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# BMJ Open

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

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Complete List of Authors:	Lee, Ahreum; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence, and Impact McArthur, Caitlin; McMaster University Faculty of Health Sciences, Department of Medicine Veroniki, Areti; University of Ioannina, Kastner, Monika; North York General Hospital, Knowledge Translation and Implementation, Research and Innovation Ioannidis, George; McMaster University Faculty of Health Sciences, Department of Medicine Griffith, Lauren; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence, and Impact Thabane, Lehana; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence, and Impact Adachi, Jonathan; McMaster University Faculty of Health Sciences, Department of Medicine Papaioannou, Alexandra; McMaster University Faculty of Health Sciences, Department of Medicine
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4 **1 Management of Social Isolation and Loneliness in Older Adults: Protocol for a Network**  
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6 **2 Meta-analysis of Randomized Controlled Trials**  
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11 4 Ahreum Lee MPH,<sup>1,2</sup> Caitlin McArthur PT, PhD,<sup>2,3</sup> Areti Angeliki Veroniki PhD,<sup>4,5,6</sup> Monika Kastner PhD,<sup>7</sup>  
12  
13 <sup>8,9</sup> George Ioannidis PhD,<sup>2,3</sup> Lauren E. Griffith PhD,<sup>1</sup> Lehana Thabane PhD,<sup>1,2,10</sup> Jonathan D. Adachi MD,<sup>2</sup>  
14  
15 <sup>3</sup> and Alexandra Papaioannou MD<sup>1,2,3,\*</sup>  
16  
17  
18

19  
20 <sup>1</sup>Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario,  
21  
22 Canada  
23

24 <sup>2</sup>GERAS Centre for Aging Research, Hamilton, Ontario, Canada  
25

26 <sup>3</sup>Department of Medicine, McMaster University, Hamilton, Ontario, Canada  
27

28 <sup>4</sup>Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece  
29

30 <sup>5</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada  
31

32 <sup>6</sup>Institute of Reproductive and Development Biology, Department of Surgery & Cancer, Faculty of  
33  
34 Medicine, Imperial College, London, United Kingdom  
35

36 <sup>7</sup>Knowledge Translation and Implementation, Research and Innovation, North York General Hospital,  
37  
38 Toronto, Ontario, Canada  
39

40 <sup>8</sup>Health Service Research, Institute of Health Policy, Management and Evaluation, University of Toronto,  
41  
42 Toronto, Ontario, Canada  
43

44 <sup>9</sup>Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada  
45

46 <sup>10</sup>Biostatistics Unit, St Joseph's Healthcare Hamilton, Ontario, Canada  
47

48  
49 22 Emails: [leea94@mcmaster.ca](mailto:leea94@mcmaster.ca); [mcarthurc@hhsc.ca](mailto:mcarthurc@hhsc.ca); [averoniki@uoi.gr](mailto:averoniki@uoi.gr); [monika.kastner@nygh.on.ca](mailto:monika.kastner@nygh.on.ca);

50  
51 23 [ioannidis@hhsc.ca](mailto:ioannidis@hhsc.ca); [griffith@mcmaster.ca](mailto:griffith@mcmaster.ca); [thabal@mcmaster.ca](mailto:thabal@mcmaster.ca); [jd.adachi@sympatico.ca](mailto:jd.adachi@sympatico.ca);

52  
53 24 [papaioannou@hhsc.ca](mailto:papaioannou@hhsc.ca)  
54

55 25 ORCID IDs: Ahreum Lee 0000-0003-0882-6256; Caitlin McArthur 0000-0001-9985-2796; Areti Angeliki  
56  
57

1  
2  
3  
4 26 Veroniki 0000-0001-6388-4825; Monika Kastner 0000-0002-2838-7417; George Ioannidis 0000-0001-  
5  
6 27 6956-5737; Lauren E. Griffith 0000-0002-2794-9692; Lehana Thabane 0000-0003-0355-9734; Jonathan  
7  
8 28 D. Adachi 0000-0001-9142-2767; Alexandra Papaioannou 0000-0001-9412-0932  
9

10  
11 29  
12  
13 30 **\*Corresponding Author:** Alexandra Papaioannou; GERAS Centre for Aging Research; Department of  
14  
15 31 Medicine, McMaster University, Hamilton ON, Canada

16  
17 32 Email: [papaioannou@hhsc.ca](mailto:papaioannou@hhsc.ca)

18  
19 33 Tel: +1-905-521-2100 ext. 12405  
20  
21 34

22  
23 35 **Word count** Abstract (282) Main text (3773)  
24  
25 36

## 37 **ABSTRACT**

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

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

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

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4 60 **Trial registration number** CRD42020155789

5  
6 61 **Keywords** Social isolation, Loneliness, Older adults, Systematic review, Randomized controlled  
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9 62 trials, Network meta-analysis

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11 63  
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13 64 **Strengths and limitations of this study**

- 15  
16 65 ▶ This study will be the first systematic review and network meta-analysis about social  
17  
18 66 isolation and loneliness for community-dwelling older adults.
- 19  
20 67 ▶ With the growing aging population systematic review strategies are needed inform which  
21  
22 68 interventions are most effective for alleviating social isolation and loneliness at both an  
23  
24 69 individual and community level.
- 25  
26 70 ▶ It might be difficult to interpret the effects when pooling estimates from trials using different  
27  
28 71 tools to measure social isolation and loneliness combined with high heterogeneity.  
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## 73 INTRODUCTION

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

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



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4 96 analysis (NMA) is required to provide effect estimates for all comparisons by considering the  
5  
6 97 relative efficacy of multiple intervention alternatives.<sup>30 31</sup> There is some evidence that several  
7  
8 98 interventions such as physical activity, social activities, social or health services, psychotherapy,  
9  
10 99 befriending interventions, and leisure or skill development intervention may reduce social  
11  
12 100 isolation and loneliness. A systematic review and NMA are required to incorporate recent studies  
13  
14 101 and compare the direct, indirect as well as mixed interventions for social isolation and loneliness.  
15  
16 102 The aim of this study is to determine the comparative effect of interventions to alleviate social  
17  
18 103 isolation and loneliness in older adults. Research question is “What the comparative effects of  
19  
20 104 interventions to alleviate social isolation and loneliness in older adults?”  
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## 27 106 **METHODS AND ANALYSIS**

### 28 29 107 **Protocol and registration**

30  
31  
32 108 This study will follow the Preferred Reporting Items for The PRISMA Extension Statement for  
33  
34 109 Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care  
35  
36 110 Interventions.<sup>32</sup> The completed PRISMA NMA checklist is provided in online supplementary file  
37  
38  
39 111 1. The protocol of this NMA has been submitted for registration in PROSPERO (registration  
40  
41 112 number CRD42020155789).  
42  
43  
44

### 45 114 **Study selection criteria**

#### 46 115 **Types of studies to be Included**

47  
48 116 We will include randomized controlled studies (RCTs) that assess the effects of different  
49  
50 117 interventions to alleviate social isolation and loneliness in older adults aged 60 years or older  
51  
52  
53 118 living in the community. Observational studies including prospective, retrospective cohort, case-  
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4 119 control, nested case-control, case cohort, cross-sectional, and simulation, comments, editorials,  
5  
6 120 letters to the editor, case series, conference abstract, and animal studies will be excluded. Studies  
7  
8  
9 121 without information of social isolation or loneliness will be excluded (see online supplementary  
10  
11 122 file 2).  
12

13  
14 123

#### 15 16 124 Types of participants

17  
18 125 Community-dwelling older adults aged 60 years or older will be included in this study. If the  
19  
20 126 mean or median (depending on what the original authors report) age of participants is 60 years or  
21  
22 127 older, it will be included. RCTs including older adults not residing in the community (e.g.,  
23  
24 128 hospitalized patients or long-term care homes) will be excluded. Older adults from institutional  
25  
26  
27 129 settings may have limited contact with friends or family, which could increase the risk of  
28  
29 130 loneliness.<sup>33 34</sup> RCTs including older adults who are healthy or who have chronic disease (e.g.,  
30  
31 131 hypertension and diabetes) will be included. RCTs must include older adults who are mobile  
32  
33 132 (i.e., able to walk independently with or without an assistive aid or can self-propel wheelchair)  
34  
35 133 will be included. Participants without dementia, moderate to severe cognitive dysfunction (Mini-  
36  
37 134 Mental State Examination (MMSE) <24, Montreal Cognitive Assessment (MoCA) <26, or Short  
38  
39 135 Portable Mental Status Questionnaire (SPMSQ) >6) will be included. Vulnerable people with  
40  
41 136 dementia or severe cognitive dysfunction might be more socially isolated or lonely due to lack of  
42  
43 137 contact with friends or family,<sup>28</sup> which may confound the measurement of social functioning and  
44  
45 138 loneliness.<sup>28</sup> We will exclude the following severe diseases as they might make it difficult to  
46  
47 139 identify the effects of alleviating social isolation and loneliness: cancer, AIDS (HIV), chronic  
48  
49 140 heart failure, recent surgery, dialysis, transplant, or intractable rare disease. Because patients  
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51 141 with such severe diseases need intensive treatment for the diseases, it may be difficult to identify  
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4 142 whether effects from the intervention for social isolation and loneliness or from the intensive  
5  
6 143 treatment for severe diseases. In addition, older adults experiencing unstable mental health  
7  
8 144 disorders such as bipolar disorder, active psychosis, or suicidal plans will be excluded because  
9  
10 145 these factors could work as confounders for the efficacy on social isolation or loneliness. (see  
11  
12 146 online supplementary file 2).  
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16 147

#### 18 148 Types of interventions

19  
20 149 RCTs will examine one or more of the following interventions: 1) social activities such as social  
21  
22 150 engagement, social facilitation or shared interest topic groups in community centers, and  
23  
24 151 social/recreational services such as social support and psychotherapy including counselling  
25  
26 152 therapy, music, art or animal intervention; 2) exercise programs including group (e.g., tai-chi,  
27  
28 153 aerobic or yoga class), individual exercise in a gym or at home, web, or telephoned-based; 3)  
29  
30 154 health services such as health care provisions including care management, home visits from  
31  
32 155 nurses or other professionals; 4) befriending interventions such as charity-funded friendship  
33  
34 156 clubs and friendship enrichment programs; 5) leisure or skill development interventions such as  
35  
36 157 gardening programs, computer or internet use, voluntary work, and holiday; 6) multifaceted  
37  
38 158 interventions including any combination of intervention (e.g., social activities combined with  
39  
40 159 exercise programs, social/health support combined with psychotherapy).  
41  
42  
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45 160 Comparators will be a control, usual care or placebo intervention (see online supplementary file  
46  
47 161 2).  
48  
49

50 162

#### 52 163 Types of outcomes – The primary outcomes

53  
54  
55 164 Because social isolation and loneliness not only are intricately related but also distinct concepts  
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4 165 that are frequently used interchangeably,<sup>35</sup> data for both social isolation and loneliness will be  
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6 166 included.

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9 167 Social isolation will be defined as an objective lack of contact with appropriate quality or  
10  
11 168 quantity or a lack of social encounters.<sup>36-38</sup> The following outcomes for social isolation will be  
12  
13 169 included: social support, social networks such as network size, frequency of contact with  
14  
15 170 network members, social function, and social participation. Any measures of social isolation,  
16  
17 171 social support, social networks, social function and social participation will be included as long  
18  
19  
20 172 as they assess social isolation based on our definition.

21  
22  
23 173 Commonly used instruments for social isolation are the Lubben Social Network Scale-6<sup>39</sup> for  
24  
25 174 social network, the Revised Social Support Questionnaire (SSQ6)<sup>40</sup> and the Multidimensional  
26  
27 175 Scale of Perceived Social Support<sup>41</sup> for social support, and the Subjective Social Participation  
28  
29 176 Index<sup>42</sup> for social participation. The Lubben Social Network Scale-6<sup>39</sup> for social network  
30  
31 177 measures social isolation by measuring frequency, size, and closeness of contacts of the  
32  
33 178 respondent's social network by assessing the perceived level of support they get from friends and  
34  
35 179 families. Scoring is as follows: 0 = none, 1 = one, 2 = two 3 = three or four, 4 = five to eight, 5 =  
36  
37 180 nine or more. Total scores from 0 to 30 with higher scores indicating larger social networks. The  
38  
39 181 SSQ6<sup>40</sup> for social support has six item measure of social support wherein respondents indicate  
40  
41 182 the number of people they feel they have available to provide support in six areas. The  
42  
43 183 Multidimensional Scale of Perceived Social Support<sup>41</sup> for social support has 12-item scale that is  
44  
45 184 broken into three factor groups (i.e., family, friends, and significant other). This scale is scored  
46  
47 185 on a 1 (very strongly disagree) to 7 (very strongly agree) Likert-type scale. Higher scores  
48  
49 186 indicate high levels of social support. The subjective Social Participation Index<sup>42</sup> for social  
50  
51 187 participation has a 15-question scale broken into three "Factors" – perception of social support,  
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188 use of new technologies, and index of subjective social participation. Answers to these four  
189 questions are always = 0, sometimes = 1, or never = 2. Low scores indicate increased social  
190 participation.

191  
192 Types of outcomes – The secondary outcome

193 The secondary outcome will be loneliness. Loneliness will be defined as unpleasant feelings  
194 experienced because one's interactions with others do not meet one's expectations.<sup>2 25 43</sup> Any  
195 measures of loneliness will be included as long as they meet our definition of loneliness.

196 Commonly used instruments for loneliness are the De Jong Gierveld Loneliness Scale,<sup>44</sup> and the  
197 University of California Los Angeles (UCLA) Loneliness Scale.<sup>45</sup> The De Jong Gierveld  
198 Loneliness Scale<sup>44</sup> measures emotional and social loneliness and has six statements, three  
199 measuring emotional loneliness and three measuring social loneliness, each with three choices  
200 including yes, more or less, and no. Scores range from 0-6, with 6 indicating higher loneliness.  
201 The UCLA Loneliness Scale Version 3<sup>45</sup> has 20-question tool used to assess subjective feelings  
202 of loneliness or social isolation. All questions are framed using “how often do you feel....” and  
203 choices include never, rarely, sometimes, and often. Scores range from 20 to 80, with a higher  
204 score indicating greater loneliness.

