Title

The association of recreational and competitive running with hip and knee osteoarthritis: a systematic review and meta-analysis

Authors

Eduard Alentorn-Geli, MD, MSc, PhD[1-4], Kristian Samuelsson, MD, MSc, PhD[5], Volker Musahl, MD, PhD[6], Cynthia L. Green, PhD[7], Mohit Bhandari, MD, PhD[8], Jón Karlsson, MD, PhD[5]

Affiliations

[1]Fundación García-Cugat, Barcelona, Spain

[2]Artroscopia GC, SL, Hospital Quirón, Plaza Alfonso Comín 5-7, 08023, Barcelona, Spain

[3]Mutualidad Catalana de Futbolistas – Delegación Cataluña, Federación Española de Fútbol, Barcelona, Spain

[4]Department of Orthopedic Surgery, Mayo Clinic, Rochester MN, USA

[5]Department of Orthopedic Surgery, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, SE-431 80 Mölndal, Sweden

[6]Department of Orthopedic Surgery, University of Pittsburgh, 3200 South Water Street, Pittsburgh, PA, 15203 USA

[7]Department of Biostatistics and Bioinformatics, Duke University Medical Center, 2424 Erwin Road, Suite 1102 Hock Plaza, Box 2721, Durham, NC, 27710 USA

[8]Department of Orthopedic Surgery, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada

Corresponding author

Eduard Alentorn-Geli, MD, MSc, PhD, FEBOT

Artroscopia GC, Hospital Quirón

Plaza Alfonso Comín 5-7, Planta -1, 08023 Barcelona, Spain.

E-mail: ealentorngeli@gmail.com

Phone: +34-932172252

No funding was received for the present investigation.

Word count: 4175

No Institutional Review Board approval was needed for the present study.

ABSTRACT

Study design

Systematic review and meta-analysis

Background

Running is a healthy and popular activity worldwide, but data regarding its association with osteoarthritis (OA) are conflicting.

Objectives

To evaluate the association of hip and knee OA with running and to explore the influence of running intensity on this association

Methods

PubMed, EMBASE and Cochrane Library databases were used to identify studies investigating the occurrence of OA of the hip and/or knee among runners. Studies comparing this occurrence between runners and controls (sedentary, non-running individuals) were meta-analyzed. Runners were regarded as 'competitive' if they were reported as professionals/elite athletes, or participated in International competitions. Recreational runners were individuals running in a non-professional (amateur) manner. The prevalence and odds ratio (95% CI) for OA between runners (at competitive and recreational level) and controls were calculated. Subgroup analyses were conducted for OA location (hip or knee), gender and years of exposure to running (less or more than 15 years).

Results

Twenty-four studies (n=123,173 individuals) were included and 16 (n=112,192 individuals) were meta-analyzed. The overall prevalence (95% CI) of hip and knee OA was 13.3% (11.62-15.2) in competitive runners, 3.5% (3.38-3.63) in recreational runners and 10.23% (9.89-10.58) in controls. The odds ratio (95% CI) for hip and/or knee OA between recreational runners and controls was 0.66 (0.57-0.76). The odds ratio (95% CI) for hip and/or knee OA in competitive runners was higher than that in recreational runners (OR (95% CI) 1.34 (0.97-1.86) and 0.66 (0.57-0.76) respectively (controls as reference group); p=0.0001).

Conclusions

Recreational runners had a lower occurrence of OA compared with competitive runners and controls. These results indicated that a more sedentary lifestyle or long exposure to high-volume and/or high-intensity running are both associated with hip and/or knee OA. However, it was not possible to determine whether these associations are causative or confounded by other risk factors, such as previous injury.

Level of evidence

Etiology/Harm, Level 2a

Keywords

Runners; Osteoarthritis; Hip; Knee

INTRODUCTION

It is well accepted in the scientific and medical community that exercise is good for health. Running for health-related purposes is one of the best exercises to improve cardiovascular, musculoskeletal, respiratory and general health.[13] In fact, running is a regular physical activity among millions of persons around the world. However, is running safe and healthy for weight-bearing joints in all circumstances? Some concerns have been raised about whether prescribing exercise such as running can cause osteoarthritis (OA) in weight-bearing joints, particularly in certain scenarios.[57] Given the fact that OA may cause severe impairment to the patient's quality of life and require joint replacement, clarification of the influence of running on the development of OA is warranted. This clarification may help determine whether health-care providers can safely prescribe running for health-related purposes.

A clear distinction must first be made between running and other sports. It has been observed that the risk of OA may not be equivalent among exercise activities.[1] It has been demonstrated that, in general, previous injury or a heavy occupational workload increase the risk of OA [16, 49, 54] and the level of sports participation (whether elite/professional or recreational) may play an important role in the development of OA in sports.[8, 9, 21, 29, 45] Regarding exposure to running, specifically, there are contradictory data on the risk of OA. Some studies have found that running was not associated with an increased risk of OA (in fact, some researchers even found that it was protective),[5, 7, 24, 47, 56] but a fair number of studies have observed a higher risk of OA, or abnormal cartilage changes in animal and human studies.[2, 4, 10, 11, 15, 26, 32, 33, 35, 36, 38-40, 43, 46, 48] A likely explanation for these controversial results is the presence of differences in the type of running (level, intensity and length of exposure) and the presence of confounding factors (i.e. other risk factors for OA) not considered in the risk analysis for OA in runners. However, the influence of the level of exercise (elite/professional versus recreational) and the influence of other potential risk factors for OA (particularly body mass index (BMI), occupational workload and previous injury) on the risk of OA from running have not been well studied. The relevance of a better knowledge of the influence of these factors on the risk of OA in runners is to obtain a better definition of the patients that could acquire health-related benefits from running, without increasing the risk of joint damage that would end up in the impairment of their function and quality of life.

The purpose of this study was to evaluate the association of hip and knee OA with running and to further explore the influence of running intensity and years of exposure on this association. The study also aimed to assess the influence of concomitant risk factors on the association of running with hip and knee OA. It was hypothesized that running is not associated with OA of the hip and knee, at least in recreational runners, or whenever other risk factors are controlled.

METHODS

The methodology of this study was reported following the PRISMA Statement for systematic reviews and meta-analyses.[37]

Eligibility criteria

All prospective, cross-sectional or retrospective human studies investigating the relationship between OA of the hip and/or knee and running were evaluated for eligibility. Studies were included in the qualitative analysis if: 1) the level of evidence was I-III; 2) they were written in English; 3) there was clearly defined physician-based hip and/or knee (tibiofemoral joint) OA (clinical and/or radiographic findings); and 4) running activity was clearly reported in the sample. Studies with a self-reported diagnosis of OA were included if the diagnosis was specifically made by a physician. In studies where this information was not detailed enough, but the individuals had undergone joint replacement, it was assumed that the patients had physician-diagnosed OA and were therefore included in the present study. OA was not considered to be equivalent to pain, osteophytes, or subchondral sclerosis alone. To be included in the meta-analysis, studies had to report the incidence or prevalence of OA in runners and a control group. Review articles, systematic reviews and meta-analyses were not included, but reference lists were examined to ensure the completeness of relevant studies. Studies including subjects exposed to running and different types of physical activity altogether were not included.

Information sources and search

Electronic search

A systematic electronic literature search was conducted using PubMed (MEDLINE; with no start date), EMBASE (starting in 1980) and The Cochrane Library (no start date) in November 2016. Two librarians expert in electronic search methods performed the literature search. The search strategy and keywords employed in this study are summarized in Appendix 1.

Other search methods

The reference lists of all included articles and review studies were scrutinized to search for potential studies not previously identified.

Data collection and analysis

Study selection

All abstracts were read and articles of potential interest were reviewed in detail (full text) by two co-authors to decide on inclusion or exclusion from this systematic review.

In cases of disagreement, both co-authors reviewed and discussed the study and a final decision was made in consensus.

Data collection process

Information regarding the type of study, study and patient characteristics, quantification of the exposure to running, main results relating to OA and running, confounding factors considered, observations and main conclusions were extracted from all the included studies. For the studies included in the meta-analysis, a database spreadsheet was created to extract the information for the analysis. The database included information on the joint involved, additional risk factors for OA considered in the analysis (age, gender, weight, occupational workload and previous injury), years of exposure to running, running level (professional/competitive versus recreational), group (runners or controls) and the number of patients (total, men and women) with and without OA in each of the two groups. Runners were regarded as being part of the elite/competitive group if the authors specifically reported that the runners were professional, elite, or ex-elite athletes, or in any case in which runners represented their countries in International competitions. The control group consisted of mainly sedentary, non-running individuals. One co-author performed all the data extraction, which was then verified by a second co-author.

Assessment of the risk of bias

The assessment of the risk of bias was based on the recommendations of the Cochrane Collaboration.[14] The most important items considered for the risk of bias included selection bias (random sequence generation and allocation concealment): systematic differences between the baseline characteristics of the groups that are compared); performance bias (blinding of participants and personnel): systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest; detection bias (blinding of outcome assessment):

systematic differences between groups in how outcomes are determined; attrition bias (incomplete outcome data): systematic differences between groups in withdrawals from a study; and reporting bias (selective reporting): systematic differences between reported and unreported findings.[14] Each study was classified according to high risk, low risk, or unknown risk of bias for each item.

Statistical analysis

Three different analyses were conducted. First, a comparison of the association of OA for hip and/or knee, hip alone and knee alone between runners and controls (for the overall population, males and females, whenever available) was made depending on the level of running (competitive versus recreational). Each subgroup (competitive or recreational) was compared with its respective control group in the included study. The same comparison was made depending on the years of exposure to running (less or more than 15 years), including the studies that reported this specific information. Finally, the association of OA of the hip and/or knee, hip alone and knee alone was compared in the overall population, males and females (whenever data were available), depending on the confounding factors adjusted in the risk analysis of the included studies. The level of adjustment of the included studies was divided into five categories: studies not adjusting the risk of OA for any parameter, studies adjusting for age, studies adjusting for age and BMI, studies adjusting for age, BMI and occupational workload and studies adjusting for age, BMI, occupational workload and previous injury.

