

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and characteristics of physical fitness training on aerobic fitness in vulnerable older adults: an umbrella review of systematic reviews.
AUTHORS	Visser, Dennis; Wattel, Elizabeth; Gerrits, Karin; van der Wouden, Johannes; Meiland, Franka; de Groot, Aafke; Jansma, Elise; Hertogh, Cees; Smit, Ewout

VERSION 1 – REVIEW

REVIEWER	Liguori , Gary University of Rhode Island, Health Sciences
REVIEW RETURNED	21-Jan-2022

GENERAL COMMENTS	<p>The authors have submitted an umbrella review of systematic reviews to determine the feasibility of fitness training improving cardiovascular fitness in older adults, particularly those who are 'vulnerable'. While I applaud the effort made in putting this paper together, there are a number of significant concerns upon my review which lead to me to reject the paper.</p> <p>-Broadly, I would strongly suggest that if the paper is to be revised, someone who has English as a first language assists with the writing, as it is not up to standards as is.</p> <p>More specifically, some of my concerns are as follows:</p> <p>-Abstract: should only include the standard headings of Objective, Methods, Results, Conclusions. I would strongly encourage following the same flow in the main body of the paper. There are too many categories as is (in part could be resolved as noted above with the writing assistance), with some of these taking away from the main thrust of the paper, or some of them nothing more than one sentence that adds no value.</p> <p>-Stated Outcomes of the Research: two outcomes are stated, and the first is 'effectiveness' of training. Effectiveness is a highly subjective term, which I feel is far too broad to be an important research question. Please consider revising this with some specificity. Q2 in the Outcomes asks about characteristics associated with the 'significant effects' of training. Again, this is difficult to interpret. I think what you are asking is about those training studies that showed an improvement, and if that is the case, please state that more clearly.</p> <p>-Vulnerable. This is a term used often early in the paper to describe a particular population of interest, however the term vulnerable is never defined, which is critically important in this case.</p>
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	<p>-Of the ~50 reviews that were included, I counted at least 16 with a total duration of as little as 4 days to 4 weeks (including at least 2 with duration listed as 'length of in-patient stay', which is likely in this same range, but maybe even shorter). I note this because decades of research on CV training have concluded that significant improvements in V02 and other CV measures need at least 6 weeks to occur, and that is on the very short end of likeliness to see change. Therefore, I have serious concerns about including reviews that are noticeably shorter than this. In this case, at least one-third of the reviews included have durations that I believe are too short to measure meaningful change.</p> <p>-Outcomes broken down by condition. The results are separated into 8 different categories ('healthy older', 'frail', etc.). Many of these categories include only 1-3 reviews, which seems insufficient to draw any conclusions. Further, if only one review is included, is this really an umbrella review, or simply restating someone else's review? n Healthy Older, oncology (3 reviews, but each on a different type of cancer), and trauma all had one review paper only. Frail (each with differing results) and Cognitive each had only two. Therefore, I am really struggling to see how this is an umbrella review, when the results are separated out and there is very little review per category.</p> <p>I am not suggesting combining all the results, which you actually do in the conclusions. I don't agree with this as each condition is so unique, the results across all of these can't be generalized (comparing healthy older adults, for instance, with those suffering from COPD).</p> <p>Therefore, if the paper were to be revised, I would encourage that one particular subgroup be identified, and the review be conducted for that population.</p>
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REVIEWER	Cadore, E Public University of Navarre, Department of Health Sciences
REVIEW RETURNED	25-Feb-2022

GENERAL COMMENTS	<p>This review presented an overview of effectiveness and training characteristics of physical training on aerobic fitness, compared to other or no training, in adults over 65 years with various health statuses, providing a basis for guidelines for aerobic training of vulnerable older adults , that can be used in geriatric rehabilitation. The review is well written and brings an interesting summary on the approached topic. I have only two comments that I believe will improve the manuscript:</p> <p>Did the authors include or excluded reviews that included aerobic combined to resistance training? Please clarify in the "Methods" and "Results" sections.</p> <p>In order to update the state of the art on the current guidelines of exercise prescription, authors must include in the "Introduction" as well as "Discussion" sections the recent International Consensus by Izquierdo et al. 2021 (J Nutr Health Aging - 25(7):824-853. doi: 10.1007/s12603-021-1665-8)</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author:

The authors have submitted an umbrella review of systematic reviews to determine the feasibility of fitness training improving cardiovascular fitness in older adults, particularly those who are 'vulnerable'. While I applaud the effort made in putting this paper together, there are a number of significant concerns upon my review which lead to me to reject the paper.

4. Broadly, I would strongly suggest that if the paper is to be revised, someone who has English as a first language assists with the writing, as it is not up to standards as is.

Answer: Thank you for this suggestion. The manuscript has now been edited by a sworn translator who has English as a first language. We believe the text has improved by this intervention.

More specifically, some of my concerns are as follows:

5. Abstract: should only include the standard headings of Objective, Methods, Results, Conclusions. I would strongly encourage following the same flow in the main body of the paper. There are too many categories as is (in part could be resolved as noted above with the writing assistance), with some of these taking away from the main thrust of the paper, or some of them nothing more than one sentence that adds no value.

