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Benefits of Exercise in Heart Failure: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review

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ABSTRACT

Objective: To update Sagar et.al. systematic review and meta-analysis on exercise-based rehabilitation for heart failure.
Methods: A systematic review and meta-analysis of randomized clinical trials on exercised-based cardiac rehabilitation. MEDLINE, OVID and cross references were searched for RCTs published between February 2013 up to August 2018. Trials with at least 6 months follow up were included if exercise training program alone or as a component of comprehensive cardiac rehabilitation was compared with groups without exercise prescription.
Results: A total of 11,989 patients were included in the 43 randomized clinical trials predominantly with reduced EF and NYHA class ll -lll. Exercise training program prescription in heart failure patients reduced the all-cause mortality (RR=0.76; 95%CI= 0.66, 0.87; P= 0.001), all cause hospitalization after 12 months (RR=0.70; 95% CI= 0.52, 0.96; P= 0.02) rehospitalization due to heart failure (RR= 0.49; 95% CI= 0.44, 0.55; P= <0.0001) and improvement in quality-of-life scores

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(RR= -0.36; 95% CI= -0.58, -0.14; P= 0.002). Among these health quality related outcomes, the all-cause mortality and the hospitalization admission after 12 months follow up showed a significant association with exercise therapy program, particularly on exercise setting(p=0.026) and exercise dose (p=0.013), respectively, as revealed by the univariate meta-regression results.

Conclusion: This study has shown that exercise therapy either in center or home based has benefited heart failure patients in reducing the risk of all-cause mortality up to 12 months, hospital admission up 12 months, and has given a better quality of life. The new studies included have further strengthened the findings of previous studies that an exercise therapy program provides benefit to heart failure patients, either as an "alone" intervention or together with a cardiac rehabilitation program; and that the setting and dose of an exercise therapy program provide significant contribution to a reduced risk in all-cause mortality and hospitalization after 12 months follow up, respectively.

Keywords: Heart Failure; exercise therapy; cardiac rehabilitation.

1. INTRODUCTION

A progressive heart disease leading to chronic heart failure, regardless of its etiology would lead to poor quality of life and depression to a previously active person. Dyspnea, fatigue, and inability to do activities of daily living worst outcomes [1] would include decrease mobility, low quality of life, frequent hospital readmissions and eventually increase in mortality [2]. Exercise and cardiac rehabilitation studies on heart failure patients have revealed effectiveness of an exercise program in improving the functional capacity, quality of life, clinical outcomes, and cost effectiveness of patients with chronic heart failure. Thus, exercise training has been recommended by different guidelines as a reasonable adjunctive therapy in chronic heart failure. Moderate continuous endurance exercise has been demonstrated to be effective and safe for this subset of patients [3].

Published studies on exercise benefits in heart failure, in both preserved and reduced EF condition in randomized clinical trials, with follow up of at least 6 months was done using different search engines to update the findings of a systematic and meta-analysis published in 2014 by Sagar et al with objective of updating the 2010 Cochrane systematic review on exercised-based rehabilitation for heart failure, focusing on the effectiveness of exercise on mortality, readmission and health related quality of life. Three studies included elderly patients aged >70 years old [4-6] [7-10], women [9] critically ill patients [7] and patients with atrial fibrillation [11]. Two studies reevaluated the cost effectiveness of the intervention [12-15].

The aim of this update review is to reassess the effectiveness of exercise therapy/cardiac rehabilitation, either in center- or home- based, to heart failure patients.

2. METHODS

2.1 Protocol and Registration

The protocol followed the PRISMA statement, and the methods done by the Viral Sagar et al. in their systemic review (http://dx. Doi.org/10.1136 /openhrt- 2014-000163). Database (Medline and OVID) was searched from January 2013 (the searching end date of the previous Cochrane review) to present date using the following search terms: exercise, physical exertion, heart failure, HFpEF, HFrEF and rehabilitation. References of journals were also reviewed for potential studies.

2.2 Eligibility Criteria

All randomized clinical trials from February 2013 up to August 2018 that have subjects with heart failure (both HFrEF and HFpEF) who are at least 18 years old and observed a follow up period of 6 months or more were included in the analysis. Studies with patients with previous exercise therapy/cardiac rehabilitation program were excluded. Studies included were those that have control groups that did not receive any form of exercise intervention but on optimal medical treatment and intervention groups have received exercise therapy or a programmed cardiac rehabilitation. Further, the studies have findings on four outcomes, namely: 1) death (all-cause, HF-related and sudden death); [2] hospital readmission (all-cause or HF-related); [3] quality of life assessed using validated outcomes questionnaires and [4] treatment cost-effectiveness. Investigators screened the titles,

abstract and full text journals for eligibility. Some of the authors were contacted for information not found or clarifications of data in the manuscripts.

2.3 Data Extraction

In every study included in this study, the design, patients' characteristics, intervention group details (including type frequency, duration, and intensity of the exercise), nature of control group, length of follow-up and outcomes were extracted manually and through RevMan 5.3 (Table7). Trial quality was also assessed based on Cochrane risk of bias tool.

