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Management of Social Isolation and Loneliness in Older Adults: Protocol for a Network Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Introduction Social isolation and loneliness in older adults are significant public health issues. Various interventions such as exercise programs or social activities are used in the management of social isolation and loneliness in older adults. Network meta-analysis provides effect estimates for all comparisons by considering the relative efficacy of multiple intervention alternatives. Therefore, this study will determine the comparative efficacy of intervention to alleviate social isolation and loneliness of older adults by comparing direct and indirect interventions through systematic review and network meta-analysis.

Methods and analysis We will include all relevant randomized controlled trials for interventions of social isolation and loneliness in older adults written in English without any limitation of publication date through electronic databases: MEDLINE via OVID, EMBASE, Cochrane Central Registry of Controlled Trials (CENTRAL), PsycINFO, and CINAHL. Independent teams of reviewers will screen trial eligibility, collect data, identify duplication, and assess risk of bias, by using the Cochrane revised risk of bias tool. The interventions for the management of social isolation and loneliness will be included. The primary outcome is social isolation. The secondary outcomes are loneliness and quality of life/health-related quality of life. We will conduct a network meta-analysis through a Bayesian hierarchical model, by testing assumption (i.e., transitivity) for network meta-analysis. We will also estimate the ranking probabilities for all interventions at each possible rank for each intervention. For estimation of each intervention efficacy, we will assess the certainty and credibility using the GRADE approach.

Ethics and dissemination Ethics approval will not be obtained for this systematic review as it will be conducted with published papers. The review results will be presented at a field-specific conference and published in a relevant peer-reviewed journal.

Trial registration number CRD42020155789

Keywords Social isolation, Loneliness, Older adults, Systematic review, Randomized controlled trials, Network meta-analysis

Strengths and limitations of this study

- This study will be the first systematic review and network meta-analysis about social isolation and loneliness for community-dwelling older adults.
- With the growing aging population systematic review strategies are needed inform which interventions are most effective for alleviating social isolation and loneliness at both an individual and community level.
- It might be difficult to interpret the effects when pooling estimates from trials using different tools to measure social isolation and loneliness combined with high heterogeneity.

INTRODUCTION

Social isolation is an objective and quantitative reflection of reduced social network size and limited social contact. This phenomenon is especially important to examine for older adults, when there are often decreased economic resources, increased mobility impairment, and the death of contemporaries.[1] Loneliness is a psychological embodiment of social isolation that demonstrates limited frequency and intimacy of social contacts and discrepancies between relationships and desired relationships.[2] With loneliness, social loneliness means a lack of feelings of social integration, and emotional loneliness is the feeling one feels when one does not have an attachment figure.[3] According to the 2016 Statistics Canada report, approximately 0.75 million older adults aged 60 years or older experienced social isolation and loneliness.[4] A recent national survey reported that 40% of older adults reported being lonely[5] and 24% reported being socially isolated.[6] In particular, older adults are more vulnerable because their meaningful social contacts are eventually replaced by family and close friends after retirement from work.[7]

Social isolation and loneliness in older adults are significant public health issues. Both social isolation and loneliness are associated with increased risk of cardiovascular disease,[8] hypertension,[9-12] inflammatory responses to stress,[13-16] decreased quality of life, physical and mental health,[1 17] and mortality.[18-23] As age increases, approximately one half and one third of older adults experience social isolation[24] and loneliness,[25 26] respectively. Previous studies examining the effect of physical activity interventions on social isolation and loneliness demonstrate inconsistent effects.[27] Physical activity interventions improve social functioning, whereas they have no effects on loneliness, social support and social networks.[28] Since clinical trials and previous traditional meta-analyses assessed the relative effects of two interventions at a time,[29] the relative effects of different interventions have not been explored. Network meta-

analysis (NMA) is required to provide effect estimates for all comparisons by considering the relative efficacy of multiple intervention alternatives.[30 31] There is some evidence that several interventions such as physical activity, social activities, social or health services, psychotherapy, befriending interventions, and leisure or skill development intervention may reduce social isolation and loneliness. A systematic review and NMA are required to incorporate recent studies and compare the direct, indirect as well as mixed interventions for social isolation and loneliness. The aim of this study is to determine the comparative effect of interventions to alleviate social isolation and loneliness in older adults. Research question is "What the comparative effects of interventions to alleviate social isolation and loneliness in older adults?".

METHODS AND ANLYSIS

Protocol and registration

This study will follow the Preferred Reporting Items for The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions.[32] The completed PRISMA NMA checklist is provided in online supplementary file 1. The protocol of this NMA has been submitted for registration in PROSPERO (registration number CRD42020155789).

Study selection criteria

Types of studies to be Included

We will include randomized controlled studies (RCTs) that assess the effects of different interventions to alleviate social isolation and loneliness in older adults aged 60 years or older living in the community. Observational studies including prospective, retrospective cohort, case-

control, nested case-control, case cohort, cross-sectional, and simulation, comments, editorials, letters to the editor, case series, conference abstract, and animal studies will be excluded. Studies without information of social isolation or loneliness will be excluded (see online supplementary file 2).

Types of participants

Community-dwelling older adults aged 60 years or older will be included in this study. If the mean or median (depending on what the original authors report) age of participants is 60 years or older, it will be included. RCTs including older adults not residing in the community (e.g., hospitalized patients or long-term care homes) will be excluded. Older adults from institutional settings may have limited contact with friends or family, which could increase the risk of loneliness.[33 34] RCTs including older adults who are healthy or who have chronic disease (e.g., hypertension and diabetes) will be included. RCTs must include older adults who are mobile (i.e., able to walk independently with or without an assistive aid or can self-propel wheelchair) will be included. Participants without dementia, moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE) <24, Montreal Cognitive Assessment (MoCA) <26, or Short Portable Mental Status Questionnaire (SPMSQ) >6) will be included. Vulnerable people with dementia or severe cognitive dysfunction might be more socially isolated or lonely due to lack of contact with friends or family,[28] which may confound the measurement of social functioning and loneliness.[28] We will exclude the following severe diseases as they might make it difficult to identify the effects of alleviating social isolation and loneliness: cancer, AIDS (HIV), chronic heart failure, recent surgery, dialysis, transplant, or intractable rare disease. Because patients with such severe diseases need intensive treatment for the diseases, it may be difficult to identify

whether effects from the intervention for social isolation and loneliness or from the intensive treatment for severe diseases. In addition, older adults experiencing unstable mental health disorders such as bipolar disorder, active psychosis, or suicidal plans will be excluded because these factors could work as confounders for the efficacy on social isolation or loneliness. (see online supplementary file 2).

Types of interventions

RCTs will examine one or more of the following interventions: 1) social activities such as social engagement, social facilitation or shared interest topic groups in community centers, and social/recreational services such as social support and psychotherapy including counselling therapy, music, art or animal intervention; 2) exercise programs including group (e.g., tai-chi, aerobic or yoga class), individual exercise in a gym or at home, web, or telephoned-based; 3) health services such as health care provisions including care management, home visits from nurses or other professionals; 4) befriending interventions such as charity-funded friendship clubs and friendship enrichment programs; 5) leisure or skill development interventions such as gardening programs, computer or internet use, voluntary work, and holiday; 6) multifaceted interventions including any combination of intervention (e.g., social activities combined with exercise programs, social/health support combined with psychotherapy).

Comparators will be a control, usual care or placebo intervention (see online supplementary file 2).

Types of outcomes – The primary outcomes

Because social isolation and loneliness not only are intricately related but also distinct concepts

that are frequently used interchangeably,[35] data for both social isolation and loneliness will be included.

Social isolation will be defined as an objective lack of contact with appropriate quality or quantity or a lack of social encounters.[36-38] The following outcomes for social isolation will be included: social support, social networks such as network size, frequency of contact with network members, social function, and social participation. Any measures of social isolation, social support, social networks, social function and social participation will be included as long as they assess social isolation based on our definition.

Commonly used instruments for social isolation are the Lubben Social Network Scale-6[39] for social network, the Revised Social Support Questionnaire (SSQ6)[40] and the Multidimensional Scale of Perceived Social Support[41] for social support, and the Subjective Social Participation Index[42] for social participation. The Lubben Social Network Scale-6[39] for social network measures social isolation by measuring frequency, size, and closeness of contacts of the respondent's social network by assessing the perceived level of support they get from friends and families. Scoring is as follows: 0 = none, 1 = one, 2 = two 3 = three or four, 4 = five to eight, 5 = nine or more. Total scores from 0 to 30 with higher scores indicating larger social networks. The SSQ6[40] for social support has six item measure of social support wherein respondents indicate the number of people they feel they have available to provide support in six areas. The Multidimensional Scale of Perceived Social Support[41] for social support has 12-item scale that is broken into three factor groups (i.e., family, friends, and significant other). This scale is scored on a 1 (very strongly disagree) to 7 (very strongly agree) Likert-type scale. Higher scores indicate high levels of social support. The subjective Social Participation Index[42] for social participation has a 15-question scale broken into three "Factors" – perception of social support,

use of new technologies, and index of subjective social participation. Answers to these four questions are always = 0, sometimes = 1, or never = 2. Low scores indicate increased social participation.

Types of outcomes – The secondary outcome

The secondary outcome will be loneliness. Loneliness will be defined as unpleasant feelings experienced because one's interactions with others do not meet one's expectations.[2 25 43] Any measures of loneliness will be included as long as they meet our definition of loneliness. Commonly used instruments for loneliness are the De Jong Gierveld Loneliness Scale,[44] and the University of California Los Angeles (UCLA) Loneliness Scale.[45] The De Jong Gierveld Loneliness Scale[44] measures emotional and social loneliness and has six statements, three measuring emotional loneliness and three measuring social loneliness, each with three choices including yes, more or less, and no. Scores range from 0-6, with 6 indicating higher loneliness. The UCLA Loneliness Scale Version 3[45] has 20-question tool used to assess subjective feelings of loneliness or social isolation. All questions are framed using "how often do you feel...." and choices include never, rarely, sometimes, and often. Scores range from 20 to 80, with a higher score indicating greater loneliness.

Search strategy

Electronic databases

The search strategy will be developed using a combination of controlled vocabulary and free-text words related to study participants and study design. Electronic database searches will be performed in MEDLINE via OVID, EMBASE, Cochrane Central Registry of Controlled Trials

(CENTRAL), PsycINFO, and CINAHL to identify RCTs published on interventions for social isolation and loneliness in older adults. The following keywords alone and in combination will be searched: “social isolation”, “loneliness”, “social relationships”, “social support”, “social network”, “social alienation, “community networks”, “social distance”, “interpersonal relations”, “friends”, “psychosocial deprivation”, and “social participation”. No date limit will be applied. An experienced librarian will review our search strategies in individual databases and updated them where needed. We will manually search reference lists of all included studies and relevant reviews. We will limit articles to those written in English (see online supplementary file 3).

Data Extraction

Titles and/or abstracts identified using the search strategy will be screened for potential eligibility independently by two reviewers, and the team will obtain full texts of any articles that either reviewer believes may be eligible. A team of two reviewers will evaluate each full text article for potential eligibility. Any disagreement will be resolved by discussion or if necessary, adjudication by a third reviewer. Two reviewers will perform data extraction independently and in duplicate. A pilot form will be tested on randomly selected studies by two reviewers to ensure consistency in extraction form. We will extract the following information: 1) study characteristics (design, year, duration of follow-up, recruitment settings, country, study aim, and number of participants allocated to intervention and control); 2) participant characteristics (sample size, eligible criteria, age, sex, participant’s chronic disease, and residential settings); 3) intervention or exposure details (type of intervention, frequency of intervention, intensity/level of intervention, length of intervention, intervention content and a control group comparison, format of the delivery, and information about the intervention provider); 4) methodological

information (effects on main outcomes, assessment tools, and information about validation of assessment tools); 5) results related to effect size calculation (means or mean change, standard deviations (SDs), the information from which SD could be derived, such as standard error or confidence interval (CI), number of participants in each intervention group, measurement period, and relevant effect sizes (e.g., odds ratio and rate ratio) with a measure of uncertainty such as standard error (SE) or 95% CI, and/or p-value). If means or SDs are available and instead studies report SEs, CI, t-or p-value, effect sizes will be computed based on the provided data from between group values according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[46] In case of disagreement in the extracted data, reviewers will come to consensus through discussion. If a consensus cannot be reached, a third reviewer will be involved. If possible, we will conduct an intention-to-treat analysis, but otherwise we will use the available data (i.e., per-protocol analysis results). The agreement between the two reviewers screening title and abstract full-text articles will be assessed by the Kappa *(k)* estimates. The agreement between reviewers will be assessed according to the following cut-off points: 1) ≤0 as poor agreement; 2) 0.01 to 0.20 as slight agreement; 3) 0.21 to 0.40 as fair agreement; 4) 0.41 to 0.60 as moderate agreement; 5) 0.61 to 0.80 as substantial agreement; 6) >0.80 as almost perfect agreement.[47]

Risk of bias assessment

The risk of bias will be assessed by two reviewers independently. Any discrepancies on the results of risk of bias will be resolved by the third reviewer. Risk of bias will be assessed according to the Cochrane revised tool for assessing risk of bias in randomized trials (RoB 2)[48] as follows: 1) bias arising from the randomization; 2) bias due to deviations from intended

interventions; 3) bias due to missing out come data; 4) bias in measurement of the outcome; 5) bias is selection of the reported result. The two reviewers will independently judge each domain as high, low, or some concerns risk of bias.

