Supplementary file 2. GRADE: Grading the body of evidence

Injury

Population: Adults 18 years of age and older
Exposure: Duration, frequency and/or intensity of LTPA, or a composite score reflecting total volume of LTPA
Comparison: No LTPA, or LTPA of a lesser duration, frequency and/or intensity, or composite score of total volume of LTPA.
Outcome: Adverse health outcomes (especially injury, osteoarthritis, erectile dysfunction, and exposure to pollution)

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of injuries in Brazilian recreational street runners: meta-analysis (Borel et al., 2019) *(82)*									

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
23[a]	20 cross-sectional 3 prospective cohort	Serious[b]	Not serious	Not serious	Not serious	None	**Adverse health outcomes** The pooled prevalence of injuries was 36.5% (95% CI 30.8-42.5%). Based on a total population of 3,786 runners. Injury prevalence were given by location and type: • knee injury: 32.9% (95% CI 26.7-39.6%). • ankle injury: 17.7% (95% CI 11.2-26.9%). • hip injury: 13.3% (95% CI 6.9-24.1%). • muscle injuries (including strains and contractures): 27.9% (95% CI 18.2-40.1%). • The prevalence of ligament injuries (e.g. sprains and dislocations): 27.8% (95% CI 19.4-38.1%). • inflammatory lesions (i.e. plantar fasciitis, tendinitis, synovitis, bursitis, and medial tibial stress syndrome): 26.5% (95% CI 14.9-40.1%). • bone injuries (i.e. fracture, chondromalacia patella and bone oedema): 5.6% (95% CI 1.8-16.3%). The following LTPA exposure relationships were reported: • six studies showed a relationship between running distance of 20km or more per week and the occurrence of injury. • five studies showed a relationship between running experience of more than five years and the occurrence of injury. • four studies showed a relationship between a training frequency > 3 days/week and the occurrence of injury. **Dose-response relationship** No effects to report, due to heterogeneity no meta-analysis was performed and hence no ORs or RRs were provided. **Type of LTPA** No effects to report, while only one type of LTPA (i.e. running) was included in the review.	Moderate[rr]	CRITICAL

Is there evidence for an association between changes in training load and running-related injuries? A systematic review (Damsted et al., 2018) *(83)*

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
4	1 randomized controlled trial[c] 1 cross-sectional[d] 2 prospective cohort[e]	Serious[f]	Serious[g]	Not serious	Not serious	None	**Adverse health outcomes** The following LTPA exposure relationships were reported: • 2 out of 4 reviews found an association between sudden increases in training load (>30%) and an increased risk of running-related injury: i.e. increasing the weekly running distance by more than 30% compared to a less than 10% change in the previous week Evidence from two studies defined sudden increases in training load as: • Changing one or more of the running variables (velocity, distance, , frequency, or volume) compared with the non-injured runners • The mean difference between the increase in the running distance the week before the onset of an injury and the average weekly increase during other weeks was found to be 86% **Dose-response relationship** No effects to report, due to heterogeneity no meta-analysis was performed and hence no ORs or RRs were provided. **Type of LTPA** No effects to report, only one type of LTPA (i.e. running) was included in the review.	Low[ss]	CRITICAL

The associations between training load and baseline characteristics on musculoskeletal injury and pain in endurance sport populations: a systematic review (Johnston et al., 2018) *(84)*

10	10 prospective cohorts[h]	Serious[i]	Serious[j]	Serious[k]	Not serious	None	**Adverse health outcomes** No effects to report; this review only looked at dose-response relationships. **Dose-response relationship** • medium effect size association between high total training distances per week/month (not specified in the review) and increased rate of injury and/or pain • medium effect size association between low training frequency (<2 sessions/week) and increased rate of injury and/or pain. • large effect size association between short training duration (<2 hours/week) and increased rate of injury and/or pain; however, this finding may be less applicable given that recreational endurance participation was defined by some studies as a training frequency of three to six training sessions/week *(97, 98)* and training duration of two to four hours/week *(99)*. Definitions of the effect sizes: • Small: OR ≥ 1.5 or RR ≥ 2 • Medium: OR ≥ 2 or RR ≥ 3 • Large: OR ≥ 3 or RR ≥ 4 **Type of LTPA** Running and Triathlon as LTPA were included in the review.	Very Low[tt]	CRITICAL