2.4 Statistical Analysis

Cochrane Handbook for Systematic Reviews of Interventions was followed to analyze all data. Nominal or binary variables are reported as the number of patients with events and without events in both the control and intervention groups and quality of life. Continuous variables are reported as standard deviations or mean for the different variables and when these are not available median was used (also a measure of central tendency). The absolute mean and standard deviation at follow up for both groups were used. Heterogeneity was assessed qualitatively by comparing the characteristics of the studies (Table 2) and I^2 statistics for quantitative data. Funnel plot was used to identify small study bias and publication bias. Data on the three outcomes from the studies published February 2013 to present were incorporated in the previous data to increase the number of studies and patients to obtain accurate results. All data were analyzed using the Stata/SE 15 and RevMan 5.3. To further the analysis, the F-test for equality of variances and the t-test for pooled-variances based on the result of the F-test for equality of variances were also used.

3. RESULTS

3.1 Descriptive Summary of Included Studies

The searches yielded 1065 studies. After the review of the abstracts, 41 full papers were included. However, 31 papers were excluded and only 10 full papers (RCTs) fulfilled the review inclusion criteria. The 2014 updated Cochrane review conducted by Sagar et al provided 33 RCTs resulting to a total of 43 studies. This is summarized in Fig. 1.

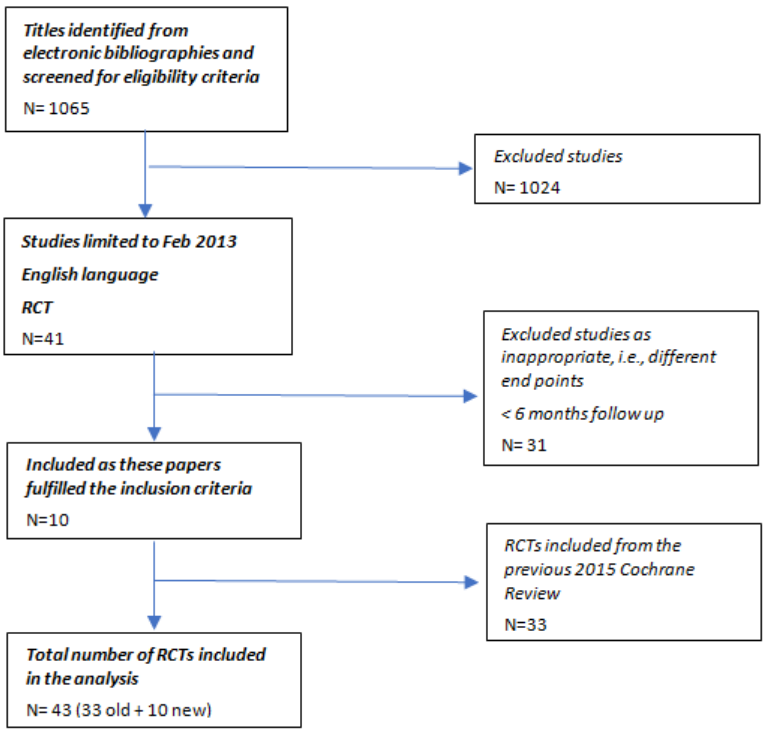

Fig. 1. Summary of study inclusion/exclusion process

From the 43 studies, as shown in Table 1, a total of 11,989 (4740 old and 7249 new) patients were included in the randomized clinical trials, predominantly with reduced EF and NYHA class ll -lll. Selected characteristics of the 33 RCTs (old) were found in the previous Cochrane review [16]. These are also found in the 10 new RCTs included in the update review. The study by I. Pina et.al (2013), which is a sub-study of the HF ACTION, contributed 2331 patients in the new RCTs included. The mean age of patients ranged from 58 to 76 years (51 to 81 years for the old studies). Both sexes were recruited in the new RCTs in contrast to more females in the previous review. There are six trials with more than 12 months follow period. Details of the interventions done in the new RCTs vary from marching in place to walking, resistance/strength and aerobic exercises for both center- and home- based settings. Majority of the exercise sessions were done first in exercise centers/hospital rehabilitation sections followed by exercises done at home. The duration of the exercise training varied widely with sessions duration of 20 to 250 minutes per week with intensity of up to 70% of maximal heart rate or Borg rating of 12-15 and delivered from six months to more than 36 months.

3.2 Risk of Bias

Table 2 shows that several clinical trials did not give sufficient data to allow complete assessment of risk of bias. The overall risk of bias was moderate. Majority [17]of the trials did not elaborate on how randomization was done [4-11] and 2 trials did not mention randomization in the methodology [7-12] All studies had group balanced at baseline and only two studies [18-19] had an intention to do a treat analysis. Given the nature of intervention, it was impossible to blind the caregivers and participants and not all participants were accounted for at the end of the study.

3.3 Outcomes

3.3.1 Mortality

There was significant difference in pooled mortality of up to 12 months follow up between the control and exercise training groups (28 trials, RR=0.76; 95% CI= 0.66,0.87; P= <0.00001). There was a reduction in all-cause mortality in heart failure patients in favor of exercise training program. This was driven by the study of Pina [20] which contributed to 54.0% and Doukky [21] 24.4% of the effect.

