

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Therapeutic effects of exercise interventions for patients with chronic kidney disease: an umbrella review of systematic reviews and meta-analyses
AUTHORS	Zhang, Fan; Bai, Yan; Zhao, Xing; Huang, Liuyan; Wang, Weiqiong; Zhou, Wenqin; Zhang, Huachun

VERSION 1 – REVIEW

REVIEWER	Shibagaki, Yugo St Marianna University School of Medicine
REVIEW RETURNED	18-Aug-2021

GENERAL COMMENTS	<p>Authors conducted an umbrella review of systematic reviews and meta-analyses regarding therapeutic effects exercise in patients with CKD. Although the objective and the method of the study is appropriate, the current version of the manuscript cannot be accepted unless authors respond to the comments appropriately.</p> <p>* In the RESULTS section, (1) "cardiovascular risk factor" should be changed to "blood pressure" since other CV risks are not investigated at all. (2) For most of the outcomes, the directions of the effects of exercise are not specified so that the how exercise affect the outcomes is uncertain. For example, overall effect of blood pressure should be specified if it is lowering or elevating. Authors should specify the directions of effect in each outcome. (3) Dialysis adequacy is not symptom so it should not be included in Dialysis-related "symptoms".</p> <p>* In the Discussion (second last paragraph) and in the Conclusion section, authors exaggerate the beneficial effect of exercise despite the effect sizes are so small and the evidence levels by GRADE are mostly very low or low. Even though I personally believe the effect of the exercise, the way authors states it seems to be exaggerated, which would be misleading the readers.</p>
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REVIEWER	Prasannarong, Mujalin Chiang Mai University Faculty of Associated Medical Sciences, Physical Therapy
REVIEW RETURNED	03-Sep-2021

GENERAL COMMENTS	The overview of meta-analysis (MA) of the therapeutic effects of exercise interventions in CKD patients is very interesting, and the methods are well planned. However, some information should be included in the manuscript. I hope that all suggestions and questions may be helpful for the manuscript.
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	<p>1. The title of the study focuses on the therapeutic effects of exercise intervention in CKD. It would be more appropriate if the introduction focuses on the beneficial effects of exercise on the outcomes.</p> <p>2. Table 2: VO₂peak and 6MWT are aerobic capacity measurements. Therefore, the author should find another term for Heiwe (2011) and Heiwe (2012).</p> <p>3. Tables: please define the “Mixed” exercise type. Most MAs are mixed-exercise type. More discussion should be included.</p> <p>4. There are many cardiovascular factors in CKD. This review presented SBP and DBP. The authors should discuss other factors, which were not included in this study.</p> <p>5. Body composition is a common term. However, to gain more clinical application, the specific body composition, such as fat mass, muscle mass, bone mass, should be analyzed or discussed.</p> <p>6. Page 11: although there is a low incidence of adverse events in CKD due to exercise, the author should discuss the relationship between exercise and reported adverse events. This information will help the therapeutic team to be careful. Moreover, This may support “Exercise appears to be safe way to affect...” that stated in the abstract's conclusion (page 2).</p> <p>7. Figure S2 should be included in the main manuscript. In figure and table number limitation, the author may combine muscle strength and endurance in the same table.</p>
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REVIEWER	Ho, Roger C. M. Natl Univ Singapore, Psychological Medicine
REVIEW RETURNED	05-Jan-2022

GENERAL COMMENTS	<p>I am invited to perform the statistical review. Under statistical analysis, please define fixed-effects and random-effects model and state which model was used. Please add the following definitions:</p> <p>Fixed-effect models assume that the population effect sizes are the same for all studies ((Cheung et al 2012). In contrast, random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Loh et al 2018).</p> <p>References: Cheung MW et al. Conducting a meta-analysis: basics and good practices. Int J Rheum Dis. 2012 Apr;15(2):129-35. PMID:22462415</p> <p>Loh AZH et al Postoperative Psychological Disorders Among Heart Transplant Recipients: A Meta-Analysis and Meta-Regression. Psychosom Med. 2020 Sep;82(7):689-698. doi: 10.1097/PSY.0000000000000833. PMID: 32541547.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr. Yugo Shibagaki, St Marianna University School of Medicine

(1) In fact, our original idea was to obtain evidence for the effect of exercise on cardiovascular risk factors in patients with CKD; however, the results of most meta-analyses did not meet our eligibility

criteria, leaving only blood pressure as the final factor; in order not to mislead readers, we have followed the reviewer's suggestion and have changed the “cardiovascular risk factors” in the results section to “blood pressure”.

(2) Compared to systematic reviews/meta-analyses, umbrella reviews are more about grading the reliability of the evidence obtained from the study, so we did not further synthesize the data to determine the direction of impact.

(3) We have separated out the dialysis adequacy.

(4) We have made appropriate revisions to the penultimate paragraph of the Discussion section and the Conclusion (See the Discussion and Conclusion).

Reviewer 2: Dr. Mujalin Prasannarong, Chiang Mai University Faculty of Associated Medical Sciences

(1) We have added the corresponding content in the Introduction (See the Introduction).

