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SUMMARY WITH CRITICAL APPRAISAL

Physical Activity for Chronic Osteoarthritic Knee Pain: A Review of Clinical Effectiveness

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AMSTAR	A Measurement Tool to Assess Systematic Reviews
CI	Confidence intervals
ES	Effect size
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HRQoL	Health-related quality of life
KOA	Knee osteoarthritis
KOOS	Knee Injury and Osteoarthritis Outcome Score
MA	Meta-analysis
OA	Osteoarthritis
PICO	Population, intervention, comparator, and outcome
RCT	Randomized controlled trial
RoB	Risk of bias
RR	Risk ratio
SF-36	Short-Form 36 Questionnaire
SMD	Standardized mean differences
SR	Systematic review

Context and Policy Issues

Osteoarthritis is caused by the wearing down of cartilage in the joints of the body and thickening of the bones underneath.[1,2] The condition causes varying degrees of pain, stiffness and swelling, and may lead to joint damage. Risk factors include age, heredity, obesity, and previous joint injury.[2] Among individuals older than 55 years of age, the prevalence of osteoarthritis is greater in women than men (33.6% for women and 24.3% for men).[1,3] However, the prevalence is the same among men and women of younger age, with men being slightly more vulnerable.[1]

Although osteoarthritis typically affects hands, feet, knees, spine, and hips, it occurs more frequently at the knee than the other joints.[4] The pain, joint stiffness, instability, and decreased physical function associated with KOA lead to declines in activity and disability that can result in a higher risk of obesity, cardiovascular disease, diminished quality of life, and death among affected patients compared with the general population.[3]

Treatments aimed to decrease pain and improve joint mobility include analgesics and anti-inflammatory drugs, exercise, physiotherapy, weight loss or healthy weight programs, and self- management education programs.[2] In severe cases, surgery to replace the entire joint may be recommended.[2] Exercise is generally recommended as a core non-pharmacological therapy to improve symptoms and the general well-being of people with KOA due to its relative safety compared with pharmacological treatments.[5]

In 2017, CADTH produced a Rapid Response report summarizing evidence on the clinical effectiveness of exercise for the management of KOA.[6] In 2019, a CADTH Rapid Response Reference List report[7] indicated availability of new and potentially relevant publications on the clinical effectiveness of physical activity on chronic non-cancer pain. Therefore, the objective of this report is to review and summarize any new evidence that may have become available since the 2017.

Research Question

What is the clinical effectiveness of physical activity for chronic, non-cancer knee pain from osteoarthritis?

Key Findings

Evidence from two traditional systematic reviews and one systematic umbrella review suggested that in patients with knee osteoarthritis, physical activity significantly reduced pain and improved function, performance, and health-related quality of life compared with usual care (not consistently defined), no treatment, or sham interventions.

Limited evidence from one systematic review suggested higher temporary increases in minor pain with exercise than with sham interventions, and no difference in worsening pain, falls, or death between exercise and control groups. Also, limited evidence from a systematic review included in the systematic umbrella review indicated that three to 30 weeks of low-impact activity combining muscle-strengthening, stretching, and aerobic elements were not associated with serious adverse events in older adults, and the number of total knee replacement surgeries was not significantly different between patients who underwent physical activity compared to no-activity control groups over a two month to 24-month observation period.

Sources of uncertainty included the fact that the systematic reviews were based on studies of unclear or low methodological quality. Also, all three included systematic reviews reported significant heterogeneity of their included studies, lacked a standardized definition of ‘‘usual care’’, and had no information on symptom duration, clinical characteristics, comorbid conditions, and concomitant treatments. Therefore, it was difficult to determine if the findings were due entirely to the investigated interventions and controls or if other factors influenced the results.

There was no study identified that examined the comparative clinical effectiveness of physical activity versus pharmacological interventions in individuals with knee osteoarthritis.

Methods

Literature Search Methods

This report is an upgrade of a previously published CADTH report.[7] It makes use of a limited literature search (for the previous report) conducted by an information specialist on key resources, including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The original search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine’s MeSH (Medical Subject Headings), and keywords. The main search concepts were exercise and knee pain. Also in the original search, filters were applied to limit the retrieval to health technology assessments, systematic reviews, and meta analyses, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014, and October 15, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults living with chronic, non-cancer knee pain from osteoarthritis, excluding pregnant patients
Intervention	Physical activity (i.e., strength training, resistance training, aerobic exercise, running, cycling, swimming, excluding physical activity/therapy guided by a physical therapist or physiotherapy exercises and Pilates or yoga)
Comparator	Pharmacological interventions No treatment (e.g., waitlist, sham interventions) Usual care (if usual care is pharmacological interventions only)
Outcomes	Clinical effectiveness (e.g., pain reduction, functional performance, quality of life, disability level, safety, global impression of recovery)
Study Designs	Health technology assessments and systematic reviews

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were published before 2014, or included in at least one of the already selected systematic reviews or the previous CADTH Rapid Response report[6] for which the current review is an update. Also, studies were excluded if they involved patients with osteoarthritis occurring at a variety of anatomical joints (e.g., knee, hip, or hand) without reporting outcomes specific to knee osteoarthritis (KOA). However, studies were considered for inclusion if they had mixed study populations comprising predominantly of KOA patients.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using version two of A Measurement Tool to Assess systematic Reviews (AMSTAR 2).[8] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 597 citations were identified in the literature search. Following screening of titles and abstracts, 578 citations were excluded, and 19 potentially relevant reports from the electronic search were retrieved for full-text review. A grey literature search did not identify any potentially relevant publications. Of these potentially relevant articles, 16 papers were excluded for various reasons, including three systematic reviews and meta-analyses[9-11] that were excluded because they have already been reviewed in the previous CADTH Rapid Response report[6] of which the current report is an update. Thus, three publications - two

traditional systematic reviews[5,12] and one systematic umbrella review (i.e., a systematic review of systematic reviews)[13] - met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA[14] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2