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
What are the main running-related musculoskeletal injuries? A systematic review (Lopes et al., 2012) *(85)*									
8	2 prospective cohorts[l] 1 clinical trial[m] 2 retrospective cohorts[n] 3 cross-sectional[o]	Serious[p]	Serious[q]	Not serious	Not serious	Electronic searches were conducted only in the main databases related to the sports injuries field	**Adverse health outcomes** • Prevalence and incidence numbers based on a total population of 3,500 runners • The highest incident rate of running-related musculoskeletal injury (RRMIs) was found for patellar tendinopathy (22.7%) • The most prevalent general RRMI was found for plantar fasciitis (17.5%) • The most prevalent RRMI during ultra-marathon races was found for ankle dorsi-flexors tendinopathy (29.6%). • The most frequently general RRMIs reported were: 1) medial tibial stress syndrome (incidence rate ranging from 13.6% to 20.0%; prevalence rate of 9.5%) 2) Achilles tendinopathy (incidence rate ranging from 9.1% to 10.9%; prevalence rate ranging from 6.2% to 9.5%) 3) plantar fasciitis (incidence rate ranging from 4.5% to 10.0%; prevalence rate ranging from 5.2% to 17.5%) • For RRMIs sustained during ultra-marathon races, the most frequently reported injuries were: 1) Achilles tendinopathy (prevalence rate ranging from 2.0%to 18.5%) 2) Patellofemoral syndrome (prevalence rate ranging from 7.4% to 15.6%) **Dose-response relationship** No effects to report; this review only looked at the adverse health outcomes. **Type of LTPA** No effects to report; only one type of LTPA (i.e. running) was included in the review.	Low[uu]	CRITICAL
Stress fractures of the femoral neck: a review (Neubauer et al., 2016) *(86)*									

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							Due to **Critically Low** rating on the AMSTAR 2 scale, this systematic review did **NOT** qualify for assessing the GRADE evidence.		CRITICAL

Training errors and running related injuries: a systematic review (Nielsen et al., 2012) *(87)*

28	7 Retrospective cohort[r] 12 Prospective cohort[s] 6 Case-control[t] 3 Randomized controlled trial[u]	Serious[v]	Serious[w]	Not serious	Not serious	None	**Adverse health outcomes** • In several studies, an increased risk, relative risk, or odds ratio for sustaining an RRI was reported when the weekly running frequency increased: persons running 6-7 times per week had the highest risk of RRI. • Based on the studies reviewed, it was not possible to identify which training errors were related to running related injuries. **Dose-response relationship** No effects to report, due to heterogeneity no meta-analysis was performed and hence no ORs or RRs were provided. **Type of LTPA** No effects to report; only one type of LTPA was included in the review.	Low[vv]	CRITICAL

Association between physical activity and risk of fracture (Qu et al., 2014) *(88)*

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
15	15 Prospective Cohort[x]	Serious[y]	Serious[z]	Not serious	Not serious	None	**Adverse health outcomes** • In the meta-analysis, the participants (total of 1,235,768) with the highest category of LTPA had an approximately 29% lower risk of total fractures compared to those in the lowest category, with 95% CIs of 0.63–0.80 (p<0.01) and moderate heterogeneity across studies (p=0.0, I^2=74.2%). • The analysis for subtypes of fracture showed a statistically significant inverse relationship between higher category of LTPA and risk of hip or wrist fracture (39% and 28% lower risk, respectively): i.e. among individuals in the highest category of LTPA, compared to those in the lowest category (95% CIs were 0.54–0.69 and 0.49–0.96, respectively, all p<0.01). • The association between LTPA and vertebral fracture risk was not statistically significant (RR, 0.87; 95% CI, 0.72–1.03; p<0.01). • Regarding age: the stratified analysis found an RR of 0.76 (95% CI, 0.60-0.91; p=0.52; I^2= 85.0%) for adults <62 years old. **Dose-response relationship** The review did not conduct a dose-response analysis, the existence of a dose-response relationship between LTPA and fracture risk remains unknown. **Type of LTPA** No effects to report; the review did not specify the type of LTPA in their high vs. low or moderate vs. sedentary comparisons.	Low[ww]	CRITICAL

