

**INTERVENTIONS FOR REDUCING LONELINESS:
AN UMBRELLA REVIEW OF INTERVENTION STUDIES**

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ABSTRACT

Loneliness is a common phenomenon associated with several negative health outcomes. Current knowledge regarding interventions for reducing loneliness in randomized controlled trials (RCTs) is still conflicting. The aim of the present work is to provide an overview of interventions to reduce loneliness, using an umbrella review of previously published systematic reviews and meta-analyses. For each intervention for reducing loneliness, random-effects summary effect size and 95% confidence intervals (CIs) were calculated. For significant outcomes (p-value <0.05), the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool was used, grading the evidence from very low to high. From 211 studies initially evaluated, 7 meta-analyses for seven different types of interventions were included (median number of RCTs: 8; median number of participants: 600). Three interventions were statistically significant for reducing loneliness, i.e. meditation/mindfulness, social cognitive training and social support. When applying GRADE criteria, meditation/mindfulness (mean difference, MD= -6.03; 95%CI: -9.33 to -2.73; very low strength of the evidence), social cognitive training (8 RCTs; SMD= -0.49; 95%CI: -0.84 to -0.13; very low strength of the evidence) and social support (9 RCTs; SMD=-0.13; 95%CI: -0.25 to -0.01; low strength of the evidence) significantly decreased the perception of loneliness. In conclusion, three intervention types may be utilised for reducing loneliness, but they are supported by a low/very low certainty of evidence indicating the need for future large scale RCTs to further investigate the efficacy of interventions for reducing loneliness.

Key words: loneliness; meta-analysis; randomized controlled trial; social; umbrella review.

WHAT IS KNOWN ABOUT THIS TOPIC

- Loneliness is a common condition across all ages
- The effectiveness of interventions for decreasing loneliness is poorly explored
- To know which interventions are able to decrease loneliness is of importance

WHAT THIS PAPER ADDS

- Three interventions were statistically significant for reducing loneliness, i.e. meditation/mindfulness, social cognitive training and social support
- The interventions for reducing loneliness are supported by a low/very low certainty of evidence
- Our umbrella underlines the need for future larger RCTs.

INTRODUCTION

Loneliness, perceived as a deficit between actual and desired quality or quantity of relationships(Cacioppo & Patrick, 2008), is a common condition.(Victor, Scambler, Bowling, & Bond, 2005) Several social and clinical factors have been proposed as putative risk factors for loneliness and it is widely known that loneliness itself can be considered as risk factor for other medical conditions, including psychiatric and physical disorders. (Solmi et al., 2020)

Whilst the epidemiological research regarding the factors predicting loneliness is wide, the research regarding interventions able to reduce loneliness is limited. To the best of our knowledge, only a few studies are available. Approximately 15 years ago, Cattam et al. found, among 30 quantitative publications focusing on the effectiveness of loneliness prevention programs in older people that only six can be considered as high-quality, effective interventions.(Cattan, White, Bond, & Learch, 2005) In particular, this seminal paper evidenced that educational and social activity group interventions targeting specific groups might alleviate loneliness in older people. In a recent umbrella review of previous systematic reviews and meta-analyses(Jarvis, Padmanabhanunni, Balakrishna, & Chipps, 2020), the authors found that, in older adults, active interventions are able to reduce the sense of loneliness. However, several aspects still need to be clarified. First, loneliness is common in adults and adolescents(Beutel et al., 2017), as well as older adults. Second, data of this umbrella review were pooled together, without giving the estimates for the type of intervention.(Jarvis et al., 2020) Finally, another possible important limitation is that the evidence of meta-analyses of randomized controlled trials (RCTs) is better evaluated with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool that may provide a reproducible and transparent framework for grading certainty in evidence(Siemieniuk & Guyatt, 2019) and that these works included both RCTs and other types of publication having less strength of evidence (e.g. open label studies).

Given this background, the aim of the present work is to provide an overview of interventions that are able to reduce loneliness using an umbrella review of previously published systematic reviews and meta-analyses.