For each parameter, the odds ratio (OR) with 95% confidence interval (CI) was calculated based on the number of individuals with and without OA among the runners and controls. The overall prevalence (95% CI) was also calculated for competitive runners, recreational runners, controls and runners for < 15 and > 15 years). A meta-analysis of the association between running and OA was then conducted within each exposure group to produce combined estimates of measurements of effect (OR, with 95% CI), based on a random-effects model. For each meta-analysis conducted, overall OR estimates were calculated using an inverse variance-weighted random-effects model with 95% CIs. Random-effects analysis was used because the overall heterogeneity was moderate. Heterogeneity was characterized using the I^2 statistics. All analyses were made using SAS Version 9.4 (SAS Institute, Cary, NC), Comprehensive Meta-Analysis Version 3.0 (Biostat, Englewood, NJ) and RevMan 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Study selection

The literature search elicited a total of 1,907 references, of which 354 were duplicates and another 1,515 were excluded (Figure 1). A total of 38 studies were reviewed in full text and 17 were included. In addition, eight articles were added after reviewing the reference lists of the included studies. These eight articles were not identified by the literature search but met the inclusion criteria. As a result, 25 articles (involving 125,810 individuals) met the final inclusion criteria for the current systematic review. Seventeen of them (involving 114,829 individuals) could be included in the quantitative analysis.

Characteristics of the studies

Of the 25 studies, seven were prospective cohort studies and 18 case-control or cross-sectional studies. Table 1 summarizes the characteristics and principal findings of the 25 studies included in the qualitative analysis. An assessment of the risks of bias is summarized in Table 2. It is worth noting that most of the studies had a high risk of bias for most of the evaluated parameters.

Running level

The occurrence of hip and/or knee OA in the sample (overall population, males and females) depending on the level of running is summarized in Table 3. The overall prevalence (95% CI) of hip and/or knee OA was 3.66% (3.54-3.79) in runners and 10.23% (9.89-10.58) in control individuals. The overall prevalence (95% CI) was 13.3% (11.62-15.20) in the competitive runners and 3.5% (3.38-3.63) in recreational runners. Compared with the control group, recreational runners had a significantly lower association with hip and/or knee OA (OR 0.66; 95% CI 0.57-0.76; I^2 50%) and knee OA alone (OR 0.72; 95% CI 0.63-0.83; I^2 0%) in the overall population and in males (OR 0.78; 95% CI 0.68-0.89; I^2 0%; and OR 0.7; 95% CI 0.5-0.97; I^2 0% respectively). Compared with the control group, female recreational runners had a lower association with hip and/or knee OA (OR 0.54; 95% CI 0.41-0.71; I^2 43%). Compared with recreational runners, competitive runners had a significantly higher association with hip and/or knee OA and knee OA alone in the overall population (p=0.0001 and p=0.005 respectively) and in males (p=0.004 and p=0.01 respectively). In females, competitive runners had a higher association with hip and/or knee OA compared with recreational runners (p= 0.006) (Table 3).

Years of running

The association of hip and/or knee OA in the sample (overall population, males and females) depending on years of running (less or more than 15 years) is summarized in Table 4. All studies in the > 15 years subgroup corresponded to competitive runners (Table 4). The overall prevalence (95% CI) of hip and/or knee OA was 3.03% (2.92-3.15) in people running for less than 15 years and 17.2% (13.3-22.01) in people running for more than 15 years. Compared with the control group, individuals with exposure to running of less than 15 years had a lower association with hip and/or knee OA in the overall population (OR 0.6; 95% CI 0.49-0.73; I^2 47%), males (OR 0.79; 95% CI 0.68-0.91; I^2 0%) and females (OR 0.52; 95% CI 0.47-0.57; I^2 0%). Compared with people running for less than 15 years, those running for more than 15 years had a higher association with hip and/or knee OA in the overall population (p=0.01) and females (p=0.0006) (Table 4).

Influence of potential confounding factors

The association of hip and/or knee OA in the sample (overall population, males and females), depending on the adjustment of potential confounding factors, is summarized in Tables 5-7. It was observed that the two studies in which a larger number of variables were controlled in the risk analysis (both including recreational runners) had a significantly lower association with hip and/or knee OA compared with controls (Table 5). For the other level of adjustments, and for males and females separately, the association of running with hip and/or knee OA could not be demonstrated (Tables 5-7).

DISCUSSION

The principal finding in this study was that, in general, running was not associated with OA. In fact, running at recreational level was associated with lower odds of hip and/or knee OA compared with individuals running competitively and more sedentary, non-running individuals. While competitive running led to an increased association with OA compared with recreational running, non-runners also had a higher risk of joint degeneration compared with recreational runners. The influence of associated risk factors (age, gender, weight, occupational workload and previous injury) on the association with OA in runners could not be clearly demonstrated. These findings are relevant for physicians, physical therapists, nurses, athletic trainers and athletes planning to prescribe running for training, return to sports, or health-related purposes.

The ideal study to investigate the risk of OA associated with running would have been a prospective, randomized, double-blind study with one group running regularly over a long period of time, compared with another sedentary group and excluding or controlling the influence of previous injury, highly demanding occupational workload and overweight. In addition, individuals should be exposed only to running and no other activities, which is also difficult to control. No study of this kind exists and it would be extremely difficult to perform. Moreover, having a group behave as sedentary individuals could be ethically questionable. Most of the studies included in this review were case-control or cross-sectional studies. In addition, these studies were found to involve a high risk of the principal types of bias: selection, performance, detection, attrition and reporting (Tables 1 and 2). Despite the inherent limitations of the included studies, this investigation provides valuable information for health-related professionals.

There have been recent similar studies with comparable conclusions.[3, 28, 50-52] Overall, these systematic review and meta-analyses have not been able to demonstrate an association between running and hip and knee OA. However, some of these meta-analyses included cases series, missed some relevant studies for inclusion and did not differentiate the association depending on the intensity of running. Overall, our study drew similar conclusions. The novel finding in our investigation is the increased association between running and OA in competitive but not in recreational runners. In fact, running at recreational level was even found to have a protective effect on hip and/or knee OA.

The mileage of exposure to running very likely has a strong influence on the development of OA. Konradsen et al. found that running (orienteering running) was not associated with hip and knee OA with a median kilometers per week ranging between 21 and 42.[20] In contrast, Marti et al. observed an increased prevalence of hip OA in elite long-distance runners who were exposed to a mean of 92 kilometers per week.[35] The present study was unable to establish the association of OA with running according to mileage, because most studies did not quantify the exposure to running or did so using different measurements. In terms of the level of running, the definition of elite/competitive or recreational is not always clear and there is no quantification of the amount of running that is considered elite. Some individuals may run a high mileage per week at a considerably high intensity for recreational purposes. In general, the lower the number of miles per week, the lower the level of running, but the distinction between elite/competitive or recreational has not been quantified. Studies included in this investigation were grouped according to the authors' definition of the level of running. In general, running at elite/competitive level increases the association with OA compared with the recreational level, particularly for the knee in the overall population and males (Table 3). However, there are no original studies specifically comparing the prevalence or incidence of hip and/or knee OA in elite/competitive versus recreational runners. Interestingly, most of the studies demonstrating an increased risk of OA from running or sports in general included elite, ex-elite, professional, or high-level athletes.[8, 9, 21, 29, 35, 36, 45, 48]

McDermott and Freyne found that runners with OA had been running for significantly more years compared with runners without OA (mean 19.6 years versus 11.9 years respectively).[36] This would correspond to the findings in the present study, where runners exposed to this activity for less than 15 years had a lower association with OA in the overall population compared with an exposure of more than 15 years (Table 4). The potential influence of number of years or mileage on the risk of OA may be explained by the findings observed by Galois et al.[11] These researchers found a chondroprotective effect of slight or moderate (intensity determined by the distance run) running in rats that was no longer present under intense (highest distance run by rats) running. Interestingly, all studies grouped as less than 15 years corresponded to recreational running,[5, 6, 41, 42, 56] whereas studies grouped as more than 15 years corresponded to competitive runners.[20, 44, 48] As a result, no information on the effects of recreational running for more than 15 years on the association with hip and knee OA is available.

The risk of OA from sports participation is influenced by the control of other risk factors by either excluding their presence or performing an adjusted risk analysis.[16, 49, 54] Specifically for running, a very limited number of studies that adjusted the risk analysis for many of the most important associated risk factors, particularly obesity, occupational workload and previous injury, were included in the present investigation (Tables 5-7). These factors were found to influence the risk of OA and should therefore be considered whenever the risk of OA is investigated.[16, 49, 54] The present meta-analysis was unable to demonstrate a clear association with OA in studies adjusting the risk analysis for other risk factors for OA compared with studies not performing this adjustment. A limitation of this comparison is that some studies appeared in more than one of the subgroups created for the level of adjustment. It was then recommended not to perform a direct between-subgroups comparison (no p-value) of the influence of associated risk factors. It still remains unclear whether prescribing running in the overweight/obese patient with an additional high-impact occupational workload and previous injury is safe for joints. It is very likely that the combination of these three factors together in a patient who begins to run may increase the risk of OA.[16, 31, 49, 54] Further original investigations should be conducted to obtain a response to this research question.

