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Systematic Review/Meta-analysis

The Effect of Cardiac Rehabilitation on Health-Related Quality of Life in Patients With Coronary Artery Disease: A Meta-analysis

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See editorial by Goodman and Marzolini, pages 235–237 of this issue.

ABSTRACT

Background: The clinical effectiveness of cardiac rehabilitation (CR) on health-related quality of life (HRQOL) is an area that has not been consistently explored. The objective of this systematic review was to evaluate the effectiveness of providing any core component of CR on HRQOL domains.

Methods: We performed a meta-analysis and meta-regression of randomized controlled trials (RCTs) on the core components of CR. RCTs included adult patients with diagnosed coronary artery disease via angiography, myocardial infarction, angina, or who had undergone coronary revascularization. The Cochrane Library, MEDLINE, EMBASE, CINAHL, SCI-EXPANDED, Psych INFO, and Web of Science were searched from inception to April 27, 2017. Outcomes included overall, physical, emotional, and social HRQOL. Outcomes were reported as standardized mean change (SMC) with 95% confidence intervals (CIs). Effect size changes of 0.2, 0.5, and 0.8 SD units reflect a small, moderate, and large effect, respectively.

RÉSUMÉ

Contexte : L'efficacité clinique de la réadaptation cardiaque (RC) sur la qualité de vie liée à la santé (QVLS) est un domaine qui n'a pas été exploré de façon méthodique. L'objectif de cette revue systématique était d'évaluer l'efficacité de l'un ou l'autre des éléments centraux de la RC sur les domaines de la qualité de vie liée à la santé.

Méthodologie : Nous avons réalisé une méta-analyse et une méta-régression des essais contrôlés avec répartition aléatoire (ECRA) portant sur les éléments centraux de la RC. Les participants des ECRA étaient des patients adultes ayant reçu un diagnostic de coronaropathie par angiographie, ayant eu un infarctus du myocarde, atteints d'angine ou ayant subi une revascularisation coronarienne. Une recherche a été effectuée dans les bases de données Cochrane Library, MEDLINE, EMBASE, CINAHL, SCI-EXPANDED, Psych INFO et Web of Science de leur date de création au 27 avril 2017. Les paramètres d'évaluation étaient la QVLS globale, physique, émotionnelle et sociale. Les résultats étaient présentés sous la forme de variation

Although there has been a steady reduction in coronary heart disease (CHD) mortality over the past few decades, CHD morbidity appears to be increasing. Myocardial infarction (MI) survivors and heart failure patients are living longer, in part, because of improvements in cardiac care.[1-3] The economic burden of CHD when accounting for direct and indirect costs worldwide was estimated to be USD$108.9 billion and is predicted to reach USD$218.7 billion by 2030.[4]

Cardiac rehabilitation (CR) is a vital tool in improving outcomes in CHD. CR programs are typically multidisciplinary and include nutritional counselling, risk factor management, psychosocial management, patient education, and individualized exercise training.[5,6]

CR has been shown to reduce total mortality, cardiovascular mortality, and hospitalizations, while simultaneously

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Results: Forty-nine reports of 41 RCTs with 11,747 patients were included. Summary effect sizes were: overall HRQOL SMC, 0.28 (95% CI, 0.05-0.50), physical HRQOL SMC, 0.47 (95% CI, 0.13-0.81), emotional HRQOL SMC, 0.37 (95% CI, −0.02 to 0.77), and social HRQOL SMC, 0.13 (95% CI, −0.06 to 0.32). Meta-regression revealed type of CR intervention and year of publication as positive statistically significant treatment effect modifiers.

Conclusions: Receiving CR was shown to improve HRQOL, with exercise-, nonexercise-, and psychological-based interventions playing a vital role. Although these improvements in HRQOL were modest they still reflect an incremental benefit compared with receiving usual care.

Résultats : Quarante-neuf rapports portant sur 41 ECRA auxquels avaient participé 11 747 patients ont été inclus. En résumé, les variations de l'ampleur de l'effet étaient les suivantes : VMS de la QVLS globale, 0,28 (IC à 95 %, 0,05-0,50), VMS de la QVLS physique, 0,47 (IC à 95 %, 0,13-0,81), VMS de la QVLS émotionnelle, 0,37 (IC à 95 %, −0,02-0,77), et VMS de la QVLS sociale, 0,13 (IC à 95 %, −0,06-0,32). La méta-régression a révélé que le type d'intervention de RC et l'année de publication étaient des modificateurs positifs de l'effet du traitement statistiquement significatifs.

Conclusions : Il a été montré que le fait de suivre une RC avait pour conséquence d'améliorer la QVLS, et que les interventions de nature psychologiques, ou encore fondées sur l'activité physique ou sur d'autres éléments que l'activité physique jouent un rôle vital. Ces améliorations de la QVLS, même si elles sont légères, n'en constituent pas moins un avantage supplémentaire par rapport aux soins usuels.

improving physical function.[7,8] However, whether health-related quality of life (HRQOL) is improved by CR is less clear. The clinical effectiveness of CR on long-term outcomes such as HRQOL is an area that has not been fully explored. Recent Cochrane reviews of CR in CHD patients showed that comparing HRQOL findings in CR studies is difficult because of the complexity of the intervention, heterogeneity in the HRQOL instruments used and patient populations, as well as a lack of studies consistently reporting patient-reported health status.[2,8,9] Improvements in patient HRQOL after CR and secondary prevention programs have not been consistently reported with many studies reporting no improvement. Accordingly, additional research is needed to explore the effect of the core components of CR on HRQOL domains.

The aims of the present study were to evaluate the effectiveness of providing any core component of CR delivered in the context of CR on overall, physical, emotional, and social HRQOL domains in adult patients with CHD. Additionally, in this study we intended to explore the potential effect of the study-level predictors of CR and secondary prevention programs on HRQOL in patients with CHD using meta-regression.

Methods

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) on CR interventions for CHD patients using Cochrane methods.[10] We reported outcomes using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting standards.[11] The PRISMA checklist is shown in Supplemental Table S1. No review protocol exists for this study.

Information sources

Studies were identified through a systematic search of the following databases: MEDLINE (Ovid), EMBASE (Ovid), CINHAL (Ebsco), PsycINFO (Ovid), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Web of Science (SCI-EXPANDED). There was no date or language limits applied. The final Medline strategy was translated into syntax appropriate for each database used. Database searches were supplemented with manual searching of journals. Authors were contacted as necessary to provide missing details on Results.

Search strategy

The search strategy was designed and implemented by an information specialist (J.B.). The search was updated on April 27, 2017 to ensure that the most recent eligible articles were captured. A detailed search strategy for MEDLINE (Ovid) is provided in the Supplemental Methods S1.

Eligibility criteria

RCTs evaluating any core component of CR delivered in the context of CR (home, community, or hospital) that measured patient HRQOL (mean ± SD) at baseline and follow-up in the active and control arms were included.[12] Studies were also required to have a minimum of 6 months follow-up.

HRQOL instruments could be psychometric profiles that measure patient symptoms and function, or preference/utility-based measures that use either direct or indirect preference elicitation methods.[13] Additionally, instruments could be generic or disease-specific but needed to be validated for use in CHD patients, and encompass 1 or all of the relevant HRQOL domains.

