Running and knee osteoarthritis: a systematic review and meta-analysis

Abstract

Background

Osteoarthritis (OA) is a chronic condition characterised by pain, impaired function and reduced quality of life. A number of risk factors for knee OA have been identified such as obesity, occupation and injury. The association between physical activity or particular sports such as running and knee OA is less clear. Previous reviews, and the evidence which informs them, present contradictory or inconclusive findings.

Purpose

This systematic review aimed to determine the association between running and the development of knee OA.

Study Design

Systematic review and meta-analysis.

Method

Four electronic databases were searched, along with citations in eligible articles and reviews, and the contents of recent journal issues. Two reviewers independently screened the titles and abstracts using pre-specified eligibility criteria. Full-text articles were also independently assessed for eligibility. Eligible studies were those in which running or running-related sports (e.g. triathlon or orienteering) were assessed as a risk factor for the onset or progression of knee OA in adults. Relevant outcomes included 1) diagnosis of knee OA, 2) radiographic markers of knee OA, 3) knee joint surgery for OA, 4) knee pain or 5) knee-associated disability. Risk of bias was judged using the Newcastle-Ottowa scale. A random-effects meta-analysis was performed with case-control studies investigating arthroplasty.

Results

After de-duplication, the search returned 1322 records. 153 full-text articles were assessed. 25 were eligible, describing 15 studies: 11 cohort (6 retrospective) and 4 case-control studies. Findings of studies with a diagnostic OA outcome were mixed. There were some radiographic differences observed in runners, but only at baseline within some subgroups. Meta-analysis suggested a protective effect of running against surgery due to OA: pooled OR 0.46 (95% CI 0.30, 0.71). The I^2 was 0% (95% CI 0%, 73%). Evidence relating to symptomatic outcomes was sparse and inconclusive.

Conclusion

On this evidence, it is not possible to conclude the role of running in knee OA. Moderate to low quality evidence suggests: no association with OA diagnosis, a positive association with OA diagnosis, and a negative association with knee OA surgery. Conflicting results may reflect methodological heterogeneity. More well-designed, prospective evidence is needed to clarify the contradictions.

Keywords

Osteoarthritis, Running, Physical activity, Knee joint, Systematic review

What is known about the subject

The conclusions of previous reviews exploring the role of sport and physical activity in the development of knee osteoarthritis are inconsistent. The knee joint structures may respond differently to different types of physical activity, but it is unclear what the effect of running may be.

What this study adds to existing knowledge

This systematic review offers a comprehensive and up-to-date synthesis of the evidence surrounding running and knee OA, incorporating a number of OA related markers and symptoms. Scant, low quality prospective evidence suggests either no association or an increased risk of diagnosis. On the other hand, the first published meta-analysis of case-control evidence suggests a protective role of running against knee replacement surgery.

Background

Osteoarthritis (OA) is a chronic condition that is characterised by pain, impaired function and reduced quality of life. In the US, estimates suggest almost 27 million adults have clinically diagnosed OA[30]. An estimated 3.5 million people over the age of 50 in the UK currently have disabling OA [48]. The knee is one of the most commonly affected joints [31], with over 9 million people estimated to have knee OA in the US[30]. Despite significant progress over recent decades, much remains unknown regarding the aetiology of knee OA. A number of risk factors have been identified, such as obesity, occupational activity level and joint injury [3]. Other factors which have been demonstrated to influence OA susceptibility include age, gender, genetics and ethnicity [17]. The association between physical activity or exercise and knee OA is less clear.

It has been postulated that OA develops following either excessive physiological loading on normal joint structures, or normal loading on compromised structures (following injury, for example) [11]. OA is a mechanically driven condition[41]. How the individual knee structures respond to dynamic, cyclical loading patterns during running (particularly over prolonged periods) is unclear. If the mechanical loading stimulus of running helps elicit beneficial adaptation to the joints and surrounding structures, it may have a protective effect. Conversely, if a joint's tolerance to loading is exceeded as a result of running, it could be a risk factor. The relationship is further complicated as running itself is directly (and indirectly) associated with other risk factors such as joint injury and BMI [3, 49]. There is variation in the risk of knee joint injury across different sports and physical activities [22, 32]. Therefore, studying running independently from other sports may help to understand the relationship between physical activity and OA risk.

A number of reviews have investigated the role of physical activity, or particular sports, in the development of OA and have been inconclusive or contradictory [3, 8, 50, 51]. One explanation for discrepant conclusions may lie in the different methods used by studies to measure and classify physical activity. [3] The review by Urquhart et al [50], for example, excluded studies investigating physical activities of daily living. In addition, the type of sporting activity may be relevant, if different activities affect the knee joint structures in non-consistent ways [6]. Some previous reviews reported on the role of running in knee OA [8, 12, 43]. However, one of these is now over 10 years old [43] whilst the two more recent reviews were restricted in scope: one examining elite-level running only [12] and one was limited by language (English only) and date (post 1990)[8]. The objective of this review is to determine from the published literature what the role is of running in the development of knee OA.

Methods

Recommendations by the Cochrane Collaboration [14] were adopted for this review. The protocol was registered on PROSPERO database (reg. no. CRD42015024001)[4].

Search strategy

Four electronic databases (MEDLINE via OvidSP, Embase via OvidSP, SPORTDiscus via EBSCOhost, and PEDro (Physiotherapy Evidence Database)) were searched (for search terms see online appendix 1). Searches were not limited by language or date. Database searches were supplemented by hand-searching the citations in identified reviews and eligible articles, as well as of the contents of recent/in-press editions of four pre-specified relevant journals (AJSM, JAMA, Osteoarthritis and Cartilage, Journal of Bone and Joint Surgery). Searches took place from June to November 2015, and results were imported and de-duplicated using EndNote X6.

