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Systematic Review/Meta-analysis

Sex Differences in Cardiac Rehabilitation Enrollment: A Meta-analysis

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ABSTRACT

Background: The present systematic review and meta-analysis examines studies published in the past 10 years that described cardiac rehabilitation (CR) enrollment among women and men, to determine whether a significant sex difference persists despite the evidence supporting the benefits of CR to women as well as men.

Methods: Scopus, MEDLINE, CINAHL, PsycINFO, PubMed, and The Cochrane Library databases were systematically searched for peer-reviewed articles published from July 2000 to July 2011. Titles and abstracts were screened, and the 623 selected full-text articles were independently screened based on predefined inclusion/exclusion criteria (guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA) and assessed for quality using the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement form. The meta-analysis was undertaken using Review Manager software.

Cardiovascular disease continues to be the leading cause of morbidity and mortality among men and women globally. However, women who suffer an acute coronary event might be more likely than men to incur morbidity and mortality within the first year of recovery.¹ In addition, they often have lower physical function, are less physically active, of lower socioeconomic status, and are at greater risk in the context of smoking and diabetes than men.² For these reasons, secondary prevention is key, particularly among women.

Cardiac rehabilitation (CR) programs offer structured exercise, education, counselling, and risk reduction to promote secondary prevention. CR participation is associated with an overall reduction in recurrent cardiac events,³ improved survival, functional status, and psychosocial well-being.⁴ Considering the abundance of empirical evidence, Class I,

RÉSUMÉ

Introduction : Les présentes revue systématique et méta-analyse examinent les études publiées au cours des 10 dernières années sur la participation des femmes et des hommes à la réadaptation cardiaque (RC) pour déterminer s'il persistait une différence importante entre les sexes en dépit des données scientifiques soutenant les avantages de la RC tant pour les femmes que pour les hommes.

Méthodes : Les bases de données Scopus, MEDLINE, CINAHL, PsycINFO, PubMed et la Bibliothèque Cochrane ont été consultées de façon systématique pour relever des articles évalués par des pairs de juillet 2000 à juillet 2011. Les titres et les résumés ont été examinés, et les 623 textes intégraux des articles sélectionnés ont été examinés indépendamment selon les critères préétablis d'inclusion et d'exclusion (en se guidant sur l'énoncé PRISMA; *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) et évalués sur la qualité à l'aide de l'énoncé STROBE (*Strengthening the Reporting of Observational*

Level A clinical practice guideline recommendations^{5,6} promote CR access for patients.

Unfortunately, however, CR is grossly underutilized.⁷ The reasons for underuse are well documented, and include patient-, provider-, and health system-level factors.⁸ There have been reviews of interventions demonstrated to promote greater enrollment among eligible patients,⁹ with a multisite, controlled observational study setting a benchmark of 70% patient enrollment.¹⁰ Nevertheless, underuse persists, and moreover, sex disparities in access are widespread in the United States, Canada, and other health care systems.

More specifically, a treatment-risk paradox is observed, such that although women might be in greater need of the secondary prevention offered through CR, they are significantly less likely to access it than men.^{8,11,12} This sex bias has been recognized for well over a decade,⁸ and indeed there are women-specific guideline recommendations promoting their access to CR.² Although intervention research has tested sex-specific interventions that are tailored to improve the enrollment of women in CR, the literature is limited and little is known what progress has been made (if any) to close the sex gap in CR utilization. To our knowledge, a meta-analysis of

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See page 799 for disclosure information.

Results: Twenty-six eligible observational studies reporting data for 297,719 participants (128,499 [43.2%] women) were included. On average, 45.0% of men and 38.5% of women enrolled in CR. In the pooled analysis, men were more likely to be enrolled in CR compared with women (female enrollment vs male enrollment odds ratio, 0.64; 95% confidence interval, 0.57-0.72; $P < 0.00001$). Heterogeneity was considered high ($I^2 = 78\%$). In the subgroup analyses, systematic CR referral during inpatient tertiary care resulted in significantly greater enrollment among women than nonsystematic referral.