The present study has some limitations. First, it was difficult to find studies with a clearly sedentary control group. This is associated with the normal activities the general population may perform every day. Some studies did not clearly specify whether the control group was sedentary or reported anecdotal exposure to sports.[5, 17, 22, 24, 44, 47, 48, 56] As a result, the control group in some studies was not completely sedentary. Secondly, in some studies, the runners were also exposed to other types of sport (i.e. tennis), the runners included some individuals performing only walking exercise, or involved orienteering running.[6, 17, 20, 22, 48, 55] Considering both limitations, the presence of joint-impact exercises in the control group or the presence of high-impact joint forces other than running in runners has to be considered when interpreting the risk of OA from running per se. Third, the running level could only be classified according to the researchers' information but not based on any quantified parameter for running (mileage per week, velocity of running and so on). It is therefore not possible to formulate any recommendation from a practical standpoint on the quantity of running that would be safe for the hip and knee. Fourth, the inclusion of studies written only in English may imply a language bias.[12] This language restriction is commonly used in studies due to obvious linguistic limitations. Fifth, the assessment of the risk of bias was conducted using a tool not specifically designed for observational, etiologic association studies and the use of other appraisal tools might therefore provide different insights. Lastly, due to high between-studies heterogeneity (high I^2 statistic), the random-effects model, which can inappropriately weight smaller studies in some instances, was necessary. In some comparisons, the I^2 heterogeneity statistic was very low (Tables 3-7). The use of a fixed-effects model did not significantly change the results in parameters with low I^2 and a decision was made to use the random-effects model throughout the statistical analysis. Overall, the heterogeneity was considerably lower for comparisons involving the knee joint alone as compared with the hip and knee or hip alone.

Despite these limitations, the present study is the first meta-analysis investigating the occurrence of OA between competitive and recreational runners and it involves a very large sample (114,829 individuals from different countries). The study has high external validity and the conclusions are of general health interest given the high popularity of running worldwide.

CONCLUSIONS

Running at recreational level was associated with significantly lower odds of OA compared with competitive runners or control individuals. These results indicate that a more sedentary lifestyle or long exposure to high-volume and/or high-intensity running are both associated with hip and/or knee OA. Running was associated with lower hip and/or knee OA if it was performed for as long as up to 15 years; for more than 15 years, there were few studies and no clear conclusion could be drawn. It was also not possible clearly to demonstrate the influence of associated risk factors (age, gender, weight, occupational workload and previous injury) on the risk of OA in runners.

KEY POINTS

Findings: Recreational runners had a lower association with OA compared with competitive runners and controls. The beneficial association of running with a lower OA risk was not observed in long-term competitive runners.

Implications: Running at recreational level can be safely recommended as a general health exercise, with the evidence suggesting that it has benefits for hip- and knee-joint health. The amount of running that is safe for the joints could not be determined.

Caution: The present results must be interpreted with caution due to the absence of high-quality prospective, randomized, controlled trials, the small number of studies for some comparisons, the potentially high risk of bias in included studies, the high heterogeneity of studies and the wide confidence intervals for some parameters.

REFERENCES

1. Alentorn-Geli E, Puig Verdié L. Osteoarthritis in sports and exercise: risk factors and preventive strategies. In: Rotschild BD, ed. *Principles of osteoarthritis. Its definition, character, derivation and modality*. Rijeka, Croatia: InTech; 2012:173-232.
2. Arokoski J, Kiviranta I, Jurvelin J, Tammi M, Helminen HJ. Long-distance running causes site-dependent decrease of cartilage glycosaminoglycan content in the knee joints of beagle dogs. *Arthritis Rheum.* 1993;36(10):1451-1459.
3. Bastick AN, Belo JN, Runhaar J, Bierma-Zeinstra SMA. What are the prognostic factors for radiographic progression of knee osteoarthritis? A meta-analysis. *Clin Orthop Relat Res.* 2015;473:2969-2989.
4. Beckett J, Jin W, Schultz M, et al. Excessive running induces cartilage degeneration in knee joints and alters gait of rats. *J Orthop Res.* 2012;30(10):1604-1610.
5. Chakravarty EF, Hubert HB, Lingala VB, Zatarain E, Fries JF. Long distance running and knee osteoarthritis. A prospective study. *Am J Prev Med.* 2008;35(2):133-138.
6. Cheng Y, Macera CA, Davis DR, Ainsworth BE, Troped PJ, Blair SN. Physical activity and self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor? *J Clin Epidemiol.* 2000;53(3):315-322.
7. Dahaghin S, Tehrani-Banihashemi SA, Faezi ST, Jamshidi AR, Davatchi F. Squatting, sitting on the floor, or cycling: are life-long daily activities risk factors for clinical knee osteoarthritis? Stage III results of a community-based study. *Arthritis Rheum.* 2009;61(10):1337-1342.
8. Deacon A, Bennell K, Kiss ZS, Crossley K, Brukner P. Osteoarthritis of the knee in retired, elite Australian Rules footballers. *Med J Aust.* 1997;166(4):187-190.
9. Felson DT, Zhang Y, Hannan MT, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis Rheum.* 1997;40(4):728-733.
10. Franciozi CE, Tarini VA, Reginato RD, et al. Gradual strenuous running regimen predisposes to osteoarthritis due to cartilage cell death and altered levels of glycosaminoglycans. *Osteoarthritis Cartilage.* 2013;21(7):965-972.
11. Galois L, Etienne S, Grossin L, et al. Dose-response relationship for exercise on severity of experimental osteoarthritis in rats: a pilot study. *Osteoarthritis Cartilage.* 2004;12(10):779-786.
12. Gregoire G, Derderian F, Le Lorier J. Selecting the language of the publications included in a meta-analysis: is there a Tower of Babel bias? *J Clin Epidemiol.* 1995;48(1):159-163.
13. Hespanhol Junior LC, Pillay JD, van Mechelen W, Verhagen E. Meta-Analyses of the Effects of Habitual Running on Indices of Health in Physically Inactive Adults. *Sports Med.* 2015;45(10):1455-1468.
14. Higgins JPT, Altman DG. Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions*. Chichester: John Wiley & Sons, Ltd; 2008:187-241.

15. Horisberger M, Fortuna R, Valderrabano V, Herzog W. Long-term repetitive mechanical loading of the knee joint by in vivo muscle stimulation accelerates cartilage degeneration and increases chondrocyte death in a rabbit model. *Clin Biomech (Bristol, Avon).* 2013;28(5):536-543.
16. Imeokparia RL, Barrett JP, Arrieta MI, et al. Physical activity as a risk factor for osteoarthritis of the knee. *Ann Epidemiol.* 1994;4(3):221-230.
17. Kettunen JA, Kujala UM, Kaprio J, Koskenvuo M, Sarna S. Lower-limb function among former elite male athletes. *Am J Sports Med.* 2001;29(1):2-8.
18. Kettunen JA, Kujala UM, Raty H, Sarna S. Jumping height in former elite athletes. *Eur J Appl Physiol Occup Physiol.* 1999;79(2):197-201.
19. Kohatsu ND, Schurman DJ. Risk factors for the development of osteoarthrosis of the knee. *Clin Orthop Relat Res.* 1990;261:242-246.
20. Konradsen L, Hansen EM, Sondergaard L. Long distance running and osteoarthrosis. *Am J Sports Med.* 1990;18(4):379-381.
21. Kujala UM, Kaprio J, Sarna S. Osteoarthritis of weight bearing joints of lower limbs in former elite male athletes. *BMJ.* 1994;308(6923):231-234.
22. Kujala UM, Sarna S, Kaprio J, Koskenvuo M, Karjalainen J. Heart attacks and lower-limb function in master endurance athletes. *Med Sci Sports Exerc.* 1999;31(7):1041-1046.
23. Lane NE, Bloch DA, Jones HH, Marshall WH, Jr., Wood PD, Fries JF. Long-distance running, bone density, and osteoarthritis. *JAMA.* 1986;255(9):1147-1151.
24. Lane NE, Michel B, Bjorkengren A, et al. The risk of osteoarthritis with running and aging: a 5-year longitudinal study. *J Rheumatol.* 1993;20(3):461-468.
25. Lane NE, Oehlert JW, Bloch DA, Fries JF. The relationship of running to osteoarthritis of the knee and hip and bone mineral density of the lumbar spine: a 9 year longitudinal study. *J Rheumatol.* 1998;25(2):334-341.
26. Lapvetelainen T, Nevalainen T, Parkkinen JJ, et al. Lifelong moderate running training increases the incidence and severity of osteoarthritis in the knee joint of C57BL mice. *Anat Rec.* 1995;242(2):159-165.
27. Lau EC, Cooper C, Lam D, Chan VN, Tsang KK, Sham A. Factors associated with osteoarthritis of the hip and knee in Hong Kong Chinese: obesity, joint injury, and occupational activities. *Am J Epidemiol.* 2000;152(9):855-862.
28. Lefèvre-Colau MM, Nguyen C, Haddad R, et al. Is physical activity, practicated as recommended for health benefit, a risk factor for osteoarthritis? *Ann Phys Rehabil Med.* 2016;59:196-206.
29. Lindberg H, Roos H, Gardsell P. Prevalence of coxarthrosis in former soccer players. 286 players compared with matched controls. *Acta Orthop Scand.* 1993;64:165-167.
30. Lo GH, Driban JB, Kriska AM, et al. History of Running is Not Associated with Higher Risk of Symptomatic Knee Osteoarthritis: A Cross-Sectional Study from the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken).* 2016.
31. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med.* 2007;35(10):1756-1769.
32. Lucchinetti E, Adams CS, Horton WE, Jr., Torzilli PA. Cartilage viability after repetitive loading: a preliminary report. *Osteoarthritis Cartilage.* 2002;10(1):71-81.

