Background

Historically, women have been under-represented as study participants in clinical trials and particularly in cardiovascular research. Within cardiovascular disease, the topic of cardiac rehabilitation for women has been particularly neglected. The National Institute of Health’s (NIH) Office of Research on Women’s Health (ORWH) issued a report in 2010 entitled “A Vision for 2020 for Women’s Health Research” which specifically noted the need for “clinical practice studies” devoted to “women-centered cardiac rehabilitation.” Similarly, the American Heart Association stated in 2005 that “randomized trials are needed to better define the role of exercise therapy [such as cardiac rehabilitation] for … specific subgroups of CVD patients, particularly females.”

The Women’s Movement and Women’s Health Research

There is a clear need for further attention to certain women’s health topics, and there are still significant challenges to achieving sex-based equality in clinical research. At the same time, the mere fact that prominent organizations such as the AHA and the NIH’s ORWH are both focusing on and systematically assessing disparities in women’s health research represents real progress; this progress, though still incomplete, is built upon several decades of social, political, and policy-level change.

The Women’s Movement of the 1960s, 70s, and 80s focused on both equality at work and home as well as reproductive/medical rights and served to set the stage for the equality
movement in women’s health research. Bernadine Healy, former director of the NIH, connected feminism to this new women’s health movement by calling the new movement to “acknowledge that [women are biologically] different from men” the third stage of feminism. Some social scientists such as Steven Epstein assert that the women’s health movement is actually “post-feminist” because it is a byproduct of “previous feminist struggles.” In either view, this movement towards greater attention to women’s health developed in a context created by earlier feminist activism and new scholarly and policy analysis.

Task Force on Women’s Health

In 1983, as the second wave of the Women’s Movement was waning in many ways, the US Assistant Secretary of Health and former Surgeon General, Edward Brandt, created the Task Force on Women’s Health Issues “to identify those women’s health issues that are important in our society today.” He explained that he believed the Task Force was necessary largely due to the changing roles and responsibilities of American women who are now “involved in a spectrum of activities today that were barely discernible on yesterday’s horizon.” The circumstances leading up to Brandt’s appointment of the Task Force are beyond the scope of the present essay, but it is clear that the Task Force’s Report drew national attention to the issue of women’s health. The Task Force Report, moreover, asserted that the lack of women’s health research seriously compromised the quality of women’s health care. This criticism would lead to several further but gradual steps towards equality in health research over the course of the next decade.
The first step was the NIH’s creation of the Advisory Committee on Women’s Health Issues in 1985 to evaluate implementation of the Task Force’s recommendations. In 1986, the Committee attempted to advance women’s health research by strongly encouraging NIH grant applicants to include women in their research study populations. Unfortunately, the Committee had little real authority, and it was unclear whether there was any real improvement in the inclusion of women in clinical research. Several groups including the Congressional Caucus for Women’s Issues and the Society for Women’s Health Research pressured the government to evaluate the inclusion of female subjects in NIH research. As a result, the Government Accounting Office (GAO) was commissioned to evaluate the situation, and the GAO’s 1990 Report frankly stated that the “National Institutes of Health has made little progress in implementing its policy to encourage the inclusion of women in research study populations.”

Reacting to the GAO’s assessment, the NIH created the Office of Research on Women’s Health (ORWH) just two months later in September of 1990. The Office was expressly designed to “ensure that previously articulated NIH policies to support research on women’s health issues” were followed and to “ensure that women are appropriately represented in biomedical and behavioral research studies supported by NIH.” While the creation of the ORWH within the NIH represented a positive development, the ORWH still lacked the explicit authority to enforce policies. As such, the ORWH would continue to have real difficulty effecting any meaningful change for the next several years.
National Institutes of Health Revitalization Act

To promote women’s health research and provide the Office of Research on Women’s Health with greater authority, Congress crafted and debated various pieces of legislation over the next several years. The first proposed piece of legislation was the NIH Revitalization Act of 1990, which failed to pass the House. The second proposed piece of legislation was the NIH Revitalization Act of 1991, which passed the House and Senate only to be stopped at the hand of then President George H.W. Bush. Finally, in January 1993, Massachusetts Senator Edward Kennedy introduced a modified version of the initial Act, called the NIH Revitalization Act of 1993. This new Act both ensured the inclusion of women and minorities in NIH sponsored research and reaffirmed the creation of the Office of Research on Women’s Health by the NIH. Specifically, the Act provided the ORWH with clear responsibilities and powers to “ensure that women are included as subjects in each project of [clinical, NIH funded] research.”