Study selection

Two reviewers independently assessed each reference against pre-specified inclusion and exclusion criteria (see protocol on PROSPERO) using a two-stage process: firstly, titles and abstracts, and, secondly, full-text articles. Discrepancies were settled by discussion between reviewers or consultation with a third author. Eligible studies were cohort, case-control studies or randomised trials which included adult samples, measured exposure to any form of running or jogging (including running-related sports such as triathlon and orienteering), included a comparison group, and assessed the following outcomes:

1. any definition of diagnosed knee OA and/or
2. radiographic/imaging markers of knee OA and/or
3. knee arthroplasty for OA and/or
4. knee pain and/or
5. disability specifically associated with the knee.

Excluded studies were those that reported outcomes not specific to the knee joints, and those in which the time between exposure to running and the outcome was inadequate (a minimum of one year). Retrospective cohorts, defined as cohorts in which prior running exposure was established at recruitment, were eligible. Studies were also excluded where running exposure was combined with other sports or activities, therefore running exposure could not be identified independently. This review did not consider grey literature. More detailed eligibility criteria are available in the review protocol. Studies were not excluded on the basis of language or date. Translators were sought for non-English references.

Data extraction and synthesis

Data were extracted for each eligible article by a single reviewer, using a pre-piloted extraction form. Data extraction was checked by a second reviewer. Where multiple publications were found for a study, the most recent results for each outcome were extracted. Where a study included more than one comparator, comparisons with community controls were prioritised (over, for example, comparisons against athletes from other sports).

All eligible studies are included in a narrative synthesis, organised by outcome and study design. Meta-analysis was considered for each eligible outcome; however, due to high levels of between-study methodological heterogeneity and small numbers of studies for each outcome, meta-analysis was appropriate for only one outcome: knee arthroplasty (case-control studies). Due to the observational nature of case-control studies, a random-effects model was conducted in RevMan, using the Mantel-Haenszel method of weighting [34]. All rates entered were crude (unadjusted). Missing data were not accounted for. Measurement effects are expressed as odds ratios (OR) with 95% confidence intervals (CI). Due to the small number of studies (n=3), subgroup or sensitivity analyses (as pre-specified in the protocol) were not undertaken. The I^2 statistic was used as a measure of heterogeneity, with 95% confidence intervals using the non-central Chi^2 approach [16].

Meta-analyses were performed using Review Manager (RevMan) version 5.3 [46].

Risk of bias

The Newcastle Ottawa scale [53] was used to assess each eligible study for risk of bias. Two reviewers independently assessed each study. Disagreements in ratings were resolved by consensus or on consultation with a third reviewer. Studies were not excluded on the basis of risk of bias.

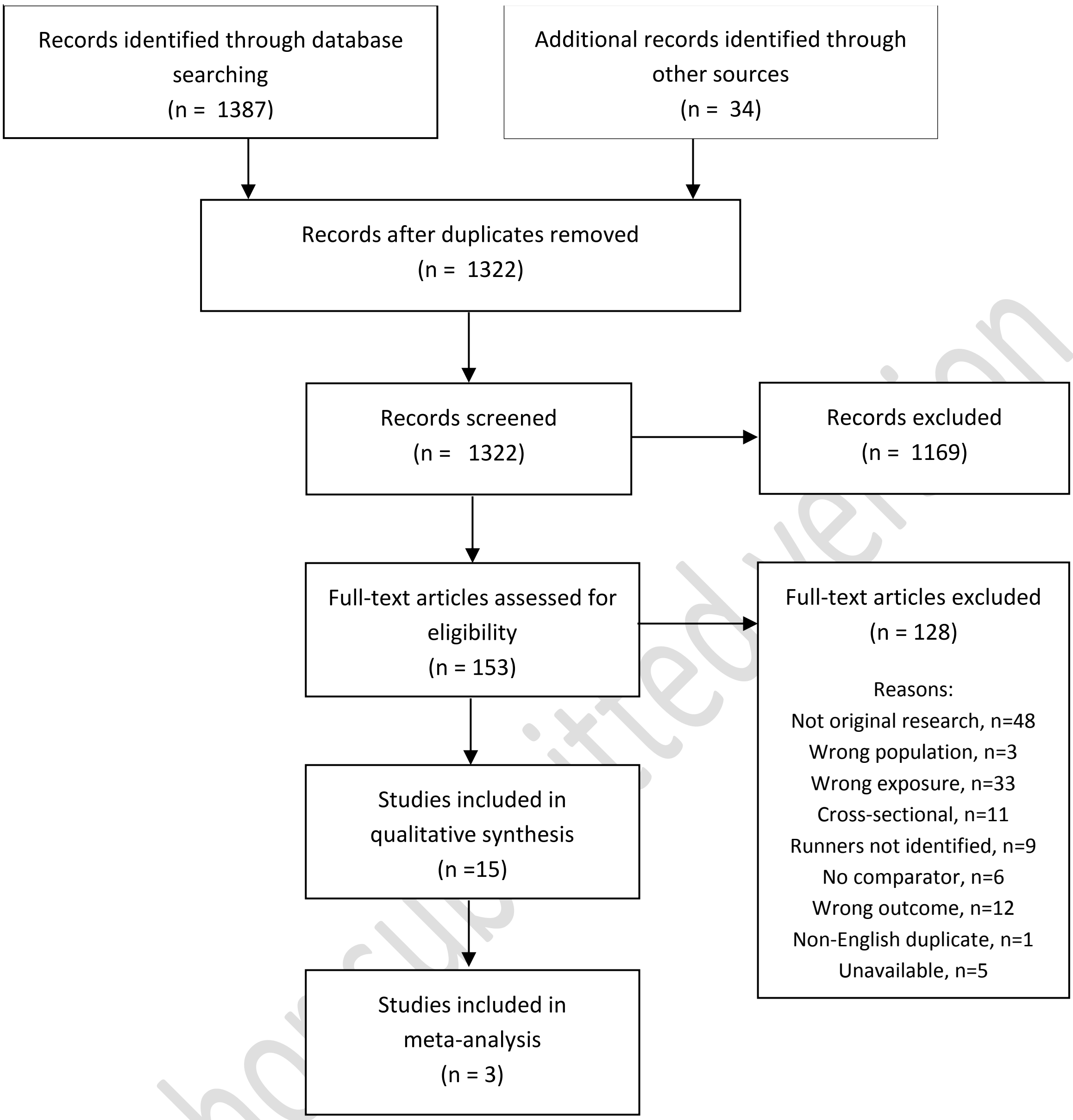
The possibility of publication bias cannot be excluded. Funnel plots were not attempted because there were too few studies included the meta-analysis [45].

