

**Reviewer #1:**

- Why the methodological rigor and risk of bias of included RCTs assessed by PEDro instead of using the Cochrane risk of bias assessment tool?

*Answer:* We would like to thank you for your comment. Indeed, we used PEDro scale instead of the Cochrane risk of bias assessment tool to assess methodological rigor and risk of bias of the included RCTs. Although both tools have different approaches to assessing risk of bias, however, they have six items in common and either instrument can be used to quantify risk of bias. PEDro scale is a widely used assessment tool in articles and there is a good agreement for most of the PEDro and the Cochrane risk of bias items that evaluate similar constructs (Moseley AM, et al. Agreement between the Cochrane risk of bias tool and Physiotherapy Evidence Database (PEDro) scale: A meta-epidemiological study of randomized controlled trials of physical therapy interventions. *PLoS One*. 2019;14:e0222770). This is the reason we preferred PEDro instead of Cochrane risk of bias tool.

- In search strategy: “The search was conducted within 1-month time period, from December 2022 until January of 2023,” the length of the search is not clear.

*Answer:* The reviewer is right. The specific time period was from December 20, 2022 until January 20, 2023. We corrected this sentence in Methods.

- The ID for registration in PROSPERO should be presented in methods.

*Answer:* We tried to register our review in PROSPERO database but, unfortunately, we had already started data extraction before the time of initial submission. Thus, it could not be eligible for inclusion in PROSPERO.

- Quality assessment in the method needs citation. The following references can be used: (10.1093/ptj/pzab144) and (10.1016/j.physio.2021.04.005)

*Answer:* According to the reviewer’s comment, we added citation in quality assessment in Methods. (Rahmati M, Malakoutinia F. Aerobic, resistance and

*combined exercise training for patients with amyotrophic lateral sclerosis: a systematic review and meta-analysis. Physiotherapy. 2021;113:12-28)*

- In limitation, “A significant limitation of the systematic review is that the included studies may present heterogeneity of the study samples, due to different mean age, different duration since diagnosis, and different functional capacity at baseline.” Without evaluation of heterogeneity by meta-analysis, how did the authors conclude this issue?

*Answer:* We would like to thank you for your comment. Indeed, we did not perform a meta-analysis for evaluation of heterogeneity. The reason was that we did not have the possibility to have access to data of all the included RCTs. Our hypothesis of heterogeneity was based on simple observation of differences between means of age, years of diagnosis, etc. and cannot be confirmed by statistical methods without raw data. We rephrased this sentence in limitations.

- Another concern that should be mentioned in the limitation, is why the authors could not do a meta-analysis of the current results.

*Answer:* As already mentioned in the previous comment, we did not perform a meta-analysis because we did not have access to data of all the included RCTs and, thus, we decided to present only the part of the systematic review. We added this sentence in limitations.

## Reviewer #2:

- First, the question of the present study (The aim of this systematic review is to evaluate the effectiveness of high intensity interval training on cardiorespiratory fitness and endothelial function in patients with type 2 diabetes and present the most updated knowledge in literature. Please, see the abstract as well as the final paragraph of the introduction to the manuscript) has already been reviewed and answered by other researchers. In other words, the positive effect of HIIT exercises on various indicators related to metabolic syndrome and cardiorespiratory fitness is quite clear, and even meta-analysis articles have been published in this field (Please, see the references of 1 to 13).  
[1. da Silva DE, Grande AJ, Roevers L, Tse G, Liu T, Biondi-Zoccai G, de Farias JM. High-Intensity Interval Training in Patients with Type 2 Diabetes Mellitus: a Systematic Review. *Curr Atheroscler Rep*. 2019 Feb 2;21(2):8. doi: 10.1007/s11883-019-0767-9. PMID: 30712240. 2. de Oliveira Teles G, da Silva CS, Rezende VR, Rebelo ACS. Acute Effects of High-Intensity Interval Training on Diabetes Mellitus: A Systematic Review. *Int J Environ Res Public Health*. 2022 Jun 9;19(12):7049. doi: 10.3390/ijerph19127049. PMID: 35742298; PMCID: PMC9223048. 3. Wormgoor SG, Dalleck LC, Zinn C, Harris NK. Effects of High-Intensity Interval Training on People Living with Type 2 Diabetes: A Narrative Review. *Can J Diabetes*. 2017 Oct;41(5):536-547. doi: 10.1016/j.jcjd.2016.12.004. Epub 2017 Mar 30. PMID: 28366674. 4. Liu, Jx., Zhu, L., Li, Pj. et al. Effectiveness of high-intensity interval training on glycemic control and cardiorespiratory fitness in patients with type 2 diabetes: a systematic review and meta-analysis. *Aging Clin Exp Res* 31, 575–593 (2019). <https://doi.org/10.1007/s40520-018-1012-z> 5. De Nardi AT, Tolves T, Lenzi TL, Signori LU, Silva AMVD. High-intensity interval training versus continuous training on physiological and metabolic variables in prediabetes and type 2 diabetes: A meta-analysis. *Diabetes Res Clin Pract*. 2018 Mar;137:149-159. doi: 10.1016/j.diabres.2017.12.017. Epub 2018 Jan 9. PMID: 29329778. 6. Jiménez-Maldonado A, García-Suárez PC, Rentería I, Moncada-Jiménez J, Plaisance EP. Impact of high-intensity interval training and sprint interval training on peripheral markers of glycemic control in metabolic syndrome and type 2 diabetes. *Biochim*

