



BMJ Open Psychological interventions for inflammatory bowel disease: a systematic review and component network meta-analysis protocol

Natalia Tiles-Sar ¹, Johanna Neuser,¹ Dominik de Sordi,¹ Gerta Rücker ², Anne Baltes,³ Jan Preiss,⁴ Gabriele Moser,⁵ Antje Timmer¹

To cite: Tiles-Sar N, Neuser J, de Sordi D, *et al.* Psychological interventions for inflammatory bowel disease: a systematic review and component network meta-analysis protocol. *BMJ Open* 2022;**12**:e056982. doi:10.1136/bmjopen-2021-056982

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-056982>).

Received 31 August 2021

Accepted 19 May 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Natalia Tiles-Sar;
natalia.tiles-sar@uni-oldenburg.de

ABSTRACT

Introduction Patients with inflammatory bowel diseases (IBD) often report psychological problems, unemployment, disability, sick leave and compromised quality of life. The effect of psychological interventions on health-related outcomes in IBD is controversial as previous reviews faced the obstacle of high heterogeneity among provided multimodal interventions. The heterogeneity can be addressed with network meta-analysis (NMA) and (multi)component NMA (CNMA). We aim to investigate whether psychological interventions can improve quality of life, clinical and social outcomes in IBD using NMA and CNMA. This is the study protocol.

Methods and analysis We will consider randomised, quasi-randomised and non-randomised controlled trials, including cluster randomised and cross-over trials with 2 months of minimum follow-up. The conditions to be studied comprise Crohn's disease and ulcerative colitis in children, adolescents and adults. We will include any psychological intervention aiming to change the health status of the study participant. We will search Medline, Embase, Web of Science, CENTRAL, LILACS, Psynex, PsycINFO, Google Scholar and trial registries from inception (the search will be updated before the review completion). Two authors will independently screen all references based on titles and abstracts. For data extraction, standard forms are developed and tested before extraction. All information will be assessed independently by at least two reviewers, and disagreements solved by consensus discussion or a third rater if necessary.

The data synthesis will include a pairwise meta-analysis supported by meta-regression. We will conduct NMA (all treatments will constitute single nodes of the network) and CNMA (we will define all treatments as sums of core components, eg, cognitive +behaviour, or cognitive +behaviour + relaxation, and additionally consider interactions) using the R Package netmeta.

Ethics and dissemination No ethical approval is required. Reports will include the final report to the funder, conference presentation, peer-reviewed publication and a patient report.

PROSPERO registration number CRD42021250446.

INTRODUCTION

Inflammatory bowel diseases (IBD), that is, Crohn's disease (CD) and ulcerative

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The topic is of high importance for patients, their families and service providers.
- ⇒ This review will use a novel method of network meta-analysis and component network meta-analysis to tackle heterogeneity in multimodal interventions.
- ⇒ The limitation is the expected heterogeneity among the psychological interventions.
- ⇒ The variable methodological rigour of individual studies is also expected to challenge the validity and interpretation of review results.

colitis (UC), are characterised by a chronic course with an unpredictable sequence of periods with increased inflammatory activity (relapses) and a wide variety of potential complications.¹ Patients face increased unemployment rates, disability status, sick leave and substantially compromised quality of life (QoL).^{2,3} A significant proportion of patients experience psychological health problems: based on 13 studies in a systematic review, the mean prevalence of anxiety was calculated at 19% (healthy controls: 10%) and of depression at 21% (healthy controls 13%).⁴

Psychological therapy in IBD is discussed as a relevant component of disease management.^{5,6} The term encompasses a range of very diverse interventions, including psychodynamic-oriented therapies, commonly applied cognitive-behavioural approaches, mindfulness and relaxation techniques (eg, autogenic training and feedback methods), solution-focused or acceptance and commitment therapy.^{7,8} Often, psychological interventions in IBD target to improve coping skills and general stress management; change of thoughts, emotions processing, and consequently alter behaviour; educate about mental health concerns; provide overall support. High importance has been attached to psychological therapy in IBD,

as these therapies are expected to improve associated psychological health problems, QoL and possibly impact clinical outcomes.^{9–12}