Interestingly, this part of the Act was not particularly contentious. Several other provisions of the Act, however, were hotly debated; ultimately, the only significant change to the Act was the Nickles Amendment, which prevented HIV positive immigrants from entering the country. The Revitalization Act of 1993, with only minor modification, successfully passed through Congress in May 1993 and would later be signed into law on June 10th 1993 by then President Bill Clinton.

In July of 1993, just a month after the passage of the NIH Revitalization Act, the NIH issued guidelines that required grantees to not only include female subjects but also analyze and report outcomes by sex. This requirement would help evaluate whether various interventions, from surgery to medications to CR, were equally effective in male and female patients. Although
issued in 1993, the NIH Revitalization Act and these guidelines only went into effect a year later on July 1, 1994.\textsuperscript{25}

**Food and Drug Administration and the Office of Women’s Health**

It is important to note that we, thus far, have focused on the NIH and the NIH’s ORWH; in 1994, the Food and Drug Administration (FDA) created its own Office of Women’s Health through an agency ruling. The OWH is responsible for funding research on “women’s conditions and diseases” and for “encouraging industry to include women in their clinical trials.”\textsuperscript{36} (para 25) Of note, the OWH in 2012 received just $6 million of funding, significantly less than ORWH’s $42.3 million.\textsuperscript{37} (para 4) In addition, the OWH is only able to encourage the drug industry to include women in clinical trials, which are ultimately funded by pharmaceutical companies; the ORWH, on the other hand, has a clear statutory mandate to ensure that NIH funded research studies adequately address women’s health issues. In theory, therefore, the ORWH has significantly greater influence over the direction of NIH research than the OWH has over the direction of pharmaceutical research. After the founding of the OWH in 1994, several years would pass before the next government ruling on women’s health research.

**2001 Clarifying NIH Guidelines on Women’s Health Research**

In 2001, the NIH issued the “NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research.”\textsuperscript{38} This statement served to clarify the details of what constitutes a clinical study and what specific sex-based analysis and reporting are required of NIH funded studies.\textsuperscript{38} In these guidelines, the NIH explicitly stated that research analysis must analyze and report the effects of an intervention by sex.\textsuperscript{38} This 2001 guideline represents the final
clarification statement for the NIH Revitalization Act; following its release, there have been no official changes or modifications to the national policy on women’s health research.

**Effect of Agencies, Rulings, and Legislation on Women’s Health Research**

We have discussed the laws, policies, and organizations established to direct women’s health research. We turn now to the question of how these changes have affected the actual practice of women’s health research. It is important to note, from the beginning, that the answer is quite nuanced and complicated. Various groups both within and outside of the government have reached differing conclusions about this question. These groups include the Department of Health and Human Services (HHS), the General Accounting Office (GAO; known since 2004 as the Government Accountability Office), and the Institute of Medicine (IOM). HHS and GAO both operate within the federal government; HHS includes the NIH, Center for Disease Control (CDC), and many other health-related federal agencies; the GAO is an independent government agency that monitors the use of federal moneys. The IOM, on the other hands, is a non-profit organization, separate from the government. Interestingly, each of these groups paints a somewhat different picture of the current state of women’s health research. Although the Department of Health and Human Services (HHS) focuses on the progress made, the Institute of Medicine highlights the persistent shortcomings, and the GAO presents a more moderate assessment of the state of women’s health research. We will examine each of these reports in turn before attempting to draw any conclusions about the actual state of women’s health research.

The Department of Health and Human Service reported in 2009 that NIH-funded extramural research (which represents over 80% of all NIH research) had successfully included a
relatively balanced number of male and female participants. The HHS report specifically noted
that in 2007 and 2008, 46% of participants in NIH funded extramural research were women and
53% were men. This report, however, did not release the number of studies
analyzing/reporting their results by sex. Moreover, given that the NIH is a part of HHS, it is
difficult to determine whether other agendas affected HHS oversight of the report.