Study Design

One systematic review and meta-analysis was authored by Goh et al., and published in 2019.[5] Systematic searches for relevant literature for this systematic review were performed from inception up to December 2017 with no language restriction.[5] A total of 77 randomized controlled trials (RCTs) published between 1993 and 2017 were included. Sixty-two of the trials were conducted in patients with knee osteoarthritis, whereas eight involved patients with hip osteoarthritis and seven studies included patients with mixed KOA and hip osteoarthritis (OA).[5]

The final study included in this report was a systematic umbrella review authored by Kraus et al., and published in 2019.[13] Systematic umbrella reviews synthesise data from existing systematic reviews (SR) and meta-analyses (MA) instead of primary studies usually included traditional systematic reviews. Systematic searches for SR, MA, and pooled analyses to include in the umbrella reviews were performed from 2011 to February 2018. A total of nine SR or MA published from 2003 to 2011, and comprising a total of 261 primary studies, were included in the systematic umbrella review.[13]

The second included systematic review was authored by Skelly et al., and published in 2018.[12] It included 218 publications on 202 RCTs, including 18 unique RCTs reporting outcomes on KOA. The studies were identified by systematic literature searches conducted from database inception through November 2017.

Country of Origin

Authors of the systematic review by Goh et al.[5] were from The United Kingdom, China, and Malaysia. The authors of the systematic review by Skelly et al., 2018[12], and of the systematic umbrella review by Kraus et al.,[13] were from the United States of America.

Patient Population

The systematic review and meta-analysis by Goh et al., 2019[5] involved a total of 6,472 patients with knee or hip osteoarthritis, who had not undergone joint replacement surgery. Patient characteristics were reported separately for each outcome for which analysis was performed, but not for the overall populations by type of osteoarthritis (KOA or hip OA). The median (range) age in the outcome analysis groups was 64.8 (41.3–84.4) years for assessment of pain and 65 (41.3–84.4) years for function. For each of the outcome groups, most participants (≥72.6%) were female patients.

The systematic umbrella review by Kraus et al.[13] involved a total of 25,924 participants with KOA and/or hip osteoarthritis. Specifically, 24,583 (94.8%) of the participants had KOA. The mean age of study participants ranged from 52 to 79 years across the nine included SR. Information was not provided about the sex of the study participants.

The portion of the systematic review by Skelly et al.[12] involving patients with KOA had a total of 2,981 patients (from 18 RCTs). The participants ranged in age from 42 to 76 years. For each of the RCTs, most study participants (>50%) were female.

Interventions and Comparators

The systematic review by Goh et al.[5] evaluated the effects of exercise interventions without additional treatment compared with usual care (defined as usual physician follow-up, usual physical activity, or on a waiting list for the active intervention after the study period). The most commonly reported outcomes were after, at, or nearest to eight weeks after baseline or randomization. Information was not available about the frequency and intensity of the exercise programs assessed.

The systematic umbrella review by Kraus et al.[13] compared physical activity, including exercise, to a no-activity control group. The authors defined physical activity as bodily movement produced by skeletal muscles that results in energy expenditure. Various physical activities, including land and pool, aerobic, resistance, and flexibility exercises, were examined, and results were classified according to land-based and aquatic exercises.

In the systematic review by Skelly et al.,[12] exercise was compared with usual care, no treatment, or sham interventions. Exercise interventions consisted of muscle performance exercise, aerobic exercise, mobility exercise, and gait training. The duration of interventions ranged from two to 24 weeks, and the number of sessions ranged from four to 36. A clear description of the intensity or duration of sessions of physical activity was not provided. The duration of follow-up post-intervention was reported and categorized as short term (<6 months), intermediate term (≥6 to <12 months) and long-term (≥12 months). Information about the frequency, duration, and intensity of activity was not provided in the systematic umbrella review[13] or the systematic review by Goh et al.[5]

There was minimal overlap in the primary studies that were included in two of the systematic reviews.[5,12] Of the 77 and 218 included primary studies in the systematic reviews by Goh et al.[5] and Skelly et al.,[12] respectively; seven RCTs were common to both reviews. Thus, the estimates pooled separately from these systematic reviews,[5,12] contain some of the same data. The primary studies of the systematic reviews and meta-analysis included in the systematic umbrella review[13] were not provided. Therefore, the systematic umbrella review[13] could not be included in the comparison to assess overlap of primary studies. However, neither of the systematic reviews by Goh et al.[5] and Skelly et al.[12] was included in the systematic umbrella review.[13]

Outcomes

All the three included publications reported on pain, physical function, and health-related quality of life (HRQoL). The studies included in the reviews used a variety of tools to assess outcomes. For pain, evaluations were commonly carried out on visual analogue scales (VAS) or by the Western Ontario & McMaster Universities Osteoarthritic Index (WOMAC).[5,12,13] The assessment of function was commonly performed using WOMAC or Knee injury and Osteoarthritis Outcome Score (KOOS) tool.