205

## 206 **Search strategy**

207 Electronic databases

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

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4 211 (CENTRAL), PsycINFO, and CINAHL to identify RCTs published on interventions for social  
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6 212 isolation and loneliness in older adults. The following keywords alone and in combination will  
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8  
9 213 be searched: “social isolation”, “loneliness”, “social relationships”, “social support”, “social  
10  
11 214 network”, “social alienation”, “community networks”, “social distance”, “interpersonal relations”,  
12  
13 215 “friends”, “psychosocial deprivation”, and “social participation”. No date limit will be applied.  
14  
15 216 An experienced librarian will review our search strategies in individual databases and updated  
16  
17 217 them where needed. We will manually search reference lists of all included studies and relevant  
18  
19 218 reviews. We will limit articles to those written in English (see online supplementary file 3).  
20  
21  
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23 219

#### 24 25 220 Data Extraction

26  
27 221 Titles and/or abstracts identified using the search strategy will be screened for potential  
28  
29 222 eligibility independently by two reviewers, and the team will obtain full texts of any articles that  
30  
31 223 either reviewer believes may be eligible. A team of two reviewers will evaluate each full text  
32  
33 224 article for potential eligibility. Any disagreement will be resolved by discussion or if necessary,  
34  
35 225 adjudication by a third reviewer. Two reviewers will perform data extraction independently and  
36  
37 226 in duplicate. A pilot form will be tested on randomly selected studies by two reviewers to ensure  
38  
39 227 consistency in extraction form. We will extract the following information: 1) study  
40  
41 228 characteristics (design, year, duration of follow-up, recruitment settings, country, study aim, and  
42  
43 229 number of participants allocated to intervention and control); 2) participant characteristics  
44  
45 230 (sample size, eligible criteria, age, sex, participant’s chronic disease, and residential settings); 3)  
46  
47 231 intervention or exposure details (type of intervention, frequency of intervention, intensity/level  
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49 232 of intervention, length of intervention, intervention content and a control group comparison,  
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51 233 format of the delivery, and information about the intervention provider); 4) methodological  
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4 234 information (effects on main outcomes, assessment tools, and information about validation of  
5  
6 235 assessment tools); 5) results related to effect size calculation (means or mean change, standard  
7  
8 236 deviations (SDs), the information from which SD could be derived, such as standard error or  
9  
10 237 confidence interval (CI), number of participants in each intervention group, measurement period,  
11  
12 238 and relevant effect sizes (e.g., odds ratio and rate ratio) with a measure of uncertainty such as  
13  
14 239 standard error (SE) or 95% CI, and/or p-value). If means or SDs are available and instead studies  
15  
16 240 report SEs, CI, t-or p-value, effect sizes will be computed based on the provided data from  
17  
18 241 between group values according to the methods described in the Cochrane Handbook for  
19  
20 242 Systematic Reviews of Interventions.<sup>46</sup> In case of disagreement in the extracted data, reviewers  
21  
22 243 will come to consensus through discussion. If a consensus cannot be reached, a third reviewer  
23  
24 244 will be involved. If possible, we will conduct an intention-to-treat analysis, but otherwise we will  
25  
26 245 use the available data (i.e., per-protocol analysis results). The agreement between the two  
27  
28 246 reviewers screening title and abstract full-text articles will be assessed by the Kappa (*k*)  
29  
30 247 estimates. The agreement between reviewers will be assessed according to the following cut-off  
31  
32 248 points: 1)  $\leq 0$  as poor agreement; 2) 0.01 to 0.20 as slight agreement; 3) 0.21 to 0.40 as fair  
33  
34 249 agreement; 4) 0.41 to 0.60 as moderate agreement; 5) 0.61 to 0.80 as substantial agreement; 6)  
35  
36 250  $>0.80$  as almost perfect agreement.<sup>47</sup>  
37  
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## 251 Risk of bias assessment

252  
253 The risk of bias will be assessed by two reviewers independently. Any discrepancies on the  
254  
255 results of risk of bias will be resolved by the third reviewer. Risk of bias will be assessed  
256  
257 according to the Cochrane revised tool for assessing risk of bias in randomized trials (RoB 2)<sup>48</sup>  
258  
259 as follows: 1) bias arising from the randomization; 2) bias due to deviations from intended  
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4 257 interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; 5)  
5  
6 258 bias is selection of the reported result. The two reviewers will independently judge each domain  
7  
8  
9 259 as high, low, or some concerns risk of bias.  
10

11 260

### 12 13 261 **Strategy for data synthesis**

#### 14 15 262 Network geometry

16  
17  
18 263 A qualitative description of network geometry will be provided and accompanied by a network  
19  
20 264 plot,<sup>49</sup> allowing us to also assess for intervention connectedness. The quantitative metrics  
21  
22 265 assessing features of network geometry such as diversity (i.e., number of interventions and how  
23  
24 266 frequent they are examined) and co-occurrence (i.e., whether certain intervention comparisons  
25  
26 267 are more or less common and the extent of comparisons between different interventions) will be  
27  
28  
29 268 evaluated.<sup>49</sup>  
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31 269

#### 32 33 270 Methods for direct and indirect or mixed intervention comparisons

34  
35 271 A standard pairwise meta-analysis through random-effects model will be conducted because the  
36  
37 272 included studies are expected to differ methodologically and clinically in terms of between-study  
38  
39 273 variability.<sup>50</sup> Dichotomous outcome data will be pooled and the odds ratio (OR) and the 95% CI  
40  
41 274 will be reported. Continuous outcome data will be pooled and the standardized mean difference  
42  
43 275 (SMD) and 95% CI will be reported for study-specific follow-up mean values. We will use  
44  
45 276 followed up means instead of mean change because a mixture of the two cannot be combined  
46  
47 277 using SMD in the same model. In case there are missing SDs in follow-up means, it will be  
48  
49 278 assumed to be equal with SDs in baseline mean values. We will quantify heterogeneity (i.e.,  
50  
51 279 between-study variability) of intervention effects within each intervention comparison using the  
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4 280  $I^2$ <sup>51</sup> with its 95% CI. We will estimate the magnitude of the between study variance  $\tau^2$  and its  
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6  
7 281 95% CI by using the restricted maximum likelihood estimator and the Q-profile approach,  
8  
9 282 respectively.<sup>52 53</sup>  
10  
11 283 In addition, results of the NMA will be performed through a Bayesian statistical approach using  
12  
13 284 Markov-chain Monte Carlo (MCMC) simulation. For each NMA, the transitivity and consistency  
14  
15 285 assumptions will be preferentially assessed.<sup>54</sup> Transitivity assumptions will be assessed by  
16  
17 286 average age, percentage women, health status (e.g., chronic disease or mental health status), and  
18  
19 287 trials with low risk of bias compared to high risk of bias as potential intervention effect  
20  
21 288 modifiers, by comparing their distributions across intervention comparisons in each outcome<sup>55</sup> to  
22  
23 289 ensure that they are on average balanced. As a comparative function between each individual  
24  
25 290 intervention, the intervention contrast (i.e., mean difference or SMD, log odds for dichotomous  
26  
27 291 outcomes, or rate ratio for count outcomes) for the two interventions will be modeled.  
28  
29  
30 292 A hierarchical Bayesian model using a non-informative prior for the intervention effect  
31  
32 293 parameter and between-trial variance will be used because of lack of previous evidence for social  
33  
34 294 isolation and loneliness.<sup>56 57</sup> Model convergence will be assessed using established methods such  
35  
36 295 as MCMC errors, deviance information criterion (DIC), and trace/density plot.<sup>58</sup>  
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38  
39 296 A random-effects design by intervention interaction model will be used to assess the consistency  
40  
41 297 assumption (i.e., whether direct and indirect evidence agree) globally for each network  
42  
43 298 separately.<sup>54 59</sup> We will also assess for the consistency assumption locally, within each closed  
44  
45 299 loop, using the loop-specific approach.<sup>60 61</sup> When statistically significant inconsistency is  
46  
47 300 detected, data for potential abstraction errors will be tested.<sup>50</sup> If no data errors are identified,  
48  
49 301 direct, indirect, and mixed estimates will be separately reported.<sup>50</sup> Further, significant  
50  
51 302 inconsistency will be explored by performing meta-regression using the above mentioned  
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4 303 potential effects modifiers.<sup>50</sup> Inconsistency tests have low power to detect true inconsistency<sup>62 63</sup>  
5  
6 304 and hence, we will assess for the transitivity assumption even in the absence of evidence for  
7  
8  
9 305 inconsistency.

10  
11 306 Vague priors for all model parameters and a half-normal prior distribution for the between-study  
12  
13 307 SD will be assumed in all Bayesian NMA models.<sup>50</sup> The models will be run for 50,000 iterations  
14  
15 308 to ensure model convergence, which will be checked by visual inspection of the mixing of 4  
16  
17 309 chains or by using Gelman-Rubin convergence diagnostics,<sup>64</sup> after discarding the first 5,000  
18  
19 310 iterations and thinning of 1. The posterior median values and their 95% credible intervals (CrIs)  
20  
21 311 for the relevant model parameters will be reported with intervention effects and between-study  
22  
23 312 variance.<sup>65</sup> Each NMA estimate will be presented with a 95% prediction interval,<sup>66</sup> which  
24  
25 313 captures the magnitude of the between-study variance and indicates the interval at which the  
26  
27 314 intervention effect of future studies are expected.<sup>67</sup>

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31 315 For relative intervention ranking, the ranking probabilities for all interventions at each possible  
32  
33 316 rank for each intervention will be estimated.<sup>68</sup> Through the surface under the cumulative ranking  
34  
35 317 (SUCRA) curve and mean ranks, the intervention hierarchy will be defined with a cumulative  
36  
37 318 probability of an intervention that can be ranked first without uncertainty.<sup>69</sup> The rank-heat plot  
38  
39 319 (<http://rh.ktss.ca/>) to visually present the intervention hierarchy across the multiple outcomes of  
40  
41 320 the study will be shown.<sup>70</sup> The higher the SUCRA value, which ranges from 0% to 100%, will  
42  
43 321 indicate the higher the likelihood of intervention<sup>71</sup> for social isolation and loneliness.

44  
45 322 Standard pairwise meta-analyses will be conducted through the R statistical package (version  
46  
47 323 3.6.2) and the metafor package. NMA will be also conducted through the R statistical package  
48  
49 324 (version 3.6.2) with BUGSnet R package (version 1.0.3) for Bayesian NMA.  
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4 326 Analysis of sensitivity  
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6 327 We will perform sensitivity analyses on low risk of bias and excluding any studies with imputed  
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9 328 values if enough studies are available.  
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12  
13 330 Analysis of subgroup  
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15 331 For multicomponent/multimodal interventions, we will perform subgroup analyses by types of  
16  
17 332 specific individual intervention. For example, the implications of “social activities combined  
18  
19 333 with exercise interventions” and “psychotherapy combined with social/health service” are  
20  
21 334 different even though they are categorized as multicomponent interventions.  
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26  
27 336 Certainty of the evidence and summary of findings table  
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29 337 Through the GRADE (Grading of Recommendations Assessment, Development and Evaluation)  
30  
31 338 approach of NMA,<sup>72</sup> the certainty of direct, indirect and mixed NMA effect estimates for each  
32  
33 339 outcome will be assessed. The certainty of evidence of direct effect estimates for each outcome  
34  
35 340 will be assessed as follows according to the GRADE rating system:<sup>73</sup> high, moderate, low or  
36  
37 341 very low.  
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39  
40 342 We will use the available loops of evidence including loops with a single common comparator  
41  
42 343 (i.e., first-order) or more than one intervening treatment (i.e., higher orders) connecting the two  
43  
44 344 interventions of the comparison of interest in order to calculate the indirect effect estimated.<sup>29</sup>  
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46

47 345 For the quality of indirect evidence, the dominant first-order loop (i.e., loops with a single  
48  
49 346 common comparator connecting the two interventions of the comparison of interest) will be  
50  
51 347 assessed.<sup>29</sup> The quality of evidence rating for indirect comparisons will be the lower of the rating  
52  
53 348 for quality for the two direct estimates that contribute to the first-order loop of the indirect  
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4 349 comparison.<sup>29</sup>  
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6 350 In the case to use both direct and indirect evidence, the rate of NMA estimate quality will be  
7  
8 351 from the higher quality of the two.<sup>29</sup> The similarity between direct and indirect effect estimates  
9  
10 352 will be estimated in the final quality rating.<sup>29</sup> If there is any inconsistency between direct and  
11  
12 353 indirect effect estimates (i.e., it is estimated by the difference of point estimates and the extent of  
13  
14 354 overlap of 95% CIs and of direct and indirect effect estimates), the quality of the NMA effect  
15  
16 355 will be assessed.<sup>29</sup>  
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### 23 357 **Patient and public involvement**

24  
25 358 As this study is a systematic review, patients and the public will not be directly involved.  
26  
27 359 However, we will consult key stakeholder groups (e.g., older adult networks and relevant service  
28  
29 360 provider associations) to determine the best channels through which to disseminate the results of  
30  
31 361 our study.  
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### 35 363 **DISCUSSION**

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38 364 As the numbers of older adults increase, so does the resulting social and economic burden of  
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40 365 social isolation and loneliness. There is need for evidence-based therapeutic programs to mitigate  
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42 366 social isolation and loneliness. A high-quality systematic review of the comparative therapeutic  
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44 367 effects of interventions for improving social isolation and loneliness in older adults is essential.  
45  
46 368 To our knowledge, there are few systematic reviews and NMAs combining direct and indirect  
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48 369 effects of intervention for social isolation and loneliness in older adults. This study will include a  
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50 370 comparison of different interventions for social isolation and loneliness through not only a single  
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52 371 (e.g., exercise program or social/health service) intervention, but also combination (e.g., exercise  
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4 372 program combined with social/health service) of interventions. This study has several strengths:  
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6 373 1) including recent RCTs social isolation and loneliness for older adults; 2) screening rigorous  
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8 374 trial eligibility and collecting data from independent teams of reviews; 3) assessing credibility  
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10 375 and providing certainty for intervention effects, by using GRADE approach; 4) performing meta-  
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12 376 regression and subgroup analyses, consistent with the best current practice;<sup>66</sup> 5) providing  
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14 377 ranking intervention (i.e., the intervention sequence is determined according to their relative  
15  
16 378 efficacy)<sup>73</sup> for social isolation and loneliness.

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20 379 Although this study has several strengths, there are also potential challenges and limitations.  
21  
22 380 First, it might be difficult to interpret the effects when pooling estimates from trials using  
23  
24 381 different tools to measure social isolation (e.g., the Lubben Social Network Scale-6 and SSQ6)  
25  
26 382 and loneliness (e.g., the De Jong Gierveld Loneliness Scale and UCLA loneliness scale)  
27  
28 383 combined with high heterogeneity (i.e., differences in effect estimates between studies that  
29  
30 384 evaluated the same comparison).<sup>73</sup> Further, social isolation has a variety of surrogate outcomes  
31  
32 385 such as social support and social network. Such surrogate outcomes might down rate the  
33  
34 386 directness identified through the GRADE approach<sup>73</sup> because it means that an outcome of  
35  
36 387 interest (i.e., social isolation) might differ from the measured in surrogate outcomes (i.e., social  
37  
38 388 support and social network). Additionally, dealing with multicomponent interventions in NMA is  
39  
40 389 a methodological challenge because single or combined (i.e., consisting of several possibly  
41  
42 390 interacting components) interventions are different nodes in the network.<sup>74</sup>

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44  
45 391 It is expected that the findings of this study will provide evidence for clinicians (e.g., when  
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47 392 selecting which interventions are best for older adults), health policy makers (e.g., when making  
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49 393 decision which programs or services should be supported) as well as stakeholders (e.g., when  
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51 394 operating how programs effectively) managing social isolation and loneliness in community  
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dwelling older adults and for older adults in choosing therapeutic options.