METHODS

We performed an umbrella review (i.e. a review of other systematic reviews and meta-analyses)(Aromataris et al., 2015) adhering to the adapted forms of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations (Moher, Liberati, Tetzlaff, Altman, & Group, 2009) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.(Stroup et al., 2000)

Search strategy and selection criteria

We searched PubMed and PsycInfo databases (last search performed on March 31st 2020) to identify systematic reviews with meta-analyses including RCTs investigating any intervention for reducing loneliness. The following search key was used: “(loneliness) AND (Meta-Analysis[ptyp] OR metaanaly*[tiab] OR metaanaly*[tiab] OR Systematic review [ptyp] OR “systematic review” [tiab])).mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, tc, id, tm, mh]”. Two reviewers (DG, NV) independently searched titles/abstracts for eligibility, and assessed the full text of those articles surviving title/abstract phase. A third reviewer resolved any conflict (JD).

Inclusion criteria were: 1) Participants: any; 2) Intervention: any; 3) Comparator: non active group; 4) Outcome: loneliness evaluated with validated tools such as the UCLA Loneliness Scale(Russell, 1996); 5) Study design: RCTs. Exclusion criteria were: 1) meta-analyses of observational studies or non-RCT; 2) studies published in languages other than English.

When more than one meta-analysis assessed the same intervention, we only included the one with the larger number of studies, as previously described(Radua et al., 2018; Raglan et al., 2018; Theodoratou, Tzoulaki, Zgaga, & Ioannidis, 2014), considering the excluded papers as doubled.

Data extraction

Two investigators (NV, DG) independently extracted data in a pre-defined Microsoft Excel spreadsheet. For each meta-analysis, the following was extracted PMID/DOI, first author, publication year, population included in the study, type of intervention, study design, total sample size and the participants randomized to intervention or control group. The type of interventions was grouped in befriending interventions, technological interventions, meditation (mindfulness), animal therapy/robotpets, social cognitive training, social skills training and social support according to a previous relevant review in this topic.(C. M. Masi, H.-Y. Chen, L. C. Hawkley, & J. T. Cacioppo, 2011)

Quality assessment

The methodological quality of each included meta-analysis was assessed with the Assessment of multiple systematic reviews (AMSTAR) 2 tool (available at <https://amstar.ca/Amstar-2.php>), which is a recent update of AMSTAR(Shea et al., 2017), by two independent investigators (JD, DG).

Data analysis and assessment of the credibility of the evidence

For each association of meta-analyses providing individual study data, we extracted effect sizes of individual studies and re-performed the meta-analysis calculating the pooled effect sizes and the 95% confidence intervals, under the assumption of random-effects models.(DerSimonian & Laird, 1986) Heterogeneity was assessed with the I^2 statistic.(Higgins, Thompson, Deeks, & Altman, 2003)

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect, using a p-value <0.05. When the p-value for the random effect was <0.05, we evaluated the evidence using the GRADE assessment, that takes in account several important domains in the

certainty of the evidence, including study design, risk of bias, inconsistency, indirectness, imprecision and other aspects, such as publication bias. (Guyatt et al., 2008) The GRADE assessment was made by an investigator (DG) and checked and corrected, if needed, by the senior author of the present manuscript (NV).

RESULTS

Literature search

Figure 1 reports the flow diagram of the search, selection and inclusion process. Among 211 articles initially included, 43 full texts were retrieved with a final selection of 7 meta-analyses, all published in the last 10 years.(Abbott et al., 2019; Choi, Kong, & Jung, 2012; Cohen-Mansfield & Perach, 2015; Hagan, Manktelow, Taylor, & Mallett, 2014; C. M. Masi, H. Y. Chen, L. C. Hawkley, & J. T. Cacioppo, 2011; Quan, Lohman, Resciniti, & Friedman, 2019; Siette, Cassidy, & Priebe, 2017)

Main findings

Table 1 reports the descriptive findings of the seven meta-analyses included. The median number of the RCTs included was 8 (range: 2-9) with a median number of participants of 600 (282 to the active interventions and 288 to controls). The UCLA loneliness scale was the most used among the scales investigating loneliness. In one outcome, high heterogeneity was found (social cognitive training, $I^2=61\%$). No study suffered from possible publication bias. Three interventions reached the statistical significance at the p-value <0.05 : these interventions were meditation/mindfulness, social cognitive training and social support.

Table 2 shows the evidence according to the GRADE for the three statistically significant interventions. In two RCTs, meditation/mindfulness significantly decreased perception of loneliness (MD= -6.03; 95%CI: -9.33 to - 2.73), however, this evidence was supported by a very low strength of the evidence, mainly owing to high risk of bias and indirectness. Similarly, social cognitive training (8 RCTs; SMD= -0.49; 95%CI: -0.84 to -0.13) and social support (9 RCTs; SMD=-0.13; 95%CI: - 0.25 to - 0.01) were supported by a very low and low strength of evidence, respectively. Again, the risk of bias in the RCTs included was high.