Answer: We revised the formatting of the abstract according to the suggestions of the editor (see comment nr. 1). Although we followed the headings of the PRISMA guidelines in the Method section, we understand that the flow of the paper might indeed improve by revising the formatting of this section to fewer categories. In order to do so, we aligned the formatting of the method section to the formatting of the abstract.

For the Results section we believe that the subheadings improve the readability of the paper and left the subheadings in this section unchanged.

6. Stated Outcomes of the Research: two outcomes are stated, and the first is 'effectiveness' of training. Effectiveness is a highly subjective term, which I feel is far too broad to be an important research question. Please consider revising this with some specificity. Q2 in the Outcomes asks about characteristics associated with the 'significant effects' of training. Again, this is difficult to interpret. I think what you are asking is about those training studies that showed an improvement, and if that is the case, please state that more clearly.

Answer: We agree that the suggested modifications will improve the research questions, and reformulated them into

1. What is the effect of physical fitness training on aerobic fitness outcomes compared to other or no training in adults over 65 years old, with various health statuses?
2. What are the training characteristics in studies that showed an improvement in aerobic fitness in adults over 65 years old?

7. Vulnerable. This is a term used often early in the paper to describe a particular population of interest, however the term vulnerable is never defined, which is critically important in this case.

Answer: We agree with the suggestion that the term vulnerability should be defined. We did this adding a sentence on this topic in the first paragraph of the introduction:

"Patients in geriatric rehabilitation are vulnerable with regard to their health status, meaning that is characterized by a large variety in frailty, comorbidity and disability.1-3 "(referring to the papers of Bachmann, the Boston Working group and Fried).

8. Of the ~50 reviews that were included, I counted at least 16 with a total duration of as little as 4 days to 4 weeks (including at least 2 with duration listed as 'length of in-patient stay', which is likely in this same range, but maybe even shorter). I note this because decades of research on CV training have concluded that significant improvements in V02 and other CV measures need at least 6 weeks to occur, and that is on the very short end of likeliness to see change. Therefore, I have serious concerns about including reviews that are noticeably shorter than this. In this case, at least one-third of the reviews included have durations that I believe are too short to measure meaningful change.

Answer: We thank the reviewer for this interesting suggestion that indeed deserves attention in the discussion paragraph. As we did not use an exclusion criterion for the duration of the intervention, those studies are part of our results and we have to take them into account. In order to adjust the Discussion paragraph we explored the short duration studies (<6 weeks intervention) within the reviews included in our study, and found significant positive effects on walking tests in 12 out of 18 studies, and in all four meta-analyses, in studies comparing aerobic training to no training. We found significant positive effects on $\dot{V}O_2$ peak in 1 out of 2 studies and in both meta-analyses. To further explore this issue, we took a closer look at the literature concerning the time course and the mechanisms of adaptations in cardiorespiratory fitness with endurance training. Generally, in a healthy population, the cardiovascular system turned out to be the major limiting factor in maximal oxygen consumption that can be improved by training, for example cardiac output and oxygen transport capacity of the blood.⁴⁻⁶ Structural adaptations to the cardiovascular system are expected to take longer than six weeks.⁷ The second potential limiting factor is the muscle's capacity to use the delivered oxygen, for example capillary density and mitochondrial content and function.^{5, 6} The role of peripheral factors is greater as the active muscle mass is smaller, typically seen in patients. In fact, in patients with cardiovascular or pulmonary disease skeletal muscle dysfunction seems highly associated with the limited exercise performance.⁸ From fundamental animal studies on effects of chronic electrical stimulation on muscle plasticity it is known that changes in metabolic(oxidative) profile following exercise precede those in structural muscle adaptation such as hypertrophy and even fibre type conversion.⁹ Therefore early changes in muscle oxidative capacity likely contribute to improvement of endurance capacity.

Several studies show increases in $\dot{V}O_2$ peak faster than expected from cardiovascular perspective in young and older men and woman,^{10, 11} in type 2 diabetes¹² and as a result of HITT training in healthy young to middle aged adults.¹³ This can be explained by the findings of Hoier et al., who illustrated that the initiation of capillary and mitochondrial adaptations occurs within 14 days of endurance training.¹⁴ Hence, Burgomaster et al. showed that only six sessions of sprint interval training can increase muscle oxidative potential and endurance capacity.¹⁵ The findings of the studies with short interventions in our review suggest that in those patients the peripheral factor might be the limiting factor in $\dot{V}O_2$ peak, and that the improvements are induced by capillary and / or mitochondrial adaptations rather than by adaptations in the cardiac output.

