BMJ Open

Subgroup effects of non-surgical and non-pharmacological treatment of patients with hand osteoarthritis: a protocol for an individual patient data meta-analysis

Giesleen C E Thissen ,[1] Marienke van Middelkoop,[1] Joost W Colaris,[2] Ruud W Selles ,[3,4] Krysia Dziedzic,[5] Elaine Nicholls,[6,7] Sita M A Bierma-Zeinstra[1]

To cite: Thissen GCE, van Middelkoop M, Colaris JW, *et al*. Subgroup effects of non-surgical and non-pharmacological treatment of patients with hand osteoarthritis: a protocol for an individual patient data meta-analysis. *BMJ Open* 2022;**12**:e057156. doi:10.1136/bmjopen-2021-057156

► 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-2021-057156).

Received 06 September 2021
Accepted 20 December 2021

For numbered affiliations see end of article.

Correspondence to
Giesleen C E Thissen;
g.thissen@erasmusmc.nl

ABSTRACT

Introduction Hand osteoarthritis (OA) is a common joint disorder in the adult population. No cure for hand OA is known yet, but treatment aims to reduce symptoms. Non-surgical and non-pharmacological therapy interventions can include splinting, patient education, and strengthening and range of movement exercises. However, it is still unclear which treatment is most beneficial for which patient. This study aims to identify subgroups of patients with hand OA that benefit most from the different non-surgical and non-pharmacological treatments.

Methods and analysis We will conduct an individual patient data (IPD) meta-analysis by extracting IPD of eligible published randomised controlled trials (RCTs). A systematic literature search through Embase, Medline and Cochrane was performed on 8 February 2021. The primary outcome will be hand pain, and our secondary outcomes are objective and subjective hand physical functions. Subgroups include age, sex, body mass index, hypermobility and other comorbidities, pain medication, occupation, baseline pain, erosive OA, type and the number of hand joints involved, radiological severity of OA, and duration of symptoms. IPD of RCTs with homogeneous treatment interventions will be pooled and analysed using a two-stage approach to evaluate treatment effect on different subgroups.

Ethics and dissemination No new data will be collected, so research ethical or governance approval is exempt. Findings will be disseminated via national and international conferences, publications in peer-reviewed journals, and summaries posted on websites accessed by the public and clinicians.

Strengths and limitations of this study

- We designed our protocol in collaboration with the Osteoarthritis Trial Bank, which is an internationally recognised organisation with considerable individual patient data (IPD) meta-analyses experience and facilitates a safe transfer and storage of IPD.
- IPD meta-analyses are considered the gold standard for subgroup analyses.
- A general limitation to IPD analyses relates to the barriers of data collection when contacting authors, data delivery agreements and the availability of data.

INTRODUCTION

Hand osteoarthritis (OA) is a common joint disorder in the adult population.[1] Hand OA can manifest as soft-tissue swelling, inflammation, bony enlargement and bone erosion. The most frequently affected joints of the hand are the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the second through fifth fingers, and the first carpometacarpal (CMCI) joint of the thumb joint, which is also known as the trapeziometacarpal joint.[2] In some cases of CMCI OA, the scaphotrapezial-trapezoid (STT) joint and metacarpal phalangeal (MCP) joints are involved as well. Patients with hand OA experience symptoms of pain, stiffness, loss of mobility, and reduced strength which can lead to loss in hand function and can affect quality of life.[3] van der Oest *et al* found that CMCI OA is strongly associated with increasing age.[4] Similar results are found in PIP and DIP joints.[5 6] So with the increasing ageing population, it is expected that the number of patients who suffer from hand OA will increase in future years.[6]

Currently, there is no cure for OA, but treatment aims to reduce pain, functional disability and to optimise hand function. Non-pharmacological and non-surgical treatment interventions for hand OA patients can include splinting, patient education, and strengthening and range of movement (ROM) exercises by a hand therapist, but there remains a lack of evidence as to which

conservative therapy is most beneficial.[7 8] Earlier studies found discrepancies in the effect of interventions in RCTs due to heterogeneity in the patients in the studies and found also different responses to the same treatment.[9]

