Fransen M, McConnell S, Harmer AR, and et al. Exercise for osteoarthritis of the knee (Review). *Cochrane Database of Systematic Reviews* 2015, Issue 1.

Design: Meta-analysis of randomized clinical trials
Date: 4-27-15 LM

Study Question: To determine whether land-based therapeutic exercise is beneficial for people with knee OA in terms of reduced joint pain and improved physical function and quality of life.

PICOs:

- **Patients:** Male and female adults, 18 years of age or over given an established diagnosis of knee osteoarthritis as defined using accepted criteria, or self-reported knee OA based on chronic joint pain with or without clinical radiographic confirmation.
- **Interventions:** Any land-based non-perioperative therapeutic exercise regimens aiming to relieve the symptoms of knee OA, regardless of content, duration, frequency or intensity. This includes any exercise designed to improve muscle strength, range of joint movement or aerobic capacity (or combinations of the 3) and could be supervised or designed as a home program.
- **Comparison interventions:** The control group could be active, including any non-exercise intervention or placebo, including a no treatment or waiting list group.
- **Outcomes:** Each RCT needed to include assessment of at least one of:
  • knee pain;
  • self-reported physical function;
  • quality of life.
  Each outcome was assessed at 3 time points: immediately at the end of treatment (post-treatment), two to 6 months after the end of treatment, and long-term follow-up which was more than 6 months after the end of study treatment. Each study was required to report outcome measurements in at least one of these time periods. If data on more than one pain or physical function scale were reported in a trial, data were extracted from the scale according to a pre-determined hierarchy of outcome scales.
- **Study types:** Randomized controlled trials (RCTs) or controlled clinical (quasi-randomized) trials published in English, comparing some form of land-based therapeutic exercise with a non-exercise group.

Study selection:

- Databases included MEDLINE, EMBASE, CINAHL, PEDro, and the Cochrane Library through May 2013. Also searched were ClinicalTrials.gov and the WHO trials portal.
- Three teams of 2 review authors independently assessed articles on trial quality for inclusion and resolved any disagreements through consensus or consulting a third review author. The three teams independently extracted data from included studies and assessed articles for risk of bias, with 3 levels of quality of evidence; low risk, high risk or unclear risk.

- Risk of bias was assessed using the Cochrane Collaboration 'risk of bias' tool which uses the following criteria; random sequence generation, allocation concealment, blinding of participants, providers, and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias.
- If the random sequence generation, allocation concealment, and incomplete outcome data domain were adequately met in a study, the overall risk of bias was judged as low for that study.
- As the studies used a variety of continuous scales to measure pain and physical function, a unitless measure of treatment effect size was needed to allow the results of the various RCTs to be pooled. Standardized mean differences (SMD) were used to calculate treatment effect sizes from the end of treatment scores and related standard deviation (SD) scores, and to obtain a summary estimate.
- Heterogeneity in meta-analysis was assessed with the I^2 statistic. Data was pooled and outcomes combined using the random-effects model for a meta-analysis. If $I^2 \geq 30\%$ and $\leq 60\%$, this represented moderate heterogeneity, while I^2 greater than 50% was considered as representing substantial heterogeneity.
- Subgroup analyses were planned to assess for potential small-study bias in the meta-analyses by comparing effect estimates derived from a random-effects model and a fixed-effect model. Subgroup analyses were also conducted according to treatment content and delivery mode, and number of face-to-face contacts.
- The minimal clinically important difference (MCID) for each outcome was determined to be 15 points on a 0- to 100-point pain scale, and 10 points on a 0- to 100-point function scale.
- A sensitivity analysis was planned to evaluate potential selection, attrition, and detection bias on the outcomes of pain and physical function.

Results:

- Twenty-three new studies since the last update in 2008 were included in this update.
- Overall 54 studies providing data on 5362 participants for outcomes on pain and on 5222 participants for outcomes on physical function with mostly mild-to-moderate symptomatic knee OA were included.
- Five RCTs evaluated a Tai Chi based program and all the others consisted of traditional muscle strengthening, functional training, and aerobic fitness programs. Exercise regimens were individually supervised or were provided during a class.
- Most of the studies consisted of between 50 and 150 participants, but 19 (35%) studies consisted of less than 25 participants in one or both allocation groups.
- There was large variability in treatment dosage. Supervised exercise sessions ranged from 20 to 60 minutes with a total of 0 to 72 monitored sessions that continued for one to 6 months. Two studies prescribed home exercise programs for up to 2 years.
- Symptom duration varied among study participants from less than one year to longer than 10 years.
- Forty-four studies (3537 participants) provided immediate post-treatment outcomes assessments, while 12 RCTs (1468 participants) evaluated follow-up two to six months after completion of the exercise program.

