Postoperative exercise therapy in subgroups of patients with knee osteoarthritis: outcomes on pain and function after TKA/UKA – A protocol for an individual patient data systematic review

Protocol paper for website OA trial bank

Upasna Sharma[1*], Jos Runhaar[1], P. Koen Bos[2], Desirée M. J. Dorleijn[3], Marijn Vis[4], Patrick J. E. Bindels[1], Max Reijman[2], Marienke van Middelkoop[1,5] and Sita M. A. Bierma-Zeinstra[1,2]

Author affiliations
[1]Department of General Practice, Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands
[2]Department of Orthopedics & Sports Medicine, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands
[3]Department of Orthopedics, Leiden University Medical Center, Leiden, The Netherlands
[4]Department of Rheumatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands
[5] OA Trial Bank Steering Group, Rotterdam, Netherlands
[*]Corresponding author: r.sharma@erasmusmc.nl
Department of General Practice, Erasmus MC University Medical Center Rotterdam, PO-box 2040, 3000, CA, Rotterdam, The Netherlands

Abstract

Introduction Osteoarthritis (OA) is a common disorder in the ageing people, which mostly affects the knee joint. Several treatment options are available to reduce pain or improve knee function with a possibility of surgical interventions at end-stage knee OA, taking complications and comorbidities into account. Exercise therapy (ET) is one of the non-surgical, non-pharmacological therapy interventions with beneficial effects, recommended by international clinical guidelines. Several studies have shown a beneficial effect of ET on pain, stiffness, muscle weakness and physical function. Still it is unknown which patients benefit from ET given post-surgery, as the overall effects of postoperative ET are rather small and patients with knee OA consist of an heterogeneous group. Therefore this study aims to identify subgroups of patients with knee OA who have better outcome after postoperative ET compared to usual care. This could be an approach to individualized patient care to improve treatment and patient outcomes.

Methods and analysis We will perform an individual patient data (IPD) analysis with IPD data of relevant published randomized controlled trials (RCTs). We will conduct a systematic literature search through Embase, Medline, Web of Science, CINAHL and Scopus. The primary outcome will be the difference of self-reported pain and knee function 6 months post-surgery and post ET on a WOMAC/KOOS scale between the subgroups and the secondary outcomes are pain and physical function measured at other time points and scales, hospital stay duration, adverse events, analgesic use and quality of life.

The subgroups will be defined based on age, sex, body mass index (BMI), severity of pain and physical disability, muscle strength, mental health complaints, presence of comorbidities, daily physical activity, radiographic involvement of patellofemoral compartment and swelling of the knee joint. IPD of RCTs will be pooled if the exercise interventions are homogenous and analysed using a two-stage approach to evaluate the treatment effect in different subgroups.

Ethics and dissemination For this study no new data is collected and therefore research ethical or governance approval is exempted. Findings shall be presented and shared via national and international conferences, publications in peer-reviewed journals and summaries on websites, which are accessible by the public and professionals.

Keywords Osteoarthritis, knee joint, exercise therapy, postoperative, individual patient data

Introduction

Osteoarthritis (OA) is a disabling disease, affecting the knee joint most commonly.(1) Knee OA is a clinical diagnosis, with knee pain as one of the most disabling symptoms, supported by radiographic imaging.(2) Management of knee OA after surgery consists of different types of pharmacological and non-pharmacological treatments. At end-stage knee OA the recommended treatment is joint replacement surgery, such as total knee joint replacement, for patients with severe functional impairment. This intervention is more common due to the ageing population. Postoperative immobilization was the former treatment preference, but recent studies have shown that early postoperative mobilization is beneficial for the recovery of range of motion of the knee joint.(2-4) As per the OARSI guidelines for non-surgical management of knee OA, exercise therapy (ET) might have a small but clinically relevant short-term beneficial outcome for pain and physical function.(5) However, the effectiveness of post-operative ET and moreover which patients would benefit in the postoperative recovery process, is still uncertain due to overall small effect sizes and variable outcomes. Also a suboptimal content of exercise programmes and heterogeneous OA population influence the effectiveness of postoperative ET.(6) By looking at individual patient level, it might be possible to target a subgroup which will have better outcomes with postoperative ET on pain and physical function.