RESULTS

The search results are shown in Figure 1, according to PRISMA guidelines [35]. Following screening, 25 articles[1] were identified as eligible, describing 15 studies. Study names were assigned comprising first author and year of first publication (see Table 1). Year of (first) publication ranged from 1977 to 2010. Two studies were not published in English: one was Danish [7], one was German [15].

[1] References # 5, 7, 9-10, 15, 18-21, 23-29, 32, 35-40, 42, 45

Figure 1: Flowchart of search results, adapted from PRISMA[35]



STUDY CHARACTERISTICS

Study characteristics are summarised in Table 1. The majority (n=11) were cohort studies, 6 of which were retrospective [7, 15, 21, 36, 37, 44]. The remaining 4 studies used a case-control design [20, 33, 42, 47]. All of the eligible studies were based in either European or USA populations.

Cohort studies

Three studies, all investigating radiographic outcomes, identified fewer than 5 years running exposure, and could be described as short-term [15, 36, 37]. Three studies were long-term (exposure and outcome separated by at least 25yr) [19, 21, 44], and four were medium-term (between 5 and 25 years' exposure) [5, 10, 25, 39]. One study [7] did not report the study duration.

In the majority of the cohort studies (n=7), exposure to running was defined as membership of a club or association or as having taken part in competition. One cohort was recruited from a broader community, rather than via clubs or competition records [10]. Several studies [15, 37, 38] did not describe recruitment nor how the exposure was determined.

Sample sizes of cohorts ranged from 15 to 1279 (see Table 1) with seven of the 11 cohorts including small (n≤100) samples. Five of the cohorts included both males and females, one included only females [44], and five studies included only males. Mean age at outcome assessment ranged from 27.4 to around 69 years. All but 3 of the studies investigated running or jogging as the exposure. The other 3 studies investigated orienteering or triathlon. No studies specifically reported on exposure to short-distance running.

Five of the cohorts recruited only elite athletes (or ex-professional athletes). Non-runners were recruited from a variety of sources: public military archives; the community; hospital radiology departments; from within the cohort or from other studies. Two studies additionally compared against ex-elite athletes from other sports[23, 44]. Two studies did not report how 'non-runners' were defined, identified or recruited [37, 38].

Case control studies

Three of the case control studies based their case definition on hospital registries of knee arthroplasty procedures: in Sweden [42], Finland [33] and the USA [20]. The other case control study [47] was based in Sweden and used listed diagnosis of knee OA from hospital registers to define cases. To assess exposure to running (and other sports and activities), participants were mailed questionnaires[20, 42, 47] or were interviewed[33].

The studies based in Finland and Sweden[33, 42, 47] were able to randomly select controls from national registers of the base population. The US-based study[20] recruited controls from the Stanford Lipid Research Study. Three of the case control studies matched on age and sex. Thelin 2006 additionally matched on residency area. Sandmark 1999 did not report matching.

Two of the studies[20, 33] investigated running, whilst one study[47] focussed on orienteering, and one study[42] measured both jogging and orienteering. All case-control studies included both males and females.

Table 1: Characteristics of included studies (chronological order of 1st publication)