33. Luke AC, Stehling C, Stahl R, et al. High-field magnetic resonance imaging assessment of articular cartilage before and after marathon running: does long-distance running lead to cartilage damage? *Am J Sports Med.* 2010;38(11):2273-2280.
34. Manninen P, Riihimaki H, Heliovaara M, Suomalainen O. Physical exercise and risk of severe knee osteoarthritis requiring arthroplasty. *Rheumatology (Oxford).* 2001;40(4):432-437.
35. Marti B, Knobloch M, Tschopp A, Jucker A, Howald H. Is excessive running predictive of degenerative hip disease? Controlled study of former elite athletes. *Br Med J.* 1989;299:1-3.
36. McDermott M, Freyne P. Osteoarthrosis in runners with knee pain. *Br J Sports Med.* 1983;17(2):84-87.
37. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;18:264-269.
38. Neidhart M, Muller-Ladner U, Frey W, et al. Increased serum levels of non-collagenous matrix proteins (cartilage oligomeric matrix protein and melanoma inhibitory activity) in marathon runners. *Osteoarthritis Cartilage.* 2000;8(3):222-229.
39. Ni GX, Zhan LQ, Gao MQ, Lei L, Zhou YZ, Pan YX. Matrix metalloproteinase-3 inhibitor retards treadmill running-induced cartilage degradation in rats. *Arthritis Res Ther.* 2011;13(6):R192.
40. Niehoff A, Muller M, Bruggemann L, et al. Deformational behaviour of knee cartilage and changes in serum cartilage oligomeric matrix protein (COMP) after running and drop landing. *Osteoarthritis Cartilage.* 2011;19(8):1003-1010.
41. Panush RS, Hanson CS, Caldwell JR, Longley S, Stork J, Thoburn R. Is Running Associated with Osteoarthritis? An Eight-Year Follow-up Study. *J Clin Rheumatol.* 1995;1(1):35-39.
42. Panush RS, Schmidt C, Caldwell JR, et al. Is running associated with degenerative joint disease? *JAMA.* 1986;255(9):1152-1154.
43. Pap G, Eberhardt R, Sturmer I, et al. Development of osteoarthritis in the knee joints of Wistar rats after strenuous running exercise in a running wheel by intracranial self-stimulation. *Pathol Res Pract.* 1998;194(1):41-47.
44. Puranen J, Ala-Ketola L, Peltokallio P, Saarela J. Running and primary osteoarthritis of the hip. *Br Med J.* 1975;2:424-425.
45. Roos H, Lindberg H, Gardsell P, Lohmander LS, Wingstrand H. The prevalence of gonarthrosis and its relation to meniscectomy in former soccer players. *Am J Sports Med.* 1994;22(2):219-222.
46. Siebelt M, Groen HC, Koelewijn SJ, et al. Increased physical activity severely induces osteoarthritic changes in knee joints with papain induced sulfate-glycosaminoglycan depleted cartilage. *Arthritis Res Ther.* 2014;16(1):R32.
47. Sohn RS, Micheli LJ. The effect of running on the pathogenesis of osteoarthritis of the hips and knees. *Clin Orthop Relat Res.* 1985;198:106-109.
48. Spector TD, Harris PA, Hart DJ, et al. Risk of osteoarthritis associated with long-term weight-bearing sports: a radiologic survey of the hips and knees in female ex-athletes and population controls. *Arthritis Rheum.* 1996;39(6):988-995.

49. Thelin N, Holmberg S, Thelin A. Knee injuries account for the sports-related increased risk of knee osteoarthritis. *Scand J Med Sci Sports.* 2006;16(5):329-333.
50. Timmins KA, Leech RD, Batt ME, Edwards KL. Running and Knee Osteoarthritis: A Systematic Review and Meta-analysis. *Am J Sports Med.* 2016.
51. Tran G, Smith TO, Grice A, Kingsbury SR, McCrory P, Conaghan PG. Does sports participation (including level of performance and previous injury) increase risk of osteoarthritis? A systematic review and meta-analysis. *Br J Sports Med.* 2016;Sep 28. doi: 10-1136/bjsports-2016-096142. [Epub ahead of print].
52. Vigdorchik JM, Nepple JJ, Eftekhary N, Leunig M, Clohisy JC. What is the association of elite sporting activities with the development of hip osteoarthritis? *Am J Sports Med.* 2016;Jul 29. pii: 0363546516656359. [Epub ahead of print].
53. Vingard E, Alfredsson L, Goldie I. Sports and osteoarthritis of the hip. An epidemiologic study. *Am J Sports Med.* 1993;21:195-200.
54. Vingard E, Alfredsson L, Malchau H. Osteoarthrosis of the hip in women and its relationship to physical load from sports activities. *Am J Sports Med.* 1998;26:78-82.
55. Vrezas I, Elsner G, Bolm-Audorff U, Abolmaali N, Seidler A. Case-control study of knee osteoarthritis and lifestyle factors considering their interaction with physical workload. *Int Arch Occup Environ Health.* 2010;83(3):291-300.
56. Williams PT. Effects of running and walking on osteoarthritis and hip replacement risk. *Med Sci Sports Exerc.* 2013;45(7):1292-1297.
57. Willick SE, Hansen PA. Running and osteoarthritis. *Clin Sports Med.* 2010;29(3):417-428.

TABLE 1. Summary of studies evaluating the risk of osteoarthritis after exposure to running.

Author	Type of study	Study / Patient characteristics	Exposure to running	Results	Confounding factors considered	Observations	Conclusion
Chakravarty et al., 2008[5]	Cohort study, level II evidence	45 long-distance runners (mean age 71y, 65% men, 44% previous knee injury, BMI 23) and 53 age-, education-, and occupation-matched controls (mean age 72y, 70% men, 36% previous knee injury, BMI 25) followed for nearly two decades for radiographic knee OA	Vigorous exercise: runners 293 min/week, controls 199 min/week Running: runners 95 min/week, controls one min week	Knee OA: runners 20%, controls 32% (p=0.2). Severe knee OA: runners 2.2%, controls 9.4% (p=0.2) Knee OA associated with BMI, initial radiographic damage and longer follow-up. Knee OA not associated with gender, education, previous knee injury and mean exercise time.	Adjusted for age, gender, BMI, education, previous knee injury and initial radiographic and disability scores Not clearly adjusted for occupational workload	Running not isolated Controls also exposed to running earlier in life	Running not associated with accelerated radiographic knee OA
Cheng et al., 2000[6]	Cohort study, level II evidence	16,961 subjects aged 20-87y (median age 44y for men (76%) and 43y for women (24%)) followed up for a mean of 10.9y for incidence of hip and knee OA Self-reported physician-diagnosed hip and knee OA	Physical activity: high (walking or jogging >20 miles/week), moderate (between 10-20 miles/week), low (<10 miles/week), other (other activities than walking/jogging)	439 incident cases in men (3.4%) and 162 in women (3.9%); subjects >50y: incident OA higher in women; subjects <50y: incident OA similar between men and women Physical activity <50y: men high HR 2.4 (1.5-3.9), moderate 1.2 (1-1.4), low 1 (0.6-1.5), other 1.4 (0.9-2); women high HR 1.5 (0.4-5.1), moderate 1.2 (0.9-1.5), low 0.8 (0.4-1.6), other 1.1 (0.6-2). Physical activity >50y: men high HR 1.2 (0.6-2.3), moderate 1 (0.8-1.2), low 1.3 (0.9-1.8), other 1.1 (0.7-1.5); women high HR 1.4 (0.4-4.6), moderate 1.2 (0.9-1.5), low 0.6 (0.3-1.2), other 0.7 (0.4-1.3).	Adjusted for age, gender, BMI, smoking and ethanol and caffeine use History of joint injury and occupational workload not controlled in the analysis	Kappa agreement 0.68 between self-reported physician-diagnosed OA and chart review for OA Running not isolated	High levels of physical activity associated with increased incidence of hip and knee OA in men < 50y, but not in the rest of the sample
Dahaghin et al., 2009[7]	Case-control, level III evidence	480 cases with knee OA (mean age 57y SD 12y) and 490 controls without knee OA (mean age 46y SD15y) (p<0.00001); 70% women in cases, 65% in controls; BMI 30 cases, 27 controls (p<0.00001)	Not reported	Participation in sports: 32% cases, 40% controls Running OR 1.05 (0.7-1.58)	Age-, gender- and BMI-adjusted History of knee injuries not reported Occupational workload collected Adjustment of knee OA in runners depending on workload not known	Running not isolated Minimum exposure to sports = 6 mo Low participation in sports in both groups	Running not associated with increased risk of knee OA
Kettunen et al., 1999[18]	Case-control, level III evidence	Initial sample: male ex-elite athletes for runners, shooters, soccer, WL Follow-up in 1992: 80% responded (28 runners)	Not reported; former athletes at an elite level	Long-distance runners 14% knee OA and 12% hip OA, compared with 3% and 30% in shooters resp.	Not adjusted for the running and OA comparison between groups	Controls not sedentary No statistics for running and OA	Running not clearly associated with hip or

