

# Effectiveness of Laser Therapy in Adults with Knee Osteoarthritis: A Bivariate Meta-Analysis of Placebo-Controlled Randomized Controlled Trials

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## BACKGROUND

Knee pain represents the second most common musculo-skeletal disorder after low back pain [1]. Knee osteoarthritis (OA) represents the leading cause of knee pain, as well as the most common site for OA, with a projected increase of 74.9% [uncertainty interval 59.4-89.9%] in the number of cases by 2050 compared to 2020 [2]. Laser therapy (LT) represents a non-invasive treatment modality that is frequently provided to adults with knee OA due to its anti-inflammatory effects, despite not being recommended in major OA treatment guidelines [3]. Trials usually report measures of function and pain in this population, which are correlated when measured on the same participants. Nevertheless, meta-analyses typically ignore such correlations and perform univariate meta-analyses on the two outcomes independently, which may impact the estimates and their precision [4]. Conversely, multivariate meta-analyses consider the correlation between different outcomes and have the potential for the estimate of one effect to borrow strength from the data on other effects of interest [5].

## OBJECTIVES

To assess the effectiveness of LT compared to sham LT on function and pain in adults with knee OA, taking advantage of the correlation between the two outcomes.

## METHODS

PubMed and Embase were systematically searched from inception to May 6th, 2025 for placebo-controlled randomized controlled trials (RCTs) comparing LT to sham LT, alone or in addition to other conservative interventions (e.g., physio-

therapy, exercise), in adults with knee OA. Studies were included if they measured function and pain with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Physical Function and Pain subscales, respectively. In case of multiple relevant study groups, the sample size of the control group was split accordingly. Within-group mean changes and corresponding standard deviations of change (SDs) were extracted. When not reported, mean changes were computed and the SD of change was calculated following the Cochrane Handbook guideline [6] and assuming a correlation of 0.5 between baseline and post-treatment values.

A frequentist random-effect bivariate meta-analysis was performed on function and pain at the end of treatment, assuming a common correlation between outcomes ( $r=0.824$ , from external reference [7]) for all included studies. Sensitivity analyses assuming different correlation values (i.e., 0.2, 0.4, 0.6) were also performed. Univariate random-effects meta-analyses for the two outcomes disjointly were performed estimating the between-study heterogeneity using the restricted maximum likelihood estimator (REML) and computing the 95% confidence interval (95%CI) using the Hartung-Knapp (HK) method. Mean differences (MD) and 95%CI were calculated for both univariate and bivariate meta-analysis. Bivariate estimates were compared with univariate estimates and the impact of bivariate meta-analysis was assessed using the Borrowing of Strength (BoS) index [5] and the estimated number of additional studies using correlated evidence [8]. All the analysis were performed in R version 4.4.1.

## RESULTS

From 233 individual records identified, 14 RCTs (16 effect sizes) involving 728 adults with knee OA were included. Main bivariate meta-analyses supported the effectiveness of

LT compared to sham LT (function: MD -3.57, 95%CI -5.27 to -1.86; pain: MD -1.37, 95%CI -2.12 to -0.61). Similar estimates have been computed in univariate meta-analyses and in sensitivity analyses (Figure 1).

Compared to univariate meta-analyses, the main model improved the precision of the estimates (i.e., reduced standard error), with a BoS of 15.5% and 9.5% for function and pain, respectively. The extra information gained by using correlated evidence is similar to finding direct evidence from approximately three and two additional studies, respectively. When considering sensitivity analyses, bivariate models improved the precision of the estimate for function for every assumed correlation, while bivariate models with lower correlations (i.e.,  $r < 0.4$ ) resulted in reduced precision and, consequently, larger confidence intervals compared to the univariate model for pain. Heterogeneity statistics were similar in univariate and bivariate models.