Study ID	Study type	Sport(s)	Sport level	Follow-up (yr)	Number of participants	Exposed group/Cases, n	Non-exposed group/controls, n	Exposure definition & measurement
de Carvalho 1977[7]	Retrospective cohort	Running	NR	NR	64	Runners recruited from club: 100% M, mean age 47.7yr, n=32	Radiology patients (excl hip/knee disorder or arthritis): 100% M, age- and weight-matched, n=32	Membership of club Mean yr running 23.9; mean distance/wk 33.65km
Lane 1986[5, 26-29]	Prospective cohort	Running	NR	18	98	Runners recruited from club: 56% M, mean age at recruitment 57.5, n=45	Drawn from Stanford Lipid Research Study: 56% M, mean age 57.7, age-, sex-, occupation- and education-matched, n=53	Membership of club OR questionnaire-reported current running
Panush 1986[38, 39]	Ambispective* cohort	Running	NR	5 retro, 8 prosp	35	'Runners': recruitment unclear, 100% M, mean age at recruitment 56, n=17	'Controls': recruitment unclear, 100% M, mean age at recruitment 61, n=18	'Runners' ran ≥32km/wk for ≥5yr
Kohatsu 1990[20]	Case-control	Running	NR	n/a	92	Patients with TKR for severe knee OA (≥Grade 3 + history) from hospital registers 1977-88: 39% M, mean age 71.3, n=46	Drawn from Stanford Lipid Research Study: 39% M, mean age 70.8, age- and sex-matched, n=46	Leisure-time running assessed by mailed questionnaire
Konradsen 1990[21]	Retrospective cohort	Orienteering	Competitive/elite	~35-40	60	Qualifiers for county teams 1950-55: 100% M, median age 58, n=30	Radiology patients (abdominal): 'sedentary', 100% M, age-, height-, weight- and occupational activity-matched, n=30	Qualification for county teams 1950-55
Kujala 1994[18, 19, 23, 24, 40]	Ambispective* cohort	Long-distance running	Competitive/elite	~28-72 retro, 3 prosp	117 or 1911**	Competitors in international events 1920-65: 100% M, mean age at recruitment 59.7, n=28 or 199**	1 Drawn from public archives: 100% M, age- and residence area-matched, n=1712 [19, 23] 2 Competitors in international events 1920-65 (soccer, weight-lifting, shooting): 100%M, mean ages 56.5, 59.3, 61, n=89 [18, 23, 24, 40]	Representation in international competition 1920-65
Spector 1996[44]	Retrospective cohort	Middle- and long-distance running	Competitive/elite	~20-46	1044 or 282**	Competitors in national/international events 1950-79: 0% M, mean age 52.3	1 Drawn from Chingford cohort or twin study: 0% M, mean age 54.2, n=977 2 Competitors in national/international tennis events 1950-79: 0% M, mean age 52.3, n=215	Representation in international competition 1950-79
Kujala 1999[25]	Prospective cohort	Orienteering	Competitive/elite	11	529	Orienteers recruited from 1984 ranking records: 100% M, mean age at recruitment 48.6, n=300	Drawn from public archives (excl obese, smokers, CHD, OA): 100% M, mean age 60.3, age- and residence area-matched, n=229	Inclusion in national ranking in 1984
Sandmark 1999[42]	Case-control	Running, jogging, orienteering	NR	n/a	1173	Patients with knee surgery 1991-93 (primary reason TF OA), from national register: 52% M, born 1921-38, n=625	Randomly selected from population register, born 1921-38: 48% M, n=548	Physical activities aged 15-50yr, inc marathon, jogging, orienteering assessed by mailed questionnaire
Muhlbauer 2000[9, 37]	Retrospective cohort	Triathlon	NR	≥3	36	'Triathletes': recruitment unclear, 50% M, mean age 27.4 (M), 26.1 (F), n=18	'Controls': recruitment unclear, 'physically inactive', 50% M, mean age 22.2 (M), 22.3 (F), n=18	Trained for triathlon ≥10hr/wk for ≥3yr
Manninen 2001[33]	Case-control	Running	NR	n/a	907	Patients with knee prosthetic surgery (primary reason TF OA), from national	Randomly selected from population register: 48% M, age- and sex-matched, mean ages	Lifetime recreational exercise, inc running,

						register: 20% M, mean ages (M, F) 67.5, 69.2	(M, F) 67.2, 67.1, n=548	assessed by interview
Hohmann 2005[15]	Retrospective cohort	Long-distance running	Competitive/elite	≥5	15	'Advanced and professional' marathon runners: recruitment unclear: 100% M, median age 34 and 33, n=8	'Beginner' marathon runners: recruitment unclear, 86% M, median age 39, n=7	Reported running ≥5yr with marathon time <4hr
Thelin 2006[47]	Case-control	Orienteering	Any	n/a	1473	Patients with diagnosis of TF OA (Ahlback level 3 or more or knee surgery or noted moderate cartilage reduction or joint gap ≤3mm) from 6 hospital registers: 43.2% M, mean age 62.6, n=778	Selected from population register: 42.2% M, mean age 62.6, age-, sex- and municipality-matched, n=695	Reported regular orienteering ≥1yr since age 16yr, assessed by mailed questionnaire
Felson 2007[10]	Prospective cohort	Running or jogging	NR	8.75	1279	Participants in Framingham Offspring cohort who reported jogging or running: 44% M, mean age 53.2, n=1279 (full sample)	Participants in Framingham Offspring cohort who reported never jogging or running: 44% M, mean age 53.2, n=1279 (full sample)	Reported ever being exposed to jogging/running
Mosher 2010[36]	Retrospective cohort	Long-distance running	NR	≥5	37	Marathon runners recruited from clubs: 59% M, (2 age groups) mean ages 25.7 and 52.6, n=22	Community controls (excl if regularly ran over past 5yr): 40% M, (2 age groups) mean ages 28.4 and 54	Self-described marathon runners, mean ≥10mi/wk over prior 5yr

Abbreviations: M = male, F = female, n/a = not applicable, NR = not reported, CHD = coronary heart disease, OA = osteoarthritis, TF = tibiofemoral, TKR = total knee replacement; *Ambispective = both retrospective and prospective data collection. ** Sample size depends on comparison made.

NARRATIVE SYNTHESIS

Findings from each study are summarised in Table 2.

Diagnosis of knee OA

Seven cohort studies included diagnosis as an outcome, three of which measured incidence prospectively. The diagnostic criteria used were different in almost every study (see Table 2). Of the 4 studies which reported formal statistical comparisons, three found no differences in knee OA diagnoses between groups, though two were small in size and likely under-powered [21, 39]. The two large studies found: firstly, no difference in knee OA rates between runners and controls within the same cohort, over 8 years [10]; and secondly, significantly increased odds of knee OA diagnosis amongst elite orienteers compared to controls [25].

One case control study [47] identified cases of tibiofemoral OA diagnosis from 6 hospital registers (see Table 3). The findings indicated no significant difference in the odds of knee OA in patients who had previously participated regularly in orienteering.

One publication from a prospective cohort reported the results of a case-cohort analysis [28]. This result was not extracted because the analysis was not in keeping with the original study design.

Radiographic/imaging markers

Nine cohort studies examined radiographic outcomes: six measured osteophytes; one sclerosis; three assessed cartilage thickness, volume or joint surface area; one measured knee joint angle; one looked at joint space; and one study employed a composite score (Table 2).

For all but two of these outcomes, no significant differences were reported. Lane 1986 [26] found female, but not male, runners had a higher mean sclerosis score at baseline; and Muhlbauer 2000 [37] found male triathletes had a greater joint surface area than controls.