Clinical guidelines typically recommend psychological treatment as a supportive measure, although they disagree concerning the level of evidence regarding its effectiveness.^{13 14} Previous reviews do not formally address heterogeneity and complexity among psychological interventions—either only one type of therapy is evaluated, or narrative or qualitative analyses are performed.^{15–26} Since there have been substantial advances in both the analysis methods and reporting of clinical trials, we will, in our meta-analysis, deal with heterogeneity by applying meta-regression, NMA and component NMA (CNMA) complementing the standard pairwise approach.^{27–29} Meta-regression is used as a means to identify clinical sources of heterogeneity in study results, emerging from differences in populations studied and the type of index and control interventions. Network meta-analysis (NMA) will allow for simultaneous evaluation of different interventions used in different trials to establish a ranking of therapeutic approaches. Lastly, CNMA will be used to assess the relative efficacy of different components of interventions (eg, change of cognitions, relaxation, education, support) and their interaction.

OBJECTIVES

Primary research objective

To assess whether psychological interventions as add-on therapy improve the QoL in persons with IBD (any type, any disease activity stage, any age) compared with no therapy, sham or any other therapy (pairwise comparison).

Secondary research objectives

1. To assess whether psychological interventions improve other indicators of health status in IBD (pairwise comparisons, secondary outcomes).
2. To identify sources of heterogeneity of effects arising from differences in populations, index and control interventions (meta-regression).
3. To rank the effectiveness of different types of psychological interventions (NMA).
4. To rank the effectiveness of specific components of psychological interventions and identify potential interactions between components CNMA).

METHODS AND ANALYSIS

This is a protocol for a systematic review on the effectiveness of complex psychological interventions and their components on health-related outcomes in patients with IBD. We will comprise randomised, quasi-randomised and non-randomised controlled trials. This includes cluster randomised and cross-over trials. The minimum follow-up is 2 months.

Participants

The conditions to be studied comprise UC and CD in children, adolescents, and adults. Studies with mixed IBD populations will also be included. Studies in more diverse populations will be included if separate results are available for the subgroup of patients with IBD. There will be no restriction based on age, sex and disease-specific characteristics, such as duration, inflammatory activity and disease severity.

Interventions

We will include any psychological intervention aiming to change the health status of the individual study participant. These will be grouped as psychotherapy and psychological support or counselling, patient education and relaxation techniques. Combinations of these will also be included. All application modes are eligible, including face-to-face interventions, application by phone, web-based interventions and written materials. We will not include interventions aiming at gain of knowledge and lifestyle changes, such as smoking cessation, diet or weight management and physical activity.

Any control intervention is allowed, including none, sham or any other psychological intervention.

Outcomes

Our primary outcome is health-related QoL, preferably measured as change from baseline by a validated disease-specific QoL measure. Absolute scores at predefined time points, failure to improve or failure to maintain at follow-up will be considered if change from baseline is unavailable. Where disease-specific QoL measures are not available, generic measures may also be used.

Our secondary outcomes include measures of anxiety and depression, disease activity as defined in the trial (preferably using validated clinical scores), healthcare use (time in hospital, emergency room visits) and time off work or school. Adverse events will include all events declared severe as well as all adverse events leading to withdrawal. Trial withdrawal will also be examined as a measure of intervention acceptability.

Search methods

We will search Web of Science Core Collection, KCI-Korean Journal Database, Russian Science Citation Index via Web of Science, Medline, Psynex, PsycINFO via Ovid, Embase, Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library and LILACS. Both MESH and free text terms will be used for disease and intervention terms (online supplemental appendix 1). For MEDLINE, the highly sensitive search strategy for clinical trials will be applied. LILACS, Psynex and PsycINFO will be searched based on disease terms only (Lilacs: in Spanish and Portuguese; Psynex: in German and English, PsycINFO: in English).

Electronic searches will include clinical trial registries (International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, ISRCTN registry, German Registry of

Clinical Trials (DRKS)) and Publisher Databases (eg, Springer, ScienceDirect, Wiley Online Library) as available. Search in the registries will be based on disease terms only for smaller registries or those with limited search tools.

There will be no language, date, document/publication type, publication status (published or unpublished) or status of study (ongoing or completed) restrictions for all databases. All databases will be searched from inception. The search will be updated prior to the completion of the review.