Due to the small and moderate effect sizes on treatment of hand OA, and since different responses to treatment between patient subgroups have been found, it is recommended to identify responsive subgroups in treating hand OA.[10] Identifying subgroups where interventions are effective could improve clinical decision making for the individual patient. Subgroups that differ based on demographic characteristics (e.g., age,[11] sex,[12] body mass index (BMI),[13] hypermobility[14]) and clinical characteristics (e.g., baseline pain, radiological grade of OA, erosive OA,[15] type, and the number of affected joints, and duration of symptoms[12]) are expected to show different treatment effects. An individual patient data (IPD) meta-analysis to quantify the effect, modified by these different subgroups, is suggested by the Steering Group of the OA Trial Bank. The OA Trial Bank is an initiative to identify subgroup effects of treatments by conducting IPD meta-analyses in OA patients.[16 17]

This study aims to identify subgroups of patients with hand OA that most benefit, in terms of pain and hand function, from different non-surgical and non-pharmacological treatments.

METHODS

This study will be conducted in collaboration with the OA Trial Bank (www.oatrialbank.com). We will use their methods of previously published protocols.[18–21] The final database with IPD of included RCTs will be deposited within the OA Trial Bank.

In collaboration with an Erasmus MC librarian, W.M. Bramer, we will develop a search strategy to collect all relevant RCTs by using the following databases; Embase, Medline and Cochrane.[22] The literature search was performed on 8 February 2021. Full search terms used for the specific online databases are shown in online supplemental appendix 1. We will include all available RCTs that meet the following criteria:

Participants

We will include all patients aged over 18 years old, who are diagnosed with OA of the hand according to American College of Rheumatology classification criteria[2] or on the basis of detailed clinical and/or radiographic information, or diagnosed by a health professional. OA of the STT, CMCI, MCP, PIP and/or DIP joints will be included. Studies including subgroups of hand OA patients will be included as well.

Interventions

Any intervention that is non-surgical or non-pharmacological will be included in this study. For instance, orthoses, patient education programmes and strengthening and ROM exercises by a hand therapist.

Comparison

Any comparison will be included.

Outcomes

Studies will need to have assessed a hand pain severity measure. Our primary outcome will be general hand pain, but as different measures of pain severity will be used, these may also be taken into account, dependent on the availability of data. Pain severity is described as a core outcome domain in the last OARSI recommendations. Our secondary outcomes are core outcome domains as well, including objective hand physical function (e.g., ROM, grip strength) and subjective physical functions (e.g., Disabilities of the Arm, Shoulder and Hand Questionnaire, Functional Index of Hand Osteoarthritis, Australian/Canadian Osteoarthritis Hand Index, Michigan Hand Outcomes Questionnaire).[23 24] Outcome data will be extracted at all available time points and classified into short term (closest to 12 weeks), mid-term (closest to 6 months) and long term (closest to 12 months). These time points will be used for further analyses.

Types of baseline assessments

As a minimum, studies will need to have assessed the level of baseline pain. Next to that, important patient characteristics, including sex, age, hypermobility, medication, BMI, occupation, type, and the number of affected joints, radiological severity, and duration of symptoms at baseline will be extracted if available.

Predictors

Next to that, important patient characteristics including sex, age, hypermobility, pain medication, BMI, occupation, erosive OA, type and the number of affected joints, radiological severity, and duration of symptoms will be considered potential predictor terms, if they are available.

Study design

Only RCTs will be included, no other study design. English, Dutch, and German written articles will be included.

Data collection

After finishing the literature search, titles and abstracts will be imported into EndNote V.X9. All titles and abstracts will be double screened by the authors (GT, MvM, JWC and RWS). Thereafter, selected full papers will be double reviewed by these authors. Then, the corresponding author of the included RCT of interest will be contacted following the procedures of the OA Trial Bank. The corresponding authors were asked to participate and consequently deliver anonymised IPD of the RCTs, that started in April 2021. All data deliverers will be asked to sign a data delivery license agreement, including items on input data, obligations, ownership of data, terms, authorship, statistical analyses and publications. We expect the data collection to be finished in June 2022. To ensure the quality of the data, it will be checked for data-entry mistakes and consistency, and all individual patient results

that we will receive will be compared with the published summary results of the primary studies. In case of differences, authors will be contacted to resolve the discrepancies. All datasets will be converted into a common format in R software (freely available at https://cran.r-project.org) to create one complete and homogeneous dataset. A new variable will identify the original RCT. The data will be contributed to the OA Trial Bank.

