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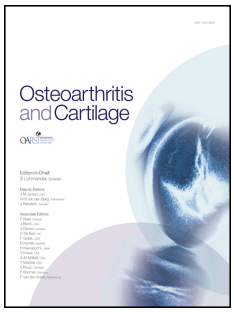

Is long-term physical activity safe for older adults with knee pain?: A systematic review

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Title:

Is long-term physical activity safe for older adults with knee pain?: A systematic review

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Abstract

Objective

To determine whether long-term physical activity is safe for older adults with knee pain.

Design

A comprehensive systematic review and narrative synthesis of existing literature was conducted using multiple electronic databases from inception until May 2013. Two reviewers independently screened, checked data extraction and carried out quality assessment.

Inclusion criteria for study designs were randomised controlled trials (RCTs), prospective cohort studies or case control studies, which included adults of mean age over 45 years old with knee pain or osteoarthritis (OA), undertaking physical activity over at least three months and which measured a safety related outcome (adverse events, pain, physical functioning, structural OA imaging progression or progression to total knee replacement (TKR)).

Results

Of the 8614 unique references identified, 49 studies were included in the review, comprising 48 RCTs and one case control study. RCTs varied in quality and included an array of low impact therapeutic exercise interventions of varying cardiovascular intensity. There was no evidence of serious adverse events, increases in pain, decreases in physical function, progression of structural OA on imaging or increased TKR at group level. The case control study concluded that

increasing levels of regular physical activity was associated with lower risk of progression to TKR.

Conclusions

Long-term therapeutic exercise lasting three to thirty months is safe for most older adults with knee pain. This evidence supports current clinical guideline recommendations. However, most studies investigated selected, consenting older adults carrying out low impact therapeutic exercise which may affect result generalizability.

Systematic review registration

PROSPERO 2014:CRD42014006913

Key words

- Osteoarthritis;
- Knee pain;
- Safety;
- Physical activity;
- Exercise;
- Systematic review;

Introduction

Knee pain in older adults (aged 45 years and over) is common, with the majority of pain in this age group being attributable to osteoarthritis (OA)[1,2]. Physical activity including both local muscle strengthening and increased general physical activity is consistently recommended for older adults with knee pain[2,3,4] and its effectiveness for pain reduction and physical function improvement has been well established from large, high quality systematic reviews[5,6,7]. Furthermore, the general health benefits of regular physical activity are unequivocal; it is positively associated with both life expectancy and quality of life[8,9], as well as being negatively associated with multimorbidity[10].

However, physical activity levels in older adults with knee pain are low[11,12,13,14] and both health care professionals and older adults with knee pain express concerns over the safety of long-term physical activity[15,16]. For example, common and persisting narratives regarding joint "wear and tear" may link to the belief that physical activity will cause further joint damage, whilst pain during activity may be perceived as an indicator of harm[16,17]. In addition, some older adults fear adverse events with physical activity, such as falls, which may in turn lead to reductions in physical activity[18].

No systematic review has focussed specifically on the safety of long-term physical activity for older adults with knee pain by collating both randomised control trial (RCT) and observational study evidence from multiple safety outcome domains including adverse events, pain, physical function, structural progression and total knee replacement frequency. Hence, the aim of this systematic review was to

synthesise existing literature from multiple safety related outcome domains to determine whether long-term physical activity is safe for older adults with knee pain.

Method

Safety definition and systematic review premise

Within the context of this systematic review, "*Safety*" is considered as a construct comprising multiple factors relating to harm and condition progression. For physical activity to be considered safe in this population, at a group level, it must not result in; a) serious adverse events; b) increased pain; c) worsening physical function; d) structural progression of OA on imaging; or e) increased incidence of total knee replacements.

Search strategy and study selection

The systematic review was developed from a centre protocol and was prospectively registered on PROSPERO (International prospective register of systematic reviews)[19]. A comprehensive search strategy was developed combining keywords and database MESH headings for knee pain and osteoarthritis, exercise and physical activity (shown in Appendix 1). The search was adapted and run in several electronic databases including MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, AMED, PEDro, SPORTDiscus, International Occupational Safety and Health Information Centre database (CISDOC), National Institute for Occupational Safety and Health (NIOSHTIC-2) and the Health and Safety Executive database (HSELINE) from inception until May 2013.

Study inclusion criteria were randomised controlled trials (RCT), prospective cohort studies or case control studies, which included adults of mean age over 45 years old with knee pain or adults with OA, undertaking physical activity over at least three months. In addition, included studies had to have measured a safety related outcome (adverse events, pain, physical functioning, structural progression of OA on imaging, or progression to total knee replacement (TKR)). Exclusion criteria were: a) non randomised controlled trials, cross-sectional observational studies and retrospective cohort studies; b) studies including participants with serious knee pathology not attributable to OA, or mixed participants (for example, some with knee pain and some with other conditions such as rheumatoid arthritis or hip OA without separate knee pain subgroup analysis). Further detail is provided in Table 1.

Two reviewers (JQ and either MH, NF, MT) independently screened all titles, abstracts and full texts for study inclusion and exclusion criteria. Disagreements were resolved by discussion or consensus with a third reviewer where necessary. Reference lists of the included studies were also screened.

TABLE 1

Methodological risk of bias

Included RCTs were assessed for risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias using the Cochrane Risk of Bias Tool[20]. “Other bias” was used to cover aspects of precision (adequate sample size), contamination and issues of sampling frame generalizability. Observational studies were assessed for risk of bias from study participation, study attrition, prognostic

factor measurement, outcome measurement, study confounding, statistical analysis and reporting using the Quality in Prognostic Studies (QUIPS) tool[21].

Risk of bias assessment was carried out by two independent reviewers. Disagreement was resolved by discussion or consultation with a third reviewer where necessary. Overall risk of bias was used to inform conclusion strength rather than as a cut off inclusion criterion within the systematic review.

Data extraction

Safety outcome data extraction was carried out by one reviewer (JQ) and independently verified by a second reviewer (either MH, NF, MT) whilst study descriptive data extraction and physical activity categorisation was carried out by one reviewer (JQ). Information was extracted on: a) study title, authors, year of publication, type, and country; b) participants including total number, key baseline characteristics (e.g. age, specific comorbidities and knee malalignment) and diagnosis method (e.g. knee pain or radiographic OA); c) physical activity type, intensity, session frequency and intervention duration; d) safety outcome data at baseline and immediately post intervention, including: adverse events, pain and function (statistical significance performed, in comparison with either a non-physical activity control group post-intervention or within group over time), radiographic/ MRI structural OA progression, and TKR data. Numbers of TKRs occurring during RCTs within physical activity and non-physical activity intervention/ control groups were extracted. Adjusted odds ratios and confidence intervals for progression to TKR for varying levels of physical activity exposure were also extracted from case control studies.

Narrative synthesis

Narrative synthesis was completed rather than meta-analysis due to the substantial heterogeneity within studies and the focus on safety rather than treatment effect size. The synthesis included collating and summarising safety outcomes from separate domains and subsequently integrating the results from different domains to draw conclusions about safety. Within each safety outcome domain, patterns of physical activity and exercise safety were summarised. In order to allow comparisons between individual studies, intensity of physical activity interventions were categorised into low, moderate and vigorous using a combination of reported target maximum heart rate percentage and activity metabolic equivalent of task (MET) whilst impact of physical activity was classified into low and high impact (see Appendix 2 for detail). In addition, RCT adverse events were categorised into mild, moderate and severe by one reviewer (JQ) and independently verified by a second reviewer (MH)[22]. Mild adverse events were defined as bothersome but not requiring change in therapy, moderate adverse events were those requiring change in therapy, additional therapy or hospitalisation whilst severe adverse events were defined as disabling or life threatening.

