PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Is exercise-based cardiac rehabilitation effective: a systematic review and meta-analysis to re-examine the evidence.
AUTHORS	Powell, Richard; McGregor, Gordon; Ennis, Stuart; Kimani, Peter; Underwood, Martin

VERSION 1 – REVIEW

REVIEWER	ter Hoeve, Nienke Erasmus Medical Center, the Netherlands
REVIEW RETURNED	09-Oct-2017

GENERAL COMMENTS	The manuscript determines the effects of standard cardiac rehabilitation (CR) programs performed after 2000 on survival rates and re-hospitalization. The paper is relevant (and interesting) to the field of secondary prevention of CHD. Overall, the paper is well written. Methods seem appropriate. In my opinion, the discussion and conclusions need major revisions, the authors draw very strong and not always appropriate conclusions. Some nuance is needed. The paper has the potential to start a (very interesting) discussion which outcomes define the success of CR in the current (medical) era. Major issues 1. In the manuscript, the effects of CR on relative young (mean age 59.5 years) patients with CHD is investigated. As described in the paper, medical treatment of this group of patients has changed tremendously over the last years. Due to better preventive medication and medical interventions, patients leave the hospital with much better preserved cardiac function and nearly optimal cardiovascular risk profile (such as blood pressure and cholesterol). Due to these improvements, short-term mortality in this group of patients is expected to be very low. Therefore, the outcomes of this meta-analysis are not completely surprising. However, reducing mortality is by far not the single goal of CR programs. The conclusion in the abstract that continued used of CR is not supported is therefore inappropriate. Based on your results it can only by concluded that CR is not effective with regard to short-term mortality (which is stated more correctly in lines 36-39 on page 10). 2. Several studies have shown effects on quality of life, physical fitness, return to work (which is relevant for economical evaluation!!), participation in society, depressive mood etc. etc. All highly important and relevant goals of CR and outcomes that determine success of CR! Could the authors expand a bit more in the discussion on what determines the success of CR?

	Is this really only short-term mortality…?? In the current era with medical improvements and the results of this meta-analysis, a shift towards putting more emphasize on these 'softer' outcomes in research (and subsequently updating CR goals and probably CR programs) might be needed. 3. Authors discuss quality of life (and draw conclusions) based on one study (line 37-41, page 9). It seems inappropriate to draw strong (negative) conclusions based on one study, while the Cochrane review did report some evidence for improvements. 4. Could the authors give information on average follow-up time in the included studies? Possibly, the follow-up time was too short to detect benefits in mortality? 5. Did the authors consider to give some additional information on baseline characteristics? For instance blood pressure levels, cholesterol and LVEF function? It might be relevant for the conclusions to have better insight whether the investigated population is a high or low-risk population. In the discussion it would be of relevance to discuss this matter. Probably, more effects with regard to mortality and re-hospitalization are seen in patients with higher risk profiles. 6. The discussion section could be more convincing, when critical analysis is done in context of previous studies, reviews, meta-analyses. Could the authors expand in the discussion sessions on the difference in findings between their meta-analyses and previously performed reviews and meta-analyses? Now, outcomes are only compared to one study (the RAMIT trial). 7. On page 5, lines 37-43 you describe that the controls did receive education and advice on healthy lifestyle and psychosocial issues. Probably, the contrast between the interventions was not large enough for differences in mortality/ rehospitalization? Could it be that the educational program in which controls participated improved lifestyle and as such cardiovascular risk factors and mortality? And does this mean that mainly the exercise component seems to not lead to an improvement in mortality? 8. On page 8, lines 32-33, you describe that 6 studies were included that compared exercise as a stand-alone. In the methods (page 5, lines 42-43), however, you describe to only include studies that also included an educational/psychosocial component. Why did you choose to include these 6 studies? 9. The finding (page 9, line 3) that hospital admissions reached borderline statistical significance is very interesting and relevant. As mentioned in point 1, mortality is expected to be low in this group of patients, therefore lowering hospital admissions is clinically relevant in this population (also with regard to economic impact). Could the authors expand a bit more on this very interesting outcome in the discussion and conclusions. 10. The authors mention a high heterogeneity between the content of investigated CR programs. On page 10, lines 10-31, the authors argue that it would not be of interest to look whether a certain content is more effective with regard to mortality. Since hospital readmissions did reach borderline significance, it does seem interesting to look for this outcome measure whether a certain content (e.g. exercise dose or more elaborated educational/behavioral program) is more effective. Minor issues 1. In the results section of the abstract you mention in line 28 that no differences were found at their longest follow-up period.