Quality assessment

Supplementary Table 1 reports the quality assessment. Among the 7 meta-analyses included, 5 were rated as critically low, one low and one moderate. Six of the 7 meta-analyses did not previously publish the protocol and no one reported the sources of funding. These two items were the most important in decreasing the quality of the meta-analyses included.

DISCUSSION

In the present umbrella review including seven systematic reviews with meta-analysis with a mean of 8 RCTs and 600 participants, it was found that among seven explored interventions, only three reached a statistical significance; these were: 1) meditation/mindfulness; 2) social cognitive training; and, 3) social support. Using the GRADE, these interventions are supported by a low/very low strength of evidence.

Previous to the present review, literature had identified both successful and unsuccessful loneliness reduction strategies, as summarized in reference(Christopher M Masi et al., 2011). Among them, five of the six reviews concluded that loneliness can be mitigated with specific interventions. (Christopher M Masi et al., 2011) However, it is important to note that all these reviews concluded that the efficacy of the interventions are unclear and that more rigorous research is needed in this area. This is in agreement with findings from the present review.(Christopher M Masi et al., 2011) Our umbrella review further indicates that only some intervention types are able to reduce the perception of loneliness. In particular, mindfulness (a psychological process purposely bringing – through meditation - one's attention to experiences occurring in the present moment without judgment) is able to significantly reduce the perception of loneliness (Creswell, 2017). However, this evidence is supported by only two RCTs with high risk of bias. One can speculate that simply bringing greater awareness to the present moment is somewhat able to positively impact loneliness and social interactions.(Lindsay, Young, Brown, Smyth, & Creswell, 2019) It is likely that bringing greater awareness to social interactions might increase attentiveness to social cues and one's own emotional reactions to them, finally reducing perceived loneliness.(Lindsay et al., 2019) At the same time, social cognitive training (i.e. the mental operations involved in understanding, perceiving, and interpreting our social world)(Kurtz & Richardson, 2012) and social support (i.e. is the perception and actuality that one is cared for, has assistance available from other people)(Vaux, 1988) seem to be able to significantly reduce the sense of loneliness, again supported by a low/very low certainty of evidence.

Social support is fundamental, especially for lonely people who live in disadvantaged places (e.g. mountain district), also in terms of the development of neighbourhood.(Gelmini et al., 2020) These findings are somewhat surprising, but they support the concept that, despite the utility of the theoretic social cognitive training and social supports, the causes of loneliness are probably unique in each person and matching specific therapies with specific interventions is challenging.(Christopher M Masi et al., 2011)

Importantly, several interventions expected to reduce perceptions of loneliness did not. For example, among the interventions included in this umbrella review, technological interventions did not significantly affect the sense of loneliness in the RCTs included in the analysis. In this period of Corona Virus Disease 2019 (COVID-19) pandemic, several articles have reported that new technologies, such as video calls, can reduce loneliness, particularly in older people living in nursing home.(Vilendrer et al., 2020) However, a recent Cochrane review including three cluster quasi-randomised trials, reported that there is currently uncertain evidence on the effectiveness of video call interventions to reduce loneliness in older adults.(Noone et al., 2020) One can similarly speculate that pets (or robopets) are not able to reduce loneliness. Indeed, for these specific interventions, we found only three small RCTs (only 89 participants), making it difficult to reach robust conclusions. Observational research, on the contrary, has reported that these interventions are associated with a reduced perception of loneliness, for example in women who are not married or cohabiting.(Zasloff & Kidd, 1994)

The present umbrella review has both strengths and limitations. A strength is that a stringent quantitative criteria to grade the evidence using the GRADE was applied (the same tool used by the Cochrane reviews(Siemieniuk & Guyatt, 2019)). Moreover, this review only included RCTs, differently from previous reviews, and this choice may attenuate the risk of clinical heterogeneity. In this sense, only one intervention reported a high I^2 , i.e. >50%. Among the limitations, potentially the most important is that five of the systematic reviews and meta-analyses included were of poor quality.

A second limitation is that the detected evidence, even if significant, was supported by a high risk of bias in the RCTs included.

In conclusion, a few interventions are available for reducing loneliness and, among them, only three (i.e. meditation/mindfulness, social cognitive training and social support) show promise to reduce this phenomenon. These interventions are, however, supported by a low/very low certainty of evidence according to the GRADE criteria. We believe that our research further shows that we have a great difference between the relevant negative health and social outcomes traditionally associated with loneliness and the interventions that we have available so far, indicating the necessity of further research regarding this important issue.