The Institute of Medicine, as an independent non-profit, produced a much more critical
report in 2010 entitled “Women’s Health Research: Progress, Pitfalls, and Promise.” The report
states that there “has been inadequate enforcement of requirements that representative numbers
of women be included in clinical trials and that women’s results be reported.” Unlike the
HHS study which focuses on equal numbers of study participants, the IOM study focuses
primarily on the reporting of results by sex. The IOM asserts that a “lack of reporting on sex and
gender differences has hindered identification of potentially important sex differences and
slowed progress in women’s health research and its translation to clinical practice.” In
2010, the IOM thus reached very different conclusions from those reached by HHS just one year
earlier.

The Government Accounting Office, meanwhile, seems to have found a middle ground.
Despite its optimistic title, the GAO Report “NIH Has Increased Its Efforts to Include Women in
Research” reaches a relatively balanced conclusion. While the GAO report was released in 2000,
it still resonates with both the HHS report of 2009 as well as the IOM report of 2010, and it
manages to integrate the two in a single coherent assessment of women’s health research. The
GAO report states that the NIH has achieved a near-equal balance of male and female study
participants by implementing a new system to evaluate and monitor the number of female study
participant. The GAO report, however, notes that while the “NIH has made substantial
progress in ensuring that women are included in studies … [it has made] less progress in encouraging analysis by sex**40 (p7)** which is also the primary criticism made by the IOM report.

Without access to the primary data, it is difficult to assess whether the HHS, IOM, or the GAO report most accurately reflects the current state of women’s health research. Drawing upon the collective insights from these reports, however, we see that while there may be more female subjects in NIH funded research, it appears that few studies analyze and report results by sex. This is definitely the case for the discipline of cardiac rehabilitation, which serves as the focus of this paper. While cardiac rehabilitation has been available to patients for over thirty years, only five studies have evaluated the effectiveness of CR in men and women. There is a great need for more sex-based cardiac rehabilitation research. Studies evaluating the relative benefits of CR components for each sex and studies assessing the relative effectiveness of tailored CR interventions may prove particularly useful.
Appendix 2: Systematic Review of Cardiac Rehabilitation

Background

Cardiac rehabilitation (CR) is a multifaceted program designed to assist patient recovery from various forms of heart disease. The history of cardiac rehabilitation involves a gradual paradigm shift that occurred over several decades. In the early 20th century, prevailing medical wisdom dictated that physicians place their patients on complete bed rest for at least six weeks following a heart attack.41 (p1793) By the 1950s, however, this dogma was increasingly brought into question by Levine, Lown, and others.41 By the 1960s, Hellerstein had developed a comprehensive activity program for heart attack patients. Moreover, in 1968, he published his pivotal work, “Exercise Therapy in Coronary Disease,” which still acts as the foundation for modern cardiac rehabilitation.41 (p1795)

Modern cardiac rehabilitation involves several key components: a supervised/tailored exercise program, nutritional/dietary counseling, and emotional/motivational support 42,42. In the words of the American Heart Association, the goal of cardiac rehabilitation is to help patients “increase physical fitness, reduce cardiac symptoms, improve health and reduce the risk of future heart problems.”42 (para 4) CR is supported by a wide array of medical organizations including the American College of Cardiology Foundation, the American Association of Cardiovascular and Pulmonary Rehabilitation, and the American Heart Association.43 This systematic review examines whether this broad support for cardiac rehabilitation is grounded in current research. We specifically seek to answer the question: how effective is cardiac rehabilitation at improving functional capacity in heart attack (myocardial infarction/MI) patients? The results of this review
will help inform and provide background for my master’s paper as whole, which examines the effectiveness of CR in men and women with ischemic heart disease.

Methods

Types of Studies

We restricted our review to randomized controlled trials (RCTs) comparing patients randomized to receive either standard treatment, ie control, or cardiac rehabilitation in addition to standard treatment, ie intervention. We chose not to include observational studies because of the difficulty in determining whether potential differences in outcome in such studies are the result of CR itself or the result of baseline intervention/control differences. This issue of baseline differences is especially concerning because previous studies have documented significant baseline differences between those patients who decide to enroll in CR and those who opt not to.