Strategy for data synthesis

Network geometry

A qualitative description of network geometry will be provided and accompanied by a network plot,[49] allowing us to also assess for intervention connectedness. The quantitative metrics assessing features of network geometry such as diversity (i.e., number of interventions and how frequent they are examined) and co-occurrence (i.e., whether certain intervention comparisons are more or less common and the extent of comparisons between different interventions) will be evaluated.[49]

Methods for direct and indirect or mixed intervention comparisons

A standard pairwise meta-analysis through random-effects model will be conducted because the included studies are expected to differ methodologically and clinically in terms of between-study variability.[50] Dichotomous outcome data will be pooled and the odds ratio (OR) and the 95% CI will be reported. Continuous outcome data will be pooled and the standardized mean difference (SMD) and 95% CI will be reported for study-specific follow-up mean values. We will use followed up means instead of mean change because a mixture of the two cannot be combined using SMD in the same model. In case there are missing SDs in follow-up means, it will be assumed to be equal with SDs in baseline mean values. We will quantify heterogeneity (i.e., between-study variability) of intervention effects within each intervention comparison using the

I^2 [51] with its 95% CI. We will estimate the magnitude of the between study variance $\boldsymbol{\tau}^2$ and its 95% CI by using the restricted maximum likelihood estimator and the Q-profile approach, respectively.[52 53]

In addition, results of the NMA will be performed through a Bayesian statistical approach using Markov-chain Monte Carlo (MCMC) simulation. For each NMA, the transitivity and consistency assumptions will be preferentially assessed.[54] Transitivity assumptions will be assessed by average age, percentage women, health status (e.g., chronic disease or mental health status), and trials with low risk of bias compared to high risk of bias as potential intervention effect modifiers, by comparing their distributions across intervention comparisons in each outcome[55] to ensure that they are on average balanced. As a comparative function between each individual intervention, the intervention contrast (i.e., mean difference or SMD, log odds for dichotomous outcomes, or rate ratio for count outcomes) for the two interventions will be modeled.

A hierarchical Bayesian model using a non-informative prior for the intervention effect parameter and between-trial variance will be used because of lack of previous evidence for social isolation and loneliness.[56 57] Model convergence will be assessed using established methods such as MCMC errors, deviance information criterion (DIC), and trace/density plot.[58]

A random-effects design by intervention interaction model will be used to assess the consistency assumption (i.e., whether direct and indirect evidence agree) globally for each network separately.[54 59] We will also assess for the consistency assumption locally, within each closed loop, using the loop-specific approach.[60 61] When statistically significant inconsistency is detected, data for potential abstraction errors will be tested.[50] If no data errors are identified, direct, indirect, and mixed estimates will be separately reported.[50] Further, significant inconsistency will be explored by performing meta-regression using the above mentioned

potential effects modifiers.[50] Inconsistency tests have low power to detect true inconsistency[62 63] and hence, we will assess for the transitivity assumption even in the absence of evidence for inconsistency.

Vague priors for all model parameters and a half-normal prior distribution for the between-study SD will be assumed in all Bayesian NMA models.[50] The models will be run for 50,000 iterations to ensure model convergence, which will be checked by visual inspection of the mixing of 4 chains or by using Gelman-Rubin convergence diagnostics,[64] after discarding the first 5,000 iterations and thinning of 1. The posterior median values and their 95% credible intervals (Crls) for the relevant model parameters will be reported with intervention effects and between-study variance.[65] Each NMA estimate will be presented with a 95% prediction interval,[66] which captures the magnitude of the between-study variance and indicates the interval at which the intervention effect of future studies are expected.[67]

For relative intervention ranking, the ranking probabilities for all interventions at each possible rank for each intervention will be estimated.[68] Through the surface under the cumulative ranking (SUCRA) curve and mean ranks, the intervention hierarchy will be defined with a cumulative probability of an intervention that can be ranked first without uncertainty.[69] The rank-heat plot (http://rh.ktss.ca/) to visually present the intervention hierarchy across the multiple outcomes of the study will be shown.[70] The higher the SUCRA value, which ranges from 0% to 100%, will indicate the higher the likelihood of intervention[71] for social isolation and loneliness.

Standard pairwise meta-analyses will be conducted through the R statistical package (version 3.6.2) and the metafor package. NMA will be also conducted through the R statistical package (version 3.6.2) with BUGSnet R package (version 1.0.3) for Bayesian NMA.

Analysis of sensitivity

We will perform sensitivity analyses on low risk of bias and excluding any studies with imputed values if enough studies are available.

Analysis of subgroup

For multicomponent/multimodal interventions, we will perform subgroup analyses by types of specific individual intervention. For example, the implications of "social activities combined with exercise interventions" and "psychotherapy combined with social/health service" are different even though they are categorized as multicomponent interventions.

Certainty of the evidence and summary of findings table

Through the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach of NMA,[72] the certainty of direct, indirect and mixed NMA effect estimates for each outcome will be assessed. The certainty of evidence of direct effect estimates for each outcome will be assessed as follows according to the GRADE rating system:[73] high, moderate, low or very low.

We will use the available loops of evidence including loops with a single common comparator (i.e., first-order) or more than one intervening treatment (i.e., higher orders) connecting the two interventions of the comparison of interest in order to calculate the indirect effect estimated.[29] For the quality of indirect evidence, the dominant first-order loop (i.e., loops with a single common comparator connecting the two interventions of the comparison of interest) will be assessed.[29] The quality of evidence rating for indirect comparisons will be the lower of the rating for quality for the two direct estimates that contribute to the first-order loop of the indirect

comparison.[29]

In the case to use both direct and indirect evidence, the rate of NMA estimate quality will be from the higher quality of the two.[29] The similarity between direct and indirect effect estimates will be estimated in the final quality rating.[29] If there is any inconsistency between direct and indirect effect estimates (i.e., it is estimated by the difference of point estimates and the extent of overlap of 95% CIs and of direct and indirect effect estimates), the quality of the NMA effect will be assessed.[29]

Patient and public involvement

As this study is a systematic review, patients and the public will not be directly involved. However, we will consult key stakeholder groups (e.g., older adult networks and relevant service provider associations) to determine the best channels through which to disseminate the results of our study.

DISCUSSION

As the numbers of older adults increase, so does the resulting social and economic burden of social isolation and loneliness. There is need for evidence-based therapeutic programs to mitigate social isolation and loneliness. A high-quality systematic review of the comparative therapeutic effects of interventions for improving social isolation and loneliness in older adults is essential. To our knowledge, there are few systematic reviews and NMAs combining direct and indirect effects of intervention for social isolation and loneliness in older adults. This study will include a comparison of different interventions for social isolation and loneliness through not only a single (e.g., exercise program or social/health service) intervention, but also combination (e.g., exercise

program combined with social/health service) of interventions. This study has several strengths: 1) including recent RCTs social isolation and loneliness for older adults; 2) screening rigorous trial eligibility and collecting data from independent teams of reviews; 3) assessing credibility and providing certainty for intervention effects, by using GRADE approach; 4) performing meta-regression and subgroup analyses, consistent with the best current practice;[66] 5) providing ranking intervention (i.e., the intervention sequence is determined according to their relative efficacy)[73] for social isolation and loneliness.

Although this study has several strengths, there are also potential challenges and limitations. First, it might be difficult to interpret the effects when pooling estimates from trials using different tools to measure social isolation (e.g., the Lubben Social Network Scale-6 and SSQ6) and loneliness (e.g., the De Jong Gierveld Loneliness Scale and UCLA loneliness scale) combined with high heterogeneity (i.e., differences in effect estimates between studies that evaluated the same comparison).[73] Further, social isolation has a variety of surrogate outcomes such as social support and social network. Such surrogate outcomes might down rate the directness identified through the GRADE approach[73] because it means that an outcome of interest (i.e., social isolation) might differ from the measured in surrogate outcomes (i.e., social support and social network). Additionally, dealing with multicomponent interventions in NMA is a methodological challenge because single or combined (i.e., consisting of several possibly interacting components) interventions are different nodes in the network.[74]

It is expected that the findings of this study will provide evidence for clinicians (e.g., when selecting which interventions are best for older adults), health policy makers (e.g., when making decision which programs or services should be supported) as well as stakeholders (e.g., when operating how programs effectively) managing social isolation and loneliness in community

dwelling older adults and for older adults in choosing therapeutic options.

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Competing interests None declared.

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Management of Social Isolation and Loneliness in Older Adult: Protocol for a Network Meta-analysis of Randomized Controlled Trials

Supplementary files

Supplementary file 1: PRISMA NMA checklist

Table A.1: PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*_	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	6-9 Additional file 2

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9-10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9-10 Additional file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10-11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10-11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	12
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11-12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	12-14
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	13-14
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	13-14

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	15
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	15
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	n/a
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g.*	n/a

		placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	n/a
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	16-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	17

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Supplementary file 2: PICOS statement

PICOS	Inclusion	Exclusion
Participants	□ Community-dwelling older adults ≥ 60 years of age (If mean or median age of participants is 60 year or older, it can be included.) □ Healthy or have a chronic disease, but mobile (i.e., older adults are able to walk independently with or without gait aid, or can self-propel wheelchair.) □ A mild or moderate dementia or cognitive dysfunction	□ Adults < 60 years of age □ Not community residing (inpatients, nursing home, hospital wards, or long-term care facilities) □ Dementia or moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE)<24, Montreal Cognitive Assessment (MoCA) <26, or Short Portable Mental Status Questionnaire (SPMSQ)>6) □ Chronic diseases related to death or serious risk: cancer, AIDS (HIV), chronic heart failure, recent surgery or transplant or intractable rare disease □ Unstable diseases such as bipolar disorder, active psychosis, or suicidal plans □ Caregivers
Interventions	1) Social activities (with others) and social/recreational services: social engagement, social facilitation, or shared interest topic groups in community centres, etc. and social support and psychotherapy (counselling therapy, music, art or animal intervention, etc.) 2) Exercise programs: group (e.g., tai-chi, aerobic or yoga class), one-to-one exercise in gym, outdoor, home, web, or telephone-based, etc. 3) Health services: health care provision (care management, home visits from nurses or other	□ Pharmaceutical interventions including medications and nutritional supplements (vit D, calcium, or protein) for mental health, anxiety, or depression

	professionals) and etc. 4) Befriending interventions: charity-funded friendship clubs, etc. 5) Leisure/skill development intervention: gardening programs, computer/internet use, voluntary work, holidays, etc. 6) Multicomponent/ Multifaced interventions: any combination of intervention (e.g., social activity combined with exercise programs or social/health service)	
Comparison intervention	□ Usual care, a control, or placebo	
Outcomes	1) Loneliness (e.g., De Jong Gierveld Loneliness Scale, UCLA Loneliness Scale Version #, other (such as Italian) Loneliness Scale or loneliness from The Philadelphia Geriatric Morale Scale (PGMS)) 2) Social isolation (e.g., the Turkish version of the Nottingham Health Profile questionnaire) 3) Social support (e.g., Revised Social Support Questionnaire, Multidimensional Scale of Perceived Social Support (MSPSS), Duke Social Support Index-10, the short version of the Medical Outcomes Study [17] Social Support Survey, or the Chinese version of the Inventory of Social Supportive Behaviours) 4) Social network (size) including frequency of contact with network members (e.g., Lubben Social Network Scale-6)	□ Social or family wellbeing □ Happiness □ Satisfaction with life □ Depression

	5) Social functioning as a sub-domain of health-related quality of life 6) Social participation (e.g., Subjective Social Participation Index) 7) Quality of life or health quality of life (e.g., The Short Form (SF-36) Health Survey, The World Health Organization Quality of Life Assessment questionnaire (WHOQOL-BREF), or the 12-item Short Form Health Survey) Although it is the same trial number, if there are different outcomes in each study, it will be included respectively.	
Study design	□ All RCTs or quasi-RCTs regardless of sample size	□ Non-RCTs □ Observational studies (prospective, retrospective cohort, case-control, nested case-control, case cohort, cross-sectional, and simulation studies), comments, editorials, letters to the editor, case series, conference abstract, and animal studies
Setting	□ Community settings	
Language	□ English	□ Non-English