What are the main risk factors for running-related injuries? (Saragiotto et al., 2014) *(89)*

9	9 Prospective Cohort[aa]	Serious[bb]	Serious[cc]	Not serious	Not serious	Even though the electronic search was conducted in the main databases related to the sports-injuries field, it is possible that eligible articles have been published in journals not indexed in any of the searched databases.	**Adverse health outcomes** No effects to report; this review only looked at risk factors for adverse health outcomes. Two of the five studies that investigated weekly distance as a risk factor identified that training for more than 64 km a week was a risk factor for lower extremity injuries. **Dose-response relationship** No effects to report, due to heterogeneity no meta-analysis was performed and hence no ORs or RRs were provided. **Type of LTPA** No effects to report; only one type of LTPA was included in the review.	Low[xx]	CRITICAL

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Epidemiology of ankle and foot overuse injuries in sports: a systematic review (Sobhani et al., 2013) *(90)*									
6	4 Prospective cohort[dd] 2 Cross-sectional[ee]	Serious[ff]	Serious[gg]	Serious[hh]	None	None	**Adverse health outcomes** The highest incidences of ankle and foot injury, expressed per 1000 athletes per season, were reported for: • sports dance (ballet), 338.5 (95% CI: 283.2-401.4) • running, 250.0 (95% CI: 100.5-515.1), • gymnastics, 188.7 (95% CI: 90.5-347.0) **Dose-response relationship** No effects to report, due to heterogeneity no meta-analysis was performed and hence no ORs or RRs were provided. **Type of LTPA** No effects to report; multiple sports were included in the review, but all summarizing conclusions were based on elite sports.	Very Low[yy]	CRITICAL
Incidence, risk factors and prevention of running related injuries in long-distance running: a systematic review (Tonoli et al., 2010) *(91)*									
							Due to **Critically Low** rating on the AMSTAR 2 scale, this systematic review did **NOT** qualify for assessing the GRADE evidence.		CRITICAL
Injuries in runners: a systematic review on risk factors and sex differences (van der Worp et al., 2015) *(92)*									

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
13	11 Prospective cohort[ii] 2 Retrospective cohort[ij]	Serious[kk]	Serious[il]	Serious[mm]	Not Serious	Selection & Publication bias[kk]	**Adverse health outcomes** This review only looked at risk factors for adverse health outcomes. Factors that increased the risk of running-related injuries in women were: • older age: not specified • previous participation in non-axial sports (e.g. cycling, swimming, etc.) • participating last year in a marathon • running on concrete surface • longer weekly running distance (> 48–63.8 km) • wearing the same running shoes for > 4 to 6 months Men were at greater risk of running-related injuries if they had: • restarted running • history of previous injuries • running experience of 0–2 years • weekly running distance between 32–47.8 km • weekly running distance more than 64 km per week **Dose-response relationship** No effects to report, due to heterogeneity no meta-analysis was performed and hence no ORs or RRs were provided. **Type of LTPA** No effects to report; only one type of LTPA (i.e. running) was included in the review.	Very Low[zz]	CRITICAL

Incidence of Running-Related injuries per 1000 h of running in different types of runners: a systematic review and meta-analysis (Videbaek et al., 2015) *(93)*

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
12	7 Prospective cohort[nn] 5 Randomized controlled trials[oo]	Serious[pp]	Serious[qq]	Not Serious	Not Serious	None	**Adverse health outcomes** The weighted estimates showed that novice runners faced a significantly greater injury rate of 17.8 (95 % CI 16.7–19.1; population of 2,480) than recreational runners, who sustained 7.7 (95 % CI 6.9–8.7; population of 946) running-related injuries per 1000 hours of running. The weighted estimate showed an injury incidence for all types of runners combined of 1.07 (95 % CI 1.01–1.13) per 1000 km of running. (Based on a total population of 2,248 runners). **Dose-response relationship** No effects to report; the meta-analysis only looked at the adverse health outcomes relationship. **Type of LTPA** No effects to report; only one type of LTPA (i.e. running) was included in the review.	Low[aaa]	CRITICAL