Two studies specifically used MRI to identify joint changes in response to jogging (30mins) [36] or running a marathon [15]. Hohmann 2005 was a small study with no comparison reported. Mosher 2010 found a significant difference in femoral cartilage thickness between marathon runners and controls before, but not after, a 30-minute 'jog', and only amongst older participants.

No case control studies identified cases using radiographic markers of knee OA.

Arthroplasty for knee OA

None of the cohort studies assessed this outcome.

Three case control studies identified cases of knee arthroplasty from hospital registers [20, 33, 42]. No formal comparison was made between runners or orienteers and controls in the Sandmark 1999 study, although crude numbers of participants reporting jogging were lower amongst cases than controls. The other two studies found no significant differences.

Knee pain

Three cohort studies assessed knee pain as an outcome. Two of the studies did not report comparisons [18, 39]. The other study found no significant difference in the odds of knee pain between elite orienteers and controls [25].

No case control studies identified cases of knee pain.

Knee-associated disability

Only two studies investigated knee-related function or disability as an outcome [19, 25]. Only Kujala 1999 presented formal statistical comparisons, showing no significant difference in the odds of knee associated disability between male elite orienteers and controls.

No case control studies defined cases on the basis of knee-associated disability.

Table 2: Summary of cohort study findings, arranged by outcome and sport

Study ID	Comparison	Outcome definition	Results	Risk of bias			Knee injury accounted for?
				Selection†	Comparability ‡	Outcome§	
Diagnosis of knee OA							
de Carvalho [7]	Male club runners (n=22) vs radiology patients (n=25)	Joint space<3mm or joint space ≤50% of other knee/opposite side or sclerosing of articulation surface or subchondral cysts	1/22 runners, 0/25 controls had PF diagnosis. 1/22 runners, 1/25 controls had TF diagnosis. No statistical comparison.	***	*	*	NR
Panush 1986[39]	Male runners (n=12) vs unspecified controls (n=10)	Ahlback grade ≥1	0/12 runners, 2/10 controls. NS (statistical methods NR).	*		**	N
Kujala 1994[23]	Male elite runners (n=163) vs community controls (n=1403)	ICD code from hospital discharge report	2.5% (95% CI 0.7, 6.3) of runners and 1.3% (95% CI 0.8, 2.0) controls. No statistical comparison.	***	*	**	N
Kujala 1994[18]	Male elite runners (n=28) vs other elite sportsmen (n=89)	Kellgren-Lawrence grade ≥2	4/28 runners, 1/29 shooters, 9/31 soccer players, 9/29 weightlifters. No statistical comparison.	****	*	**	NR
Felson 2007[10]	Runners/joggers (n=68) vs non-runners/joggers in Framingham Offspring cohort	Kellgren-Lawrence grade ≥2 AND reported knee pain, aching or stiffness on most days	Runners/joggers compared to controls: OR 1.00 (95% CI 0.27, 3.68). NS (logistic regression)	****	**	***	Y - covariate
Konradsen 1990[21]	Male elite orienteers (n=27) vs radiology patients (n=27)	Ahlback grade	Grade 3: 4/54 runners' knees, 0/54 controls'. Grade 2: 0/54 runners, 0/54 controls. Grade 1: 31/54 runners, 27/54 controls. NS (Mann-Whitney) NB - Excluded orienteers who were 'no longer active'.	**	**	**	NR
Kujala 1999[25]	Male elite orienteers (n=264) vs community controls (n=179)	Self-report	Runners compared to controls (OR 1.79; 95% CI 1.10, 3.54). (logistic regression)	***	**	**	N
Radiographic markers							
Osteophytes							
de Carvalho 1977[7]	Male club runners (n=22) vs radiology patients (n=25)	Dichotomous (presence Y/N)	1/22 runners, 3/25 controls had unilateral PF osteophytes. 9/22 runners, 9/25 controls had bilateral. 5/22 runners, 4/25 controls had unilateral TF osteophytes. 9/22 runners, 6/25 controls had bilateral. No statistical comparison.	***	*	*	NR
Lane 1986[29]	Club runners (n=28) vs community controls (n=27)	Score (sum of scores for each spur, 0-3) Change in score from baseline (1993-1984)	Runners' mean score 1.24 (SE 0.32) vs controls 1.13 (SE 0.42). NS (t test) Runners' mean score change 0.80 (SE0.23) vs controls 0.67 (SE 0.32). NS (t test)	**	*	***	N
Panush 1986[39]	Male runners (n=12) vs unspecified controls (n=10)	Number	Runners' mean 0.4 (SD 1.4) vs controls' 1.3 (SD 4.1). NS (statistical methods not reported)	*		**	N
Konradsen 1990[21]	Male elite orienteers (n=27) vs radiology patients (n=27)	Number	Runners' median 1 (range 0 to 3) vs controls median 1 (range 0 to 5). NS (Mann-Whitney) NB - Excluded orienteers who were 'no longer active'.	**	**	**	NR
Kujala 1994[24]	Male elite runners (n=28) vs	Dichotomous (≥1 osteophyte graded ≥2	4/28 runners, 1/29 shooters, 9/31 soccer players,	****	**	*	N