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Figure 1. PRISMA flow-chart

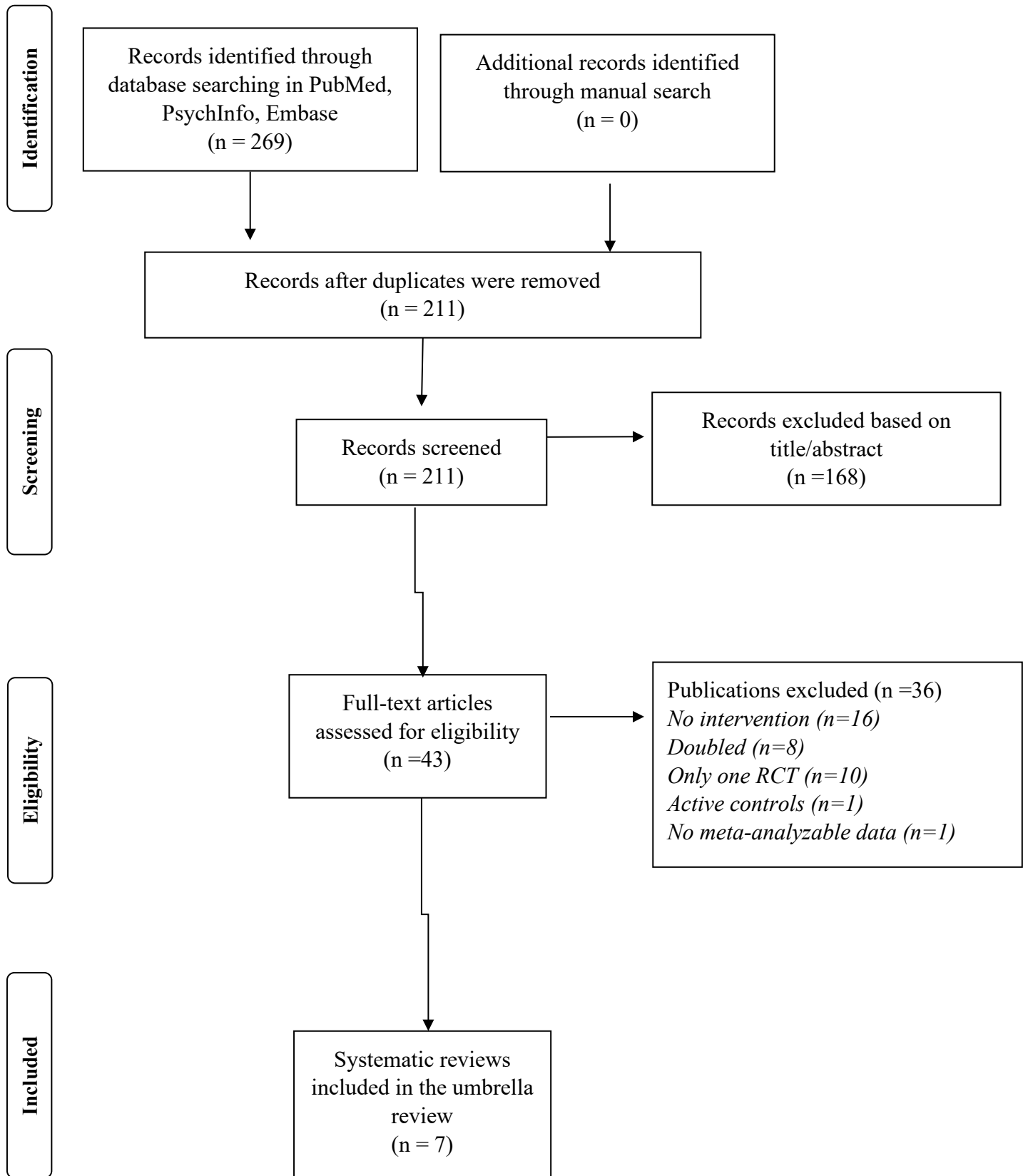


Table 1. Descriptive findings of the meta-analyses included

Type of intervention	Number of studies	Scale for assessing loneliness	Intervention	Controls	Sample size	Type of metric	Effect size (95%CI)	P	I ²	P-value Egger
Befriending intervention	5	Own scale (n=2); EQ-5D ONS (n=1); SELSA-S (n=1); QOL-BREF (n=1)	382	388	770	SMD	-0.003 (-0.16 to 0.16)	0.98	0	0.85
Technological interventions	4	de Jong Gierveld loneliness scale (n=3); UCLA loneliness scale (n=1)	209	181	529	Hedges's g	0.20 (-0.04 to 0.43)	0.10	0	0.92
Meditation (mindfulness)	2	UCLA loneliness scale (n=2)	65	67	132	MD	-6.03 (-9.33 to -2.73)	0.0003	20	NA
Animal therapy/robopets	3	UCLA loneliness scale (n=3) UCLA loneliness scale (n=5); Ando-Osada-Kodama loneliness scale (n=1); de Jong Gierveld loneliness scale (n=2)	44	45	89	SMD	-0.38 (-0.80 to 0.05)	0.08	31	0.24
Social cognitive training	8	Asher Loneliness Scale (n=1); de Jong Gierveld loneliness scale (n=1)	453	469	941	SMD	-0.49 (-0.84 to -0.13)	0.007	61	0.89
Social skills training	2		121	137	258	SMD	0.02 (-0.24 to 0.78)	0.89	0	NA

Type of intervention	Number of studies	Scale for assessing loneliness	Intervention	Controls	Sample size	Type of metric	Effect size (95%CI)	P	I ²	p-value Egger
Social support	9	UCLA loneliness scale (n=6); de Jong Gierveld loneliness scale (n=1); own scale (n=1); OARS social resource rating scale (n=1)	703	732	1483	SMD	-0.13 (-0.25 to -0.01)	0.03	2.4	0.29
Total (median)	8		282	288	600					

Abbreviations: CI: confidence interval; SELSA-S: Social and Emotional Loneliness Scale for Adults (short form); QOL-BREF: World Health Organization Quality of Life: Brief Version; UCLA: University of California, Los Angeles; NA: not available; MD: mean difference; SMD: standardized mean difference; OARS: Older Americans Resources and Services.

AMSTAR 2 quality assessment of meta-analyses.

	AMSTAR 2 items ^{a, c}																
Author, Year [Reference]	1	2 ^b	3	4 ^b	5	6	7 ^b	8	9 ^b	10	11 ^b	12	13 ^b	14	15 ^b	16	Overall rating (based on critical domains) ^d
Siette 2016	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Choi, 2012	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Cohen-Mansfield, 2015	Y	N	Y	Y	N	N	N	Y	Y	N	NMA	NMA	N	N	NMA	N	Critically low