Conclusions: Overall, rates of CR enrollment among women are significantly lower compared with men, with women being 36% less likely to enroll in a rehabilitation program.

recent studies reporting rates of CR enrollment among women and men has yet to be undertaken, and could ascertain whether sex differences persist in the current era. Therefore, the objectives of this study were first to review studies published in the past 10 years that describe CR enrollment among women and men, and second to quantitatively test whether a significant sex difference still exists.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and recommendations were used to guide the development and completion of this meta-analysis¹³ (<http://www.prisma-statement.org/>). The methods were specified and documented in a protocol to ensure consistency in approach.

Search strategy and data sources

Comprehensive literature searches of Scopus, MedLine, CINAHL, PsycINFO, PubMed, and The Cochrane Library databases were conducted for peer-reviewed articles published from July 2000 to July 2011 with support from staff librarians. PubMed “related article” links were used as a complement to the other databases and were searched to identify further articles meeting inclusion criteria. Reference lists of key studies and reviews were also searched.

Examples of subject heading search terms used were “Heart Disease,” “Coronary Disease,” “Rehabilitation Centre,” “Health Services Accessibility,” and “Patient Participation.” Some key words used in the search included “Cardiac Rehabilitation,” “Access,” and “Program Utilization.” The search strategy for MedLine is shown in [Supplemental Figure S1](#). RefWorks¹⁴ software was used to create a database of citations identified using electronic and manual searches.

Inclusion criteria

(i) Articles were included in the review if the following criteria were met: (1) study design consisted of a primary observational study (cross-sectional, prospective, retrospective) or an interventional study (randomized controlled trials

Studies in Epidemiology). La méta-analyse a été entreprise en utilisant le logiciel Review Manager.

Résultats : Vingt-six (26) études observationnelles admissibles rapportant les données de 297 719 participants (128 499 [43,2 %] femmes) ont été incluses. En moyenne, 45,0 % des hommes et 38,5 % des femmes ont participé à la RC. Dans les analyses groupées, les hommes ont été plus susceptibles de participer à la RC que les femmes (ratio d'incidence approché de la participation des femmes c. la participation des hommes, 0,64; intervalle de confiance à 95 %, 0,57-0,72; $P < 0,00001$). L'hétérogénéité a été considérée comme étant élevée ($I^2 = 78\%$). Dans les analyses en sous-groupes, l'orientation systématique en RC durant l'hospitalisation en soins tertiaires a entraîné une participation considérablement plus grande chez les femmes que l'orientation non systématique.

Conclusions : Dans l'ensemble, les taux de participation des femmes à la RC sont considérablement plus faibles que ceux des hommes, soit que les femmes sont 36 % moins susceptibles de participer à un programme de réadaptation.

[RCT] or non-randomized studies); (2) outcome: enrollment was defined as attending a minimum of 1 session of an outpatient CR (phase II) program. Numerators and denominators for the rates were required to be reported in the publication, or calculated from the data presented. The numerator consisted of the number of study participants that were enrolled in CR. The denominator consisted of the total number of CR-eligible patients from a registry or circumscribed in an in- or outpatient setting. (3) Participants who were eligible for outpatient CR based on the Canadian⁵ and American Guidelines for Cardiac Rehabilitation,¹⁵ specifically those with acute coronary syndrome (ie, myocardial infarction or unstable angina), chronic stable angina, stable chronic heart failure, and those who underwent 1 of the following procedures: percutaneous coronary intervention, coronary artery bypass graft surgery, cardiac valve surgery, cardiac transplantation, or cardiac resynchronization therapy. (4) The article was a full-length report, published in a peer-reviewed journal, and written in the English language. (5) Rates of CR enrollment were reported for men and women separately, or could be calculated based on the data provided.