The WOMAC is a 24-item, validated, condition-specific questionnaire used in hip and knee osteoarthritis.[15] The instrument consists of three subscales: pain (five questions), stiffness (two questions), and physical function (17 questions). The subscale scores vary, with pain ranging from 0 to 20 points, stiffness from 0 to 8 points, and physical function from 0 to 68 points. Higher scores represent worse pain, stiffness, and functional limitations.[15] The

KOOS is a 42-item knee-specific instrument developed to assess the short-term and long-term consequences of knee injury.[16] It is a validated tool with five subscales; pain (nine items), other symptoms (seven items), function in daily living (17 items), function in sport and recreation (five items), and knee-related quality of life (four items). The subscales are scored separately using a Likert scale in which all items have five possible answer options scored from 0 (No Problems) to 4 (Extreme Problems) and each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0–100 scale, with zero representing extreme knee problems and 100 representing no knee problems.[16]

Quality of life was evaluated using a variety of tools, including the Short-Form 36 (SF-36).[5,12,13] The Short Form-36 (SF-36) is a 36-item patient-reported questionnaire that covers eight health domains: physical functioning (10 items), bodily pain (2 items), role limitations due to physical health problems (4 items), role limitations due to personal or emotional problems (4 items), emotional well-being (5 items), social functioning (2 items), energy/fatigue (4 items), and general health perceptions (5 items).[17,18] The items for each domain are scored and averaged together on a scale ranging from 0 to 100, where a higher score represents better health. A physical component summary (PCS) and mental component summary (MCS) can be calculated from the scores of the eight.[17,18] In addition to pain, function, and HRQOL, the systematic review by Goh et al.[5] evaluated performance using objective measures such as timed movements, maximum walking speed, knee range of motion, and strength.[5]

Limited information on safety outcomes were reported in the systematic umbrella review[13] and the systematic review by Skelly et al.[12] The systematic umbrella review[13] reported about serious adverse events, defined as increased pain, decreased physical function, progression of structural OA on imaging, or increased total knee replacement. Skelly et al.[12] reported on incidences of minor temporary increase in pain, worsening pain, falls, and death. Safety data were not available in the systematic review by Goh et al.[5]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3

All the three systematic reviews[5,12,13] included in this report stated their objectives and provided definitions for their populations, interventions, comparators, and outcomes. All RCTs in the traditional systematic reviews,[5,12] and the SRs or MAs in the systematic umbrella review,[13] were identified from comprehensive literature searches. Although the authors did not provide rationale for selecting the types of study designs to include in the reviews, the eligibility strategies seemed reasonable given that enough RCTs and SRs or MAs were available to answer the questions of interest, without the need to include study designs of lower quality. The limitations of the systematic umbrella review[13] design include incomplete stratification of the evidence due to residual overlap within the included MAs or SRs, heterogeneity of exposures making it challenging to determine the exact relationships between physical activity and outcomes, and heterogeneity of studied populations potentially limiting the generalizability of results.[13]

The investigators of each systematic review[5,12,13] reported that they developed and registered a review protocol before undertaking the study. There was no indication from any of the publications that a deviation from protocol occurred. The eligibility of studies for inclusion in each systematic review[5,12,13] was determined individually by two reviewers (at least), with disagreements resolved by consensus[12] or through the involvement of a third

reviewer.[5,13] Each systematic review[5,12,13] described characteristics of included studies in tabular form, with one providing a list of excluded studies with reasons for exclusion.[12]

Authors of all the three systematic reviews[5,12,13] declared that they had no competing interests that could influence their reports. One systematic review[12] provided information about the funding sources for each of its primary studies.

Two systematic reviews[5,12] evaluated the quality of included studies using the Cochrane risk of bias assessment tool, which is a well-known and widely-used instrument for such purposes. While one of the reviews[12] reported that the assessment was performed independently by two investigators, the other review[5] did not provide details on whether or not the evaluations were done in duplicate. The systematic umbrella review[13] reported the quality of the included SRs as assessed using a modified AMSTAR instrument referred to as $AMSTAR_{ExB}$.[13] There was no further information about the $AMSTAR_{ExB}$ instrument or how it was applied. Thus, the rigor of the quality evaluation of the included SRs and MAs is unknown.

Abstracted data were independently verified for completeness and accuracy in two reviews,[5,12] but the systematic umbrella review[13] did not provide information about the strategy for data abstraction and verification. Two systematic reviews[5,12] conducted meta-analysis using a random effects model, and adjusted for heterogeneity by sequentially excluding studies identified as high contributors from analyses until the level of heterogeneity was considered acceptable (i.e., I^2 statistic < 30%). While one review[5] assessed publication bias to evaluate any potential impact of small samples, the other review[12] did not. In all of the included systematic reviews,[5,12,13] the authors considered the risk of bias in the included studies when discussing and interpreting in the results.

Overall, the methodological quality of the systematic reviews included in this Rapid Response report was good.

Summary of Findings

Clinical Effectiveness of Physical Activity for Chronic, Non-cancer Knee Pain from Osteoarthritis

Appendix 4 presents a table of the main study findings and authors' conclusions.

Pain reduction

All three included systematic reviews[5,12,13] reported that physical activity was associated with statistically significantly greater reduction in KOA pain than usual care,[5,12] no activity,[13] no treatment, or sham interventions.[12]

In one systematic review,[5] analysis of data from 55 comparisons comprising 3,750 patients with KOA found that exercise therapy resulted in a significantly better improvement in pain score compared to usual care. The effect size was 0.64 (95% confidence interval [CI] 0.51 to 0.78; *P* = 0.02).

The systematic umbrella review[13] found that compared with no-activity, physical activity resulted in reduced KOA pain as indicated by a standard mean difference (SMD) and 95% CI of -0.49 (-0.59 to -0.39) for land-based exercise (17 studies; n = 3,537) and -0.31 (-0.47 to -0.15) for aquatic exercise (12 studies; n = 1,076).