The aim of this study is to investigate moderators of the effect of postoperative ET on subgroups of patients with knee OA compared to usual care (no exercise controls) to pain and physical function postoperatively. This will be performed by an individual patient data (IPD) analysis.

Methods

We will perform an IPD analysis of randomized clinical trials (RCTs) studying the effectiveness of postoperative ET in patients with knee OA after a total knee arthroplasty (TKA) or uni-compartmental knee arthroplasty (UKA). This study will be conducted in collaboration with and adhering to the protocols of the OA Trial Bank (www.oatrialbank.com). The OA Trial Bank and data deliverer will have a data sharing agreement. All data of the included RCTs will be submitted and stored within the OA Trial Bank. This protocol is not registered in the PROSPERO database.

A systematic search strategy has been developed in collaboration with Erasmus MC librarian, W.M. Bramer. This search strategy is to collect all relevant RCTs by using different databases, such as Embase, Medline, Web of Science, CINAHL and Scopus.(7) This literature search was performed on 13th June 2022. The full search strategy with all search terms for each specific online database are shown in online supplemental appendix 1.

The following criteria will be applied to identify all relevant RCTs for this IPD analysis.

Study design

We will include all peer-reviewed RCTs studying postoperative ET in all adult patients with knee OA after a primary knee replacement surgery (TKA or UKA).

Participants

We will include all patients, men or women, undergoing a primary knee joint replacement for OA. Studies with other surgery treatment than TKA or UKA or with patients having a previous prosthesis of the affected knee joint will be excluded. In case it is not mentioned in the article, the IPD will be

screened on these criteria. RCTs studying subgroups will also be included, because individual patient data are collected.

Intervention

To select the RCTs we will follow the WHO definition of ET, which is defined as participation in physical activity, existing of many forms: aerobic, strength, flexibility, balance or body-region specific exercises. This should be supervised, structured, repetitive and purposeful for the improvement or maintenance of (physical fitness, physical performance or) a specific health condition, like OA. (8, 9) This definition is to ensure the dose, frequency and intensity of the intervention, and which will not be considered as criteria to in- or exclude studies for this IPD analysis.
The postoperative exercise therapy should be initiated within 1 year after surgery. ET given directly after the surgery and for the length of hospital stay only, with no further therapy after discharge, will not be considered as an intervention, but as control group. Education/self-management/ motivational techniques or other treatments (i.e. pharmacological, but no other surgical treatment) can be part of the interventions. Studies will be excluded if exercise therapy is combined with other form of interventions (i.e. pharmacological treatment, other surgical treatment), so that treatments effects attributed to exercise therapy alone could be measured.(8)

Comparison

RCTs should compare the postoperative exercise therapy with control groups, having usual care, such as usual physician follow up with no intervention (usual physical activity), education and advice, pharmacological treatment, unsupervised home training (e.g. with a maximum of one physiotherapist consult) or exercise therapy given directly after surgery and limited for the length of hospital stay, with no further supervised, repetitive or structured therapy after discharge.

Outcomes

The outcome of the RCTs should at least include one or more adequate patient reported outcome measure (PROM) on pain or physical function, measured minimal one time point within a year after surgery. The measurement scales should be one of the following: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS).

Types of baseline assessments

As a minimum, the potential RCTs will need to have assessed at least one or more of the subgroup factors (see next paragraph). Also, there should be baseline PROMs either pre-surgery or before or at start of the postoperative ET. At least the level of baseline pain or function, age and sex should be mentioned. Besides that, other important patient characteristics, including body mass index (BMI), comorbidities, occupation, radiological severity and duration of symptoms at baseline (i.e. how long on the waiting list), will be extracted if available. These characteristics will be used to classify the patients in the subgroups and taken into account for bias evaluation.

