9. Lee AC, Driban JB, Price LL, Harvey WF, Rodday AM, Wang C. Responsiveness and minimally important differences for 4 patient-reported outcomes measurement information system short forms: Physical function, pain interference, depression, and anxiety in knee osteoarthritis. *J Pain*. 2017;18(9):1096–1110.

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Second letter to the Editor about the article ''The addition of blood flow restriction to resistance exercise in individuals with knee pain: a systematic review and meta-analysis''

We read with interest the recent systematic review entitled ''The addition of blood flow restriction to resistance exercise in individuals with knee pain: a systematic review and meta-analysis'' by Cuyul-Vásquez et al.[1]

The use of blood flow restriction (BFR) by musculoskeletal rehabilitation and sports medicine professionals is increasingly popular which makes this systematic review an important addition. Although the authors reported that they conducted the review following recommendations in the Cochrane Handbook,[2] there are some important departures, which have likely introduced biases and inconsistencies we would like to draw attention to.

Our first concern is how the data for pain reduction (Fig. 3A in Cuyul-Vásquez et al.[1]) were extracted and pooled. Their results suggest no difference between interventions (SMD = −0.37, 95% CI: −0.93, 0.19) at short-term follow-up.

On close inspection of the raw data used to generate the described effect sizes, we suspect a few critical errors may have inadvertently crept into the final analyses which have influenced the ultimate outcomes as calculated and reported. Firstly, the authors appear to have not imported and pooled homogenous outcome measures, but instead different methods of calculating these measures. Specifically, it is hard to justify pooling ''mean ± standard deviation (SD)'' values for Numerical Pain Rating Scale (NPRS), Visual Analogue Scale (VAS), and Western Ontario and McMaster Universities Osteoarthritis Index pain subscale ($WOMAC_{pain}$),[3–5] along with ''mean difference ± SD'' values for Knee injury and Osteoarthritis Outcome Score pain subscale ($KOOS_{pain}$),[6] and ''percentage (%) mean difference ± SD'' values for $KOOS_{pain}$,[7] notwithstanding the use of standardized mean differences (SMD). Furthermore, it would appear that the direction of the effect estimate has been reversed in one study.[7] The net effect of this is that the effect estimate in the study of Segal et al.[7] is overestimated 4.5 times, and the overall effect size has been extremely (37 times) overestimated based on our calculations (SMD = −0.010, 95% CI: −0.267, 0.247) as depicted in Fig. 1A. In addition, they excluded from the meta-analyses a study[8] that reported pain outcomes ($KOOS_{pain}$) that appears to meet their inclusion criteria for quantitative synthesis (SMD = −0.058, 95% CI: −0.311, 0.236 — Fig. 1B) given the clinical heterogeneity of the studies pooled in this review.[9]

Another concern is how the authors' reported and selected data throughout the review. Specifically: (a) the corresponding sample sizes for the included studies deviate from the numbers reported in original publications, for example in Giles et al.,[5] the sample of the strengthening group was n = 39 and not 30; (b) the inclusion of a single-session study by Korakakis et al.,[10] that does not meet the inclusion criteria (i.e. treatment duration between two weeks to three months); (c) the exclusion from the knee function meta-analysis of studies reporting relevant outcome measures, such as the Kujala patellofemoral score[5] and KOOS.[8]

The pooling of heterogeneous outcome measures, the discrepancies in eligible studies, and the overestimation of the pooled effect estimate suggest that these recommendations on the effectiveness of BFR should be interpreted with some caution until the authors provide clarification. Anecdotally, BFR training is very common,[11,12] however is also associated with potentially serious side effects[13,14] and decisions on its use need to be based upon unbiased summaries of the available evidence.