One systematic review[12] reported that from analysis of seven studies (n = 706), exercise demonstrated more significant beneficial effects in the short-term (1 to <6 months) on pain than usual care, no treatment, or sham interventions, as indicated by SMD (95% CI) of −0.44 (−0.82 to −0.05). However, after excluding poor-quality trials, analysis of the remaining five trials resulted in a similar the SMD although no longer statistically significant (SMD = −0.40; 95% CI −0.85 to 0.08). In the same systematic review,[12] data from two trials (n = 944) found no apparent difference in the long-term (≥12 months) effects of exercise and usual care on KOA (pooled difference on a 0 to 10 scale = −0.24, 95% CI −0.72 to 0.24).

Functional performance

All three included systematic reviews[5,12,13] reported that physical activity was associated with statistically significantly better improvement in functional performance among patients with KOA than usual care,[5,12] no activity,[13] no treatment, or sham intervention.[12]

In one systematic review,[5] a separate KOA-related endpoint for functional performance was not reported. However, effect sizes of 0.50 (0.38 to 0.63) and 0.46 (0.35 to 0.57) for function and performance respectively in favour of exercise versus usual care, were reported for an overall sample that combined populations with knee OA, hip OA, or mixed KOA and hip OA patients (77 RCTs; n= 6,472). Most (71.13%) of the patients in the analysis were KOA patients, with 13.3% of patients having hip OA and 15.5% of patients in whom KOA and hip OA co-occurred (i.e., having mixed KOA and hip OA).

Analysis in the systematic umbrella review[13] found that compared with no activity, physical activity resulted in statistically significantly improved functional performance in KOA patients as indicated by SMD (95% CI) of -0.52 (-0.64 to -0.39) for land-based exercise (17 studies; n = 1,660) and -0.32 (-0.47 to -0.17) for aquatic exercise (12 studies; n = 1,059).

In one systematic review,[12] a meta-analysis of seven studies (n = 706) demonstrated that in the short-term exercise compared with usual care, no treatment, or sham interventions, was associated with small but statistically significantly higher physical function beneficial effects (SMD = −0.25; 95% CI −0.40 to −0.09).

In the same systematic review,[12] pooled data from two trials (n = 944) showed a small but statistically significant improvement in long-term physical function for KOA patients with exercise than with usual care (SMD = −0.24, 95% CI −0.37 to −0.11). However, results from the individual trials did not show a statistically significant difference between exercise and usual care.

Quality of life

Two included systematic reviews[5,13] reported that among KOA patients, physical activity resulted in statistically significant improvements in HRQoL compared with usual care or no-activity.

In one systematic review,[5] HRQoL was not reported separately for KOA patients. However, an analysis involving patients with KOA, hip OA, or mixed KOA and hip OA (77 RCTs; n= 6472) found a small but statistically significant benefit in HRQoL with exercise compared with usual care (effect size = 0.21, 95% CI 0.11 to 0.31). Most (71.13%) of the patients in the analysis had KOA; 13.3% had hip OA and 15.5% had mixed KOA and hip OA (i.e., both KOA and hip OA).

The systematic umbrella review[13] found that compared with no-activity, physical activity resulted in significant improvement in HRQoL among KOA patients as indicated by a SMD (95% CI) of 0.28 (0.15 to 0.40) for land-based exercises (13 studies; n = 1,073) and -0.28 (-0.49 to -0.01) for aquatic exercises (10 studies; n = 971).

However, analysis of data from two trials in one systematic review[12] found no association between exercise and HRQoL on either a 0 to 100 KOOS scale or using the SF-36 instrument. The quality of the evidence was rated as fair in both trials.

Safety

Limited information on safety outcomes was reported in two of the included systematic reviews.[12,13] Safety data were not available in the systematic review by Goh et al.[5]

In the systematic umbrella review,[13] one included SR found that three to 30 weeks of low-impact activity combining muscle-strengthening, stretching, and aerobic exercise were not associated with serious adverse events in older adults (n = 8,614) with KOA. In four RCTs (n = 985) out of a total of 49 trials included in that SR, there was no significant difference in the number of total knee replacements over a two month to 24-month observation period within the group of patients who underwent physical activity compared to nonphysical activity groups (n = 8 versus n = 10 groups, respectively).

In one systematic review,[12] one out of 18 unique RCTs reporting outcomes on KOA found that the increase in temporary, minor pain was higher in the exercise group than a sham group (relative risk 14.7, 95% CI: 2.0 to 107.7). The wide CI indicates high variability in the reported effect. Also, in the same systematic review,[12] four RCTs found no difference in worsening pain versus controls, and one RCT reported no difference in falls or death. The quality of evidence was rated as moderate.

Limitations

Most of the primary studies (67%) reporting on KOA that were included in the systematic review by Skelly et al.[12] were graded by the authors as being of poor quality, and the rest were graded as fair-quality. Although the systematic review by Goh et al.[5] reportedly assessing the quality of primary studies, the quality scores were not adequately reported. However, the authors reported that the quality of the primary studies was low due to factors such as inadequate blinding of participants and investigators, reporting bias, allocation concealment, and small sample size. The systematic umbrella review by Kraus et al.[13] did not provide a measure of the overall methodological quality of the included systematic reviews and meta-analyses. Thus, taken together, the strength of evidence from the included systematic reviews[5,12,13] was not high.

All three included systematic reviews[5,12,13] reported substantial heterogeneity in their included studies due to variations in patient characteristics, disease severity, co-morbidity status, types of interventions used and choice of controls, and methodological characteristics. The interpretation of the effect of the reported heterogeneity is challenging because the heterogeneity potentially limits to the generalizability of results (i.e., making it unclear to whom the results apply), but conversely is likely to be consistent with the heterogeneity seen in clinical practice (i.e., suggesting the findings may be applicable to broad primary care clinical settings).