Subgroup definitions

We have pre-defined potential subgroups by reviewing the literature and by expert opinion. A thorough search of the literature has been conducted to identify clinical important moderators. These possible moderators have been discussed with clinical experts (project group, see author list) to get a definitive set of potential moderators for postoperative exercise therapy. We have identified the following possible effect modifiers: age, sex, pain severity, severity of physical disability, muscle strength, mental

health (anxiety or depression), radiographic involvement of patellofemoral compartment and swelling of the knee joint. The previous mentioned primary effect modifiers, if not available, will be substituted by other variables as secondary effect modifiers, such as comorbidities (osteoarthritis elsewhere, cardiovascular, respiratory diseases, neurologic (not able to perform ET)), daily usual physical activity, working status, use of a walking aid, use and need of analgesics and length of stay in hospital. (10-13) To identify potential clinical relevant subgroups with clinical implications, we will dichotomize some of these moderators, before analyzing the data, by determining cut-off values based on the distribution of the data, the prevalence and consensus within the project group. Few studies have been performed on the effectiveness of postoperative rehabilitation and therefore the hypothesized direction of the effect for some potential moderators is variable due to lack of evidence.(14)

IPD analysis

For this IPD analysis there will be no language restriction and animal studies will be excluded. Inclusion criteria of the population, intervention and comparison are based on the criteria for the RCTs. The purpose of post-operative ET should be reduction of pain and improvement of function (e.g. range of motion of the knee joint).

Outcome measures

A recent IPD review of Georgopoulos et al. (OARSI 2022 (15)) found substantial heterogeneity within data of individuals due to which caution is required in PROMs harmonization for IPD analysis. Although a hierarchy of outcome measures has been presented by the Cochrane Musculoskeletal Review Group (16), PROMs should be selected according to the clinical population and research question. All trials will be clustered based on their outcomes (e.g. PROMs or performance-based outcome). Outcomes measured on different scales will be standardized to pool the data.

Primary outcome

For this IPD analysis the difference in self-reported pain and function score (e.g. WOMAC/KOOS) between the subgroups, at any outcome measure point closest to 6 months postoperative and post ET, will be the primary outcome.

Secondary outcome

The following measurements will be considered as secondary outcomes, if trials have measured them at any other time point (e.g. after 8 weeks, 3 months or 12 months of follow-up post-surgery or post ET):

- Self-reported pain (measured on VAS/NRS),
- Self-reported physical function score (WOMAC/KOOS),
- Range of motion,
- Performance-based score

The OARSI guidelines recommended a core set of performance-based tests of physical function (30-second chair stand test, 4x10 m fast-paced walk test and stair climb test). These have also been assessed by Tolk et al. (17, 18). We will consider the change in these performance-based outcome measures, if two or more studies have analysed one of these.

- Hospital stay duration,
- Adverse events,
- (reduction of) analgesic use,
- Quality of life (measured by KOOS, QALY, SF-36)

Data collection

Multiple reviewers will independently select studies based on titles and abstracts and import these articles into EndNote 20.0.1. Full articles fulfilling the inclusion criteria will be obtained for those citations and screened by two authors, independently. A third author will be consulted if consensus is not reached. Then, the first author and/or corresponding author of the included RCTs will be contacted following the procedures of the OA Trial Bank. If the corresponding author cannot be reached, we will contact the other authors or institutes in which the trials have taken place. They will be requested to participate and consequently share anonymized IPD of the RCTs. Full protocol details for the IPD meta-analysis are pre-specified in the data delivery license agreement, that was approved by all members of the OA trial Bank Steering Committee.

A data delivery license agreement has been set up by the OA Trial Bank, including items on input data, obligations, ownership of data, terms, authorship, statistical analyses and publications. All data deliverers will be asked to sign this agreement. Data-entry mistakes and consistency will be checked to ensure the quality of the data. Also all individual patient results will be compared with the published summary results of the primary studies. If there will be differences, authors will be contacted to resolve the discrepancies.