Data extraction

The data extracted from the published RCTs will include patient characteristics, disease-specific characteristics and all relevant outcome measures on all time points that are available. This will be presented alongside information on study design, target population, country of study and funding source. Preferably, we will conduct analyses using IPD. But in studies where we are unable to obtain IPD, but aggregate data is available, this will extract aggregate data instead.

Risk of bias

The risk of bias will be evaluated by two independent authors (GT and MvM) for every included study, using the revised version of the Cochrane Risk of Bias (RoB) tool, known as RoB 2.0.[25] Both original publications and IPD datasets will be graded ('low RoB,' 'high RoB,' or 'some concerns') on five domains: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. The overall study will be reported as high RoB if at least one domain is rated as high RoB or if some concerns are identified in multiple domains. The study will be reported as low RoB if all domains are rated with low RoB. If there will be any disagreement, a third author (SMAB-Z) will be contacted for discussion.

Analyses

All data will be cleaned and merged after data collection using R. The continuous data will be checked for normality for each study. When a considerable amount of data is missing at random, a multiple imputation method will be used within each trial before pooling the data. Data analyses will be conducted using R. The primary outcome, hand pain, will be standardised in order to pool the data. Secondary outcomes on hand physical function will be standardised as well. Subgroups were predefined by professionals in the field. The possible subgroups include age, sex, BMI, hypermobility and other comorbidities, pain medication, occupation, baseline pain, type and the number of hand joints involved, erosive OA, radiological severity of OA and duration of symptoms. If possible and homogenous, interventions will be clustered. Decisions will be made on consensus among the project group.

For this study, a two-stage approach of IPD analyses will be performed. During the first stage, from each trial, all IPD will be analysed separately to obtain aggregate data of effect estimates of interest and its CIs. When only aggregate data is available instead of IPD, this aggregate data can also be collected during the first stage of the two-stage analysis. Then, all aggregate data of included RCTs will be synthesised in the second stage to produce summary meta-analysis results. Treatment effects will be analysed using a random-effects model to account for between-study heterogeneity. Interaction terms will be used in the model to identify the predictors of response. The heterogeneity between the separate trials will be summarised by the estimated between-trial variance and be tested with I^2 statistics. A $p<0.05$ will be regarded as statistically significant.[26]

If studies with small study sizes will be identified, or few studies will be involved, a one-stage approach will be performed as alternative for the two-stage approach, by combining all IPD using a regression model that takes into account clustering of patients within studies.[27 28]

ETHICS AND DISSEMINATION

No new data will be collected, so research ethical or governance approval is exempt. The existing protocols of previous OA Trial Bank projects will be used to guide the confidential and secure transfer of IPD. We will store all data in a secured digital research environment, where all IPD of the OA Trial Bank projects are stored. Findings will be disseminated via national and international conferences, publications in peer-reviewed journals, and summaries posted on websites accessed by the public and clinicians. To inform patients, we will post our updates on our institutional patient platform. We aim to reach all types of professionals who are involved in non-surgical and non-pharmacological treatment of hand OA.

Author affiliations
[1]Department of General Practice, Erasmus MC, Rotterdam, Netherlands
[2]Department of Orthopaedics and Sports Medicine, Erasmus MC, Rotterdam, Netherlands
[3]Department of Rehabilitation Medicine, Erasmus MC, Rotterdam, Netherlands
[4]Department of Plastic and Reconstructive Surgery, Erasmus MC, Rotterdam, Netherlands
[5]School of Medicine, Keele University, Staffordshire, UK
[6]Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Keele, UK
[7]Keele Clinical Trials Unit, Keele University, Keele, UK

Twitter Ruud W Selles @ruudselles

Acknowledgements We thank Dr Wichor Bramer, librarian at Erasmus MC for assisting us during our literature search, and we thank the patient members of the advisory board for their contribution to this project

Contributors GT, MvM, RWS, JWC and SMAB-Z contributed to the initial conception of the study. GT and MvM drafted the manuscript. GT, MvM, RWS, JWC, KD, EN and SMAB-Z reviewed the manuscript. The OA Trial Bank Steering Committee peer-reviewed and approved the study protocol. The guarantor of the study is SMAB-Z.