A standardised definition of ‘‘usual care’’ was not provided and there was no information on symptom duration, clinical characteristics, comorbid conditions and concomitant treatments

in any of the studies. Therefore, it was unclear if the observed outcomes were entirely due to the interventions and controls of interest or the results were influenced by other factors. Also, none of the included systematic reviews[5,12,13] provided enough information about the type, intensity, duration, or frequency of physical activity to achieve optimal clinical effectiveness for KOA patients.

There were no studies identified that examined the comparative clinical effectiveness of physical activity versus pharmacological interventions in individuals with KOA. Furthermore, information about adherence to exercise programs and adverse events associated with exercise in patients with KOA was limited.

Conclusions and Implications for Decision or Policy Making

Two traditional systematic review[5,12] and one systematic umbrella review[13] (that synthesized information from existing systematic reviews and meta-analyses) provided information for this report. Across the three publications,[5,12,13] there were a total of 311 RCTs that examined the effect of physical activity or exercise on KOA, involving a total of 34,036 study participants. None of the included systematic reviews[5,12,13] provided enough information about the specific type, intensity, duration, or frequency of physical activity to achieve optimal clinical effectiveness for KOA patients.

Evidence from the included reviews[5,12,13] suggested that in patients with KOA, physical activity significantly reduced pain and improved function, performance, and HRQoL compared with usual care, no treatment, or sham interventions, at least in the short-term (i.e., up to six months).

Limited evidence from one systematic review[12] suggested a higher temporary increase in minor pain with exercise than with sham interventions, and no difference in worsening pain, falls, or death between exercise and control groups. Also, limited evidence from a systematic review included in the systematic umbrella review[13] indicated that three to 30 weeks of low-impact activity combining muscle-strengthening, stretching, and aerobic elements did not cause serious adverse events in older adults, and the number of total knee replacements surgeries over a two month to 24-month observation period was not significantly different between patients who underwent physical activity compared to no-activity control groups.

The findings in the current report were consistent with results of a previous CADTH Rapid Response review.[6] That report found evidence from 18 systematic reviews suggesting that overall, exercise therapy was associated with significantly higher clinical effectiveness compared with no intervention, placebo, or minimal intervention for KOA patients with regards to reducing pain and stiffness and improving physical function and performance.[6] The previous report[6] did not identify enough information to effectively compare incidence of adverse events associated with exercise to that of control interventions.[6]

Sources of uncertainty in the current report included the fact that the systematic reviews were based on studies of unclear[5,13] or low methodological quality.[5,12] Also, the included studies in all three included systematic reviews[5,12,13] had significant heterogeneity, lacked a standardized definition of ‘‘usual care’’, and had no information on symptom duration, clinical characteristics, comorbid conditions and concomitant treatments. Therefore, it was difficult to determine if the findings were due entirely to the investigated interventions and controls or if other factors influenced the results.

There were no studies identified that examined the comparative clinical effectiveness of physical activity versus pharmacological interventions in individuals with KOA.

Given these limitations and others described elsewhere in the report, future research should evaluate various physical activity interventions in KOA patients to identify optimal techniques and mode of delivery, as well as potential differences in effectiveness according to different ages, symptom duration, clinical characteristics, comorbid conditions, and concomitant treatments.