396

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401

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3 **Management of Social Isolation and Loneliness in Older Adult: Protocol for a Network Meta-**  
4 **analysis of Randomized Controlled Trials**  
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10 **Supplementary files**  
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21 Supplementary file 1: PRISMA NMA checklist..... 2  
22  
23 Supplementary file 2: PICOS statement ..... 6  
24  
25 Supplementary file 3: Search strategy..... 9  
26  
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## 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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed</i> . <i>Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity</i> . <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	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
<b>Geometry of the network</b>	<b>S1</b>	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). <i>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.</i>	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: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	13-14
<b>Assessment of Inconsistency</b>	<b>S2</b>	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: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	15
<b>RESULTS†</b>			
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
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
<b>Summary of network geometry</b>	<b>S4</b>	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. <i>Modified approaches may be needed to deal with information from larger networks.</i>	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g.</i>	n/a

		<i>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.</i>	
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> 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, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	n/a
<b>DISCUSSION</b>			
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). <i>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).</i>	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
<b>FUNDING</b>			
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	<ul style="list-style-type: none"> <li><input type="checkbox"/> Community-dwelling older adults <math>\geq 60</math> years of age (If mean or median age of participants is 60 year or older, it can be included.)</li> <li><input type="checkbox"/> 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.)</li> <li><input type="checkbox"/> A mild or moderate dementia or cognitive dysfunction</li> </ul>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Adults <math>&lt; 60</math> years of age</li> <li><input type="checkbox"/> Not community residing (inpatients, nursing home, hospital wards, or long-term care facilities)</li> <li><input type="checkbox"/> Dementia or moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE)<math>&lt;24</math>, Montreal Cognitive Assessment (MoCA) <math>&lt;26</math>, or Short Portable Mental Status Questionnaire (SPMSQ)<math>&gt;6</math>)</li> <li><input type="checkbox"/> Chronic diseases related to death or serious risk: cancer, AIDS (HIV), chronic heart failure, recent surgery or transplant or intractable rare disease</li> <li><input type="checkbox"/> Unstable diseases such as bipolar disorder, active psychosis, or suicidal plans</li> <li><input type="checkbox"/> Caregivers</li> </ul>
Interventions	<ol style="list-style-type: none"> <li>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.)</li> <li>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.</li> <li>3) Health services: health care provision (care management, home visits from nurses or other</li> </ol>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Pharmaceutical interventions including medications and nutritional supplements (vit D, calcium, or protein) for mental health, anxiety, or depression</li> </ul>

	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	<input type="checkbox"/> 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))	<input type="checkbox"/> Social or family wellbeing <input type="checkbox"/> Happiness <input type="checkbox"/> Satisfaction with life <input type="checkbox"/> Depression
	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 <sup>17</sup> 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) 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	<input type="checkbox"/> All RCTs or quasi-RCTs regardless of sample size	<input type="checkbox"/> Non-RCTs <input type="checkbox"/> 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	<input type="checkbox"/> Community settings	
Language	<input type="checkbox"/> English	<input type="checkbox"/> 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*

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28	26 OR 27
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For peer review only

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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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted.</i>	4
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i>	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
<b>Geometry of the network</b>	<b>S1</b>	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). <i>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.</i>	12-14

1 2 3 4 5 6 7 8 9 10 11 12 13 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: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses;</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	13-14
15 16 17 18 19 20	<b>Assessment of Inconsistency</b>	<b>S2</b>	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
21 22 23 24	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
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44	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: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network;</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	15
45 46 47	<b>RESULTS†</b>			
48 49 50 51	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
52 53 54	<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
55 56 57	<b>Summary of</b>	<b>S4</b>	Provide a brief overview of characteristics of the treatment	n/a

<b>network geometry</b>		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. <i>Modified approaches may be needed to deal with information from larger networks.</i>	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>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.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	n/a
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> 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, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,</i> and so forth).	n/a
<b>DISCUSSION</b>			

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). <i>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).</i>	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
<b>FUNDING</b>			
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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Complete List of Authors:	Lee, Ahreum; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence, and Impact McArthur, Caitlin; McMaster University Faculty of Health Sciences, Department of Medicine Veroniki, Areti; University of Ioannina, Kastner, Monika; North York General Hospital, Knowledge Translation and Implementation, Research and Innovation Ioannidis, George; McMaster University Faculty of Health Sciences, Department of Medicine Griffith, Lauren; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence, and Impact Thabane, Lehana; McMaster University Faculty of Health Sciences, Health Research Methods, Evidence, and Impact Adachi, Jonathan; McMaster University Faculty of Health Sciences, Department of Medicine Papaioannou, Alexandra; McMaster University Faculty of Health Sciences, Department of Medicine
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4 **1 Management of Social Isolation and Loneliness in Community Dwelling Older Adults:**  
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6 **2 Protocol for a Network Meta-analysis of Randomized Controlled Trials**  
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11 4 Ahreum Lee MPH,<sup>1,2</sup> Caitlin McArthur PT, PhD,<sup>2,3</sup> Areti Angeliki Veroniki PhD,<sup>4,5,6</sup> Monika Kastner PhD,<sup>7</sup>  
12  
13 <sup>8,9</sup> George Ioannidis PhD,<sup>2,3</sup> Lauren E. Griffith PhD,<sup>1</sup> Lehana Thabane PhD,<sup>1,2,10</sup> Jonathan D. Adachi MD,<sup>2</sup>  
14  
15 <sup>3</sup> and Alexandra Papaioannou MD<sup>1,2,3,\*</sup>  
16  
17  
18

19  
20 <sup>1</sup>Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario,  
21  
22 Canada  
23

24 <sup>2</sup>GERAS Centre for Aging Research, Hamilton, Ontario, Canada  
25

26 <sup>3</sup>Department of Medicine, McMaster University, Hamilton, Ontario, Canada  
27

28 <sup>4</sup>Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece  
29

30 <sup>5</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada  
31

32 <sup>6</sup>Institute of Reproductive and Development Biology, Department of Surgery & Cancer, Faculty of  
33  
34 Medicine, Imperial College, London, United Kingdom  
35

36 <sup>7</sup>Knowledge Translation and Implementation, Research and Innovation, North York General Hospital,  
37  
38 Toronto, Ontario, Canada  
39

40 <sup>8</sup>Health Service Research, Institute of Health Policy, Management and Evaluation, University of Toronto,  
41  
42 Toronto, Ontario, Canada  
43

44  
45 <sup>9</sup>Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada  
46

47 <sup>10</sup>Biostatistics Unit, St Joseph's Healthcare Hamilton, Ontario, Canada  
48

49 22 Emails: [leea94@mcmaster.ca](mailto:leea94@mcmaster.ca); [mcarthurc@hhsc.ca](mailto:mcarthurc@hhsc.ca); [averoniki@uoi.gr](mailto:averoniki@uoi.gr); [monika.kastner@nygh.on.ca](mailto:monika.kastner@nygh.on.ca);

50  
51 23 [ioannidis@hhsc.ca](mailto:ioannidis@hhsc.ca); [griffith@mcmaster.ca](mailto:griffith@mcmaster.ca); [thabal@mcmaster.ca](mailto:thabal@mcmaster.ca); [jd.adachi@sympatico.ca](mailto:jd.adachi@sympatico.ca);

52  
53 24 [papaioannou@hhsc.ca](mailto:papaioannou@hhsc.ca)  
54

55 25 ORCID IDs: Ahreum Lee 0000-0003-0882-6256; Caitlin McArthur 0000-0001-9985-2796; Areti Angeliki  
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60

26 Veroniki 0000-0001-6388-4825; Monika Kastner 0000-0002-2838-7417; George Ioannidis 0000-0001-  
27 6956-5737; Lauren E. Griffith 0000-0002-2794-9692; Lehana Thabane 0000-0003-0355-9734; Jonathan  
28 D. Adachi 0000-0001-9142-2767; Alexandra Papaioannou 0000-0001-9412-0932

30 **\*Corresponding Author:** Alexandra Papaioannou; GERAS Centre for Aging Research; Department of  
31 Medicine, McMaster University, Hamilton ON, Canada  
32 Email: [papaioannou@hhsc.ca](mailto:papaioannou@hhsc.ca)  
33 Tel: +1-905-521-2100 ext. 12405

35 **Word count** Abstract (283) Main text (4879)



## 37 **ABSTRACT**

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

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

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

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4 60 **Trial registration number** CRD42020155789

5  
6 61 **Keywords** Social isolation, Loneliness, Older adults, Systematic review, Randomized controlled  
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9 62 trials, Network meta-analysis

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13 64 **Strengths and limitations of this study**

- 15  
16 65 ▶ This study will be the first systematic review and network meta-analysis about social  
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18 66 isolation and loneliness for community-dwelling older adults.
- 19  
20 67 ▶ With the growing aging population systematic review strategies are needed inform which  
21  
22 68 interventions are most effective for alleviating social isolation and loneliness at both an  
23  
24 69 individual and community level.
- 25  
26 70 ▶ It might be difficult to interpret the effects when pooling estimates from trials using different  
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28 71 tools to measure social isolation and loneliness combined with high heterogeneity.  
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## 73 INTRODUCTION

74 Social isolation is an objective and quantitative reflection of reduced social network size and  
75 limited social contact. This phenomenon is especially important to examine for older adults,  
76 when there are often decreased economic resources, increased mobility impairment, and the  
77 death of contemporaries.<sup>1</sup> Loneliness is a psychological embodiment of social isolation that  
78 demonstrates limited frequency and intimacy of social contacts and discrepancies between  
79 relationships and desired relationships.<sup>2</sup> With loneliness, social loneliness means a lack of  
80 feelings of social integration, and emotional loneliness is the feeling one feels when one does not  
81 have an attachment figure.<sup>3</sup> According to the 2016 Statistics Canada report, approximately 0.75  
82 million older adults aged 60 years or older experienced social isolation and loneliness.<sup>4</sup> A recent  
83 national survey reported that 40% of older adults reported being lonely<sup>5</sup> and 24% reported being  
84 socially isolated.<sup>6</sup> In particular, older adults are more vulnerable because their meaningful social  
85 contacts are eventually replaced by family and close friends after retirement from work.<sup>7</sup>  
86 Social isolation and loneliness in older adults are significant public health issues. Both social  
87 isolation and loneliness are associated with increased risk of cardiovascular disease,<sup>8</sup>  
88 hypertension,<sup>9-12</sup> inflammatory responses to stress,<sup>13-16</sup> decreased quality of life, physical and  
89 mental health,<sup>1 17</sup> and mortality.<sup>18-23</sup> As age increases, approximately one half and one third of  
90 older adults experience social isolation<sup>24</sup> and loneliness,<sup>25 26</sup> respectively. Previous studies  
91 examining the efficacy of physical activity interventions on social isolation and loneliness  
92 demonstrate inconsistent effects.<sup>27</sup> Physical activity interventions improve social functioning,  
93 whereas they have no efficacy on loneliness, social support and social networks.<sup>28</sup> Since clinical  
94 trials and previous traditional meta-analyses assessed the relative efficacy of two interventions at  
95 a time,<sup>29</sup> the relative efficacy of different interventions have not been explored.

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4 96 Regarding the effect of other interventions, one systematic review showed that two interventions  
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6 97 (i.e., group tai-chi and facilitated group discussion) alleviated loneliness but did not improve  
7  
8 98 quality of life. On the other hands, a physical/leisure activity improved quality of life but not  
9  
10 99 social support.<sup>27</sup> Another systematic review suggested that educational interventions for social  
11  
12 100 networks maintenance and enhancement for alleviating loneliness.<sup>30</sup> Additionally, two  
13  
14 101 systematic reviews<sup>31 32</sup> showed that social activity or support interventions in group format  
15  
16 102 reduce social isolation and loneliness. In contrast to the findings from two reviews, one  
17  
18 103 integrative study<sup>33</sup> found that solitary or one-to-one intervention such as solitary pet intervention,  
19  
20 104 solitary video-conference and computer/internet use was more effective.  
21  
22 105 A recent review<sup>34</sup> suggested a new approach for interventions for social isolation and loneliness.  
23  
24 106 Since social isolation and loneliness are complex constructs with various dimensions, it is  
25  
26 107 suggested that the approach should be taken to consider various predictors of them (e.g.,  
27  
28 108 relationship provisions).<sup>34</sup> For example, emotional loneliness (i.e., micro level) can be alleviated  
29  
30 109 through interventions dealing with cognition, and evaluation on a personal level.<sup>7 35 36</sup> Social  
31  
32 110 loneliness (i.e., meso level) may be mitigated through interventions targeting increasing social  
33  
34 111 networks and connectedness with community activities or social media.<sup>37</sup> As an approach of a  
35  
36 112 macro level, programs that improve general health such as treating hearing loss can be  
37  
38 113 implemented.<sup>38</sup> These factors have all been shown to be social determinants of loneliness, well-  
39  
40 114 being, and health.<sup>30 31 39 40</sup>  
41  
42 115 Network meta-analysis (NMA) is required to provide effect estimates for all comparisons by  
43  
44 116 considering the relative efficacy of multiple intervention alternatives.<sup>41 42</sup> There is some evidence  
45  
46 117 that several interventions such as physical activity, social activities, social or health services,  
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48 118 psychotherapy, befriending interventions, and leisure or skill development intervention may  
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4 119 reduce social isolation and loneliness. A systematic review and NMA are required to incorporate  
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6 120 recent studies and compare the direct, indirect as well as mixed interventions for social isolation  
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9 121 and loneliness.

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11 122 The objective of this study is to determine the comparative efficacy of interventions to alleviate  
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13 123 social isolation and loneliness in community dwelling older adults aged 60 years or older

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15 124 Research question is “What are the comparative efficacy of interventions to alleviate social  
16  
17 125 isolation and loneliness in community dwelling older adults aged 60 years or older?”

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20 126 Since social isolation and loneliness are concepts that have been understood and defined in many  
21  
22 127 different ways, interventions often vary. Nevertheless, previously most studies conducted only  
23  
24 128 direct treatment comparison through pairwise meta-analysis. However, multiple comparisons of  
25  
26 129 interventions are necessary in line with the characteristics of social isolation and loneliness. We  
27  
28 130 expect to provide the ranking comparative efficacy of interventions for social isolation and  
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30 131 loneliness.

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## 35 36 133 **METHODS AND ANALYSIS**

### 37 38 134 **Protocol and registration**

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41 135 This study will follow the Preferred Reporting Items for The PRISMA Extension Statement for  
42  
43 136 Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care  
44  
45 137 Interventions.<sup>43</sup> The completed PRISMA NMA checklist is provided in online supplementary file  
46  
47  
48 138 1. The protocol of this NMA has been submitted for registration in PROSPERO (registration  
49  
50 139 number CRD42020155789).