Results

Study characteristics

In total, 8,614 unique references were identified from the electronic databases which reduced to 715, 168 and 46 after screening titles, abstracts and full texts

117 respectively. Two further studies were identified following reference list screening
118 and one from peer review, resulting in 49 included studies (see Figure 1).

119 FIGURE 1

120 The included studies comprised 8,920 participants from 48 RCTs[23-70] and a single
121 case control study[71]. Supplementary online material gives a full table of included
122 studies including intervention detail (Table SI). The studies were undertaken in 16
123 different countries. All of the included studies were written in English except
124 Olejarova et al 2008 which was translated from Czech. Participants included those
125 with knee pain and /or a diagnosis of OA with severity of OA ranging from Kellgren
126 Lawrence I-IV in those studies utilising radiographs. Four studies specifically
127 included participants with knee pain/OA who were overweight or obese[39.50,57,64] and
128 one additional study included overweight participants who also had Type II
129 diabetes[37]. Levels of individual comorbidities varied within the remaining studies
130 although many excluded participants who had cardiovascular disease or those who
131 were deemed “unfit to exercise” for other health reasons.

132 The RCTs included 78 physical activity intervention groups. Physical activity type,
133 intensity and duration varied widely. All of the RCTs investigated therapeutic
134 exercise physical activity. “*Mixed*” exercise interventions combining strengthening,
135 stretching and aerobic elements were most common and were investigated within 46
136 intervention groups. 17 intervention groups focussed on strengthening exercises,
137 five on aerobic exercises (including walking and cycling), five on balance and agility,
138 whilst four included Tai Chi and a single intervention carried out range of motion
139 exercises. Two RCT physical activity interventions were classified as low
140 cardiovascular intensity, 71 as moderate intensity and five as vigorous intensity. All

of the physical activity interventions were considered low impact. RCT physical activity intervention duration ranged from three months to thirty months whilst frequency varied from one to three sessions per week.

Study safety outcome domain results

The number of RCTs within the review that provided information on each safety outcome domain are shown in Figure 2.

FIGURE 2

Adverse events

Adverse events were explicitly reported in only 22 of the included RCTs (see Table 2 for details). Some authors reported adverse events generally without attributing severity whilst others split adverse events into "*minor*" or "*mild*" and "*serious*", however, definitions of these terms were often lacking. According to the standardised adverse event categorisation[22], no studies reported serious adverse events related to physical activity. Moderate adverse events were rare being reported in between 0-6% of physical activity intervention participants in any included study. These included five falls with one resulting in a fractured wrist and one a head laceration, one foot fracture (caused by a participant dropping a weight on their foot), four drop outs related to increased knee or other joint pain and one inguinal hernia attributed to physical activity. Mild adverse events were reported in between 0-22% of physical activity participants within individual studies and usually involved muscle soreness and temporary or mild joint pain increase.

TABLE 2

Pain

In total, 46 studies measured pain. The Western Ontario and McMaster Arthritis Index (WOMAC) pain scale[72] and numerical pain scales were the two most common outcome measures. No studies found significantly higher pain with physical activity (Table 3). Only 29 carried out between group statistical testing comparing physical activity to non-physical activity interventions. Of these, 19 showed pain to be significantly lower in the physical activity groups whilst seven found no significant difference between groups and two showed a combination of significantly lower and non-significant difference with multiple physical activity intervention groups.

Of the studies that statistically explored change in pain over time within physical activity group (n=28), most showed significant improvement (n=20) with only five studies showing no significant change and three showing mixed improvement and no change within multiple physical activity interventions.

Physical function

In total, 43 studies measured physical function with WOMAC function[72] and various objective function tests being the most common outcome measures. No studies found physical function to be lower with physical activity (see Table 3). Only 28 carried out between group statistical testing comparing physical activity to non-physical activity interventions. The majority showed physical function was significantly better in physical activity groups (n=15) whilst a minority found no significant difference between groups (n=11) and two studies a combination of

significantly better and non-significant difference with multiple physical activity intervention groups.

Of the studies that explored change in function over time within physical activity groups (n=28), most showed significant improvement (n=19) with only two studies showing no significant change and seven showing mixed improvement and no change within multiple physical activity interventions .

TABLE 3

Structural OA biomarker imaging

Six studies reported heterogeneous measures of OA from imaging of the tibiofemoral joint, including: Kellgren and Lawrence score, joint space width, joint space narrowing, OA severity and cartilage volume (see Table 4). Of the five RCTs that measured changes in radiographic OA using imaging, none provided any evidence of significantly greater structural progression of OA between those in physical activity versus non-physical activity groups or those within physical activity group over time. A single small RCT found trends for improvements in the majority of OA parameters measured using MRI over time within the physical activity group[32] whilst a single RCT found trends towards joint space narrowing within physical activity groups[49].

TABLE 4

Total knee replacement

Four RCTs reported TKRs within the study intervention period in enough detail to permit data extraction[28,35,39,46], as did the case control study[71]. Summing the four RCTs, there was no evidence of more TKRs within physical activity groups compared to non-physical activity groups (n=8 and 10 respectively). The case control study[71] investigated cases of Finnish adults who underwent TKR and age matched controls. They concluded that TKR risk decreased with increasing recreational physical activity. Using adults with a history of no regular physical activity as a reference, adjusted odds ratios (and 95% confidence intervals) of TKR were 0.91 (0.31-2.63) in men with low cumulative hours of physical activity and 0.35 (0.12-0.95) in those with a high number of accumulative hours. In women the respective results for low and high cumulative hours of physical activity were 0.56 (0.30-0.93) and 0.56 (0.32-0.98).

Risk of bias assessment

Risk of bias from included studies varied widely. 18 studies (38%) were judged to be at high risk of bias in one or more risk of bias domains. The risk of bias domains of "sequence generation", "allocation concealment", and "incomplete outcome data" were assessed as low risk of bias in 31 (65%), 16 (33%) and 19 (40%) of studies respectively. Blinding of participants to physical activity intervention was not possible and hence judged as unclear throughout, whilst blinding of "outcome assessment" was assessed as low risk of bias in 26 (54%) of studies. Only four studies published protocols hence selective reporting was unclear for most studies and only low in three (6%). Figure 3 shows the RCT Cochrane risk of bias tool summary scores for each outcome domain (Table SII in the supplementary online

material shows individual study scores). Studies were not excluded on the basis of methodological risk of bias and although there was wide variation in the risk of bias within included studies, safety findings were consistent for studies at both low and high risk of bias.

Using the QUIPs tool, the case control study[71] was considered at moderate risk of bias in four domains (attrition, prognostic factor measurement, confounding and statistical analysis and reporting) and low risk in two (selection, and statistical analysis and reporting).

FIGURE 3

Discussion

This systematic review is the first to specifically investigate whether long-term physical activity is safe for older adults with knee pain. However, the vast majority of evidence meeting our inclusion criteria related specifically to therapeutic exercise hence our conclusions relate to therapeutic exercise rather than physical activity more generally. Based on consistent evidence from 49 included studies we conclude that long-term therapeutic exercise is safe for most older adults with knee pain. At the group level, there was no evidence of serious adverse events, increases in pain, worsening of physical function, progression of structural OA on imaging or higher rates of TKR associated with therapeutic exercise. Moderate adverse events, such as falls or pain that resulted in participants dropping out of studies, were very rare, whilst a minority of individuals experienced mild adverse events.

This evidence builds on previous expert consensus that exercise appears to be safe for adults with knee pain attributable to OA[73]. Together with existing systematic reviews that evidence the effectiveness of therapeutic exercise in improving pain and physical functioning[6,7,74], and those showing physical activity is not associated with condition progression[75,76], the findings reinforce clinical guidelines recommending therapeutic exercise as a core part of condition management[2,3,4].