Study ID	Comparison	Outcome definition	Results	Risk of bias			Knee injury accounted for?
				Selection†	Comparability ‡	Outcome§	
	other elite sportsmen (n=89)	on 0-3 scale)	10/29 weightlifters. NS (runners vs shooters, generalized Fisher's exact test)				
Spector 1996[44]	Female elite runners (n=67) vs controls (n=977)	Dichotomous ((≥1 osteophyte graded ≥1 on 0-3 scale)	13/67 runners, 145/977 controls had TF osteophytes. 30/67 runners, 60/215 controls had PF osteophytes. No statistical comparison	**	**	***	N
Spector 1996[44]	Female elite runners (n=67) vs elite tennis players (n=14)	Dichotomous ((≥1 osteophyte graded ≥1 on 0-3 scale)	13/67 runners, 5/14 tennis players had TF osteophytes. 30/67 runners, 4/14 tennis players had PF osteophytes. No statistical comparison	**	**	***	N
Sclerosis							
Lane 1986[26]	Club runners (n=41) vs community controls (n=41)	Score (sum of rating, 0-3, for each 'area of sclerosis'). At baseline only.	Female runners mean score 6.7 (SE 0.5) vs controls 5.1 (SE 0.3). p<0.05 (t test). Male runners mean 5.5 (SE 0.4) vs controls 5.5 (SE 0.5). NS (t test)	*	*	*	N
Cartilage							
Panush 1986 [39]	Male runners (n=12) vs unspecified controls (n=10)	Sum of thickness (mm) both knees, radiograph	Mean medial thickness 5.18mm (SD 0.71) runners vs 4.94mm (SD 1.12) controls. Lateral thickness 6.58mm (SD 1.06) runners vs 5.85mm (SD 1.08) controls. NS (statistical methods NR)	*		**	N
Konradsen 1990 [21]	Male elite orienteers (n=27) vs radiology patients (n=27)	Cartilage height (mm) at medial & lateral compartments, radiograph	Median medial thickness 4mm runners, 4mm controls. Median lateral thickness 5mm runners, 5.5 in controls. NS (Mann-Whitney) NB - Excluded orienteers who were 'no longer active'.	**	**	**	NR
Muhlbauer 2000 [9]	Triathletes (n=18) vs unspecified controls (n=18)	Cartilage volume (ml) taken from MRI, right knee	Mean volume males 25.3ml triathletes, 23ml controls; females 18.9ml triathletes, 17.9ml controls. NS Mean cartilage thickness males 1.99mm triathletes, 2.01mm controls; females 1.93mm triathletes, 1.86mm controls. NS Knee joint surface area males 120cm^2 triathletes, 110cm^2 controls. p<0.01 (Mann-Whitney). Females 95.2cm^2 triathletes, 88.9cm^2 controls. NS		*	*	Y - excluded
Knee joint angle							
Hohmann 2005 [15]	Advanced (n=8) vs beginner (n=7) marathon runners	Knee joint angle >2º, radiograph	Varus knees 4/7 beginners, 4/6 advanced, 1/2 professionals. Valgus knees 1/7 beginners, 1/6 advanced and 0/2 professionals. No statistical comparison.	*	*	**	Y- excluded
Joint space							
Lane 1986 [29]	Club runners (n=28) vs community controls (n=27)	Joint space narrowing score in 1993 (0-12 scale) Change in score (1993-1984)	Mean score 1.12 (SE 0.22) runners, 1.32 (SE 0.24) controls. NS (t test) Mean score change 0.20 (SE 0.10) runners, 0.32 (SE 0.12) controls. NS (t test)	**	*	***	N
Lane 1986 [5]	Club runners (n=45) vs	Joint space width (mm)	1/45 runners, 5/53 controls had joint space 0mm (or	**	**	***	Y - covariate

Study ID	Comparison	Outcome definition	Results	Risk of bias			Knee injury accounted for?
				Selection†	Comparability ‡	Outcome§	
	community controls (n=53)		TKR). 4/45 runners, 6/53 controls had width ≤1mm. 5/45 runners, 7/53 controls had width ≤2mm. 11/45 runners, 12/53 controls had width ≤3mm. No statistical comparison. Running not associated with joint space width (-0.15 (95% CI -0.71, 0.41). NS (linear regression)				
Total knee score							
Lane 1986 [5, 29]	1. Club runners (n=28) vs community controls (n=27) 2. Club runners (n=45) vs community controls (n=53)	Knee score (sum of scores for osteophytes, joint space, sclerosis, cysts or erosions) (0-66 scale)	1. TKS in 1993 not associated with pace per mile (0.27 (SE 0.15). p=0.088 (stepwise linear regression) [29] 2. Running not associated with TKS (0.72 (95% CI -1.64, 3.08). NS (linear regression) [5]	**	*	***	1. N 2. Y - covariate
Radiographic outcomes in response to running							
Joint effusion							
Hohmann 2005 [15]	Advanced (n=8) vs beginner (n=7) marathon runners	'Stage 2' edema (T2 sequence by MRI): pre- and post-marathon	Pre-marathon, 1/8 advanced, 0/7 beginners. Post-marathon, 1/8 advanced, 5/7 beginners. No statistical comparison.	*	*	**	Y - excluded
Cartilage							
Mosher 2010 [36]	Club marathon runners vs community controls	Femoral and tibial cartilage thickness (mm) and cartilage T2, pre- and post-30-min jog, MRI	Cartilage thicker in marathoners than controls. NS except in older age group (≥46 years) for femoral cartilage pre-running (ANOVA , p value NR; group means only presented graphically). No difference runners and controls in T2 (values NR).	***	*	**	Y - excluded
Knee pain							
Panush 1986 [39]	Male runners (n=12) vs unspecified controls (n=10)	Unclear	0/12 runners, 0/19 controls reported pain. No statistical comparison. NB – sample likely biased due to drop-out (29% runners reported pain at baseline).	*		**	N
Kujala 1994 [18]	Male elite runners (n=28) vs other elite athletes (n=89)	Knee pain reported ≥monthly for prior 12mo	6/28 runners, 5/29 shooters, 14/31 soccer players, 8/29 weightlifters reported pain. No statistical comparison.	****	*	**	N
Kujala 1999 [25]	Male elite orienteers (n=264) vs community controls (n=179)	Knee pain reported by questionnaire, ≥weekly for prior 12mo	Compared to controls, runners OR 1.75 (95% CI 0.96, 3.18). NS (logistic regression)	***	**	**	N
Knee associated disability							
Kujala 1994 [19]	Male elite runners (n=71) vs community controls (n=460)	Score ≥3 assessed on a 7-point scale, based on 7 different activities.	5/71 runners, 59/460 controls reported disability. No statistical comparison.	***	*	*	N
Kujala 1999 [25]	Male elite orienteers (n=264) vs community controls (n=179)	Score ≥1 on 5-point scale, based on 5 activities. Pain or discomfort in knee(s) when	Compared to controls, runners OR 0.69 (95% CI 0.39, 1.21). NS (logistic regression) Compared to controls, runners OR 0.78 (95% CI 0.43,	***	**	**	N