Supplementary file 3: Search strategy

Table A.3.1: MEDLINE via OVID from 1946 to Nov 20, 2019

Searches	Search Terms
1	loneliness/
2	social isolation/
3	social alienation/
4	social support/
5	community networks/
6	social distance/
7	interpersonal relations/
8	friends/
9	psychosocial deprivation/
10	social participation/
11	(lonely or loneliness or solitude).ti,ab.
12	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
13	(social wellbeing or social health or social capital).ti,ab.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	randomized controlled trial.pt.
16	randomized.mp.
17	controlled clinical trial.pt.
18	placebo.mp.
19	15 or 16 or 17 or 18
20	14 and 19
21	exp aged/ or older aged/
22	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
23	21 or 22
24	20 and 23

Table A.3.2: EMBASE from 1974 to Nov 20, 2019

Searches	Search Terms
1	loneliness/
2	social isolation/
3	social alienation/
4	social support/
5	community networks.mp.
6	social distance/
7	human relation/
8	friend/
9	psychosocial deprivation.mp.
10	social participation/
11	(lonely or loneliness or solitude).ti,ab.
12	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
13	(social wellbeing or social health or social capital).ti,ab.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	random:.tw.
16	placebo:.mp.
17	double-blind:.tw.
18	15 or 16 or 17
19	14 and 18
20	exp aged/ or older aged/
21	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
22	20 or 21
23	19 and 22

Table A.3.3: PsycINFO from 1806 to Nov 20, 2019

Searches	Search Terms
1	exp loneliness/
2	exp social deprivation/
3	exp social support/
4	exp alienation/
5	exp friendship/
6	exp social networks/
7	exp interpersonal relationships/
8	(lonely or loneliness or solitude).ti,ab.
9	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
10	(social wellbeing or social health or social capital).ti,ab.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	double-blind.tw.
13	control.tw.
14	random: assigned:.tw.
15	12 or 13 or 14
16	11 and 15
17	exp aged/ or older aged.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measure, mesh]
18	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
19	17 and 18
20	16 and 19

Table A.3.4: CENTRAL from - to Nov 20, 2019

Searches	Search Terms
1	loneliness
2	social isolation
3	social alienation
4	social support
5	community networks
6	social distance
7	interpersonal relations
8	friends
9	psychosocial deprivation
10	social participation
11	lonely or loneliness or solitude
12	MeSH descriptor: [Social Isolation] explode all trees
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	MeSH descriptor: [Aged] in all MeSH products
15	senior* OR elder*
16	#14 OR #15
17	#13 AND #16

Table A.3.5: CINAHL from - to Nov 20, 2019

Searches	Search Terms
1	(MH “Loneliness”)
2	(MH “Social Isolation”)
3	(MH “Social Alienation”)
4	(MH “Support, Psychosocial”)
5	(MH “Community networks”)
6	(MH “Interpersonal Relations”)
7	(MH “Social Networks”)
8	(MH “Psychosocial Deprivation”)
9	(MH “Social Participation”)
10	TI lonely or loneliness or solitude
11	AB lonely or loneliness or solitude
12	TI ((social* or societ* or perce* or person*) N2 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*))
13	AB ((social* or societ* or perce* or person*) N2 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*))
14	TI (social wellbeing or social health or social capital)
15	AB (social wellbeing or social health or social capital)
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17	TI randomized
18	AB randomized
19	TI placebo
20	AB placebo
21	“placebo”
22	TI double-blind
23	AB double-blind
24	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25	16 AND 26
26	(MH “Aged”)
27	TI aged or elder* or geriatric* or gerontol*

28	26 OR 27
29	25 AND 28

PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	5

Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	6-9 Additional file 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9-10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9-10 Additional file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10-11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10-11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-11
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	12
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11-12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	12-14

Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	13-14
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	13-14
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	15
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	15
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
Summary of	**S4**	Provide a brief overview of characteristics of the treatment	n/a

network geometry		network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	n/a
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	n/a
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	n/a
DISCUSSION			

Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	16-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	17

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

BMJ Open

Management of Social Isolation and Loneliness in Community Dwelling Older Adults: Protocol for a Network Meta-analysis of Randomized Controlled Trials

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Management of Social Isolation and Loneliness in Community Dwelling Older Adults: Protocol for a Network Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Introduction Social isolation and loneliness in older adults are significant public health issues. Various interventions such as exercise programs or social activities are used in the management of social isolation and loneliness in older adults. Network meta-analysis provides effect estimates for all comparisons by considering the relative efficacy of multiple intervention alternatives. Therefore, this study will determine the comparative efficacy of intervention to alleviate social isolation and loneliness of older adults in community dwelling by comparing direct and indirect interventions through systematic review and network meta-analysis.

Methods and analysis We will include all relevant randomized controlled trials for interventions of social isolation and loneliness in older adults written in English without any limitation of publication date through electronic databases: MEDLINE via OVID, EMBASE, Cochrane Central Registry of Controlled Trials (CENTRAL), PsycINFO, and CINAHL. Independent teams of reviewers will screen trial eligibility, collect data, identify duplication, and assess risk of bias, by using the Cochrane revised risk of bias tool. The interventions for the management of social isolation and loneliness will be included. The primary outcome is social isolation. The secondary outcomes are loneliness and health-related quality of life. We will conduct a network meta-analysis through a Bayesian hierarchical model, by testing assumption (i.e., transitivity) for network meta-analysis. We will also estimate the ranking probabilities for all interventions at each possible rank for each intervention. For estimation of each intervention efficacy, we will assess the certainty and credibility using the GRADE approach.

Ethics and dissemination Ethics approval will not be obtained for this systematic review as it will be conducted with published papers. The review results will be presented at a field-specific conference and published in a relevant peer-reviewed journal.

Trial registration number CRD42020155789

Keywords Social isolation, Loneliness, Older adults, Systematic review, Randomized controlled trials, Network meta-analysis

Strengths and limitations of this study

- This study will be the first systematic review and network meta-analysis about social isolation and loneliness for community-dwelling older adults.
- With the growing aging population systematic review strategies are needed inform which interventions are most effective for alleviating social isolation and loneliness at both an individual and community level.
- It might be difficult to interpret the effects when pooling estimates from trials using different tools to measure social isolation and loneliness combined with high heterogeneity.

INTRODUCTION

Social isolation is an objective and quantitative reflection of reduced social network size and limited social contact. This phenomenon is especially important to examine for older adults, when there are often decreased economic resources, increased mobility impairment, and the death of contemporaries.[1] Loneliness is a psychological embodiment of social isolation that demonstrates limited frequency and intimacy of social contacts and discrepancies between relationships and desired relationships.[2] With loneliness, social loneliness means a lack of feelings of social integration, and emotional loneliness is the feeling one feels when one does not have an attachment figure.[3] According to the 2016 Statistics Canada report, approximately 0.75 million older adults aged 60 years or older experienced social isolation and loneliness.[4] A recent national survey reported that 40% of older adults reported being lonely[5] and 24% reported being socially isolated.[6] In particular, older adults are more vulnerable because their meaningful social contacts are eventually replaced by family and close friends after retirement from work.[7]

Social isolation and loneliness in older adults are significant public health issues. Both social isolation and loneliness are associated with increased risk of cardiovascular disease,[8] hypertension,[9-12] inflammatory responses to stress,[13-16] decreased quality of life, physical and mental health,[1 17] and mortality.[18-23] As age increases, approximately one half and one third of older adults experience social isolation[24] and loneliness,[25 26] respectively. Previous studies examining the efficacy of physical activity interventions on social isolation and loneliness demonstrate inconsistent effects.[27] Physical activity interventions improve social functioning, whereas they have no efficacy on loneliness, social support and social networks.[28] Since clinical trials and previous traditional meta-analyses assessed the relative efficacy of two interventions at a time,[29] the relative efficacy of different interventions have not been explored.

Regarding the effect of other interventions, one systematic review showed that two interventions (i.e., group tai-chi and facilitated group discussion) alleviated loneliness but did not improve quality of life. On the other hands, a physical/leisure activity improved quality of life but not social support.[27] Another systematic review suggested that educational interventions for social networks maintenance and enhancement for alleviating loneliness.[30] Additionally, two systematic reviews[31 32] showed that social activity or support interventions in group format reduce social isolation and loneliness. In contrast to the findings from two reviews, one integrative study[33] found that solitary or one-to-one intervention such as solitary pet intervention, solitary video-conference and computer/internet use was more effective.

A recent review[34] suggested a new approach for interventions for social isolation and loneliness. Since social isolation and loneliness are complex constructs with various dimensions, it is suggested that the approach should be taken to consider various predictors of them (e.g., relationship provisions).[34] For example, emotional loneliness (i.e., micro level) can be alleviated through interventions dealing with cognition, and evaluation on a personal level.[7 35 36] Social loneliness (i.e., meso level) may be mitigated through interventions targeting increasing social networks and connectedness with community activities or social media.[37] As an approach of a macro level, programs that improve general health such as treating hearing loss can be implemented.[38] These factors have all been shown to be social determinants of loneliness, well-being, and health.[30 31 39 40]

Network meta-analysis (NMA) is required to provide effect estimates for all comparisons by considering the relative efficacy of multiple intervention alternatives.[41 42] There is some evidence that several interventions such as physical activity, social activities, social or health services, psychotherapy, befriending interventions, and leisure or skill development intervention may

reduce social isolation and loneliness. A systematic review and NMA are required to incorporate recent studies and compare the direct, indirect as well as mixed interventions for social isolation and loneliness.

The objective of this study is to determine the comparative efficacy of interventions to alleviate social isolation and loneliness in community dwelling older adults aged 60 years or older

Research question is "What are the comparative efficacy of interventions to alleviate social isolation and loneliness in community dwelling older adults aged 60 years or older?"

Since social isolation and loneliness are concepts that have been understood and defined in many different ways, interventions often vary. Nevertheless, previously most studies conducted only direct treatment comparison through pairwise meta-analysis. However, multiple comparisons of interventions are necessary in line with the characteristics of social isolation and loneliness. We expect to provide the ranking comparative efficacy of interventions for social isolation and loneliness.

METHODS AND ANLYSIS

Protocol and registration

This study will follow the Preferred Reporting Items for The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions.[43] The completed PRISMA NMA checklist is provided in online supplementary file 1. The protocol of this NMA has been submitted for registration in PROSPERO (registration number CRD42020155789).

Study selection criteria

Types of studies to be Included

We will include randomized controlled studies (RCTs) that assess the efficacy of different interventions to alleviate social isolation and loneliness in older adults aged 60 years or older living in the community. Observational studies including prospective, retrospective cohort, case-control, nested case-control, case cohort, cross-sectional, and simulation, comments, editorials, letters to the editor, case series, conference abstract, and animal studies will be excluded. Studies without information of social isolation or loneliness will be excluded (see online supplementary file 2).

Types of participants

Community-dwelling older adults aged 60 years or older will be included in this study. If the mean or median (depending on what the original authors report) age of participants is 60 years or older, it will be included. RCTs including older adults not residing in the community (e.g., hospitalized patients or long-term care homes) will be excluded. Older adults from institutional settings may have limited contact with friends or family, which could increase the risk of loneliness.[44 45] RCTs including older adults who are healthy or who have chronic disease (e.g., hypertension and diabetes) will be included. RCTs must include older adults who are mobile (i.e., able to walk independently with or without an assistive aid or can self-propel wheelchair). Participants without dementia, moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE) <24, Montreal Cognitive Assessment (MoCA) <26, or Short Portable Mental Status Questionnaire (SPMSQ) >6) will be included. Vulnerable people with dementia or severe cognitive dysfunction might be more socially isolated or lonely due to lack of contact with friends or family,[28] which may confound the measurement of social functioning and

loneliness.[28] We will exclude the following severe diseases as they might make it difficult to identify the efficacy of alleviating social isolation and loneliness: cancer, AIDS (HIV), chronic heart failure, recent surgery, dialysis, transplant, or intractable rare disease. Because patients with such severe diseases need intensive treatment for the diseases, it may be difficult to identify whether efficacy from the intervention for social isolation and loneliness or from the intensive treatment for severe diseases. In addition, older adults experiencing unstable mental health disorders such as bipolar disorder, active psychosis, or suicidal plans will be excluded because these factors could work as confounders for the efficacy on social isolation or loneliness. (see online supplementary file 2).

Types of interventions

RCTs will examine one or more of the following interventions: 1) social activities and social or recreational services such as social engagement including social involvement and social participation, social facilitation, social support including emotional instrumental and informational support, psychotherapy (e.g., counselling therapy, music, art or animal intervention) and education program; 2) exercise programs such as group exercise (e.g., tai-chi, aerobic or yoga class) and one-to-one or individual exercise in a gym or at home, web, or telephoned-based; 3) health services such as health care provisions including care management, home visits from nurses or other professionals; 4) befriending interventions such as charity-funded friendship clubs and friendship enrichment programs; 5) leisure or skill development interventions such as gardening programs, computer or internet use, voluntary work, and holiday; 6) multifaceted interventions including any combination of intervention (e.g., social activities combined with exercise programs, social/health support combined with

psychotherapy).