The study population consisted of adult men and women with CHD who were eligible for CR. This included patients who have had an MI, have undergone revascularization (coronary artery bypass grafting or percutaneous coronary interventions), or who had angina pectoris.

Studies had to include any core component of CR: nutritional counselling, risk factor management, psychosocial interventions, patient education, and individualized exercise training.[6] The comparator (usual care) could include standard medical care, such as drug therapy, but patients could not be randomized to receive CR or any of its core components.

Studies of participants who completed CR programs before randomization, had patients randomized before cardiovascular

surgery, and trials in which both arms evaluated the same CR treatment strategy were excluded. Studies involving patients with heart failure, heart valve surgery, heart transplantation, or patients implanted with either cardiac resynchronization therapy or implantable defibrillators were also omitted.

Study selection

The titles and abstracts of all identified references were examined for inclusion by 2 reviewers (N.K. and T.F.) working independently. Full texts of potentially eligible studies were retrieved by the same reviewers, who independently determined study eligibility using a standardized inclusion form. Any disagreements were resolved by discussion and, if necessary, a third reviewer (M.K.) was asked to arbitrate.

Data extraction and quality assessment

Data from included studies were extracted independently by 2 reviewers (N.K. and T.F.) using a standardized data extraction sheet and risk of bias was independently evaluated using the Cochrane risk assessment tool.[14] Blinding was reported as completed when outcome assessors were concealed of treatment allocation. With regard to the inconsistency in the reporting of outcomes in the absence of mean scores medians were used as a replacement. Additionally, in cases in which no SDs were given for associated means SDs were estimated by transforming given standard errors or confidence intervals (CIs).

Conceptualization of HRQOL domains

The heterogeneity in CR programs and the multitude of instruments that can be used to measure HRQOL all create problems when attempting to pool the data. To pool HRQOL scores 2 important requirements must be met. First, instruments must measure similar constructs. Second, each measure must have similar responsiveness to change. If instruments are less responsive than their counterparts treatment effects can be underestimated.[15-17]

When performing a meta-analysis of continuous HRQOL data challenges in interpretation occur because of the different instruments used to measure similar constructs.[15] To determine whether the HRQOL instruments identified within the systematic review were appropriate to pool the content each instrument was assessed. By reviewing each instruments' primary article outlining its development and intended use we were able to determine if each instrument was measuring the same underlying constructs. Each of the validated HRQOL instruments were independently examined for the domains of interest and subsequently grouped into 4 discrete conceptual categories.[17]

To measure the essential dimensions of health outcomes they were stratified into overall, physical, emotional, and social HRQOL domains. The **Q**uality of **L**ife after **M**yocardial **I**nfarction (QLMI), MacNew Heart Disease Questionnaire (MacNew), **A**ngina **P**ectoris **Q**uality of **L**ife **Q**uestionnaire (AP-QLQ), **S**eattle **A**ngina **Q**uestionnaire (SAQ), the **M**yocardial **I**nfarction **D**imensional **A**ssessment **S**cale (MIDAS), **Q**uality of **L**ife **I**ndex-Cardiac Version III (QLI), **S**hort **F**orm-36 (SF-36), **S**hort **F**orm-12 (SF-12), **D**uke **A**ctivity **S**tatus **I**ndex (DASI), **S**hort **F**orm-**6D** (SF-6D), **E**uro**QOL**-**5** **D**imension (EQ-5D), and **T**ime **T**rade **O**ff (TTO) were used to evaluate changes in each HRQOL domain. Subscales of these selected instruments that measured the outcomes of interest were extracted, standardized, and pooled into the appropriate domains. A complete list of instruments is shown in Supplemental Table S2.

The overall domain included perspectives on one's life as a whole and was calculated using preference-based measures (EQ-5D, SF-6D, and TTO), which provided a subjective assessment of patients' total health and psychometric profiles (AP-QLQ, QLMI, QLI, MacNew), which produced global scores reflecting patients overall HRQOL. Physical domain included performance of self-care activities, mobility, and physical activities and was calculated using the SF-36, SF-12, MacNew, QLMI, QLI, MIDAS, AP-QLQ, DASI, and SAQ. Emotional domain functions were estimated using the SF-36, SF-12, MacNew, QLI, MIDAS, QLI, and AP-QLQ and included emotional distress and emotional reactions; the social domain included social interactions, behaviours, and isolation and was estimated using the SF-36, QLI, and MacNew.[18] A complete list of the subscales used to create each domain is shown in Supplemental Table S3.

Outcome measures

Study outcomes were measured at baseline (entry to CR) and at follow-up (minimum 6 months). The collected variables included overall, physical, emotional, and social HRQOL domains.

Statistical analysis

To pool outcomes of studies using heterogeneous HRQOL instruments, we used an effect size summary statistic to standardize treatment effects for all scales.[15] In this research we used a repeated measure design investigating the change in HRQOL scores over time and as such the metric of standardized mean change (SMC) was used. SMC is the mean pre−post change in the treatment group minus the mean pre−post change in the control group, divided by the pretest SD.[12] This approach provided a single unit-free estimate of treatment effect in SD units. Additional details of the effect size calculations are shown in the Supplemental Methods S2. To interpret the meta-analysis effect sizes the criterion created by Cohen, which states that effect size changes of 0.2 SD units reflects a small change, 0.5 SD units a moderate change, and 0.8 SD units a large change were used.[19]

Data synthesis and analyses were performed using R software and the package "metafor" (R Institute for Statistical Computing, Vienna, Austria).[20,21] A direct head-to-head pairwise frequentist analysis was used to compare outcomes for those who received CR with those who received usual care. Continuous outcomes are expressed using the metric of SMC and 95% CIs were calculated for each effect estimate.[12]

A multilevel meta-analytic model using independent pairwise crossed random effects were used to account for the correlation between HRQOL instruments and studies with multiple reports of HRQOL outcomes. Crossed random effects were needed to deal with the correlation between each independent study using the same instrument and the clustering that occurred because of the repeated administration of multiple HRQOL instruments in some studies.[15-17]

Additional model statistics are shown in the Supplemental Methods S3.

Stratified meta-analysis using random or fixed effects were performed according to the CR intervention (exercise; studies providing exercise, nonexercise; studies providing no exercise, or psychosocial; studies providing only psychological interventions) and HRQOL instrument used to further explore heterogeneity. Random effects subgroup analyses were performed when there was a large amount of studies; otherwise fixed effects models were used.

Heterogeneity among included studies was quantitatively assessed using the I^2 and tau^2 (T^2) statistics. Because using the I^2 statistic is not precise, an uncertainty interval (UI) was also given.[22,23]

To examine small study and publication bias, funnel plots and Egger tests were performed for each domain.[24] Sensitivity analyses were performed to determine if any single observation was driving the model using identified influential observations and a leave-one-out method.