Long-term therapeutic exercise (up to thirty months), was consistently safe across a broad range of types and intensities of interventions. However, no studies focussed on domestic physical activity, occupational physical activity, travel activity or sports. Whilst various types and intensities of therapeutic exercise within this systematic review may be similar to physical activities within these different categories, caution is required in drawing inferences from the findings. For example, cycling on an exercise bike is safer than on roads due to the risk of road traffic accidents. Varying therapeutic exercise frequencies, ranging from one to three hours per week, and cardiovascular intensities from low to vigorous were also safe regardless of level. Hence, all these components can be considered in therapeutic exercise programs for older adults with knee pain. However, given that all the studies included in the review included low impact interventions, it is not possible to confidently draw conclusions about the safety of higher impact exercise, such as running.

Long-term therapeutic exercise was also safe across a broad range of study populations including older adults with varying levels of knee pain severity, those diagnosed with both radiographic OA and clinical OA, varus malalignment[44], and common comorbidity subgroups such as overweight and Type II diabetic participants[37,39,50,57,64,77,78]. However, despite exercise being a core part of cardiac rehabilitation recommended for multiple cardiovascular diseases[79], many RCTs

excluded older adults with a history of cardiovascular disease or those considered "unfit for exercise" which is a limitation in generalising the results to this comorbid subgroup.

Falling was the most common moderate severity adverse event (n=5). Falls are a common problem for older adults, with 30% of adults over the age of 65 falling at least once a year[80,81]. Although existing systematic review evidence has shown therapeutic exercise reduces the number of falls in community dwelling older adults[81], five falls appears relatively low for the number of included participants and may also be explained by the different characteristics of RCT participants compared to adults in the general population or under reporting of falls. Adverse events were only explicitly reported in 22 of the 48 RCTs hence it is not clear whether they occurred in the remaining studies. Finally, although only a minority of older adults experienced mild or temporary increases in pain with therapeutic exercise (ranging from 0-22% of participants within individual RCT exercise groups), this finding is still clinically meaningful, especially if it contributes to physical activity avoidance behaviour through fear of "hurt meaning harm"[16,17,82].

Study risk of bias

Of particular concern to the validity of the conclusions was the unclear or high risk of attrition bias due to incomplete outcome data in just over half of the studies. Even low numbers of unexplained loss to follow up may bias the conclusions if they were associated with adverse events or increased pain. However, safety findings were consistent regardless of individual study risk of bias. For example, three large RCTs

with low risk of attrition bias still found safe outcomes and no serious adverse events after two years of moderate intensity strengthening and mixed exercise[39,46,67].

Strengths and limitations of the systematic review

Systematic review strengths included the prospective registration with PROSPERO which offered transparency in the planned method and reduced the chance of the research being duplicated. The search strategy was comprehensive and included double author screening, data extraction and quality assessment to decrease the risk of individual subjectivity and human error[83]. The safety conclusions were triangulated from multiple safety outcome domains including adverse events hence strengthening their validity.

There are several limitations. Firstly, despite efforts to include observational studies, all but one of the studies meeting the inclusion criteria were RCTs. This may lead to a participant selection bias. Participants who consent and are included in therapeutic exercise intervention trials may be systematically different from the wider population of older adults with knee pain. Furthermore, RCT evidence pertained to therapeutic exercise carried out for up to thirty months, hence any conclusions for longer periods must be made with caution. Secondly, although there was no evidence of increased frequency of TKR or increased OA structural progression with physical activity, these results should also be interpreted with caution. This is because relatively few studies (five and six for each respective safety domain) contributed extractable data whilst the responsiveness of radiographs to detect OA structural change over periods less than two years is suboptimal[84] which would tend to bias these safety outcomes towards the null. Thirdly, two studies were identified

through the reference list search and one from peer review so the electronic database search, despite being comprehensive, was not exhaustive. Fourthly, there is a possibility of publication bias with studies showing positive outcomes more likely to be published[85]. If a small number of unpublished studies exist that show therapeutic exercise to be unsafe this could alter the conclusions, however, given the large number of papers investigating a broad range of exercise yielding similar safety findings this situation seems unlikely. Finally, caution is required in inferring safety to subgroups and physical activity categories not included within the review.

Research and clinical implications

Future research needs to investigate the safety of physical activity for specific subgroups of older adults with knee pain such as those with cardiovascular conditions and multimorbidities. Research into the safety of physical activity associated with sport, travel, occupation and domestic tasks is also warranted in this patient group.

Many types of long-term therapeutic exercise have been shown to be safe for most older adults with knee pain regardless of pain severity. This allows choice in therapeutic exercise selection based on individual health goals, preferences and factors likely to facilitate adherence such as enjoyment[17,86]. Patients can be reassured that mild or temporary increases in pain with therapeutic exercise occur in a minority of individuals but pain does not equal harm or mean structural progression of knee OA and most will experience less pain if they persist with long-term exercise.

The long-term therapeutic exercise safety profile and risk of serious adverse events appears favourable when compared to common pharmacological treatment options such as paracetamol and non-steroidal anti inflammatories[2,87]. Our findings may increase the frequency and confidence with which therapeutic exercise is recommended and offer reassurance to some clinicians and older adults with knee pain who perceive that knee pain attributed to OA is a “wear and tear” condition that deteriorates with time and is made worse by regular physical activity[15,16,17,88].

To conclude, the findings from this systematic review suggest that long-term therapeutic exercise can safely be recommended for older adults with knee pain. However, there are limitations in generalising the safety findings to all types of patient subgroups and physical activity as a result of the current available evidence.

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Contributions

Jonathan Quicke was the overall lead for the work for the systematic review and was involved at all stages of the paper. The lead author can be contacted by email:

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Jonathan Quicke, Prof Nadine Foster and Dr Melanie Holden were involved with the conception of the design. Jonathan Quicke, Prof Nadine Foster, Dr Melanie Holden and Martin Thomas were involved in study searching, quality assessment and data extraction checking and editing drafts of the paper.

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Competing interests

There is no conflict of interest for any of the authors

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683 **Figure legends**

684 Fig.1. Flow chart for study selection

685 Fig. 2. Bar chart of RCTs providing safety outcome domain evidence

686 Fig. 3. Summary of risk of bias within the 47 included RCTs

687

688 **Illustrations and tables**

689 Table I. Inclusion and exclusion criteria

690 Table II. Adverse events

691 Table III. Summary of RCT pain and physical function outcomes

692 Table IV. Summary of osteoarthritis biomarker imaging results

693

694 **Appendices**

695 Appendix 1. Medline search filter

696 Appendix 2. Cardiovascular intensity categorisation

697

Supplementary online material

Table IS. Table of included studies

Table IIS. RCT risk of bias judgements

MEDLINE search filter

1	exp osteoarthritis/
2	osteoathr$.tw.
3	OA.ti
4	arthrosis.mp.
5	exp pain/
6	1 OR 2 OR 3 OR 4 OR 5
7	knee/
8	exp knee joint/
9	6 AND (7 OR 8)
10	(knee adj3 pain).mp.
11	6 OR 9 OR 10
12	exp exercise/
13	exp sports/
14	exp rehabilitation/
15	exp physical exertion/
16	exp physical endurance/
17	exp physical fitness/
18	exp exercise tolerance/
19	exp occupational exposure/
20	exp occupational medicine/
21	exp physical therapy modalities/
22	exp exercise test/
23	exp recreation/
24	exp leisure activities/
25	exp activities of daily living/
26	exertion$.tw.
27	exercis$.tw.
28	sport$.tw.
29	((physical OR motion) adj5 (fitness OR therp$)).tw.
30	(physical$ adj2 endu$).tw.
31	((strength$ OR isometric$ OR isotonic$ OR isokinetic$ OR aerobic$ OR endurance or weight$) adj5 (aerobic$ OR endurance or weight$) adj5 (train$)).tw.
32	physiotherap$.tw.
33	kinesiotherap$.tw.
34	rehab$.tw.
35	(skate$ OR skating).tw.
36	run$.tw.
37	jog$.tw.
38	treadmill$.tw.
39	swim$.tw.
40	bicycle$.tw.
41	(cycle$ OR cycling).tw.
42	walk$.tw.
43	(row OR rows OR rowing).tw.
44	muscle strength$.tw.
45	activit$ of daily living.tw.
46	((leisure OR travel OR work OR physical or occupation$ or recreation$) adj5 (activit$ OR exercise$ or train$)).tw.
47	(activit$) adj5 (daily living).tw.
48	OR/12-47
49	11 AND 48