Comparators will be an inactive control group such as usual care, placebo intervention or no intervention (i.e., it means any comparison targets that can compare the results of post interventions or follow-up outcomes for the intervention group). .

Types of outcomes – The primary outcomes

Because social isolation and loneliness not only are intricately related but also distinct concepts that are frequently used interchangeably,[46] data for both social isolation and loneliness will be included.

Social isolation will be defined as an objective lack of contact with appropriate quality or quantity or a lack of social encounters.[31 47 48] The following outcomes for social isolation will be included: social support, social networks such as network size, frequency of contact with network members, social function, and social participation. Any measures of social isolation, social support, social networks, social function and social participation will be included as long as they assess social isolation based on our definition.

Commonly used instruments for social isolation are the Lubben Social Network Scale-6[49] for social network, the Revised Social Support Questionnaire (SSQ6)[50] and the Multidimensional Scale of Perceived Social Support[51] for social support, and the Subjective Social Participation Index[52] for social participation. The Lubben Social Network Scale-6[49] for social network measures social isolation by measuring frequency, size, and closeness of contacts of the respondent's social network by assessing the perceived level of support they get from friends and families. Scoring is as follows: 0 = none, 1 = one, 2 = two 3 = three or four, 4 = five to eight, 5 = nine or more. Total scores from 0 to 30 with higher scores indicating larger social networks. The

SSQ6[50] for social support has six item measure of social support wherein respondents indicate the number of people they feel they have available to provide support in six areas. The Multidimensional Scale of Perceived Social Support[51] for social support has 12-item scale that is broken into three factor groups (i.e., family, friends, and significant other). This scale is scored on a 1 (very strongly disagree) to 7 (very strongly agree) Likert-type scale. Higher scores indicate high levels of social support. The subjective Social Participation Index[52] for social participation has a 15-question scale broken into three "Factors" – perception of social support, use of new technologies, and index of subjective social participation. Answers to these four questions are always = 0, sometimes = 1, or never = 2. Low scores indicate increased social participation. Additionally, we will use the validated tools and ones on the list of 54 tools according to the systematic review[53] since we will only be able to pool results of those that used the same tools. Validated tools will be defined as those supported by an academic reference and evidence of their psychometric properties.[32] Studies using selected items, rather than the full scales of validated tools, will be categorized as 'partially validated'.[32]

Types of outcomes – The secondary outcome

The secondary outcomes are loneliness and health-related quality of life. Loneliness will be defined as unpleasant feelings experienced because one's interactions with others do not meet one's expectations.[2 25 54] Any measures of loneliness will be included as long as they meet our definition of loneliness.

Commonly used instruments for loneliness are the De Jong Gierveld Loneliness Scale,[55] and the University of California Los Angeles (UCLA) Loneliness Scale.[56] The De Jong Gierveld Loneliness Scale[55] measures emotional and social loneliness and has six statements, three

measuring emotional loneliness and three measuring social loneliness, each with three choices including yes, more or less, and no. Scores range from 0-6, with 6 indicating higher loneliness. The UCLA Loneliness Scale Version 3[56] has 20-question tool used to assess subjective feelings of loneliness or social isolation. All questions are framed using "how often do you feel...." and choices include never, rarely, sometimes, and often. Scores range from 20 to 80, with a higher score indicating greater loneliness. In addition, commonly used tools for health-related quality of life are World Health Organization Quality of Life Scale (WHOQOL-BREF),[57] the 36-Item Short From Health Survey (SF-36),[58] and the Duke Health Profile.[59] WHOQOL-BREF[57] measures 26 items, including 4 domains of physical health, psychological, social relationships and environmental. The 4 domain scores represent an individual's perception of the quality of life in each specific domain, and the higher the score, the higher the quality of life.[57] SF-36[58] measures 36 items, including 8 domains of physical function, mental health, social function, role physical, role emotional, pain, vitality, and general health. The scores are converted directly using the weighted sum of the questions in the 8 domains, and the lower the scores, the greater the disability.[58] In the converted scale of 0-100, 0 means maximum disability and 100 means no disability.[58] The Duke Health Profile[59] measures 17 items, including 10 domains of physical, mental, and social health, general and perceived health, self-esteem, anxiety, depression, pain, and disability. It is self-measured in a ram item scoring within the range of 0-100 and means that the higher the score, the healthier.[59]

Search strategy

Electronic databases

The search strategy will be developed using a combination of controlled vocabulary and free-text

words related to study participants and study design. Electronic database searches will be performed in MEDLINE via OVID, EMBASE, Cochrane Central Registry of Controlled Trials (CENTRAL), PsycINFO, and CINAHL to identify RCTs published on interventions for social isolation and loneliness in older adults. The following keywords for social isolation and loneliness alone and in combination will be searched with terms describing characteristics for them: “social isolation”, “loneliness”, “social relationships”, “social support”, “social network”, “social alienation, “community networks”, “social distance”, “interpersonal relations”, “friends”, “psychosocial deprivation”, and “social participation”. Since the subject of the study is older adults, “older adults” will also be added to the search terms. No date limit will be applied. An experienced librarian will review our search strategies in individual databases and updated them where needed. We will manually search reference lists of all included studies and relevant reviews. We will limit articles to those written in English. Furthermore, in order to identify ongoing trials, three clinical trial registries such as Clinical Trial Registry, Current Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform will be searched. Additionally, unpublished studies will be searched through ProQuest Dissertations and Theses, E-Thos, and Opengrey.(see online supplementary file 3)

Data Extraction

Through the electronic databases, titles and/or abstracts identified using the search strategy will be screened for potential eligibility independently by two reviewers, and the team will obtain full texts of any articles that either reviewer believes may be eligible. ENDNOTE X9 will automatically filter out duplicates and one reviewer will also remove those in the step of title and/or abstract screening. A team of two reviewers will evaluate each full text article for

potential eligibility. Any disagreement will be resolved by discussion or if necessary, adjudication by a third reviewer. Two reviewers will perform data extraction independently and in duplicate. A pilot form will be tested on randomly selected studies by two reviewers to ensure consistency in extraction form. We will extract the following information: 1) study characteristics (design, year, duration of follow-up, recruitment settings, country, study aim, and number of participants allocated to intervention and control); 2) participant characteristics (sample size, eligible criteria, age, sex, participant's chronic disease, and residential settings); 3) intervention or exposure details (type of intervention, frequency of intervention, intensity/level of intervention, length of intervention, intervention content and a control group comparison, format of the delivery, and information about the intervention provider). More specifically, it will first be classified as a single or multifaceted intervention. Single intervention will have only one intervention, while multifaceted interventions will have more than one. Then by the type of intervention (e.g., social activities and social services, exercise programs, health services, befriending intervention, and leisure/skill development). Each type of intervention will then be more specifically classified. The duration (i.e., months), frequency (e.g., once or twice a week, weekly, biweekly, or monthly), time (i.e., minutes) of the specific intervention type will be investigated. For example, if it is an intervention of social activities, it is specifically classified such as social engagement, social facilitation, or social support. If it is the intervention of social engagement, the duration (e.g., 6 months), frequency (e.g., monthly), and time (e.g., 60 minutes) of the social engagement will be investigated.; 4) methodological information (effects on main outcomes, assessment tools, and information about validation of assessment tools); 5) results related to effect size calculation (means or mean change, standard deviations (SDs), the information from which SD could be derived, such as standard error or confidence interval (CI),

number of participants in each intervention group, measurement period, and relevant effect sizes (e.g., odds ratio and rate ratio) with a measure of uncertainty such as standard error (SE) or 95% CI, and/or p-value). If means or SDs are available and instead studies report SEs, CI, t-or p-value, effect sizes will be computed based on the provided data from between group values according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[60] In case of disagreement in the extracted data, reviewers will come to consensus through discussion. If a consensus cannot be reached, a third reviewer will be involved. If possible, we will conduct an intention-to-treat analysis, but otherwise we will use the available data (i.e., per-protocol analysis results). The agreement between the two reviewers screening title and abstract full-text articles will be assessed by the Kappa *(k)* estimates. The agreement between reviewers will be assessed according to the following cut-off points: 1) ≤0 as poor agreement; 2) 0.01 to 0.20 as slight agreement; 3) 0.21 to 0.40 as fair agreement; 4) 0.41 to 0.60 as moderate agreement; 5) 0.61 to 0.80 as substantial agreement; 6) >0.80 as almost perfect agreement.[61]

Risk of bias assessment

The risk of bias will be assessed by two reviewers independently. Any discrepancies on the results of risk of bias will be resolved by the third reviewer. Risk of bias will be assessed according to the Cochrane revised tool for assessing risk of bias in randomized trials (RoB 2)[62] as follows: 1) bias arising from the randomization; 2) bias due to deviations from intended interventions; 3) bias due to missing out come data; 4) bias in measurement of the outcome; 5) bias is selection of the reported result. The two reviewers will independently judge each domain as high, low, or some concerns risk of bias.

Strategy for data synthesis

Network geometry

A qualitative description of network geometry will be provided and accompanied by a network plot,[63] allowing us to also assess for intervention connectedness. The quantitative metrics assessing features of network geometry such as diversity (i.e., number of interventions and how frequent they are examined) and co-occurrence (i.e., whether certain intervention comparisons are more or less common and the extent of comparisons between different interventions) will be evaluated.[63]

Methods for direct and indirect or mixed intervention comparisons

A standard pairwise meta-analysis through random-effects model will be conducted because the included studies are expected to differ methodologically and clinically in terms of between-study variability.[64] Dichotomous outcome data will be pooled and the odds ratio (OR) and the 95% CI will be reported. Continuous outcome data will be pooled and the standardized mean difference (SMD) and 95% CI will be reported for study-specific follow-up mean values. We will use followed up means instead of mean change because a mixture of the two cannot be combined using SMD in the same model. In case there are missing SDs in follow-up means, it will be assumed to be equal with SDs in baseline mean values. We will quantify heterogeneity (i.e., between-study variability) of intervention effects within each intervention comparison using the I^2 [65] with its 95% CI. We will estimate the magnitude of the between study variance $\boldsymbol{\tau}^2$ and its 95% CI by using the restricted maximum likelihood estimator and the Q-profile approach, respectively.[66 67] If the ratio of the actual variance (I^2) to the total variance is 50% or more and

the significant p-value for test of homogeneity is less than 0.10, heterogeneity of the effect size will be judged to be substantial.[68] Subgroup analysis or meta-regression will be performed if the studies are not available due to high heterogeneity.

Regarding dealing with dependent effect sizes, several methods (e.g., Robust meta-analysis[69] and Three level meta-analysis[70]) are discussed. If the correlation between the dependent effect sizes is unknown, such as when multiple measures are used in a study,[71] a three level meta-analysis will be performed. The three level meta-analysis is an extension of the use of two-level random-effect models in meta-analysis[70] (i.e., Level 2 variance represents the difference between studies in effect size estimates with the assumption that all studies provide independent effect sizes), in which the dependent effect sizes will be clustered within-study at Level 2 and then the effect between-study will be estimated at Level 3.[71] In other words, by modelling the within-study dependence at Level 2 and the between-study mean effect size and variance at Level 3, where the variance in the effect is greatest will be determined.[72]

In addition, results of the NMA will be performed through a Bayesian statistical approach using Markov-chain Monte Carlo (MCMC) simulation. For each NMA, the transitivity and consistency assumptions will be preferentially assessed.[73] Transitivity assumptions will be assessed by average age, percentage women, health status (e.g., chronic disease or mental health status), and trials with low risk of bias compared to high risk of bias as potential intervention effect modifiers, by comparing their distributions across intervention comparisons in each outcome[74] to ensure that they are on average balanced. As a comparative function between each individual intervention, the intervention contrast (i.e., mean difference or SMD, log odds for dichotomous outcomes, or rate ratio for count outcomes) for the two interventions will be modeled.

A hierarchical Bayesian model using a non-informative prior for the intervention effect

parameter and between-trial variance will be used because of lack of previous evidence for social isolation and loneliness.[75 76] Model convergence will be assessed using established methods such as MCMC errors, deviance information criterion (DIC), and trace/density plot.[77]

A random-effects design by intervention interaction model will be used to assess the consistency assumption (i.e., whether direct and indirect evidence agree) globally for each network separately.[73 78] We will also assess for the consistency assumption locally, within each closed loop, using the loop-specific approach.[79 80] When statistically significant inconsistency is detected, data for potential abstraction errors will be tested.[64] If no data errors are identified, direct, indirect, and mixed estimates will be separately reported.[64] Further, significant inconsistency will be explored by performing meta-regression using the above mentioned potential effects modifiers.[64] Inconsistency tests have low power to detect true inconsistency[81 82] and hence, we will assess for the transitivity assumption even in the absence of evidence for inconsistency.