Handsearch: we will search 2019–2021 contributions for major gastroenterological and selected other IBD-related conferences (Digestive Disease Week, Canadian Digestive Disease Week, World Congress of Gastroenterology, European Crohn's and Colitis Organisation Conference, Advances in Inflammatory Bowel Diseases Conference, Crohn's and Colitis Congress, Annual Meeting of British Society of Gastroenterology, United European Gastroenterology Week, Viszeralmedizin).

Google Scholar will be used for forward searching (using the 'cited by' function) of relevant articles (ie, all included articles as well as relevant systematic reviews). Specialists in the fields will be questioned, and reference lists of available reviews and relevant publications will be searched.

Data collection

The primary selection of eligible studies will be performed manually by at least two independent reviewers using Covidence.³⁰ The primary selection will be based on the title and abstract screening for eligibility following inclusion and exclusion criteria. Full-text screening will be performed where the title and abstract were not informative. A flow diagram will be presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

The data extraction will be used via Covidence based on the predefined items and completed independently for each study by at least two trained persons from the core review team. Item selection for extraction takes into account the extended Consolidated Standards of Reporting Trials (CONSORT) criteria for psychological intervention trials and the Template for Intervention Description and Replication (TIDieR) checklist.^{28,31} Given critical debates and variation surrounding effectiveness evaluation of complex interventions, we will also collect information on the development of the intervention at question if available from trial reports, incorporating items from the Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare (CRDeCI_2) list, the Medical Research Council (MRC) framework on complex interventions and suggested extensions.^{27,32–35} We will also record whether and how interventions applied have been based on theory, for example, using the taxonomy by O'Cathain, as the lack of theory is occasionally reported as invalidating findings,

although so far, to our knowledge, without empirical support.³⁵

The main variables will include general information, setting, population characteristics, intervention and comparison treatment description (eg, intervention duration, intensity, mode of application, format and intervention provider), instruments and timing of the outcome assessment, study quality assessment, number of patients at each trial stage and in each arm, baseline and follow-up values per each outcome of interest, details of withdrawals and adverse events. The expert team members will be consulted if consensus is not achieved on details or categorisation of interventions or outcomes. An additional person will be designated as the final arbiter in case of any other dissent.

Assessment of risk of bias in included studies will be done independently by at least two review authors. Disagreements will be solved by discussion. If a consensus is not reached, one of the participating experts will serve as a final arbiter. Quality assessment of studies will be based on the revised Cochrane risk-of-bias tool 2.³⁶ Bias will also be considered where non validated outcome measures are used. The bias will be assessed at the study and outcome level (primary focusing on QoL). We will exclude studies with a high risk of bias from the following analysis. Publication bias will be examined by inspection of funnel plots and comparison-adjusted funnel plots, based on all included trials.³⁷ If 10 studies or more are identified, Egger's test will be performed. The potential for outcome reporting bias will be explored by examining the number and types of outcomes reported to be evaluated as compared with those reported, with a focus on QoL. The overall quality of the evidence will be assessed with Grading of Recommendations, Assessment, Development and Evaluations (GRADE) for the pairwise meta-analysis (will be published with Cochrane) and with Confidence in Network Meta-Analysis (CINeMA) for the NMA.^{38–40}

Missing information will be requested from the investigators of the primary studies. Missing outcome data will be presented in an intention-to-treat approach for dichotomous outcomes, where all lost to follow-up will be considered as treatment failure. For continuous outcomes, we will use intention-to-treat analysis as available from the reports. If unavailable, per-protocol results may be used, but this will be considered to increase the risk of bias as formulated in the risk of bias tool.

Data synthesis

We will only pool studies with a low or moderate risk of bias. Pairwise meta-analysis will be done by calculating random-effects pooled standardised mean differences with 95% CIs (for QoL) or pooled relative risks for binary outcomes. We will not pool across the three main categories of interventions (psychotherapy/psychological support, patient education, relaxation techniques) and age groups (children, youth, adults) but perform separate meta-analyses for each of these. Multicomponent intervention trials may be assigned to more than one meta-analysis. In case of substantial statistical heterogeneity (eg,

$I^2 > 50\%$, or $p < 0.001$), we will also refrain from pooling within these categories.