Old studies and new studies have statistically the same RRs (F-prob $_{(0.05)}$ = 0.098; t-prob $_{(0.05)}$ = 0.179). However, it has to be noted that the new studies revealed a reduced risk in the exercise training groups than those revealed in old studies ($Mean_{(new)}$ = 0.54 < $Mean_{(old)}$ = 1.27). They also have less varied composition of RRs than the old studies included in this update review study ($CV_{(new)}$ = 54.06% < $CV_{(old)}$ = 70.74%). These risk ratios retrieved from the new studies signify the benefit of exercise training program in reducing mortality among heart failure patients and strengthen the findings of previous studies.

Table 1. Selected Characteristics of the new included RCTs

Characteristics	Number
Exercise only	0
Setting	
Center based	0
Home based	3
Both	7
Sample size	37 to 2331
Publication date	
Feb 2013 to present	10
Single center	4
Multi center	6
Study Locations	
Europe	4
America	3
Others	3
Sex	
Men only	0
Women only	1
Both	9
Age (years)	58.5 to 76.9
Diagnosis	
HFREF	8
HFPEF	0
Both	2
Left ventricular ejection fraction (%0	25% to 50%
Included NYHA IV	3

Legend: HFREF, heart failure with reduced ejection fraction; HFPEF, heart failure with preserved ejection fraction

3.3.2 Hospital admissions

A significant reduction in hospital admissions after 12 months (8 trials, RR= 0.70; 95% CI= 0.52,0.96; P=0.02) and heart failure rehospitalizations (18 trials, RR=0.49; 95% CI= 0.44,0.55; P=<0.00001) were observed in the exercise training groups compared to the no exercise (usual care) group (Figs 3 and 4).

Table 2. Summary didactic categorical description of risk of bias assessment of new studies by author

Author(year)	Adequate sequence generation	Allocation concealment	Outcome blinding	Intention to treat analysis	Group balanced at baseline	Complete outcome report
Hollriegel (2016)	yes	yes	?	?	yes	yes
Chen (2017	yes	yes	yes	?	yes	no
Hagglund (2017(	yes	?	?	no	yes	yes
Denehy (2013)	yes	yes	yes	?	yes	yes
Krainer (2013)	no	no	no	?	?	?
Mudge (2018)	yes	yes	no	yes	yes	yes
Pina (2014)	yes	yes	yes	yes	yes	No
Antonicelli (2016)	yes	yes	yes	no	no	no
Lou (2017)	yes	yes	yes	yes	yes	yes
Doukky (2016)	no	no	no	?	?	?