- Nineteen (20%) of the included RCTs were assessed as ’low risk of bias’ reporting adequate sequence generation and allocation concealment. Four of the 54 included RCTs were able to blind participants to treatment allocation. Just over half (57%) of the 54 included RCTs reported blinding of the outcomes assessor to group allocation. Studies were largely free from selection bias, but results may be vulnerable to performance and detection bias, since outcomes were participant self-reported.
- High-quality evidence from 44 trials (3537 participants) showed that exercise reduced pain (standardized mean difference (SMD) -0.49, 95% confidence interval (CI) -0.39 to -0.59) immediately after treatment. The mean pain after treatment in the control group was 44 points, and 32 points in the exercise group on a 100 point pain scale. (0 indicated no pain). Exercise significantly reduced pain by an equivalent of 12 points (95% CI 10 to 15 points). This equates to a 27% relative improvement. This statistically significant effect size would be considered moderate. Between-study heterogeneity was moderate (I^2 = 47%). These effect sizes are statistically significant. The MCID of 15 points for pain is not attained, but the confidence intervals do include the MCID, so the effect may reach clinical relevance.
- Moderate-quality evidence from 44 trials (3913 participants) showed that exercise improved physical function (SMD -0.52, 95% CI -0.39 to -0.64) immediately after treatment. Physical function was estimated at 38 points on a 0 to 100-point scale (0 indicated no loss of physical function) in the control group and 28 points in the exercise group. Exercise significantly improved physical function by an equivalent of 10 points (95% CI 8 to 13 points). This equates to a 26% relative improvement. This statistically significant effect size would be considered moderate and clinically important. Between-study heterogeneity was substantial (I^2 = 68%).
- High-quality evidence from 13 studies (1073 participants) revealed that exercise improved quality of life (SMD 0.28, 95% CI 0.15 to 0.40) immediately after treatment. Quality of life was estimated at 43 points on a 0 to 100-point scale (100 indicated best quality of life) in the control group and 47 points in the exercise group. Exercise improved quality of life by an equivalent of 4 points (95% CI 2 to 5 points). This equates to a 9% relative improvement. This statistically significant effect size would be considered small. Between-study heterogeneity was negligible (I^2 = 0%).
- The reduction in pain and improvement in physical function was sustained at least two to six months after ceasing monitored treatment. There was evidence from 12 studies (1468 participants) for knee pain and 10 studies (1279 participants) for physical function that showed that exercise does have a statistically significant beneficial effect for patient pain reduction 2 to 6 months after treatment (SMD -0.24, 95% CI -0.35 to -0.14) with an equivalent reduction of 6 (3 to 9) points on 0 to 100-point scale, and of physical function (SMD -0.15 95% CI -0.26 to -0.04), with an equivalent improvement of 3 (1 to 5) points on 0 to 100-point scale. These effect sizes would be considered small to very small. Even though these effect sizes are statistically significant, they are clinically unimportant.
- Marked variability was noted across included studies among participants recruited, symptom duration, exercise interventions assessed and important aspects of study methodology.
- Individually delivered exercise programs tended to result in greater reductions in pain and improvements in physical function, compared to class-based exercise programs

or home-based programmes, but between-study heterogeneity was marked within the individually provided treatment delivery subgroup analysis.

- Most of the studies provided no precise information on side effects or adverse effects of exercise. Eight studies reported increased knee or low back pain attributed to the exercise program, and all identified studies reported no injuries.

Authors' conclusions:

- The overall results of the meta-analysis (high-level evidence) suggest that land-based exercise is beneficial in the short-term at the completion of a supervised exercise program for reducing pain, and improving quality of life, and improving physical function (moderate quality evidence) and that these benefits are sustained for at least another two to six months among people with symptomatic knee OA.
- The magnitude of the treatment effect would be considered moderate (immediate) to small (two to six months) but comparable with estimates reported for non-steroidal anti-inflammatory drugs and could be considered clinically important for a low risk intervention such as exercise. Confidence intervals around demonstrated pooled results for pain reduction and improvement in physical function do not exclude a minimal clinically important treatment effect.
- Since the participants in most trials were aware of their treatment, this may have contributed to their improvement in pain and function. Despite the lack of blinding, studies were not downgraded on the quality of evidence for risk of performance or detection bias.
- Healthcare professionals and people with knee OA can be reassured that any type of exercise program that is done regularly and is closely monitored by healthcare professionals can improve pain and physical function related to knee OA in the short term. This allows a great deal of choice, ranging from individual physiotherapy-led sessions and exercise classes to home-based programs.
- Exercise programs that were individually administered appeared to be associated with greater improvements in knee pain and physical function.
- Further research in this area is unlikely to change the findings of this review. Future research should include developing multi-armed placebo-controlled randomized clinical trials to help provide evidence of optimal exercise content and dosage. In addition, future research should assess the long-term effectiveness of exercise for people with knee OA in terms of structural disease progression.