Appendix 2 Cardiovascular intensity and physical activity impact categorisation

Cardiovascular intensity and physical activity impact categorisation were carried out by one author (JQ). Where target heart rates were stipulated, <50% of maximum heart rate was defined as low intensity, 50-70% as moderate intensity, and >70%-85% as vigorous intensity[87]. If no target heart rate information was available physical activities were classified by MET score. A MET score of <3 was defined as low intensity, 3-6 as moderate intensity whilst >6 was considered vigorous[88]. Physical activity intervention impact was categorised on a case by case basis into high and low impact based on the likely amount of compressive load and whether both feet were intermittently off the ground. For example, jogging, running and jumping were considered high impact whilst cycling, swimming and walking were considered low impact.

Table I Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Study Methods	
• **RCTs/ prospective cohort studies/ case control studies**	• Cross-sectional observational studies/ retrospective cohort studies/ non-randomised controlled trials • Knee pain/ OA incidence studies
Publications	
• **Full text, published studies** • **All countries/ languages**	• Abstracts, posters, non-peer reviewed, thesis, books
Participants	
• **Adults with mean age 45 years old and over with knee pain OR adults with knee OA**	• Serious pathology not attributable to OA (Inflammatory arthropathies / fracture/ Cancer / metabolic disorder) • Heterogeneous lower limb joint OA participants
Intervention	
• **Three month or more of physical activity intervention or exposure**	• Physical activity not explicitly carried out for 3 months or more
Outcomes	
• **Contains at least one safety related outcome from: adverse events, pain, physical function, radiographic/MRI biomarkers of structural OA progression**	

Abbreviations: OA= osteoarthritis; MRI= magnetic resonance imaging,

Table II Adverse events

Study author	Adverse event outcomes from physical activity groups	
	Description	**Frequency and severity summary**
Abbott et al 2013	One inguinal hernia related to physical activity.	**very rare/ moderate**
Baker et al 2001	No adverse events due to physical activity.	**N/A**
Bennell et al 2005	Minor pain with physical activity reported in 22% of the physical activity group.	**minority/ mild**
Bennell et al 2010	Three participants reported back pain, one back and hip pain, one aggravated varicose veins/ knee pain.	**minority/ mild**
Brismee et al 2007	Minor muscle soreness, foot and knee pain reported.	**minority/ mild**
Ettinger et al 1997+	Two falls in I1 and I2, one participant dropped weight on foot causing foot fracture in I2.	**very rare/ moderate**
Faroughi et al 2011	Two minor adverse events.	**very rare/ mild**
Fitzgerald et al 2011	No adverse events reported.	**N/A**
Hasegawa et al 2010	No adverse events reported.	**N/A**
Kawasaki et al 2009	No subjects needed to halt treatment due to severe adverse events.	**unclear**
Lim et al 2008	Four reported increased knee pain and two reported hip and groin pain attributed to the intervention in I1 Three had increased knee pain and one withdrew with neck pain in I2 Two participants (one from each alignment group) stopped the treatment due to increased knee pain	**minority/ mild-moderate**
McKnight et al 2010	15 adverse events were definitely related to the study, 13 were probably related 30 were possibly related. These consisted of: increased knee pain, accident/ injury related to strength training and pain/ soreness from strength training. One participant withdrew due to exacerbating pre-existing back pain.	**minority/ mild** **very rare/ moderate**
Mikesky et al 2006	One participant dropped out due to increased knee pain with strength training	**very rare/ moderate**
Miller et al 2006	No serious adverse events	**unclear**
Ni et al 2010	Five subjects complained of minor muscle soreness, foot and knee pain	**very rare/ mild**
Peloquin et al 1999	One participant dropped out due to knee inflammation from physical activity	**very rare/ moderate**
Rejeski et al 2002+	One adverse event during physical activity- a participant tripped and sustained a laceration to his head	**very rare/ moderate**
Rogind et al 1998	No adverse events were reported	**N/A**
Song et al 2003	Temporary mild pain in I1. Dropouts were mainly due to personal reasons not activity related factors.	**unclear/ mild**
Thomas et al 2002	Fifty two (11%) of those in the physical activity group reported minor side effects.	**very rare/ mild**
Wang et al 2009	One participant in I1 reported an increase in knee pain. #	**very rare/ mild**
Wang et al 2011	One participant in I1 reported dizziness during physical activity. Two I2 participants reported increased pain after physical activity.	**very rare/ mild**

Key: +=findings from primary paper and follow up papers ; I1= physical activity intervention group 1, I2= physical activity intervention group 2, N/A= none reported, **very rare**= 0-15%, **minority**= 16-25% (modified from Hubal and Day 2006), **mild=** bothersome but requiring no change in therapy, **moderate=** requiring change in therapy, additional treatment, or hospitalisation, **severe**= disabling or life-threatening (Calis 2004), **unclear**: Insufficient adverse event reporting detail, #= one participant reported a newly diagnosed cancer that was not attributed to physical activity.

Table III Summary of RCT pain and physical function outcomes

Study author N=48	Pain		Physical function	
	Between group N=29	Within group N=28	Between group N=28	Within group N=28
Abbott et al 2013				
Aglamis et al 2008	✓	✓	✓	✓
Avelar et al 2011		✓		#
Baker et al 2001	✓	✓	↔	✓
Bautch et al 1997		✓		
Bennell et al 2005	↔	✓	↔	✓
Bennell et al 2010	✓		✓	
Brismee et al 2007	✓	✓	✓	✓
Dias et al 2003			✓	✓
Durmus et al 2012		✓		✓
Ettinger et al 1997+	✓		✓	
Farr et al 2010		✓		
Fitzgerald et al 2011		↔		✓
Foroughi et al 2011		✓		✓
Foy et al 2011	✓		✓	
Hasegawa 2010	✓	✓	✓	✓
Jenkinson et al 2009	✓	↔	✓	✓
Kawasaki et al 2008		✓		✓
Kawasaki et al 2009	↔		↔	
Keefe et al 2004	↔			
Kirkley et al 2008				
Lim et al 2008	✓		↔	
McCarthy et al 2004				
McKnight et al 2010		✓		✓
Messier et al 2000		#		✓
Messier et al 2007		↔		#
Mikesky et al 2006		↔		
Miller et al 2006	✓		✓	
Ni et al 2010	✓		✓	
Olejerova et al 2008				
O'Reilly et al 1999	✓	✓	✓	✓
Osteras et al 2012	↔			
Peloquin et al 1999	✓	✓	#	#
Pisters et al 2010		✓		✓
Rejeski et al 2002+	#	✓	#	#
Rogind et al 1998	↔	#	↔	#
Salancinski et al 2012	✓	✓	↔	↔
Sayers et al 2012	↔	↔	↔	↔
Schlenk et al 2011			↔	✓
Silva et al 2008		✓		✓
Simao et al 2012	#		↔	
Somers et al 2012	✓	#	✓	#
Song et al 2003	✓		✓	
Talbot et al 2003	↔		↔	✓
Thomas et al 2002	✓		✓	
Topp et al 2002	↔	✓	↔	#
Wang et al 2009	✓	✓	✓	✓
Wang et al 2011	✓			