Risk of bias

The risk of bias will be evaluated for every included trial, by two independent authors, using the revised version of the Cochrane Risk of Bias (RoB) tool, known as RoB 2.0 (19). The criteria can be scored as 'yes' (low risk of bias), 'no' (high risk of bias) or 'unclear'. If a trial fulfilled six or more criteria items, the trial will be considered having a low risk of bias, which is supported by empirical evidence.(20) A disagreement between the reviewers will be discussed with input from a third reviewer.

Data extraction

The following data will be extracted from the published RCTs as per the availability: list of authors, target population, country of study, publication year, patient characteristics (age, sex, BMI), disease-specific characteristics (clinical criteria, radiographic information, duration of complaints, on-going treatments), details of the intervention (e.g. exercise therapy and surgery) and intervention measures, comparator groups, and all outcome measures of pain or function on all time-points that are available. Interventions will be categorized by frequency, intensity, type, duration, setting, and exercise deliverer.(8)

All trials will be allocated with an individual random trial number by creating a new variable after converting all datasets into a common format with IBM SPSS statistics software 28.0 (or any latest version). This will create one complete and homogeneous dataset with all randomized patients in the pooled database.

Data analysis

After receiving the datasets, an IPD analysis will be performed. We will follow an intention-to-treat analysis. For this study, a two-stage approach will be performed, where from each trial all IPD is analyzed separately in the first stage to obtain aggregate data of effect estimates of interest, which are then synthesized in the second stage to produce summary meta-analysis results based on a random effect model. To have a better power for the subgroup analysis, at least two or more studies should have investigated a moderator. The mixed-effect regression model (or hierarchical) method is particularly suitable for investigating interaction effects between the subgroups. Interactions will be estimated in each trial separately to avoid aggregation bias and estimate the treatment-covariate

interactions, after which they will be synthesized in the second stage. The model will include the baseline and follow-up measures of dependent variables (i.e. pain intensity or physical function score), independent variables (i.e. treatment (postoperative ET or usual care)), the effect modifier (different subgroups), and an interaction term (subgroup x treatment). A single covariate will be included in the regression model to adjust for possible residual confounding by study differences. The mean difference (for continuous outcomes) and odds ratio (for binary outcomes) will be estimated for the pooled subgroup effect of postoperative ET. A p-value of <0.05 is regarded as statistically significant. When obtaining too few studies (i.e. less than 3 RCTs or < 100 patients in total), an one-stage approach will be performed by combining all individual patient data in a single meta-analysis based on a regression model stratified by trial.(21) If there will be more than 3 RCTs with a total of > 100 patients for one type of control group, then we will analyze subgroups per control group. The control groups will be divided into non-surgical (e.g. pharmacological) treatment and no treatment.

It is important to note that the population of both surgery methods differ. Therefore at first an overall analysis will be performed, to then look for interaction between ET and type of surgery method, within the different type of surgery groups.

We assume the data to be missing at random, in case this is more than 10% observed patient characteristics will be used to impute missing data (potential covariates and outcomes) by means of multiple imputation. Missing data will be imputed within each original study, before data of the individual studies are pooled.(20)

Heterogeneity

During selection of the trials, the interventions will be screened on clinical heterogeneity. We expect the types of interventions, in the several trials, to be heterogeneous with different rehabilitation protocols. Details of the interventions will be specified in order to see if interventions are homogenous and can be clustered, if possible. The between-study differences will be assessed by a descriptive comparison.

Statistical heterogeneity of the eligible studies will be determined for the primary outcomes, using a two-stage meta-analysis approach in Review Manager V.5.3. A sensitivity analyses will be done without data from trials causing the heterogeneity, in case of high heterogeneity (I^2 index >50).

Status of project

Currently, the search strategy has been completed. We expect the study selection to be finished in February 2023. Data collection is expected to be finished by December 2023.