Masi, 2013	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Critically low
Quan, 2019	Y	N	Y	Y	Y	Y	Y	Y	Y	N	NMA	NMA	Y	Y	NMA	Y	Critically low
Abbott, 2019	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate
Hagan, 2014	Y	N	Y	Y	N	N	N	Y	Y	N	NMA	NMA	N	N	NMA	N	Critically low

^a Yes, No, Other

^b Critical Domains

^c AMSTAR 2 items:

- Did the research questions and inclusion criteria for the review include the components of PICO (Population, Intervention, Comparator group, Outcome)?** YES/NO. For yes, must have all four.
- Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?** YES, PARTIAL YES, NO. For Partial YES: the authors state that they had a written protocol or guide that included ALL the following (review question(s), a search strategy, inclusion/exclusion criteria, a risk of bias assessment). For YES: as for partial yes, plus the protocol should be registered and should also have specified: a meta-analysis/synthesis plan, if appropriate, and a plan for investigating causes of heterogeneity, justification for any deviations from the protocol.
- Did the review authors explain their selection of the study designs for inclusion in the review?** YES/NO. For YES, the review should satisfy one of the following: explanation for including only RCTs, or explanation for including only NRSI, or explanation for including both RCTs and NRSI.
- Did the review authors use a comprehensive literature search strategy?** YES, PARTIAL YES, NO. for PARTIAL YES must have all of the following: searched at least 2 databases (relevant to research question), provided key word and/or search strategy, justified publication restrictions (eg. Language). For YES should also have all of the following: searched the reference lists/biographies of included studies, searched trial/study registries, included/consulted content experts in the field, searched for grey literature where relevant, conducted search within 24 months of completion of the review.
- Did the review authors perform study selection in duplicate?** YES/NO. for YES, either ONE of the following: at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent) with the remainder selected by one reviewer.