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### 54 55 141 **Study selection criteria**

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4 142 Types of studies to be Included  
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6 143 We will include randomized controlled studies (RCTs) that assess the efficacy of different  
7  
8 144 interventions to alleviate social isolation and loneliness in older adults aged 60 years or older  
9  
10 145 living in the community. Observational studies including prospective, retrospective cohort, case-  
11  
12 146 control, nested case-control, case cohort, cross-sectional, and simulation, comments, editorials,  
13  
14 147 letters to the editor, case series, conference abstract, and animal studies will be excluded. Studies  
15  
16 148 without information of social isolation or loneliness will be excluded (see online supplementary  
17  
18 149 file 2).  
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25 151 Types of participants  
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27 152 Community-dwelling older adults aged 60 years or older will be included in this study. If the  
28  
29 153 mean or median (depending on what the original authors report) age of participants is 60 years or  
30  
31 154 older, it will be included. RCTs including older adults not residing in the community (e.g.,  
32  
33 155 hospitalized patients or long-term care homes) will be excluded. Older adults from institutional  
34  
35 156 settings may have limited contact with friends or family, which could increase the risk of  
36  
37 157 loneliness.<sup>44 45</sup> RCTs including older adults who are healthy or who have chronic disease (e.g.,  
38  
39 158 hypertension and diabetes) will be included. RCTs must include older adults who are mobile  
40  
41 159 (i.e., able to walk independently with or without an assistive aid or can self-propel wheelchair).  
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43 160 Participants without dementia, moderate to severe cognitive dysfunction (Mini-Mental State  
44  
45 161 Examination (MMSE) <24, Montreal Cognitive Assessment (MoCA) <26, or Short Portable  
46  
47 162 Mental Status Questionnaire (SPMSQ) >6) will be included. Vulnerable people with dementia or  
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49 163 severe cognitive dysfunction might be more socially isolated or lonely due to lack of contact  
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51 164 with friends or family,<sup>28</sup> which may confound the measurement of social functioning and  
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4 165 loneliness.<sup>28</sup> We will exclude the following severe diseases as they might make it difficult to  
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6 166 identify the efficacy of alleviating social isolation and loneliness: cancer, AIDS (HIV), chronic  
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9 167 heart failure, recent surgery, dialysis, transplant, or intractable rare disease. Because patients  
10  
11 168 with such severe diseases need intensive treatment for the diseases, it may be difficult to identify  
12  
13 169 whether efficacy from the intervention for social isolation and loneliness or from the intensive  
14  
15 170 treatment for severe diseases. In addition, older adults experiencing unstable mental health  
16  
17 171 disorders such as bipolar disorder, active psychosis, or suicidal plans will be excluded because  
18  
19 172 these factors could work as confounders for the efficacy on social isolation or loneliness. (see  
20  
21 173 online supplementary file 2).  
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#### 25 174 26 27 175 Types of interventions

28  
29 176 RCTs will examine one or more of the following interventions: 1) social activities and social or  
30  
31 177 recreational services such as social engagement including social involvement and social  
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33 178 participation, social facilitation, social support including emotional instrumental and  
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35 179 informational support, psychotherapy (e.g., counselling therapy, music, art or animal  
36  
37 180 intervention) and education program; 2) exercise programs such as group exercise (e.g., tai-chi,  
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39 181 aerobic or yoga class) and one-to-one or individual exercise in a gym or at home, web, or  
40  
41 182 telephoned-based; 3) health services such as health care provisions including care management,  
42  
43 183 home visits from nurses or other professionals; 4) befriending interventions such as charity-  
44  
45 184 funded friendship clubs and friendship enrichment programs; 5) leisure or skill development  
46  
47 185 interventions such as gardening programs, computer or internet use, voluntary work, and  
48  
49 186 holiday; 6) multifaceted interventions including any combination of intervention (e.g., social  
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51 187 activities combined with exercise programs, social/health support combined with  
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4 188 psychotherapy).

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6 189 Comparators will be an inactive control group such as usual care, placebo intervention or no  
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9 190 intervention (i.e., it means any comparison targets that can compare the results of post  
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11 191 interventions or follow-up outcomes for the intervention group). .

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16 193 Types of outcomes – The primary outcomes

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18 194 Because social isolation and loneliness not only are intricately related but also distinct concepts  
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20 195 that are frequently used interchangeably,<sup>46</sup> data for both social isolation and loneliness will be  
21  
22 196 included.

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24  
25 197 Social isolation will be defined as an objective lack of contact with appropriate quality or  
26  
27 198 quantity or a lack of social encounters.<sup>31 47 48</sup> The following outcomes for social isolation will be  
28  
29 199 included: social support, social networks such as network size, frequency of contact with  
30  
31 200 network members, social function, and social participation. Any measures of social isolation,  
32  
33 201 social support, social networks, social function and social participation will be included as long  
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35 202 as they assess social isolation based on our definition.

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39 203 Commonly used instruments for social isolation are the Lubben Social Network Scale-6<sup>49</sup> for  
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41 204 social network, the Revised Social Support Questionnaire (SSQ6)<sup>50</sup> and the Multidimensional  
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43 205 Scale of Perceived Social Support<sup>51</sup> for social support, and the Subjective Social Participation  
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45 206 Index<sup>52</sup> for social participation. The Lubben Social Network Scale-6<sup>49</sup> for social network  
46  
47 207 measures social isolation by measuring frequency, size, and closeness of contacts of the  
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49 208 respondent's social network by assessing the perceived level of support they get from friends and  
50  
51 209 families. Scoring is as follows: 0 = none, 1 = one, 2 = two 3 = three or four, 4 = five to eight, 5 =  
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53 210 nine or more. Total scores from 0 to 30 with higher scores indicating larger social networks. The  
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4 211 SSQ6<sup>50</sup> for social support has six item measure of social support wherein respondents indicate  
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6 212 the number of people they feel they have available to provide support in six areas. The  
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8 213 Multidimensional Scale of Perceived Social Support<sup>51</sup> for social support has 12-item scale that is  
9  
10 214 broken into three factor groups (i.e., family, friends, and significant other). This scale is scored  
11  
12 215 on a 1 (very strongly disagree) to 7 (very strongly agree) Likert-type scale. Higher scores  
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14 216 indicate high levels of social support. The subjective Social Participation Index<sup>52</sup> for social  
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16 217 participation has a 15-question scale broken into three “Factors” – perception of social support,  
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18 218 use of new technologies, and index of subjective social participation. Answers to these four  
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20 219 questions are always = 0, sometimes = 1, or never = 2. Low scores indicate increased social  
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22 220 participation. Additionally, we will use the validated tools and ones on the list of 54 tools  
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24 221 according to the systematic review<sup>53</sup> since we will only be able to pool results of those that used  
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26 222 the same tools. Validated tools will be defined as those supported by an academic reference and  
27  
28 223 evidence of their psychometric properties.<sup>32</sup> Studies using selected items, rather than the full  
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30 224 scales of validated tools, will be categorized as ‘partially validated’.<sup>32</sup>  
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39 226 Types of outcomes – The secondary outcome

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41 227 The secondary outcomes are loneliness and health-related quality of life. Loneliness will be  
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43 228 defined as unpleasant feelings experienced because one’s interactions with others do not meet  
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45 229 one’s expectations.<sup>2 25 54</sup> Any measures of loneliness will be included as long as they meet our  
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47 230 definition of loneliness.

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50 231 Commonly used instruments for loneliness are the De Jong Gierveld Loneliness Scale,<sup>55</sup> and the  
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52 232 University of California Los Angeles (UCLA) Loneliness Scale.<sup>56</sup> The De Jong Gierveld  
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54 233 Loneliness Scale<sup>55</sup> measures emotional and social loneliness and has six statements, three

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4 234 measuring emotional loneliness and three measuring social loneliness, each with three choices  
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6 235 including yes, more or less, and no. Scores range from 0-6, with 6 indicating higher loneliness.  
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9 236 The UCLA Loneliness Scale Version 3<sup>56</sup> has 20-question tool used to assess subjective feelings  
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11 237 of loneliness or social isolation. All questions are framed using “how often do you feel....” and  
12  
13 238 choices include never, rarely, sometimes, and often. Scores range from 20 to 80, with a higher  
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15 239 score indicating greater loneliness. In addition, commonly used tools for health-related quality of  
16  
17 240 life are World Health Organization Quality of Life Scale (WHOQOL-BREF),<sup>57</sup> the 36-Item  
18  
19 241 Short Form Health Survey (SF-36),<sup>58</sup> and the Duke Health Profile.<sup>59</sup> WHOQOL-BREF<sup>57</sup>  
20  
21 242 measures 26 items, including 4 domains of physical health, psychological, social relationships  
22  
23 243 and environmental. The 4 domain scores represent an individual’s perception of the quality of  
24  
25 244 life in each specific domain, and the higher the score, the higher the quality of life.<sup>57</sup> SF-36<sup>58</sup>  
26  
27 245 measures 36 items, including 8 domains of physical function, mental health, social function, role  
28  
29 246 physical, role emotional, pain, vitality, and general health. The scores are converted directly  
30  
31 247 using the weighted sum of the questions in the 8 domains, and the lower the scores, the greater  
32  
33 248 the disability.<sup>58</sup> In the converted scale of 0-100, 0 means maximum disability and 100 means no  
34  
35 249 disability.<sup>58</sup> The Duke Health Profile<sup>59</sup> measures 17 items, including 10 domains of physical,  
36  
37 250 mental, and social health, general and perceived health, self-esteem, anxiety, depression, pain,  
38  
39 251 and disability. It is self-measured in a ram item scoring within the range of 0-100 and means that  
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41 252 the higher the score, the healthier.<sup>59</sup>  
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## 254 **Search strategy**

255 Electronic databases

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

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3  
4 257 words related to study participants and study design. Electronic database searches will be  
5  
6 258 performed in MEDLINE via OVID, EMBASE, Cochrane Central Registry of Controlled Trials  
7  
8  
9 259 (CENTRAL), PsycINFO, and CINAHL to identify RCTs published on interventions for social  
10  
11 260 isolation and loneliness in older adults. The following keywords for social isolation and  
12  
13 261 loneliness alone and in combination will be searched with terms describing characteristics for  
14  
15 262 them: “social isolation”, “loneliness”, “social relationships”, “social support”, “social network”,  
16  
17 263 “social alienation, “community networks”, “social distance”, “interpersonal relations”, “friends”,  
18  
19 264 “psychosocial deprivation”, and “social participation”. Since the subject of the study is older  
20  
21 265 adults, “older adults” will also be added to the search terms. No date limit will be applied. An  
22  
23 266 experienced librarian will review our search strategies in individual databases and updated them  
24  
25 267 where needed. We will manually search reference lists of all included studies and relevant  
26  
27 268 reviews. We will limit articles to those written in English. Furthermore, in order to identify  
28  
29 269 ongoing trials, three clinical trial registries such as Clinical Trial Registry, Current Controlled  
30  
31 270 Trials, and the World Health Organization International Clinical Trials Registry Platform will be  
32  
33 271 searched. Additionally, unpublished studies will be searched through ProQuest Dissertations and  
34  
35 272 Theses, E-Thos, and Opengrey.(see online supplementary file 3)  
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#### 43 274 Data Extraction

44  
45 275 Through the electronic databases, titles and/or abstracts identified using the search strategy will  
46  
47 276 be screened for potential eligibility independently by two reviewers, and the team will obtain full  
48  
49 277 texts of any articles that either reviewer believes may be eligible. ENDNOTE X9 will  
50  
51 278 automatically filter out duplicates and one reviewer will also remove those in the step of title  
52  
53 279 and/or abstract screening. A team of two reviewers will evaluate each full text article for  
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4 280 potential eligibility. Any disagreement will be resolved by discussion or if necessary,  
5  
6 281 adjudication by a third reviewer. Two reviewers will perform data extraction independently and  
7  
8  
9 282 in duplicate. A pilot form will be tested on randomly selected studies by two reviewers to ensure  
10  
11 283 consistency in extraction form. We will extract the following information: 1) study  
12  
13 284 characteristics (design, year, duration of follow-up, recruitment settings, country, study aim, and  
14  
15 285 number of participants allocated to intervention and control); 2) participant characteristics  
16  
17 286 (sample size, eligible criteria, age, sex, participant's chronic disease, and residential settings); 3)  
18  
19 287 intervention or exposure details (type of intervention, frequency of intervention, intensity/level  
20  
21 288 of intervention, length of intervention, intervention content and a control group comparison,  
22  
23 289 format of the delivery, and information about the intervention provider). More specifically, it  
24  
25 290 will first be classified as a single or multifaceted intervention. Single intervention will have only  
26  
27 291 one intervention, while multifaceted interventions will have more than one. Then by the type of  
28  
29 292 intervention (e.g., social activities and social services, exercise programs, health services,  
30  
31 293 befriending intervention, and leisure/skill development). Each type of intervention will then be  
32  
33 294 more specifically classified. The duration (i.e., months), frequency (e.g., once or twice a week,  
34  
35 295 weekly, biweekly, or monthly), time (i.e., minutes) of the specific intervention type will be  
36  
37 296 investigated. For example, if it is an intervention of social activities, it is specifically classified  
38  
39 297 such as social engagement, social facilitation, or social support. If it is the intervention of social  
40  
41 298 engagement, the duration (e.g., 6 months), frequency (e.g., monthly), and time (e.g., 60 minutes)  
42  
43 299 of the social engagement will be investigated.; 4) methodological information (effects on main  
44  
45 300 outcomes, assessment tools, and information about validation of assessment tools); 5) results  
46  
47 301 related to effect size calculation (means or mean change, standard deviations (SDs), the  
48  
49 302 information from which SD could be derived, such as standard error or confidence interval (CI),  
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4 303 number of participants in each intervention group, measurement period, and relevant effect sizes  
5  
6 304 (e.g., odds ratio and rate ratio) with a measure of uncertainty such as standard error (SE) or 95%  
7  
8 305 CI, and/or p-value). If means or SDs are available and instead studies report SEs, CI, t-or p-  
9  
10 306 value, effect sizes will be computed based on the provided data from between group values  
11  
12 307 according to the methods described in the Cochrane Handbook for Systematic Reviews of  
13  
14 308 Interventions.<sup>60</sup> In case of disagreement in the extracted data, reviewers will come to consensus  
15  
16 309 through discussion. If a consensus cannot be reached, a third reviewer will be involved. If  
17  
18 310 possible, we will conduct an intention-to-treat analysis, but otherwise we will use the available  
19  
20 311 data (i.e., per-protocol analysis results). The agreement between the two reviewers screening title  
21  
22 312 and abstract full-text articles will be assessed by the Kappa (*k*) estimates. The agreement  
23  
24 313 between reviewers will be assessed according to the following cut-off points: 1)  $\leq 0$  as poor  
25  
26 314 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  
27  
28 315 as moderate agreement; 5) 0.61 to 0.80 as substantial agreement; 6)  $>0.80$  as almost perfect  
29  
30 316 agreement.<sup>61</sup>  
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### 39 318 Risk of bias assessment

40  
41 319 The risk of bias will be assessed by two reviewers independently. Any discrepancies on the  
42  
43 320 results of risk of bias will be resolved by the third reviewer. Risk of bias will be assessed  
44  
45 321 according to the Cochrane revised tool for assessing risk of bias in randomized trials (RoB 2)<sup>62</sup>  
46  
47 322 as follows: 1) bias arising from the randomization; 2) bias due to deviations from intended  
48  
49 323 interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; 5)  
50  
51 324 bias is selection of the reported result. The two reviewers will independently judge each domain  
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53 325 as high, low, or some concerns risk of bias.  
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## 327 **Strategy for data synthesis**

### 328 Network geometry

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

335

### 336 Methods for direct and indirect or mixed intervention comparisons

337 A standard pairwise meta-analysis through random-effects model will be conducted because the  
338 included studies are expected to differ methodologically and clinically in terms of between-study  
339 variability.<sup>64</sup> Dichotomous outcome data will be pooled and the odds ratio (OR) and the 95% CI  
340 will be reported. Continuous outcome data will be pooled and the standardized mean difference  
341 (SMD) and 95% CI will be reported for study-specific follow-up mean values. We will use  
342 followed up means instead of mean change because a mixture of the two cannot be combined  
343 using SMD in the same model. In case there are missing SDs in follow-up means, it will be  
344 assumed to be equal with SDs in baseline mean values. We will quantify heterogeneity (i.e.,  
345 between-study variability) of intervention effects within each intervention comparison using the  
346  $I^2$ <sup>65</sup> with its 95% CI. We will estimate the magnitude of the between study variance  $\tau^2$  and its  
347 95% CI by using the restricted maximum likelihood estimator and the Q-profile approach,  
348 respectively.<sup>66 67</sup> If the ratio of the actual variance ( $I^2$ ) to the total variance is 50% or more and