Vague priors for all model parameters and a half-normal prior distribution for the between-study SD will be assumed in all Bayesian NMA models.[64] The models will be run for 50,000 iterations to ensure model convergence, which will be checked by visual inspection of the mixing of 4 chains or by using Gelman-Rubin convergence diagnostics,[83] after discarding the first 5,000 iterations and thinning of 1. The posterior median values and their 95% credible intervals (Crls) for the relevant model parameters will be reported with intervention effects and between-study variance.[84] Each NMA estimate will be presented with a 95% prediction interval,[85] which captures the magnitude of the between-study variance and indicates the interval at which the intervention effect of future studies are expected.[86]

For relative intervention ranking, the ranking probabilities for all interventions at each possible

rank for each intervention will be estimated.[87] Through the surface under the cumulative ranking (SUCRA) curve and mean ranks, the intervention hierarchy will be defined with a cumulative probability of an intervention that can be ranked first without uncertainty.[88] The rank-heat plot (http://rh.ktss.ca/) to visually present the intervention hierarchy across the multiple outcomes of the study will be shown.[89] The higher the SUCRA value, which ranges from 0% to 100%, will indicate the higher the likelihood of intervention[90] for social isolation and loneliness.

Standard pairwise meta-analyses will be conducted through the R statistical package (version 3.6.2) and the metafor package. NMA will be also conducted through the R statistical package (version 3.6.2) with BUGSnet R package (version 1.0.3) for Bayesian NMA.

Analysis of sensitivity

According to Cochrane reviews,[91] the major approach to incorporating risk of bias assessments is to restrict meta-analyses to studies at low risk of bias, or to stratify studies depending on risk of bias. We will perform sensitivity analyses on low risk of bias and excluding the following studies: 1) studies with high risk of bias, 2) studies with missing data, and 3) studies with imputed data (i.e., in order to ensure that imputed research results are not one-sided in NMA) if enough studies are available.

Analysis of subgroup

For multicomponent/multimodal interventions, we will perform subgroup analyses by types of specific individual intervention. For example, the implications of "social activities combined with exercise interventions" and "psychotherapy combined with social/health service" are different even though they are categorized as multicomponent interventions.

Certainty of the evidence and summary of findings table

Through the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach of NMA,[92] the certainty of direct, indirect and mixed NMA effect estimates for each outcome will be assessed. The certainty of evidence of direct effect estimates for each outcome will be assessed as follows according to the GRADE rating system:[93] high, moderate, low or very low.

We will use the available loops of evidence including loops with a single common comparator (i.e., first-order) or more than one intervening treatment (i.e., higher orders) connecting the two interventions of the comparison of interest in order to calculate the indirect effect estimated.[29] For the quality of indirect evidence, the dominant first-order loop (i.e., loops with a single common comparator connecting the two interventions of the comparison of interest) will be assessed.[29] The quality of evidence rating for indirect comparisons will be the lower of the rating for quality for the two direct estimates that contribute to the first-order loop of the indirect comparison.[29]

In the case to use both direct and indirect evidence, the rate of NMA estimate quality will be from the higher quality of the two.[29] The similarity between direct and indirect effect estimates will be estimated in the final quality rating.[29] If there is any inconsistency between direct and indirect effect estimates (i.e., it is estimated by the difference of point estimates and the extent of overlap of 95% CIs and of direct and indirect effect estimates), the quality of the NMA effect will be assessed.[29]

Patient and public involvement

As this study is a systematic review, patients and the public will not be directly involved. However, we will consult key stakeholder groups (e.g., older adult networks and relevant service provider associations) to determine the best channels through which to disseminate the results of our study.

DISCUSSION

As the numbers of older adults increase, so does the resulting social and economic burden of social isolation and loneliness. There is need for evidence-based therapeutic programs to mitigate social isolation and loneliness. A high-quality systematic review of the comparative therapeutic effects of interventions for improving social isolation and loneliness in older adults is essential. To our knowledge, there are few systematic reviews and NMAs combining direct and indirect effects of intervention for social isolation and loneliness in older adults. This study will include a comparison of different interventions for social isolation and loneliness through not only a single (e.g., exercise program or social/health service) intervention, but also combination (e.g., exercise program combined with social/health service) of interventions. This study has several strengths: 1) including recent RCTs social isolation and loneliness for older adults; 2) screening rigorous trial eligibility and collecting data from independent teams of reviews; 3) assessing credibility and providing certainty for intervention effects, by using GRADE approach; 4) performing meta-regression and subgroup analyses, consistent with the best current practice;[85] 5) providing ranking intervention (i.e., the intervention sequence is determined according to their relative efficacy)[93] for social isolation and loneliness.

Although this study has several strengths, there are also potential challenges and limitations. First, it might be difficult to interpret the effects when pooling estimates from trials using

different tools to measure social isolation (e.g., the Lubben Social Network Scale-6 and SSQ6) and loneliness (e.g., the De Jong Gierveld Loneliness Scale and UCLA loneliness scale) combined with high heterogeneity (i.e., differences in effect estimates between studies that evaluated the same comparison).[93] Further, social isolation has a variety of surrogate outcomes such as social support and social network. Such surrogate outcomes might down rate the directness identified through the GRADE approach[93] because it means that an outcome of interest (i.e., social isolation) might differ from the measured in surrogate outcomes (i.e., social support and social network). Additionally, dealing with multicomponent interventions in NMA is a methodological challenge because single or combined (i.e., consisting of several possibly interacting components) interventions are different nodes in the network.[94]

It is expected that the findings of this study will provide evidence for clinicians (e.g., when selecting which interventions are best for older adults), health policy makers (e.g., when making decision which programs or services should be supported) as well as stakeholders (e.g., when operating how programs effectively) managing social isolation and loneliness in community dwelling older adults and for older adults in choosing therapeutic options.

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Management of Social Isolation and Loneliness in Community Dwelling Older Adult: Protocol for a Network Meta-analysis of Randomized Controlled Trials

Supplementary Files

Supplementary file 1: PRISMA NMA checklist

Table A.1: PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*	8-12 Additional file 2

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	12-13
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12-13 Additional file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	13-15
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	13-15
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	13-15
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	16
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	15-16
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	16-18
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	17-18
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	17-18

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	15
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	19
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	n/a
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g.*	n/a

		placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	n/a
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	22

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Supplementary file 2: PICOS statement

PICOS	Inclusion	Exclusion
Participants	□ Community-dwelling older adults ≥ 60 years of age (If mean or median age of participants is 60 year or older, it can be included.) □ Healthy or have a chronic disease, but mobile (i.e., older adults are able to walk independently with or without gait aid, or can self-propel wheelchair.) □ A mild or moderate dementia or cognitive dysfunction	□ Adults < 60 years of age □ Not community residing (inpatients, nursing home, hospital wards, or long-term care facilities) □ Dementia or moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE)<24, Montreal Cognitive Assessment (MoCA) <26, or Short Portable Mental Status Questionnaire (SPMSQ)>6) □ Chronic diseases related to death or serious risk: cancer, AIDS (HIV), chronic heart failure, recent surgery or transplant or intractable rare disease □ Unstable diseases such as bipolar disorder, active psychosis, or suicidal plans □ Caregivers
Interventions	1) Social activities (with others) and social/recreational services: social engagement (also, social involvement, social participation), social facilitation, social support (including emotional instrumental and informational support), psychotherapy (e.g., counselling therapy, music, art or animal intervention, etc.), and education program 2) Exercise programs: group exercise (e.g., tai-chi, aerobic or yoga class) and one-to-one/individual exercise (in gym, outdoor, home, web, telephone-	□ Pharmaceutical interventions including medications and nutritional supplements (vit D, calcium, or protein) for mental health, anxiety, or depression

	based, and etc.) 3) Health services: health care provision (e.g., care management, home visits from nurses or other professionals) and etc. 4) Befriending interventions: peer or partnership program, charity-funded friendship clubs and etc. 5) Leisure/skill development intervention: gardening programs, computer/internet use, voluntary work, holidays and sports (for hobby), productive activities (e.g., reading or engaging in hobbies), passive consumptive activities (e.g., watching TV or listening to radio) and etc. 6) Multicomponent/ Multifaced interventions: any combination of intervention (e.g., social activity combined with exercise programs or social/health service)	
Comparison intervention	□ Usual care, a control, or placebo	
Outcomes	1) Loneliness (e.g., De Jong Gierveld Loneliness Scale, UCLA Loneliness Scale Version #, other (such as Italian) Loneliness Scale or loneliness from The Philadelphia Geriatric Morale Scale (PGMS)) 2) Social isolation (e.g., the Turkish version of the Nottingham Health Profile questionnaire) 3) Social support (e.g., Revised Social Support Questionnaire, Multidimensional Scale of Perceived Social Support (MSPSS), Duke Social Support Index-10, the	□ Social or family wellbeing □ Happiness □ Satisfaction with life □ Depression

	short version of the Medical Outcomes Study [17] Social Support Survey, or the Chinese version of the Inventory of Social Supportive Behaviours) 4) Social network (size) including frequency of contact with network members (e.g., Lubben Social Network Scale-6) 5) Social functioning as a sub-domain of health-related quality of life 6) Social participation (e.g., Subjective Social Participation Index) 7) Health quality of life (e.g., The Short Form (SF-36) Health Survey, The World Health Organization Quality of Life Assessment questionnaire (WHOQOL-BREF), or the 12-item Short Form Health Survey) Although it is the same trial number, if there are different outcomes in each study, it will be included respectively.	
Study design	□ All RCTs or quasi-RCTs regardless of sample size	□ Non-RCTs □ Observational studies (prospective, retrospective cohort, case-control, nested case-control, case cohort, cross-sectional, and simulation studies), comments, editorials, letters to the editor, case series, conference abstract, and animal studies
Setting	□ Community settings	
Language	□ English	□ Non-English

Supplementary file 3: Search strategy

Table A.3.1: MEDLINE via OVID from 1946 to Nov 20, 2019

Searches	Search Terms
1	loneliness/
2	social isolation/
3	social alienation/
4	social support/
5	community networks/
6	social distance/
7	interpersonal relations/
8	friends/
9	psychosocial deprivation/
10	social participation/
11	(lonely or loneliness or solitude).ti,ab.
12	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
13	(social wellbeing or social health or social capital).ti,ab.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	randomized controlled trial.pt.
16	randomized.mp.
17	controlled clinical trial.pt.
18	placebo.mp.
19	15 or 16 or 17 or 18
20	14 and 19
21	exp aged/ or older aged/
22	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
23	21 or 22
24	20 and 23

Table A.3.2: EMBASE from 1974 to Nov 20, 2019

Searches	Search Terms
1	loneliness/
2	social isolation/
3	social alienation/
4	social support/
5	community networks.mp.
6	social distance/
7	human relation/
8	friend/
9	psychosocial deprivation.mp.
10	social participation/
11	(lonely or loneliness or solitude).ti,ab.
12	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
13	(social wellbeing or social health or social capital).ti,ab.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	random:.tw.
16	placebo:.mp.
17	double-blind:.tw.
18	15 or 16 or 17
19	14 and 18
20	exp aged/ or older aged/
21	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
22	20 or 21
23	19 and 22

Table A.3.3: PsycINFO from 1806 to Nov 20, 2019

Searches	Search Terms
1	exp loneliness/
2	exp social deprivation/
3	exp social support/
4	exp alienation/
5	exp friendship/
6	exp social networks/
7	exp interpersonal relationships/
8	(lonely or loneliness or solitude).ti,ab.
9	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
10	(social wellbeing or social health or social capital).ti,ab.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	double-blind.tw.
13	control.tw.
14	random: assigned:.tw.
15	12 or 13 or 14
16	11 and 15
17	exp aged/ or older aged.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measure, mesh]
18	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
19	17 and 18
20	16 and 19

Table A.3.4: CENTRAL from - to Nov 20, 2019

Searches	Search Terms
1	loneliness
2	social isolation
3	social alienation
4	social support
5	community networks
6	social distance
7	interpersonal relations
8	friends
9	psychosocial deprivation
10	social participation
11	lonely or loneliness or solitude
12	MeSH descriptor: [Social Isolation] explode all trees
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	MeSH descriptor: [Aged] in all MeSH products
15	senior* OR elder*
16	#14 OR #15
17	#13 AND #16