Exclusion criteria

Meta-analyses, systematic reviews, qualitative studies, published letters, comments, editorials, case-series and case reports, nonempirical, and publications not peer-reviewed (eg, dissertations) were excluded. Additionally, published articles were excluded if they included a double cohort with identical CR enrollment data, in which case the publication presenting the most relevant and higher-quality evidence in relation to the objectives herein was included.

A flow chart based on the PRISMA guidelines¹³ depicting study selection is presented in [Figure 1](#).

Study selection

Citations from all databases were independently evaluated by 2 authors (S.G. and T.J.F.C.). Citations were rejected if the reviewer determined that the study did not examine outpatient CR enrollment according to the title or abstract. Original articles of relevant abstracts were obtained. When enrollment

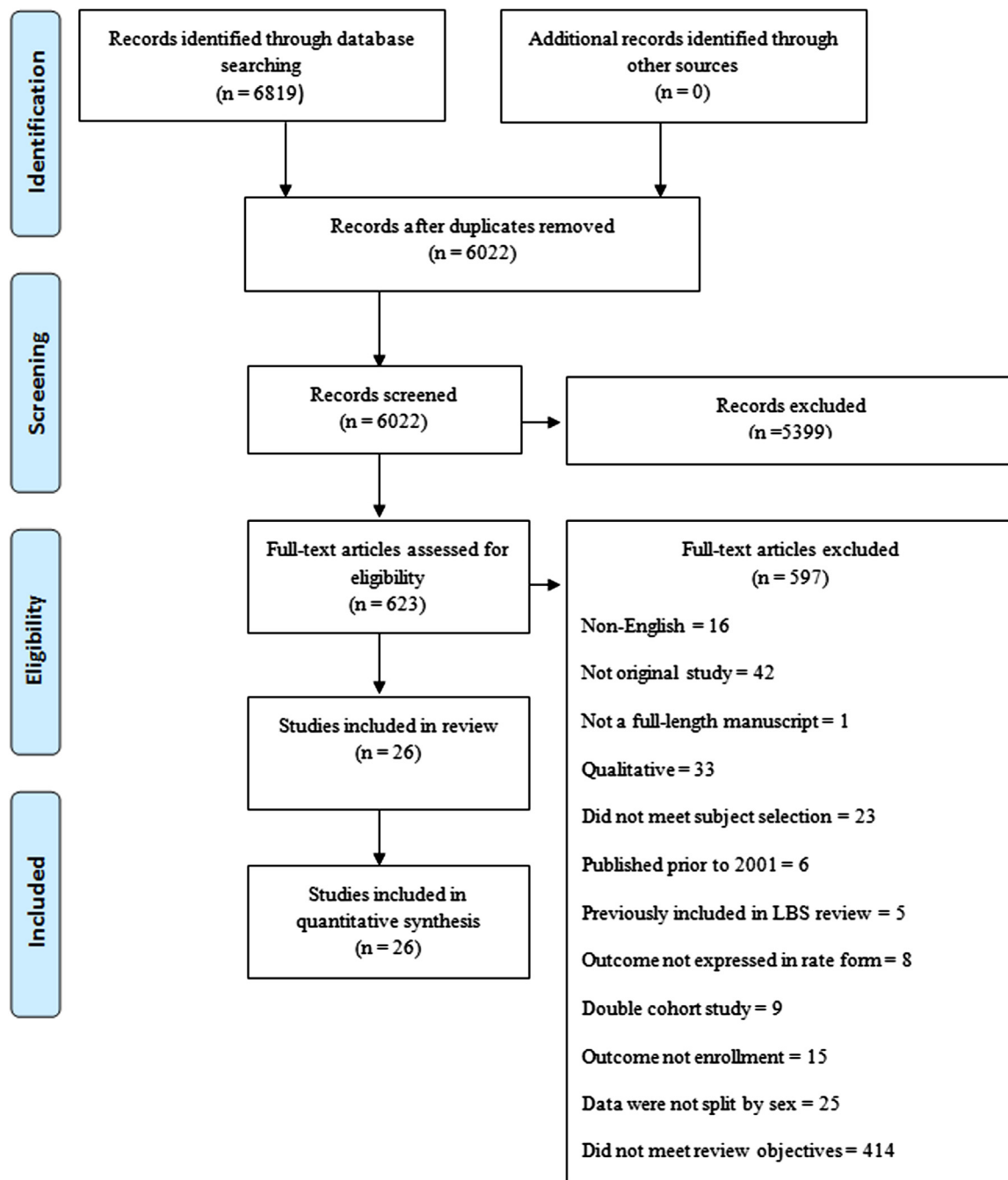


Figure 1. PRISMA chart of study selection process. LBS, Lisa Benz Scott; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

numerators or denominators were missing according to sex, authors were contacted to ascertain this information. Two reviewers (L.S. and Casey McGloin [C.M.]) then independently assessed the articles for inclusion using a standardized, piloted form based on the criteria outlined. Discrepancies were resolved by discussion and consensus with a third reviewer (T.J.F.C.).

Data extraction process and quality assessment

A standardized, piloted data extraction form created by the authors was used when extracting data from studies meeting

inclusion criteria. Two reviewers then independently extracted data from each article (L.S. and C.M.). Any discrepancies were resolved according to independent verification of the data in consultation with a third reviewer (S.G.). The included studies are presented in [Supplemental Table S1](#).

The quality of the studies that were observational in design was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement form.¹⁶ Two reviewers independently assessed the quality of the included articles (L.S. and C.M.), which were rated as “good,” “fair,” or “poor” quality.¹⁷ Any discrepancies were

resolved using independent verification in consultation with third reviewer (S.G. or T.J.F.C.). Quality ratings are also shown in [Supplemental Table S1](#).

Data synthesis and analysis