Moderator variables

Five *a priori* covariates were explored: HRQOL instrument type (generic health profile, disease-specific health profile, or generic preference); type of intervention (exercise, nonexercise, psychosocial only); year of publication; duration of follow-up; and proportion of MI patients. Type of instrument was used to determine if there was a significant difference in the type of measure used to conceptualize HRQOL scores. Disease-specific instruments are thought to be more responsive than generic instruments, which could possibly lead to an underestimation of treatment effect.[25] The type of CR program was included to determine if type of intervention had a differential effect on HRQOL scores. Year of publication was included to explore the change in the improvement of the standard of care over time. The duration of follow-up was explored to determine if the length of the follow-up was associated with HRQOL scores. The proportion of MI patients was used to explore if having more post-MI patients in the program was associated with HRQOL scores. The proportion of variance explained (R^2) in the meta-regression analysis was calculated by comparing the estimate of T^2 with the covariate to T^2 when no covariate was used in the model.[26]

Results

Study demographic characteristics

Figure 1 shows the selection of potentially eligible studies. A total of 1462 potential studies were identified for full-text review with 1413 trials being excluded. Forty-nine reports of 41 RCTs with 11,747 participants met the eligibility criteria and were included in the meta-analysis. Characteristics of included trials are shown in Supplemental Table S4.

The study and patient demographic characteristics are shown in Table 1. Studies were conducted primarily in Europe (46%) and Asia (20%). In terms of publication dates studies ranged from 1991 to 2017. The mean age of participants was 62 (range, 49-77) years and participants were mostly male (62%). Thirteen percent of patients were diagnosed with diabetes and 24% were previous smokers. The median duration of follow-up across all studies was 12 months with the largest follow-up time being reported at 108 months. There were 11 studies using exercise-based CR, with 15 using nonexercise and an additional 15 using psychosocial interventions.

Risk of bias

For each trial the risk of bias was presented using the risk of bias summary (Supplemental Fig. S1). Several studies did not sufficiently report in detail their potential risk of bias resulting in many unclear reports. Details on selection, performance, and detection bias were poorly reported. Because of the nature of CR, it is difficult to blind patients and clinicians to group allocation. Because of the large number of "unclear" reports and the complex nature of some CR programs all studies were included in the analysis regardless of their risk level.

Overall HRQOL

Using fixed effects models, instrument-specific effect sizes were: MacNew SMC, 0.23 (95% CI, 0.10-0.37), EQ-5D SMC, 0.12 (95% CI, 0.02-0.22), and TTO SMC, 0.31 (95% CI, 0.31-0.49), which all represent a small but statistically significant treatment effect. When examining studies according to type of intervention, exercise-based CR was shown to produce an SMC of 0.25 (95% CI, −0.05 to 0.54), which represents a small, but nonsignificant statistical treatment effect, with an I^2 of 84.4%. Nonexercise-based CR produced an SMC of 0.17 (95% CI, 0.01-0.33), which represents a small significant treatment effect, with an $I^2$of 51.2% (Table 2). Investigating all of the studies together irrespective of type of CR and instrument, individuals who received CR had an improved overall HRQOL compared with those who received usual care. Using 16 reports of 14 trials and 3055 participants the SMC was 0.28 (95% CI, 0.05-0.50), which represents a small to moderate treatment effect (Fig. 2). There was a substantial amount of heterogeneity when all of the studies were combined in the SMC model ($I^2 = 90.2\%$; 95% UI, 80%-95%). From the I^2 of 90% all of the inconsistency was attributed to between study variance. The Egger test provided no evidence of publication bias ($P = 0.49$) in terms of funnel plot asymmetry (Fig. 3).

Physical HRQOL

Using fixed effects models, instrument-specific effect sizes were: SF-12 SMC, 0.06 (95% CI, 0.00-0.11), SAQ SMC, 0.19 (95% CI, 0.08-0.29), and MacNew SMC, 0.27 (95% CI, 0.13-0.44), which all represent small, statistically significant treatment effects. Using random effects models instrument-specific effect sizes were: SF-36 Physical Functioning SMC, 0.23 (95% CI, 0.00-0.47) and SF-36 Physical Component Score (PCS) SMC, 0.59 (95% CI, −0.24 to 1.43) with an I^2 of 95.6% and 99.2%, respectively. The SF-36 Physical Functioning showed a small to moderate significant treatment effect. In an examination of studies according to type of CR, exercise-based CR produced an SMC of 1.07 (95% CI, −0.49 to 2.64), which presents a nonsignificant but large treatment effect with an $I^2$of 99.6%. Nonexercise SMC was 0.17 (95% CI, −0.05 to 0.38) and presented a nonsignificant small treatment effect with an $I^2$of 90.9%. Psychological-based CR interventions produced an SMC of 0.52 (95% CI, 0.06-0.98), which

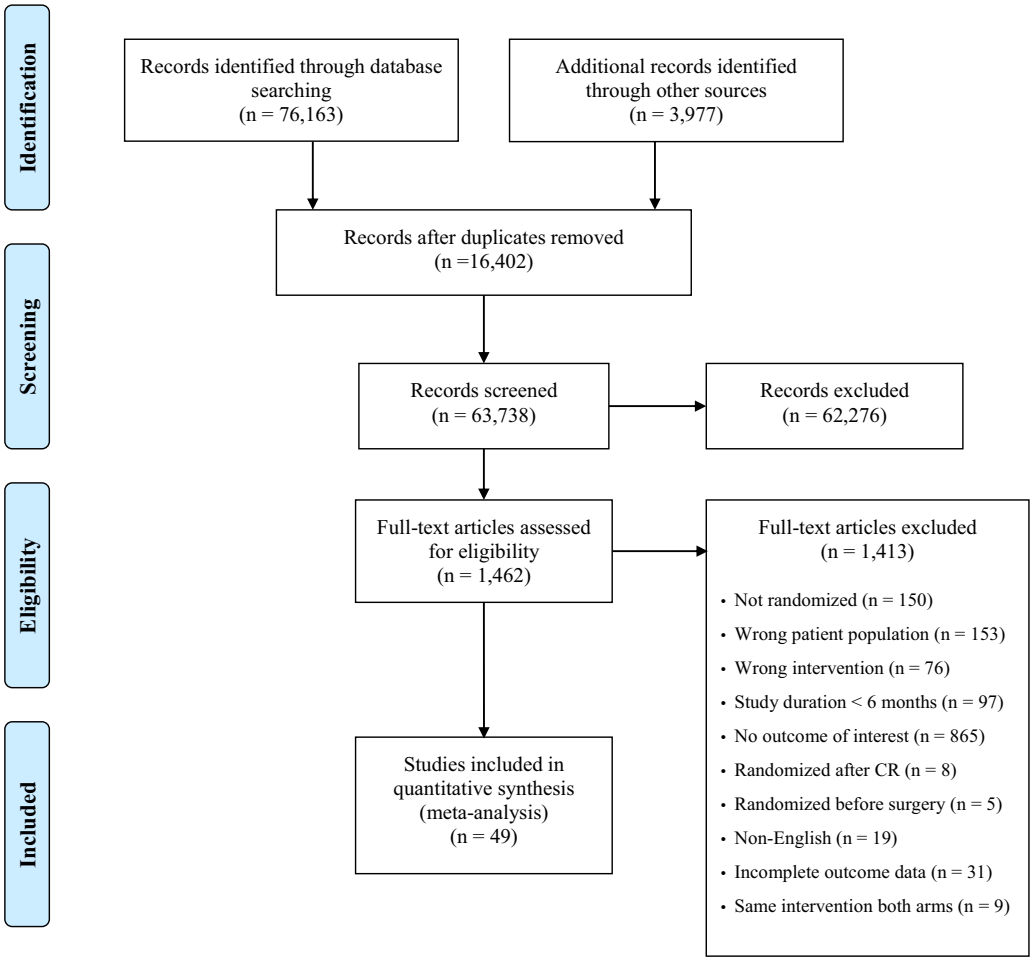

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart of study selection process. CR, cardiac rehabilitation.

represents a significant moderate treatment effect and an I^2 of 96.1% (Table 2). When all of the studies were pooled together, receiving CR improved physical HRQOL compared with receipt of usual care. Using 40 reports of 35 RCTs with 9631 patients the SMC, regarding physical HRQOL was 0.47 (95% CI, 0.13-0.81; Fig. 4). A moderate to large treatment effect was observed. However, there was a considerable amount of heterogeneity when all of the studies were combined in the SMC model (I^2 = 99%; 95% UI, 98%-99%). In relation to the I^2approximately 87% of the inconsistency observed was because of between study variance with 11% because of within study variance. The Egger test provided evidence of publication bias ($P = 0.0001$) in terms of funnel plot asymmetry (Fig. 5). This asymmetry appeared to be due to an absence of small- to medium-sized studies with positive treatment effects.