Table A.3.5: CINAHL from - to Nov 20, 2019

Searches	Search Terms
1	(MH “Loneliness”)
2	(MH “Social Isolation”)
3	(MH “Social Alienation”)
4	(MH “Support, Psychosocial”)
5	(MH “Community networks”)
6	(MH “Interpersonal Relations”)
7	(MH “Social Networks”)
8	(MH “Psychosocial Deprivation”)
9	(MH “Social Participation”)
10	TI lonely or loneliness or solitude
11	AB lonely or loneliness or solitude
12	TI ((social* or societ* or perce* or person*) N2 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*))
13	AB ((social* or societ* or perce* or person*) N2 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*))
14	TI (social wellbeing or social health or social capital)
15	AB (social wellbeing or social health or social capital)
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17	TI randomized
18	AB randomized
19	TI placebo
20	AB placebo
21	“placebo”
22	TI double-blind
23	AB double-blind
24	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25	16 AND 26
26	(MH “Aged”)
27	TI aged or elder* or geriatric* or gerontol*

28	26 OR 27
29	25 AND 28

PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*_	5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	8-12 Additional file 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	12-13
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12-13 Additional file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	13-15

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	13-15
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	13-15
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	16
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	15-16
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	16-18
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	17-18
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	17-18
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	15
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	19
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the	n/a

		network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	n/a
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	n/a
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	22

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance

from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

BMJ Open

Management of Social Isolation and Loneliness in Community Dwelling Older Adults: Protocol for a Network Meta-analysis of Randomized Controlled Trials

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Keywords:	MENTAL HEALTH, GERIATRIC MEDICINE, STATISTICS & RESEARCH METHODS

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Management of Social Isolation and Loneliness in Community Dwelling Older Adults: Protocol for a Network Meta-analysis of Randomized Controlled Trials

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ABSTRACT

Introduction Social isolation and loneliness in older adults are significant public health issues. Various interventions such as exercise programs or social activities are used in the management of social isolation and loneliness in older adults. Network meta-analysis provides effect estimates for all comparisons by considering the relative efficacy of multiple intervention alternatives. Therefore, this study will determine the comparative efficacy of intervention to alleviate social isolation and loneliness of older adults in community dwelling by comparing direct and indirect interventions through systematic review and network meta-analysis.

Methods and analysis We will include all relevant randomized controlled trials for interventions of social isolation and loneliness in older adults written in English without any limitation of publication date through electronic databases: MEDLINE via OVID, EMBASE, Cochrane Central Registry of Controlled Trials (CENTRAL), PsycINFO, and CINAHL. Independent teams of reviewers will screen trial eligibility, collect data, identify duplication, and assess risk of bias, by using the Cochrane revised risk of bias tool. The interventions for the management of social isolation and loneliness will be included. The primary outcome is social isolation. The secondary outcomes are loneliness and health-related quality of life. We will conduct a network meta-analysis through a Bayesian hierarchical model, by testing assumption (i.e., transitivity) for network meta-analysis. We will also estimate the ranking probabilities for all interventions at each possible rank for each intervention. For estimation of each intervention efficacy, we will assess the certainty and credibility using the GRADE approach.

Ethics and dissemination Ethics approval will not be obtained for this systematic review as it will be conducted with published papers. The review results will be presented at a field-specific conference and published in a relevant peer-reviewed journal.

Trial registration number CRD42020155789

Keywords Social isolation, Loneliness, Older adults, Systematic review, Randomized controlled trials, Network meta-analysis

Strengths and limitations of this study

- This study will be the first systematic review and network meta-analysis about social isolation and loneliness for community-dwelling older adults.
- With the growing aging population systematic review strategies are needed inform which interventions are most effective for alleviating social isolation and loneliness at both an individual and community level.
- This study will provide a rank order list, by their relative efficacy, of interventions for social isolation and loneliness through the intervention sequence.
- It might be difficult to interpret the effects when pooling estimates from trials using different tools to measure social isolation and loneliness combined with high heterogeneity.
- Given that single or combined (i.e., consisting of several possibly interacting components) interventions are different nodes in the network, an issue of multicomponent interventions in NMA may be a methodological challenge.

INTRODUCTION

Social isolation is an objective and quantitative reflection of reduced social network size and limited social contact. This phenomenon is especially important to examine for older adults, when there are often decreased economic resources, increased mobility impairment, and the death of contemporaries.[1] Loneliness is a psychological embodiment of social isolation that demonstrates limited frequency and intimacy of social contacts and discrepancies between relationships and desired relationships.[2] With loneliness, social loneliness means a lack of feelings of social integration, and emotional loneliness is the feeling one feels when one does not have an attachment figure.[3] According to the 2016 Statistics Canada report, approximately 0.75 million older adults aged 60 years or older experienced social isolation and loneliness.[4] A recent national survey reported that 40% of older adults reported being lonely[5] and 24% reported being socially isolated.[6] In particular, older adults are more vulnerable because their meaningful social contacts are eventually replaced by family and close friends after retirement from work.[7]

Social isolation and loneliness in older adults are significant public health issues. Both social isolation and loneliness are associated with increased risk of cardiovascular disease,[8] hypertension,[9-12] inflammatory responses to stress,[13-16] decreased quality of life, physical and mental health,[1 17] and mortality.[18-23] As age increases, approximately one half and one third of older adults experience social isolation[24] and loneliness,[25 26] respectively. Previous studies examining the efficacy of physical activity interventions on social isolation and loneliness demonstrate inconsistent effects.[27] Physical activity interventions improve social functioning, whereas they have no efficacy on loneliness, social support and social networks.[28] Since clinical trials and previous traditional meta-analyses assessed the relative efficacy of two interventions at a time,[29] the relative efficacy of different interventions have not been explored.

Regarding the effect of other interventions, one systematic review showed that two interventions (i.e., group tai-chi and facilitated group discussion) alleviated loneliness but did not improve quality of life. On the other hands, a physical/leisure activity improved quality of life but not social support.[27] Another systematic review suggested that educational interventions for social networks maintenance and enhancement for alleviating loneliness.[30] Additionally, two systematic reviews[31 32] showed that social activity or support interventions in group format reduce social isolation and loneliness. In contrast to the findings from two reviews, one integrative study[33] found that solitary or one-to-one intervention such as solitary pet intervention, solitary video-conference and computer/internet use was more effective.

A recent review[34] suggested a new approach for interventions for social isolation and loneliness. Since social isolation and loneliness are complex constructs with various dimensions, it is suggested that the approach should be taken to consider various predictors of them (e.g., relationship provisions).[34] For example, emotional loneliness (i.e., micro level) can be alleviated through interventions dealing with cognition, and evaluation on a personal level.[7 35 36] Social loneliness (i.e., meso level) may be mitigated through interventions targeting increasing social networks and connectedness with community activities or social media.[37] As an approach of a macro level, programs that improve general health such as treating hearing loss can be implemented.[38] These factors have all been shown to be social determinants of loneliness, well-being, and health.[30 31 39 40]

Network meta-analysis (NMA) is required to provide effect estimates for all comparisons by considering the relative efficacy of multiple intervention alternatives.[41 42] There is some evidence that several interventions such as physical activity, social activities, social or health services, psychotherapy, befriending interventions, and leisure or skill development intervention may

reduce social isolation and loneliness. A systematic review and NMA are required to incorporate recent studies and compare the direct, indirect as well as mixed interventions for social isolation and loneliness.

The objective of this study is to determine the comparative efficacy of interventions to alleviate social isolation and loneliness in community dwelling older adults aged 60 years or older

Research question is "What are the comparative efficacy of interventions to alleviate social isolation and loneliness in community dwelling older adults aged 60 years or older?"

Since social isolation and loneliness are concepts that have been understood and defined in many different ways, interventions often vary. Nevertheless, previously most studies conducted only direct treatment comparison through pairwise meta-analysis. However, multiple comparisons of interventions are necessary in line with the characteristics of social isolation and loneliness. We expect to provide the ranking comparative efficacy of interventions for social isolation and loneliness.

METHODS AND ANLYSIS

Protocol and registration

This study will follow the Preferred Reporting Items for The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions.[43] The completed PRISMA NMA checklist is provided in online supplementary file 1. The protocol of this NMA has been submitted for registration in PROSPERO (registration number CRD42020155789).

Study selection criteria

Types of studies to be Included

We will include randomized controlled studies (RCTs) that assess the efficacy of different interventions to alleviate social isolation and loneliness in older adults aged 60 years or older living in the community. Observational studies including prospective, retrospective cohort, case-control, nested case-control, case cohort, cross-sectional, and simulation, comments, editorials, letters to the editor, case series, conference abstract, and animal studies will be excluded. Studies without information of social isolation or loneliness will be excluded (see online supplementary file 2).

Types of participants

Community-dwelling older adults aged 60 years or older will be included in this study. If the mean or median (depending on what the original authors report) age of participants is 60 years or older, it will be included. RCTs including older adults not residing in the community (e.g., hospitalized patients or long-term care homes) will be excluded. Older adults from institutional settings may have limited contact with friends or family, which could increase the risk of loneliness.[44 45] RCTs including older adults who are healthy or who have chronic disease (e.g., hypertension and diabetes) will be included. RCTs must include older adults who are mobile (i.e., able to walk independently with or without an assistive aid or can self-propel wheelchair). Participants without dementia, moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE) <24, Montreal Cognitive Assessment (MoCA) <26, or Short Portable Mental Status Questionnaire (SPMSQ) >6) will be included. Vulnerable people with dementia or severe cognitive dysfunction might be more socially isolated or lonely due to lack of contact with friends or family,[28] which may confound the measurement of social functioning and

loneliness.[28] We will exclude the following severe diseases as they might make it difficult to identify the efficacy of alleviating social isolation and loneliness: cancer, AIDS (HIV), chronic heart failure, recent surgery, dialysis, transplant, or intractable rare disease. Because patients with such severe diseases need intensive treatment for the diseases, it may be difficult to identify whether efficacy from the intervention for social isolation and loneliness or from the intensive treatment for severe diseases. In addition, older adults experiencing unstable mental health disorders such as bipolar disorder, active psychosis, or suicidal plans will be excluded because these factors could work as confounders for the efficacy on social isolation or loneliness. (see online supplementary file 2).

Types of interventions

RCTs will examine one or more of the following interventions: 1) social activities and social or recreational services such as social engagement including social involvement and social participation, social facilitation, social support including emotional instrumental and informational support, psychotherapy (e.g., counselling therapy, music, art or animal intervention) and education program; 2) exercise programs such as group exercise (e.g., tai-chi, aerobic or yoga class) and one-to-one or individual exercise in a gym or at home, web, or telephoned-based; 3) health services such as health care provisions including care management, home visits from nurses or other professionals; 4) befriending interventions such as charity-funded friendship clubs and friendship enrichment programs; 5) leisure or skill development interventions such as gardening programs, computer or internet use, voluntary work, and holiday; 6) multifaceted interventions including any combination of intervention (e.g., social activities combined with exercise programs, social/health support combined with

psychotherapy).

Comparators will be an inactive control group such as usual care, placebo intervention or no intervention (i.e., it means any comparison targets that can compare the results of post interventions or follow-up outcomes for the intervention group). .

Types of outcomes – The primary outcomes

Because social isolation and loneliness not only are intricately related but also distinct concepts that are frequently used interchangeably,[46] data for both social isolation and loneliness will be included.

Social isolation will be defined as an objective lack of contact with appropriate quality or quantity or a lack of social encounters.[31 47 48] The following outcomes for social isolation will be included: social support, social networks such as network size, frequency of contact with network members, social function, and social participation. Any measures of social isolation, social support, social networks, social function and social participation will be included as long as they assess social isolation based on our definition.

Commonly used instruments for social isolation are the Lubben Social Network Scale-6[49] for social network, the Revised Social Support Questionnaire (SSQ6)[50] and the Multidimensional Scale of Perceived Social Support[51] for social support, and the Subjective Social Participation Index[52] for social participation. The Lubben Social Network Scale-6[49] for social network measures social isolation by measuring frequency, size, and closeness of contacts of the respondent's social network by assessing the perceived level of support they get from friends and families. Scoring is as follows: 0 = none, 1 = one, 2 = two 3 = three or four, 4 = five to eight, 5 = nine or more. Total scores from 0 to 30 with higher scores indicating larger social networks. The

SSQ6[50] for social support has six item measure of social support wherein respondents indicate the number of people they feel they have available to provide support in six areas. The Multidimensional Scale of Perceived Social Support[51] for social support has 12-item scale that is broken into three factor groups (i.e., family, friends, and significant other). This scale is scored on a 1 (very strongly disagree) to 7 (very strongly agree) Likert-type scale. Higher scores indicate high levels of social support. The subjective Social Participation Index[52] for social participation has a 15-question scale broken into three "Factors" – perception of social support, use of new technologies, and index of subjective social participation. Answers to these four questions are always = 0, sometimes = 1, or never = 2. Low scores indicate increased social participation. Additionally, we will also include the 54 tools that measure social isolation and loneliness that are described and listed in the systematic review.[53] Validated tools will be defined as those supported by an academic reference and evidence of their psychometric properties.[32]

Types of outcomes – The secondary outcome

The secondary outcomes are loneliness and health-related quality of life. Loneliness will be defined as unpleasant feelings experienced because one's interactions with others do not meet one's expectations.[2 25 54] Any measures of loneliness will be included as long as they meet our definition of loneliness.