PA = physical activity; OR = odds ratio; CI = confidence interval; RRMI = running-related musculoskeletal injury; RRI = running-related injury; RR = relative risk;

a: Authors did not provide breakdown of the cross-sectional and prospective cohort studies. Abiko et al., 2017; Araujo et al., 2015; Campos et al., 2016; Fernandes et al., 2014; Ferreira et al., 2012; Hespanhol Junior et al., 2012; Hespanhol Junior et al., 2013; Hino et al., 2009; Ishida et al., 2013; Lopes et al., 2011; Oliveira et al., 2012; Oliveira EGA, Santos-Filho SD, 2018; Pazin et al., 2008; Pileggi et al., 2010; Purim et al., 2014; Rangel et al., 2016; Rios et al., 2017; Rolim et al. 2015; Salicio et al., 2017; Saragiotto et al., 2016; Souza et al., 2014; Yamato et al., 2011
b: Most studies did not use a standard definition of injury. The limitations of the study include the moderate quality of evidence, use of self-administered questionnaires that can lead to memory bias, and lack of standard collected information, thus compromising a more detailed interpretation of the data.
c: Buist et al., 2008
d: Cantidio Ferreira et al., 2012
e: Nielsen et al., 2013; Nielsen et al., 2014
f: Among the non-randomized studies, the most frequent reasons for decreased quality scores were: low external validity, a follow-up period shorter than 12 weeks, and lack of reporting a measure of association, while the risk of bias was more related to the absence of blinding procedures in the included randomized trial.
g: Due to the heterogeneity observed in the study designs, the runners' profiles, as well as the methods used for data collection and analysis of changes in training load, comparison of the results of the four studies included in the present systematic review must be performed with caution.
h: Bovens et al., 1989; Hein et al., 2014; Hespanhol Junior et al., 2013; Lysholm and Wiklander, 1987; Malisoux et al., 2015; Nielsen et al., 2013; Nielsen et al., 2014; Taunton et al., 2003; van Middelkoop et al., 2007; Zwingenberger et al., 2014
i: There was variability in definitions of injury and/or pain, external training load, baseline assessments, data collection and statistical analysis.
j: No heterogeneity I^2 tests were performed or provided.
k: The generalizability of results should be considered given that nine studies involved a recreational ESP whereas three involved an elite ESP.
l: Lysholm, Wiklander, 1987; Pileggi et al., 2010
m: Jakobsen et al., 1994
n: Jacobs, Berson, 1986; McKean et al., 2006
o: Fallon 1996; Hutson 1984; Scheer, Murray, 2011
p: (Outcome) Although most of the studies have a clear definition of RRMIs the definitions always differ between studies. In terms of the participants, only one study performed a random sample