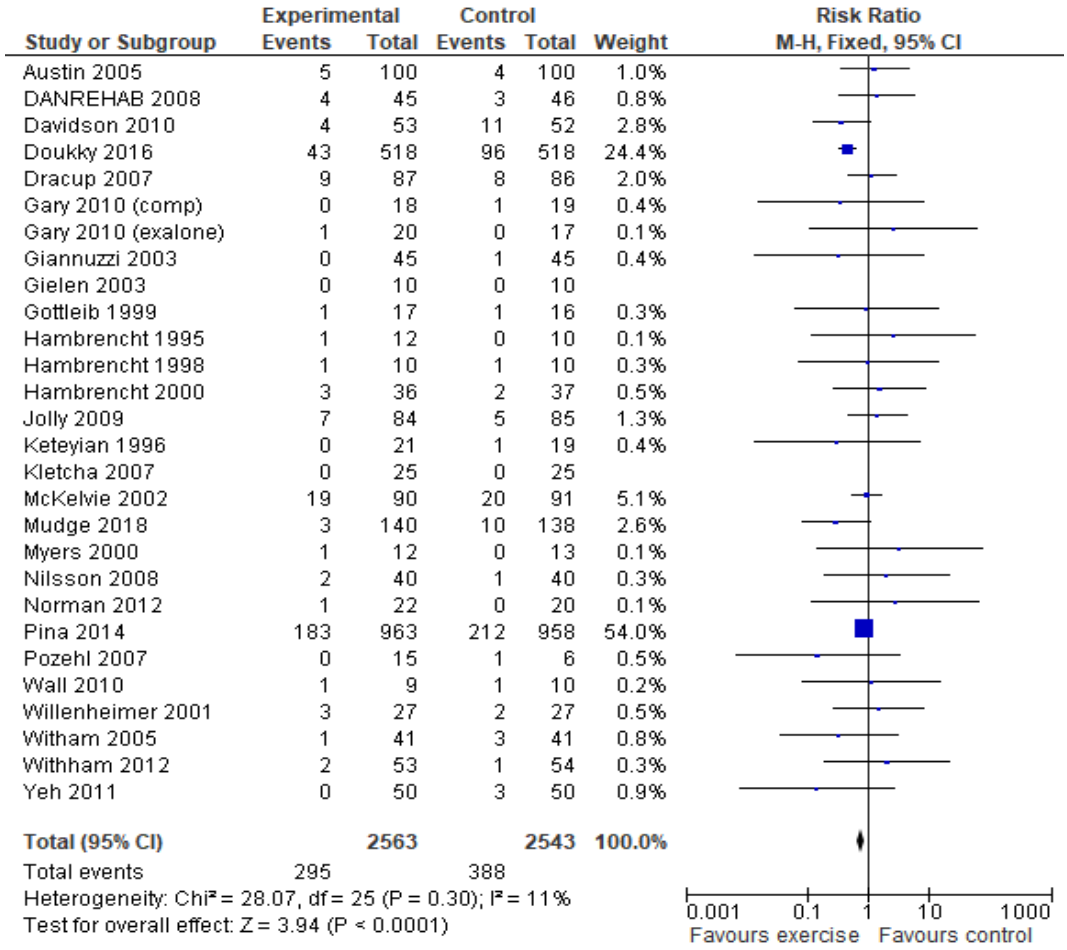

Fig. 2. Pooled all-cause mortality of all trials (old and new) up to 12 months follow up

Table 3. Comparative summary of all-cause mortality risk ratios

Studies Included	Mean	SD	CV	F-prob $_{(0.05)}$	t-prob $_{(0.05)}$
Old	1.27	0.90	70.74%	0.098	0.179
New	0.54	0.29	54.06%		

Findings on hospitalization outcomes have further revealed that old studies and new studies have statistically the same RRs (Hospitalization Admission after 12 months follow-up: F-prob $_{(0.05)}$ = 0.297; t-prob $_{(0.05)}$ = 0.717; Hospitalization Admission Due to Heart Failure rehospitalization: F-prob $_{(0.05)}$ = 0.083; t-prob $_{(0.05)}$ = 0.535). Though the new studies revealed a better reduced risk in hospital admission after 12 months follow up in the exercise training groups than those revealed in old studies, this is not the case in hospitalization admission due to heart failure rehospitalization (Hospitalization Admission after 12 months follow-up: Mean$_{(new)}$ = 0.69 < Mean$_{(old)}$ = 0.81; Hospitalization Admission Due to Heart Failure Rehospitalization: Mean$_{(new)}$ = 0.86 > Mean$_{(old)}$ = 0.66). Nevertheless, these results have still further signified the benefit of exercise training program in heart failure patients.

3.3.3 Health-related quality of life

There are 24 trials (18 old and 4 new) that reported a validated health related quality of life measures. Majority of the trials used the Minnesota Living with Heart Failure questionnaire. Lou (2017) and the HF-ACTION trial, however, used the Kansas City Cardiomyopathy questionnaire. Figs 5 shows that there was an improvement in all quality-of-life scores of up to 12 months follow up in the trials included in the analysis (24 trials: SMD=-0.36; 95% CI= -0.58-0.14; P=0.002). However, a favorable significant improvement is detected in

the exercise training groups. The new studies included in this study given more weight on this finding than the old studies (Mean $_{(weight\ new)}$ = 4.10 > Mean $_{(weight\ old)}$ = 3.67). This is further strengthened by the size of the intervention effect of the new studies than the old studies (Mean $_{(SMD\ new)}$ = -0.22 > Mean $_{(SMDold)}$ = -0.61)

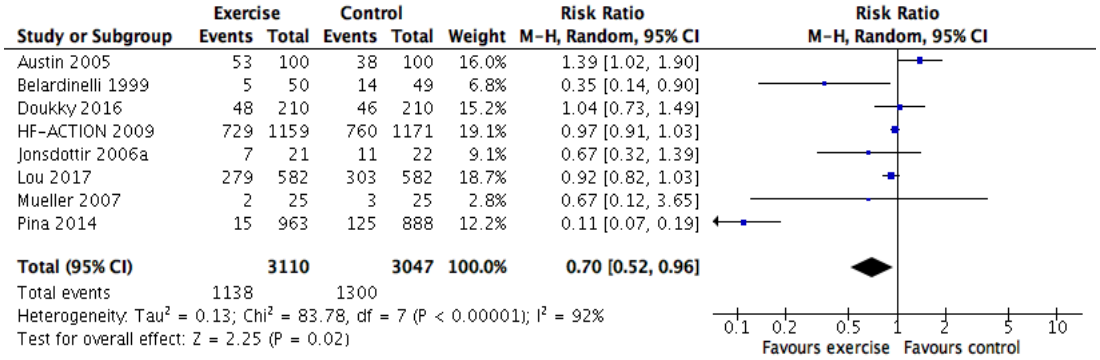

Fig. 3. Hospital admission outcomes after 12 months of follow up

Table 4. Comparative summary of hospital admission outcomes (after 12 months follow up) risk ratios

Studies Included	Mean	SD	CV	F-prob $_{(0.05)}$	t-prob $_{(0.05)}$
Old	0.81	0.39	48.32%	0.297	0.717
New	0.69	0.51	73.31%		

