# Comparing unequal volumes of HIIT and MICT does not introduce bias

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We would like to thank Andreato *et al.* [1] and Stern [2] for their further contributions to the discussion about the perceived need to 'equalise' HIIT and MICT for energy expenditure, work done, or session duration, to avoid bias in the interpretation of comparison studies. We read their letters with interest, but we fail to find further justification for the need to equalise protocols, and remain unconvinced by the arguments presented. Unfortunately, we have insufficient space to rebut all claims made by Andreato [1] and Stern [2], or to expand the argument to research into sports performance. Therefore, we will limit ourselves to the key presenting issue.

Andreato [3] originally proposed that "*an important risk of bias common in research comparing HIIT and MICT [is] the lack of equalisation among protocols*", and that this "*limits the conclusions of many studies*". Despite our criticisms [4], Andreato and Stern still fail to elaborate on exactly what bias is introduced if protocols are not equalised. We have no other choice than to make an assumption again: that the bias referred to entails that if a greater volume of MICT is associated with superior adaptations compared to a lower volume of HIIT, it might not be MICT *per se* that was superior to HIIT, it might be that the unequal volume caused the difference. This, however, is not sufficient justification for the assertion that protocols must be equalised.

A number of scenarios are possible when comparing 'unequal' HIIT and MICT. Firstly, if HIIT provides either equal or more pronounced adaptations compared to a greater volume of MICT, then there is no bias. In these cases, it can be confidently concluded that HIIT is superior to, or as effective as MICT. This is the case in the majority of studies that we are aware of. Secondly, if a greater volume of MICT leads to greater adaptations compared to HIIT, the comparison is not biased *if* the purpose of the HIIT intervention was clearly stated as offering a time-efficient alternative to MICT. In this case, the lack of equality was by design and does not lead to biased conclusions. Such studies can conclude that the time-efficient alternative to MICT was less effective. Bias is *only* present in the third possible scenario, which involves a greater volume of MICT leading to greater adaptations compared to HIIT, where HIIT is not specifically studied as a time-efficient alternative to MICT. In this case, it cannot be determined whether the superior adaptations with MICT were caused by the greater volume of exercise or by the different type of exercise. This scenario may occur in a small minority of studies.

Considering that i) HIIT is often associated with adaptations similar to, or greater than those with MICT, and ii) by design, HIIT is often structured to require a smaller volume of exercise than MICT, the argument for a generalised need to equalise HIIT and MICT can be rejected. The authors make a sweeping statement that equalisation of protocols is required ("*not if, but how*" [2]), with a brief disclaimer that an exception is "*when the goal is to investigate whether HIIT can be time-efficient*". We propose there is generally no need for equalisation of HIIT and MICT, with a brief disclaimer that there is a small risk of bias in cases when the goal is not to investigate whether HIIT can be used as a time-efficient alternative to MICT.

There are other reasons why equalisation of protocols is not warranted. For example, matching solely for either energy expenditure, duration, or volume results in false equivalence as this will leave the other two 'unequal', as will many other parameters (e.g., average heart rate, perceived exertion, amount of glycogen breakdown, etc). Why is equalisation for one parameter enough? Why does the lack of equality for many other parameters not lead to bias? This remains unaddressed. Stern suggests that to "*equalize the*

*adaptation and measure the difference in volume*" would be an alternative way to equalise protocols, but matching adaptations would be an unattainable methodological challenge.

Andreato *et al.* justify the need to equalise protocols by stating that the results of meta-analyses are altered according to the analysis carried out, e.g., when considering equalised protocols vs. 'unequal' protocols). We fail to see why that is a problem. These can be considered unique research questions; if you ask a different research question, then you will (potentially) get a different answer.

Stern contends that "*the only way to determine whether the physiological adaptation mechanisms of HIIT and MICT are differentiated is to measure the dependent variable through the manipulation of an equalized independent variable*". We disagree with this assertion. If identical volumes of MICT and HIIT have different effects on a given parameter, then this does not tell us whether the mechanisms of adaptation were different. It merely confirms that exercise intensity is likely an important factor in training adaptations *per se*, not whether this is because the same mechanism is activated more strongly, or because different mechanisms are activated. Indeed, the molecular mechanisms of adaptation are different for resistance training and MICT [5], but this has not been revealed by comparing equalised protocols based on energy expenditure, duration, or volume.

Stern further suggests that "*as an analogy, two similar drugs would be tested for efficacy by either holding dose equivalence and testing which drug therapy has the greater effect, or dosing each drug to equivalent effect and measuring the difference in dose*". This is not standard practice; head-to-head drug comparison trials tend to use different doses (see for example [6-8]). How can the doses of two drugs be equalised? One approach would be based on mass, but the active components may have different molecular masses, so the same dose may involve different numbers of molecules. You could match the dose by the number of molecules, but the drugs may have entirely different mechanisms of action, so a higher number of molecules may be required to achieve a similar effect. Further issues, like differences in bioavailability, half-life, etc, make this approach unworkable. This analogy actually strengthens our argument that HIIT and MICT protocols do not need to be equalised. The correct approach would be to titrate the therapeutic dose of each drug based on efficacy and side effects, and then compare the two drugs. This is similar to developing an effective exercise protocol (like HIIT), and then comparing it to a known effective exercise protocol (like MICT). No dose-equivalence is needed.

In conclusion, we repeat our agreement with the assertion that clear and standardised terminology needs to be used to define HIIT and MICT, and studies should report in full the protocol parameters that have been applied. However, although researchers are free to equalise HIIT and MICT protocols for energy expenditure, session workload, or session duration in comparison studies, only rarely is there a need to do so.

**Disclaimer Statement**

The authors report no relationships that could be construed as a conflict of interest.

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