Key: +=findings from primary paper and follow up papers, ✓= significantly lower pain in physical activity group over time or compared to non-physical activity group/ significantly better physical function in physical activity group over time or compared to non-physical activity group. ↔ = no

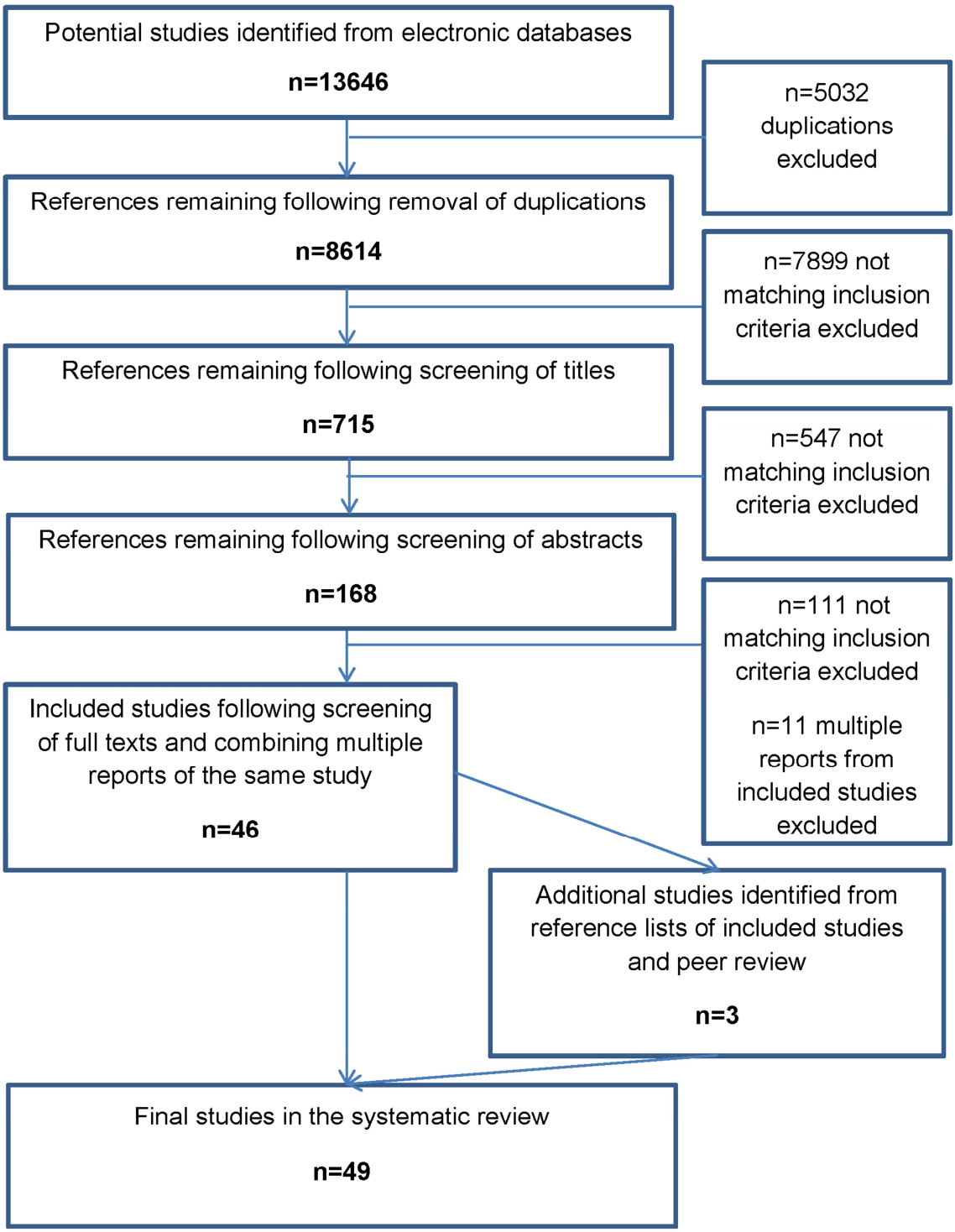
significant difference over time or between groups. #=mixed significant improvements and non-significant results across multiple physical activity interventions. All significance tests set at $\alpha = 0.05$.

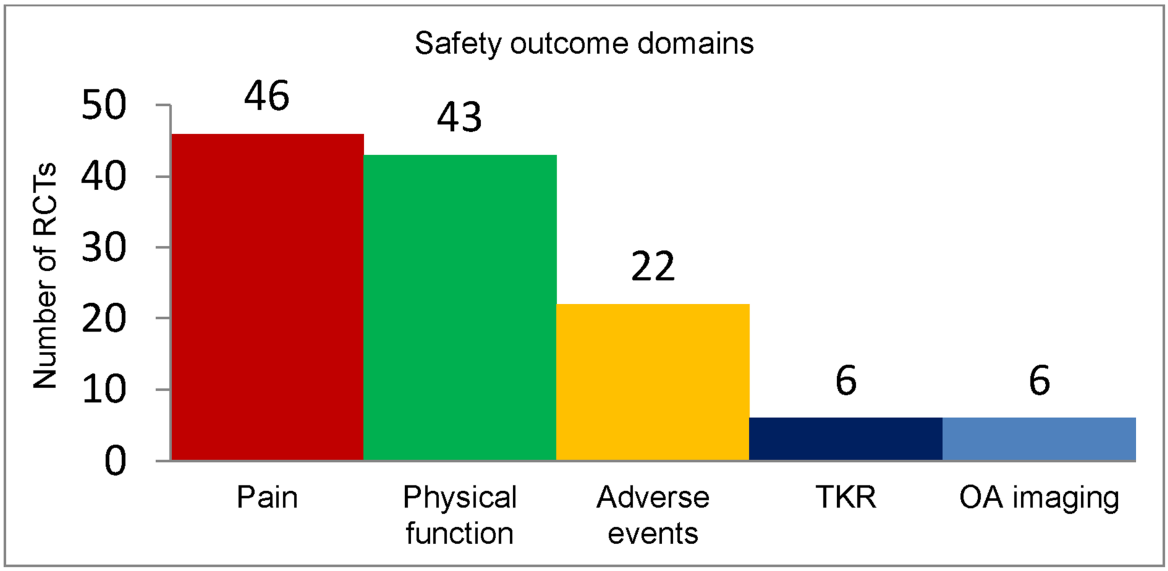
Table IV Summary of osteoarthritis biomarker imaging results

Study author	Radiographic or MRI biomarker outcomes	
	Outcome measure	**Result**
Bautch et al 1997	Radiographic/ tibiofemoral/ antero-posterior/ KL severity	No within physical activity group change over time
Durmus et al 2012	MRI /tibiofemoral/ cartilage volume	Some MRI parameter improvements within physical activity group over time
Ettinger et al 1997+	Radiographic/ tibiofemoral/ antero-posterior and lateral/ OA severity	No between group difference post intervention
Mikesky et al 2006	Radiographic/ tibiofemoral/ antero-posterior/ joint space width, joint space narrowing and and ostophytosis severity	Both physical activity groups showed non-significant trends towards joint space width narrowing over time
Kawasaki et al 2008	Radiographic/ tibiofemoral/ anteroposterior/ joint space width	No between group difference post intervention
Rejeski et al 2002+	Radiographic/ tibiofemoral and patellofemoral/ anteroposterior and sunrise/ joint space width and KL	No between group difference post intervention No within physical activity group change over time

Key: += results were taken from the primary trial paper and additional follow up papers pertaining to the same trial.