selection and two studies sampled the entire target population of runners. There are only three prospective studies that could enable the assessment of the loss to a follow-up criterion, and all of them fulfilled this criterion, which indicated a lower risk of bias in these studies.
q: No heterogeneity I^2 tests were performed or provided.
r: Koplan 1982; Koplan 1995; Marti 1988a; Marti 1988b; McKean 2006; Valliant 1981; Wen 1997
s: Bovens 1989; Fields 1990; Hootman 2002; Kelsey 2007; Lysholm 1987; Macera 1989; Middelkoop 2008; Pollock 1977; Satterthwaite 1999; Taunton 2003; Walter 1989; Wen 1998
t: Colbert 2000; Duffey 2000; McCrory 1999; Messier 1995; Messier 1991; Messier 1988
u: Buist 2008; Jakobsen 1994; Mechelen 1993
v: The types of participants (novice, recreational, and elite), and the injury definition used varied considerably between the studies.
w: No heterogeneity I^2 tests were performed or provided.
x: Mussolino et al., 1998; Hoidrup et al., 2001; Lau et al., 2001; Feskanich et al., 2002; Roy et al., 2003; Samelson et al., 2006; Thorpe et al., 2006; Michaelsson et al., 2007; Robbins et al., 2007; Appleby et al., 2008; Lee et al., 2010; Trimpou et al., 2010; Armstron et al., 2011; Nikander et al., 2011; Morseth et al., 2012
y: The quality of individual studies varied; some of these may have had limited adjustments for potential statistical confounders. The classification of the quantity of physical activity is difficult to evaluate, a fact that inevitably weakens the strength of the identified association. Differences in methodology between studies may also introduce heterogeneities.
z: Most of the I^2 estimates calculated in this meta-analysis were assessed as moderate. The overall I^2 value of 74.2% is considered as substantial.
aa: Bredeweg et al., 2012; Pileggi et al., 2010; Buist et al., 2009; Lun et al., 2004; Taunton et al., 2003; Wen et al., 1998; Fields et al., 1990; Macera et al., 1989; Walter et al., 1989
bb: The inconsistencies among studies complicate inter-study comparisons and prevent us from confirming the relationship between all risk factors and running injuries. In addition, relatively few prospective studies were identified in this review, reducing the overall ability to detect risk factors.
cc: We found a great heterogeneity of statistical methods between studies, which prevented us from performing a meta-analysis. No heterogeneity I^2 tests were performed or provided.
dd: Dannenberg et al., 1996; Olsen et al., 2006; Seil et al., 1998; van Ginckel et al., 2009
ee: Weiss 1985; Tuffery 1989
ff: Methodological information was missing or provided poorly in most studies. Lack of adequate description of population characteristics, sampling method, and participation rate makes it impossible to generalize results to relevant populations.
gg: Due to the heterogeneity across studies in terms of population characteristics, overuse definitions, assessment tools and sampling methods, data pooling and a meta-analysis were not possible. No heterogeneity I^2 tests were performed or provided.
hh: Incidence and Prevalence rates ranged considerably across studies.
ii: Thijs et al., 2011; Buist et al., 2010; Buist et al., 2010; Hesar et al., 2009; van Ginckel et al., 2009; van Middelkoop et al., 2008; Thijs et al., 2008; Lun et al., 2004; Taunton et al., 2003; Wen et al., 1998; Macera et al., 1989
jj: McKean et al., 2006; Wen et al., 1997
kk: By our inclusion criteria (e.g. long-distance runners recreational and/or competitive) for selecting the original studies, a broad spectrum in the type of runners (novice, track and field, etc.) was selected. Although we performed an extensive literature search, it is likely that both selection and publication bias influenced the results.
ll: The heterogeneity in study populations, in operationalization of both outcomes and risk factors, and time to follow-up prevented us from following a formal meta-analytical approach. No heterogeneity I^2 tests were performed or provided.
mm: Indirect comparisons = A point of concern is that many of the included studies did not clearly describe the participation rate of the target group, which limits the generalizability of findings.
nn: Bovens et al., 1989; Buist et al., 2010; Nielsen et al., 2013; Malisoux et al., 2015; Wen et al., 1998; Krabak et al., 2011; Lysholm et al., 1987
oo: Bredeweg et al., 2012; Buist et al., 2008; Jakobsen et al., 1994; Theisen et al., 2014; van Mechelen et al., 1993
pp: The definition of injury varies considerably across studies. Second, runners from the included studies were classified into four groups according to the type of runner, enabling relevant intergroup comparison. Third, the method of gathering data on exposure time may be questionable. Further, some studies specified the premise that the same runner was included and was contributing exposure time, if running was resumed after an injury occurrence (e.g. the can contribute two injuries from one individual).
qq: No heterogeneity I^2 tests were performed or provided.
rr: Certainty was downgraded from High to Moderate because of serious risk of bias.
ss: Certainty was downgraded from High to Low because of serious risk of bias and inconsistency.
tt: Certainty was downgraded from High to Very Low because of serious risk of bias, inconsistency, and indirectness.
uu: Certainty was downgraded from High to Low because of serious risk of bias and inconsistency.
vv: Certainty was downgraded from High to Low because of serious risk of bias and inconsistency.
ww: Certainty was downgraded from High to Low because of serious risk of bias and inconsistency.

xx: Certainty was downgraded from High to Low because of serious risk of bias and inconsistency.
yy: Certainty was downgraded from High to Very Low because of serious risk of bias, inconsistency, and indirectness.
zz: Certainty was downgraded from High to Very Low because of serious risk of bias, inconsistency, and indirectness.
aaa: Certainty was downgraded from High to Low because of serious risk of bias and inconsistency.