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4 349 the significant p-value for test of homogeneity is less than 0.10, heterogeneity of the effect size  
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6 350 will be judged to be substantial.<sup>68</sup> Subgroup analysis or meta-regression will be performed if the  
7  
8 351 studies are not available due to high heterogeneity.  
9  
10  
11 352 Regarding dealing with dependent effect sizes, several methods (e.g., Robust meta-analysis<sup>69</sup> and  
12  
13 353 Three level meta-analysis<sup>70</sup>) are discussed. If the correlation between the dependent effect sizes  
14  
15 354 is unknown, such as when multiple measures are used in a study,<sup>71</sup> a three level meta-analysis  
16  
17 355 will be performed. The three level meta-analysis is an extension of the use of two-level random-  
18  
19 356 effect models in meta-analysis<sup>70</sup> (i.e., Level 2 variance represents the difference between studies  
20  
21 357 in effect size estimates with the assumption that all studies provide independent effect sizes), in  
22  
23 358 which the dependent effect sizes will be clustered within-study at Level 2 and then the effect  
24  
25 359 between-study will be estimated at Level 3.<sup>71</sup> In other words, by modelling the within-study  
26  
27 360 dependence at Level 2 and the between-study mean effect size and variance at Level 3, where the  
28  
29 361 variance in the effect is greatest will be determined.<sup>72</sup>  
30  
31  
32 362 In addition, results of the NMA will be performed through a Bayesian statistical approach using  
33  
34 363 Markov-chain Monte Carlo (MCMC) simulation. For each NMA, the transitivity and consistency  
35  
36 364 assumptions will be preferentially assessed.<sup>73</sup> Transitivity assumptions will be assessed by  
37  
38 365 average age, percentage women, health status (e.g., chronic disease or mental health status), and  
39  
40 366 trials with low risk of bias compared to high risk of bias as potential intervention effect  
41  
42 367 modifiers, by comparing their distributions across intervention comparisons in each outcome<sup>74</sup> to  
43  
44 368 ensure that they are on average balanced. As a comparative function between each individual  
45  
46 369 intervention, the intervention contrast (i.e., mean difference or SMD, log odds for dichotomous  
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48 370 outcomes, or rate ratio for count outcomes) for the two interventions will be modeled.  
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50 371 A hierarchical Bayesian model using a non-informative prior for the intervention effect  
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4 372 parameter and between-trial variance will be used because of lack of previous evidence for social  
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6 373 isolation and loneliness.<sup>75 76</sup> Model convergence will be assessed using established methods such  
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9 374 as MCMC errors, deviance information criterion (DIC), and trace/density plot.<sup>77</sup>

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11 375 A random-effects design by intervention interaction model will be used to assess the consistency  
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13 376 assumption (i.e., whether direct and indirect evidence agree) globally for each network  
14  
15  
16 377 separately.<sup>73 78</sup> We will also assess for the consistency assumption locally, within each closed  
17  
18 378 loop, using the loop-specific approach.<sup>79 80</sup> When statistically significant inconsistency is  
19  
20 379 detected, data for potential abstraction errors will be tested.<sup>64</sup> If no data errors are identified,  
21  
22 380 direct, indirect, and mixed estimates will be separately reported.<sup>64</sup> Further, significant  
23  
24 381 inconsistency will be explored by performing meta-regression using the above mentioned  
25  
26  
27 382 potential effects modifiers.<sup>64</sup> Inconsistency tests have low power to detect true inconsistency<sup>81 82</sup>  
28  
29 383 and hence, we will assess for the transitivity assumption even in the absence of evidence for  
30  
31 384 inconsistency.

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34 385 Vague priors for all model parameters and a half-normal prior distribution for the between-study  
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36 386 SD will be assumed in all Bayesian NMA models.<sup>64</sup> The models will be run for 50,000 iterations  
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38  
39 387 to ensure model convergence, which will be checked by visual inspection of the mixing of 4  
40  
41 388 chains or by using Gelman-Rubin convergence diagnostics,<sup>83</sup> after discarding the first 5,000  
42  
43 389 iterations and thinning of 1. The posterior median values and their 95% credible intervals (CrIs)  
44  
45 390 for the relevant model parameters will be reported with intervention effects and between-study  
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47  
48 391 variance.<sup>84</sup> Each NMA estimate will be presented with a 95% prediction interval,<sup>85</sup> which  
49  
50 392 captures the magnitude of the between-study variance and indicates the interval at which the  
51  
52 393 intervention effect of future studies are expected.<sup>86</sup>

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55 394 For relative intervention ranking, the ranking probabilities for all interventions at each possible  
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4 395 rank for each intervention will be estimated.<sup>87</sup> Through the surface under the cumulative ranking  
5  
6 396 (SUCRA) curve and mean ranks, the intervention hierarchy will be defined with a cumulative  
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8 397 probability of an intervention that can be ranked first without uncertainty.<sup>88</sup> The rank-heat plot  
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10  
11 398 (<http://rh.ktss.ca/>) to visually present the intervention hierarchy across the multiple outcomes of  
12  
13 399 the study will be shown.<sup>89</sup> The higher the SUCRA value, which ranges from 0% to 100%, will  
14  
15 400 indicate the higher the likelihood of intervention<sup>90</sup> for social isolation and loneliness.  
16  
17 401 Standard pairwise meta-analyses will be conducted through the R statistical package (version  
18  
19 402 3.6.2) and the metafor package. NMA will be also conducted through the R statistical package  
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21 403 (version 3.6.2) with BUGSnet R package (version 1.0.3) for Bayesian NMA.  
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#### 27 405 Analysis of sensitivity

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29 406 According to Cochrane reviews,<sup>91</sup> the major approach to incorporating risk of bias assessments is  
30  
31 407 to restrict meta-analyses to studies at low risk of bias, or to stratify studies depending on risk of  
32  
33 408 bias. We will perform sensitivity analyses on low risk of bias and excluding the following  
34  
35 409 studies: 1) studies with high risk of bias, 2) studies with missing data, and 3) studies with  
36  
37 410 imputed data (i.e., in order to ensure that imputed research results are not one-sided in NMA) if  
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39 411 enough studies are available.  
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#### 45 413 Analysis of subgroup

46  
47 414 For multicomponent/multimodal interventions, we will perform subgroup analyses by types of  
48  
49 415 specific individual intervention. For example, the implications of “social activities combined  
50  
51 416 with exercise interventions” and “psychotherapy combined with social/health service” are  
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54 417 different even though they are categorized as multicomponent interventions.  
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7 419 Certainty of the evidence and summary of findings table  
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9 420 Through the GRADE (Grading of Recommendations Assessment, Development and Evaluation)  
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11 421 approach of NMA,<sup>92</sup> the certainty of direct, indirect and mixed NMA effect estimates for each  
12  
13 422 outcome will be assessed. The certainty of evidence of direct effect estimates for each outcome  
14  
15 423 will be assessed as follows according to the GRADE rating system:<sup>93</sup> high, moderate, low or  
16  
17 424 very low.

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19  
20 425 We will use the available loops of evidence including loops with a single common comparator  
21  
22 426 (i.e., first-order) or more than one intervening treatment (i.e., higher orders) connecting the two  
23  
24 427 interventions of the comparison of interest in order to calculate the indirect effect estimated.<sup>29</sup>  
25  
26  
27 428 For the quality of indirect evidence, the dominant first-order loop (i.e., loops with a single  
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29 429 common comparator connecting the two interventions of the comparison of interest) will be  
30  
31 430 assessed.<sup>29</sup> The quality of evidence rating for indirect comparisons will be the lower of the rating  
32  
33 431 for quality for the two direct estimates that contribute to the first-order loop of the indirect  
34  
35 432 comparison.<sup>29</sup>

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38  
39 433 In the case to use both direct and indirect evidence, the rate of NMA estimate quality will be  
40  
41 434 from the higher quality of the two.<sup>29</sup> The similarity between direct and indirect effect estimates  
42  
43 435 will be estimated in the final quality rating.<sup>29</sup> If there is any inconsistency between direct and  
44  
45 436 indirect effect estimates (i.e., it is estimated by the difference of point estimates and the extent of  
46  
47 437 overlap of 95% CIs and of direct and indirect effect estimates), the quality of the NMA effect  
48  
49 438 will be assessed.<sup>29</sup>

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## 53 440 **Patient and public involvement**

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4 441 As this study is a systematic review, patients and the public will not be directly involved.  
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6 442 However, we will consult key stakeholder groups (e.g., older adult networks and relevant service  
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9 443 provider associations) to determine the best channels through which to disseminate the results of  
10  
11 444 our study.  
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## 16 446 **DISCUSSION**

17  
18 447 As the numbers of older adults increase, so does the resulting social and economic burden of  
19  
20 448 social isolation and loneliness. There is need for evidence-based therapeutic programs to mitigate  
21  
22 449 social isolation and loneliness. A high-quality systematic review of the comparative therapeutic  
23  
24 450 effects of interventions for improving social isolation and loneliness in older adults is essential.  
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26  
27 451 To our knowledge, there are few systematic reviews and NMAs combining direct and indirect  
28  
29 452 effects of intervention for social isolation and loneliness in older adults. This study will include a  
30  
31 453 comparison of different interventions for social isolation and loneliness through not only a single  
32  
33 454 (e.g., exercise program or social/health service) intervention, but also combination (e.g., exercise  
34  
35 455 program combined with social/health service) of interventions. This study has several strengths:  
36  
37 456 1) including recent RCTs social isolation and loneliness for older adults; 2) screening rigorous  
38  
39 457 trial eligibility and collecting data from independent teams of reviews; 3) assessing credibility  
40  
41 458 and providing certainty for intervention effects, by using GRADE approach; 4) performing meta-  
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43 459 regression and subgroup analyses, consistent with the best current practice;<sup>85</sup> 5) providing  
44  
45 460 ranking intervention (i.e., the intervention sequence is determined according to their relative  
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47 461 efficacy)<sup>93</sup> for social isolation and loneliness.  
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52 462 Although this study has several strengths, there are also potential challenges and limitations.  
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54  
55 463 First, it might be difficult to interpret the effects when pooling estimates from trials using  
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4 464 different tools to measure social isolation (e.g., the Lubben Social Network Scale-6 and SSQ6)  
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6 465 and loneliness (e.g., the De Jong Gierveld Loneliness Scale and UCLA loneliness scale)  
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8  
9 466 combined with high heterogeneity (i.e., differences in effect estimates between studies that  
10  
11 467 evaluated the same comparison).<sup>93</sup> Further, social isolation has a variety of surrogate outcomes  
12  
13 468 such as social support and social network. Such surrogate outcomes might down rate the  
14  
15 469 directness identified through the GRADE approach<sup>93</sup> because it means that an outcome of  
16  
17 470 interest (i.e., social isolation) might differ from the measured in surrogate outcomes (i.e., social  
18  
19 471 support and social network). Additionally, dealing with multicomponent interventions in NMA is  
20  
21 472 a methodological challenge because single or combined (i.e., consisting of several possibly  
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23 473 interacting components) interventions are different nodes in the network.<sup>94</sup>  
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26  
27 474 It is expected that the findings of this study will provide evidence for clinicians (e.g., when  
28  
29 475 selecting which interventions are best for older adults), health policy makers (e.g., when making  
30  
31 476 decision which programs or services should be supported) as well as stakeholders (e.g., when  
32  
33 477 operating how programs effectively) managing social isolation and loneliness in community  
34  
35 478 dwelling older adults and for older adults in choosing therapeutic options.  
36  
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40

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42  
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49  
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52  
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54  
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critically revised the protocol draft and the present manuscript. All authors read and approved the final manuscript.

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For peer review only

**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.....	2
Supplementary file 2: PICOS statement.....	6
Supplementary file 3: Search strategy.....	9

For peer review only

## 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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed</i> . <i>Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity</i> . <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> . <sub>2</sub>	5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
<b>METHODS</b>			
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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> . <sub>2</sub>	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
<b>Geometry of the network</b>	<b>S1</b>	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). <i>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.</i>	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: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	17-18
<b>Assessment of Inconsistency</b>	<b>S2</b>	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: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	19
<b>RESULTS†</b>			
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
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
<b>Summary of network geometry</b>	<b>S4</b>	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. <i>Modified approaches may be needed to deal with information from larger networks.</i>	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g.</i>	n/a

		<i>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.</i>	
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> 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, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	n/a
<b>DISCUSSION</b>			
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). <i>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).</i>	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
<b>FUNDING</b>			
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	<ul style="list-style-type: none"> <li><input type="checkbox"/> Community-dwelling older adults <math>\geq 60</math> years of age (If mean or median age of participants is 60 year or older, it can be included.)</li> <li><input type="checkbox"/> 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.)</li> <li><input type="checkbox"/> A mild or moderate dementia or cognitive dysfunction</li> </ul>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Adults <math>&lt; 60</math> years of age</li> <li><input type="checkbox"/> Not community residing (inpatients, nursing home, hospital wards, or long-term care facilities)</li> <li><input type="checkbox"/> Dementia or moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE)<math>&lt;24</math>, Montreal Cognitive Assessment (MoCA) <math>&lt;26</math>, or Short Portable Mental Status Questionnaire (SPMSQ)<math>&gt;6</math>)</li> <li><input type="checkbox"/> Chronic diseases related to death or serious risk: cancer, AIDS (HIV), chronic heart failure, recent surgery or transplant or intractable rare disease</li> <li><input type="checkbox"/> Unstable diseases such as bipolar disorder, active psychosis, or suicidal plans</li> <li><input type="checkbox"/> Caregivers</li> </ul>
Interventions	<ol style="list-style-type: none"> <li>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</li> <li>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-</li> </ol>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Pharmaceutical interventions including medications and nutritional supplements (vit D, calcium, or protein) for mental health, anxiety, or depression</li> </ul>

	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	<input type="checkbox"/> 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	<input type="checkbox"/> Social or family wellbeing <input type="checkbox"/> Happiness <input type="checkbox"/> Satisfaction with life <input type="checkbox"/> Depression



short version of the Medical Outcomes Study <sup>17</sup> 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	<input type="checkbox"/> All RCTs or quasi-RCTs regardless of sample size	<input type="checkbox"/> Non-RCTs <input type="checkbox"/> 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	<input type="checkbox"/> Community settings	
Language	<input type="checkbox"/> English	<input type="checkbox"/> 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*

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28	26 OR 27
29	25 AND 28

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## 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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted.</i>	5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
<b>METHODS</b>			
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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i>	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
<b>Geometry of the network</b>	<b>S1</b>	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). <i>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.</i>	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: <ul style="list-style-type: none"> <li>• Handling of multi-arm trials;</li> <li>• Selection of variance structure;</li> <li>• Selection of prior distributions in Bayesian analyses; and</li> <li>• Assessment of model fit.</li> </ul>	17-18
<b>Assessment of Inconsistency</b>	<b>S2</b>	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: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• Alternative formulations of the treatment network; and</li> <li>• Use of alternative prior distributions for Bayesian analyses (if applicable).</li> </ul>	19
<b>RESULTS†</b>			
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
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
<b>Summary of network geometry</b>	<b>S4</b>	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. <i>Modified approaches may be needed to deal with information from larger networks.</i>	n/a
Synthesis results	21		Present results of each meta-analysis done, including confidence/credible intervals. <i>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.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	n/a
<b>Exploration for inconsistency</b>	<b>S5</b>		Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> 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, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	n/a
<b>DISCUSSION</b>				
Summary 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). <i>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).</i>	21-22
Conclusions	26		Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
<b>FUNDING</b>				
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

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2  
3 from the PRISMA statement.