Meta-analysis was performed using Review Manager Analysis software (version 5.0).¹⁸ The combined results were examined using the random effects model because heterogeneity in the methodology of the studies was perceived as inevitable. To determine the effect of heterogeneity on the meta-analysis, we used I^2 statistics. I^2 scores of $\leq 40\%$ were interpreted as unimportant heterogeneity. For each study, the effect was plotted according to the inverse of its standard error. A funnel plot was constructed to test the presence of publication bias.

Potential causes of heterogeneity were explored by performing subgroup analyses. The influence of low-quality studies on the pooled estimates was tested in a subgroup analysis by including and excluding them, using a test of interaction with a predetermined 2-tailed α of 0.05 to compare differences between original and corrected effect sizes. The current meta-analysis also explored: the influence of the source of the sample (registry vs nonregistry); the source for enrollment ascertainment (self-report vs other); the number of sites investigated in the study (single-site vs multisite); the definition of enrollment (no definition vs unclear definition vs outlined criteria for at least a minimum number of sessions attended vs attending at least 1 CR session); the geographic location (Australia vs United Kingdom vs other countries); and systematic referral (systematic referral vs no systematic referral) on the effect sizes among studies.

Results

In [Figure 1](#) the results of the search, and application of inclusion/exclusion criteria are shown. Of the 623 articles identified as potentially eligible for inclusion, 26 full-length articles that reported CR enrollment rates among men and women, and/or examined differences between enrollment rates of men and women were included in this review.

Characteristics of included studies

Each study is described in [Supplemental Table S1](#). With regard to quality assessment, 6 (23.1%) studies were rated as good quality, 15 (57.7%) studies were rated as fair, and 5 (19.2%) studies were rated as poor quality (see [Supplemental Table S1](#)).

All studies were observational in design. Thirteen (50%) were multisite studies (of which 3 [23.1%] were registry-based). The included studies reported on data collected between 1997 and 2007, except for 1 article based on a registry in which the data go back to 1982.¹⁹

Most studies were conducted in the United States (US; $n = 10$; 38.5%), and 5 (19.2%) were conducted in the United Kingdom (UK), 4 (15.4%) in Australia, 2 (7.7%) in China, and 1 (3.8%) in each of Canada, Denmark, France, Germany, and Japan.