	Could the authors specify between which intervention no differences found? 2. Strength and limitation: in the last point the word "is" is missing (page 3, line 17). 3. Page 5, line 29: What do you mean with "optimal secondary preventative medical treatment"? 4. Although understandable, it is a pity that patients were not involved in the interpretation of results. It might be very interesting to discuss what outcomes measures should define the success of CR in their opinion. 5. In line 47 on page 7, the word "only" should be removed (is used double in this sentence). 6. In page 10, line 45-47, you suggest to only perform RCT's. Currently, CR is recommended by the guidelines of several countries. Would it be ethical to randomize patients to no-CR? 7. In the conclusion on page 10, the authors suggest high intensity interval training as an alternative. I think this sessions should be moved to the discussion.

REVIEWER	Lis Neubeck Edinburgh Napier University
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	This systematic review and meta-analyses aims to investigate the differences between exercise-based CR and control in a contemporary setting. It builds on the recent Cochrane systematic review of exercise-based CR, using the papers included in this review and categorising the papers according to a cut-off defined by the authors, when, they argue, access to cardioprotective medications increased. The outcomes selected were all-cause mortality, cardiovascular mortality and hospital readmissions. Major comments: 1. The stated findings of this study need to be more cautiously phrased, as although the results suggest there may be less benefit of exercise-based CR than previously believed, it would be an overstatement to suggest that there is no benefit. 2. This review overlooks the value of improvements in cardiovascular risk factors, psychosocial factors and adherence to medication. Although this was not the stated aim of the review, it should be articulated more clearly in the discussion. 3. The authors interpret their findings to show that there is no benefit of exercise-based CR, but also acknowledge the immense variation between the intensity, duration, and delivery settings of the included interventions. It would be useful to understand how that would impact on outcomes in this study. 4. The importance of reporting of complex interventions needs further elucidation.

	5. As the authors acknowledge in the limitations section, the RAMIT study results raised many concerns about the quality of the intervention. There are other limitations of the RAMIT, including the failure to recruit sufficient participants (only 22% of targeted sample size). 20% of participants dropped out, and it is unknown what contamination occurred in the control group over the duration of the follow up. This should be discussed earlier and not just in the limitations. 6. Other systematic reviews have suggested that comprehensive CR which includes multiple risk factor reduction is more effective than exercise only CR (van Halewijn G, Deckers J, Tay HY, van Domburg R, Kotseva K, Wood D. Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis. International Journal of Cardiology. 2017;232(Supplement C):294-303.) These are important findings which should be included in the discussion. 7. The limitations should acknowledge the limitations of the present study, and not those of other studies (eg RAMIT). The limitations of the included papers should form an important part of the discussion, particularly the issues around reporting as per comment 4 8. Please remove any new concepts and recommendations from the conclusion. The introduction of HIIT, if considered important, should form part of the discussion. The conclusions should relate only to the findings of your review.

REVIEWER	Dr Louise Marston, Principal Research Statistician UCL, London.
REVIEW RETURNED	25-Oct-2017

GENERAL COMMENTS	Abstract and Background. Please write CR in full on first use. P3, last paragraph, line 53. Insert "significant" between "no" and "reduction" p9, line 46. "failed to report a p-value" - it should be possible to determine statistical significance from the 95% CI. Please consider that mortality and hospital admissions are relatively long term outcomes, so benefits in terms of reduced mortality and admissions may not be seen in the lifetime of these studies due to their relative short term natures. However, CR may be affecting some of the intermediate "softer" outcomes you mention. These in turn may be working to decrease mortality and hospital admissions in the longer term. Page 10, line 11. Give actual p-values rather than p>0.01. I would say p=0.01 is highly significant, so depends on how much greater than 0.01 it is to determine how significant it is. It is also better to highlight this information in the results rather than include new information in the discussion. Table 1. Support for "groups balanced at baseline" does not match the item. This should be whether the group randomised to exercise is similar to the group randomised to control at baseline. This is unlikely to have p-values.