4 † Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this  
5 section.  
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# 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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<b>Primary Subject Heading</b>:	Mental health
Secondary Subject Heading:	Geriatric medicine, Public health, Research methods
Keywords:	MENTAL HEALTH, GERIATRIC MEDICINE, STATISTICS & RESEARCH METHODS

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4 **1 Management of Social Isolation and Loneliness in Community Dwelling Older Adults:**  
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6 **2 Protocol for a Network Meta-analysis of Randomized Controlled Trials**  
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11 4 Ahreum Lee MPH,<sup>1,2</sup> Caitlin McArthur PT, PhD,<sup>2,3</sup> Areti Angeliki Veroniki PhD,<sup>4,5,6</sup> Monika Kastner PhD,<sup>7</sup>  
12  
13 <sup>8,9</sup> George Ioannidis PhD,<sup>2,3</sup> Lauren E. Griffith PhD,<sup>1</sup> Lehana Thabane PhD,<sup>1,2,10</sup> Jonathan D. Adachi MD,<sup>2</sup>  
14  
15 <sup>3</sup> and Alexandra Papaioannou MD<sup>1,2,3,\*</sup>  
16  
17  
18  
19

20 <sup>1</sup>Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario,  
21  
22 Canada  
23

24 <sup>2</sup>GERAS Centre for Aging Research, Hamilton, Ontario, Canada  
25

26 <sup>3</sup>Department of Medicine, McMaster University, Hamilton, Ontario, Canada  
27

28 <sup>4</sup>Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece  
29

30 <sup>5</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada  
31

32 <sup>6</sup>Institute of Reproductive and Development Biology, Department of Surgery & Cancer, Faculty of  
33  
34 Medicine, Imperial College, London, United Kingdom  
35

36 <sup>7</sup>Knowledge Translation and Implementation, Research and Innovation, North York General Hospital,  
37  
38 Toronto, Ontario, Canada  
39

40 <sup>8</sup>Health Service Research, Institute of Health Policy, Management and Evaluation, University of Toronto,  
41  
42 Toronto, Ontario, Canada  
43

44 <sup>9</sup>Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada  
45

46 <sup>10</sup>Biostatistics Unit, St Joseph's Healthcare Hamilton, Ontario, Canada  
47

48  
49 22 Emails: [leea94@mcmaster.ca](mailto:leea94@mcmaster.ca); [mcarthurc@hhsc.ca](mailto:mcarthurc@hhsc.ca); [averoniki@uoi.gr](mailto:averoniki@uoi.gr); [monika.kastner@nygh.on.ca](mailto:monika.kastner@nygh.on.ca);

50  
51 23 [ioannidis@hhsc.ca](mailto:ioannidis@hhsc.ca); [griffith@mcmaster.ca](mailto:griffith@mcmaster.ca); [thabal@mcmaster.ca](mailto:thabal@mcmaster.ca); [jd.adachi@sympatico.ca](mailto:jd.adachi@sympatico.ca);

52  
53 24 [papaioannou@hhsc.ca](mailto:papaioannou@hhsc.ca)  
54

55 25 ORCID IDs: Ahreum Lee 0000-0003-0882-6256; Caitlin McArthur 0000-0001-9985-2796; Areti Angeliki  
56  
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26 Veroniki 0000-0001-6388-4825; Monika Kastner 0000-0002-2838-7417; George Ioannidis 0000-0001-  
27 6956-5737; Lauren E. Griffith 0000-0002-2794-9692; Lehana Thabane 0000-0003-0355-9734; Jonathan  
28 D. Adachi 0000-0001-9142-2767; Alexandra Papaioannou 0000-0001-9412-0932

30 **\*Corresponding Author:** Alexandra Papaioannou; GERAS Centre for Aging Research; Department of  
31 Medicine, McMaster University, Hamilton ON, Canada  
32 Email: [papaioannou@hhsc.ca](mailto:papaioannou@hhsc.ca)  
33 Tel: +1-905-521-2100 ext. 12405

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## 37 **ABSTRACT**

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

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

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



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4 60 **Trial registration number** CRD42020155789

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6 61 **Keywords** Social isolation, Loneliness, Older adults, Systematic review, Randomized controlled  
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9 62 trials, Network meta-analysis  
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13 64 **Strengths and limitations of this study**

- 15 65 ▶ This study will be the first systematic review and network meta-analysis about social  
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17 isolation and loneliness for community-dwelling older adults.  
18 66  
19 67 ▶ With the growing aging population systematic review strategies are needed inform which  
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21 interventions are most effective for alleviating social isolation and loneliness at both an  
22 68  
23 individual and community level.  
24 69  
25 70 ▶ This study will provide a rank order list, by their relative efficacy, of interventions for social  
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27 isolation and loneliness through the intervention sequence.  
28 71  
29 72 ▶ It might be difficult to interpret the effects when pooling estimates from trials using different  
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31 tools to measure social isolation and loneliness combined with high heterogeneity.  
32 73  
33 74 ▶ Given that single or combined (i.e., consisting of several possibly interacting components)  
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35 interventions are different nodes in the network, an issue of multicomponent interventions in  
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37 NMA may be a methodological challenge.  
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## 78 INTRODUCTION

79 Social isolation is an objective and quantitative reflection of reduced social network size and  
80 limited social contact. This phenomenon is especially important to examine for older adults,  
81 when there are often decreased economic resources, increased mobility impairment, and the  
82 death of contemporaries.<sup>1</sup> Loneliness is a psychological embodiment of social isolation that  
83 demonstrates limited frequency and intimacy of social contacts and discrepancies between  
84 relationships and desired relationships.<sup>2</sup> With loneliness, social loneliness means a lack of  
85 feelings of social integration, and emotional loneliness is the feeling one feels when one does not  
86 have an attachment figure.<sup>3</sup> According to the 2016 Statistics Canada report, approximately 0.75  
87 million older adults aged 60 years or older experienced social isolation and loneliness.<sup>4</sup> A recent  
88 national survey reported that 40% of older adults reported being lonely<sup>5</sup> and 24% reported being  
89 socially isolated.<sup>6</sup> In particular, older adults are more vulnerable because their meaningful social  
90 contacts are eventually replaced by family and close friends after retirement from work.<sup>7</sup>  
91 Social isolation and loneliness in older adults are significant public health issues. Both social  
92 isolation and loneliness are associated with increased risk of cardiovascular disease,<sup>8</sup>  
93 hypertension,<sup>9-12</sup> inflammatory responses to stress,<sup>13-16</sup> decreased quality of life, physical and  
94 mental health,<sup>1 17</sup> and mortality.<sup>18-23</sup> As age increases, approximately one half and one third of  
95 older adults experience social isolation<sup>24</sup> and loneliness,<sup>25 26</sup> respectively. Previous studies  
96 examining the efficacy of physical activity interventions on social isolation and loneliness  
97 demonstrate inconsistent effects.<sup>27</sup> Physical activity interventions improve social functioning,  
98 whereas they have no efficacy on loneliness, social support and social networks.<sup>28</sup> Since clinical  
99 trials and previous traditional meta-analyses assessed the relative efficacy of two interventions at  
100 a time,<sup>29</sup> the relative efficacy of different interventions have not been explored.

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4 101 Regarding the effect of other interventions, one systematic review showed that two interventions  
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6 102 (i.e., group tai-chi and facilitated group discussion) alleviated loneliness but did not improve  
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9 103 quality of life. On the other hands, a physical/leisure activity improved quality of life but not  
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11 104 social support.<sup>27</sup> Another systematic review suggested that educational interventions for social  
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13 105 networks maintenance and enhancement for alleviating loneliness.<sup>30</sup> Additionally, two  
14  
15 106 systematic reviews<sup>31 32</sup> showed that social activity or support interventions in group format  
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18 107 reduce social isolation and loneliness. In contrast to the findings from two reviews, one  
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20 108 integrative study<sup>33</sup> found that solitary or one-to-one intervention such as solitary pet intervention,  
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22 109 solitary video-conference and computer/internet use was more effective.  
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25 110 A recent review<sup>34</sup> suggested a new approach for interventions for social isolation and loneliness.  
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27 111 Since social isolation and loneliness are complex constructs with various dimensions, it is  
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29 112 suggested that the approach should be taken to consider various predictors of them (e.g.,  
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31 113 relationship provisions).<sup>34</sup> For example, emotional loneliness (i.e., micro level) can be alleviated  
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33 114 through interventions dealing with cognition, and evaluation on a personal level.<sup>7 35 36</sup> Social  
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35 115 loneliness (i.e., meso level) may be mitigated through interventions targeting increasing social  
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37 116 networks and connectedness with community activities or social media.<sup>37</sup> As an approach of a  
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39 117 macro level, programs that improve general health such as treating hearing loss can be  
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42 118 implemented.<sup>38</sup> These factors have all been shown to be social determinants of loneliness, well-  
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44 119 being, and health.<sup>30 31 39 40</sup>  
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48 120 Network meta-analysis (NMA) is required to provide effect estimates for all comparisons by  
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50 121 considering the relative efficacy of multiple intervention alternatives.<sup>41 42</sup> There is some evidence  
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52 122 that several interventions such as physical activity, social activities, social or health services,  
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54 123 psychotherapy, befriending interventions, and leisure or skill development intervention may  
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4 124 reduce social isolation and loneliness. A systematic review and NMA are required to incorporate  
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6 125 recent studies and compare the direct, indirect as well as mixed interventions for social isolation  
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9 126 and loneliness.

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11 127 The objective of this study is to determine the comparative efficacy of interventions to alleviate  
12  
13 128 social isolation and loneliness in community dwelling older adults aged 60 years or older

14  
15  
16 129 Research question is “What are the comparative efficacy of interventions to alleviate social  
17  
18 130 isolation and loneliness in community dwelling older adults aged 60 years or older?”

19  
20 131 Since social isolation and loneliness are concepts that have been understood and defined in many  
21  
22 132 different ways, interventions often vary. Nevertheless, previously most studies conducted only  
23  
24 133 direct treatment comparison through pairwise meta-analysis. However, multiple comparisons of  
25  
26 134 interventions are necessary in line with the characteristics of social isolation and loneliness. We  
27  
28 135 expect to provide the ranking comparative efficacy of interventions for social isolation and  
29  
30 136 loneliness.

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## 35 36 138 **METHODS AND ANALYSIS**

### 37 38 139 **Protocol and registration**

39  
40  
41 140 This study will follow the Preferred Reporting Items for The PRISMA Extension Statement for  
42  
43 141 Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care  
44  
45 142 Interventions.<sup>43</sup> The completed PRISMA NMA checklist is provided in online supplementary file  
46  
47  
48 143 1. The protocol of this NMA has been submitted for registration in PROSPERO (registration  
49  
50 144 number CRD42020155789).

51  
52  
53 145

### 54 55 146 **Study selection criteria**

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4 147 Types of studies to be Included  
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6 148 We will include randomized controlled studies (RCTs) that assess the efficacy of different  
7  
8 149 interventions to alleviate social isolation and loneliness in older adults aged 60 years or older  
9  
10  
11 150 living in the community. Observational studies including prospective, retrospective cohort, case-  
12  
13 151 control, nested case-control, case cohort, cross-sectional, and simulation, comments, editorials,  
14  
15 152 letters to the editor, case series, conference abstract, and animal studies will be excluded. Studies  
16  
17 153 without information of social isolation or loneliness will be excluded (see online supplementary  
18  
19 154 file 2).  
20  
21  
22  
23  
24

25 156 Types of participants  
26

27 157 Community-dwelling older adults aged 60 years or older will be included in this study. If the  
28  
29 158 mean or median (depending on what the original authors report) age of participants is 60 years or  
30  
31 159 older, it will be included. RCTs including older adults not residing in the community (e.g.,  
32  
33 160 hospitalized patients or long-term care homes) will be excluded. Older adults from institutional  
34  
35 161 settings may have limited contact with friends or family, which could increase the risk of  
36  
37 162 loneliness.<sup>44 45</sup> RCTs including older adults who are healthy or who have chronic disease (e.g.,  
38  
39 163 hypertension and diabetes) will be included. RCTs must include older adults who are mobile  
40  
41 164 (i.e., able to walk independently with or without an assistive aid or can self-propel wheelchair).  
42  
43 165 Participants without dementia, moderate to severe cognitive dysfunction (Mini-Mental State  
44  
45 166 Examination (MMSE) <24, Montreal Cognitive Assessment (MoCA) <26, or Short Portable  
46  
47 167 Mental Status Questionnaire (SPMSQ) >6) will be included. Vulnerable people with dementia or  
48  
49 168 severe cognitive dysfunction might be more socially isolated or lonely due to lack of contact  
50  
51 169 with friends or family,<sup>28</sup> which may confound the measurement of social functioning and  
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4 170 loneliness.<sup>28</sup> We will exclude the following severe diseases as they might make it difficult to  
5  
6 171 identify the efficacy of alleviating social isolation and loneliness: cancer, AIDS (HIV), chronic  
7  
8 172 heart failure, recent surgery, dialysis, transplant, or intractable rare disease. Because patients  
9  
10 173 with such severe diseases need intensive treatment for the diseases, it may be difficult to identify  
11  
12 174 whether efficacy from the intervention for social isolation and loneliness or from the intensive  
13  
14 175 treatment for severe diseases. In addition, older adults experiencing unstable mental health  
15  
16 176 disorders such as bipolar disorder, active psychosis, or suicidal plans will be excluded because  
17  
18 177 these factors could work as confounders for the efficacy on social isolation or loneliness. (see  
19  
20 178 online supplementary file 2).  
21  
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25 179

26  
27 180 Types of interventions

28  
29 181 RCTs will examine one or more of the following interventions: 1) social activities and social or  
30  
31 182 recreational services such as social engagement including social involvement and social  
32  
33 183 participation, social facilitation, social support including emotional instrumental and  
34  
35 184 informational support, psychotherapy (e.g., counselling therapy, music, art or animal  
36  
37 185 intervention) and education program; 2) exercise programs such as group exercise (e.g., tai-chi,  
38  
39 186 aerobic or yoga class) and one-to-one or individual exercise in a gym or at home, web, or  
40  
41 187 telephoned-based; 3) health services such as health care provisions including care management,  
42  
43 188 home visits from nurses or other professionals; 4) befriending interventions such as charity-  
44  
45 189 funded friendship clubs and friendship enrichment programs; 5) leisure or skill development  
46  
47 190 interventions such as gardening programs, computer or internet use, voluntary work, and  
48  
49 191 holiday; 6) multifaceted interventions including any combination of intervention (e.g., social  
50  
51 192 activities combined with exercise programs, social/health support combined with  
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1  
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4 193 psychotherapy).

5  
6 194 Comparators will be an inactive control group such as usual care, placebo intervention or no  
7  
8  
9 195 intervention (i.e., it means any comparison targets that can compare the results of post  
10  
11 196 interventions or follow-up outcomes for the intervention group). .