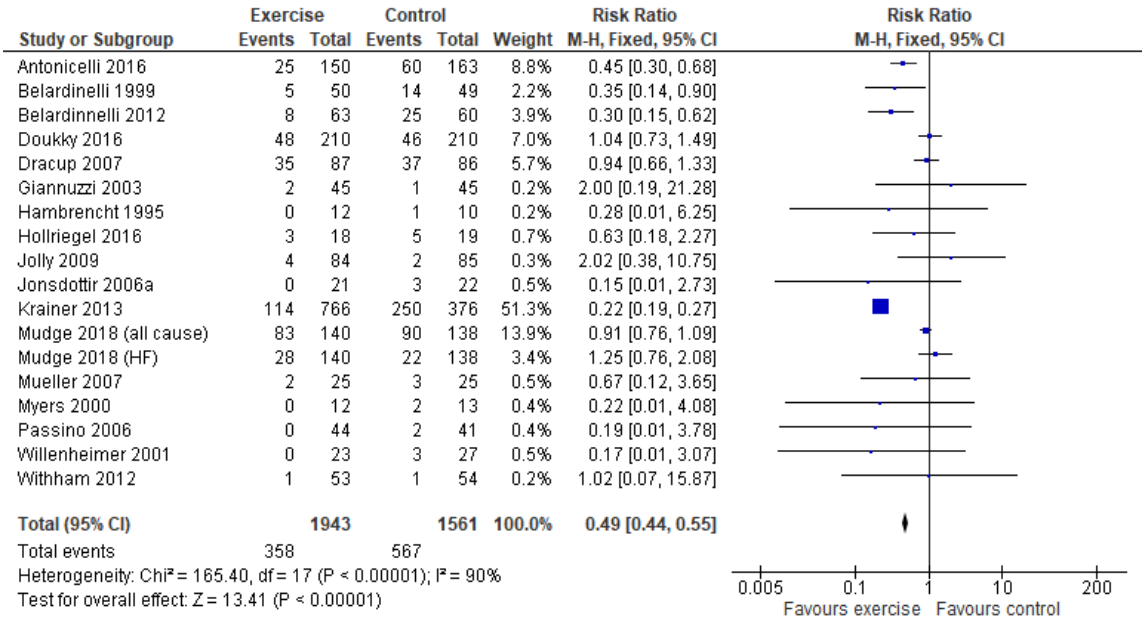

Fig. 4. Hospital admissions outcomes due heart failure rehospitalization

Table 5. Comparative summary of hospital admission outcomes (due to hf rehospitalization) risk ratios

Studies Included	Mean	SD	CV	F-prob $_{(0.05)}$	t-prob $_{(0.05)}$
Old	0.66	0.67	101.58%	0.083	0.535
New	0.86	0.32	37.31%		

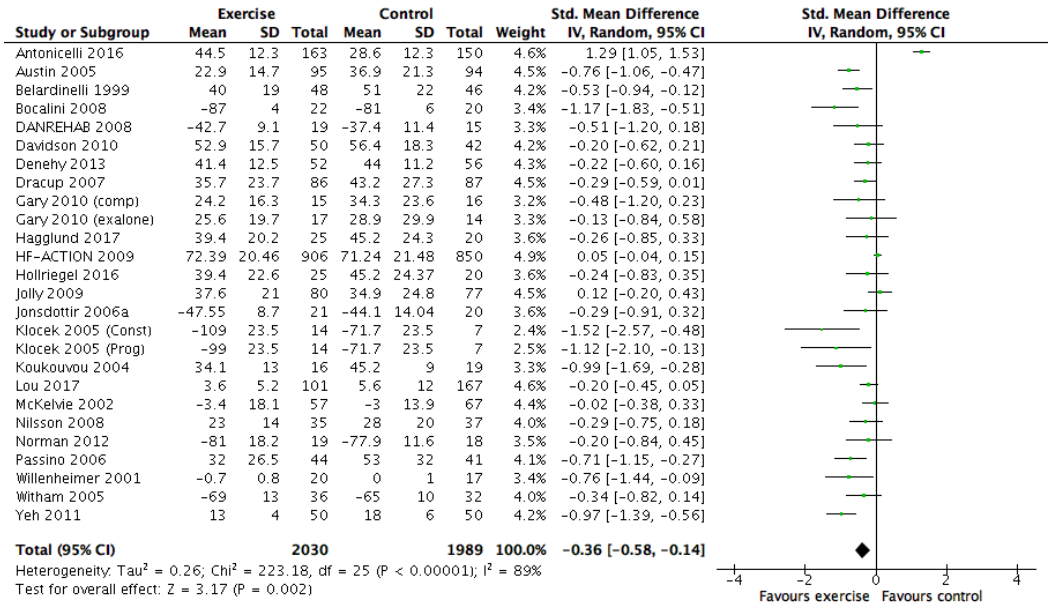

Fig. 5. Forrest plot of comparison: All Quality-of-Life scores up to 12 months follow up

Table 6. Comparative summary of old and new studies

	Mean	SD	CV	F-prob $_{(0.05)}$	t-prob $_{(0.05)}$
Weight					
Old	3.67	0.62	16.72%	0.265	0.373
New	4.10	0.71	12.19%		
Std. Mean Difference					
Old	-0.61	0.40	66.55%	0.055	0.201
New	-0.22	0.03	12.86%		

3.3.4 Meta regression analysis

Among the health quality related outcomes, only the all-cause mortality and the hospitalization admission after 12 months follow up have significant association with exercise setting and exercise dose, respectively, as revealed by the univariate meta-regression results. The risk of bias is also revealed to be significantly associated with the MLWHF and the all HRQol. The risk of bias in the quality of life is significant because results of smaller studies are subject to greater variation in sampling hence are less precise [22] as reflected in the smaller weights each study contributed to the Forrest plot (Fig. 4, 5).