Participants

Diagnoses qualifying patients for cardiac rehabilitation (CR) are extremely diverse. Medicare and most private insurance companies will cover CR for a variety of indications including MI within the last 12 months, coronary artery bypass surgery, angina pectoris, heart

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1 It is important to note that while this systematic review specifically examines CR for heart attack patients, the original research in this paper evaluates CR for a broad range of ischemic heart disease (IHD) conditions including heart attack, angina, CABG, and PCI. Also, while the systematic review examines men and women together, our research evaluates these groups separately. These differences are intentional, with the systematic review assessing whether there appears to be any benefit to CR while our research attempts to measure the degree of benefit in various groups (men compared to women, heart attack patients compared to angina patients, etc).

2 For the purposes of this systematic review, standard treatment does not include cardiac rehabilitation or any of the components of CR.
valve repair/replacement, angioplasty or coronary stenting, and heart or heart/lung transplant.

These CR diagnoses are each quite distinct and involve very different disease processes; consequently, it is not clear that cardiac rehabilitation is equally effective in addressing each condition. We have thus specifically chosen to limit the review to studies of heart attack patients, as heart attack is one of the most common qualifying conditions for CR.\textsuperscript{46}

\textbf{Intervention}

We required that included studies specifically and explicitly assess the effectiveness of cardiac rehabilitation. The core components of cardiac rehabilitation are patient assessment, exercise training, physical activity counseling, nutritional counseling, and psychosocial management.\textsuperscript{47} We excluded any study that did not include all of these core CR components as part of the intervention.

\textbf{Control}

We limited studies to those in which control participants received only standard care. Any studies offering control participants more than standard care \textsuperscript{ii} were excluded. As part of standard care, all participants in the included studies were instructed to continue to follow-up with their previous (non-study) physicians.
Outcome

We restricted studies to those evaluating the outcome of exercise capacity. Exercise capacity was chosen both because it is an important patient-oriented outcome and because our research is, similarly, aimed at addressing the effect of CR on exercise capacity. Two different indices of exercise capacity were used by the included studies: peak VO2 and total work capacity. Peak VO2 is the volume of oxygen consumed per min per kg by an individual at maximal exertion. Total work capacity (TWC) is the amount of work that an individual can undertake without becoming symptomatic; TWC is measured in kg per meter.

In terms of the timeframe for measuring outcomes, we only required that studies measure outcomes at baseline (before CR) and upon completion of CR. Some included studies additionally measured outcomes at time points several months to years after participants’ completion of CR.

Search Methods for Study Identification

On February 24, 2012, we searched the MEDLINE database using the MESH term “myocardial infarction” and the keyword “cardiac rehabilitation”³. We limited the search results to English language papers published within the last ten years (2003 to 2012). We retrieved a total of 368 articles. After we used the previously elaborated criteria to screen the abstracts of these articles, only nineteen articles remained. We then closely reviewed the eligibility of these nineteen articles and were left with only three articles. To be thorough, we also conducted a hand search of two of the most recent systematic reviews on the topic, which were published in the

³ Unfortunately, cardiac rehabilitation is not a MESH term in MEDLINE.
American Heart Journal and Cochrane. From this hand search, only three articles were obtained, and we had previously found each of these three articles using MEDLINE. Thus, despite assessing 368 articles for inclusion, our review includes only three studies because of stringent eligibility criteria.

Results

The three included studies are Lee, Chen, Hsu, et al.’s “The Effect of Cardiac Rehabilitation on Myocardial Perfusion Reserve in Postinfarction Patients”, Marchionni, Fattorolli, Fumagelli, et al.’s “Improved Exercise Tolerance and Quality of Life with Cardiac Rehabilitation of Older Patients after Myocardial Infarction” and Giallauria, De Lorenzo, Pilerci, et al.’s “Favorable Effects of Exercise Training on N-terminal Pro-Brain Natriuretic Peptide (pro-BNP) Plasma Levels in Elderly Patients after Acute Myocardial Infarction.”43,48-50 (Of note, in addition to examining exercise capacity, some of the studies also looked at other outcomes such as myocardial perfusion or pro-BNP levels.) Both Lee et al.’s study and Giallauria et al.’s study measure peak VO2 to assess exercise capacity48,50 while Marchionni et al.’s study relied on bicycle ergometry testing to assess total work capacity.49