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15  
16 198 Types of outcomes – The primary outcomes

17  
18 199 Because social isolation and loneliness not only are intricately related but also distinct concepts  
19  
20 200 that are frequently used interchangeably,<sup>46</sup> data for both social isolation and loneliness will be  
21  
22 201 included.

23  
24  
25 202 Social isolation will be defined as an objective lack of contact with appropriate quality or  
26  
27 203 quantity or a lack of social encounters.<sup>31 47 48</sup> The following outcomes for social isolation will be  
28  
29 204 included: social support, social networks such as network size, frequency of contact with  
30  
31 205 network members, social function, and social participation. Any measures of social isolation,  
32  
33 206 social support, social networks, social function and social participation will be included as long  
34  
35 207 as they assess social isolation based on our definition.

36  
37  
38  
39 208 Commonly used instruments for social isolation are the Lubben Social Network Scale-6<sup>49</sup> for  
40  
41 209 social network, the Revised Social Support Questionnaire (SSQ6)<sup>50</sup> and the Multidimensional  
42  
43 210 Scale of Perceived Social Support<sup>51</sup> for social support, and the Subjective Social Participation  
44  
45 211 Index<sup>52</sup> for social participation. The Lubben Social Network Scale-6<sup>49</sup> for social network  
46  
47 212 measures social isolation by measuring frequency, size, and closeness of contacts of the  
48  
49  
50 213 respondent's social network by assessing the perceived level of support they get from friends and  
51  
52 214 families. Scoring is as follows: 0 = none, 1 = one, 2 = two 3 = three or four, 4 = five to eight, 5 =  
53  
54  
55 215 nine or more. Total scores from 0 to 30 with higher scores indicating larger social networks. The

1  
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4 216 SSQ6<sup>50</sup> for social support has six item measure of social support wherein respondents indicate  
5  
6 217 the number of people they feel they have available to provide support in six areas. The  
7  
8 218 Multidimensional Scale of Perceived Social Support<sup>51</sup> for social support has 12-item scale that is  
9  
10 219 broken into three factor groups (i.e., family, friends, and significant other). This scale is scored  
11  
12 220 on a 1 (very strongly disagree) to 7 (very strongly agree) Likert-type scale. Higher scores  
13  
14 221 indicate high levels of social support. The subjective Social Participation Index<sup>52</sup> for social  
15  
16 222 participation has a 15-question scale broken into three “Factors” – perception of social support,  
17  
18 223 use of new technologies, and index of subjective social participation. Answers to these four  
19  
20 224 questions are always = 0, sometimes = 1, or never = 2. Low scores indicate increased social  
21  
22 225 participation. Additionally, we will also include the 54 tools that measure social isolation and  
23  
24 226 loneliness that are described and listed in the systematic review.<sup>53</sup> Validated tools will be defined  
25  
26 227 as those supported by an academic reference and evidence of their psychometric properties.<sup>32</sup>  
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34 229 Types of outcomes – The secondary outcome

35  
36 230 The secondary outcomes are loneliness and health-related quality of life. Loneliness will be  
37  
38 231 defined as unpleasant feelings experienced because one’s interactions with others do not meet  
39  
40 232 one’s expectations.<sup>2 25 54</sup> Any measures of loneliness will be included as long as they meet our  
41  
42 233 definition of loneliness.

43  
44 234 Commonly used instruments for loneliness are the De Jong Gierveld Loneliness Scale,<sup>55</sup> and the  
45  
46 235 University of California Los Angeles (UCLA) Loneliness Scale.<sup>56</sup> The De Jong Gierveld  
47  
48 236 Loneliness Scale<sup>55</sup> measures emotional and social loneliness and has six statements, three  
49  
50 237 measuring emotional loneliness and three measuring social loneliness, each with three choices  
51  
52 238 including yes, more or less, and no. Scores range from 0-6, with 6 indicating higher loneliness.  
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4 239 The UCLA Loneliness Scale Version 3<sup>56</sup> has 20-question tool used to assess subjective feelings  
5  
6 240 of loneliness or social isolation. All questions are framed using “how often do you feel....” and  
7  
8  
9 241 choices include never, rarely, sometimes, and often. Scores range from 20 to 80, with a higher  
10  
11 242 score indicating greater loneliness. In addition, commonly used tools for health-related quality of  
12  
13 243 life are EQ-5D by the EuroQol Group,<sup>57</sup> World Health Organization Quality of Life Scale  
14  
15 244 (WHOQOL-BREF),<sup>58</sup> the 36-Item Short Form Health Survey (SF-36),<sup>59</sup> and the Duke Health  
16  
17 245 Profile.<sup>60</sup> EQ-5D<sup>57</sup> represents the best and worst states with five dimensions of measurement,  
18  
19  
20 246 such as mobility, self-care, usual activities, pain/discomfort and anxiety/depression, on a scale of  
21  
22 247 100 (best) and 0 (worst), indicating how good people’s health is today. WHOQOL-BREF<sup>58</sup>  
23  
24 248 measures 26 items, including 4 domains of physical health, psychological, social relationships  
25  
26  
27 249 and environmental. The 4 domain scores represent an individual’s perception of the quality of  
28  
29 250 life in each specific domain, and the higher the score, the higher the quality of life.<sup>58</sup> SF-36<sup>59</sup>  
30  
31 251 measures 36 items, including 8 domains of physical function, mental health, social function, role  
32  
33 252 physical, role emotional, pain, vitality, and general health. The scores are converted directly  
34  
35  
36 253 using the weighted sum of the questions in the 8 domains, and the lower the scores, the greater  
37  
38 254 the disability.<sup>59</sup> In the converted scale of 0-100, 0 means maximum disability and 100 means no  
39  
40 255 disability.<sup>59</sup> The Duke Health Profile<sup>60</sup> measures 17 items, including 10 domains of physical,  
41  
42  
43 256 mental, and social health, general and perceived health, self-esteem, anxiety, depression, pain,  
44  
45 257 and disability. It is self-measured in a ram item scoring within the range of 0-100 and means that  
46  
47 258 the higher the score, the healthier.<sup>60</sup>  
48  
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50 259

## 52 260 **Search strategy**

54  
55 261 Electronic databases

1  
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3  
4 262 The search strategy will be developed using a combination of controlled vocabulary and free-text  
5  
6 263 words related to study participants and study design. Electronic database searches will be  
7  
8 264 performed in MEDLINE via OVID (from 1946 to Nov. 20, 2019), EMBASE (from 1974 to Nov.  
9  
10 265 20, 2019), Cochrane Central Registry of Controlled Trials (CENTRAL) (to Nov. 20, 2019),  
11  
12 266 PsycINFO (from 1806 to Nov. 20, 2019), and CINAHL (to Nov. 20, 2019) to identify RCTs  
13  
14 267 published on interventions for social isolation and loneliness in older adults. The following  
15  
16 268 keywords for social isolation and loneliness alone and in combination will be searched with  
17  
18 269 terms describing characteristics for them: “social isolation”, “loneliness”, “social relationships”,  
19  
20 270 “social support”, “social network”, “social alienation”, “community networks”, “social distance”,  
21  
22 271 “interpersonal relations”, “friends”, “psychosocial deprivation”, and “social participation”. Since  
23  
24 272 the subject of the study is older adults, “older adults” will also be added to the search terms. No  
25  
26 273 date limit will be applied. An experienced librarian will review our search strategies in individual  
27  
28 274 databases and updated them where needed. We will manually search reference lists of all  
29  
30 275 included studies and relevant reviews. We will limit articles to those written in English.  
31  
32 276 Furthermore, in order to identify ongoing trials, three clinical trial registries such as Clinical  
33  
34 277 Trial Registry, Current Controlled Trials, and the World Health Organization International  
35  
36 278 Clinical Trials Registry Platform will be searched. Additionally, unpublished studies will be  
37  
38 279 searched through ProQuest Dissertations and Theses, E-Thos, and Opengrey. (see online  
39  
40 280 supplementary file 3)  
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## 50 282 Data Extraction

51  
52 283 Through the electronic databases, titles and/or abstracts identified using the search strategy will  
53  
54 284 be screened for potential eligibility independently by two reviewers, and the team will obtain full  
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3  
4 285 texts of any articles that either reviewer believes may be eligible. ENDNOTE X9 will  
5  
6 286 automatically filter out duplicates and one reviewer will also remove those in the step of title  
7  
8  
9 287 and/or abstract screening. A team of two reviewers will evaluate each full text article for  
10  
11 288 potential eligibility. Any disagreement will be resolved by discussion or if necessary,  
12  
13 289 adjudication by a third reviewer. Two reviewers will perform data extraction independently and  
14  
15 290 in duplicate. A pilot form will be tested on randomly selected studies by two reviewers to ensure  
16  
17 291 consistency in extraction form. We will extract the following information: 1) study  
18  
19 292 characteristics (design, year, duration of follow-up, recruitment settings, country, study aim, and  
20  
21 293 number of participants allocated to intervention and control); 2) participant characteristics  
22  
23 294 (sample size, eligible criteria, age, sex, participant's chronic disease, and residential settings); 3)  
24  
25 295 intervention or exposure details (type of intervention, frequency of intervention, intensity/level  
26  
27 296 of intervention, length of intervention, intervention content and a control group comparison,  
28  
29 297 format of the delivery, and information about the intervention provider). More specifically, it  
30  
31 298 will first be classified as a single or multifaceted intervention. Single intervention will have only  
32  
33 299 one intervention, while multifaceted interventions will have more than one. Then by the type of  
34  
35 300 intervention (e.g., social activities and social services, exercise programs, health services,  
36  
37 301 befriending intervention, and leisure/skill development). Each type of intervention will then be  
38  
39 302 more specifically classified. The duration (i.e., months), frequency (e.g., once or twice a week,  
40  
41 303 weekly, biweekly, or monthly), time (i.e., minutes) of the specific intervention type will be  
42  
43 304 investigated. For example, if it is an intervention of social activities, it is specifically classified  
44  
45 305 such as social engagement, social facilitation, or social support. If it is the intervention of social  
46  
47 306 engagement, the duration (e.g., 6 months), frequency (e.g., monthly), and time (e.g., 60 minutes)  
48  
49 307 of the social engagement will be investigated.; 4) methodological information (effects on main  
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4 308 outcomes, assessment tools, and information about validation of assessment tools); 5) results  
5  
6 309 related to effect size calculation (means or mean change, standard deviations (SDs), the  
7  
8 310 information from which SD could be derived, such as standard error or confidence interval (CI),  
9  
10 311 number of participants in each intervention group, measurement period, and relevant effect sizes  
11  
12 312 (e.g., odds ratio and rate ratio) with a measure of uncertainty such as standard error (SE) or 95%  
13  
14 313 CI, and/or p-value). If means or SDs are available and instead studies report SEs, CI, t-or p-  
15  
16 314 value, effect sizes will be computed based on the provided data from between group values  
17  
18 315 according to the methods described in the Cochrane Handbook for Systematic Reviews of  
19  
20 316 Interventions.<sup>61</sup> In case of disagreement in the extracted data, reviewers will come to consensus  
21  
22 317 through discussion. If a consensus cannot be reached, a third reviewer will be involved. If  
23  
24 318 possible, we will conduct an intention-to-treat analysis, but otherwise we will use the available  
25  
26 319 data (i.e., per-protocol analysis results). The agreement between the two reviewers screening title  
27  
28 320 and abstract full-text articles will be assessed by the Kappa (*k*) estimates. The agreement  
29  
30 321 between reviewers will be assessed according to the following cut-off points: 1)  $\leq 0$  as poor  
31  
32 322 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  
33  
34 323 as moderate agreement; 5) 0.61 to 0.80 as substantial agreement; 6)  $> 0.80$  as almost perfect  
35  
36 324 agreement.<sup>62</sup>  
37  
38  
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41  
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43  
44

#### 325 326 Risk of bias assessment

327 The risk of bias will be assessed by two reviewers independently. Any discrepancies on the  
328 results of risk of bias will be resolved by the third reviewer. Risk of bias will be assessed  
329 according to the Cochrane revised tool for assessing risk of bias in randomized trials (RoB 2)<sup>63</sup>  
330 as follows: 1) bias arising from the randomization; 2) bias due to deviations from intended  
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4 331 interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; 5)  
5  
6 332 bias is selection of the reported result. The two reviewers will independently judge each domain  
7  
8  
9 333 as high, low, or some concerns risk of bias.  
10

11 334

### 13 335 **Strategy for data synthesis**

#### 15 336 Network geometry

16 337 A qualitative description of network geometry will be provided and accompanied by a network  
17  
18 338 plot,<sup>64</sup> allowing us to also assess for intervention connectedness. The quantitative metrics  
19  
20 339 assessing features of network geometry such as diversity (i.e., number of interventions and how  
21  
22 340 frequent they are examined) and co-occurrence (i.e., whether certain intervention comparisons  
23  
24 341 are more or less common and the extent of comparisons between different interventions) will be  
25  
26 342 evaluated.<sup>64</sup>  
27  
28  
29  
30