		at age 20y; Follow-up in 1995: 1,321 athletes available, 814 in controls Hip and knee OA in <45y / >45y Study through questionnaires	championships, European championships	(0.36-0.82) -Knee disability: team sport OR 1.76 (1.03-3) -Hip OA: no differences -Knee OA: team sport OR 2.04 (1.35-3.07) -Hip pain: endurance OR 0.32 (0.17-0.61), shooting OR 0.32 (0.12-0.87), all sports OR 0.66 (0.5-0.88) -Knee pain: team sports OR 1.56 (1.07-2.28)	OA	and knee pain, disability and OA	risk of hip or knee OA
Kohatsu and Schurman, 1990[19]	Case-control, level III evidence	46 subjects (cases) with knee OA (mean age 71y, 60% females, BMI 27, years of school 14) and 46 matched controls (mean age 71y, 60% females, BMI 27, years of school 14) Diagnosed knee OA in patients undergoing TKA	Not reported	Similar exposure to running, team sports, racquet sports, and other sports in cases compared with controls (4.5% vs 8.7%, 12.2% vs 17.4%, 15.8% vs 22.2%, 59.5% vs 65.2% resp) Cases less exposed to walking compared with controls (35.7% vs 56.5%, p<0.01)	Age-, gender- and education-matched controls Unmatched for BMI Cases participated in heavier work for ages between 30 to 49y compared with controls Cases had more history of knee injuries (p<0.01)	Participation 68% Cases had higher BMI (p<0.0001) Running not isolated Running not quantified	General leisure-time physical activity not associated with significant risk of knee OA
Konradsen et al., 1990[20]	Cross-sectional, level III evidence	27 male orienteering runners (median age 58y, range 50-68; median weight 71kg, range 60-81) and 27 matched controls (median age 57y, range 53-65; median weight 75kg, range 55-82) Clinical and radiological OA	Running: median ages 40y (range 32-50); median km/week <30y: 42 (range 20-65); 31-40y: 34 (15-65); 41-50y: 30 (13-63); 51-60y: 28 (13-63); >61y: 21 (13-43)	No significant differences between runners and controls with regard to OA and osteophytosis of hip and knee, ankle No differences in joint alignment, range of motion, or complaints of pain between groups 22% of runners had pain during running, with no radiological differences compared with subjects without pain	Age-, height-, weight- and occupational load-matched controls No major joint injuries in the sample, except three subjects, one of them excluded from the analysis	Participation 90% Statistics not very detailed Runners no longer active excluded Small sample	Running at recreational level was not associated with hip, knee and ankle OA
Kujala et al., 1994[21]	Cohort study, level II evidence	2,448 male ex-elite athletes representing Finland in sport events from 1920-1965 vs 1,712 healthy age-matched controls at age 20y; follow-up in 1970: 2,049 athletes available, mean age 46y (range 21-85), 1,403 in controls, mean age 44y (range 24-86); follow-up in 1990: 1,436 athletes available, 959 in controls Study through questionnaires	Not reported; former athletes at an elite level: Olympic games, World championships, European championships	More admissions for hip, knee, ankle OA in athletes (5.9%) than controls (2.6%) (p<0.0001) Endurance (long-distance running): hip OA 5.2% (95% CI 2.6-10.2), knee OA 2.5% (0.7-6.3%), ankle OA 0%, compared with 1.4% (0.9-2.2), 1.3% (0.8-2), and 0% in the control group resp OR for hip, knee, or ankle OA in runners compared with controls: 1.84 (95% CI 0.93-3.61) Adjusted OR for hip, knee, or ankle OA in runners compared with controls: 2.42 (1.26-4.68) Mean age at first admission: higher in endurance than others: 70.6y compared with 58.2y, 61.9y, and 61.2y in mixed sports, power sports and controls resp.	Adjusted for age, weight and occupation History of joint injury not controlled	Only considering admission may hide other patients with OA at lower stages Exposure not quantified Endurance mixes running and cross-country skiing	Running not associated with increased risk of hip, knee, or ankle OA Endurance athletes had admissions for hip, knee or ankle OA at older age
Kujala et al., 1999[22]	Cohort study, level II evidence	264 male orienteering runners (mean age 58y, range 47-71; mean BMI 23) compared with 188 male non-smoking controls (mean age 60y, range 50-71; mean BMI 25) Clinical OA at 11 years of follow-up	Not specified	Hip OA: running OR 0.78 (0.35-1.73) Knee OA: running OR 1.79 (1.1-3.54) Hip pain: running OR 0.74 (0.37-1.46) Knee pain: running OR 1.75 (0.96-3.18) Hip pain on stairs: running OR 0.47 (0.2-1.08) Knee pain on stairs: running OR 0.78 (0.4-1.4) Runners: 23.5% had ligament or meniscus injury (vs 16.8% in controls); 38% of runners with knee	Age-, gender- and area of residence-adjusted analysis Not adjusted for BMI and occupational workload History of previous knee injury likely influencing development of OA	Exposure to running not quantified Controls (11%) participated in other physical activities Differences in	Overall, running not associated with greater lower-limb disability, except for knee OA

				injuries had OA (vs 7% without injury)		weight and BMI	
Lane et al., 1986[23]	Cross-sectional, level III evidence	41 long-distance runners (aged 50-72y) compared with 41 matched controls Clinical and radiological lumbar, knee and hands OA	Running: min/week 224, years run 8.5, mean total miles run 9,552	Female, but not male, runners had more sclerosis and spur formation in spine and knee, but not hand, radiographs. No differences in JSN, crepitation, joint stability, or symptomatic OA between groups	Age-, gender-, education- and occupation-matched controls Control for history of joint injury in the analysis not reported	Controls heavier than runners Controls also exposed to running	Running not associated with increased risk of lumba spine, knee and hand O.
Lane et al., 1993[24]	Cohort study, level II evidence	33 runners (mean age 63.3y, 60% males, weight 67.8kg) vs 33 matched controls (mean age 63.5y, 60% males, weight 73.1kg) Clinical and radiological OA at baseline and five years later	Runners (mean values): exercise (min/week) 304, running (min/week) 185	Lumbar OA: both groups progressed in spurs Knee OA: runners had no progression of spurs and combined JSN, sclerosis and spurs; controls had progression of both parameters Hand OA: both groups progressed in spurs and combined JSN, sclerosis and spurs No differences in age, gender, weight, exercise, running and disability between subjects with and without hand and knee OA Running was not predictive of lumbar spine, knee or hand OA	Age, gender, occupation and years of school-matched controls Injuries collected but their influence not reported	Follow-up 80% Controls were heavier than runners, $p<0.05$ Running not isolated Spurs alone not enough for OA	Running not associated with increased risk of lumba spine, knee, and hands OA
Lane et al., 1998[25]	Cohort study, level II evidence	28 runners mean age 66y (range 60-77), 60% males, mean BMI 23.6, and 27 non-runners mean age 66y, 74% males, mean BMI 24.7. Clinical and radiological OA at nine years of follow-up	Runners: mean 279 min/week of exercise; mean 107 min/week running; mean miles run/week 18; mean years running 17	Hip joint: osteophytes, JSN, total hip score not significantly different between both groups Knee joint: both groups progressed significantly in osteophytes; only controls progressed significantly in JSN; only runners progressed significantly in total knee score	Age-, gender-, education- and occupation-adjusted History of injury not clearly controlled	Controls also exercised Small sample Potential risk of selection bias.	Running not associated with increased hi OA or progression of knee OA
Lau et al., 2000[27]	Case-control, level III evidence	138 subjects with hip OA and 414 controls. 658 subjects with knee OA, 658 controls. Clinical and radiological hip or knee OA	Not detailed	Hip OA: small number of cases in all sports, except gymnastics in women; Knee OA: small number of cases except running, soccer in men and running, gymnastics, kung-fu in women Hip OA: men: running OR 0.7 (0.2-2.3), soccer 1.3 (0.3-5.4), gymnastics 1.2 (0.2-6.9), kung-fu 0.8 (0.08-6.7); women: running 0.9 (0.2-3.3), badminton 1 (0.2-5), gymnastics 6 (2.1-17.6) Knee OA: men: running OR 0.6 (0.3-1.4), soccer 1.3 (0.6-2.8), gymnastics 2 (0.8-5.3), kung-fu 1.4 (0.4-4.4); women: running 1.4 (0.7-2.8), badminton 0.5 (0.1-2.7), gymnastics 7.2 (3.1-16.8), kung-fu 20 (2.7-149)	Age-, gender-, weight-, occupation-, hip/knee injuries-controlled, but analysis only differentiating for gender	Only includes worst grades of OA Risk of type II error in sports with small number of cases No data on number of injuries in each group or sport	Running not associated with increased risk of hip and knee O. in both men and women
Lo et al., 2016[30]	Case-control, level III evidence	2,637 cases compared retrospectively for history of running and evaluated in a cross-sectional manner for knee OA; mean age 64y, 56% females, mean BMI 28.5	Runners (30%): 75% at least 250 bouts of running in their lives, 50% at least 800 bouts, 25% at least 2000 bouts. Competitive 2-5%	Radiographic knee OA: prior runners OR 0.98 (0.78-1.25) and current runners OR 0.91 (0.7-1.19) compared with reference group (never running) (p non-significant) Symptomatic knee OA: prior runners OR 0.88 (0.67-1.14) and current runners OR 0.71 (0.53-0.97) compared with reference group (never running)	Age, gender, BMI, prior to knee injury	Risk of recall bias. Running not isolated in the sample Minor proportion of competitive	Running not associated with symptomati knee OA