*Biophys Acta Mol Basis Dis.* 2020 Aug 1;1866(8):165820. doi: 10.1016/j.bbadis.2020.165820. Epub 2020 Apr 29. PMID: 32360396. Review 7. Martland R, Mondelli V, Gaughran F, Stubbs B. Can high-intensity interval training improve physical and mental health outcomes? A meta-review of 33 systematic reviews across the lifespan. *J Sports Sci.* 2020 Feb;38(4):430-469. doi: 10.1080/02640414.2019.1706829. Epub 2019 Dec 31. PMID: 31889469. 8. Sultana RN, Sabag A, Keating SE, Johnson NA. The Effect of Low-Volume High-Intensity Interval Training on Body Composition and Cardiorespiratory Fitness: A Systematic Review and Meta-Analysis. *Sports Med.* 2019 Nov;49(11):1687-1721. doi: 10.1007/s40279-019-01167-w. PMID: 31401727. 9. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med.* 2015 May;45(5):679-92. doi: 10.1007/s40279-015-0321-z. PMID: 25771785. 10. Way KL, Sultana RN, Sabag A, Baker MK, Johnson NA. The effect of high Intensity interval training versus moderate intensity continuous training on arterial stiffness and 24h blood pressure responses: A systematic review and meta-analysis. *J Sci Med Sport.* 2019 Apr;22(4):385-391. doi: 10.1016/j.jsams.2018.09.228. Epub 2018 Sep 22. PMID: 30803498. 11. Qiu S, Cai X, Yin H, Sun Z, Zügel M, Steinacker JM, Schumann U. Exercise training and endothelial function in patients with type 2 diabetes: a meta-analysis. *Cardiovasc Diabetol.* 2018 May 2;17(1):64. doi: 10.1186/s12933-018-0711-2. PMID: 29720185; PMCID: PMC5930739. 12. You Q, Yu L, Li G, He H, Lv Y. Effects of Different Intensities and Durations of Aerobic Exercise on Vascular Endothelial Function in Middle-Aged and Elderly People: A Meta-analysis. *Front Physiol.* 2022 Jan 21;12:803102. doi: 10.3389/fphys.2021.803102. PMID: 35126182; PMCID: PMC8814456. 13. Khalafi M, Sakhaei MH, Kazeminasab F, Symonds ME, Rosenkranz SK. The impact of high-intensity interval training on vascular function in adults: A systematic review and meta-analysis. *Front Cardiovasc Med.* 2022 Nov 17;9:1046560. doi: 10.3389/fcom.2022.1046560. PMID: 36465439; PMCID: PMC9713318. 14. Holmes, D. High-intensity interval training benefits patients with T2DM. *Nat Rev Endocrinol* 11, 632 (2015). <https://doi.org/10.1038/nrendo.2015.171> 15. Li J, Cheng W, Ma H. A Comparative Study of Health Efficacy Indicators in Subjects with T2DM Applying Power Cycling