In terms of participants, a total of 297,719 study subjects were included in this review, with the largest study accounting for 267,427 (89.8%) of the total participants.⁷ Mean ages, where reported, ranged from 56.0 to 78.0 years. Women accounted for less than half of study participants (total of

128,499 [43.2%]; range, 9.7%-51.0%). Eleven (42.3%) of the included studies enrolled patients with multiple eligible cardiac diagnoses or procedures, and 8 (30.8%) studies enrolled patients with myocardial infarction only, 2 (7.7%) enrolled patients with acute coronary syndrome only, 2 (7.7%) enrolled patients with coronary artery disease, 2 (7.7%) studies enrolled patients after coronary artery bypass graft surgery only, and 1 (3.8%) study enrolled patients with heart failure only.

Most of the studies relied on self-report alone to ascertain enrollment rates ($n = 8$; 30.8%). In 8 (30.8%) studies, enrollment rates were ascertained using a combination of methods, in 4 (15.4%) studies they were ascertained via CR program report only, in 4 (15.4%) studies via medical records only, and in 3 (11.5%) studies according to registry data only.

Most of the studies operationalized enrollment as attending at least 1 CR session ($n = 9$; 34.6%). In 8 (30.8%) studies, there was no clear definition presented but it was evident that patients were enrolled because they were reported as "participating" in CR, in 6 (23.1%) studies there was no explicit definition of enrollment given, and 3 (11.5%) studies outlined criteria for at least a minimum number of sessions attended. Finally, 3 (11.5%) studies undertook adjusted analysis of sex differences.

CR enrollment rates

Overall, CR enrollment rates ranged from 7.1%²⁰ to 73.0%.²¹ The overall mean rate of CR enrollment was 42.3% (SD, 18.7; median, 39.3%).

When examining the CR enrollment rates according to sex among all studies, as shown in [Supplemental Table S1](#), rates for men ranged from 8.4%²⁰ to 72.0%,²¹ and rates for women ranged from 3.4%²⁰ to 77.1%.²² The mean enrollment rate for men among these studies was $45.0 \pm 18.5\%$ (median, 42.2%), and for women it was $38.5 \pm 20.7\%$ (median, 38.2%). Among studies rated as good quality, enrollment rates for men ranged from 22.1%⁷ to 67%,¹⁹ and rates for women ranged from 14.3%⁷ to 38.2%.^{19,23}

Sex differences in CR enrollment

Inferential tests for sex differences in CR enrollment were undertaken in 21 of the 26 included of the studies (80.8%).

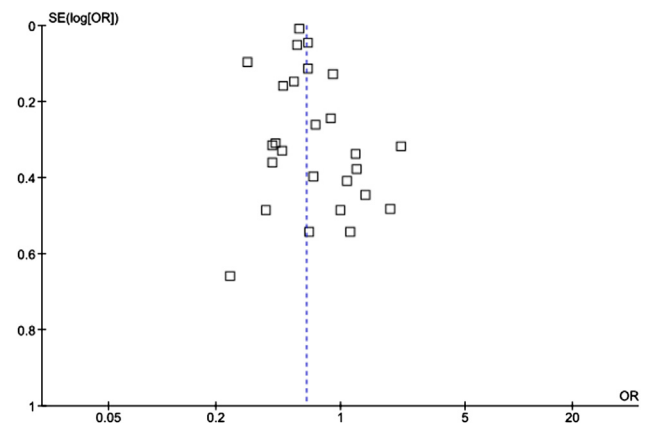


Figure 2. Funnel plot evaluating for publication bias among 26 studies used in the meta-analysis. OR, odds ratio.