	Table 1. Needs some supporting information on why ITT is high risk. I could not see figure 1 as it was too small. Also check that the tops of the other figures are showing as they are not showing well on the version I used for review. Please check the 95% CI of individual studies in Figures 2, 3 and 4. These affect the weights, which in turn affects the result of the study. Usually, weights are largest in larger studies, so surprised about the distribution of weights you have.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Nienke ter Hoeve
Institution and Country: Erasmus Medical Center, the Netherlands
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The manuscript determines the effects of standard cardiac rehabilitation (CR) programs performed after 2000 on survival rates and re-hospitalization. The paper is relevant (and interesting) to the field of secondary prevention of CHD. Overall, the paper is well written. Methods seem appropriate. In my opinion, the discussion and conclusions need major revisions, the authors draw very strong and not always appropriate conclusions. Some nuance is needed. The paper has the potential to start a (very interesting) discussion which outcomes define the success of CR in the current (medical) era.

Major issues

1. In the manuscript, the effects of CR on relative young (mean age 59.5 years) patients with CHD is investigated. As described in the paper, medical treatment of this group of patients has changed tremendously over the last years. Due to better preventive medication and medical interventions, patients leave the hospital with much better preserved cardiac function and nearly optimal cardiovascular risk profile (such as blood pressure and cholesterol). Due to these improvements, short-term mortality in this group of patients is expected to be very low. Therefore, the outcomes of this meta-analysis are not completely surprising. However, reducing mortality is by far not the single goal of CR programs. The conclusion in the abstract that continued used of CR is not supported is therefore inappropriate. Based on your results it can only by concluded that CR is not effective with regard to short-term mortality (which is stated more correctly in lines 36-39 on page 10).

Thank you for your comment. We interpret the findings differently to the reviewer. We have conclusively demonstrated that there is no effect on mortality. The other available evidence shows a borderline reduction in hospital admissions that may, or may, not be clinically important. We have changed the conclusion to match with the conclusion in the manuscript. We have recognised in both conclusions (abstract and manuscript) the borderline difference between groups for hospital admissions. Pg 2, lines 38-32. Pg 11, lines 35-36. The evidence on health-related quality of life is sparse and not suitable for pooling with very few data on overall quality of life on incremental cost-effectiveness. This does not mean that it does not have an effect on overall health-related quality of life, rather there is an absence of evidence to show that it does. Without new studies to demonstrating an effect on health-related quality of life, this intervention cannot be supported. If exercise-based CR was not already, it would be difficult to use these data to supports its introduction.

2. Several studies have shown effects on quality of life, physical fitness, return to work (which is relevant for economical evaluation!!), participation in society, depressive mood etc. etc. All highly important and relevant goals of CR and outcomes that determine success of CR! Could the authors expand a bit more in the discussion on what determines the success of CR? Is this really only short-term mortality…?? In the current era with medical improvements and the results of this meta-analysis, a shift towards putting more emphasize on these 'softer' outcomes in research (and subsequently updating CR goals and probably CR programs) might be needed.

Thank you for your comment, we have now expanded on these points and suggested these to be the focus of exercise-based CR in the short-term, rather than the outcomes measured in the review. Pg 10, lines 35-39. Exercise-based CR has the potential to influence these 'softer outcomes'. Nevertheless, there is not a current consistent body of work to suggest a positive effect on these outcomes.

3. Authors discuss quality of life (and draw conclusions) based on one study (line 37-41, page 9). It seems inappropriate to draw strong (negative) conclusions based on one study, while the Cochrane review did report some evidence for improvements.

This negative conclusion has now been extracted and instead, we draw our conclusion based on studies taken from the 2016 Cochrane review that met the criteria for our review; which overall does not provide sufficient evidence to support the use of exercise-based CR. Pg 10, lines 23-25.

4. Could the authors give information on average follow-up time in the included studies? Possibly, the follow-up time was too short to detect benefits in mortality?

Thank you for your comment, we have now included the maximum follow-up period for individual studies in table 2. We have also reported on this in the results Pg. 7 line 21-23 and discussed it in the discussion Pg 10, lines 14-17.

5. Did the authors consider to give some additional information on baseline characteristics? For instance blood pressure levels, cholesterol and LVEF function? It might be relevant for the conclusions to have better insight whether the investigated population is a high or low-risk population. In the discussion it would be of relevance to discuss this matter. Probably, more effects with regard to mortality and re-hospitalization are seen in patients with higher risk profiles.