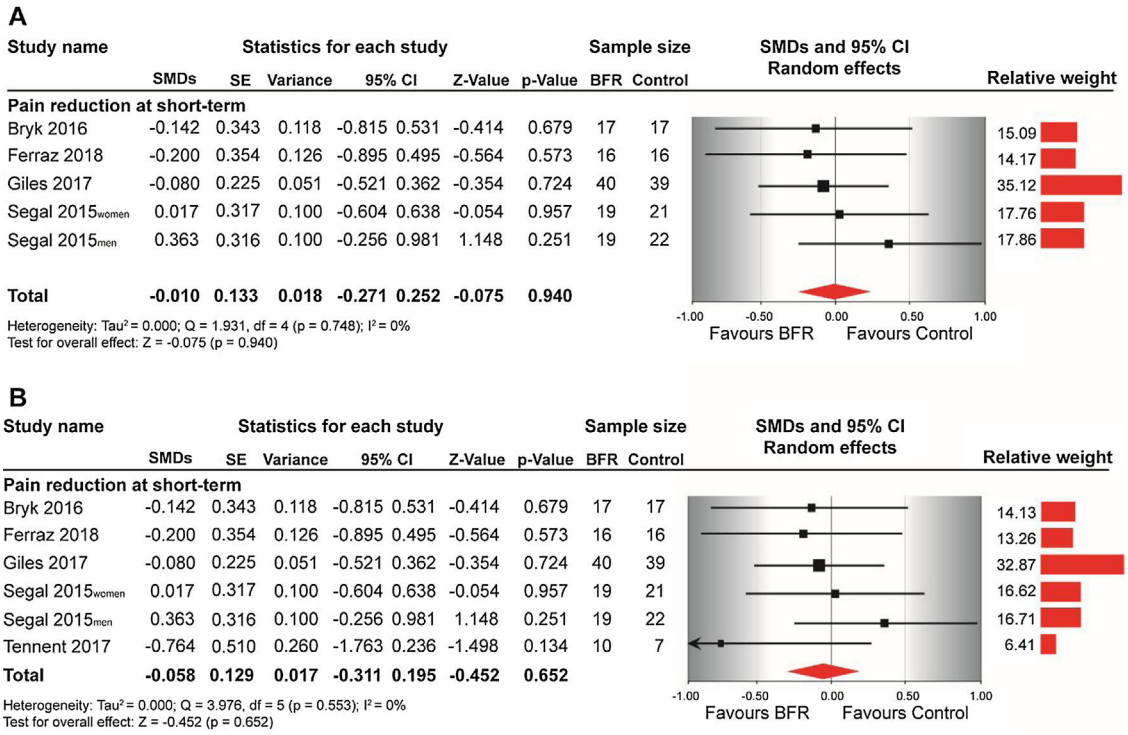

Figure 1 Pain reduction pooled results at short-term follow-up. (A) Re-calculation of pooled effect size of included studies in the systematic review. (B) Pooled effect size with the additional study[8] that was excluded from quantitative synthesis.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Cuyul-Vásquez I, Leiva-Sepúlveda A, Catalán-Medalla O, Araya-Quintanilla F, Gutiérrez-Espinoza H. The addition of blood flow restriction to resistance exercise in individuals with knee pain: a systematic review and meta-analysis. *Braz J Phys Ther*. 2020;24(6):465–478.
2. Higgins JPT, Green S, Version 5.1.0 ed. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration; 2011.
3. Bryk FF, dos Reis AC, Fingerhut D, et al. Exercises with partial vascular occlusion in patients with knee osteoarthritis: a randomized clinical trial. *Knee Surg Sports Traumatol Arthrosc*. 2016;24(5):1580–1586.
4. Ferraz RB, Gualano B, Rodrigues R, et al. Benefits of resistance training with blood flow restriction in knee osteoarthritis. *Med Sci Sports Exerc*. 2018;50(5):897–905.
5. Giles L, Webster KE, Mcclelland J, Cook JL. Quadriceps strengthening with and without blood flow restriction in the treatment of patellofemoral pain: a double-blind randomised trial. *Br J Sports Med*. 2017;51(23):1688–1694.
6. Segal NA, Williams GN, Davis MC, Wallace RB, Mikesky AE. Efficacy of blood flow-restricted, low-load resistance training in women with risk factors for symptomatic knee osteoarthritis. *PMR*. 2015;7(4):376–384.
7. Segal N, Davis MD, Mikesky AE. Efficacy of blood flowrestricted low-load resistance training for quadriceps strengthening in men at risk of symptomatic knee osteoarthritis. *Geriatr Orthop Surg Rehabil*. 2015;6(3):160–167.
8. Tennent DJ, Hylden CM, Johnson AE, Burns TC, Wilken JM, Owens JG. Blood flow restriction training after knee arthroscopy: a randomized controlled pilot study. *Clin J Sport Med*. 2017;27(3):245–252.
9. Cerqueira MS, Brito Vieira WH. Letter to the Editor about the article ''The addition of blood flow restriction to resistance exercise in individuals with knee pain: a systematic review and meta-analysis''. *Braz J Phys Ther*. 2020;24(6):560–561.
10. Korakakis V, Whiteley R, Giakas G. Low load resistance training with blood flow restriction decreases anterior knee pain more than resistance training alone. A pilot randomised controlled trial. *Phys Ther Sport*. 2018;34:121–128.
11. Yasuda T, Meguro M, Sato Y, Nakajima T. Use and safety of KAATSU training: results of a national survey in 2016. *Int J KAATSU Train Res*. 2017;13(1):1–9.
12. Patterson SD, Brandner CR. The role of blood flow restriction training for applied practitioners: a questionnaire-based survey. *J Sports Sci*. 2018;36(2):123–130.
13. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. *Br J Sports Med*. 2017;51(13):1003–1011.
14. Whiteley R. Blood flow restriction training in rehabilitation: a useful adjunct or Lucy's latest trick? *J Orthop Sports Phys Ther*. 2019;49(5):294–298.