Emotional HRQOL

Using fixed effects models, instrument-specific effects sizes were: SF-Emotional Limitation SMC, 0.04 (95% CI, 0.00-0.09), SF-12 SMC, −0.03 (95% CI, −0.08 to 0.03), and MacNew SMC, 0.16 (95% CI, 0.07-0.24), with only the MacNew showing a small significant treatment effect. Using a random effects model the instrument-specific effect size for the

Table 1. Baseline demographic characteristics

Characteristics	Overall sample size (n = 11,747)
Study location, n (%)	
Europe	19 (46)
Asia	8 (20)
North America	7 (17)
Australia	6 (15)
South America	1 (2)
Publication date, n (%)	
1990-1999	3 (7)
2000-2009	16 (39)
2010-2017	22 (54)
Mean age ± SD	61.80 ± 6.00
Male sex, n (%)	7298 (62)
Previous myocardial infarction, n (%)	3692 (31)
Previous angina, n (%)	2163 (19)
Previous coronary artery bypass grafting, n (%)	649 (6)
Previous percutaneous coronary intervention, n (%)	1231 (10)
Diabetes, n (%)	1401 (13)
Smoker, n (%)	2765 (24)
Type of intervention, n (%)	
Exercise-based	11 (27)
Not exercise-based	15 (37)
Psychosocial interventions	15 (37)

Table 2. Stratified meta-analysis, CR intervention type

Domain (number of studies)	Effect size, SMC (95% CI)	*P* value	I^2 (inconsistency)
Overall HRQOL			
Exercise (9)	0.25 (−0.05 to 0.54)	0.104	84.42
Non−Exercise (6)	**0.17 (0.01-0.33)**	**0.041**	**51.67**
Physical HRQOL			
Exercise (10)	1.07 (−0.49 to 2.64)	0.179	99.64
Non-exercise (12)	0.17 (−0.05 to 0.38)	0.128	90.85
Psychological (18)	**0.52 (0.06-0.98)**	**0.026**	**96.09**
Emotional HRQOL			
Exercise (8)	1.16 (−0.79 to 3.11)	0.244	99.76
Non-exercise (12)	**0.15 (0.01-0.30)**	**0.034**	**88.46**
Psychological (13)	**0.43 (0.05-0.81)**	**0.027**	**97.48**
Social HRQOL			
Exercise (6)	−0.08 (−0.44 to 0.28)	0.666	93.45
Non-exercise (6)	**0.13 (0.04-0.22)**	**0.004**	**37.02**
Psychological (5)	0.56 (−0.40 to 1.52)	0.25	96.07

Bold text refers to statistical significance for the type of CR intervention which has been shown to improve HRQOL in each respective domain.

CI, confidence interval; CR, cardiac rehabilitation; HRQOL, health-related quality of life; SMC, standardized mean change.

SF-36 Mental Component Score (MCS) was an SMC of 0.85 (95% CI, −0.04 to 1.74) with an I^2 of 99.5% and a nonsignificant treatment effect. Subgroup analyses according to CR type determined that receiving nonexercise- and psychological-based CR interventions resulted in an SMC of 0.15 (95% CI, 0.01-0.30) and 0.43 (95% CI, 0.05-0.81) which represent a significant small and moderate treatment effect, respectively. The inconsistency seen in the nonexercise- and psychological-based CR models were 88.5% and 97.5%, respectively (Table 2). In a meta-analysis of all studies receiving CR did not improve emotional HRQOL compared with usual care. Using 33 reports of 32 RCTs with 9762 patients the SMC was 0.37 (95% CI, −0.02 to 0.78; Fig. 6). There was a considerable amount of heterogeneity when all of the studies in the SMC model were combined (I^2 = 99%; 95% UI, 98%-99%). Ninety-three percent of the inconsistency seen in I^2 was due to between study variance, with 6% being due to within study variance. The Egger test provided evidence of publication bias ($P = 0.0001$) in terms of funnel plot asymmetry (Fig. 7). This asymmetry once again appeared to be due to an absence of small- to medium-sized studies with a positive treatment effect.