to 12 Weeks of Low-Volume High-Intensity Interval Training and Moderate-Intensity Continuous Training. *J Diabetes Res.* 2022 Jan 13;2022:9273830. doi: 10.1155/2022/9273830. PMID: 35071605; PMCID: PMC8776485. 16. Costa EC, Hay JL, Kehler DS, Boreskie KF, Arora RC, Umpierre D, Sz wajcer A, Duhamel TA. Effects of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training On Blood Pressure in Adults with Pre- to Established Hypertension: A Systematic Review and Meta-Analysis of Randomized Trials. *Sports Med.* 2018 Sep;48(9):2127-2142. doi: 10.1007/s40279-018-0944-y. PMID: 29949110. 17. Leal JM, Galliano LM, Del Vecchio FB. Effectiveness of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training in Hypertensive Patients: a Systematic Review and Meta-Analysis. *Curr Hypertens Rep.* 2020 Mar 3;22(3):26. doi: 10.1007/s11906-020-1030-z. PMID: 32125550. 18. Sawyer BJ, Tucker WJ, Bhammar DM, Ryder JR, Sweazea KL, Gaesser GA. Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults. *J Appl Physiol* (1985). 2016 Jul 1;121(1):279-88. doi: 10.1152/japplphysiol.00024.2016. Epub 2016 Jun 2. PMID: 27255523; PMCID: PMC4967258. 19. O'Brien MW, Johns JA, Robinson SA, Bungay A, Mekary S, Kimmerly DS. Impact of High-Intensity Interval Training, Moderate-Intensity Continuous Training, and Resistance Training on Endothelial Function in Older Adults. *Med Sci Sports Exerc.* 2020 May;52(5):1057-1067. doi: 10.1249/MSS.0000000000002226. PMID: 31876667. 20. Francois ME, Little JP. Effectiveness and safety of high-intensity interval training in patients with type 2 diabetes. *Diabetes Spectr.* 2015 Jan;28(1):39-44. doi: 10.2337/diaspect.28.1.39. PMID: 25717277; PMCID: PMC4334091.] Almost, in all articles published, the effect of high intensity interval training on cardiorespiratory fitness and endothelial function in type 2 diabetes has been investigated, even in the older individuals.

**Answer:** We would like to thank the reviewer for his/her comment. Indeed, the effects of HIIT on various indicators related to metabolic syndrome and cardiorespiratory fitness are being investigated, especially the last years. However, the aim of our systematic review was to present the most recent data, published even after 2020. Moreover, most of these reviews either presented

only the effects of HIIT in aerobic capacity without data on endothelial function or included other types of studies (observational) except for RCTs where bias due to confounders could be quite possible. We recognize that our systematic review may lack a meta-analysis that could increase the impact of this article, but it includes recently published RCTs that investigate both cardiorespiratory fitness and endothelial function, trying to provide updated knowledge about potential pathophysiological mechanisms in exercise and diabetes.

- Second, really, what is the main challenge and question of the respected researchers in this study? In such a way that even the explanation of the researchers in the final part of the introduction shows that the current study did not investigate a new challenge? The researchers stated in the final part of the introduction of the manuscript that previous studies have been conducted on cardiovascular and metabolic syndrome patients, but studies on type 2 diabetes patients are limited. “However, most studies focus on the effectiveness of HIIT in patients with cardiovascular diseases and metabolic syndrome. The beneficial effects of HIIT in patients with T2DM still remain under investigation and number of studies is limited”. Really, what is the distinguishing difference between patients with metabolic syndrome and type 2 diabetes? Undoubtedly, metabolic syndrome and its components have an effect on the occurrence of type 2 diabetes. It seems that the new message of the present manuscript should be rewritten. In this regard, it is suggested to evaluate the effectiveness of HIIT exercises compared to herbal supplements on vascular function or arterial stiffness.

*Answer:* This is a quite good comment by the reviewer. We already mentioned the main challenges of our review in the previous comment. We aimed to investigate the effectiveness of HIIT in both cardiorespiratory fitness and endothelial function and compare it over MICT. We also tried to relate these variables and present potential pathophysiological mechanisms about exercise and diabetes. Indeed, metabolic syndrome and its components are predictors

of the occurrence of type 2 diabetes, indicating an association. However, metabolic syndrome and type 2 diabetes are not the same clinical syndromes. Type 2 diabetes is the result of metabolic syndrome. If metabolic syndrome is treated on time, then the occurrence of diabetes is less possible (*Najarian RM, Sullivan LM, Kannel WB, Wilson PW, D'Agostino RB, Wolf PA. Metabolic syndrome compared with type 2 diabetes mellitus as a risk factor for stroke: the Framingham Offspring Study. Arch Intern Med. 2006;166:106-11*). Under the same way of thinking, id est. there is no reason to investigate similar, but different, clinical syndromes, researchers would not investigate the effects of exercise in patients with stable angina and in patients after an acute myocardial infarction separately, because stable angina could lead in an acute cardiovascular event. As far as the reviewer's suggestion to evaluate the effectiveness of HIIT exercises compared to herbal supplements on vascular function or arterial stiffness is concerned, it seems quite promising for a future systematic review, but it was not the aim of our study. We believe that it is more important to compare different aerobic exercise regimens (HIIT and MICT) in diabetic patients and demonstrate the most updated results in literature.