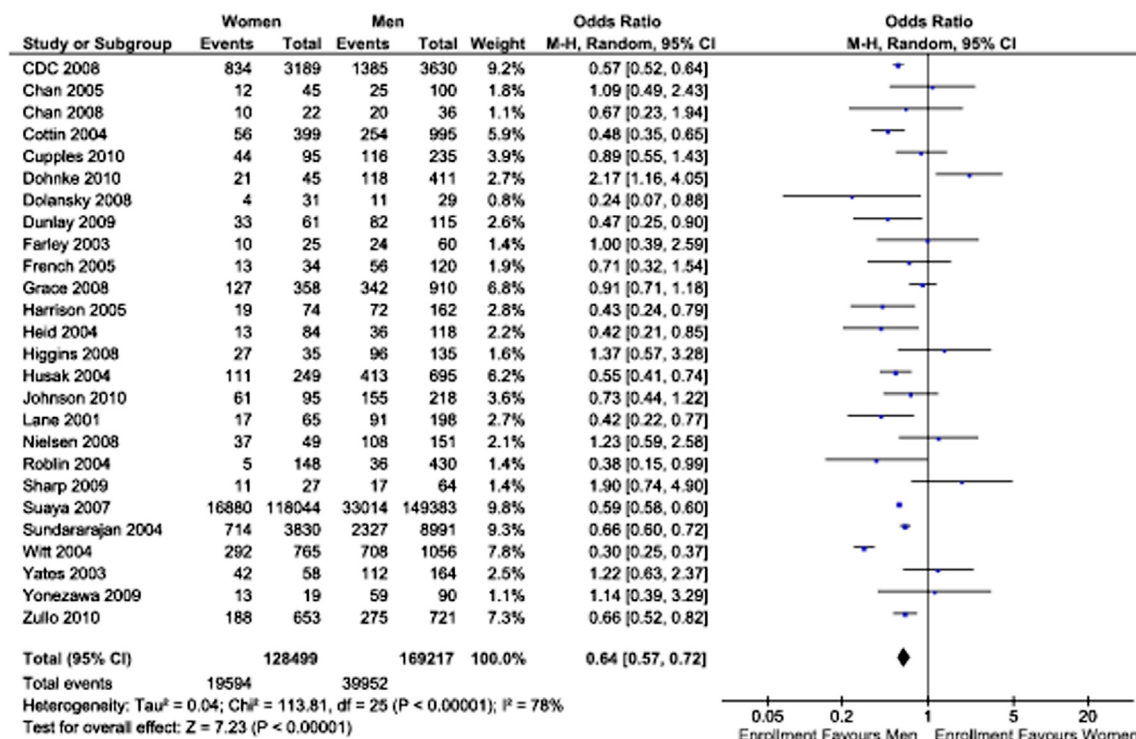


Figure 3. Forest plot presenting relative odds of men and women to enroll in a CR program. Error bars indicate 95% CIs for each study. CI, confidence interval; CR, cardiac rehabilitation; M-H, Mantel-Haenszel.

In Supplemental Table S1 available results are presented. Overall, 14 (66.7%) studies reported no significant sex differences, and 7 (33.3%) studies reported sex differences in CR enrollment, with women significantly less likely to be enrolled than men. No studies found that women were significantly more likely to be enrolled than men. Of the 3 studies that tested sex differences and undertook adjusted analyses,^{20,24,25} 1 (33.3%) adjusted for age reported significant sex differences.

Meta-analysis

The symmetrical shape of the funnel plot (Fig. 2) suggested the results are not influenced by publication bias. Figure 3 indicates the enrollment rates according to sex for each included study, and the effect size and confidence interval. In the pooled analysis, CR enrollment was significantly greater in men compared with women when female enrollment vs male enrollment was compared (odds ratio, 0.64; 95% confidence