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Reply to second letter to the editor about the article ''The addition of blood flow restriction to resistance exercise in individuals with knee pain: a systematic review and meta-analysis''

We appreciate the comments by Korokakis et al.[1] on our article 'The addition of blood flow restriction to resistance exercise in individuals with knee pain: a systematic review and meta-analysis'.[2] We would like to take the opportunity to address several points raised in these comments which adds to the discussion that this review already generated.[3,4]

First, we do not agree with the comment 'Although the authors reported that they conducted the review following recommendations in the Cochrane Handbook, there are some important departures, which have likely introduced biases and inconsistencies. . .' Our systematic review was performed according to the recommendations of the Cochrane Handbook and the PRISMA statement, which are the current guideline recommendations regarding systematic review design and methodologies.[5,6] In addition, the results of the analysis of pooled data as performed by Korokakis et al[1] and illustrated in their Figures (Figure 1A, p= 0.94, Figure 1B, p=0.65) seem to be consistent with our conclusion of a lack of effect of blood flow restriction (BFR).

Second, despite the fact that the extracted data used different scales and scores, it was possible to perform a meta-analysis, according to the recommendations of the current Cochrane Handbook, using standardised mean differences to unify and adjust the values. Although this is not ideal and could be a source of heterogeneity, it allowed assessing the data in a more categorical manner with quantitative results.[5]

Additionally, it was suggested that we should have included the study by Tennent et al.[7] Considering that its effect measures are expressed in medians and interquartile range, this is why it was not possible to include these data in the meta-analysis with our other data using RevMan 5.3 software.[5] However, we tried to contact the corresponding author to request the data, but did not receive a response. In fact, the authors of the letter should change the estimator measure of standard error and variance in their forest plots (Figure 1A and 1B),[1] as it is not advisable in intervention studies reporting the effect with this estimator as it makes the interpretation of the results difficult.[8,9] Despite this, the magnitude of the effect remains small and not statistically significant.

Regarding the meta-analysis of knee function, unlike the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Knee Injury and Osteoarthritis Outcome Score (KOOS) functional scales, the Kujala score is a specific outcome measure for patellofemoral pain that includes symptoms, function, and quality of life in a single score.[10] For this reason, the results of Giles et al.[11] were not considered in this quantitative analysis.

Regarding the inclusion of Korakakis et al.[12] this study was only considered for the descriptive and qualitative analysis and, therefore, did not influence the results of our meta-analysis.

Regarding the final statement '*The pooling of heterogeneous outcome measures, the discrepancies in eligible studies, and the overestimation of the pooled effect estimate suggest that these recommendations on the effectiveness of BFR should be interpreted with some caution*', while we understand the importance and caution about heterogeneity, the random effect model used in our meta-analysis attenuated this effect. Additionally, it is advisable to conduct a meta-analysis despite the presence of substantial heterogeneity as this is considered under the inconsistency domain when assessing the overall quality of evidence using the GRADE approach. These methodological aspects are described in the statistical methods' section of our review and follows the Cochrane Handbook, the PRISMA statement, and the GRADE recommendations.[5,6,13,14]

Finally, we thank the authors of the letter for their concern for our study. We used a transparent method of assessing and reporting the evidence. All authors of systematic reviews with a meta-analysis must make methodological decisions, but these are not made with the aim of introducing bias or decreasing the evidence for effectiveness of treatment. None of the changes suggested by the authors of the letter substantially modify the results or the conclusions of our systematic review. An important aspect of our results is that it reinforces that more clinical studies and of better methodological quality are needed to demonstrate in which patients and at which dose BFR may be clinically effective.

Conflicts of interest

The authors declare no conflicts of interest.