				(p=0.03)		runners (2-5%)	
ɅManninen et al., 2001[34]	Case-control, level III evidence	281 cases undergoing TKA for knee OA (men 55, women 226, mean age 28y) and 524 age-, gender-matched controls	Only few at competitive level. High exposure: > 8,654h in men, > 6,862h in women. Low exposure lower than these values.	Men with high cumulative exercise were protected from knee OA compared with low exposure OR 0.28 (0.08-0.96) for all ages. Women with high exposure were protected from knee OA in age ranges 30-49y, and >49y compared with low exposure OR 0.51 (0.23-1.15) and 0.59 (0.3-1.16), resp. Running: men OR 0.26 (0.05-1.3), women OR 0.7 (0.48-1.02)	Analysis adjusted for age, BMI, physical work stress, knee injury and smoking.	Participation 70% Running not isolated Controls not sedentary Specific sport exposure not provided	Running not associated with increased risk of knee OA in men and women
Marti et al., 1989[35]	Case-control, level III evidence	27 former elite long-distance runners (mean age 42y) 9 former bobsleigh riders (mean age 42y), and 23 controls (mean age 35y. Clinical and radiological hip OA	Running: mean 97km/week Bobsleigh riders: mean 12km/week	Hip OA index (computed by summing JSN, sclerosis and osteophyte): mean 1.37 (0.76-1.98 95% CI) in runners, 0.33 (-0.05-0.72) in bobsleigh and 0.32 (0-0.64) in controls (p=0.006). Runners more osteophyte and sclerosis compared with controls Hip pain: 30% in runners, and 0% in bobsleigh and controls Adjusting for age: runners more hip OA Adjusting for mileage: runners not more hjp OA	Analysis not adjusted for gender, BMI, occupational workload or history of joint injury Adjusted for age and mileage	Participation 92% Small sample Radiological blinding Controls also run No baseline X-rays	Running was associated with an increased risk of OA
Panush et al., 1986[42]	Cross-sectional, level III evidence	17 male runners (mean age 56y, range 50-74) compared with 18 male non-runners (mean age 61y, range 50-74) (no differences in age, height, weight) Clinical and radiological hip, knee, or ankle OA	Runners: mean years running 12y (range 5-27); mean miles/week 28 (range 20-40); mean lifetime mileage 17,343 (range 6,500-49,140)	Runners vs non-runners: hip pain 26% vs 11%, knee pain 29% vs 22%, ankle pain 12% vs 5%. Runners vs non-runners: osteophytes per subject hip 0.6 vs 0.9, knee 3.9 vs 4.8, ankle 2.2 vs 1.8; cartilage thickness mm hip 4.65 vs 4.3, knee medial 5 vs 5 and lateral 5.8 vs 5.6, ankle 3 vs 3.1; degeneration % hip 0 vs 0, knee 0.06 vs 0.17, ankle 0 vs 0 (all differences p>0.05)	Not controlled for occupational load and history of joint injury	Controls sedentary Small sample Joint injury and occupational load influenced OA	Running was not associated with hip, knee and ankle O
Panush et al., 1995[41]	Cohort study, level II evidence	12 male runners (mean age 63y, SD 6) compared with 10 male non-runners (mean age 68y, SD 8) (no differences in age, height, weight). Clinical and radiological hip, knee, or ankle OA at eight-year follow-up	Runners: mean years running 22y (SD 14); mean miles/week 22 (SD 11); lifetime mileage 25,168; 42% marathoners	Runners vs non-runners: hip pain 9% vs 10%, knee pain 0% vs 0%, ankle pain 0% vs 10%. No differences in hip, knee and ankle OA between runners and non-runners.	Adjustment of analysis for age, gender, BMI, occupation and history of joint injury not known	Small sample Influence of joint injury and workload Running not isolated	Running was not associated with hip, knee and ankle O
Puranen et al., 1975[44]	Case-control, Cross-sectional study, level III evidence	74 ex-élite runners (mean age 55y, range 31-81) and 115 controls (mean age 56, range 40-75)	Élite running: starting age 15y (range 12-25), total participation 21y (range 8-50)	Hip OA changes: runners 4% (controls 8.6% Osteophyte formation only: runners 9.5%, controls 14.8% (none had hip pain) Clear OA changes associated with more hip pain	Control of main confounding factors not reported: gender, BMI, occupational load, other exposure to sports, history of joint injury and so on	No statistics Influence of confounding factors Controls not sedentary	Running not associated with increased risk of hip O
Sohn and Micheli, 1985[47]	Case-control, level III evidence	504 former runners (mean age 57y, range 23-77) compared with 287 ex-swimmers; mean follow-up 55y (range 2-25). Clinical hip and knee OA	Running: miles/week by age: >70y 18, 60-69y 18, 50-59y 30, 40-49y 33, 0-40y 58; number of years running by age: >70y 8, 60-69y 9, 50-59y 12,	Severe hip or knee pain: 2% runners, 2.4% swimmers; any kind of hip or knee pain: 15% runners, 19 swimmers (p>0.05); no differences in pain between groups for any age range Surgery for pain (mainly arthroplasties): runners 0.8%, swimmers 2.1% Runners with higher miles run per week did not	Age, gender, weight, educational level, socioeconomic status, cardiovascular fitness and attitude towards exercise-matched Control of occupational	Runners response 76%, swimmers 58% Controls not sedentary. Only clinical (not	There was r association between middle- and long-distanc running and risk of hip o

			40-49y 14, 0-40y 10	have significantly more pain and nor did runners with higher cumulative years of running	workload, exposure to other sports, BMI not reported	radiographic) OA	knee OA
Spector et al., 1996[48]	Case-control study, level III evidence	81 ex-elite female athletes (67 long-distance runners and 14 tennis players) aged 52y (SD 6), BMI 22 (SD 2.8) and 977 age-matched female controls Clinical and radiological OA	Mean competition for 15y in runners and 19y in tennis; mean hours of vigorous weight-bearing sports per week: runners 2.6, tennis 5.7; mean miles per week of running 14.6; mean hours per week of tennis player 5.2	Adjusted risk of TF osteophytes and JSN in ex-athletes: OR 3.57 (1.89-6.71), OR 1.17 (0.71-1.94) resp. Adjusted risk of PF osteophytes and JSN in ex-athletes: OR 3.5 (1.8-6.81), OR 2.97 (1.15-7.67) resp. Adjusted risk of hip osteophytes and JSN in ex-athletes: OR 2.52 (1.01-6.26) and OR 1.6 (0.73-3.48) resp. Adjusted mean joint space of subjects without OA greater in ex-athletes	Age-, gender-, height- and weight-adjusted analysis For knee, analysis adjusted also for knee injuries, knee pain, smoking, menopause, BMI Knee injury: ex-athletes 3.7%, controls 13.7% ($p<0.05$) Occupational workload not controlled	Participation 71% Baseline between-group differences Running not isolated Controls also exposed to exercise	Running and tennis in women were associated with a two- t three-fold increase in the risk of radiological hip and knee OA
Vingard et al., 1993[53]	Case-control, level III evidence	233 cases with hip replacement because of OA and 302 controls, aged 50-70y	Not detailed for each sport. Reported as low, medium or high exposure. Collected: hours/week, week per year, total years and level achieved	Running: risk of hip OA in moderate and high exposure compared with low exposure: RR 1.7 (0.4-6.9) and 2.1 (0.6-6.8) resp.	Controls were age, education, smoking and BM matched Sports analysis adjusted for age, BMI, occupational work load, and different kind of sport simultaneously	Participation: 92% cases, 77% controls. Running not isolated Controls not sedentary.	Running not associated with hip OA
Vingard et al., 1998[54]	Case-control, level III evidence	230 (cases) women aged 50-70y with hip OA compared with 273 age-matched controls	Details not reported Exposure to sports to the age of 50y: hours per week, weeks per year, how many years Exposure graded as: low (total of <100h), medium (total of 100-800h), high exposure (total of >800h)	Hip OA: left 26%, right 35%, both 39% Hip OA: high vs low exposure RR 2.3 (1.5-3.7), medium vs low exposure RR 1.5 (0.9-2.5) Match of sports and occupational load: risk only increased in the following combination: medium exposure to sports and high exposure to work load RR 2.7 (1.1-7), high exposure to sports and medium exposure to work load RR 2.7 (1.2-5.9) and high exposure to both RR 4.3 (1.7-11)	Adjusted for age, BMI, occupational load, number of children, smoking, and hormone therapy Not controlled for history of hip injury	Participation 95% cases, 89% controls Controls not sedentary Running not isolated Only women included Small sample	Exposure to sports not associated with increased risk of hip O in women alone but in combination with work load
Vrezas et al., 2010[55]	Case-control, level III evidence	295 male cases with knee OA and 327 male controls, aged 25-70y Radiographic knee OA	Running: exposure from 0h to 3,530h	Running, swimming, body-building, weight lifting: no increase in risk of knee OA Exposure to running: 0-700h OR 0.8 (0.4-1.7), 700-1,695h OR 1 (0.5-2.3), 1,695-3,530h 1.9 (0.8-4.1), >3,530h 1.9 (0.8-4.3)	Age, gender, BMI and occupation History of joint injury not reported	Mild OA not included Isolation of running not known Potential effect of joint injury	Running not associated with increased risk of knee OA
Williams 2013[56]	Cross-sectional, level III evidence	Runners (74,752 subjects, 46,819 men, 27,933 women, mean age 46y and 40y resp) compared with walkers (14,625 subjects, 3,122 men, 11,503 women, mean age 61y and 52y resp).	Years of running: 13y in men, 9.8y in women Marathons in last 5y: 1.9 men, 1.1 women	Runners: 2,004 cases of OA and 259 cases of hip replacement during 7.1y follow-up Walkers: 695 cases of OA and 114 cases of hip replacement during 5.7y follow-up	Not adjusted for runners vs walkers comparison for OA Age-, gender-, hormone use-adjusted for comparisons within the runners group	Controls (walkers) older than runners Running not isolated	Running associated with less risl of hip OA

BMI, body mass index; ERT, estrogen replacement therapy; h, hours; HR, hazard ratio (95% interval confidence); JSN, joint space narrowing; Kcal, kilocalories; kg, kilogram; km, kilometre; min, minutes; Mo, months; MRI, magnetic resonance imaging; OA, osteoarthritis; OR, odds ratio (95% confidence interval); PF, patellofemoral; resp, respectively; RR, relative risk (95% confidence interval); SD, standard deviation; SEM, standard error of the mean; TF, tibiofemoral; TKA, total knee arthroplasty; vs, versus; WL, weight-lifters; y, years.