6. **Did the review authors perform data extraction in duplicate?** YES/NO. For YES, either one of the following: at least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent) with the remainder extracted by one reviewer.
7. **Did the review authors provide a list of excluded studies to justify the exclusions?** YES, PARTIAL YES, NO. For partial yes must provide a list of all potentially relevant studies that were read in full text form but excluded from the review. For YES must also have justified the exclusion from the review of each potentially relevant study.
8. **Did the review authors describe the included studies in adequate detail?** YES, PARTIAL YES, NO. For PARTIAL YES, must describe all of the following: populations, interventions, comparators, outcomes, research designs. For YES should also have all of the following: described populations in detail, described intervention and comparator in detail (including doses where relevant), described study setting, timeframe or follow-up.
9. **Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?** For RCTs: YES, PARTIAL YES, NO, INCLUDES ONLY NRSI. For PARTIAL YES must have assessed RoB from unconcealed allocation and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality); for YES must also have assessed RoB from allocation sequence that was not truly random and selection of the reported result from among multiple measurements or analyses of a specified outcome. For NRSI (Non Randomized Studies of Intervention): YES, PARTIAL YES, NO, INCLUDES ONLY RCTs. For PARTIAL YES must have assessed RoB from confounding and from selection bias. For YES, must also have assessed methods used to ascertain exposures and outcomes, and selection of the reported results from among multiple measurements or analyses of a specified outcome.
10. **Did the review authors report on the sources of funding for the studies included in the review?** YES/NO. For YES: must have reported on the sources of funding for individual studies included in the review. Note: reporting that the reviewers looked for this information but it was not reported by study authors also qualifies
11. **If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?** For RCTs: YES, NO, NO META-ANALYSIS. For YES: the authors justified combining the data in a meta-analysis and they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present and investigated the causes of heterogeneity. For NRSI: YES, NO, NO META-ANALYSIS CONDUCTED. For YES: the authors justified combining the data in a meta-analysis and they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present, and they statistically combined effects estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available, and they reported separate summary estimates for RCTs and NRSI separately when both were included in the review.
12. **If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** YES, NO, NO META-ANALYSIS INCLUDED. For YES: included only low risk of bias RCTs or, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analysis to investigate possible impact of RoB on summary estimates of effect.
13. **Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?** YES/NO. for YES: included only low risk of bias RCTs or, if RCTs with moderate or high RoB, or NRSI were included, the review provided a discussion of the key impact of RoB on the results
14. **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** YES/NO. For Yes: there was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review
15. **If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** YES, NO, NO META-ANALYSIS CONDUCTED. For YES: performed graphical statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias
16. **Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** YES/NO. For Yes: the authors reported no competing interests OR the authors described their funding sources and how they managed potential conflicts of interest.

^d Rating overall confidence in the results of the review:

HIGH: *no on one non-critical weakness*: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

MODERATE: *more than one non critical weakness* (multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence): the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

LOW: *one critical flaw with or without non-critical weaknesses*: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

CRITICALLY LOW: *more than one critical flaw with or without non-critical weaknesses*: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

° AMSTAR items:

- 1. Was an 'a priori' design provided?** The research question and inclusion criteria should be established before the conduct of the review. *Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."*
- 2. Was there duplicate study selection and data extraction?** There should be at least two independent data extractors and a consensus procedure for disagreements should be in place. *Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.*
- 3. Was a comprehensive literature search performed?** At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found. *Note: If at least 2 sources + one Appendix strategy used, select "yes" (Cochrane register/Central counts as 2 sources; a grey literature search counts as Appendix).*
- 4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?** The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc. *Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.*
- 5. Was a list of studies (included and excluded) provided?** A list of included and excluded studies should be provided. *Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."*
- 6. Were the characteristics of the included studies provided?** In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported. *Note: Acceptable if not in table format as long as they are described as above.*
- 7. Was the scientific quality of the included studies assessed and documented?** 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant. *Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).*
- 8. Was the scientific quality of the included studies used appropriately in formulating conclusions?** The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations. *Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.*
- 9. Were the methods used to combine the findings of studies appropriate?** For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I²). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?). *Note: Indicate "yes" if they mention or describe heterogeneity, i.e., if they explain that they cannot pool because of heterogeneity/variability between interventions.*

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test, Hedges-Olken). *Note: If no test values or funnel plot included, score “no”. Score “yes” if mentions that publication bias could not be assessed because there were fewer than 10 included studies.*

11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies. *Note: To get a “yes,” must indicate source of funding or support for the systematic review AND for each of the included studies.*