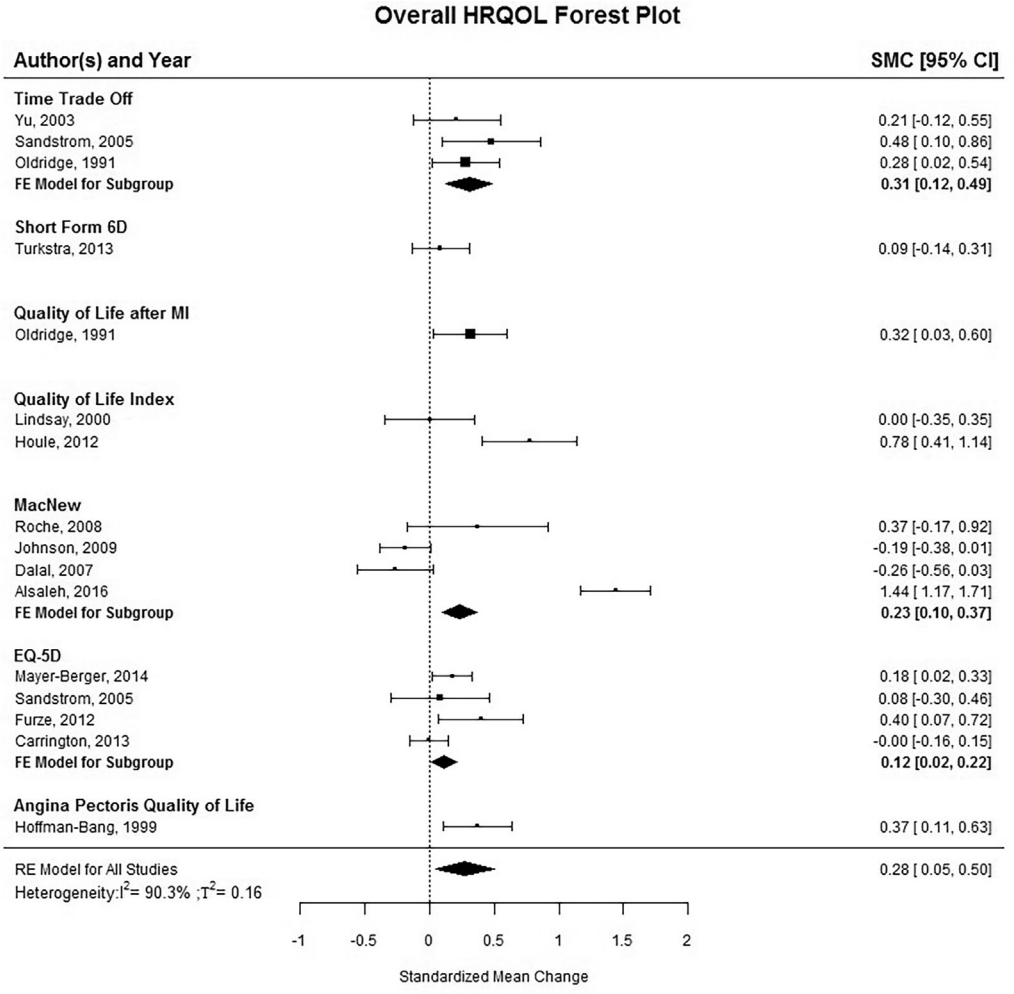

Figure 2. Overall health-related quality of life (HRQOL) forest plot shows the treatment effects of cardiac rehabilitation on HRQOL in standardized mean change (SMC) for each measure and pooled using all instruments. Error bars indicate 95% confidence interval (CI) for each study. EQ-5D, **E**uro**Q**OL-**5** **D**imension; FE, fixed effects; MI, myocardial infarction; RE, random effects.

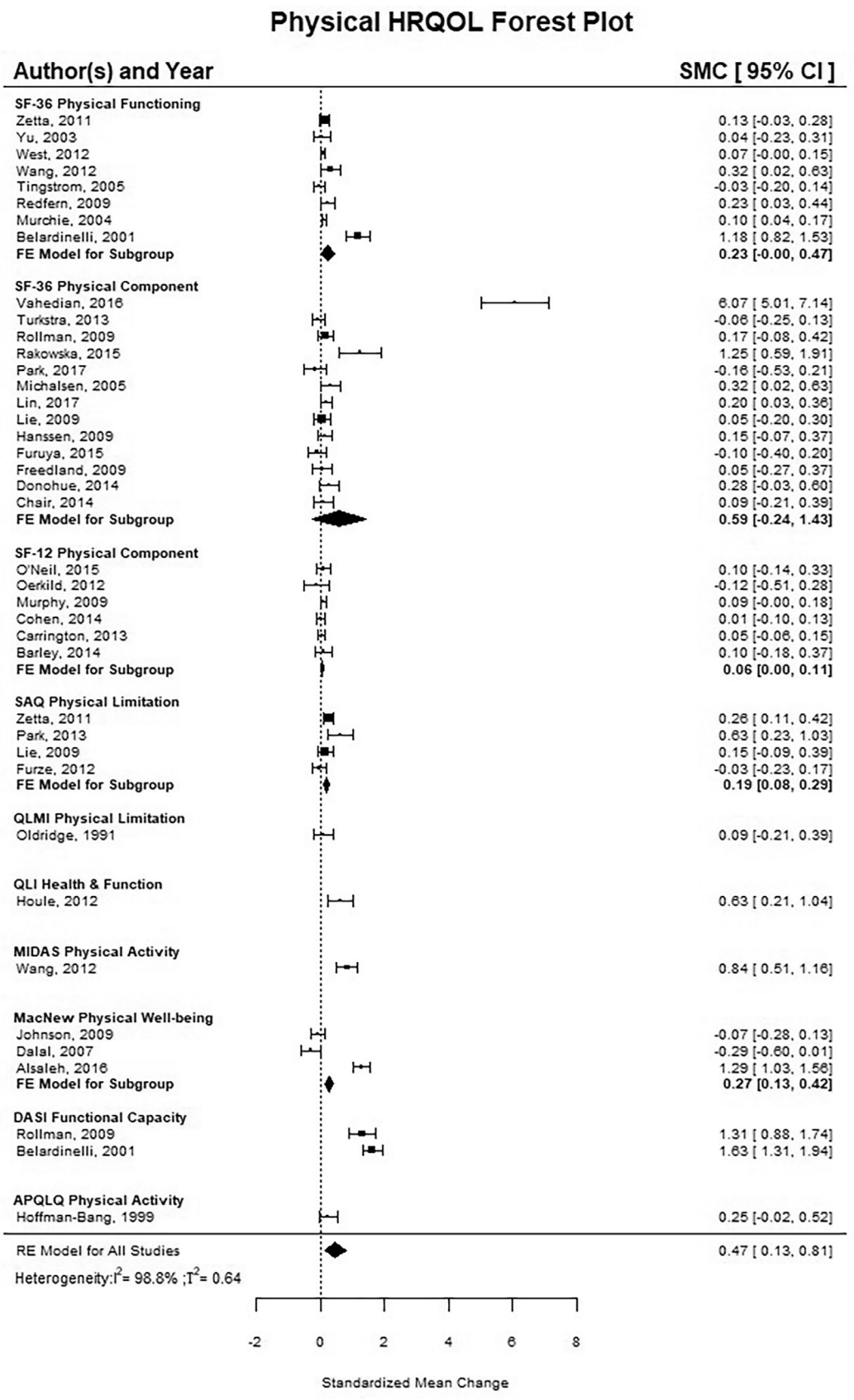

Figure 3. Physical health-related quality of life (HRQOL) forest plot showing the treatment effects of cardiac rehabilitation on HRQOL in standardized mean change (SMC) for each measure and pooled using all instruments. Error bars indicate 95% confidence interval (CI) for each study. APQLQ, angina pectoris quality of life questionnaire; DASI, **D**uke **A**ctivity **S**tatus **I**ndex; FE, fixed effects; MIDAS, **M**yocardial **I**nfarction **D**imensional **A**ssessment **S**cale; QLMI, **Q**uality of **L**ife after **M**yocardial **I**nfarction; QLI, **Q**uality of **L**ife **I**ndex-Cardiac Version III; RE, random effects; SAQ, **S**eattle **A**ngina **Q**uestionnaire; SF, short form.