Further, NMA will be conducted so that all treatments will constitute single nodes of the network.^{41 42} Next, CNMA will be planned in analogy to the work by Welton, based on the procedure described by Rücker and using the R Package netmeta.^{43–46} Thus, we will define all possible combinations as sums of core components, for example, cognitive +behaviour, or cognitive +behaviour + relaxation, and perform an additive CNMA, followed by a CNMA considering potential interaction. Results from all models will be compared with identify effects of interaction, for example, synergies of combinations. The components will be distinguished by specific interventions characteristics (eg, group and individual therapies will be differentiated).

Based on the data extraction results, classification of core components and expert consensus, a statistical analysis plan will be set up, predefining the choice of models and selection of variables before analyses are started. Programming will use the open statistical environment R, or other as appropriate.⁴⁵

Investigation of heterogeneity and subgroup analysis

In pairwise analysis, clinical heterogeneity will be assessed by predefined subanalyses (see the next paragraph). We will calculate the I^2 value to quantify statistical heterogeneity.⁴⁷ Sources of heterogeneity will also be evaluated by meta-regression applied to the total sample of all trials selected for the analysis. For NMA, total heterogeneity, measured by Cochran's Q , will be decomposed into within-design heterogeneity and between-design inconsistency, based on a treatment-design interaction model and illustrated by a net heat plot.⁴⁸ Differences between direct and indirect effects will be investigated based on a node-splitting method.⁴⁹

All meta-analyses will be performed including subgroup analyses by disease type (CD, UC). Results from trials without separate reporting by disease type will be included within a subgroup 'unspecified IBD'. Subgroup analysis will also examine the effects of common subtypes of intervention (eg, cognitive-behavioural therapy), type of comparator, treatment intensity, training of provider and mode of application. In addition, subgroup analyses by comorbidity, sex and disease activity (remission, relapse) may be performed if these factors differ between studies. If enough studies are identified, the comparison of the effect across countries, geopolitical and cultural regions will be made.

Sensitivity analysis

Sensitivity analysis will be performed restricted to studies with a low risk of bias. This will primarily relate to excluding studies with quasi-randomised or non-randomised treatment allocation, but other design features may also be considered, such as using non-validated outcome assessment or failure to perform intention-to-treat analysis. If this information is available and differs between trials, we will perform additional sensitivity analysis by excluding trials on interventions

not based on theory or without sufficient information on how they were developed. Also, we will perform meta-analysis restricted to the most common disease-specific QoL measure, where three or more studies with this instrument are available for pooling.

We used the PRISMA for systematic review protocols (PRISMA-P) checklist when writing the protocol.⁵⁰

Patient and public involvement

The German CD/UC Association (DCCV e.V.) representative (AB) contributed to the development of the protocol and will be further involved in the research process accordingly. Our findings will be disseminated through the DCCV network.

ETHICS AND DISSEMINATION

No ethical approval is required since we are not using individual participant data. Reports will include the final report to the funder, conference presentation, peer-reviewed publication and patients' reports that could be disseminated through patients' associations (eg, DCCV e.V. in Germany). The first part of the review focusing on pairwise comparison and meta-regression will constitute the update for the previous Cochrane review of 2011. Therefore, these results will be disseminated through the Cochrane Library. The results from the network and CNMA will be published as a separate non-Cochrane manuscript.

Author affiliations

¹Department of Epidemiology and Biometry, Carl von Ossietzky University of Oldenburg, Oldenburg, Germany

²Institute of Medical Biometry and Medical Informatics, Medical Faculty and Medical Center - University of Freiburg, Freiburg, Germany

³German Association for Crohn's Disease and Ulcerative Colitis (DCCV e.V.), Berlin, Germany

⁴Clinic for Internal Medicine - Gastroenterology, Diabetology and Hepatology, Vivantes Klinikum Neukölln, Berlin, Germany

⁵Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria

Acknowledgements The authors would like to thank Dr Farhad Shokraneh for peer-reviewing the search methods and strategies.