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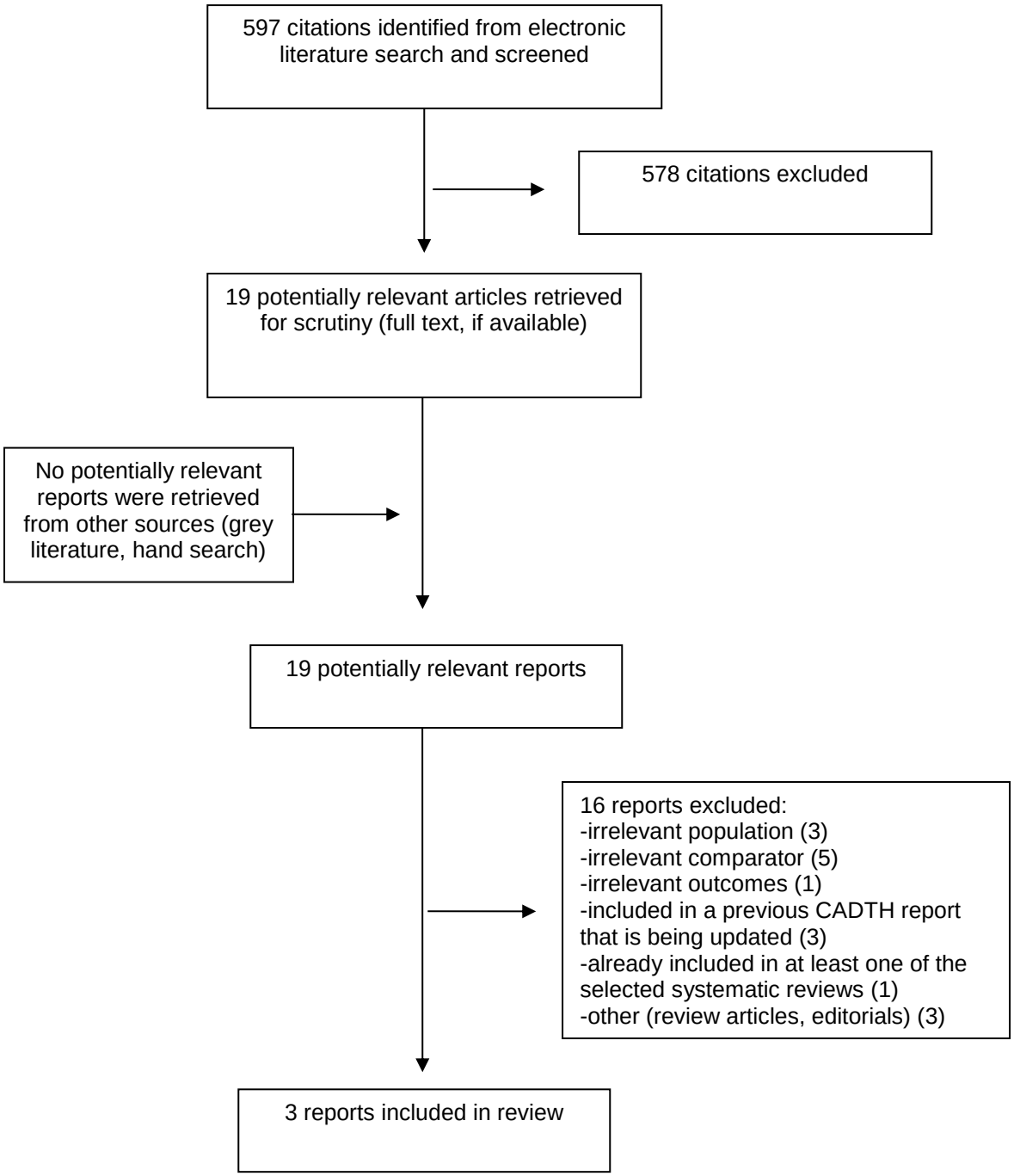
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Goh et al., 2019[5] **Authors from The United Kingdom, China, and Malaysia**	Systematic review of 77 RCTs and meta-analysis	6,472 patients with knee or hip osteoarthritis	Exercise-only (not mixed with any other intervention) versus Usual care (defined as usual physician follow-up, usual physical activity, or on a waiting list for the active intervention after the study period)	**Primary endpoint:** • Pain Secondary outcomes: Self-reported • Function • Objective performance • QoL Outcomes were commonly measured at or nearest to 8 weeks after randomization.
Kraus et al., 2019[13] **USA**	A systematic umbrella review of a total of nine SRs and/or MAs	A total of 25,924 patients with existing lower hip or knee (or both) osteoarthritis. Of these, 24,583 (94.8%) had KOA.	Physical activity (not mixed with any other intervention) versus a No-activity control group	• Pain • Physical function • HRQoL • Length of follow-up was not specified
Skelly et al., 2018[12]	Systematic review of 218 publications (202 trials), including 18 unique RCTs reporting outcomes on KOA	A total of 2866 patients with hip (n=23) or knee OA (from the 18 RCTs on KOA)	Exercise versus Usual Care, No Treatment, or Sham (“*Attention Control” was also a comparator in the SR, but it was not an eligible comparator for this Rapid Response report*)	• Pain • Physical function • HRQoL • Harms The follow-up was reported as short term (<6 months), intermediate term (≥6 to <12 months) and long-term (≥12 months)

HRQoL = health-related quality of life; MA = meta-analysis; KOA = knee osteoarthritis; OA = osteoarthritis; RCT = randomized controlled trial; SR = systematic review.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR-2[8]

Strengths	Limitations
Goh et al., 2019[5]	
• The objective of the study was provided, and the methods section of the publication adequately identified the components of PICO for the review. • The protocol for a wider project, of which the current SR/MA is a part, was registered with PROSPERO and published before the conduct of the review. • A comprehensive literature search was conducted in multiple databases for relevant RCTs. • One reviewer screened abstracts and full-text articles deemed potentially appropriate for inclusion and a second investigator validated the initial selection. Discrepancies were resolved with the involvement of a third reviewer. • The quality of the included studies was a modified Cochrane risk of bias assessment tool. • Small study effect or publication bias was assessed using funnel plots • One reviewer abstracted study data, which were verified for accuracy and completeness by a second reviewer. Discrepancies were resolved with the involvement of a third reviewer • The characteristics of included studies were provided. • A random effects model was used appropriately to pool data in meta-analysis. • The review authors assessed sources heterogeneity using the Baujat plot. Analysis considered adjusting the influence of heterogeneity to unremarkable level by sequentially excluding studies identified as high contributors until the I^2 statistic was < 30%. • The discussion and interpretation of the results considered the RoB in individual studies included in the review	• The authors did not explain why they limited inclusion to RCTs. However, the study design restriction seemed justified given that RCTs rank higher than other primary studies and there were enough of them available to address the review questions. • A list of excluded studies was not provided • The authors did not report on the sources of funding for the studies included in the SR. However, they declared no competing interests of their own that could influence with the report
Kraus et al., 2019[13]	
• The objective of the study was provided, and the elements of PICO were adequately identified in methods section of the publication. • The protocol for the study was registered with PROSPERO before the conduct of the review. • A comprehensive literature search was conducted in multiple databases and supplemented by articles identified through the expertise and familiarity of authors who are experts in the area. • The titles, abstracts, and full-text of the identified articles were independently screened by two reviewers, with disagreement resolved by discussion or by a third reviewer.	• The strategy for data abstraction was not adequately described, and it was unclear whether the abstracted study data were independently verified for accuracy and completeness. • A list of excluded studies was not provided • The rigor of the measure used to evaluate the quality of the included SR/MA is unknown because there was insufficient information about the modified AMSTAR instrument ($AMSTAR_{ExB}$) that was used. Also, it was not reported whether the evaluation was conducted independently by two or more investigators with a strategy to address disagreements.