3.3.6 Cost and cost effectiveness

In the previous Cochrane review (13), an additional healthcare cost of US$3227/patient is expected in the exercise training group with incremental life expectancy of 1.82 years/person. Recently, a cost analysis study in Columbia found that exercised-based cardiac rehabilitation in heart failure resulted in an ICER of US$3156 per life year gained and US$998 per QALY when compared with usual care [15]. The willingness-to-pay thresholds of US$7 000, US$14 000, and US$21 000 (which is equivalent to 1, 2, and 3 times the GDP per capita in Colombia in 2011), respectively was found to be cost effective [15]. Exercise training program has been found to be cost-effective if the willingness to pay is >$29,697 with ICERs of $31,624 per life year save, incremental life year saved of 0.81 and life year saved of 7.93 years per patient [17].

3.3.7 Small study bias

The hospital admission after 12 months follow-up (Egger test: estimated coefficient of 0.008; SE of 1.7 and P=0.996) and hospital admission due to heart failure (Egger test: estimated bias coefficient of -2.4; SE of 0.88 and P=0.01) did not show funnel plot asymmetry (Figs. 7,8,9).

Table 7. Univariate meta-regression results

	All-cause mortality p Value	All hospitalizations p Value	MLWHF P Value	All HRQoL outcomes p Value
Type of rehabilitation (exercise only vs comprehensive)	0.199	0.328	0.236	0.283
Type of exercise (aerobic training alone vs aerobic plus resistance training	0.618	0.701	0.776	0.442
Exercise setting	0.026	0.770	0.068	0.100
Exercise dose	0.646	0.013	0.613	0.521
Single versus multicenter	0.072	0.909	0.432	0.321
Publication date	0.687	0.196	0.398	0.023
Risk of Bias	0.831	0.259	0.005	0.020

Low risk bias: absence of > 4/6 risk of bias items; high risk: absence of bias <4/6 risk of bias items; MLWHF: Minnesota Living with heart failure questionnaire:HRQol: health related quality of life

The test provides weak evidence for the presence of small-study effects and publication bias. However, funnel plot asymmetry was seen with all-cause mortality of up to 12 months (Egger test: estimated bias coefficient of 0.68; SE of 0.24 and P= 0.009) (Fig. 6) and all quality-of-life scores (Egger test: estimated coefficient of -2.41; SE of 0.88 and P=0.011).

4. DISCUSSION

This update systematic review reveals benefit of exercise therapy/cardiac rehabilitation, either in center- or home- based, to heart failure patients, by meta-analyzing 43 studies with a total of 11,989 (4740 old and 7249 new) patients who were included in the randomized clinical trials, predominantly with reduced EF and NYHA class ll -lll. It found out that the exercise therapy has benefited the heart failure patients in reducing the risk of all-cause mortality up to 12 months, hospital admission up 12 months, and has given a better quality of life. Though this finding is revealed based on the 43 studies, where 33 are old published studies and 10 are new, the new studies included in this systematic review and meta-analysis have been detected to record a better reduced risks in all health-related outcomes covered in this study than those that were recorded by the old studies. The new studies included in this study have further strengthened the findings of previous studies that an exercise therapy program provide benefit to heart failure patients, either it is an “alone’ intervention or is together with a cardiac rehabilitation program. This is in contrast with the result of previous review by Sagar, et.al. [13] which showed no difference in pooled all-cause mortality between exercise CR with follow-up to 1 year (12 months) and the control group. But, the improvement in health-related quality of life with exercise training in heart failure revealed in this update review concurs with Sagar et all study [13].

The significant benefits of exercise therapy are specifically spotted in this study in the reduced risk in all-cause mortality and hospitalization after 12 months follow up based on exercise setting and exercise dose, respectively, as revealed by the univariate meta-regression.

5. CONCLUSION

This update review study, which aims to reassess the effectiveness of exercise therapy/cardiac rehabilitation, either in center- or home- based, to heart failure patients found out that the:

1. Exercise therapy has benefited the heart failure patients in reducing the risk of all-cause mortality up to 12 months, hospital admission up 12 months, and has given a better quality of life.
2. The new studies included have shown a better reduced risks in all health-related outcomes covered in this study than those that were recorded by the old studies. Thus, further strengthened the findings of previous studies that an exercise therapy program provide benefit to heart failure patients, either it is an “alone’ intervention or is together with a cardiac rehabilitation program.
3. The setting and dose of an exercise therapy program provide significant contribution to a reduced risk in all-cause mortality and hospitalization after 12 months follow up, respectively.

All these could change the landscape of treating heart failure by including non-conventional mode of treatment like exercise training program to improve overall patients’ outcome.