Commonly used instruments for loneliness are the De Jong Gierveld Loneliness Scale,[55] and the University of California Los Angeles (UCLA) Loneliness Scale.[56] The De Jong Gierveld Loneliness Scale[55] measures emotional and social loneliness and has six statements, three measuring emotional loneliness and three measuring social loneliness, each with three choices including yes, more or less, and no. Scores range from 0-6, with 6 indicating higher loneliness.

The UCLA Loneliness Scale Version 3[56] has 20-question tool used to assess subjective feelings of loneliness or social isolation. All questions are framed using "how often do you feel...." and choices include never, rarely, sometimes, and often. Scores range from 20 to 80, with a higher score indicating greater loneliness. In addition, commonly used tools for health-related quality of life are EQ-5D by the EuroQol Group,[57] World Health Organization Quality of Life Scale (WHOQOL-BREF),[58] the 36-Item Short From Health Survey (SF-36),[59] and the Duke Health Profile.[60] EQ-5D[57] represents the best and worst states with five dimensions of measurement, such as mobility, self-care, usual activities, pain/discomfort and anxiety/depression, on a scale of 100 (best) and 0 (worst), indicating how good people's health is today. WHOQOL-BREF[58] measures 26 items, including 4 domains of physical health, psychological, social relationships and environmental. The 4 domain scores represent an individual's perception of the quality of life in each specific domain, and the higher the score, the higher the quality of life.[58] SF-36[59] measures 36 items, including 8 domains of physical function, mental health, social function, role physical, role emotional, pain, vitality, and general health. The scores are converted directly using the weighted sum of the questions in the 8 domains, and the lower the scores, the greater the disability.[59] In the converted scale of 0-100, 0 means maximum disability and 100 means no disability.[59] The Duke Health Profile[60] measures 17 items, including 10 domains of physical, mental, and social health, general and perceived health, self-esteem, anxiety, depression, pain, and disability. It is self-measured in a ram item scoring within the range of 0-100 and means that the higher the score, the healthier.[60]

Search strategy

Electronic databases

The search strategy will be developed using a combination of controlled vocabulary and free-text words related to study participants and study design. Electronic database searches will be performed in MEDLINE via OVID (from 1946 to Nov. 20, 2019), EMBASE (from 1974 to Nov. 20, 2019), Cochrane Central Registry of Controlled Trials (CENTRAL) (to Nov. 20, 2019), PsycINFO (from 1806 to Nov. 20, 2019), and CINAHL (to Nov. 20, 2019) to identify RCTs published on interventions for social isolation and loneliness in older adults. The following keywords for social isolation and loneliness alone and in combination will be searched with terms describing characteristics for them: “social isolation”, “loneliness”, “social relationships”, “social support”, “social network”, “social alienation, “community networks”, “social distance”, “interpersonal relations”, “friends”, “psychosocial deprivation”, and “social participation”. Since the subject of the study is older adults, “older adults” will also be added to the search terms. No date limit will be applied. An experienced librarian will review our search strategies in individual databases and updated them where needed. We will manually search reference lists of all included studies and relevant reviews. We will limit articles to those written in English. Furthermore, in order to identify ongoing trials, three clinical trial registries such as Clinical Trial Registry, Current Controlled Trials, and the World Health Organization International Clinical Trials Registry Platform will be searched. Additionally, unpublished studies will be searched through ProQuest Dissertations and Theses, E-Thos, and Opengrey. (see online supplementary file 3)

Data Extraction

Through the electronic databases, titles and/or abstracts identified using the search strategy will be screened for potential eligibility independently by two reviewers, and the team will obtain full

texts of any articles that either reviewer believes may be eligible. ENDNOTE X9 will automatically filter out duplicates and one reviewer will also remove those in the step of title and/or abstract screening. A team of two reviewers will evaluate each full text article for potential eligibility. Any disagreement will be resolved by discussion or if necessary, adjudication by a third reviewer. Two reviewers will perform data extraction independently and in duplicate. A pilot form will be tested on randomly selected studies by two reviewers to ensure consistency in extraction form. We will extract the following information: 1) study characteristics (design, year, duration of follow-up, recruitment settings, country, study aim, and number of participants allocated to intervention and control); 2) participant characteristics (sample size, eligible criteria, age, sex, participant's chronic disease, and residential settings); 3) intervention or exposure details (type of intervention, frequency of intervention, intensity/level of intervention, length of intervention, intervention content and a control group comparison, format of the delivery, and information about the intervention provider). More specifically, it will first be classified as a single or multifaceted intervention. Single intervention will have only one intervention, while multifaceted interventions will have more than one. Then by the type of intervention (e.g., social activities and social services, exercise programs, health services, befriending intervention, and leisure/skill development). Each type of intervention will then be more specifically classified. The duration (i.e., months), frequency (e.g., once or twice a week, weekly, biweekly, or monthly), time (i.e., minutes) of the specific intervention type will be investigated. For example, if it is an intervention of social activities, it is specifically classified such as social engagement, social facilitation, or social support. If it is the intervention of social engagement, the duration (e.g., 6 months), frequency (e.g., monthly), and time (e.g., 60 minutes) of the social engagement will be investigated.; 4) methodological information (effects on main

outcomes, assessment tools, and information about validation of assessment tools); 5) results related to effect size calculation (means or mean change, standard deviations (SDs), the information from which SD could be derived, such as standard error or confidence interval (CI), number of participants in each intervention group, measurement period, and relevant effect sizes (e.g., odds ratio and rate ratio) with a measure of uncertainty such as standard error (SE) or 95% CI, and/or p-value). If means or SDs are available and instead studies report SEs, CI, t-or p-value, effect sizes will be computed based on the provided data from between group values according to the methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[61] In case of disagreement in the extracted data, reviewers will come to consensus through discussion. If a consensus cannot be reached, a third reviewer will be involved. If possible, we will conduct an intention-to-treat analysis, but otherwise we will use the available data (i.e., per-protocol analysis results). The agreement between the two reviewers screening title and abstract full-text articles will be assessed by the Kappa *(k)* estimates. The agreement between reviewers will be assessed according to the following cut-off points: 1) ≤0 as poor agreement; 2) 0.01 to 0.20 as slight agreement; 3) 0.21 to 0.40 as fair agreement; 4) 0.41 to 0.60 as moderate agreement; 5) 0.61 to 0.80 as substantial agreement; 6) >0.80 as almost perfect agreement.[62]

Risk of bias assessment

The risk of bias will be assessed by two reviewers independently. Any discrepancies on the results of risk of bias will be resolved by the third reviewer. Risk of bias will be assessed according to the Cochrane revised tool for assessing risk of bias in randomized trials (RoB 2)[63] as follows: 1) bias arising from the randomization; 2) bias due to deviations from intended

interventions; 3) bias due to missing out come data; 4) bias in measurement of the outcome; 5) bias is selection of the reported result. The two reviewers will independently judge each domain as high, low, or some concerns risk of bias.

Strategy for data synthesis

Network geometry

A qualitative description of network geometry will be provided and accompanied by a network plot,[64] allowing us to also assess for intervention connectedness. The quantitative metrics assessing features of network geometry such as diversity (i.e., number of interventions and how frequent they are examined) and co-occurrence (i.e., whether certain intervention comparisons are more or less common and the extent of comparisons between different interventions) will be evaluated.[64]

Methods for direct and indirect or mixed intervention comparisons

A standard pairwise meta-analysis through random-effects model will be conducted because the included studies are expected to differ methodologically and clinically in terms of between-study variability.[65] Dichotomous outcome data will be pooled and the odds ratio (OR) and the 95% CI will be reported. Continuous outcome data will be pooled and the standardized mean difference (SMD) and 95% CI will be reported for study-specific follow-up mean values. We will use followed up means instead of mean change because a mixture of the two cannot be combined using SMD in the same model. In case there are missing SDs in follow-up means, it will be assumed to be equal with SDs in baseline mean values. We will quantify heterogeneity (i.e., between-study variability) of intervention effects within each intervention comparison using the

I^2 [66] with its 95% CI. We will estimate the magnitude of the between study variance $\boldsymbol{\tau}^2$ and its 95% CI by using the restricted maximum likelihood estimator and the Q-profile approach, respectively.[67 68] If the ratio of the actual variance (I^2) to the total variance is 50% or more and the significant p-value for test of homogeneity is less than 0.10, heterogeneity of the effect size will be judged to be substantial.[69] Subgroup analysis or meta-regression will be performed if the studies are not available due to high heterogeneity.

Regarding dealing with dependent effect sizes, several methods (e.g., Robust meta-analysis[70] and Three level meta-analysis[71]) are discussed. If the correlation between the dependent effect sizes is unknown, such as when multiple measures are used in a study,[72] a three level meta-analysis will be performed. The three level meta-analysis is an extension of the use of two-level random-effect models in meta-analysis[71] (i.e., Level 2 variance represents the difference between studies in effect size estimates with the assumption that all studies provide independent effect sizes), in which the dependent effect sizes will be clustered within-study at Level 2 and then the effect between-study will be estimated at Level 3.[72] In other words, by modelling the within-study dependence at Level 2 and the between-study mean effect size and variance at Level 3, where the variance in the effect is greatest will be determined.[73]

In addition, results of the NMA will be performed through a Bayesian statistical approach using Markov-chain Monte Carlo (MCMC) simulation. For each NMA, the transitivity and consistency assumptions will be preferentially assessed.[74] Transitivity assumptions will be assessed by average age, percentage women, health status (e.g., chronic disease or mental health status), and trials with low risk of bias compared to high risk of bias as potential intervention effect modifiers, by comparing their distributions across intervention comparisons in each outcome[75] to ensure that they are on average balanced. As a comparative function between each individual

intervention, the intervention contrast (i.e., mean difference or SMD, log odds for dichotomous outcomes, or rate ratio for count outcomes) for the two interventions will be modeled.

A hierarchical Bayesian model using a non-informative prior for the intervention effect parameter and between-trial variance will be used because of lack of previous evidence for social isolation and loneliness.[76 77] Model convergence will be assessed using established methods such as MCMC errors, deviance information criterion (DIC), and trace/density plot.[78]

A random-effects design by intervention interaction model will be used to assess the consistency assumption (i.e., whether direct and indirect evidence agree) globally for each network separately.[74 79] We will also assess for the consistency assumption locally, within each closed loop, using the loop-specific approach.[80 81] When statistically significant inconsistency is detected, data for potential abstraction errors will be tested.[65] If no data errors are identified, direct, indirect, and mixed estimates will be separately reported.[65] Further, significant inconsistency will be explored by performing meta-regression using the above mentioned potential effects modifiers.[65] Inconsistency tests have low power to detect true inconsistency[82 83] and hence, we will assess for the transitivity assumption even in the absence of evidence for inconsistency.

Vague priors for all model parameters and a half-normal prior distribution for the between-study SD will be assumed in all Bayesian NMA models.[65] The models will be run for 50,000 iterations to ensure model convergence, which will be checked by visual inspection of the mixing of 4 chains or by using Gelman-Rubin convergence diagnostics,[84] after discarding the first 5,000 iterations and thinning of 1. The posterior median values and their 95% credible intervals (Crls) for the relevant model parameters will be reported with intervention effects and between-study variance.[85] Each NMA estimate will be presented with a 95% prediction interval,[86] which

captures the magnitude of the between-study variance and indicates the interval at which the intervention effect of future studies are expected.[87]

For relative intervention ranking, the ranking probabilities for all interventions at each possible rank for each intervention will be estimated.[88] Through the surface under the cumulative ranking (SUCRA) curve and mean ranks, the intervention hierarchy will be defined with a cumulative probability of an intervention that can be ranked first without uncertainty.[89] The rank-heat plot (http://rh.ktss.ca/) to visually present the intervention hierarchy across the multiple outcomes of the study will be shown.[90] The higher the SUCRA value, which ranges from 0% to 100%, will indicate the higher the likelihood of intervention[91] for social isolation and loneliness.

Standard pairwise meta-analyses will be conducted through the R statistical package (version 3.6.2) and the metafor package. NMA will be also conducted through the R statistical package (version 3.6.2) with BUGSnet R package (version 1.0.3) for Bayesian NMA.

Analysis of sensitivity

According to Cochrane reviews,[92] the major approach to incorporating risk of bias assessments is to restrict meta-analyses to studies at low risk of bias, or to stratify studies depending on risk of bias. We will perform sensitivity analyses on low risk of bias and excluding the following studies: 1) studies with high risk of bias, 2) studies with missing data, and 3) studies with imputed data (i.e., in order to ensure that imputed research results are not one-sided in NMA) if enough studies are available.