Strengths	Limitations

• The quality of each SR/MA included in the umbrella review was assessed using a modified version of AMSTAR (AMSTAR$_{ExB}$).
• The characteristics of included SR/MA were summarized in tabular form.
• The study was funded by U.S. Department of Health and Human Services (HHS). The authors declared no conflicts of interest that may have influenced the report.
	• The authors did not report on the sources of funding for the SRs/MAs included in the umbrella SR.
	• The study design (umbrella SR) is reported to be associated with limitations[13] such as:
	  ○ incomplete stratification of the evidence due to residual overlap within the included MA/SR;
	  ○ heterogeneity of exposures making it difficult to determine the exact relationships of physical activity and outcomes; and
	  ○ heterogeneity of studied populations potentially limiting the generalizability of results.

Skelly et al., 2018[12]	
• The elements of PICO were described by the research questions, inclusion criteria, and other parts of the methods section. • Key questions to address by the systematic review were developed with input from recognized professional institution and considerations of public comment and the review protocol was posted on the AHRQ Effective Health Care Program Web site (www.effectivehealthcare.ahrq.gov) and registered in the PROSPERO international database of prospectively registered systematic reviews. There was no indication of any deviation from the protocol. • A comprehensive literature search was conducted in multiple databases, and the reference lists of included articles and the bibliographies of systematic reviews published since 2010 were reviewed for potentially relevant literature. Also, efforts were made to identify includable unpublished trials by searching the ClinicalTrials.gov site and posting a Federal Register notice. Trial authors were contacted to provide additional data, where available data were inadequate. • At least two investigators reviewed abstracts, and full-text articles were retrieved for all citations deemed potentially appropriate for inclusion by at least one of the reviewers. All full-text articles were reviewed independently by two investigators for final inclusion. Discrepancies were resolved by consensus. • The quality of the included studies was independently assessed by two investigators using Risk of Bias Tool in the Cochrane Handbook for Systematic Reviews of Interventions, in conjunction with a recommended approach in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Research. Disagreements were resolved by consensus. • All abstracted study data were verified for accuracy and completeness by a second team member	• The authors did not explain why they limited inclusion to RCTs. However, the study design restriction seemed justified given that RCTs rank higher than other primary studies and there were enough of them available to address the review questions. • Non-English-language articles were excluded. It is unknown how this may have impacted the available evidence. • Assessment of publication bias was not conducted to evaluate any potential impact of small samples, methodological limitations in trials, or heterogeneity in interventions, populations or outcomes.

Strengths	Limitations
• The strength of evidence for each Key Question and primary outcome was initially assessed by one experienced researcher and independently reviewed by at least one other experienced senior investigator. • The included studies were described in tabular form, and a list of excluded studies was provided along with reasons for exclusion • The SR was funded by AHRQ. The authors declared no conflicts of interest that may have influenced the report. Information was provided about the funding sources for each study included in the SR. • The random effects model was used appropriately for the statistical combination of result in meta-analysis. Statistical heterogeneity among the studies was assessed using the standard Cochran's chi-square test and the I^2 statistic. Where necessary, the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis was assessed by excluding studies of a particular rating in quality (e.g., poor quality) from analysis. • The review authors investigated and discussed sources of observed heterogeneity and accounted for RoB in individual studies when interpreting the results of the review	

AHRQ = Agency for Healthcare Research and Quality; AMSTAR = A Measurement Tool to Assess Systematic Reviews; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MA = meta-analysis, PICO = population, intervention, comparator, and outcome; PROSPERO = International Prospective Register of Systematic Reviews, RCT = randomized controlled trial; RoB = risk of bias; SR = systematic review.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Goh et al., 2019[5]	
Pain • Analysis found that exercise therapy resulted in a significantly better improvement in pain score compared to usual care in patients with KOA (55 comparisons; n = 3,750). The ES (95% CI) was 0.64 (0.51 to 0.78); *P* = 0.02; I^2 = 71.2% **Functional Performance** • The functional performance outcome was not reported separately for KOA patients. • The ES (95% CI) from analysis involving patients with knee OA (71.1%), hip OA (13.3%), or mixed KOA and hip OA (i.e., co-occurring KOA and hip OA) (15.5%) were: ○ 0.50 (0.38 to 0.63); number of studies = 65; I^2 = 74.5% for function and ○ 0.46 (0.35 to 0.57); number of studies = 0.73; I^2 = 70.5% for performance, all in favour of exercise versus usual care**.** **Quality of life** • A HRQoL outcome was not reported separately for KOA patients. • The ES (95%) from analysis involving patients with KOA (71.1%), hip OA, or mixed KOA and hip OA (i.e., co-occurring KOA and hip OA) was 0.21 (0.11 to 0.31); number of studies 33; I^2 = 36.4%.	"Exercise significantly reduces pain and improves function, performance and QoL in people with knee and hip OA as compared with usual care at 8 weeks. The effects are maximal around 2 months and thereafter slowly diminish, being no better than usual care at 9 to 18 months. Participants with younger age, knee OA and not awaiting joint replacement may benefit more from exercise therapy."[5] (*p356*)
Kraus et al., 2019[13]	
Pain • Meta-analyses of included studies found that both land-based and aquatic exercises significantly reduced KOA pain compared with no activity. SMD (95% CI) was: ○ -0.49 (-0.59 to -0.39) for land-based exercise (17 studies; n = 3,537). Test for overall effect Z = 9.64; *P* <0.00001. Heterogeneity: Tau^2 = 0.05; Chi^2 = 84.97; df = 45; ***P*** = 0.0003; I^2 = 47%, and ○ -0.31 (-0.47 to -0.15) for aquatic exercise (12 studies; n = 1,076) Test for overall effect Z = 3.80; *P* =0.0001. Heterogeneity: Tau^2 = 0.02; Chi^2 = 16.28; df = 11; *P* = 0.13; I^2 = 32% **Physical Function** • Meta-analyses found that both land-based and aquatic exercise significantly improved physical function in KOA patients compared with no activity. SMD (95% CI) was:	"People with lower-extremity OA should be encouraged to engage in achievable amounts of physical activity, of even modest intensities. They can choose to accrue minutes of physical activity throughout the entire day, irrespective of bout duration, and be confident in gaining some health and arthritis-related benefits."[13] (*p1324*)