Contributors AT (review supervisor) initiated the review and update, wrote the funding proposal, and supervised all steps during the protocol development. NTS (review coordinator) refined the protocol, updated the search methods and modified the search strategy and extraction form. JN (2nd screener, extractor, and bias assessor) participated in writing the manuscript and did user testing of the extraction form. GR (senior statistician) devised the advanced statistical methods and wrote part of the analysis section. DdS (statistician) consulted on data management and statistical analyses. GM (psychosomatics) and JP (gastroenterology) serve as content experts consulting on the protocol. AB (patient representative) contributed advice and comments from the patient perspective. All authors read and approved the final version of the protocol.

Funding German Federal Ministry of Education and Research (BMBF, 01KG2018) sponsored this research but had no impact on the protocol development.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Natalia Tiles-Sar <http://orcid.org/0000-0001-6128-114X>

Gerta Rücker <http://orcid.org/0000-0002-2192-2560>

REFERENCES

- Knowles SR, Graff LA, Wilding H, *et al*. Quality of life in inflammatory bowel disease: a systematic review and meta-analyses-Part I. *Inflamm Bowel Dis* 2018;24:742–51.
- Büsch K, da Silva SA, Holton M, *et al*. Sick leave and disability pension in inflammatory bowel disease: a systematic review. *J Crohns Colitis* 2014;8:1362–77.
- Floyd DN, Langham S, Séverac HC, *et al*. The economic and quality-of-life burden of Crohn's disease in Europe and the United States, 2000 to 2013: a systematic review. *Dig Dis Sci* 2015;60:299–312.
- Mikocka-Walus A, Knowles SR, Keefer L, *et al*. Controversies revisited: a systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflamm Bowel Dis* 2016;22:752–62.
- Klag T, Mazurak N, Fantasia L, *et al*. High demand for psychotherapy in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;23:1796–802.
- Miehler W, Weichselberger M, Öfferlbauer-Ernst A, *et al*. Which patients with IBD need psychological interventions? A controlled study. *Inflamm Bowel Dis* 2008;14:1273–80.
- Goodhand JR, Wahed M, Rampton DS. Management of stress in inflammatory bowel disease: a therapeutic option? *Expert Rev Gastroenterol Hepatol* 2009;3:661–79.
- Paulides E, Boukema I, van der Woude CJ. The effect of psychotherapy on quality of life in IBD patients: a systematic review. *Inflamm Bowel Dis* 2020.
- Jordan C, Sin J, Fear NT, *et al*. A systematic review of the psychological correlates of adjustment outcomes in adults with inflammatory bowel disease. *Clin Psychol Rev* 2016;47:28–40.
- Mardini HE, Kip KE, Wilson JW. Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity. *Dig Dis Sci* 2004;49:492–7.
- Mittermaier C, Dejacó C, Waldhoer T, *et al*. Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosom Med* 2004;66:79–84.
- Levenstein S, Prantera C, Varvo V, *et al*. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2000;95:1213–20.
- Häuser W, Moser G, Klose P, *et al*. Psychosocial issues in evidence-based guidelines on inflammatory bowel diseases: a review. *World J Gastroenterol* 2014;20:3663–71.
- Kucharzik T, Atreya R, Bokemeyer B. Da. S3-Leitlinie–Colitis ulcerosa. *Z Gastroenterol* 2018.
- Timmer A, Preiss JC, Motschall E. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database Syst Rev* 2011;2:CD006913.
- Ewais T, Begun J, Kenny M, *et al*. A systematic review and meta-analysis of mindfulness based interventions and yoga in inflammatory bowel disease. *J Psychosom Res* 2019;116:44–53.
- Tran L, Mulligan K. A systematic review of self-management interventions for children and adolescents with inflammatory bowel disease. *Inflamm Bowel Dis* 2019;25:685–98.
- Tu W, Xu G, Du S. Structure and content components of self-management interventions that improve health-related quality of