Comments:

- Updated results of this meta-analysis concur with previously identified benefits of exercise for pain and physical function among people with knee OA. However, effect sizes are greater than those reported in the previous Cochrane review (Fransen, 2008) (SMD 0.40, 95% CI 0.30 to 0.50 for pain; SMD 0.37, 95% CI 0.25 to 0.49 for physical function). The larger effects identified in this review are likely due to separation of findings into those noted immediately post treatment and those reported at a follow-up time point. This suggests that the larger effects are a reflection of superior beneficial results immediately following treatment.

- The minimal clinically important difference (MCID) for each outcome for this meta-analysis was determined to be 15 points for pain, and 10 points for function. This meta-analysis did display statistically significant results for both pain and function, but did not attain clinically important results for pain. The difference in pain reduction and functional improvement was only 12 and 10 points, respectively, for immediate effects. However, these small clinically insignificant benefits seen here still could be considered a clinically important benefit for a low risk intervention such as exercise. Even though exercise reduced pain by only 12 points post-treatment (95% CI 10 to 15), the confidence intervals encompass the clinically important difference of 15 points, indicating a very small, but clinically important treatment effect.
- If the meta-analysis result for immediate post-treatment pain is restricted to the 14 studies (1458 participants) that had a low risk of selection and attrition bias, exercise still demonstrated significant benefit (SMD 0.47, 95% CI 0.36 to 0.59) of moderate size, equivalent to 11 (95% CI 9 to 15) points on a 0 to100-point scale. Similar results were found for physical function when restricted to the 14 studies (1456 participants) having a low risk of bias (SMD 0.45, 95% CI 0.28 to 0.63) which is equivalent to 9 (95% CI 6 to 13) points on a 0 to 100-point scale.
- The results of this review suggest that although the pain-relieving benefit of exercise is not maintained six or more months after treatment, improvements in physical function are better sustained.
- The sub-group analyses for various exercise programs did not result in any statistically significant differences between programs, but some interesting findings were revealed. For both pain and physical function, exercise programs involving Tai Chi, coordination, stretching or balancing exercises seemed to be less effective than strengthening and aerobic exercise. This may reflect the limited focus of these exercise programs on specific muscle groups, or it may reflect lower exercise intensity. For physical function in particular, exercise involving quadriceps strengthening alone (10 studies) was the most beneficial, yielding a large effect size (SMD 0.74, 95% CI 0.41 to 1.07). Medium effects on physical function were identified for exercise programs that employed general lower limb strengthening (SMD 0.54, 95% CI 0.26 to 0.83) and strengthening combined with aerobic exercise (SMD 0.52, 95% CI 0.36 to 0.67). Smaller benefits were detected for walking exercise programs.
- Differences between the various forms of exercise delivery were not statistically significant even though the effect size for pain for closely supervised individual treatments (SMD 0.76) was large. Home programs (SMD 0.38) and class-based programs (SMD 0.42) demonstrated effect sizes for pain that were much smaller.
- The effect size for both pain and physical function was influenced by the number of face-to-face contacts with the healthcare professional supervising the exercise program. The difference between fewer than 12 contacts and 12 or more contacts failed to reach statistical significance. This is likely due to considerable between study heterogeneity. These results suggest that most people with knee OA need some form of ongoing monitoring or supervision to optimize clinical benefits of exercise treatment.

- Potential study limitations may be present for pain and quality of life due to possible performance and detection bias that may overestimate effect sizes. Potential study limitations for physical function may be due to high heterogeneity between study findings causing imprecision.
- Exercise ’dosage,’ which is a factor of frequency, intensity and program duration, varied considerably between the studies included in this review. These extreme differences in treatment dosage make it impossible to develop recommendations for effective treatment.
- For immediate post-treatment pain and physical function, 14 of the 42 included RCTs had a low risk of bias. However, all the results may be vulnerable to performance and detection bias, since none of the RCTs were able to blind participants to treatment allocation, and the outcomes of pain and physical function were participant self-reported. Effect sizes may also be inflated.
- The possibility of publication bias could not be ruled out, since unpublished studies were not searched.
- One only has to wonder that if knee OA participants continued in an exercise program for the rest of their lives, the pain-relieving and improved functional benefits of exercise may be sustained indefinitely.

Assessment:

- Adequate quality Cochrane meta-analysis which supports good evidence that land-based exercise shows a moderate clinically important benefit for the relief of pain and improvement in function at the completion of a supervised exercise program, and shows that somewhat smaller benefits are sustained for at least another two to six months among people with symptomatic osteoarthritis of the knee.

Reference:

- Fransen M, McConnell S. Exercise for osteoarthritis of the knee. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004376.pub2].