TABLE 2. Assessment of the risk of bias in included studies

Study	Type of bias*				
	Selection	Performance	Detection	Attrition	Reporting
Chakravarty 2008[5]	H	H	L	U	U
Cheng 2000[6]	H	H	U	U	U
Dahaghin 2009[7]	L	H	H	U	U
Kettunen 1999[18]	H	H	H	U	H
Kettunen 2001[17]	H	H	H	U	H
Kohatsu 1990[19]	H	H	H	U	U
Konradsen 1990[20]	H	H	H	U	U
Kujala 1994[21]	H	H	H	U	U
Kujala 1999[22]	H	H	H	U	U
Lane 1986[23]	H	H	L	U	U
Lane 1993[24]	H	H	L	U	U
Lane 1998[25]	H	H	L	U	U
Lau 2000[27]	H	H	U	U	U
Lo 2016[30]	H	H	H	U	U
Manninen 2001[34]	H	H	H	U	U
Marti 1989[35]	H	H	L	H	H
Panush 1986[42]	H	H	L	U	U
Panush 1995[41]	H	H	L	U	U
Puranen 1975[44]	H	H	H	H	H
Sohn 1985[47]	H	H	H	H	H
Spector 1996[48]	H	H	H	U	U
Vingard 1993[53]	H	H	H	U	U
Vingard 1998[54]	H	H	H	U	U
Vrezas 2010[55]	H	H	H	U	U
Williams 2013[56]	H	H	H	U	U

H, high risk; L, low risk; U, unknown risk

*Selection bias: random sequence generation or allocation concealment; Performance bias: blinding of participants and personnel; Detection bias: blinding of outcome assessment; Attrition bias: incomplete data outcome; Reporting bias: selective reporting

TABLE 3. Comparison of the association between osteoarthritis and running level

Outcome	N	Runners		Controls		Odds ratio (95% CI)	I^2	p-value
		Events	Total	Events	Total			
Overall population								
Hip and/or knee								
Competitive[17, 20-22, 44, 48]	6	184	1382	721	6276	1.34 (0.97-1.86)	53	0.0001
Recreational[5-7, 19, 24, 30, 34, 41, 42, 55, 56]	11	2942	83939	2373	23959	0.86 (0.69-1.07)	50	
Hip								
Competitive[17, 20-22, 48]	5	64	651	188	3067	1.65 (0.94-2.89)	58	0.36
Recreational[41, 56]	2	2266	74764	810	14635	0.81 (0.19-3.42)	48	
Knee								
Competitive[17, 20-22, 44, 48]	6	120	731	533	3209	1.16 (0.86-1.57)	15	0.005
Recreational[5, 7, 19, 24, 30, 34, 42, 55]	8	461	1456	1328	3520	0.83 (0.7-0.99)	0	
Males								
Hip and/or knee								
Competitive[17, 20-22, 44]	5	147	1220	289	4322	1.45 (0.97-2.17)	53	0.004
Recreational[6, 34, 41, 42, 55, 56]	6	1606	52996	520	8106	0.78 (0.68-0.89)	0	
Hip								
Competitive[17, 20-22]	4	55	570	115	2090	1.67 (0.78-3.59)	68	0.17
Recreational[41, 56]	2	1352	46831	111	3132	0.86 (0.50-1.49)	8	
Knee								
Competitive[17, 20-22, 44]	5	92	650	174	2232	1.29 (0.90-1.83)	11	0.01
Recreational[34, 42, 55]	3	88	230	247	539	0.70 (0.50-0.97)	0	
Females								
Hip and/or knee								
Competitive[48]	1	37	162	432	1954	1.04 (0.71-1.53)	-	0.006
Recreational[6, 34, 56]	3	968	29726	932	13269	0.54 (0.41-0.71)	43	

CI, confidence interval; I^2, heterogeneity index; N, number of studies

TABLE 4. Comparison of the association between osteoarthritis and the length of running exposure

Outcome	N	Runners		Controls		Odds ratio (95% CI)	I^2	p-value
		Events	Total	Events	Total			
Overall population								
Hip and/or knee								
< 15 years[5, 6, 41, 42, 56]	5	2503	82545	1078	20510	0.60 (0.49-0.73)	47	0.01
> 15 years[20, 44, 48]	3	50	290	450	2123	1.01 (0.72-1.43)	0	
Hip								
< 15 years[41, 56]	2	2266	74764	810	14635	0.81 (0.19-3.42)	48	0.45
> 15 years[20, 48]	2	10	108	74	1004	1.51 (0.74-3.06)	0	
Knee								
< 15 years[5, 42]	2	22	62	33	71	0.62 (0.29-1.32)	0	0.4
> 15 years[20, 44, 48]	3	40	182	376	1119	0.90 (0.59-1.36)	0	
Males								
Hip and/or knee								
< 15 years[6, 41, 42, 56]	4	1519	52783	276	7585	0.79 (0.68-0.91)	0	0.92
> 15 years[20, 44]	2	13	128	18	169	0.83 (0.29-2.36)	38	
Hip								
< 15 years[41, 56]	2	1352	46831	111	3132	0.86 (0.50-1.49)	8	0.92
> 15 years[20]	1	1	27	1	27	1.0 (0.06-16.85)	-	
Knee								
< 15 years[42]	1	1	17	3	18	0.31 (0.03-3.34)	-	0.47
> 15 years[20, 44]	2	12	101	17	142	0.83 (0.26-2.60)	40	
Females								
Hip and/or knee								
< 15 years[6, 56]	2	963	29717	772	12872	0.52 (0.47-0.57)	0	0.0006
> 15 years[48]	1	37	162	432	1954	1.04 (0.71-1.53)	-	

CI, confidence interval; I^2, heterogeneity index; N, number of studies

TABLE 5. Comparison of the association between osteoarthritis and running depending on the level of adjustment for other risk factors in the overall population

Outcome	N	Runners		Controls		Odds ratio (95% CI)	I^2
		Events	Total	Events	Total		
Hip and/or knee							
No adjustment[5-7, 17, 19-22, 24, 34, 41, 42, 44, 48, 55, 56]	16	2942	84546	2544	28376	0.88 (0.68-1.13)	82
Adjusted by age[7, 17, 21, 22, 34, 48]	6	335	1636	1220	7226	1.15 (0.79-1.69)	79
Adjusted by age + BMI[7, 17, 34, 48]	4	263	782	1150	4062	0.94 (0.64-1.36)	73
Adjusted by age + BMI + WL[17, 34]	2	69	264	395	1494	1.00 (0.45-2.25)	68
Adjusted by age + BMI + WL + PI[30, 34]	2	191	801	744	2364	0.73 (0.61-0.89)	0
Hip							
No adjustment[17, 20-22, 41, 48, 56]	7	2330	75415	998	17702	1.35 (0.64-2.83)	90
Adjusted by age[17, 22, 48]	3	54	461	167	1637	1.34 (0.79-2.28)	50
Adjusted by age + BMI[17, 48]	2	40	197	154	1458	1.72 (1.16-2.57)	0
Adjusted by age + BMI + WL[17]	1	31	116	81	481	1.80 (1.12-2.9)	-
Adjusted by age + BMI + WL + PI	0	----	----	----	----	----	-
Knee							
No adjustment[5, 7, 17, 19-22, 24, 34, 42, 44, 48, 55]	13	397	1412	1311	4870	0.87 (0.70-1.08)	27
Adjusted by age[7, 17, 22, 34, 48]	5	268	849	1015	2783	0.94 (0.68-1.31)	58
Adjusted by age + BMI[7, 17, 34, 48]	4	223	585	996	2604	0.81 (0.65-1.01)	12
Adjusted by age + BMI + WL[17, 34]	2	38	148	314	1013	0.91 (0.52-1.6)	34
Adjusted by age + BMI + WL + PI[30, 34]	2	191	801	744	2364	0.73 (0.61-0.89)	0

[*]This study controlled for age, gender, body-mass index, other physical activities and prior knee injury.

BMI, body-mass index; CI, confidence interval; I^2, heterogeneity index; N, number of studies; PI, previous injury; WL, workload

TABLE 6. Comparison of the association between osteoarthritis and running depending on the level of adjustment for other risk factors in males

Outcome	N	Runners		Controls		Odds ratio (95% CI)	I^2
		Events	Total	Events	Total		
Hip and/or knee							
No adjustment[6, 17, 20-22, 34, 41, 42, 44, 55, 56]	11	1753	54216	809	12428	1.01 (0.76-1.33)	69
Adjusted by age[17, 21, 22, 34]	4	136	1109	305	4261	1.43 (0.85-2.40)	69
Adjusted by age + BMI[17, 34]	2	64	255	235	1097	0.76 (0.17-3.37)	74
Adjusted by age + BMI + WL[17, 34]	2	64	255	235	1097	0.76 (0.17-3.37)	74
Adjusted by age + BMI + WL + PI[34]	1	2	17	34	108	0.29 (0.06-1.34)	-
Hip							
No adjustment[17, 20-22, 41, 56]	6	1407	47401	226	5222	1.41 (0.76-2.64)	78
Adjusted by age[17, 22]	2	45	380	94	660	1.20 (0.49-2.94)	75
Adjusted by age + BMI[17]	1	31	116	81	481	1.80 (1.12-2.90)	-
Adjusted by age + BMI + WL[17]	1	31	116	81	481	1.80 (1.12-2.90)	-
Adjusted by age + BMI + WL + PI	0	----	----	----	----	----	-
Knee							
No adjustment[17, 20-22, 34, 42, 44, 55]	8	180	880	421	2771	0.99 (0.67-1.45)	47
Adjusted by age[17, 22, 34]	3	78	403	173	795	1.1 (0.58-2.1)	60
Adjusted by age + BMI[17, 34]	2	33	139	154	616	0.7 (0.2-2.41)	63
Adjusted by age + BMI + WL[17, 34]	2	33	139	154	616	0.7 (0.2-2.41)	63
Adjusted by age + BMI + WL + PI[34]	1	2	17	34	108	0.29 (0.06-1.34)	-