Funding The OA Trial Bank was supported by ReumaNederland (grant number CIO-01). ReumaNederland is not involved in aspects as the design of the protocol or analysis plan. KD is part funded by the National Institute for Health Research (NIHR) Applied Health Research Collaboration (ARC) West Midlands (NIHR 200165). KD is an NIHR Senior Investigator (ID NIHR 200259). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Disclaimer The funder will have no input on results or publication of the results. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Competing interests None declared.

Patient and public involvement statement The Dutch Arthritis Foundation is a patient-driven foundation, aiming to improve treatment in patients with OA. The advisory board of the OA Trial Bank includes researchers in the field, a delegate of the Dutch Arthritis Foundation, and Patient Involvement (PPI). The patient members advise the Steering Committee of the OA Trial Bank on their activities. There is no patient involvement in the recruitment and conduct phase of this study given the nature of the study design.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Giesleen C E Thissen http://orcid.org/0000-0002-1381-2185
Ruud W Selles http://orcid.org/0000-0002-2432-6756

REFERENCES

1 Arden N, Nevitt MC. Osteoarthritis: epidemiology. *Best Pract Res Clin Rheumatol* 2006;20:3–25.
2 Altman R, Alarcón G, Appelrouth D, *et al*. The American College of rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum* 1990;33:1601–10.
3 Neogi T. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage* 2013;21:1145–53.
4 van der Oest MJW, Duraku LS, Andrinopoulou ER, *et al*. The prevalence of radiographic thumb base osteoarthritis: a meta-analysis. *Osteoarthritis Cartilage* 2021;29:785–92.
5 Dahaghin S, Bierma-Zeinstra SMA, Ginai AZ, *et al*. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682–7.
6 Haugen IK, Englund M, Aliabadi P, *et al*. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham osteoarthritis study. *Ann Rheum Dis* 2011;70:1581–6.
7 Spaans AJ, van Minnen LP, Kon M, *et al*. Conservative treatment of thumb base osteoarthritis: a systematic review. *J Hand Surg Am* 2015;40:16–21.
8 Towheed TE. Systematic review of therapies for osteoarthritis of the hand. *Osteoarthritis Cartilage* 2005;13:455–62.
9 Veronese N, Smith L, Bolzetta F, *et al*. Efficacy of conservative treatments for hand osteoarthritis: an umbrella review of interventional studies. *Wien Klin Wochenschr* 2021;133:234–40.
10 Billig JI, Kane RL, Yue M, *et al*. Discrepancies in conservative treatment for thumb carpometacarpal arthritis: a comparison between different specialities and patient characteristics. *J Hand Surg Eur Vol* 2021;46:141–5.
11 Tsehaie J, Spekreijse KR, Wouters RM, *et al*. Outcome of a hand orthosis and hand therapy for Carpometacarpal osteoarthritis in daily practice: a prospective cohort study. *J Hand Surg Am* 2018;43:1000–9.
12 Srikanth VK, Fryer JL, Zhai G, *et al*. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage* 2005;13:769–81.
13 Bliddal H, Christensen P, Riecke BF, *et al*. Osteoarthritis - a role for weight management in rheumatology practice: an update. *Clin Obes* 2011;1:50–2.
14 Riordan E, Robbins S, Deveza L, *et al*. Radial subluxation in relation to hand strength and radiographic severity in trapeziometacarpal osteoarthritis. *Osteoarthritis Cartilage* 2018;26:1506–10.
15 Kloppenburg M, Maheu E, Kraus VB, *et al*. OARSI clinical trials recommendations: design and conduct of clinical trials for hand osteoarthritis. *Osteoarthritis Cartilage* 2015;23:772–86.
16 van Middelkoop M, Arden NK, Atchia I, *et al*. The OA trial bank: meta-analysis of individual patient data from knee and hip osteoarthritis trials show that patients with severe pain exhibit greater benefit from intra-articular glucocorticoids. *Osteoarthritis Cartilage* 2016;24:1143–52.
17 Runhaar J, Rozendaal RM, van Middelkoop M, *et al*. Subgroup analyses of the effectiveness of oral glucosamine for knee and hip osteoarthritis: a systematic review and individual patient data meta-analysis from the OA trial bank. *Ann Rheum Dis* 2017;76:1862–9.
18 Persson MSM, Fu Y, Bhattacharya A, *et al*. Relative efficacy of topical non-steroidal anti-inflammatory drugs and topical capsaicin in osteoarthritis: protocol for an individual patient data meta-analysis. *Syst Rev* 2016;5:165.
19 van Middelkoop M, Dziedzic KS, Doherty M, *et al*. Individual patient data meta-analysis of trials investigating the effectiveness of intra-articular glucocorticoid injections in patients with knee or hip osteoarthritis: an OA trial bank protocol for a systematic review. *Syst Rev* 2013;2:54.
20 Holden MA, Burke DL, Runhaar J, *et al*. Subgrouping and targeted exercise pRogrammes for knee and hip osteoarthritis (STEER OA): a systematic review update and individual participant data meta-analysis protocol. *BMJ Open* 2017;7:e018971.
21 Macri EM, Callaghan M, van Middelkoop M, *et al*. Effects of mechanical interventions in the management of knee osteoarthritis: protocol for an OA trial bank systematic review and individual participant data meta-analysis. *BMJ Open* 2021;11:e043026.
22 Bramer WM, Rethlefsen ML, Kleijnen J, *et al*. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Syst Rev* 2017;6:245.
23 Bobos P, MacDermid JC, Boutsikari EC, *et al*. Evaluation of the content validity index of the Australian/Canadian osteoarthritis hand index, the patient-rated wrist/hand evaluation and the thumb disability exam in people with hand arthritis. *Health Qual Life Outcomes* 2020;18:302.
24 Marks M. Which patient-reported outcomes shall we use in hand surgery? *J Hand Surg Eur Vol* 2020;45:5–11.
25 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
26 Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med* 2017;36:855–75.
27 Stewart GB, Altman DG, Askie LM, *et al*. Statistical analysis of individual participant data meta-analyses: a comparison of methods and recommendations for practice. *PLoS One* 2012;7:e46042.
28 Langan D, Higgins JPT, Jackson D, *et al*. A comparison of heterogeneity variance estimators in simulated random-effects meta-analyses. *Res Synth Methods* 2019;10:83–98.