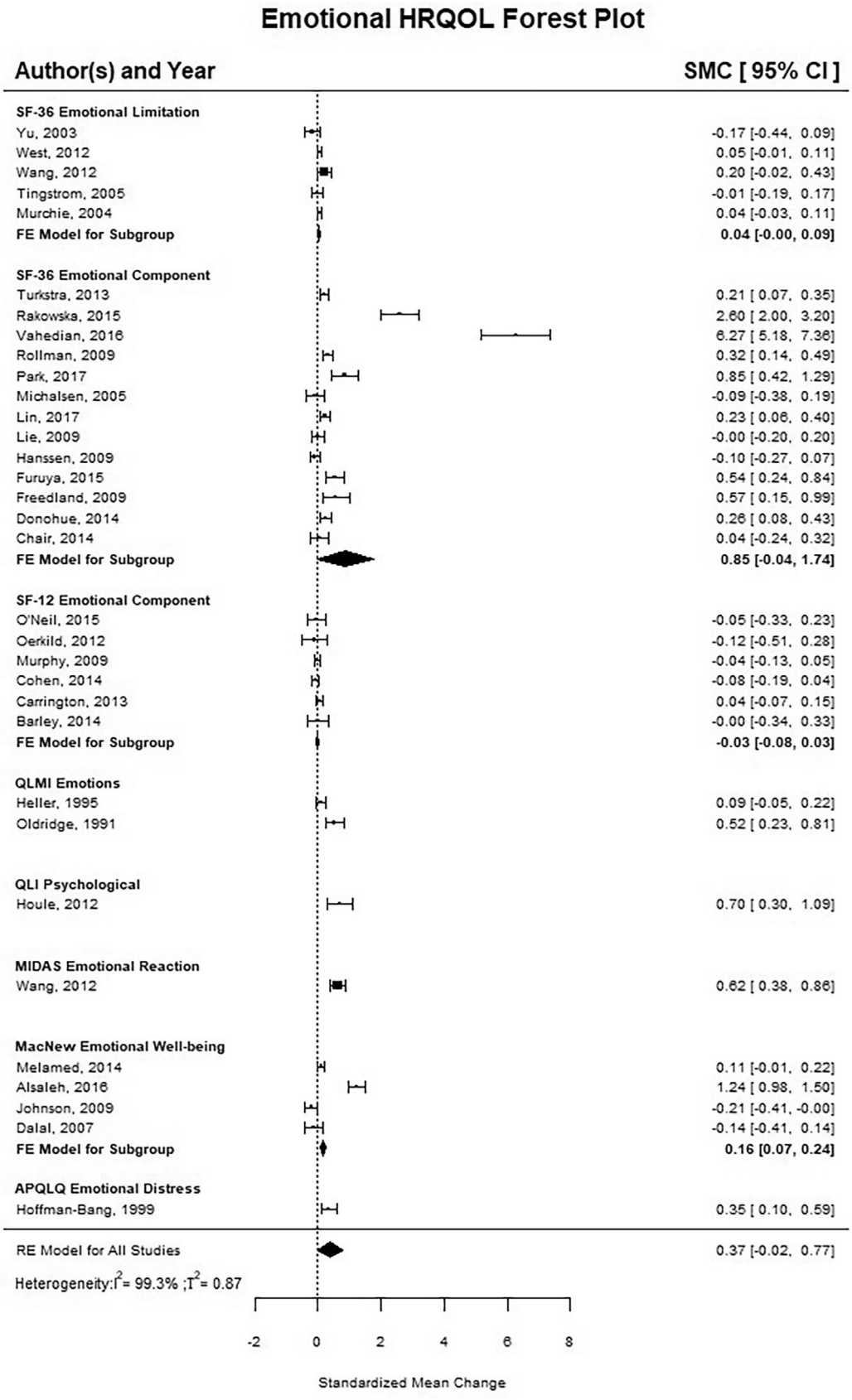

Figure 4. Emotional health-related quality of life (HRQOL) forest plot showing the treatment effects of cardiac rehabilitation on HRQOL in standardized mean change (SMC) for each measure and pooled using all instruments. Error bars indicate 95% confidence interval (CI) for each study. APQLQ, Angina Pectoris Quality of life Questionnaire FE, fixed effects MIDAS, **M**yocardial **I**nfarction **D**imensional **A**ssessment **S**cale; QLMI, **Q**uality of **L**ife after **M**yocardial **I**nfarction; QLI, **Q**uality of **L**ife **I**ndex-Cardiac Version III; RE, random effects; SF, short form.

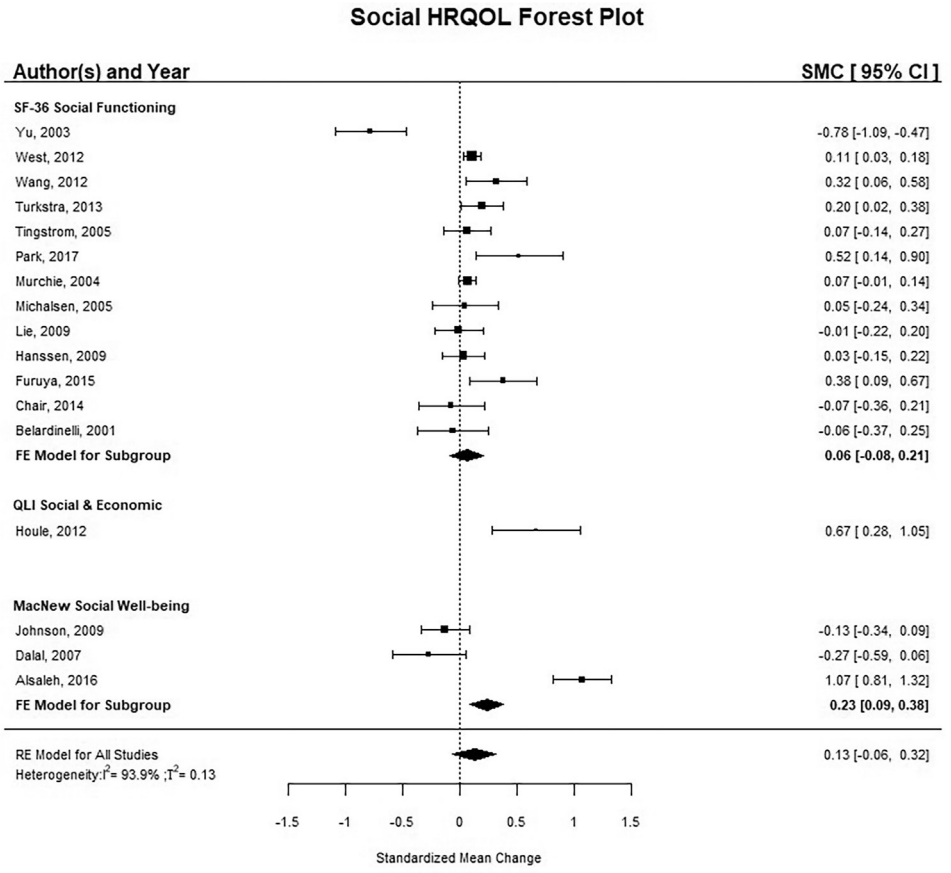

Figure 5. Social health related quality of life (HRQOL) forest plot showing the treatment effects of cardiac rehabilitation on HRQOL in standardized mean change (SMC) for each measure and pooled using all instruments. Error bars indicate 95% confidence interval (CI) for each study. FE, fixed effects; QLI, **Q**uality of **L**ife **I**ndex-Cardiac Version III; RE, random effects; SF, short form.

Social HRQOL

Using a fixed-effects model the instrument-specific effect size for the MacNew was an SMC of 0.23 (95% CI, 0.09-0.38) and produced a significant small treatment effect. Using a random-effects model the instrument-specific effect size for the SF-36 was an SMC of 0.06 (95% CI, −0.10 to 0.21) with an I^2 of 88.7% and a nonsignificant treatment effect. Subgroup analyses according to CR type determined that receiving nonexercise-based CR interventions provided a small significant treatment effect with an SMC of 0.13 (95% CI, 0.04-0.22) and an $I^2$of 37% (Table 2). Receiving CR did not improve social HRQOL compared with usual care. Using 17 RCTs with 5520 patients the SMC was 0.13 (95% CI, −0.06 to 0.32; Fig. 8). There was a substantial amount of heterogeneity when all of the studies in the SMC model were combined (I^2= 94%; 95% UI, 89%-98%). With respect to the inconsistency seen in I^2, 93% of the heterogeneity was due to between study variance and only 1% due to within study variance. The Egger test provided no evidence of publication bias ($P = 0.56$) in terms of funnel plot asymmetry (Fig. 9).

