APPENDIX 2:

The quality of the evidence is based upon 5 main domains:

Domain	Description	Considerations in our systematic review
Study Limitations	Limitations in the study design and implementation of included primary studies suggesting high likelihood of bias.[1] Study limitations in this systematic review and meta-analysis will be assessed using the PEDro scale. Primary studies which attain scores of 6 or higher on the PEDro scale are considered "high quality" and low level of study limitations. Studies with a PEDro score of 4 or 5 are considered "fair quality" and medium level of study limitations and those with scores of 3 or less are considered "poor quality" and high level of study limitations.	The quality of the evidence will be downgraded if more than 25% of LDH participants are from studies with high level of study limitations.[2 3]
Inconsistency	Inconsistency refers to an unexplained heterogeneity of finding among included studies. Inconsistency occurs when there is a wide variance of point estimates among included studies; minimal or no overlap of confidence intervals; significant heterogeneity is obvious by visual inspection; or I-squared value is > 50%.	The quality of the evidence will be downgraded if there is a significant heterogeneity by visual inspection or I-squared value is > 50%.[2-4]
Indirectness	Indirectness refers to any deviation in the research question or its operationalization between included primary studies.[5] Differences may be found in the PICO criteria [population, intervention(s), comparison(s), or in outcome measures].[5]	In this systematic review the quality of the evidence will be downgraded if > 50% of the LDH participants are outside the target group (population).[2-4]

Imprecision	Imprecision reflects conceptually the random variation in outcome estimates due to chance.[5] Sample size, number of events, and confidence intervals can influence imprecision.	According to Mueller et al., if fewer than 400 LDH participants are included in the comparison for continuous data and fewer than 300 events for dichotomous data the quality of the evidence will be downgraded.[2-4 6] In other words; findings are considered to be imprecise when studies include relatively few patients and few events but have a wide confidence intervals around the estimate of the effect.
Publication Bias	Publication bias is considered as the preferential and more rapid publication of studies with statistically significant and beneficial findings than of trials without significant findings.[7] The existence of publication bias is one of the potential sources of risk of bias in systematic reviews. Publication bias will be assessed by visually examining funnel plots for evidence of asymmetry.	The quality of evidence will be downgraded if there is no symmetrically distribution around the point estimate in the funnel plots.

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