STUDY LIMITATIONS

Funnel plot asymmetry in the all-cause mortality and quality of life scores outcomes implied evidence of small study bias and probably publication bias, thus grey literature can be searched for other unpublished studies to reduce such biases. The review was limited to English-language articles, introducing a risk of bias. There were also studies included which details limited descriptions of the interventions and controls in accordance with Consolidated Standards of Reporting Trials (CONSORT).

CONSENT

As per international standard or university standard, Participants’ written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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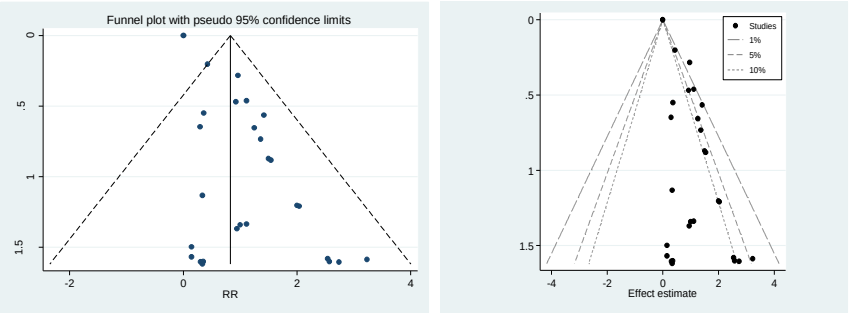
APPENDIX



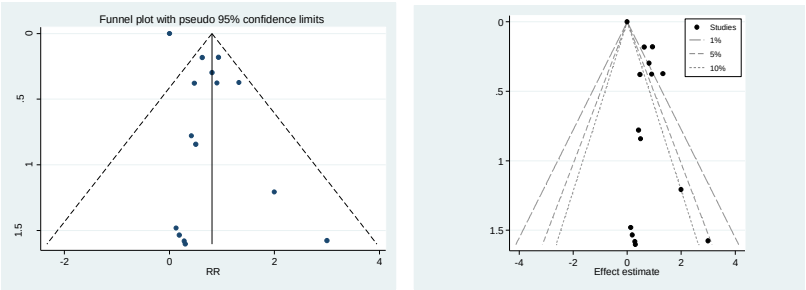
Egger's test for small-study effects:

Number of studies = 26 Root MSE= 7528

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.4946349	.1481874	3.34	0.003	.1887911	.8004787
bias	.6849844	.2413394	2.84	0.009	.1868844	1.183084

Test of H0: no small-study effects P = 0.009

Fig. 6. Funnel plot of comparison: 1 All exercise interventions versus usual care, outcome: All-cause mortality up to 12 months' follow-up



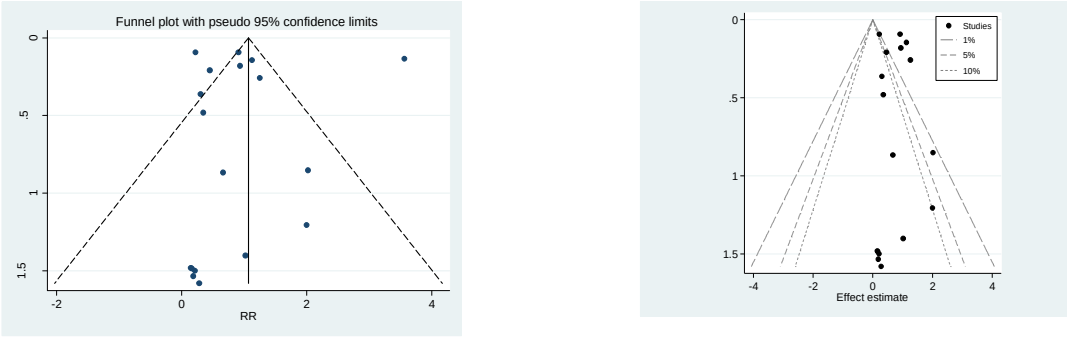
Egger's test for small-study effects:

Number of studies= 15 Root MSE= .8211

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.7876252	.1304713	6.04	0.000	.5033527	1.071898
bias	.0769059	.3472714	0.22	0.828	-.6797335	.8335452

Test of H0: no small-study effects P = 0.828

Fig. 7. Funnel plot of comparison: 1. All exercise interventions versus usual care, outcome: hospital admissions after 12 months' follow up



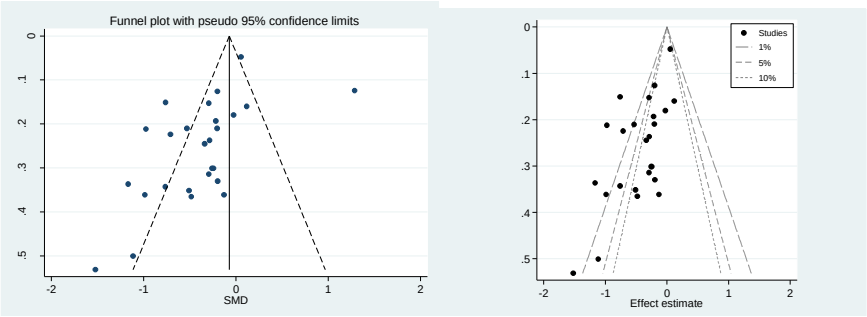
Egger's test for small-study effects:

Number of studies = 18 Root MSE = 5.271

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.067766	.368975	2.89	0.011	.285574	1.849958
bias	.0089696	1.774585	0.01	0.996	-3.752983	3.770922

Test of H0: no small-study effects P = 0.996

Fig. 8. Funnel plot of comparison: 1: All exercise interventions versus usual care, outcome: hospital admissions due to heart failure rehospitalizations



Egger's test for small-study effects:

Number of studies = 26 Root MSE = 2.661

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.2467116	.1442672	1.71	0.100	-.0510412	.5444643
bias	-2.414468	.8803689	-2.74	0.011	-4.23146	-.5974758

Test of H0: no small-study effects P = 0.011

Fig. 9. Funnel plot of comparison: All Quality of Life scores up to 12 months follow up.

Egger's Test Reference:
fmwww.bc.edu/RePEc/bocode/m/metabias

Syntax:
metabias EffectEstimate SE, egger
metafunnel EffectEstimate SE, xtitle("RR") ytitle("SE[log RR]")
metafunnel EffectEstimate SE, xtitle("MD") ytitle("SE[MD]")
confunnel EffectEstimate SE

Table 8. Characteristics of the trials included

Author	Year	Methods	Participants	Interventions	Outcome	Comparison	Country	Follow up
Lou	2017	RCT parallel group	HF <35% EF with atrial fibrillation Female:30%; Age: 58.6-63.1y	Aerobic(walking/biking) 90mins/week 60-70% HR reserve	QoL (KCCQ) All cause mortality All cause hospitalization Heart failure hospitalization	Usual care Medical tx	USA multicenter	36months
Doukky	2016	RCT multicenter Partially blinded	HF <40% EF Age: 63-65y Male:45-56%	Aerobic exercise 90 mins/week	All cause mortality HF hospitalization	Usual care No exercise Medical tx	USA	36 months
Pina	2014	RCT multicenter	HF <35% EF NYHA ll-lV Age: 57-60y Men: 70%	Aerobic exercise 30-40 mins 5x/week 60-70% HR reserve	All cause mortality QoL (KCCQ) All cause hospitalization	Usual care Medical tx	USA	24 months
Mudge	2018	RCT Blinded outcome assesors	HF <31% EF Men: 70% Age: 61.9-62.9y	Aerobic exercise (treadmill/bike) 30mins 5x/week	All cause death readmission	Usual care Medical tx HF disease Mgt program	Australia	12 months
Krainer	2013	Prospective Cohort study	High risk subjects Age: 75-78 y Women: 64-66%	Any physical activity At work and home	Heart failure admission	Usual care No active physical activity	USA	120months
Hollriegel	2016	RCT Parallel group	HF <24% EF Age: 60 y	Exercise training (not specified) 5-20mins 3-6x/week	All cause death Heart failure hospitalization	Usual care Medical tx	Germany	12 months
Antonicelli	2016	Prospective RCT	HF <50% EF Men: 56.9% Age: >70 y	Exercise training and telemonitoring Hospital Cardiac Rehab	All cause readmission QoL (MLHFH)	Usual care Medical tx	Italy	6 months
Denehy	2013	Stratified phase ll RCT Parallel group	HF Age: 60.4-61.4y Men: 58-68%	Exercise training (marching in place/standing and resistance exercises) 30-60mins 2x/week	All cause readmission All cause mortality	Usual care Medical tx Sit on bed	Australia	12 months
Hagglund	2017	Mixed method randomly assigned study	HF <50% EF Age 71-85y Men: 77%	Tai chi 60min/sesssion	Qol (MLHFQ)	Usual care Medical tx	Sweden	6 months
Chen	2017	Randomized prospective trial	HF <50% EF Age: 60-61y Men: 83%	Aerobic exercise Hospital to home 30mins 3x week 60-80%HR reserve	Qol (MLHFQ)	Usual care Medical tx	Taiwan	12 months

F-Test Two-Sample for Variances		
	RR (On or Before 2013 Stuides)	RR (Beyond 2013 Studies)
Mean	1.2726087	0.53666667
Variance	0.81049289	0.08403333
Observations	23	3

df	22	2					
F	9.64489749						
P(F<=f) one-tail	0.09804999						
F Critical one-tail	19.4503065						
F-test for Equality of Variances = p-rob 0.098 > a=0.05 Thus, the variances of the two studies are statistically the same. The t-test for pooled-variance shall then be utilized for comparison of the RRs							
	t-Test: Two-Sample Assuming Equal Variances						
		RR (On or Before 2013 Stuides)	RR (Beyond 2013 Studies)				
	Mean	1.2726087	0.53666667	sd		cv (?2013 studies)	cv (>2013 studies)
	Variance	0.81049289	0.08403333	0.90027378	0.28988504	70.7423882	54.015845
	Observations	23	3				
	Pooled Variance	0.74995459					
	Hypothesized Mean Difference	0					
	df	24					
	t Stat	1.38440766					
	P(T<=t) one-tail	0.08948588					
	t Critical one-tail	1.71088208					
	P(T<=t) two-tail	0.17897177					
	t Critical two-tail	2.06389856					

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/75586