Abbreviations: MRI= magnetic resonance imaging; OA= osteoarthritis; KL= Kellgren and Lawrence OA grading.


Potential studies identified from electronic databases
n=13646
n=5032 duplications excluded
References remaining following removal of duplications
n=8614
n=7899 not matching inclusion criteria excluded
References remaining following screening of titles
n=715
n=547 not matching inclusion criteria excluded
References remaining following screening of abstracts
n=168
n=111 not matching inclusion criteria excluded
n=11 multiple reports from included studies excluded
Included studies following screening of full texts and combining multiple reports of the same study
n=46
Additional studies identified from reference lists of included studies and peer review
n=3
Final studies in the systematic review
n=49



Abbreviations: RCT=randomised controlled trial, TKR= total knee replacement

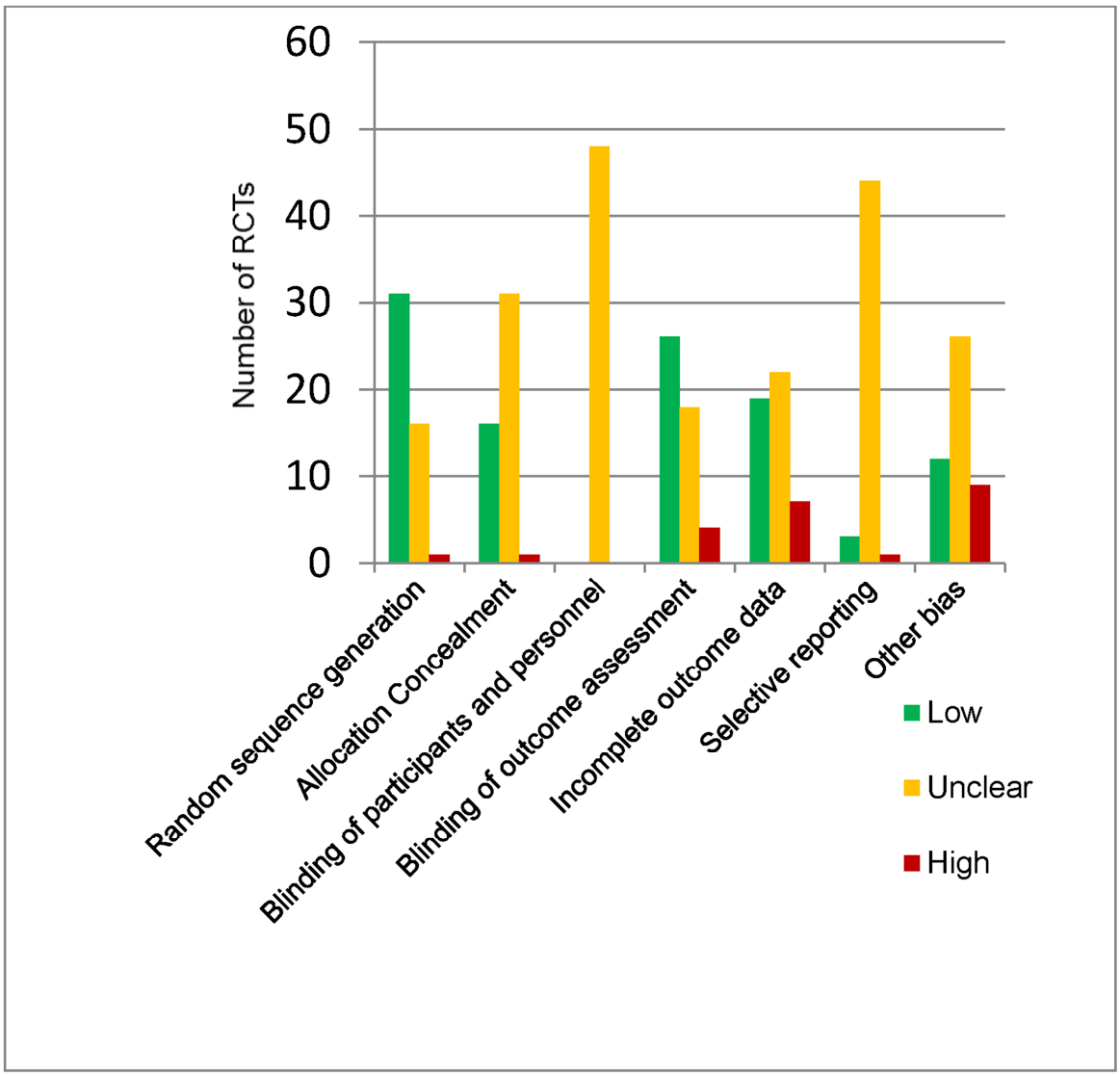


Table SII RCT risk of bias judgements

Study author N=47	Risk of bias domains						
	1	2	3	4	5	6	7
Abbott et al 2013	l	l	u	l	u	l	l
Aglamis et al 2008+	l	l	u	l	h	u	h
Avelar et al 2011	u	u	u	u	u	u	h
Baker et al 2001	u	u	u	h	l	u	l
Bautch et al 1997	u	u	u	u	u	u	u
Bennell et al 2005	l	l	u	l	h	u	u
Bennell et al 2010	l	l	u	l	l	l	l
Brismee et al 2007	l	u	u	l	u	u	u
Dias et al 2003	l	l	u	l	u	u	u
Durmus et al 2012	u	u	u	u	l	u	u
Ettinger et al 1997+	l	l	u	u	u	u	l
Farr et al 2010	l	u	u	u	u	u	l
Fitzgerald et al 2011	l	u	u	l	l	u	l
Foroughi et al 2011	u	u	u	u	l	h	u
Foy et al 2011	l	l	u	u	l	u	u
Hasegawa 2010	u	u	u	u	l	u	h
Jenkinson et al 2009+	l	h	u	u	l	u	u
Kawasaki et al 2008	u	u	u	u	h	u	u
Kawasaki et al 2009	l	u	u	l	h	u	u
Keefe et al 2004	u	u	u	u	u	u	u
Kirkley et al 2008	l	u	u	l	u	u	u
Lim et al 2008	l	l	u	l	l	u	l
McCarthy et al 2004	l	l	u	l	u	u	l
McKnight et al 2010	l	l	u	h	l	u	l
Messier et al 2000	u	u	u	l	u	u	u
Messier et al 2007	u	u	u	u	u	u	h
Mikesky et al 2006	u	u	u	l	h	u	u
Miller et al 2006	u	u	u	u	l	u	u
Ni et al 2010	l	u	u	l	u	u	u
Olejerova et al 2008	h	u	u	u	u	u	h
O'Reilly et al 1999	l	l	u	u	l	u	l
Osteras et al 2012	u	u	u	h	l	u	h
Peloquin et al 1999	l	u	u	l	u	u	u
Pisters et al 2010	l	u	u	l	u	u	u
Rejeski et al 2002+	l	l	u	l	u	u	u
Rogind et al 1998	l	u	u	l	l	u	u
Salancinski et al 2012	l	u	u	u	h	u	u
Sayers et al 2012	l	u	u	l	u	u	h
Schlenk et al 2011	u	u	u	u	u	u	u
Silva et al 2008	l	u	u	l	l	u	l
Simao et al 2012	u	l	u	l	u	u	u
Somers et al 2012	l	u	u	l	u	u	u
Song et al 2003	l	l	u	l	h	u	h
Talbot et al 2003	l	u	u	h	u	u	h
Thomas et al 2002	l	u	u	l	l	u	l
Topp et al 2002	u	u	u	u	l	u	u
Wang et al 2009	l	l	u	l	l	l	u
Wang et al 2011	l	l	u	l	l	u	u