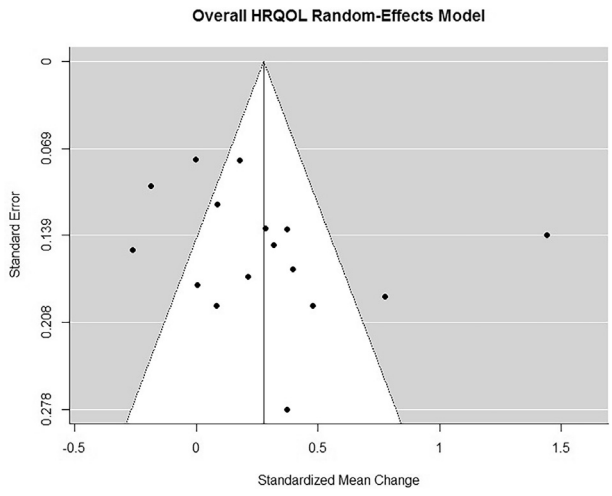

Figure 6. Overall health-related quality of life (HRQOL) funnel plot showing the treatment effects of cardiac rehabilitation on HRQOL against the variance in all studies.

Meta-regression

In our meta-regression we attempted to identify factors that *a priori* we believed to be important treatment effect modifiers. Statistically significant associations were seen in the psychosocial intervention covariate in the overall HRQOL domain (1.31; 95% CI, 0.79-1.82; $P = 0.0001$).

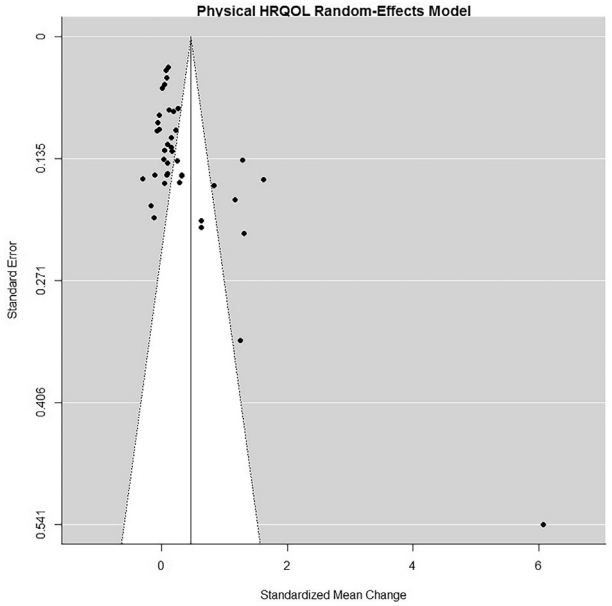

Figure 7. Physical health-related quality of life (HRQOL) funnel plot showing the treatment effects of cardiac rehabilitation on HRQOL against the variance in all studies.

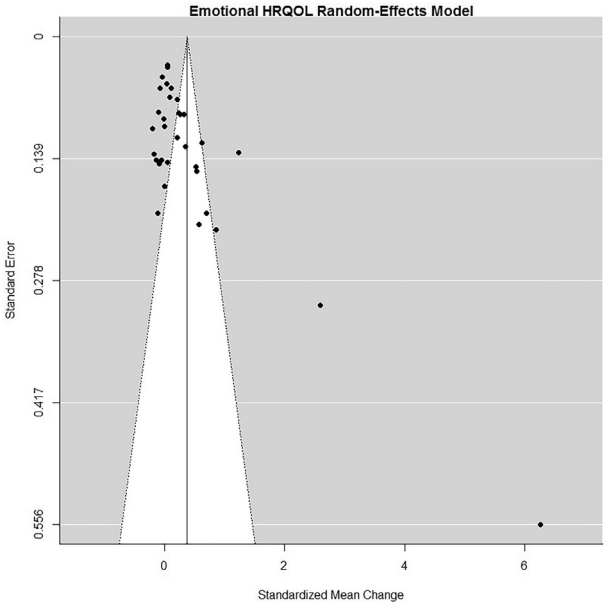

Figure 8. Emotional health-related quality of life (HRQOL) funnel plot showing the treatment effects of cardiac rehabilitation on HRQOL against the variance in all studies.

Additionally, the year of publication (0.06; 95% CI, 0.02-0.09; $P = 0.0004$) and nonexercise intervention (0.50; 95% CI, 0.17-0.84; $P = 0.003$) treatment effect modifiers were shown to be statistically significant in the social HRQOL domain (Table 3).

Sensitivity analysis

Because of the large number of "unclear" reports a sensitivity analysis according to risk of bias could not be performed. We performed sensitivity analyses using a leave-one-out method to assess the potential bias arising from the inclusion of outcome data from outliers deemed to have a strong influence on the Results: overall SMC, 0.18 (95% CI, 0.05- 0.32; $P = 0.01$), physical SMC, 0.27 (95% CI, 0.13-0.40; $P = 0.0001$), emotional SMC, 0.24 (95% CI, 0.07-0.40; $P = 0.003$), and social SMC, 0.06 (95% CI, −0.08 to 0.21; $P = 0.40$; Supplemental Table S5).

Discussion

Narrative and thematic reviews of CR have suggested that CR improves HRQOL in patients with CHD, but it has not been systematically proven.[2,8,27] We found that patients who received CR did improve their HRQOL, but the magnitude of this effect was modest. Nonexercise- and psychological-based interventions produced a significant positive effect on HRQOL. When HRQOL was evaluated using a disease-specific measure, MacNew, HRQOL significantly improved in all domains. On average HRQOL scores in all summary domains were shown to be positive but only statistically significant compared with usual care in the overall and physical dimensions. Our meta-regression further revealed significant associations in the psychological intervention, nonexercise, and year of publication covariates. Recent publications were shown to have higher social HRQOL scores compared with older studies, which might be because of the interventions progressively targeting more than just physical aspects of health. Reports by Alsaleh et al.[28] in the overall and social domain and Vahedian et al.[29] in the physical and emotional domain were shown to have a strong influence on the pooled estimates. These studies were performed within developing countries (Jordan and Iran) without established CR programs providing structured outpatient care in hospital or community settings. The absence of CR programs in these regions might have influenced the participants' willingness to participate and engage in the intervention leading to the large positive treatment effects seen in both studies in relation to those who received their local standard of care.

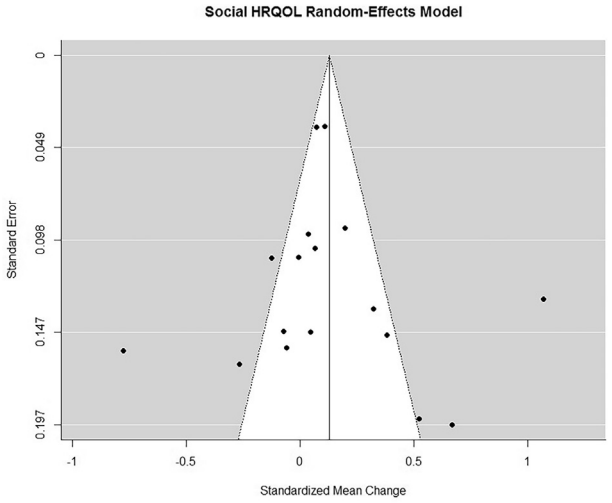

Figure 9. Social health-related quality of life (HRQOL) funnel plot showing the treatment effects of cardiac rehabilitation on HRQOL against the variance in all studies.