Study ID	Comparison	Outcome definition	Results	Risk of bias			Knee injury accounted for?
				Selection†	Comparability ‡	Outcome§	
		using stairs	1.41). NS (logistic regression)				

Abbreviations: Y = yes, N = no, n/a = not applicable, NR = not reported, NS = not significant, CI = confidence intervals, OR = odds ratio, SE = standard error, SD = standard deviation, CHD = coronary heart disease, OA = osteoarthritis, PF = patellofemoral, TF = tibiofemoral, TKS = total knee score. † Stars (of possible 4) awarded for sampling of exposed and non-exposed cohort. ‡ Stars (of possible 2) awarded for control of confounding characteristics between groups. § Stars (of possible 3 for prospective studies, possible 2 for retrospective) awarded for blind assessment of outcome and adequacy of follow-up.

Table 3 – Summary of case-control studies' findings

Study ID	Sport	Outcome definition	Results	Risk of bias			Knee injury accounted for?
				Selection†	Comparability‡	Exposure§	
Diagnosis of knee OA							
Thelin 2006 [47]	Orienteering	TF OA diagnosis or knee surgery or moderate cartilage reduction or joint gap ≤3mm – from hospital records	Males who reported orienteering (≥1yr since age 16) OR 1.07 (95% CI 0.62, 1.82). Females OR 0.91 (95% CI 0.34, 2.45). NS (logistic regression)	***	**	*	N
Knee surgery for OA							
Kohatsu 1990 [20]	Running	TKR for severe knee OA (≥Grade 3 + history knee pain)	2/46 cases, 4/46 controls reported running. NS (Chi^2)	***	*	*	N
Sandmark 1999 [42]	Running or orienteering	Knee prosthetic surgery due to primary TF OA	Males: 16/325 cases, 35/264 controls reported jogging. 30/325 cases, 27/264 controls orienteering. Females: 8/300 cases, 14/284 controls jogging. 8/300 cases, 5/284 controls orienteering. No statistical comparison.	****	**	**	Y - excluded
Manninen 2001 [33]	Running	Knee prosthetic surgery due to primary TF OA	Males who reported running OR 0.26 (95% CI 0.05, 1.30), females 0.70 (95% CI 0.48, 1.02). NS (logistic regression)	***	**	***	Y - covariate

Abbreviations: Y = yes, N = no, NS = not significant, CI = confidence intervals, OR = odds ratio, OA = osteoarthritis, TF = tibiofemoral, TKR = total knee replacement. † Stars (of possible 4) awarded for selection of cases and controls. ‡ Stars (of possible 2) awarded for control of confounding characteristics between groups. § Stars (of possible 3) awarded for ascertainment of exposure and non-response rate.

META-ANALYSIS

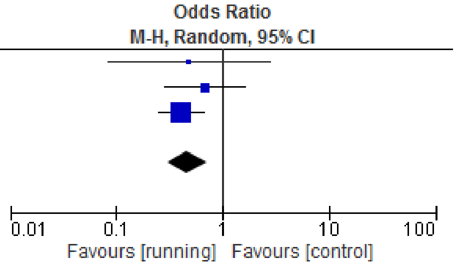
Due to the heterogeneity of outcome definition and measurement of studies, only one meta-analysis was appropriate: this combined the case-control studies which identified cases of knee surgery due to OA (Figure 1). The combined odds ratio of undergoing knee surgery due to OA was 0.46 (95% CI 0.30, 0.71) in runners or orienteers when compared with non-runners. The I^2 was 0%, with 95% CI 0% to 73%. No subgroup or sensitivity analyses were undertaken due to the small number of studies.

Figure 1

Study or Subgroup	Case Events	Case Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Kohatsu 1990	2	46	4	46	5.9%	0.48 [0.08, 2.74]
Manninen 2001	7	281	19	524	23.2%	0.68 [0.28, 1.64]
Sandmark 1999	24	625	49	548	71.0%	0.41 [0.25, 0.67]
Total (95% CI)		**952**		**1118**	**100.0%**	**0.46 [0.30, 0.71]**
Total events	33		72			

Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%

Test for overall effect: Z = 3.57 (P = 0.0004)



Discussion

This review has systematically gathered the peer-reviewed evidence regarding the role of running in the development of knee OA. Five types of outcome relating to knee OA were considered: diagnosis, radiographic markers, surgery, and the symptomatic indicators of consistent knee pain and knee-associated disability.

From this evidence, it is not possible to conclude if running was associated with diagnosis of knee OA, chiefly because the two best quality studies identified [10, 25] offered differing conclusions (one finding no association and one finding a positive relationship). Nor was there evidence to support a difference in radiographic or other imaging markers between runners and controls, with the exception being two studies which observed differences at baseline and only among subgroups (females, [26] and older adults [36]). At follow-up, observed differences in these studies were not apparent. Evidence relating to symptomatic outcomes was sparse and therefore inconclusive.