- life in people with inflammatory bowel disease: a systematic review, meta-analysis and meta-regression. *J Clin Nurs* 2015;24:2695–709.
- Fiest KM, Bernstein CN, Walker JR, *et al*. Systematic review of interventions for depression and anxiety in persons with inflammatory bowel disease. *BMC Res Notes* 2016;9:404.
- Gracie DJ, Irvine AJ, Sood R, *et al*. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2017;2:189–99.
- Hanlon I, Hewitt C, Bell K, *et al*. Systematic review with meta-analysis: online psychological interventions for mental and physical health outcomes in gastrointestinal disorders including irritable bowel syndrome and inflammatory bowel disease. *Aliment Pharmacol Ther* 2018;48:244–59.
- Hood MM, Jedel S. Mindfulness-based interventions in inflammatory bowel disease. *Gastroenterol Clin North Am* 2017;46:859–74.
- Langhorst J, Wulfert H, Lauche R, *et al*. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. *J Crohns Colitis* 2015;9:86–106.
- Li C, Hou Z, Liu Y, *et al*. Cognitive-behavioural therapy in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *Int J Nurs Pract* 2019;25:e12699.
- Peters SL, Muir JG, Gibson PR. Review article: gut-directed hypnotherapy in the management of irritable bowel syndrome and inflammatory bowel disease. *Aliment Pharmacol Ther* 2015;41:1104–15.
- Tarricone I, Regazzi MG, Bonucci G, *et al*. Prevalence and effectiveness of psychiatric treatments for patients with IBD: a systematic literature review. *J Psychosom Res* 2017;101:68–95.
- Craig P, Dieppe P, Macintyre S, *et al*. Developing and evaluating complex interventions: the new medical research council guidance. *BMJ* 2008;337:a1655.
- Grant S, Mayo-Wilson E, Montgomery P, *et al*. CONSORT-SPI 2018 explanation and elaboration: guidance for reporting social and psychological intervention trials. *Trials* 2018;19:406.
- Higgins JPT, López-López JA, Becker BJ, *et al*. Synthesising quantitative evidence in systematic reviews of complex health interventions. *BMJ Glob Health* 2019;4:e000858.
- Innovation VH. Covidence systematic review software [Internet]. Melbourne, Australia; 2021 [Accessed 27 Jul 2021].
- Hoffmann TC, Glasziou PP, Boutron I, *et al*. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ* 2014;348:g1687.
- Minary L, Trompette J, Kivits J, *et al*. Which design to evaluate complex interventions? Toward a methodological framework through a systematic review. *BMC Med Res Methodol* 2019;19:92.
- Bleijenberg N, de Man-van Ginkel JM, Trappenburg JCA, *et al*. Increasing value and reducing waste by optimizing the development of complex interventions: enriching the development phase of the medical research council (MRC) framework. *Int J Nurs Stud* 2018;79:86–93.
- Möhler R, Köpke S, Meyer G. Criteria for reporting the development and evaluation of complex interventions in healthcare: revised guideline (CReDECI 2). *Trials* 2015;16:204.
- O'Cathain A, Crook T, Sworn K, *et al*. Taxonomy of approaches to developing interventions to improve health: a systematic methods overview. *Pilot Feasibility Stud* 2019;5:41.
- Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:14898.
- Chaimani A, Higgins JPT, Mavridis D, *et al*. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;8:e76654.
- Atkins D, Best D, Briss PA, *et al*. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
- Puhan MA, Schünemann HJ, Murad MH, *et al*. A grade Working group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630.
- Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al*. Cinema: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;17:e1003082.
- Rücker G. Network meta-analysis, electrical networks and graph theory. *Res Synth Methods* 2012;3:312–24.
- Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;3:80–97.
- Rücker G, Petropoulou M, Schwarzer G. Network meta-analysis of multicomponent interventions. *Biom J* 2020;62:808–21.
- Welton NJ, Caldwell DM, Adamopoulos E, *et al*. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. *Am J Epidemiol* 2009;169:1158–65.



- 45 R Core Team. R: A language and environment for statistical computing [Internet]. Vienna, Austria R Foundation for Statistical Computing; 2021.
- 46 Rücker G, König J, Efthimiou O. *Network Meta-Analysis using Frequentist Methods [Internet]. R package version 1.3-0*. KU: netmeta, 2021.
- 47 Higgins J, Thompson S, Deeks J, *et al*. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002;7:51–61.
- 48 Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol* 2013;13:35.
- 49 Dias S, Welton NJ, Caldwell DM, *et al*. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44.
- 50 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.