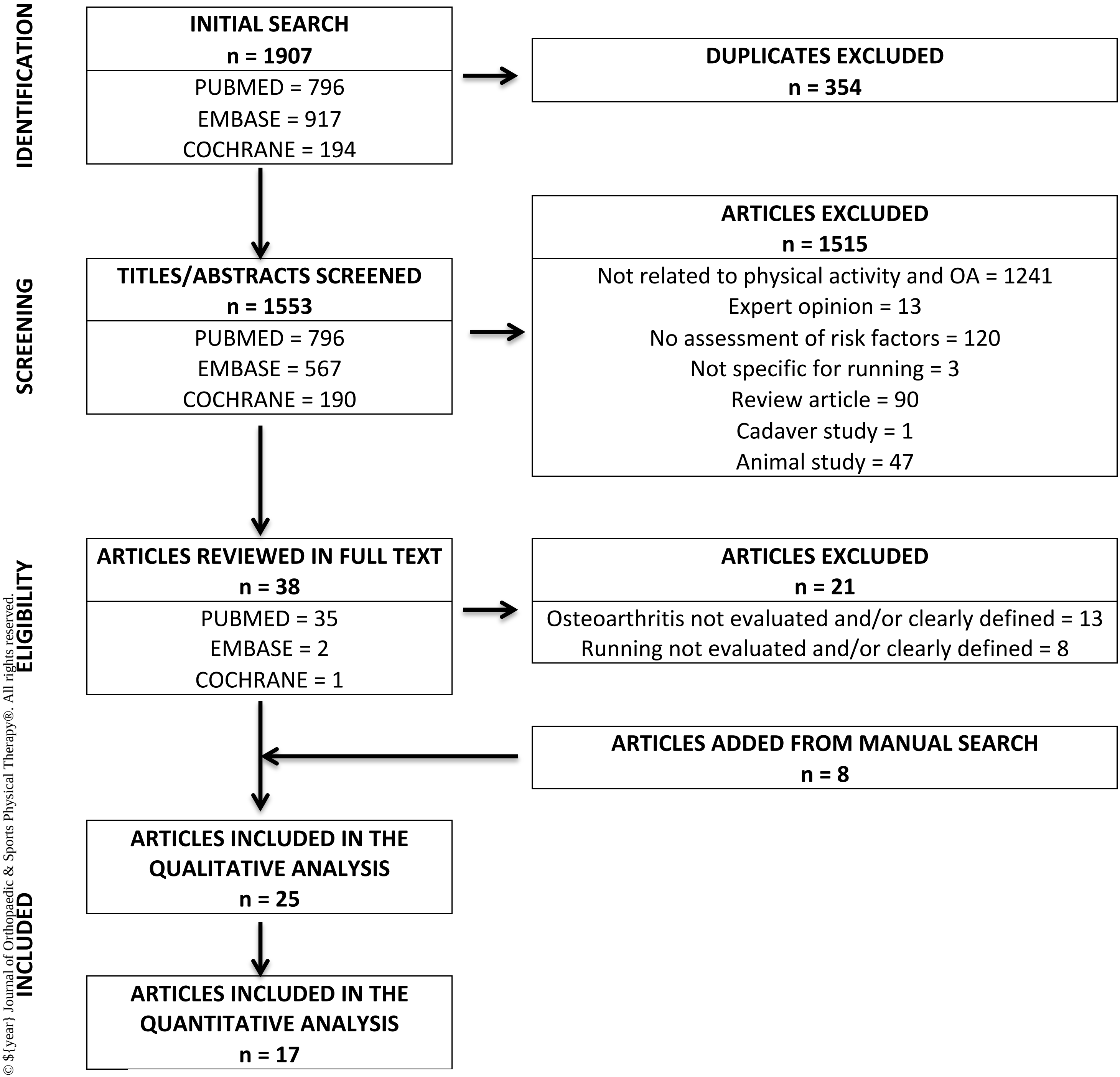
BMI, body-mass index; CI, confidence interval; I^2, heterogeneity index; N, number of studies; PI, previous injury; WL, workload

TABLE 7. Comparison of the association between osteoarthritis and running depending on the level of adjustment for other risk factors in females

Outcome	N	Runners		Controls		Odds ratio (95% CI)	I^2
		Events	Total	Events	Total		
Hip and/or knee							
No adjustment[6, 34, 48, 56]	4	1005	29888	1364	15223	0.69 (0.46-1.04)	80
Adjusted by age[34, 48]	2	42	171	592	2351	1.09 (0.75-1.57)	0
Adjusted by age + BMI[34, 48]	2	42	171	592	2351	1.09 (0.75-1.57)	0
Adjusted by age + BMI + WL[34]	1	5	9	160	397	1.85 (0.49-7)	-
Adjusted by age + BMI + WL + PI[34]	1	5	9	160	397	1.85 (0.49-7)	-
Hip							
No adjustment[48, 56]	2	923	28014	772	12480	0.84 (0.29-2.43)	88
Adjusted by age[48]	1	9	81	73	977	1.55 (0.74-3.22)	-
Adjusted by age + BMI[48]	1	9	81	73	977	1.55 (0.74-3.22)	-
Adjusted by age + BMI + WL	0	----	----	----	----	----	-
Adjusted by age + BMI + WL + PI	0	----	----	----	----	----	-
Knee							
No adjustment[34, 48]	2	33	90	519	1374	0.99 (0.63-1.54)	0
Adjusted by age[34, 48]	2	33	90	519	1374	0.99 (0.63-1.54)	0
Adjusted by age + BMI[34, 48]	2	33	90	519	1374	0.99 (0.63-1.54)	0
Adjusted by age + BMI + WL[34]	1	5	9	160	397	1.85 (0.49-7)	-
Adjusted by age + BMI + WL + PI[34]	1	5	9	160	397	1.85 (0.49-7)	-

BMI, body-mass index; CI, confidence interval; I^2, heterogeneity index; N, number of studies; PI, previous injury; WL, workload

Figure 1. Flowchart of study identification, screening, and inclusion



APPENDIX 1. Search strategy used for the electronic literature search using Pubmed, EMBASE, and The Chocrane Library databases.

	SEARCH	QUERY
PUBMED	#1	Search (degenerative[tiab] OR degeneration[tiab] OR degradation[tiab] OR damaged[tiab] OR damage[tiab]) AND (joints[mesh] OR joints[tiab] OR joint[tiab])
	#2	Search osteoarthritis[tiab] OR osteoarthrosis[tiab] OR osteoarthritic[tiab] OR osteo-arthritis[tiab] OR osteo-arthrosis[tiab] OR osteo-arthritic[tiab] OR arthritis[tiab] OR arthrosis[tiab]
	#3	Search "Osteoarthritis"[Mesh]
	#4	Search joint disease[tiab] OR joint diseases[tiab]
	#5	Search "Joint Diseases"[Mesh:NoExp]
	#6	Search "Jogging"[Mesh] OR "Running"[Mesh]
	#7	Search jogging[tiab] OR jogger*[tiab] OR runner*[tiab] OR run[tiab] OR runs[tiab] OR running[tiab]
	#8	Search #1 OR #2 OR #3 OR #4 OR #5
	#9	Search #6 OR #7
	#10	Search #8 AND #9
	#11	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))
	#12	Search Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]
	#13	Search #10 NOT #11
	#14	Search #13 NOT #12
	#15	Search #13 NOT #12 Filters: English
EMBASE	#1	exp osteoarthritis/
	#2	arthropathy/ or exp joint degeneration/
	#3	exp joint/
	#4	(degenerative or degeneration or degradation or damaged or damage).ti,ab.
	#5	(joint or joints).ti,ab.
	#6	#3 and #4
	#7	#4 and #5
	#8	#6 or #7
	#9	(joint diseases or joint disease).ti,ab.
	#10	(osteoarthritis or osteoarthrosis or osteoarthritic or osteo-arthritis or osteo-arthrosis or osteo-arthritic or arthritis or arthrosis).ti,ab.
	#11	#1 or #2 or #8 or #9 or #10
	#12	exp running/
	#13	exp jogging/
	#14	(jogging or jogger$1 or runner$1 or run or runs or running).ti,ab.
	#15	#12 or #13 or #14
	#16	#11 and #15
	#17	(animal not (animal and human)).sh.
	#18	#16 not #17
	#19	limit #18 to (embase and english and (article or conference paper or note or "review"))
THE CHOCRANE LIBRARY	#1	MeSH descriptor: [Osteoarthritis] explode all trees
	#2	MeSH descriptor: [Joint Diseases] explode all trees
	#3	osteoarthritis or osteoarthrosis or osteoarthritic or osteo-arthritis or osteo-arthrosis or osteo-arthritic or arthritis or arthrosis:ti,ab,kw (Word variations have been searched)
	#4	(joint or joints) and (degenerative or degeneration or degradation or damaged or damage):ti,ab,kw (Word variations have been searched)
	#5	joint diseases or joint disease:ti,ab,kw (Word variations have been searched)

#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Jogging] explode all trees
#8	MeSH descriptor: [Running] explode all trees
#9	jogging or jogger* or runner* or run or runs or running:ti,ab,kw (Word variations have been searched)
#10	#7 or #8 or #9
#11	#6 and #10