Analysis of subgroup

For multicomponent/multimodal interventions, we will perform subgroup analyses by types of

specific individual intervention. For example, the implications of "social activities combined with exercise interventions" and "psychotherapy combined with social/health service" are different even though they are categorized as multicomponent interventions.

Certainty of the evidence and summary of findings table

Through the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach of NMA,[93] the certainty of direct, indirect and mixed NMA effect estimates for each outcome will be assessed. The certainty of evidence of direct effect estimates for each outcome will be assessed as follows according to the GRADE rating system:[94] high, moderate, low or very low.

We will use the available loops of evidence including loops with a single common comparator (i.e., first-order) or more than one intervening treatment (i.e., higher orders) connecting the two interventions of the comparison of interest in order to calculate the indirect effect estimated.[29] For the quality of indirect evidence, the dominant first-order loop (i.e., loops with a single common comparator connecting the two interventions of the comparison of interest) will be assessed.[29] The quality of evidence rating for indirect comparisons will be the lower of the rating for quality for the two direct estimates that contribute to the first-order loop of the indirect comparison.[29]

In the case to use both direct and indirect evidence, the rate of NMA estimate quality will be from the higher quality of the two.[29] The similarity between direct and indirect effect estimates will be estimated in the final quality rating.[29] If there is any inconsistency between direct and indirect effect estimates (i.e., it is estimated by the difference of point estimates and the extent of overlap of 95% CIs and of direct and indirect effect estimates), the quality of the NMA effect

will be assessed.[29]

Patient and public involvement

As this study is a systematic review, patients and the public will not be directly involved. However, we will consult key stakeholder groups (e.g., older adult networks and relevant service provider associations) to determine the best channels through which to disseminate the results of our study.

DISCUSSION

As the numbers of older adults increase, so does the resulting social and economic burden of social isolation and loneliness. There is need for evidence-based therapeutic programs to mitigate social isolation and loneliness. A high-quality systematic review of the comparative therapeutic effects of interventions for improving social isolation and loneliness in older adults is essential. To our knowledge, there are few systematic reviews and NMAs combining direct and indirect effects of intervention for social isolation and loneliness in older adults. This study will include a comparison of different interventions for social isolation and loneliness through not only a single (e.g., exercise program or social/health service) intervention, but also combination (e.g., exercise program combined with social/health service) of interventions. This study has several strengths: 1) including recent RCTs social isolation and loneliness for older adults; 2) screening rigorous trial eligibility and collecting data from independent teams of reviews; 3) assessing credibility and providing certainty for intervention effects, by using GRADE approach; 4) performing meta-regression and subgroup analyses, consistent with the best current practice;[86] 5) providing ranking intervention (i.e., the intervention sequence is determined according to their relative

efficacy)[94] for social isolation and loneliness.

Although this study has several strengths, there are also potential challenges and limitations. First, it might be difficult to interpret the effects when pooling estimates from trials using different tools to measure social isolation (e.g., the Lubben Social Network Scale-6 and SSQ6) and loneliness (e.g., the De Jong Gierveld Loneliness Scale and UCLA loneliness scale) combined with high heterogeneity (i.e., differences in effect estimates between studies that evaluated the same comparison).[94] Further, social isolation has a variety of surrogate outcomes such as social support and social network. Such surrogate outcomes might down rate the directness identified through the GRADE approach[94] because it means that an outcome of interest (i.e., social isolation) might differ from the measured in surrogate outcomes (i.e., social support and social network). Additionally, dealing with multicomponent interventions in NMA is a methodological challenge because single or combined (i.e., consisting of several possibly interacting components) interventions are different nodes in the network.[95]

It is expected that the findings of this study will provide evidence for clinicians (e.g., when selecting which interventions are best for older adults), health policy makers (e.g., when making decision which programs or services should be supported) as well as stakeholders (e.g., when operating how programs effectively) managing social isolation and loneliness in community dwelling older adults and for older adults in choosing therapeutic options.

Ethics and Dissemination

Ethical approval is not necessary because data will be collected from published studies and there will be no concerns due to privacy. These findings will be disseminated through presentation at conferences and meetings, which will help inform interested researchers of the direction and

design of future research.

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Competing interests None declared.

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Management of Social Isolation and Loneliness in Community Dwelling Older Adults: Protocol for a Network Meta-analysis of Randomized Controlled Trials

Supplementary Files

Supplementary file 1: PRISMA NMA checklist

Table A.1: PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*_	5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	8-12 Additional file 2

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	12-13
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12-13 Additional file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	13-15
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	13-15
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	13-15
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	16
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	15-16
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	16-18
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	17-18
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	17-18

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	15
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*_	19-20
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	n/a
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g.*	n/a

		placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	n/a
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	23

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Supplementary file 2: PICOS statement

PICOS	Inclusion	Exclusion
Participants	□ Community-dwelling older adults ≥ 60 years of age (If mean or median age of participants is 60 year or older, it can be included.) □ Healthy or have a chronic disease, but mobile (i.e., older adults are able to walk independently with or without gait aid, or can self-propel wheelchair.) □ A mild or moderate dementia or cognitive dysfunction	□ Adults < 60 years of age □ Not community residing (inpatients, nursing home, hospital wards, or long-term care facilities) □ Dementia or moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE)<24, Montreal Cognitive Assessment (MoCA) <26, or Short Portable Mental Status Questionnaire (SPMSQ)>6) □ Chronic diseases related to death or serious risk: cancer, AIDS (HIV), chronic heart failure, recent surgery or transplant or intractable rare disease □ Unstable diseases such as bipolar disorder, active psychosis, or suicidal plans □ Caregivers
Interventions	1) Social activities (with others) and social/recreational services: social engagement (also, social involvement, social participation), social facilitation, social support (including emotional instrumental and informational support), psychotherapy (e.g., counselling therapy, music, art or animal intervention, etc.), and education program 2) Exercise programs: group exercise (e.g., tai-chi, aerobic or yoga class) and one-to-one/individual exercise (in gym, outdoor, home, web, telephone-	□ Pharmaceutical interventions including medications and nutritional supplements (vit D, calcium, or protein) for mental health, anxiety, or depression

	based, and etc.) 3) Health services: health care provision (e.g., care management, home visits from nurses or other professionals) and etc. 4) Befriending interventions: peer or partnership program, charity-funded friendship clubs and etc. 5) Leisure/skill development intervention: gardening programs, computer/internet use, voluntary work, holidays and sports (for hobby), productive activities (e.g., reading or engaging in hobbies), passive consumptive activities (e.g., watching TV or listening to radio) and etc. 6) Multicomponent/ Multifaced interventions: any combination of intervention (e.g., social activity combined with exercise programs or social/health service)	
Comparison intervention	□ Usual care, a control, or placebo	
Outcomes	1) Loneliness (e.g., De Jong Gierveld Loneliness Scale, UCLA Loneliness Scale Version #, other (such as Italian) Loneliness Scale or loneliness from The Philadelphia Geriatric Morale Scale (PGMS)) 2) Social isolation (e.g., the Turkish version of the Nottingham Health Profile questionnaire) 3) Social support (e.g., Revised Social Support Questionnaire, Multidimensional Scale of Perceived Social Support (MSPSS), Duke Social Support Index-10, the	□ Social or family wellbeing □ Happiness □ Satisfaction with life □ Depression

	short version of the Medical Outcomes Study [17] Social Support Survey, or the Chinese version of the Inventory of Social Supportive Behaviours) 4) Social network (size) including frequency of contact with network members (e.g., Lubben Social Network Scale-6) 5) Social functioning as a sub-domain of health-related quality of life 6) Social participation (e.g., Subjective Social Participation Index) 7) Health quality of life (e.g., EQ-5D by the EuroQol Group, The Short Form (SF-36) Health Survey, The World Health Organization Quality of Life Assessment questionnaire (WHOQOL-BREF), or the 12-item Short Form Health Survey) Although it is the same trial number, if there are different outcomes in each study, it will be included respectively.	
Study design	□ All RCTs or quasi-RCTs regardless of sample size	□ Non-RCTs □ Observational studies (prospective, retrospective cohort, case-control, nested case-control, case cohort, cross-sectional, and simulation studies), comments, editorials, letters to the editor, case series, conference abstract, and animal studies
Setting	□ Community settings	
Language	□ English	□ Non-English

Supplementary file 3: Search strategy

Table A.3.1: MEDLINE via OVID from 1946 to Nov 20, 2019

Searches	Search Terms
1	loneliness/
2	social isolation/
3	social alienation/
4	social support/
5	community networks/
6	social distance/
7	interpersonal relations/
8	friends/
9	psychosocial deprivation/
10	social participation/
11	(lonely or loneliness or solitude).ti,ab.
12	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
13	(social wellbeing or social health or social capital).ti,ab.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	randomized controlled trial.pt.
16	randomized.mp.
17	controlled clinical trial.pt.
18	placebo.mp.
19	15 or 16 or 17 or 18
20	14 and 19
21	exp aged/ or older aged/
22	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
23	21 or 22
24	20 and 23

Table A.3.2: EMBASE from 1974 to Nov 20, 2019

Searches	Search Terms
1	loneliness/
2	social isolation/
3	social alienation/
4	social support/
5	community networks.mp.
6	social distance/
7	human relation/
8	friend/
9	psychosocial deprivation.mp.
10	social participation/
11	(lonely or loneliness or solitude).ti,ab.
12	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
13	(social wellbeing or social health or social capital).ti,ab.
14	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15	random:.tw.
16	placebo:.mp.
17	double-blind:.tw.
18	15 or 16 or 17
19	14 and 18
20	exp aged/ or older aged/
21	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
22	20 or 21
23	19 and 22

Table A.3.3: PsycINFO from 1806 to Nov 20, 2019

Searches	Search Terms
1	exp loneliness/
2	exp social deprivation/
3	exp social support/
4	exp alienation/
5	exp friendship/
6	exp social networks/
7	exp interpersonal relationships/
8	(lonely or loneliness or solitude).ti,ab.
9	((social* or societ* or perce* or person*) adj3 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*)).ti,ab.
10	(social wellbeing or social health or social capital).ti,ab.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	double-blind.tw.
13	control.tw.
14	random: assigned:.tw.
15	12 or 13 or 14
16	11 and 15
17	exp aged/ or older aged.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measure, mesh]
18	(aged or elder* or geriatric* or gerontol* or nonagenarian* or octogenarian* or older or “oldest old” or senior* or septuagenarian* or sexagenarian* or “very old”).ti.
19	17 and 18
20	16 and 19

Table A.3.4: CENTRAL from - to Nov 20, 2019

Searches	Search Terms
1	loneliness
2	social isolation
3	social alienation
4	social support
5	community networks
6	social distance
7	interpersonal relations
8	friends
9	psychosocial deprivation
10	social participation
11	lonely or loneliness or solitude
12	MeSH descriptor: [Social Isolation] explode all trees
13	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14	MeSH descriptor: [Aged] in all MeSH products
15	senior* OR elder*
16	#14 OR #15
17	#13 AND #16

Table A.3.5: CINAHL from - to Nov 20, 2019

Searches	Search Terms
1	(MH “Loneliness”)
2	(MH “Social Isolation”)
3	(MH “Social Alienation”)
4	(MH “Support, Psychosocial”)
5	(MH “Community networks”)
6	(MH “Interpersonal Relations”)
7	(MH “Social Networks”)
8	(MH “Psychosocial Deprivation”)
9	(MH “Social Participation”)
10	TI lonely or loneliness or solitude
11	AB lonely or loneliness or solitude
12	TI ((social* or societ* or perce* or person*) N2 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*))
13	AB ((social* or societ* or perce* or person*) N2 (isolation or isolated or alienation or alienated or relation* or detachment or detached or contact or link or ties or support* or network* or participation or activ* or engage* or connect* or disconnect* or cohesion or cohesive or embedded* or vulnerab* or interact*))
14	TI (social wellbeing or social health or social capital)
15	AB (social wellbeing or social health or social capital)
16	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17	TI randomized
18	AB randomized
19	TI placebo
20	AB placebo
21	“placebo”
22	TI double-blind
23	AB double-blind
24	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
25	16 AND 26
26	(MH “Aged”)
27	TI aged or elder* or geriatric* or gerontol*

28	26 OR 27
29	25 AND 28

PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*_	5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).*_	8-12 Additional file 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	12-13
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	12-13 Additional file 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	13-15

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	13-15
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	13-15
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	16
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	15-16
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	16-18
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	17-18
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	17-18
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	15
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	19-20
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the	n/a

		network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	n/a
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	n/a
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	23

PICOS = population, intervention, comparators, outcomes, study design.

* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance

from the PRISMA statement.

† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.