In the discussion paragraph we summarize these findings: "Another finding of our review is the fact that many reviews included studies with short intervention durations. A deeper exploration of those studies revealed improvements in aerobic fitness for interventions with a duration of less than six weeks (not reported in the results section). Generally, in healthy people, the cardiovascular system is the major limiting factor in aerobic fitness, and structural adaptations to the cardiovascular system are expected to take longer than six weeks.⁷ The findings of the studies with short interventions in our review suggest that in those patients the improvements in aerobic fitness are induced by capillary and/or mitochondrial adaptations that can be initiated within 14 days of endurance training.^{11, 14}"

9. Outcomes broken down by condition. The results are separated into 8 different categories ('healthy older', 'frail', etc.). Many of these categories include only 1-3 reviews, which seems insufficient to draw any conclusions. Further, if only one review is included, is this really an umbrella review, or simply restating someone else's review?n Healthy Older, oncology (3 reviews, but each on a different type of cancer), and trauma all had one review paper only. Frail (each with differing results) and Cognitive each had only two. Therefore, I am really struggling to see how this is an umbrella review, when the results are separated out and there is very little review per category.

Answer: The reviewer understandably questions if our review meets the requirements of an umbrella review, and if conclusions can be drawn from categories that include a limited amount of reviews. The aim of our review is to give an overview of the existing knowledge concerning our research aims, with the ultimate goal to support GR-professionals in the determination of training characteristics for individual patients. An umbrella review offers the possibility to give an overview of the existing knowledge by thoroughly reviewing systematic reviews.¹⁶ The target group of our research consists of older adults with a vulnerable health status. This group is characterized by a large diversity in health issues. We distinguished eight groups of older adults, and decided to do a narrative analysis, as suggested by the Joanna Briggs institute.¹⁶ This analysis was more than just copying the results of the systematic reviews, but rather extracting and analyzing the data that specifically focused on aerobic fitness training: the effect on aerobic outcome measures and the associated FITT-criteria. The (large) number of groups is chosen in order to increase the applicability of our results in daily

practice and thereby to contribute to evidence based practice. If only one review is published for a specific health condition, then that is seen as the available knowledge on this topic.

10. I am not suggesting combining all the results, which you actually do in the conclusions. I don't agree with this as each condition is so unique, the results across all of these can't be generalized (comparing healthy older adults, for instance, with those suffering from COPD).

Answer: We thank the reviewer for this suggestion. We agree to this point of view and reformulated and toned down the conclusion in both the abstract and the conclusion paragraph. "In conclusion, physical fitness training can be an effective intervention to improve aerobic fitness in older adults in general, and also in the majority of categories of older adults with specific health statuses or diagnoses, including the most frail and vulnerable older adults."

11. Therefore, if the paper were to be revised, I would encourage that one particular subgroup be identified, and the review be conducted for that population.

Answer: We agree with the reviewer that a normal systematic review about one particular subgroup will potentially yield the most specific evidence for that subgroup. The target population of our umbrella review are frail older patients and more specific geriatric rehabilitation patients. We aimed to find generic evidence for this heterogeneous group of people. We agree that the evidence might be more broad and general, however the external validity or generalizability of the evidence is more suitable for the current GR practice.

So we propose to stick to our original plan.

Reviewer: 2

Comments to the Author:

This review presented an overview of effectiveness and training characteristics of physical training on aerobic fitness, compared to other or no training, in adults over 65 years with various health statuses, providing a basis for guidelines for aerobic training of vulnerable older adults, that can be used in geriatric rehabilitation. The review is well written and brings an interesting summary on the approached topic. I have only two comments that I believe will improve the manuscript:

12. Did the authors include or exclude reviews that included aerobic combined to resistance training? Please clarify in the "Methods" and "Results" sections.

Answer: We did not exclude reviews that included aerobic combined to resistance training, see for example the reviews of Bullo, Fukuta, Liao, Patel and Pengelly that were included. In the methods section we use a broad description in the eligibility criteria: "the reported intervention was a physical training that was expected to improve aerobic fitness" leaving room to any intervention, including resistance training, as long the review complies with the other criteria. In the result section this is formulated "The most common type of intervention was a mixed aerobic exercise program. Mixed programs were either combinations of different aerobic exercises or aerobic exercises combined with for example strength training".

13. In order to update the state of the art on the current guidelines of exercise prescription, authors must include in the "Introduction" as well as "Discussion" sections the recent International Consensus by Izquierdo et al. 2021 (J Nutr Health Aging - 25(7):824-853. doi: 10.1007/s12603-021-1665-8)

Answer: We thank the reviewer for this excellent suggestion and included the very interesting results of the consensus article by Izquierdo in the introduction and in the results.

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VERSION 2 – REVIEW

REVIEWER	Liguori , Gary University of Rhode Island, Health Sciences one of my works is referenced in this paper. however, to be transparent, my initial review of this paper had a recommendation of 'reject', so I don't believe this presents a competing interest.
REVIEW RETURNED	27-Apr-2022
GENERAL COMMENTS	Thank you for addressing our concerns, the improvements are much appreciated.
REVIEWER	Cadore, E Public University of Navarre, Department of Health Sciences
REVIEW RETURNED	26-Apr-2022
GENERAL COMMENTS	The authors addressed my comments. I have no further suggestions.