We agree, a higher risk profile population may have more to gain from CR. Unfortunately, this is out of scope for the current review. What we do know, however, is that in the majority of trials, participant baseline characteristics between groups were comparable. We have alluded to this in the limitations section. Pg 10, lines 50-52.

6. The discussion section could be more convincing, when critical analysis is done in context of previous studies, reviews, meta-analyses. Could the authors expand in the discussion sessions on the difference in findings between their meta-analyses and previously performed reviews and meta-analyses? Now, outcomes are only compared to one study (the RAMIT trial).

Thank you for your comment. We have altered the discussion and conclusion and instead, rather that comparing against the RAMIT trial, have discussed the difference between the previous Cochrane review. Pg 9, lines 34-42. Please note we do not compare our findings with RAMIT trial results. We compared the results of the meta-analysis with what the RAMIT trial indicate as clinically important and wanted to detect at the design stage. Pg 9, lines 52-53 & Pg 10, lines 5-7.

7. On page 5, lines 37-43 you describe that the controls did receive education and advice on healthy lifestyle and psychosocial issues. Probably, the contrast between the interventions was not large enough for differences in mortality/ rehospitalization? Could it be that the educational program in which controls participated improved lifestyle and as such cardiovascular risk factors and mortality? And does this mean that mainly the exercise component seems to not lead to an improvement in mortality?

Thank you for your comment. This may be possible. However, whether or not the educational control arms had any effect was not the purpose of the current meta-analysis. Instead, our findings show that an exercise-based intervention has no additional effect on mortality when added to such interventions.

8. On page 8, lines 32-33, you describe that 6 studies were included that compared exercise as a stand-alone. In the methods (page 5, lines 42-43), however, you describe to only include studies that also included an educational/psychosocial component. Why did you choose to include these 6 studies?

Thank you for your comment. I think there has been some misunderstanding. On Pg 5, lines 49-51, we state we would include studies with an intervention that was exercise alone or exercise as part of a comprehensive CR programme. Hopefully this clarifies why we included these 6 studies. These studies were also included in the Cochrane review.

9. The finding (page 9, line 3) that hospital admissions reached borderline statistical significance is very interesting and relevant. As mentioned in point 1, mortality is expected to be low in this group of patients, therefore lowering hospital admissions is clinically relevant in this population (also with regard to economic impact). Could the authors expand a bit more on this very interesting outcome in the discussion and conclusions.

This finding of borderline statistical significance. It would be inappropriate to use borderline data to draw any form conclusions on clinical relevance or economic impact. The most positive interpretation of these data is that there is a 5% reduction in hospital admissions (20 people would need to take part in the intervention for one fewer to be re-admitted to hospital). We feel it is difficult to conclude that this is a clinically/economically worthwhile benefit.

10. The authors mention a high heterogeneity between the content of investigated CR programs. On page 10, lines 10-31, the authors argue that it would not be of interest to look whether a certain content is more effective with regard to mortality. Since hospital readmissions did reach borderline significance, it does seem interesting to look for this outcome measure whether a certain content (e.g. exercise dose or more elaborated educational/behavioral program) is more effective.

Thank you for your comment. We think it would be of real interest to look at the content of intervention for each study and distinguish whether exercise-alone or exercise as part of a comprehensive programme has any correlation with outcomes data. Unfortunately, this is out of scope for the current review. Nevertheless, a quick inspection of the description of the interventions evaluated shows that the quality of the reporting of the interventions tested is too poor to allow for such an analysis Pg 11 lines 22-27. This was also mentioned in the previous Cochrane review, 2016 (Description of studies).

Minor issues

1. In the results section of the abstract you mention in line 28 that no differences were found at their longest follow-up period. Could the authors specify between which intervention no differences found?

Amended in abstract. Page 2, line 28.

2. Strength and limitation: in the last point the word “is” is missing (page 3, line 17).

Amended in strength and limitations. Page 3, line 25.

3. Page 5, line 29: What do you mean with “optimal secondary preventative medical treatment”?

Amended to include ‘defined by the Joint British recommendations on prevention of Coronary Heart Disease in Clinical Practice’ and a reference Page 5, lines 41-42.

4. Although understandable, it is a pity that patients were not involved in the interpretation of results. It might be very interesting to discuss what outcomes measures should define the success of CR in their opinion.