- Third, limiting keywords to search for articles in the field of diabetes significantly reduced the final articles evaluated in the systematic review process (12 articles in total). In addition, using the term sprint interval training (instead of the term rehabilitation) along with HIIT training seems to have included more relevant articles in the review process. Therefore, it is necessary to review the keyword sprint interval training (exercise) or high intensity intermittent training (exercise) and evaluate the articles in this field. Moreover, unfortunately, the effect of HIIT exercises on endothelial function and arterial stiffness in type 2 diabetics, which can be an innovation in the present study, has not been considered. Therefore, it is suggested to search the above exercise keywords along with cardiorespiratory fitness and especially endothelial function in databases (Pubmed, PEDro and CINAHL).

*Answer:* The reviewer is right. It would be wise to use more keywords in our search and thus, we followed the reviewer's suggestion. However, we did not manage to find more RCTs with the same criteria in order to include them in our study. We found some clinical trials, but they were not suitable for our review. We included the suggested keywords in Methods. Arterial stiffness in type 2 diabetics is a quite significant variable that we could investigate. However, we believe that using this variable along with endothelial function and cardiorespiratory fitness would make the pathophysiological patterns more complicated and would confuse readers more than making things more clear. It would be a suitable variable of interest in hypertensive patients and/or patients with cardiovascular disease.

- In section of the study selection criteria, what exactly is meant by the term "other indices of microcirculation"? Please mention some examples.

*Answer:* Thanks for your comment. We rephrased this sentence in order to make it clear.

- Considering the significant effect of nutrition or medication in controlling diabetes and its related problems, it is necessary to report a separate paragraph in this issue in the method section.

*Answer:* The importance of nutrition and/or medication in controlling diabetes, as well as its related problems are undeniable. In the included RCTs, all patients were considered to have controlled type 2 diabetes under medication and normal eating habits. We included this fact in Methods. However, our aim was not to investigate these parameters and, thus, we did not further extend this topic.

- We know very well that diabetes has different stages and the effect of HIIT exercise on people in the pre-diabetes stage, diabetes stage and advanced stages



of diabetes should be separated. Therefore, it is necessary to report the results of HIIT training according to the diabetes status (diabetes stage vs. advanced stages of diabetes) and especially according to their age.

*Answer:* Thanks for your comment. Indeed, it would be more comprehensive to demonstrate the effects of HIIT in type 2 diabetic patients of different severity. However, this characteristic was not clear in the included RCTs and thus, we did not manage to separate patients according to their status. In our review, we included only patients with established diabetes and we excluded studies with pre-diabetic patients. Moreover, age was similar in most studies. If a meta-analysis was possible, then we would be able to present more results according to disease severity and age.

- In the study selection criteria (Method section), the researchers announced the age of over 18 years as the inclusion criteria for entering the article into the systematic review process, while the effect of HIIT exercises on the cardiorespiratory fitness level of a young and an elderly person can be very different. In addition, the arterial stiffness of a young person is very different compared to an elderly person, and therefore, the effectiveness of HIIT training can also be different. This difference in reporting the results should also be taken seriously.

*Answer:* According to the reviewer's comment, we included more details about this situation in limitations.

- The authors reported in the method section that articles with duration of HIIT training of more than two weeks were included in the systematic review process. Although the implementation of HIIT exercises with a short duration has an effect on improving cardiorespiratory fitness, but its effect on arterial stiffness, especially in the elderly, is very questionable!!! To express the results more clearly, these issues should be separated.

*Answer:* As already mentioned in previous comments, our aim was not to investigate arterial stiffens, but cardiorespiratory fitness and endothelial function. The reviewer is right that a cardiac rehabilitation program with short duration could not result in improvement in arterial stiffness in elder patients. Although we did not present arterial stiffness in our results, we included a potential limitation regarding this variable.

- In the discussion section, the mechanisms of the HIIT exercise effect on arterial stiffness should be clearly stated.

*Answer:* The reviewer is right. We included an extra paragraph in Discussion regarding the effects of HIIT on the arterial stiffness.

- The practical importance of the research findings should be added in terms of performance as well as health.

*Answer:* We added the practical importance of the research findings in performance and health of diabetic patients in Clinical Perspectives section, according to the reviewer's suggestion.

- By carefully checking the references, it can be seen that the search was not done using specialized keywords. For example, see reference 7.

*Answer:* Thanks for your comment. We performed our research with specialized keywords that describe HIIT and type 2 diabetes. Indeed, some references may differentiate from these keywords, but they were chosen only for specific sentences or information that would be more helpful for the readers to be included in the main text (epidemiological data, pathophysiology etc.).

**Company editor-in-chief:**

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Cardiology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the

author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

*Answer:* We would like to thank you for your comments. We modified figure and tables according to the instructions. Moreover, all the reviewers' comments were answered point by point.