However, a key finding of this review was the result of the meta-analysis, which was suggestive of around a 50% reduced odds of surgery due to OA amongst runners. The meta-analysis was based on case-control evidence and presents for the first time the odds ratio for the proportions reported in the Sandmark 1999 study. The meta-analysis result contradicts the apparent increased odds of OA diagnosis reported by Kujala 1999 as well as the conclusion of Felson 2007 in which no effect of running on OA diagnosis was found. There are a few possible explanations for these inconsistencies.

Firstly, the differences could be due to the different study designs, with the latter two studies employing prospective cohorts, whilst the meta-analysis used only retrospective data, which could reflect recall bias. No cohort evidence in this review investigated surgery as an outcome.

Secondly, the populations under investigation are not the same. Kujala 1999 was based on elite-level orienteers only, in contrast to the broader exposure levels implied by the samples of Felson 2007 and the case-control studies. Although this review was broad in its definition of running, it is possible that different types and performance levels of running relate differently to knee OA.

Thirdly, the outcomes are differently defined in these studies. Whilst surgery is often taken as a proxy for severe OA diagnosis, it could be speculated that the relationship between running and OA varies according to disease severity. So, for example, running could protect against OA progressing to severe stages, if not against diagnosis of mild or moderate OA. This remains conjecture at this point, due to the paucity of evidence.

The literature on overall leisure-time physical activity and knee joint replacement is a little more plentiful, but no more conclusive. Studies have variously reported no association [1, 2, 33], a dose-response increase in risk [52], or a reduced risk but only at higher levels of activity (in men [33] and in women [1]). At least two of these studies did not adjust for knee joint injury [2, 52]. Manninen et al postulated that the relationship may be non-linear, as quadratic terms improved the fit of regression models[33], implying a 'U'-shaped curve. Comparing the findings of this review to the literature on physical activity, however, may not be useful, if, as previously discussed, running has a role independent of other sports and activities.

An important caveat in interpreting this evidence relates to its quality. Given the nature of observational studies, only low-to-moderate quality evidence could be expected [13]. However, the assessment of potential bias undertaken in this review indicated that many studies would be downgraded to low or very low quality. Just four studies were prospective (or ambispective) in design, and only one of these [10] was a large, well-designed, prospective study addressing recreational (as well as more competitive) running, with controls recruited from same source, and appropriately adjusted analyses.

Most studies failed to take previous injury into account when looking at OA outcomes. Just two studies [10, 33] adjusted for knee injury in analyses, and four studies excluded participants with prior injury [15, 36, 37, 42]. This is a key weakness in the evidence, given the strong association between injury and development of OA [3, 49]. Without this adjustment, it cannot be judged whether the positive association reported by Kujala 1999, for example, was due to exposure to running (in the form of orienteering) or because elite-level orienteers were more prone to injury, therefore increasing their odds of OA diagnosis. This confounder could have influenced the results of many of the studies presented here.

The review by Shrier et al [43] concluded that running (at recreational or moderate level) does not cause or worsen OA. However, this included OA of any joint. The current review was unable to make a similar conclusion, due to the paucity of and contradictions in the evidence relating specifically to knee OA. Another more recent review [8] reported increased odds for elite-level runners. However this was based only on two papers [23, 24], and the synthesis of data was methodologically flawed: firstly, the prevalence rates of the two papers were combined, despite both papers including runners from the same study, therefore effectively including the same participants twice; and, secondly, the authors calculated an additive odds ratio of the two studies, rather than reporting a pooled estimate from a meta-analysis).

In conducting this systematic review, the authors made every effort to minimise bias in identifying and collating the evidence: a pre-registered protocol was developed before searches began, and PRISMA guidelines have been followed. Independent reviewers assessed each article for eligibility and for risk of bias. In addition, the search was not limited by year or language, unlike many previous reviews. However, there are still limitations worth remarking on.

The meta-analysis included only a small number of studies, with odds ratios that represent unadjusted proportions (i.e. odds were not adjusted for confounding factors). Although the I^2 indicated low heterogeneity, the upper 95% CI of the I^2 is high (73%), and the pooled estimate should be interpreted with caution. Furthermore, the pooled result chiefly reflects the findings of one study, Sandmark 1999, which has been heavily weighted by the Mantel-Haenszel method. However, the smaller studies included in the meta-analysis implied the same direction of effect, albeit with wide confidence intervals.

A strength of the review was including several types of outcome which related to knee OA. This allowed exploration into the possible differences in reported relationships according to outcome. That different measures may respond differently to an exposure is not a new idea. Urquhart et al [50] offered a similar explanation for the contrasting findings of their review of physical activity and knee joint structures. The small number of studies relevant to each outcome in this review, however, makes it hard to establish if this is the case with running.

This comprehensive search revealed several gaps in the evidence base. For example, none of the cohorts had looked at arthroplasty as an outcome. In addition, most of the cohort studies recruited runners and controls from different sources, and were at risk of sampling bias, compounded by a failure to account for confounding factors. This review has also highlighted the dearth of evidence in recent years – just four publications in the past decade – which is surprising given the divergent (and often underpowered) findings previously. More well-designed, prospective evidence would help to clarify the contradictions observed.

Conclusion

This review was unable to conclude a role of running in the development of knee OA. Moderate to low quality evidence suggests both a positive association with OA diagnosis and a negative association with knee replacement surgery. Divergent results may be a reflection of methodological heterogeneity. Alternatively, they may be a result of a non-linear relationship between running exposure and risk of OA. It is surprising that research interest in this topic appears to have waned in recent years, particularly as participation rates continue to grow in many regions. This is in contrast to more studies investigating overall physical activity. However, activity- or sport-specific effects should not be ignored and the question of running remains clinically important. Given the many established beneficial effects of physical activity on other health outcomes, it is important to confidently inform the public about which forms of physical activity they can undertake without detriment to their musculoskeletal health. Currently, on the basis of published evidence, we are unable to offer advice about even one of the most popular activities, running.

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