31 343

#### 33 344 Methods for direct and indirect or mixed intervention comparisons

34 345 A standard pairwise meta-analysis through random-effects model will be conducted because the  
35  
36 346 included studies are expected to differ methodologically and clinically in terms of between-study  
37  
38 347 variability.<sup>65</sup> Dichotomous outcome data will be pooled and the odds ratio (OR) and the 95% CI  
39  
40 348 will be reported. Continuous outcome data will be pooled and the standardized mean difference  
41  
42 349 (SMD) and 95% CI will be reported for study-specific follow-up mean values. We will use  
43  
44 350 followed up means instead of mean change because a mixture of the two cannot be combined  
45  
46 351 using SMD in the same model. In case there are missing SDs in follow-up means, it will be  
47  
48 352 assumed to be equal with SDs in baseline mean values. We will quantify heterogeneity (i.e.,  
49  
50 353 between-study variability) of intervention effects within each intervention comparison using the  
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4 354  $I^2$  <sup>66</sup> with its 95% CI. We will estimate the magnitude of the between study variance  $\tau^2$  and its  
5  
6 355 95% CI by using the restricted maximum likelihood estimator and the Q-profile approach,  
7  
8 356 respectively.<sup>67 68</sup> If the ratio of the actual variance ( $I^2$ ) to the total variance is 50% or more and  
9  
10 357 the significant p-value for test of homogeneity is less than 0.10, heterogeneity of the effect size  
11  
12 358 will be judged to be substantial.<sup>69</sup> Subgroup analysis or meta-regression will be performed if the  
13  
14 359 studies are not available due to high heterogeneity.  
15  
16 360 Regarding dealing with dependent effect sizes, several methods (e.g., Robust meta-analysis<sup>70</sup> and  
17  
18 361 Three level meta-analysis<sup>71</sup>) are discussed. If the correlation between the dependent effect sizes  
19  
20 362 is unknown, such as when multiple measures are used in a study,<sup>72</sup> a three level meta-analysis  
21  
22 363 will be performed. The three level meta-analysis is an extension of the use of two-level random-  
23  
24 364 effect models in meta-analysis<sup>71</sup> (i.e., Level 2 variance represents the difference between studies  
25  
26 365 in effect size estimates with the assumption that all studies provide independent effect sizes), in  
27  
28 366 which the dependent effect sizes will be clustered within-study at Level 2 and then the effect  
29  
30 367 between-study will be estimated at Level 3.<sup>72</sup> In other words, by modelling the within-study  
31  
32 368 dependence at Level 2 and the between-study mean effect size and variance at Level 3, where the  
33  
34 369 variance in the effect is greatest will be determined.<sup>73</sup>  
35  
36 370 In addition, results of the NMA will be performed through a Bayesian statistical approach using  
37  
38 371 Markov-chain Monte Carlo (MCMC) simulation. For each NMA, the transitivity and consistency  
39  
40 372 assumptions will be preferentially assessed.<sup>74</sup> Transitivity assumptions will be assessed by  
41  
42 373 average age, percentage women, health status (e.g., chronic disease or mental health status), and  
43  
44 374 trials with low risk of bias compared to high risk of bias as potential intervention effect  
45  
46 375 modifiers, by comparing their distributions across intervention comparisons in each outcome<sup>75</sup> to  
47  
48 376 ensure that they are on average balanced. As a comparative function between each individual  
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4 377 intervention, the intervention contrast (i.e., mean difference or SMD, log odds for dichotomous  
5  
6 378 outcomes, or rate ratio for count outcomes) for the two interventions will be modeled.  
7  
8  
9 379 A hierarchical Bayesian model using a non-informative prior for the intervention effect  
10  
11 380 parameter and between-trial variance will be used because of lack of previous evidence for social  
12  
13 381 isolation and loneliness.<sup>76 77</sup> Model convergence will be assessed using established methods such  
14  
15 382 as MCMC errors, deviance information criterion (DIC), and trace/density plot.<sup>78</sup>  
16  
17  
18 383 A random-effects design by intervention interaction model will be used to assess the consistency  
19  
20 384 assumption (i.e., whether direct and indirect evidence agree) globally for each network  
21  
22 385 separately.<sup>74 79</sup> We will also assess for the consistency assumption locally, within each closed  
23  
24 386 loop, using the loop-specific approach.<sup>80 81</sup> When statistically significant inconsistency is  
25  
26 387 detected, data for potential abstraction errors will be tested.<sup>65</sup> If no data errors are identified,  
27  
28 388 direct, indirect, and mixed estimates will be separately reported.<sup>65</sup> Further, significant  
29  
30 389 inconsistency will be explored by performing meta-regression using the above mentioned  
31  
32 390 potential effects modifiers.<sup>65</sup> Inconsistency tests have low power to detect true inconsistency<sup>82 83</sup>  
33  
34 391 and hence, we will assess for the transitivity assumption even in the absence of evidence for  
35  
36 392 inconsistency.  
37  
38  
39 393 Vague priors for all model parameters and a half-normal prior distribution for the between-study  
40  
41 394 SD will be assumed in all Bayesian NMA models.<sup>65</sup> The models will be run for 50,000 iterations  
42  
43 395 to ensure model convergence, which will be checked by visual inspection of the mixing of 4  
44  
45 396 chains or by using Gelman-Rubin convergence diagnostics,<sup>84</sup> after discarding the first 5,000  
46  
47 397 iterations and thinning of 1. The posterior median values and their 95% credible intervals (CrIs)  
48  
49 398 for the relevant model parameters will be reported with intervention effects and between-study  
50  
51 399 variance.<sup>85</sup> Each NMA estimate will be presented with a 95% prediction interval,<sup>86</sup> which  
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4 400 captures the magnitude of the between-study variance and indicates the interval at which the  
5  
6 401 intervention effect of future studies are expected.<sup>87</sup>  
7  
8  
9 402 For relative intervention ranking, the ranking probabilities for all interventions at each possible  
10  
11 403 rank for each intervention will be estimated.<sup>88</sup> Through the surface under the cumulative ranking  
12  
13 404 (SUCRA) curve and mean ranks, the intervention hierarchy will be defined with a cumulative  
14  
15 405 probability of an intervention that can be ranked first without uncertainty.<sup>89</sup> The rank-heat plot  
16  
17 406 (<http://rh.ktss.ca/>) to visually present the intervention hierarchy across the multiple outcomes of  
18  
19 407 the study will be shown.<sup>90</sup> The higher the SUCRA value, which ranges from 0% to 100%, will  
20  
21 408 indicate the higher the likelihood of intervention<sup>91</sup> for social isolation and loneliness.  
22  
23  
24  
25 409 Standard pairwise meta-analyses will be conducted through the R statistical package (version  
26  
27 410 3.6.2) and the metafor package. NMA will be also conducted through the R statistical package  
28  
29 411 (version 3.6.2) with BUGSnet R package (version 1.0.3) for Bayesian NMA.  
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31  
32  
33

#### 34 413 Analysis of sensitivity

35  
36 414 According to Cochrane reviews,<sup>92</sup> the major approach to incorporating risk of bias assessments is  
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38 415 to restrict meta-analyses to studies at low risk of bias, or to stratify studies depending on risk of  
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40 416 bias. We will perform sensitivity analyses on low risk of bias and excluding the following  
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42 417 studies: 1) studies with high risk of bias, 2) studies with missing data, and 3) studies with  
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44 418 imputed data (i.e., in order to ensure that imputed research results are not one-sided in NMA) if  
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46 419 enough studies are available.  
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#### 51 52 421 Analysis of subgroup

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54 422 For multicomponent/multimodal interventions, we will perform subgroup analyses by types of  
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4 423 specific individual intervention. For example, the implications of “social activities combined  
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6 424 with exercise interventions” and “psychotherapy combined with social/health service” are  
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9 425 different even though they are categorized as multicomponent interventions.  
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13 427 Certainty of the evidence and summary of findings table

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15 428 Through the GRADE (Grading of Recommendations Assessment, Development and Evaluation)  
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18 429 approach of NMA,<sup>93</sup> the certainty of direct, indirect and mixed NMA effect estimates for each  
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20 430 outcome will be assessed. The certainty of evidence of direct effect estimates for each outcome  
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22 431 will be assessed as follows according to the GRADE rating system:<sup>94</sup> high, moderate, low or  
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24 432 very low.

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27 433 We will use the available loops of evidence including loops with a single common comparator  
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29 434 (i.e., first-order) or more than one intervening treatment (i.e., higher orders) connecting the two  
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31 435 interventions of the comparison of interest in order to calculate the indirect effect estimated.<sup>29</sup>

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34 436 For the quality of indirect evidence, the dominant first-order loop (i.e., loops with a single  
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36 437 common comparator connecting the two interventions of the comparison of interest) will be  
37  
38 438 assessed.<sup>29</sup> The quality of evidence rating for indirect comparisons will be the lower of the rating  
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40 439 for quality for the two direct estimates that contribute to the first-order loop of the indirect  
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42 440 comparison.<sup>29</sup>

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45 441 In the case to use both direct and indirect evidence, the rate of NMA estimate quality will be  
46  
47 442 from the higher quality of the two.<sup>29</sup> The similarity between direct and indirect effect estimates  
48  
49 443 will be estimated in the final quality rating.<sup>29</sup> If there is any inconsistency between direct and  
50  
51 444 indirect effect estimates (i.e., it is estimated by the difference of point estimates and the extent of  
52  
53 445 overlap of 95% CIs and of direct and indirect effect estimates), the quality of the NMA effect  
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4 446 will be assessed.<sup>29</sup>  
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## 8 448 **Patient and public involvement**

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11 449 As this study is a systematic review, patients and the public will not be directly involved.

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13 450 However, we will consult key stakeholder groups (e.g., older adult networks and relevant service  
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16 451 provider associations) to determine the best channels through which to disseminate the results of  
17  
18 452 our study.  
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## 21 22 454 **DISCUSSION**

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25 455 As the numbers of older adults increase, so does the resulting social and economic burden of  
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27 456 social isolation and loneliness. There is need for evidence-based therapeutic programs to mitigate  
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29 457 social isolation and loneliness. A high-quality systematic review of the comparative therapeutic  
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31 458 effects of interventions for improving social isolation and loneliness in older adults is essential.

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34 459 To our knowledge, there are few systematic reviews and NMAs combining direct and indirect  
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36 460 effects of intervention for social isolation and loneliness in older adults. This study will include a  
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38 461 comparison of different interventions for social isolation and loneliness through not only a single  
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40 462 (e.g., exercise program or social/health service) intervention, but also combination (e.g., exercise  
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42 463 program combined with social/health service) of interventions. This study has several strengths:  
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46 464 1) including recent RCTs social isolation and loneliness for older adults; 2) screening rigorous  
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48 465 trial eligibility and collecting data from independent teams of reviews; 3) assessing credibility  
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50 466 and providing certainty for intervention effects, by using GRADE approach; 4) performing meta-  
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52 467 regression and subgroup analyses, consistent with the best current practice;<sup>86</sup> 5) providing  
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54 468 ranking intervention (i.e., the intervention sequence is determined according to their relative  
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4 469 efficacy)<sup>94</sup> for social isolation and loneliness.  
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6 470 Although this study has several strengths, there are also potential challenges and limitations.  
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8 471 First, it might be difficult to interpret the effects when pooling estimates from trials using  
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10 472 different tools to measure social isolation (e.g., the Lubben Social Network Scale-6 and SSQ6)  
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12 473 and loneliness (e.g., the De Jong Gierveld Loneliness Scale and UCLA loneliness scale)  
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14 474 combined with high heterogeneity (i.e., differences in effect estimates between studies that  
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16 475 evaluated the same comparison).<sup>94</sup> Further, social isolation has a variety of surrogate outcomes  
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18 476 such as social support and social network. Such surrogate outcomes might down rate the  
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20 477 directness identified through the GRADE approach<sup>94</sup> because it means that an outcome of  
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22 478 interest (i.e., social isolation) might differ from the measured in surrogate outcomes (i.e., social  
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24 479 support and social network). Additionally, dealing with multicomponent interventions in NMA is  
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26 480 a methodological challenge because single or combined (i.e., consisting of several possibly  
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28 481 interacting components) interventions are different nodes in the network.<sup>95</sup>  
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30 482 It is expected that the findings of this study will provide evidence for clinicians (e.g., when  
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32 483 selecting which interventions are best for older adults), health policy makers (e.g., when making  
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34 484 decision which programs or services should be supported) as well as stakeholders (e.g., when  
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36 485 operating how programs effectively) managing social isolation and loneliness in community  
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38 486 dwelling older adults and for older adults in choosing therapeutic options.  
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## 41 488 **Ethics and Dissemination**

42 489 Ethical approval is not necessary because data will be collected from published studies and there  
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44 490 will be no concerns due to privacy. These findings will be disseminated through presentation at  
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46 491 conferences and meetings, which will help inform interested researchers of the direction and  
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492 design of future research.

493

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498

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501 critically revised the protocol draft and the present manuscript. All authors read and approved the  
502 final manuscript.

503

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6 **Management of Social Isolation and Loneliness in Community Dwelling Older Adults: Protocol**  
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8 **for a Network Meta-analysis of Randomized Controlled Trials**  
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13 **Supplementary Files**  
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23 Supplementary file 1: PRISMA NMA checklist ..... 2  
24  
25 Supplementary file 2: PICOS statement ..... 6  
26  
27 Supplementary file 3: Search strategy ..... 9  
28  
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## 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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted.</i> _	5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
<b>METHODS</b>			
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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i> _	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
<b>Geometry of the network</b>	<b>S1</b>	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). <i>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.</i>	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: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	17-18
<b>Assessment of Inconsistency</b>	<b>S2</b>	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: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	19-20
<b>RESULTS†</b>			
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
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
<b>Summary of network geometry</b>	<b>S4</b>	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. <i>Modified approaches may be needed to deal with information from larger networks.</i>	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g.</i>	n/a

		<i>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.</i>	
<b>Exploration for inconsistency</b>	<b>S5</b>	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> 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, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	n/a
<b>DISCUSSION</b>			
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). <i>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).</i>	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
<b>FUNDING</b>			
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	<ul style="list-style-type: none"> <li><input type="checkbox"/> Community-dwelling older adults <math>\geq 60</math> years of age (If mean or median age of participants is 60 year or older, it can be included.)</li> <li><input type="checkbox"/> 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.)</li> <li><input type="checkbox"/> A mild or moderate dementia or cognitive dysfunction</li> </ul>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Adults &lt; 60 years of age</li> <li><input type="checkbox"/> Not community residing (inpatients, nursing home, hospital wards, or long-term care facilities)</li> <li><input type="checkbox"/> Dementia or moderate to severe cognitive dysfunction (Mini-Mental State Examination (MMSE)&lt;24, Montreal Cognitive Assessment (MoCA) &lt;26, or Short Portable Mental Status Questionnaire (SPMSQ)&gt;6)</li> <li><input type="checkbox"/> Chronic diseases related to death or serious risk: cancer, AIDS (HIV), chronic heart failure, recent surgery or transplant or intractable rare disease</li> <li><input type="checkbox"/> Unstable diseases such as bipolar disorder, active psychosis, or suicidal plans</li> <li><input type="checkbox"/> Caregivers</li> </ul>
Interventions	<ol style="list-style-type: none"> <li>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</li> <li>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-</li> </ol>	<ul style="list-style-type: none"> <li><input type="checkbox"/> Pharmaceutical interventions including medications and nutritional supplements (vit D, calcium, or protein) for mental health, anxiety, or depression</li> </ul>

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

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short version of the Medical Outcomes Study<sup>17</sup> 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.

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Study design	<input type="checkbox"/> All RCTs or quasi-RCTs regardless of sample size	<input type="checkbox"/> Non-RCTs <input type="checkbox"/> 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
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Setting	<input type="checkbox"/> Community settings	
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Language	<input type="checkbox"/> English	<input type="checkbox"/> Non-English

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## 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 sociat* 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*

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28	26 OR 27
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For peer review only

## 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 #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: <b>Background:</b> main objectives <b>Methods:</b> data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . <b>Results:</b> number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> <b>Discussion/Conclusions:</b> limitations; conclusions and implications of findings. <b>Other:</b> primary source of funding; systematic review registration number with registry name.	3-4
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted.</i>	5-6
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
<b>METHODS</b>			
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. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i>	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
<b>Geometry of the network</b>	<b>S1</b>	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). <i>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.</i>	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: <ul style="list-style-type: none"> <li>• <i>Handling of multi-arm trials;</i></li> <li>• <i>Selection of variance structure;</i></li> <li>• <i>Selection of prior distributions in Bayesian analyses; and</i></li> <li>• <i>Assessment of model fit.</i></li> </ul>	17-18
<b>Assessment of Inconsistency</b>	<b>S2</b>	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: <ul style="list-style-type: none"> <li>• Sensitivity or subgroup analyses;</li> <li>• Meta-regression analyses;</li> <li>• <i>Alternative formulations of the treatment network; and</i></li> <li>• <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i></li> </ul>	19-20
<b>RESULTS†</b>			
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
<b>Presentation of network structure</b>	<b>S3</b>	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	n/a
<b>Summary of network geometry</b>	<b>S4</b>	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. <i>Modified approaches may be needed to deal with information from larger networks.</i>	n/a
Synthesis results	21		Present results of each meta-analysis done, including confidence/credible intervals. <i>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.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	n/a
<b>Exploration for inconsistency</b>	<b>S5</b>		Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> 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, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i> ).	n/a
<b>DISCUSSION</b>				
Summary 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). <i>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).</i>	21-22
Conclusions	26		Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
<b>FUNDING</b>				
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

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2  
3 from the PRISMA statement.

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