Thank you for your comment. Unfortunately, this was out of scope of the current meta-analysis.

5. In line 47 on page 7, the word “only” should be removed (is used double in this sentence).

Amended in results. Page 8, line 7.

6. In page 10, line 45-47, you suggest to only perform RCT’s. Currently, CR is recommended by the guidelines of several countries. Would it be ethical to randomize patients to no-CR?

Thank you for your comment. This is a difficult issue to address. We have demonstrated conclusively, however, that exercise-based CR has zero effect on the primary outcome of interest; which therefore provides little justification for including it in guidelines. Simply because an intervention is endorsed by guidelines does not mean it is effective. These guidelines are now based on outdated data. We need to challenge practice to improve patient outcomes based on research. We have removed this line and instead, concluded that the continued delivery of exercise-based CR needs to be supported by new research. Pg 11 37-38.

7. In the conclusion on page 10, the authors suggest high intensity interval training as an alternative. I think this sessions should be moved to the discussion.

This section has now been taken out of the conclusion and included into the strengths and limitations section when referring to the dose of exercise. Pg 11, lines 20-21.

Reviewer: 2
Reviewer Name: Lis Neubeck
Institution and Country: Edinburgh Napier University
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This systematic review and meta-analyses aims to investigate the differences between exercise-based CR and control in a contemporary setting. It builds on the recent Cochrane systematic review of exercise-based CR, using the papers included in this review and categorising the papers according to a cut-off defined by the authors, when, they argue, access to cardioprotective medications increased. The outcomes selected were all-cause mortality, cardiovascular mortality and hospital readmissions.

Major comments:
1. The stated findings of this study need to be more cautiously phrased, as although the results suggest there may be less benefit of exercise-based CR than previously believed, it would be an overstatement to suggest that there is no benefit.

We have now altered our conclusion in the abstract Page 2, lines 41-42 and manuscript Page 11, lines 35-36 to say that the evidence presented in our review has no effect on all-cause mortality or cardiovascular mortality. We have not stated that it does not work; except on all-cause mortality in which we have conclusively demonstrated that it is ineffective. We have mentioned the other benefits exercise-based CR may have, but have state that there are currently no data to support this Page 10, lines 34-39.

2. This review overlooks the value of improvements in cardiovascular risk factors, psychosocial factors and adherence to medication. Although this was not the stated aim of the review, it should be articulated more clearly in the discussion.

Thank you for your comment. We agree, although it wasn't the aim of the review, we have now alluded to these other factors that CR can influence in the discussion. Page 10, lines 34-39. Nevertheless, although exercise-based CR might affect these outcomes, the current data do not support the conclusion that it does.

3. The authors interpret their findings to show that there is no benefit of exercise-based CR, but also acknowledge the immense variation between the intensity, duration, and delivery settings of the included interventions. It would be useful to understand how that would impact on outcomes in this study.

We have elaborated on this statement by discussing the effects exercise-dose and exercise capacity may have on cardiovascular disease risk and all-cause mortality. Page 11, lines 14-19.

4. The importance of reporting of complex interventions needs further elucidation.

Thank you for your comment, we have now alluded to the reporting of complex interventions in the limitations section Page 11, lines 22-27.

5. As the authors acknowledge in the limitations section, the RAMIT study results raised many concerns about the quality of the intervention. There are other limitations of the RAMIT, including the failure to recruit sufficient participants (only 22% of targeted sample size). 20% of participants dropped out, and it is unknown what contamination occurred in the control group over the duration of the follow up. This should be discussed earlier and not just in the limitations.
Thank you for your comment. We agree and recognise the other limitations of the RAMIT trial you mention. However, for this point, we are using the RAMIT trial as an example of poor quality reporting and/or intervention delivery, which is apparent in many other studies included in this review, and therefore a limitation of this review. The PRISMA checklist state limitations at study and outcome level and at review-level should be discussed in the limitations section.

6. Other systematic reviews have suggested that comprehensive CR which includes multiple risk factor reduction is more effective than exercise only CR (van Halewijn G, Deckers J, Tay HY, van Domburg R, Kotseva K, Wood D. Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis. International Journal of Cardiology. 2017;232(Supplement C):294-303.) These are important findings which should be included in the discussion.