APPENDIX 1

SEARCH TERMS

embase.com

('hand osteoarthritis'/de OR (('hand joint'/exp OR 'hand bone'/exp OR hand/exp OR 'hand disease'/de OR 'hand pain'/de OR 'proximal interphalangeal joint'/de OR 'distal interphalangeal joint'/de OR 'interphalangeal joint'/de) AND (osteoarthritis/de OR arthritis/de)) OR 'hand arthritis'/de OR (((hand OR hands OR carpal OR carpometacarp* OR finger OR metacarp* OR trapeziometacarp* OR rhiz OR thumb OR trapezioscaphoid* OR interphalang* OR trapezio-scaphoid* OR inter-phalang*) NEAR/6 (osteoarthrit* OR osteo-arthrit* OR arthrosis OR oa))):ab,ti) AND ('Controlled clinical trial'/exp OR 'Crossover procedure'/de OR 'Double-blind procedure'/de OR 'Single-blind procedure'/de OR (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo* OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups):ab,ti,kw) NOT ([animals]/lim NOT [humans]/lim) NOT [conference abstract]/lim

Medline (Ovid)

(((exp Hand Joints/ OR exp Hand Bones/ OR exp Hand/) AND (Osteoarthritis/ OR Arthritis/)) OR (((hand OR hands OR carpal OR carpometacarp* OR finger OR metacarp* OR trapeziometacarp* OR rhiz OR thumb OR trapezioscaphoid* OR interphalang* OR trapezio-scaphoid* OR inter-phalang*) ADJ6 (osteoarthrit* OR osteo-arthrit* OR arthrosis OR oa))).ab,ti.) AND (Exp Controlled clinical trial/ OR "Double-Blind Method"/ OR "Single-Blind Method"/ OR "Random Allocation"/ OR (random* OR factorial* OR crossover* OR cross over* OR placebo* OR ((doubl* OR singl*) ADJ blind*) OR assign* OR allocat* OR volunteer* OR trial OR groups).ab,ti,kf.) NOT (exp Animals/ NOT Humans/)

Cochrane CENTRAL register of Trials

((((hand OR hands OR carpal OR carpometacarp* OR finger OR metacarp* OR trapeziometacarp* OR rhiz OR thumb OR trapezioscaphoid* OR interphalang* OR trapezio-scaphoid* OR inter-phalang*) NEAR/6 (osteoarthrit* OR osteo-arthrit* OR arthrosis OR oa))):ab,ti)