Table 1. Results of subgroup analyses; female OR vs male OR of enrolling in CR

Analysis	Subgrouping	OR	95% CI	P	I ² , %
(1) Study quality	Poor quality	0.61	0.47-0.78	< 0.0001	41
	Fair quality	0.76	0.59-0.97	0.03	63
	Good quality	0.56	0.45-0.70	< 0.00001	92
(2) Participant source	Registry patients	0.55	0.43-0.72	< 0.00001	91
	Non-registry patients	0.75	0.60-0.94	0.01	63
(3) Ascertainment of enrollment outcome	Self-report	0.67	0.53-0.86	0.001	71
	Other	0.64	0.54-0.76	< 0.00001	81
(4) Number of sites	Single site	0.68	0.57-0.81	< 0.0001	44
	Multisite	0.62	0.50-0.77	< 0.0001	87
(5) Outcome definition	No definition of enrollment	0.74	0.51-1.06	0.10	48
	Unclear definition (ie, "participating" in CR)	0.63	0.48-0.83	0.0009	72
	Outlined criteria for at least a minimum number of sessions attended	0.87	0.34-2.22	0.78	73
(6) Country	Attending at least 1 CR session	0.62	0.51-0.75	< 0.00001	88
	Australia	0.70	0.57-0.86	0.0008	15
	United Kingdom	0.69	0.43-1.11	0.13	61
(7) Referral strategy	Other	0.62	0.53-0.73	< 0.00001	83
	Systematic referral	1.40	1.02-1.91	0.04	78
	No systematic referral	0.58	0.52-0.65	< 0.00001	77

CI, confidence interval; CR, cardiac rehabilitation; OR, odds ratio.

interval, 0.57-0.72; $P < 0.00001$). Heterogeneity among all 26 studies was considered high ($I^2 = 78\%$).

Subgroup analyses were performed, as outlined in the Methods section. Results are presented in Table 1, and Forest plots for each are available in Supplemental Figures S2-S9. For the first analysis (Supplemental Fig. S2), the 5 low-quality studies were removed, and CR enrollment rates remained significantly different between women and men in the studies rated good or fair quality (odds ratio, 0.66; 95% confidence interval, 0.56-0.76; $P < 0.00001$). The odds ratio of female vs male CR enrollment in good quality studies alone was 0.56 (95% confidence interval, 0.45-0.70; $P < 0.00001$), and in registry-based articles it was 0.55 (95% confidence interval, 0.43-0.72; $P < 0.00001$). In most of the subsequent analyses, CR enrollment favoured men compared with women. Studies that had no significant sex bias in enrollment were “no definition of enrollment” and “outlined criteria for at least a minimum number of sessions attended” in the subgroup analysis according to outcome definition, and studies undertaken in the UK in the pooled analysis according to country. In the latter case, however, 1 study seemed to bias the pooled analysis. Of note, CR enrollment favoured women in studies in which patients were systematically referred to CR (odds ratio, 1.40; 95% confidence interval, 1.02-1.91; $P = 0.04$). Last, heterogeneity was considered low among Australian studies ($I^2 = 15$).

Discussion

Recent Presidential Advisories²⁶ have called for increasing patient enrollment in CR. The results of this review echo these calls. Only 42% of patients enroll in CR, which is much less than the 70% recommended benchmark.¹⁰ Because enrollment rates have not previously been systematically and quantitatively reviewed to our knowledge, it is not known whether these enrollment rates might be greater than the rates in previous decades.

Although results of the qualitative review of these data might suggest there are no sex differences in CR enrollment (ie, 67% of studies reported no sex differences), quantitative analyses revealed that sex bias exists in the current era. This evidence is discouraging considering that guidelines from the American Heart Association show that there is Class I, Level A evidence for women to partake in CR.² On average, results showed that 45% of men enroll in CR, and only 39% of women. Specifically, a 36% lower enrollment rate was observed overall in women compared with men. This sex bias was even more pronounced in higher-quality articles and in registries, in which there is greater generalizability. It is cause for concern that the sex bias persists despite decades-old knowledge about these inequities.⁸

Of particular interest, systematic CR referral resulted in significantly greater enrollment among women than nonsystematic referral in subgroup analysis. This was the only instance in which significantly greater rate of enrollment was observed among women than men, in the current study and in the broader literature to our knowledge. The reasons for this remain to be explored more fully, however, previous work by our group has suggested that women are more likely to utilize CR in the context of systematic compared with nonsystematic referral strategies, and that such approaches can also mitigate other disparities in CR access.²⁷

Quality and availability of evidence

Overall, the quality of studies reviewed in this meta-analysis was most commonly ‘fair.’ Although there was a high level of heterogeneity among the included studies, results were uniform regardless of how enrollment was ascertained (self-report vs other). This suggests good concordance between chart and self-report of CR utilization. Unfortunately, there were no randomized studies to assess interventions to promote CR enrollment identified in this review.