## CONCLUSIONS

Compared to sham LT, the current findings support that LT improves function and pain in adults with knee OA, irrespective of the meta-analytic model considered. Despite univariate and multivariate models provide very similar results, with apparently little information gained from considering the correlation between the two outcomes, the latter may improve the precision of the estimates. Nevertheless, the extent to which multivariate meta-analyses may provide more precise estimates and thus narrower confidence intervals depends on the assumed correlation and the considered outcome. Future research, considering situations where studies do not provide information on all outcomes or provide different measures of selected outcomes (thus requiring standardization of the effect estimates), or extending the bivariate meta-analysis to more than two outcomes, may shed light on the impact of a multivariate meta-analytic approach compared to separate univariate meta-analyses in the field.

## REFERENCES

1. Urwin M., Symmons D., Allison T., et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. *Ann Rheum Dis.* 1998;57(11):649-55.
2. Collaborators G.B.D.O. Global, regional, and national burden of osteoarthritis, 1990-2020 and projections to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Rheumatol.* 2023;5(9):e508-e22.
3. Stausholm M.B., Naterstad I.F., Joensen J., et al. Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open.* 2019;9(10):e031142.
4. Riley R.D. Multivariate meta-analysis: the effect of ignoring within-study correlation. *Journal of the Royal Statistical*

*Society Series A: Statistics in Society.* 2009;172(4):789-811.

5. Jackson D., White I.R., Price M., et al. Borrowing of strength and study weights in multivariate and network meta-analysis. *Stat Methods Med Res.* 2017;26(6):2853-68.
6. Higgins J.P.T., Li T., Deeks J.J., et al. Chapter 6: Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane, 2023. Available from [www.training.cochrane.org/handbook](http://www.training.cochrane.org/handbook).
7. Salaffi F., Leardini G., Canesi B., et al. Reliability and validity of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index in Italian patients with osteoarthritis of the knee. *Osteoarthritis Cartilage.* 2003;11(8):551-60.
8. Riley R.D., Jackson D., Salanti G., et al. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. *BMJ.* 2017;358:j3932.

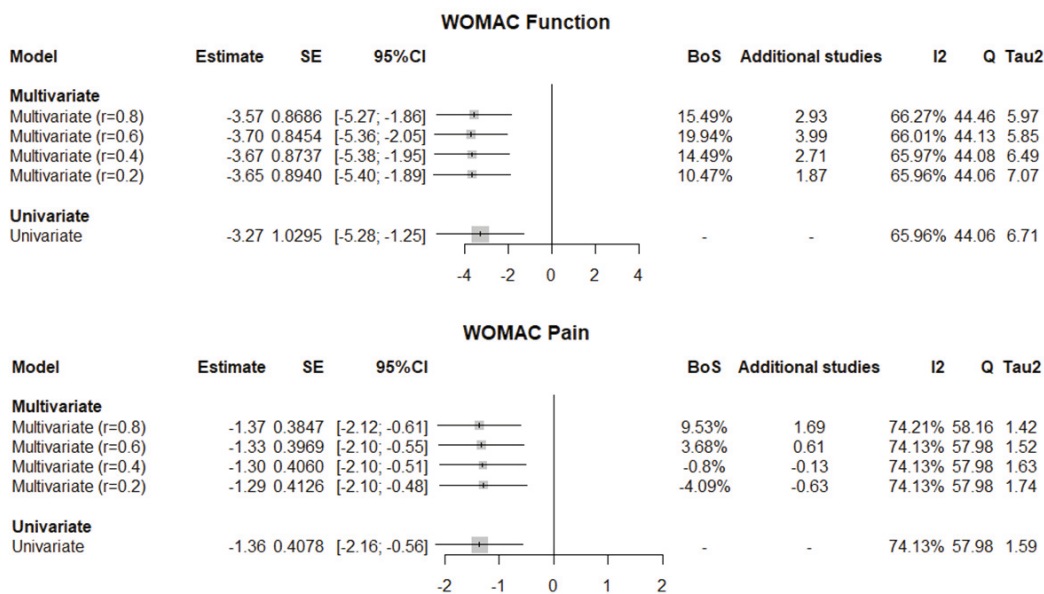


Figure 1. Comparison between multivariate and univariate meta-analyses