Thank you for this reference. We have now referred to this in our discussion. Page 10, lines 12-17. Whilst the population is different (includes not only coronary artery disease patients, but also participants with peripheral artery disease, ischaemic cerebrovascular accidents, diabetes mellitus or hypertension), it demonstrates that when a rehabilitation programme is delivered for a wider range of disorders, zero effect on all-cause mortality is observed.

7. The limitations should acknowledge the limitations of the present study, and not those of other studies (eg RAMIT). The limitations of the included papers should form an important part of the discussion, particularly the issues around reporting as per comment 4.

Thank you for your comment. We still refer to the RAMIT trial in the limitations as an example of poor quality reporting and/or intervention delivery, which is apparent in many other studies included in this review. As mentioned, the PRISMA checklist state limitations at study and outcome level and at review-level should be discussed in the limitations section.

8. Please remove any new concepts and recommendations from the conclusion. The introduction of HIIT, if considered important, should form part of the discussion. The conclusions should relate only to the findings of your review.

Thank you for your comment, we have taken the introduction to HIIT out and refer to it in the limitations. Page 11, lines 20-21.

Reviewer: 3

Reviewer Name: Dr Louise Marston, Principal Research Statistician
Institution and Country: UCL, London, UK.
Please state any competing interests or state ‘None declared’: None declared.

Abstract and Background.

1. Please write CR in full on first use.

Amended. Pg 2, line 8.

2. P3, last paragraph, line 53. Insert "significant" between "no" and "reduction"

Amended. Pg 4, line 6.

3. p9, line 46. "failed to report a p-value" - it should be possible to determine statistical significance from the 95% CI.

Thank you for your comment. After re-visiting the original paper, a between-group economic evaluation and statistical analysis was not conducted (hence no p-value). Instead, the authors compare the cost of the intervention against nationally recognised cost-effective thresholds, concluding that the intervention was ‘probably effective’.

4. Please consider that mortality and hospital admissions are relatively long term outcomes, so benefits in terms of reduced mortality and admissions may not be seen in the lifetime of these studies due to their relative short term natures. However, CR may be affecting some of the intermediate "softer" outcomes you mention. These in turn may be working to decrease mortality and hospital admissions in the longer term.

Thank you for your comment, we have recognised in the discussion that the outcome measured are mainly long term outcomes. However, it must be highlight that these outcomes although maybe long-term, are measured and reported on in studies/the Cochrane review. We have mentioned and expanded on the 'softer outcomes' as you mention, but there are no data to support this. Pg 10, lines 35-39.

5. Page 10, line 11. Give actual p-values rather than p>0.01. I would say p=0.01 is highly significant, so depends on how much greater than 0.01 it is to determine how significant it is. It is also better to highlight this information in the results rather than include new information in the discussion.

Thank you for your comment. I have now included the p value and I2 statistic to determine statistic heterogeneity for each outcome in the results section. It was at this point when we recognised there was evidence for statistical heterogeneity for hospital admissions (p= 0.002, I2= 64%). I have also alluded to this in the discussion. I have kept the p value and I2 statistic the same in the discussion Pg 11, line 6, as these are the parameters for measuring statistical heterogeneity as outlined in the 2016 Cochrane review.

6. Table 1. Support for "groups balanced at baseline" does not match the item. This should be whether the group randomised to exercise is similar to the group randomised to control at baseline. This is unlikely to have p-values.

Thank you for your comment. This has now been changed to support the bias in question. You mention this is unlikely to have a p-value, however the authors do report this in their paper. Table 1.

7. Table 1. Needs some supporting information on why ITT is high risk.

Thank you for your comment, the ITT is high risk as no ITT analysis was conducted in this study. Table 1.

8. I could not see figure 1 as it was too small. Also check that the tops of the other figures are showing as they are not showing well on the version I used for review.

Please let me know if there are any issues with this and I can look to re-send another.

9. Please check the 95% CI of individual studies in Figures 2, 3 and 4. These affect the weights, which in turn affects the result of the study. Usually, weights are largest in larger studies, so surprised about the distribution of weights you have.

Thank you for your comment. We have reconfirmed the values including the 95%CIs of the original studies. These are all correct. We performed a random effects meta-analysis. The weights in a random effects meta-analysis are a function of within-study variances and between-studies variances and so a small study whose effect is different from other studies is very likely to get weight that is way higher than its proportion of the sample size.