In all three studies, cardiac rehabilitation patients showed improvement in exercise capacity (measured either by peak VO2 or by TWC) following the intervention.48-50 In contrast, control patients showed essentially no change in exercise capacity at the end of the study.48-50 Next, we will separately examine the outcomes of peak VO2 and TWC.
Peak VO2

Peak VO2 is a commonly used measure of exercise capacity. Lee, Chen, Hsu, et al. report that study participants’ peak VO2 increased after CR from an average of 22.2 mL/kg/min to an average of 25.0 mL/kg/min. This represents an increase of 2.8 mL/kg/min or 12.6%; the peak VO2 for Lee et al.’s control group, on the other hand, decreased by 0.3 mL/kg/min or 1.3%. The associated intra-group p value for CR patients in this study is less than 0.01; unfortunately, no inter-group p value is reported. Giallauria, De Lorenzo, Pilerci, et al. likewise report that CR is associated with a marked improvement in peak VO2. Participants’ average peak VO2 improved from 16.3 mL/kg/min to 20.5 mL/kg/min after CR; this represents a change of 3.8 mL/kg/min or 23.3% which is significantly different (inter-group p value of 0.007) from the average improvement of just 0.8 mL/kg/min in controls.

TWC (Total Work Capacity)

Marchionni, Fattiorlli, Fumagelli, et al.’s study is the only included study that does not examine peak VO2. This study instead assesses total work capacity. It is difficult to evaluate the effect of CR in this study for three reasons. First, the study only evaluates the effect of CR for age-stratified groups (breaking the sample down into those 45 to 65 years old, those 65 to 75 years old, and those over 75 years old) and does not assess the overall effect of CR on the entire sample. Second, the study does not report specific values for Total Work Capacity, either before or after CR. And third, the study reports intra-group p values but not inter-group p values. Still, TWC improved in each of the age-stratified CR groups, with intra-group p value less than 0.001 for each age-stratified group. TWC for controls also tended to improve;
however, this improvement did not achieve statistical significance, based on intra-group p values.\textsuperscript{49 (p2205)} Although it would admittedly be helpful to have more information, CR does seem to benefit TWC, based on the results of this study.

**Discussion**

We’ve reviewed the results of the three RCTs assessing the effect of cardiac rehabilitation on various functional measures. The specific measures discussed include peak VO2 and Total Work Capacity (TWC). We will first discuss the measure of peak VO2 and then move on to discuss the measure of TWC.

Both of the studies which assess peak VO2 favor cardiac rehabilitation. Moreover, both Lee et al. and Giallauria et al. report a statistically significant increase in peak VO2 in the CR group compared to the control group.\textsuperscript{48,50} The specific percent improvement in peak VO2 does vary somewhat, with Lee et al, reporting a 12.6\% improvement while Giallauria et al. report a 23.3\% improvement.\textsuperscript{48 (p1398-1399), 50 (p628)} For various reasons, it is difficult to compare the percent improvement in peak VO2 across studies. First, the patient populations in these two studies are quite different, particularly in terms of participant age, sex, and fitness level.\textsuperscript{48 (p1397-1398), 50 (p626-628)} Second, the interventions themselves are somewhat different.\textsuperscript{48 (p1396), 50 (p627)} And third, the sample size for both studies is quite small, with only 39 total participants in Lee et al.’s study and 44 total participants in Giallauria et al.’s study.\textsuperscript{48 (p1395), 50 (p625)} For all of these reasons, it is not surprising that the percent improvement in peak VO2 is somewhat different between these two studies. Still, it is important to note that both studies show marked improvements in peak VO2 following CR.
The other functional outcome reported was TWC, assessed by Marchionni, Fattirolli, Fumagelli, et al. It is, however, difficult to discuss this measure at length because no specific TWC values are provided and only age-stratified results are available. Still, although Marchionni et al. are assessing a different functional outcome from Lee et al. and Giallauria et al, this study also shows marked functional improvement after cardiac rehabilitation.49 (p2205)

In conclusion, each of these randomized controlled trials shows a strong association between cardiac rehabilitation and functional improvement, measured by either peak VO2 or TWC. Cardiac rehabilitation thus seems to be beneficial, by and large, for patients who have suffered a heart attack. The question remains of whether cardiac rehabilitation is equally beneficial for men and women. And although no RCTs have been designed to address this question, we are hopeful that our observational research, in the context of previous observational studies, will begin to provide an answer to this question.
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