Key: Risk of bias domains: 1) Random sequence generation; 2) Allocation concealment; 3) Blinding of participants and personnel; 4) Blinding of outcome assessment; 5) Incomplete outcome data; 6) selective reporting; 7) Other bias. l= low risk of bias; u=unclear risk of bias; h=high risk of bias

Supplementary online material: Table SI Included studies

Study Author	Participants		Physical activity interventions/ exposure	Description of physical activity intervention/ intensity/ duration (months)	Post treatment follow-up	Safety outcome measure domains
	No.	Knee pain/ OA diagnosis				
Abbott et al 2013	206	clinical OA	I1: exercise therapy I2: manual therapy I3: exercise and manual therapy C: usual care	I1 and I3: 9 sessions of mixed exercise + HEP/ moderate intensity/ 12 months	12	Adverse events Pain TKR
Aglamis et al 2008, 2009	34	clinical and radiographic OA (KL II-IV)	I1: multicomponent exercise C: no treatment	I1: 3 x weekly mixed exercise/ moderate intensity/ 3 months	3	Pain Function
Avelar et al 2011	23	clinical and radiographic	I1: squat + body vibration I2: squat	I1: 3 x weekly squatting exercise with whole body vibration plate/ moderate intensity/ 3 months I2: As above without vibration	3	Pain Function
Baker et al 2001	46	clinical and radiographic OA	I1: strength training C: nutrition education	I1: 12 sessions of lower limb strengthening + HEP/ moderate intensity/ 4 months	4	Adverse events Pain Function
Bautch et al 1997	34	clinical and radiographic OA	I1: exercise C: minimal treatment	I1: 3 x weekly walking / low intensity/ 3months	3	Pain Structural OA
Bennell et al 2005	140	clinical and radiographic OA	I1: physiotherapy	I1: 8 sessions of individual physiotherapy including global strengthening, taping and	3, 6	Adverse events

			C: sham US	massage +HEP/ moderate intensity 6 months		Pain Function TKR
Bennell et al 2010	89	clinical and radiographic OA	I1: hip strengthening C: no treatment	I1: 7 sessions of hip strengthening exercises + HEP/ moderate intensity/ 3 months	3	Adverse events Pain Function
Brismee et al 2007	41	clinical OA	I: Tai Chi C: health and ageing related education	I1: 3 x weekly Yang style Tai Chi in a class for 6 weeks + further 6 weeks HEP/ moderate intensity/ 3 months	3, 4	Adverse events Pain Function
Dias et al 2003	50	clinical and radiographic OA	I1: exercise and walking C: educational session	I1: 2 x weekly mixed exercise and walking for 6 weeks + 6weeks HEP/ moderate intensity/ 3 months	3, 6	Function
Durmus et al 2012	39	clinical and radiographic OA	I1: exercise I2: exercise + glucosamine sulphate	I1 and I2: 3 x weekly strengthening and flexibility/ moderate intensity/ 3 months	3	Pain Function Structural OA
Ettinger et al 1997	439	clinical and radiographic tibiofemoral OA.	I1: aerobic exercise I2: resistance exercise C: health education	I1: 3 x weekly walking sesisons in the first 3 months + further HEP with ongoing support/ moderate intensity/ 18 months I2: 3 x weekly general body strengthening sessions + further HEP with ongoing support/ moderate intensity/ 18 months	3, 9,18	Adverse events Pain Function Structural OA

Farr et al 2010	171	clinical and radiographic OA (KL II)	I1: resistance training I2: self-management I3: resistance training + self-management	I1 and I3: 3 x weekly sessions of aerobic warm up, stretching and global strengthening/ moderate intensity/ 9 months	3, 9	Pain
Fitzgerald et al 2011	183	clinical and radiographic OA (KL II-IV)	I1: standard exercise I2: agility and perturbation	I1: 12 supervised sessions of lower limb stretching and strengthening + HEP with phone contact and review/ moderate intensity/ 6 months I2: as I1 + agility training with stepping directional changes and balance exercises/ moderate intensity/ 6 months	6,12	Adverse events Pain Function TKR
Foroughi et al 2011	54	clinical OA	I1: progressive resistance training I2: sham exercise	I1: 3 x weekly knee extension and hip abduction and adduction Keiser machine strengthening/ high intensity/ 6 months I2: as I1 without hip adduction or single knee extension	6	Adverse events Pain Function
Foy et al 2011	2203	knee pain, mean age >45yrs, type II DM, BMI >25	I1: intensive lifestyle intervention I2: Diabetes support and education	I1: 3 x weekly sessions including graded walking HEP, diet planning +/- supervised exercise in the first 6 months + 3 sessions a month and further HEP for 6 months/ moderate intensity/ 12 months	12	Pain Function
Hasegawa 2010	28	knee pain, mean age >45yrs	I1: strength and balance exercise	I1: weekly lower limb strength and balance exercises + 2 x weekly HEP/ moderate intensity/ 3 months	3	Adverse events Pain Function

Jenkinson et al 2009, Barton et al 2009	389	knee pain, mean age >45yrs, BMI ≥28	I1: diet advice + knee strengthening exercise I2: diet advice I3: knee strengthening exercise I4: advice leaflet	I1 and I3: contact every 4 months, phone support, staged flexibility, strengthening and aerobics HEP/ moderate intensity/ 24 months	24	Pain Function TKR
Kawasaki et al 2008	142	clinical and radiographic OA (KL II-III)	I1: exercise + glucosamine I2: exercise + risedronate I3: exercise	I1-3: twice daily lower limb strength, flexibility HEP with reviews at home every 3mths/ moderate intensity/ 18 months	18	Pain Function Structural OA
Kawasaki et al 2009	102	clinical and radiographic OA	I1: therapeutic HEP I2: hyaluronate injection	I1: twice daily lower limb strength and flexibility HEP with check-ups every month/ moderate intensity/ 6 months	6	Adverse events Pain Function
Keefe et al 2004	72	knee pain and OA diagnosis	I1:spouse assisted coping skills I2:spouse assisted coping skills and exercise I3:exercise alone C:standard care control	I2 and I3: weekly mixed exercise/ high intensity/ 3 months	3	Pain
Kirkley et al 2008	188	clinical and radiographic OA (KL II-IV)	I1: arthroscopy followed by exercise I2: individualised exercise	I1 and 2: weekly physiotherapy individualised exercise/ moderate intensity/ 3 months	3,6,12,18, 24	Pain Function
Lim et al 2008	107	clinical and radiographic OA	I1: varus alignment and quadriceps strengthening I2: neutral alignment and quadriceps strengthening	I1 and I2: 7 sessions of physiotherapy quadriceps strengthening with theraband + HEP/ moderate intensity/ 3 months	3	Adverse events Pain Function

			C1: varus alignment without new exercise C2 neutral alignment without new exercise			
Manninen et al 2001 ##	750	cases: total knee replacement due to OA control: age matched older adults	Different categories of physical activity	Retrospective cumulative lifetime hours of physical ex since leaving school divided into low/ medium/ high for different periods of life compared to no regular exercise.	lifetime	Odds ratios for progression to total knee replacement based on different cumulative life hours of physical exercise
McCarthy et al 2004	214	clinical and radiographic OA	I1: class based exercise program I2: home exercise	I1 2 x weekly mixed exercise class for 2 months + strengthening and balance individual tailored HEP/ moderate intensity/ 12 months I2: strengthening and balance individual tailored HEP/ moderate intensity/ 12 months	2,6,12	Pain Function
McKnight et al 2010	273	clinical and radiographic OA (KL II)	I1: strength training I2: self-management education I3: combined strength training and self-management	I1 and I3: 3 x weekly mixed exercise for 9months + 15 months of developing self-directed long term exercising habits with booster sessions/ moderate intensity/ 24 months	3,9,18, 24	Adverse events Pain Function TKR
Messier et al 2000	24	clinical and radiographic OA	I1: exercise + diet therapy I2: exercise	I1 and I2: 3 x weekly sessions of walking and global strength training/ moderate intensity/ 6 months	3, 6	Pain Function
Messier et al 2007	89	radiographic OA	I1: Glucosamine and Chondroitin + exercise.	I1: phase one: 6 months of Glucosamine and chondroitin then phase two: 6 months of 2 x	6, 12	Pain