Ethics and dissemination

Ethical research approval or governance approval is exempted for this IPD analysis, as no new data will be collected. To secure the confidentiality and secure transfer of IPD, existing protocols of previous OA Trial Bank projects will be used. All data will be stored in a secured digital research environment of the OA Trial Bank. Results and finding of this IPD analysis will be shared via national and international meetings, conferences, publications in peer-reviewed journals. Also summaries will be posted on websites (including our institutional patient platform) accessed by the public, clinicians and patients. Our aim is to inform all professionals involved with (all type/non-surgical and non-pharmacological) treatment modalities of knee OA.

Acknowledgements The authors wish to thank Mr. W.M. Bramer from the Erasmus MC Medical Library for developing and updating the search strategies.
Contributors JR and SMAB-Z contributed to the initial conception of the study. US and JR drafted the protocol. US, JR, PKB, DMJD, MV, PJEB, MR, MvM, and SMAB-Z reviewed the protocol. 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 Dutch Arthritis Society (Reuma Nederland) (grant number CIO-01). Reuma Nederland is not involved in aspects as the design of the protocol or analysis plan. This project (project number 839150009) is funded by ZonMw, an organization focused on health science research & innovation. ZonMw designs programs and finance projects commissioned by the Ministry of Public Health, Welfare and Sport and the Dutch Organisation of Scientific Research. Besides funding, ZonMw also reaches out to the public to discover and minimize the knowledge gaps by connecting the right people to relevant scientific developments.
Disclaimer The funder will have no input on results or publication of the results.
Competing interests None declared
Patient and public involvement statement The Dutch Arthritis Society aims to improve treatment in patients with OA being a patient-driven foundation. The advisory board of the OA Trial Bank includes researchers in the field, a delegate of the Dutch Arthritis Foundation, and Patient Involvement (PPI). Patient members advise the Steering Committee of the OA Trial Bank on their activities. Given the nature of the study design, there is no patient involvement in the recruitment and conduct phase of this study. The generated results and conclusions however will be translated into laymen text and spread to patients and the general public through regular meetings of patient-oriented organisations and info-bulletins on Artrose Gezond, an OA patient oriented webbased platform.
Patient consent for publication Not applicable.

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Supplemental appendix 1: Search strategy

embase.com

('knee osteoarthritis'/de OR 'total knee arthroplasty'/de OR (('knee pain'/de OR 'patellofemoral joint'/de OR knee/de OR 'lower limb'/de) AND osteoarthritis/de) OR (((knee* OR femorotibial* OR tibiofemoral* OR tibio-femoral* OR femoro-tibial* OR patellofemor* OR patell*-femor* OR lower-limb* OR lower-extremit*) NEAR/6 (osteoarthr* OR osteo-arthr* OR arthrosis* OR arthroses* OR arthroplast*)) OR gonarthro*):ab,ti) AND (kinesiotherapy/de OR physiotherapy/exp OR physiotherapist/de OR 'aerobic exercise'/exp OR 'anaerobic exercise'/exp OR 'aquatic exercise'/exp OR 'dynamic exercise'/exp OR 'exercise intensity'/exp OR 'high intensity exercise'/exp OR 'isokinetic exercise'/exp OR 'leg exercise'/exp OR 'low intensity exercise'/exp OR 'moderate intensity exercise'/exp OR 'muscle exercise'/exp OR 'preoperative exercise'/exp OR 'static exercise'/exp OR 'isometric exercise'/de OR 'movement therapy'/de OR 'muscle training'/de OR 'stretching exercise'/de OR (kinesiotherap* OR kinesitherap* OR (exercise* NEAR/3 (therap* OR treatment*)) OR physiotherap* OR physi*-therap* OR ((aerobic* OR anaerobic* OR aquatic* OR dynamic* OR intensity* OR isokinetic* OR leg* OR muscle* OR preoperative* OR static* OR isometr* OR stretching OR walking OR strengthen* OR postoperat*) NEAR/3 (exercise* OR training)) OR (movement NEAR/3 therap) OR ((muscle OR strength) NEAR/3 trainin*)):ab,ti) AND ('knee arthroplasty'/exp OR arthroplasty/de OR 'orthopedic surgery'/de OR 'joint surgery'/de OR 'preoperative period'/de OR 'postoperative period'/de OR 'osteoarthritis'/exp/dm_su OR (preoperati* OR pre-operati* OR presurg* OR pre-surg* OR postoperati* OR post-operati* OR postsurg* OR post-surg* OR waiting-list* OR surger* OR surgical* OR waitinglist* OR ((knee OR joint*) NEAR/3 (arthroplast* OR replacement*))):Ab,ti) NOT [conference abstract]/lim NOT ([animals]/lim NOT [humans]/lim)