(2) In fact, in Heiwe's study, aerobic capacity was covered by VO₂peak and 6MWT, and we could not separate them, so they are listed separately

(3) We have added a note at the end of the table.

(4) We have added a discussion of other cardiovascular risk factors to the discussion section.

(5) BMI is an important indicator of body composition, and we focused on assessing the effect of exercise on BMI in patients with CKD; as the reviewers noted, fat and muscle mass are also indicators of body composition; however, during our review, some meta-analyses did not meet our eligibility criteria, so they are not discussed in depth in this paper

(6) We elaborate more deeply on the relationship between exercise and safety in the Discussion section (See penultimate paragraph of the Discussion).

(7) We have put Figure S2 in the main document.

Reviewer 3: Dr. Roger C. M. Ho, Natl Univ Singapore

Thanks to Professor Roger C. M. Ho for his statistical comments, however, this study is not a Meta-analysis and does not involve the application of random effects models and fixed effects models.

VERSION 2 – REVIEW

REVIEWER	Shibagaki, Yugo St Marianna University School of Medicine
REVIEW RETURNED	09-Mar-2022

GENERAL COMMENTS	Authors commented in the response that the umbrella review are more about grading the reliability of the evidence obtained from the study, so they did not further synthesize the data to determine the direction of impact. I have a strong objection to this comment. This is a clinical paper with which readers understand the way exercise would take effect so the direction of the effect is of utmost importance.
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REVIEWER	Prasannarong, Mujalin Chiang Mai University Faculty of Associated Medical Sciences, Physical Therapy
REVIEW RETURNED	23-Mar-2022

GENERAL COMMENTS	The overview of meta-analysis (MA) of the therapeutic effects of exercise interventions in CKD patients is interesting, and the methods are well planned. However, the authors should attach responses to the reviewers and respond to all questions and suggestions point by point.
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	Therefore, I marked N/A in the review checklist and preferred to review the manuscript once the authors prepare and resubmit the revision.
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REVIEWER	Ho, Roger C. M. Natl Univ Singapore, Psychological Medicine
REVIEW RETURNED	08-Mar-2022

GENERAL COMMENTS	<p>This is my first time to review this paper. Please add the definition of fixed and random-effects model under the statistical analysis based on the following:</p> <p>Fixed-effect models assume that the population effect sizes are the same for all studies ((Cheung et al 2012). In contrast, random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population (Loh et al 2018).</p> <p>References: Cheung MW et al. Conducting a meta-analysis: basics and good practices. Int J Rheum Dis. 2012 Apr;15(2):129-35. PMID:22462415</p> <p>Loh AZH et al. Postoperative Psychological Disorders Among Heart Transplant Recipients: A Meta-Analysis and Meta-Regression. Psychosom Med. 2020 Sep;82(7):689-698. doi: 10.1097/PSY.0000000000000833. PMID: 32541547.</p> <p>Please state whether fixed or random-effects model was used in this study.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer 2: Dr. Mujalin Prasannarong, Chiang Mai University Faculty of Associated Medical Sciences

No.	Comment/Suggestion	Response
1	The title of the study focuses on the therapeutic effects of exercise intervention in CKD. It would be more appropriate if the introduction focuses on the beneficial effects of exercise on the outcomes	We have added the corresponding content in the Introduction (See Page 4, lines 19-30).
2	Table 2: VO2peak and 6MWT are aerobic capacity measurements. Therefore, the author should find another term for Heiwe (2011) and Heiwe (2012)	We had a previous discussion about this issue raised by the reviewer, aerobic capacity was covered by VO2peak and 6MWT in Heiwe's study, and we could not separate them, so they are listed separately.
3	Tables: please define the "Mixed" exercise type. Most MAs are mixed-exercise type. More discussion should be included	We have added a note at the end of the table (See Table 1-7).
4	There are many cardiovascular factors in CKD. This review presented SBP and DBP. The authors should	We have added a discussion of other cardiovascular risk factors to the discussion section (See Page 12, lines 3-10).

	discuss other factors, which were not included in this study	
5	Body composition is a common term. However, to gain more clinical application, the specific body composition, such as fat mass, muscle mass, bone mass, should be analyzed or discussed	BMI is an important indicator of body composition, and we focused on assessing the effect of exercise on BMI in patients with CKD; as the reviewers noted, fat and muscle mass are also indicators of body composition; however, during our review, some meta-analyses did not meet our eligibility criteria, so they are not discussed in depth in this paper.
6	Page 11: although there is a low incidence of adverse events in CKD due to exercise, the author should discuss the relationship between exercise and reported adverse events. This information will help the therapeutic team to be careful. Moreover, This may support “Exercise appears to be safe way to affect...” that stated in the abstract's conclusion (page 2)	We elaborate more deeply on the relationship between exercise and safety in the Discussion section (See Page 13, lines 22-28).
7	Figure S2 should be included in the main manuscript. In figure and table number limitation, the author may combine muscle strength and endurance in the same table	We have put Figure S2 in the main document (See Page 7, lines 11-12).

VERSION 3 – REVIEW

REVIEWER	Shibagaki, Yugo St Marianna University School of Medicine
REVIEW RETURNED	20-Jul-2022
GENERAL COMMENTS	No further comment