Table 3. Meta-regression output

	Explanatory variable		β (95% CI)	*P*	Heterogeneity tau^2 (between study variance)	Proportion of variance explained, %
Overall HRQOL	Instrument type	Generic health profile	0.08 (−0.62 to 0.79)	0.8155	0.1762	0
		Generic utility	−0.08 (−0.39 to 0.24)	0.6333		
	Intervention	Not exercise-based	0.20 (−0.25 to 0.66)	0.3821	0.1651	0
	Psychosocial	**Psychosocial only**	**1.31 (0.79-1.82)**	**0.0001**	**0.042**	**74**
	Proportion of MI patients		−0.003 (−0.01 to 0.00)	0.3227	0.1632	0
	Year		0.01 (−0.03 to 0.04)	0.6831	0.1757	0
	Study duration		−0.01 (−0.03 to 0.02)	0.4571	0.1691	0
Physical HRQOL	Instrument type	Generic health profile	−0.04 (−0.60 to 0.51)	0.88	0.6476	0
	Intervention	Not exercise-based	−0.43 (−1.07 to 0.22)	0.1985	0.6412	0
	Psychosocial	Psychosocial only	−0.002 (−0.57 to 0.57)	0.9957	0.6749	0
	Proportion of MI patients		0.00 (−0.004 to 0.01)	0.3649	0.6695	0
	Year		0.03 (−0.02 to 0.09)	0.2053	0.6382	0
	Study duration		0.01 (−0.01 to 0.02)	0.4846	0.6689	0
Emotional HRQOL	Instrument type	Generic health profile	−0.16 (−0.76 to 0.45)	0.6087	0.889	0
	Intervention	Not exercise-based	−0.54 (−1.33 to 0.26)	0.1763	0.8539	2
	Psychosocial	Psychosocial only	−0.07 (−0.79 to 0.65)	0.8495	0.9084	0
	Proportion of MI patients		0.01 (0.00-0.01)	0.2748	0.886	0
	Year		0.04 (−0.2 to 0.10)	0.1597	0.8436	3
	Study duration		0.01 (−0.01 to 0.03)	0.3573	0.88	0
Social HRQOL	Instrument type	Generic health profile	0.00 (− 0.91 to 0.92)	0.9949	0.1305	1
	Intervention	**Not exercise-based**	**0.50 (0.17-0.84)**	**0.0030**	**0.074**	**44**
	Psychosocial	Psychosocial only	0.26 (−0.14 to 0.66)	1.2865	0.1243	6
	Proportion of MI patients		−0.003 (−0.01 to 0.00)	0.2413	0.1297	2
	Year		**0.06 (0.02-0.09)**	**0.0004**	**0.069**	**48**
	Study duration		−0.002 (−0.01 to 0.01)	0.5804	0.1418	0

Bold text refers to exploratory variables shown to have statistical significance in their respective domains and explain some of the between study variance.
CI, confidence interval; HRQOL, health-related quality of life; MI, myocardial infarction.

The Results of this study quantitatively reinforce some of the findings of previous systematic reviews that have narratively shown CR to improve HRQOL, but provides conflicting evidence on what type of CR improves HRQOL.[2,8,30] In an overview of systematic reviews on CR conducted by Taylor and Anderson[2] it was shown that varying models of CR have a different effect on HRQOL. Patient education and psychological interventions did not consistently improve HRQOL in the studies assessed,[31,32] but exercise-based CR was shown to significantly improve HRQOL in 7 of 10 studies.[9] Additionally, Anderson et al.[8] reported evidence of higher levels of HRQOL in patients who received exercise-based CR compared with controls.

In contrast, we did not observe a statistically significant effect on HRQOL with exercise-based CR, but we did with nonexercise-based and psychological interventions. We were unable to pick apart the exercise component of CR that likely led to the uncertainty in our Results. This was because of differences in exercise intensities, frequencies, modalities, and the length of interventions of included studies.

Our findings do not take away from the value of exercise-based interventions in being a critical component of CR. In general, exercise has been associated with an improvement in quality of life in different populations. Older adults have been shown to improve their functional capacity, autonomy, and general quality of life through receiving exercise.[33] More importantly exercise training interventions have been shown to preserve and maintain HRQOL in older community dwelling adults.[34]

Implications for practice

There is more to health than mortality benefits alone. Our findings reinforce anecdotal evidence that CR is effective in not only reducing the risk of mortality and future hospitalizations, but is also effective in improving HRQOL. Our Results give credence to the varying models of CR and their ability to positively influence HRQOL. Although it might not be economically feasible for all programs to be truly comprehensive in nature, the results of this report show that program designs can be flexible and still influence overall HRQOL. Through further disseminating CR effects on patient-reported outcomes such as HRQOL, future health policies should seek to improve adherence and optimize CR delivery to suit the needs of the patient, which could lead to better public health outcomes.

Strengths and limitations

One of the major strengths of this study is that we were able to examine and organize a large number of studies and instruments that investigated at CR. Additionally, by using an extensive process to contact study authors for clarification on Results, we were able compile a more comprehensive set of data. Our analysis contains a variety of CR interventions, allowing for a more complete comparison of the varying core components of CR across HRQOL domains. Additionally, we

used the metric of SMC, which took into account the baseline mean HRQOL scores and calculated the mean treatment effect in each study.

The poor level of reporting in some trials made it difficult to assess the quality of some studies. Many RCTs that were included in the analysis did not give enough detail to allow proper assessment of risk of bias leading to many "unclear" judgements. Additionally, the vast differences in the reporting of outcomes and HRQOL instruments used from study to study created difficulties when we attempted to pool the Results. The heterogeneity of the different patient types could not be examined because of the lack of detail regarding patient diagnoses and comorbidities reported across studies. Last, the meta-regression analysis was limited with respect to the variety and detail of the covariates that could be investigated because of unreported information.

Recommendations for future research

This study shows that more research should be directed to the patient populations that receive CR, intensity of CR interventions provided, methods of CR delivery, as well as the potential treatment effect of country of recruitment.[2,8] Future research to explore the complexity within CR needs to use indirect treatment comparisons using network meta-analysis. Now that we know receiving CR can improve HRQOL, using mixed treatment comparisons will allow us to answer questions such as, "which combination of components has the greatest probability of improving HRQOL." Finally, going forward there needs to be more consistency in the conducting and reporting of HRQOL, which will allow for better comparisons across CR trials. Many studies were excluded from this review because they did not use a pre—post study design and provided incomplete HRQOL outcome data. Future studies need to use disease-specific measures that evaluate all aspects of HRQOL, such as the MacNew.

Conclusions

Our Results provide empirical evidence that shows that, in general, receiving CR can improve HRQOL, with non-exercise- and psychological-based interventions playing a vital role in addition to exercise-based models. These results should be interpreted accordingly because of the large amount of heterogeneity within some domains. It is important to note that the lack of statistical significance for any HRQOL outcome in our study does not reflect an absence of benefit of receiving CR in terms of improving HRQOL. Future trials in CR need to improve their quality of reporting, most notably in relation to risk of bias and providing full outcome data with associated measures of dispersion.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.11.013.