Medline ALL Ovid

(Osteoarthritis, Knee/ OR Arthroplasty, Replacement, Knee/ OR ((Patellofemoral Joint/ OR Knee Joint/ OR Knee/ OR Lower Extremity/) AND Osteoarthritis/) OR (((knee* OR femorotibial* OR tibiofemoral* OR tibio-femoral* OR femoro-tibial* OR patellofemor* OR patell*-femor* OR lower-limb* OR lower-extremit*) ADJ6 (osteoarthr* OR osteo-arthr* OR arthrosis* OR arthroses* OR arthroplast*)) OR gonarthro*).ab,ti.) AND (exercise therapy/ OR exp Physical Therapy Modalities/ OR Physical Therapists/ OR High-Intensity Interval Training/ OR Preoperative Exercise/ OR Muscle Stretching Exercises/ OR (kinesiotherap* OR kinesitherap* OR (exercise* ADJ3 (therap* OR treatment*)) OR physiotherap* OR physi*-therap* OR ((aerobic* OR anaerobic* OR aquatic* OR dynamic* OR intensity* OR isokinetic* OR leg* OR muscle* OR preoperative* OR static* OR isometr* OR stretching OR walking OR strengthen* OR postoperat*) ADJ3 (exercise* OR training)) OR (movement ADJ3 therap) OR ((muscle OR strength) ADJ3 trainin*)).ab,ti.) AND (Arthroplasty, Replacement, Knee/ OR Arthroplasty, Replacement/ OR Orthopedic Procedures/ OR Surgical Procedures, Operative/ OR Preoperative Period/ OR Postoperative Period/ OR Waiting Lists/ OR exp Osteoarthritis/su OR (preoperati* OR pre-operati* OR presurg* OR pre-surg* OR postoperati* OR post-operati* OR postsurg* OR post-surg* OR waiting-list* OR surger* OR surgical* OR waitinglist* OR ((knee OR joint*) ADJ3 (arthroplast* OR replacement*))).ab,ti.) NOT (exp animals/ NOT humans/)

Web of science

TS=(((((knee* OR femorotibial* OR tibiofemoral* OR tibio-femoral* OR femoro-tibial* OR patellofemor* OR patell*-femor* OR lower-limb* OR lower-extremit*) NEAR/5 (osteoarthr* OR osteo-arthr* OR arthrosis* OR arthroses* OR arthroplast*)) OR gonarthro*)) AND ((kinesiotherap* OR kinesitherap* OR (exercise* NEAR/2 (therap* OR treatment*)) OR physiotherap* OR physi*-therap* OR ((aerobic* OR anaerobic* OR aquatic* OR dynamic* OR intensity* OR isokinetic* OR leg* OR muscle* OR preoperative* OR static* OR isometr* OR stretching OR walking OR strengthen* OR postoperat*) NEAR/2 (exercise* OR training)) OR (movement NEAR/2 therap) OR ((muscle OR strength) NEAR/2 trainin*))) AND ((preoperati* OR pre-operati* OR presurg* OR pre-surg* OR postoperati* OR post-operati* OR postsurg* OR post-surg* OR waiting-list* OR surger* OR surgical* OR waitinglist* OR ((knee OR joint*) NEAR/2 (arthroplast* OR replacement*))))) AND DT=(article)