			I2: supplement placebo + exercise	weekly exercise aerobic exercise and lower limb strengthening + HEP/ moderate intensity I2: as I1 but placebo in phase 1		Function
Mikesky et al 2006	221	radiographic OA sub group within older adult sample	I1: lower extremity strength training I2: range of motion exercises	I1: 3 x weekly sessions of global strength training for first 12 months with reducing supervision, followed by HEP and 6 monthly follow ups/ moderate intensity/ 30 months I2: 3 x weekly global range of motion exercise sessions with supervision and follow up as above	12, 18, 24, 30	Adverse events Pain Function Structural OA
Miller et al 2006	87	clinical OA BMI ≥30	I1: intensive weight loss C: weight stable education	I1: 3 x weekly sessions of aerobic walking and lower limb strength exercises/ high intensity/ 6 months	6	Adverse events Pain Function
Ni et al 2010	35	clinical OA	I1: Tai Chi C: wellness education and stretching	I1: average 3 x weekly Yang style Tai Chi sessions/ moderate intensity/ 6 months C: weekly stretching sessions/ low intensity/ 6 months	6	Adverse events Pain Function
Olejerova et al 2008	157	clinical and radiographic OA	I1: combination of Glucosamine sulphate + exercise I2: Glucosamine sulphate I3: exercise	I1 and I3: 2 x weekly lower limb isometric strengthening and flexibility/ moderate intensity/ 6 months	3, 6 (all groups) 9, 12 (only I1 and I2)	Pain Function

			C: no intervention			
O'Reilly et al 1999	191	knee pain, mean age >45yrs	I1: exercise C: no treatment control	I1: daily HEP including quadriceps and hamstring exercises with 4 home visits/ moderate intensity/ 6 months	6	Pain Function
Osteras et al 2012	17	knee pain, MRI degenerative meniscus, mean age >45yrs	I1: medical exercise therapy I2: arthroscopic partial menisectomy	I1: 3 x weekly aerobic cycling and lower limb strengthening exercises/ moderate intensity/ 3 months	3	Pain Function
Peloquin et al 1999	137	clinical and radiographic OA (KL I-III)	I1: cross training exercise C: OA education	I1: 3 x weekly mixed exercise sessions/ moderate intensity/ 3 months	3	Adverse events Pain Function
Pisters et al 2010	150	clinical OA	I1: behavioural graded activity I2: usual exercise therapy	I1: ≤18 sessions of graded activity (time contingent increase in problem activities) + individually tailored exercise therapy + further HEP and up to 7 booster sessions up to a year/ moderate intensity/ 12 months. I2: ≤18 sessions of exercise therapy + further HEP	3, 15, 60	Pain Function
Rejeski et al 2002 (Messier et al 2004)	316	clinical and radiographic OA, BMI ≥28	I1: diet I2: exercise I3: diet + exercise C: healthy lifestyle education	I2 and I3: 3 x weekly aerobic walking and lower limb strength exercises for 4 months with the choice to do supported HEP or continued facility group exercise/ moderate intensity/ 18 months	6 ,18	Adverse events Pain Function Structural OA (Messier et al 2004)

Rogind et al 1998	25	clinical and radiographic OA (KL III+)	I1: physical training C: unclear control	I1: 2 x weekly global strength, flexibility and balance exercise/ moderate intensity/ 3 months	3, 12	Adverse events Pain Function
Salancinski et al 2012	37	clinical and radiographic OA (KL I-III)	I1: cycling C: control	I1: 2 x weekly cycling/ moderate intensity/ 3 months	3	Pain Function
Sayers et al 2012	33	clinical OA	I1: high speed power training I2: slow speed strength training C: stretching and cycling control	I1:3 x weekly high speed resisted concentric knee extension, cycling and stretching/ moderate intensity/ 3 months I2: as I1 but slow speed knee extension. I3: 3 x weekly cycling and stretching sessions/ moderate intensity/ 3 months	3	Pain Function
Schlenk et al 2011	26	clinical OA	I1: self-efficacy based lower extremity exercise and walking C: usual care	I1: 15 mixed exercise + self-efficacy intervention + exercise videotape + telephone counselling and monitoring sessions + HEP/ moderate intensity/ 6 months	6	Function
Silva et al 2008	64	clinical and radiographic OA	I1: water based exercise I2: land based exercise	I1: 3 x weekly heated pool lower limb stretching and strengthening exercises/ moderate intensity/ 4 months I2: 3 x weekly stretching and strengthening exercise/ moderate intensity/ 4 months	4	Pain Function

Simao et al 2012	35	clinical and radiographic OA	I1: squat group I2: platform group C: normal activities control	I1: 3 x weekly squat exercises/ moderate intensity/ 3 months I2: 3 x weekly squat exercise on a vibrating platform/ moderate intensity/ 3 months	3	Pain Function
Somers et al 2012	232	clinical and radiographic OA, BMI 25-42	I1: pain coping skills training I2: behavioural weight management I3: pain coping skills and behavioural weight management C: standard care control	I2 and I3: 3 months supervised flexibility and aerobic cycling exercise + 3 months unsupervised flexibility and aerobic exercise/ moderate intensity/ 6 months	6, 12, 18	Pain Function
Song et al 2003	72	clinical and radiographic OA	I1: Tai Chi C: control	I1: 3 x weekly supervised and HEP Sun style Tai chi sessions/ moderate intensity/ 3 months	3	Pain Function
Talbot et al 2003	34	clinical and radiographic OA	I1: arthritis self-management program I2: walking + self-management program	I2: 12 OA self-management sessions + monthly reviewed walking program with pedometers and diaries/ moderate/ 3 months	3,6	Pain Function
Thomas et al 2002	786	knee pain, mean age >45yrs	I1: exercise + telephone I2: exercise +telephone + placebo I3: exercise I4: telephone I5: placebo C: no intervention	I1-3: 4 sessions in the first 2 months then visits every 6 months + HEP of local knee strengthening exercise/ moderate intensity/ 24 months	6,12,18, 24	Pain Function

Topp et al 2002	102	clinical OA	I1: dynamic resistance training I2: isometric resistance training C: control	I1: weekly theraband resisted lower limb strengthening + HEP/ moderate intensity/ 4 months I2: weekly lower limb isometric exercise + HEP/ moderate intensity/ 4 months	4	Pain Function
Wang et al 2009	40	clinical and radiographic OA (KL II+)	I1: Tai Chi C: wellness education and stretching	I1: 2 x weekly supervised Tai Chi sessions for 3 months + 3 months further home Tai Chi/ moderate intensity/ 6 months	3, 6, 11	Adverse events Pain Function
Wang et al 2011	84	clinical and radiographic OA	I1: aquatic exercise I2: land based exercise C: control	I1: 3 x weekly global flexibility and aerobic aquatic exercise/ moderate intensity/ 3 months I2: 3 x weekly mixed exercise/ moderate intensity/ 3 months	3	Adverse events Pain Function

Key: All studies were randomised controlled trials except when labelled with ## for case control study; mixed exercise indicates strengthening, flexibility and aerobic exercise components

Abbreviations: OA= osteoarthritis; KL= Kellgren and Lawrence osteoarthritis grade; BMI=body mass index; I1= intervention group 1; I2= intervention group 2 etc; C= control; HEP= home exercise program; TKR= total knee replacement