Main Study Findings	Authors' Conclusion
○ -0.52 (-0.64 to -0.39) for land-based exercise (17 studies; n = 1,660). Test for overall effect Z = 8.23; *P* <0.00001). Heterogeneity: Tau^2 = 0.11; Chi^2 = 135.50; df = 44; *P* < 0.00001; I^2 = 68%, and ○ -0.32 (-0.47 to -0.17) for aquatic exercise (12 studies; n = 1,059). Test for overall effect Z = 4.28; *P* =0.0001. Heterogeneity: Tau^2 = 0.01; Chi^2 = 13.74; df = 11; *P* = 0.25; I^2 = 20% **Quality of life** • Meta-analyses found that both land-based and aquatic exercise significantly improved HRQoL in KOA patients compared with no activity. SMD (95% CI) was: ○ 0.28 (0.15 to 0.40) for land-based exercise (13 studies; n = 1,073). Test for overall effect Z = 4.45; *P* <0.00001. Heterogeneity: Tau^2 = 0.00; Chi^2 = 10.20; df = 12; *P* = 0.60; I^2 = 0%, and ○ -0.28 (-0.49 to -0.01) for aquatic exercise (10 studies; n = 971). Test for overall effect Z = 2.04; *P* =0.0001. Heterogeneity: Tau^2 = 0.09; Chi^2 = 25.48; df = 9; *P* = 0.002; I^2 = 65% • Following cessation of the intervention, the beneficial effects of physical activity persisted up to 6 months for pain, and beyond 6 months for physical function.[13] **Safety** • One SR that included 49 studies assessing the safety of physical activity in older adults (n = 8,614) with knee pain found that low-impact activity combining muscle-strengthening, stretching, and aerobic elements for three to 30 weeks reported no evidence of serious adverse events defined as increased pain, decreased physical function, progression of structural OA on imaging or increased total knee replacement at a group level • Based on four RCTs (n = 985) included in that SR, there were no more total knee replacements over a two month to 24-month observation period within physical activity groups compared to nonphysical activity groups (n = 8 vs. n = 10 total knee replacements, respectively).	
Skelly et al., 2018[12]	
Pain • In a meta-analysis of seven studies (n = 706), exercise compared with usual care, no treatment, or sham intervention, demonstrated a small but statistically significantly greater beneficial effects in the short-term (1 to <6 months) on pain. SMD (95% CI) was −0.44 (−0.82 to −0.05); I^2 = 35%. The quality of evidence was graded as fair in six studies and poor in one.	In patients with KOA, exercise was associated with small but significantly greater reduction in pain and improvement in physical function than usual care, no treatment, or sham intervention, at least in the short-term (i.e., one to six months). The long-term comparative benefit of exercise over usual care usual care, no treatment, or sham intervention is unclear.

Main Study Findings	Authors' Conclusion
• When the analysis excluded poor-quality trials, the estimate remained similar to the overall results, although was no longer statistically significant. The SMD (95% CI) was −0.40 (−0.85 to 0.08) (five trials; I^2 not reported) • Two trials (n = 944) that evaluated the long-term (≥12 months) effects of exercise and usual care or attention control on KOA found no clear difference (pooled difference −0.24 on a 0 to 10 scale, 95% CI −0.72 to 0.24, I^2 = 54.9%). The quality of evidence was rated as fair in one trial and poor in the other **Physical Function** • In a meta-analysis of seven studies (n = 706), exercise compared with usual care, no treatment, or sham interventions, demonstrated small but statistically significantly greater beneficial effects in the short-term on physical function. SMD (95% CI) was −0.25 (−0.40 to −0.09); I^2 = 0%. The quality of evidence was graded as fair in six studies and poor in one. • The estimate did not change significantly when the analysis excluded poor-quality trials. • Data pooled from two trials (n = 944) showed that compared to usual care, exercise produced a small but statistically significant improvement in long-term physical function, although a statistically significant difference was not observed in either of the trials separately. The pooled SMD (95% CI) was −0.24, (−0.37 to −0.11); I^2 = 0%. The quality of evidence was rated as fair in one trial and poor in the other. **Quality of life** • Two trials comparing exercise and usual care found no difference in short-term HRQoL on the KOOS 0 to 100 scale between the two groups and (pooled difference 1.76, 95% CI −2.45 to 5.97, I^2 = 0%). The quality of the evidence was rated as fair in both trials. • The adjusted (for duration of follow-up) mean (SE) SF-36 PCS were 37.6 (0.9) vs. 35.3 (0.8), respectively, and adjusted mean (SE) SF-36 MCS were 54.1 (0.8) vs. 53.7 (0.8), respectively. **Safety** • One trial (n = 140) reported minor temporary increase in pain with exercise compared with sham intervention (RR 14.7, 95% CI 2.0 to 107.7). The wide CI indicates high variability in the reported effect. • Four studies (n = 319) found no difference in worsening pain between exercise versus controls, and one trial (n = 439) found no difference in falls or death between exercise and control groups. The quality of evidence was rated as moderate.	

CI = confidence intervals; ES = effect size; HRQoL = health-related quality of life; KOA = knee osteoarthritis; KOOS = Knee Injury and Osteoarthritis Outcome Score; MCS = Mental Component Score; OA = osteoarthritis; PCS = Physical Component Score; QoL = quality of life; RR = relative risk; SE = standard error; SF-36 = Short-Form 36 Questionnaire; SMD = standardized mean differences.