VERSION 2 – REVIEW

REVIEWER	Nienke ter Hoeve Erasmus Medical Centre, the Netherlands
REVIEW RETURNED	21-Dec-2017

GENERAL COMMENTS	I would like to start with a compliment, the authors did a good job thoroughly revising their manuscript (mainly the discussion sessions)

	and did solve all main issues I raised after their original submission. I only have some minor comments left. Minor comments: 1. Abstract: please state in the objective that you determine the effectiveness in terms of mortality and hospital resubmissions. 2. Results: the authors could consider adding information about the control (no-exercise) intervention in one of the tables (like done for the exercise interventions in Table 3). I think this is very valuable information for the reader. 3. Discussion: If I understood correctly you compared CR with an exercise intervention to a non-exercise intervention (that do contain other components such as lifestyle education). This would imply that mainly the exercise component does not lead to benefits with regard to mortality and hospital resubmissions. The other multi-components of CR still need to be investigated with regard to their effectiveness (as is also mentioned by the authors in the discussion). I thinks it is important to repeat once more (in one of the first paragraphs of the discussion) what the control interventions to which you compared the exercise components include. 4. In the end of the discussion (just before the conclusions) you mention that several other studies also fail to report on the intensity of the exercise component. Is it possible to give references here?

REVIEWER	Lis Neubeck Edinburgh Napier University
REVIEW RETURNED	28-Dec-2017

GENERAL COMMENTS	Point-by-point response would be easier to follow rather than track changes in document with comments

REVIEWER	Dr Louise Marston, Principal Research Statistician UCL, UK
REVIEW RETURNED	04-Dec-2017

GENERAL COMMENTS	Thank you for your revisions to the manuscript. I still have issues with the weights of the studies, with larger studies having much larger weights than smaller studies. This is seen in the Cochrane review (ref 10).

VERSION 2 – AUTHOR RESPONSE

Response to reviewers

Reviewer: 3
Reviewer Name: Dr Louise Marston, Principal Research Statistician

Institution and Country: UCL, UK

I still have issues with the weights of the studies, with larger studies having much larger weights than smaller studies. This is seen in the Cochrane review (ref 10).
Thank you for your comment. We have since calculated the weights by hand and have confirmed the weights are correct. Just to re-iterate, the weights in a random effects meta-analysis are a function of within-study variances and between-studies variances and so a small study whose effect is different from other studies is very likely to get weight that is way higher than its proportion of the sample size. Please note a different statistical method was used in Cochrane (risk ratio).

Reviewer: 1
Reviewer Name: Nienke ter Hoeve

Institution and Country: Erasmus Medical Centre, the Netherlands

Minor comments:
1. Abstract: please state in the objective that you determine the effectiveness in terms of mortality and hospital resubmissions-

Thank you, we have now included this in the manuscript Pg 2, lines 6-7.

2. Results: the authors could consider adding information about the control (no-exercise) intervention in one of the tables (like done for the exercise interventions in Table 3). I think this is very valuable information for the reader.

Thank you, we have now included this in the manuscript Table 3.

3. Discussion: If I understood correctly you compared CR with an exercise intervention to a non-exercise intervention (that do contain other components such as lifestyle education). This would imply that mainly the exercise component does not lead to benefits with regard to mortality and hospital resubmissions. The other multi-components of CR still need to be investigated with regard to their effectiveness (as is also mentioned by the authors in the discussion). I thinks it is important to repeat once more (in one of the first paragraphs of the discussion) what the control interventions to which you compared the exercise components include.

Thank you, we have now included this in the manuscript Pg 10, lines 1-2.

4. In the end of the discussion (just before the conclusions) you mention that several other studies also fail to report on the intensity of the exercise component. Is it possible to give references here?

Thank you for your comment, we believe the way we originally worded this paragraph was confusing and have since re-worded. It was not our intention to discuss the prescribed intensity of the components delivered. We were making reference to adherence and fidelity (compliance to the prescribed exercise prescription i.e. % of time spent at intended HR range). However, we have now included the references in the manuscript as requested Pg 11, lines 30-31 as well as an additional line to suggest how the reporting of interventions could be improved Pg 11, lines 34-36.

Reviewer: 2
Reviewer Name: Lis Neubeck

Institution and Country: Edinburgh Napier University

Point-by-point response would be easier to follow rather than track changes in document with comments

Thank you, we have provided both track changes and a point by point response to the reviewers as requested.