Scopus

TITLE-ABS-KEY(((((knee* OR femorotibial* OR tibiofemoral* OR tibio-femoral* OR femoro-tibial* OR patellofemor* OR patell*-femor* OR lower-limb* OR lower-extremit*) W/5 (osteoarthr* OR osteo-arthr* OR arthrosis* OR arthroses* OR arthroplast*)) OR gonarthro*)) AND ((kinesiotherap* OR kinesitherap* OR (exercise* W/2 (therap* OR treatment*)) OR physiotherap* OR physi*-therap* OR ((aerobic* OR anaerobic* OR aquatic* OR dynamic* OR intensity* OR isokinetic* OR leg* OR muscle* OR preoperative* OR static* OR isometr* OR stretching OR walking OR strengthen* OR postoperat*) W/2 (exercise* OR training)) OR (movement W/2 therap) OR ((muscle OR strength) W/2 trainin*))) AND ((preoperati* OR pre-operati* OR presurg* OR pre-surg* OR postoperati* OR post-operati* OR postsurg* OR post-surg* OR waiting-list* OR surger* OR surgical* OR waitinglist* OR ((knee OR joint*) W/2 (arthroplast* OR replacement*))))) AND DocType(ar)

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(MH Osteoarthritis, Knee OR ((MH Knee Joint OR MH Knee OR MH Lower Extremity) AND MH Osteoarthritis) OR TI(((knee* OR femorotibial* OR tibiofemoral* OR tibio-femoral* OR femoro-tibial* OR patellofemor* OR patell*-femor* OR lower-limb* OR lower-extremit*) N5 (osteoarthr* OR osteo-arthr* OR arthrosis* OR arthroses* OR arthroplast*)) OR gonarthro*) OR AB(((knee* OR femorotibial* OR tibiofemoral* OR tibio-femoral* OR femoro-tibial* OR patellofemor* OR patell*-femor* OR lower-limb* OR lower-extremit*) N5 (osteoarthr* OR osteo-arthr* OR arthrosis* OR arthroses* OR arthroplast*)) OR gonarthro*)) AND (MH Therapeutic Exercise OR MH Lower Extremity Exercises OR MH Physical Therapy + OR MH Physical Therapists OR MH High-Intensity Interval Training OR TI(kinesiotherap* OR kinesitherap* OR (exercise* N2 (therap* OR treatment*)) OR physiotherap* OR physi*-therap* OR ((aerobic* OR anaerobic* OR aquatic* OR dynamic* OR intensity* OR isokinetic* OR leg* OR muscle* OR preoperative* OR static* OR isometr* OR stretching OR walking OR strengthen* OR postoperat*) N2 (exercise* OR training)) OR (movement N2 therap) OR ((muscle OR strength) N2 trainin*)) OR AB(kinesiotherap* OR kinesitherap* OR (exercise* N2 (therap* OR treatment*)) OR physiotherap* OR physi*-therap* OR ((aerobic* OR anaerobic* OR aquatic* OR dynamic* OR intensity* OR isokinetic* OR leg* OR muscle* OR preoperative* OR static* OR isometr* OR stretching OR walking OR strengthen* OR postoperat*) N2 (exercise* OR training)) OR (movement N2 therap) OR ((muscle OR strength) N2 trainin*))) NOT (MH animals+ NOT MH humans+) AND (MH Arthroplasty, Replacement, Knee OR MH Arthroplasty, Replacement OR MH Arthroplasty OR MH Orthopedic Surgery OR MH Surgery, Operative OR MH Preoperative Period OR MH Postoperative Period OR MH Waiting Lists OR TI(preoperati* OR pre-operati* OR presurg* OR pre-surg* OR postoperati* OR post-operati* OR

postsurg* OR post-surg* OR waiting-list* OR surger* OR surgical* OR waitinglist* OR ((knee OR joint*) N2 (arthroplast* OR replacement*))) OR AB(preoperati* OR pre-operati* OR presurg* OR pre-surg* OR postoperati* OR post-operati* OR postsurg* OR post-surg* OR waiting-list* OR surger* OR surgical* OR waitinglist* OR ((knee OR joint*) N2 (arthroplast* OR replacement*))))