The main challenge in undertaking this meta-analysis was related to definition of the enrollment numerator and denominator. With regard to the former, in a quarter of studies there was no definition provided for enrollment, and in a further third there was a vague definition related to program participation. Although the draft set of indicators has yet to be finalized, a Canadian initiative is currently under way to develop national quality indicators (<http://ddqi.ccs.ca/index.php/quality-indicators/cardiac-rehabilitation-secondary-prevention-quality-indicators-chapter>). CR enrollment is included therein and efforts are under way to fully specify the indicator in such a way that is applicable to different CR program models. It is hoped this initiative will soon be released publicly, which might promote greater consistency in enrollment reporting.

Second, there was also inconsistent definition of the enrollment rate denominator. The enrollment rate was generally defined based on: (1) the number of clinically-eligible patients from a circumscribed referral base; or (2) the number of referred patients. Of course, there will be patients who do not consent to be counted in either case. However, clearly, enrollment rates will differ significantly depending on the denominator applied. Although an attempt was made to tease this apart in the current study, it is hoped that with data definition efforts (particularly because of the increasing number of countries with national CR registries), that enrollment rate estimates based on both denominators can be robustly described. Indeed, the former rate is instructive regarding failure on behalf of the health system to ensure patient referral and coordination of care, and the latter is instructive regarding the proportion of patients who are simply not interested in participating in CR.

Clinical practice and policy implications

Interventions to improve CR enrollment rates (without particular attention to sex) have been recently reviewed,⁹ and 3 randomized trials of high quality were included.²⁸⁻³⁰ These interventions were published more than a decade ago (1995 to 2001), and each of these trials demonstrated the effectiveness of an intervention to improve CR enrollment compared with usual care. Unfortunately, however, implementation of these evidence-based interventions has not been achieved. In particular, the intervention developed and tested by Wyer et al.³⁰ is low cost and theoretically-based, consisting of a letter to patients. Although the root causes of low CR enrollment are multifactorial and complex, these 3 identified interventions should be revisited, and their potential to address sex differences in enrollment explored.

Moreover, women-only CR programs are becoming more prominent, and offering these programs to women might increase their inclination to enroll. These ideas should, but have yet to be, tested in randomized trials.

Limitations

Caution is warranted when interpreting these results. First, the literature search was limited to studies reported in English, which might limit the generalizability of the findings. Second, the results might be too heavily influenced by 1 single study, with the largest study accounting for 89.8% of the overall population that was analyzed.⁷ Furthermore, as previously mentioned, although subgroup analyses were undertaken to attempt to address differing definitions of enrollment, we must concede the enrollment rates reported herein might be affected. Last, with an I^2 value of 78%, the rate of heterogeneity among the 26 studies available in the literature was high. Again, subgroup analyses were undertaken to reduce the heterogeneity, but it is hoped this initial work will spur further attempts to quantify CR enrollment rates.

Conclusions

Patients cannot achieve the morbidity and mortality benefits associated with CR participation³¹ if they are not enrolled in a program. Yet, only approximately 40% of eligible patients enroll in CR, and women are 36% less likely to enroll compared with men. Interventions designed to specifically promote women's enrollment in CR programs are warranted. Systematic referral strategies in particular show promise, because they appear to increase enrollment rates for all types of patients in need.²⁷

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the Canadian Journal of Cardiology at www.onlinecjc.ca and at <http://dx.doi.org/10.1016/j.cjca.2013.11.007>.