Osteoarthritis

Population: Adults 18 years of age and older
Exposure: Duration, frequency and/or intensity of LTPA, or a composite score reflecting total volume of LTPA
Comparison: No LTPA, or LTPA of a lesser duration, frequency and/or intensity, or composite score of total volume of LTPA.
Outcome: Adverse health outcomes (especially injury, osteoarthritis, erectile dysfunction, and exposure to pollution)

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
The association of recreational and competitive running with hip and knee osteoarthritis: a systematic review and meta-analysis (Alentorn-Geli et al., 2017) *(94)*									

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
25	13 case-control[a] 5 cross-sectional[b] 7 prospective cohort[c]	Serious[d]	Serious[e]	Serious[f]	Not serious	None	**Adverse health outcomes** • 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%). • In fact, running at recreational level was even found to have a protective effect on hip and/or knee OA. • It was also not possible to demonstrate the confounding effect of associated risk factors (age, gender, weight, occupational workload and previous injury) on the risk of OA in runners. **Dose-response relationship** 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%) • females (OR 0.52; 95% CI 0.47-0.57; I^2 0%) **Type of LTPA** No effects to report; the meta-analysis pooled running and orienteering (e.g. runners that use a topographical map to navigate from point A to point B at speed in unfamiliar terrain) populations at the recreational level, but did not analyze these separately.	Very Low[n]	CRITICAL

Running and knee osteoarthritis: a systematic review and meta-analysis (Timmins et al., 2017) *(95)*

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
10	4 case-control[g] 1 ambispective cohort[h] 2 prospective cohort[i] 3 retrospective cohort[j]	Serious[k]	Serious[l]	Serious[m]	Not serious	None	**Adverse health outcomes** 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%. From this evidence, it is not possible to conclude whether running was associated with a diagnosis of knee OA, and studies offered differing conclusions.[p] **Dose-response relationship** No effects to report; this review only looked at the adverse health outcomes relationship for OA. **Type of LTPA** No effects to report; the meta-analysis pooled running and orienteering populations, but did not analyze these separately.	Very Low[o]	CRITICAL

PA = physical activity; OA = osteoarthritis; OR = odds ratio; CI = confidence interval

a: Oahaghin et al., 2009; Kettunen et al., 1999; Kohatsu and Schurman, 1990; Lau et al., 2000; Lo et al., 2016; Manninen et al., 2001; Marti et al., 1989; Puranen et al., 1975; Sohn and Micheli, 1985; Spector et al., 1996; Wingard et al., 1993; Wingard et al., 1998; Vrezas et al., 2010
b: Konradsen et al., 1990; Lane et al., 1986; Panush et al., 1986; Puranen et al., 1975; Williams 2013
c: Chakravarty et al., 2008; Cheng et al., 2000; Kujala et al., 1994; Kujala et al., 1999; Lane et al., 1993; Lane et al., 1998; Panush et al., 1995
d: 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. 16/25 studies scored High risk on the type of bias detection.
e: 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. 30-60% (as captured in summary of effects) may be considered moderate.
f: 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.
g: Kohatsu, 1990; Sandmark, 1999; Manninen, 2001; Thelin, 2006
h: Panush, 1986
i: Lane, 1986; Felson, 2007
j: de Carvalho, 1977; Muhlbauer, 2000; Mosher, 2010
k: Gray literature was not included in the eligibility criteria. As a result, the findings of this review may reflect publication bias. 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). Given the nature of observational studies, only low- to moderate-quality evidence could be expected. However, the assessment of potential bias undertaken in this review indicated that many studies would be downgraded to low or very low quality.
l: 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.
m: The populations under investigation are not the same. The outcomes are differently defined in these studies.
n: Certainty rated from High to Very Low because of serious risk of bias, inconsistency, and indirectness.
o: Certainty rated from High to Very Low because of serious risk of bias, inconsistency, and indirectness.
p: The review considered 5 different outcomes related to knee OA: diagnosis of knee OA, radiographic and imaging markers, arthroplasty for knee OA, knee pain, and knee-associated disability. Due to heterogeneity of outcome definition and measurement of studies, only 1 meta-analysis was appropriate: This combined the case-control studies that identified cases of knee surgery due to OA. Hence overall, there was no conclusion to be made on the relationship between running and knee OA as a long-term adverse health outcome.

Erectile Dysfunction

Population: Adults 18 years of age and older
Exposure: Duration, frequency and/or intensity of LTPA, or a composite score reflecting total volume of LTPA
Comparison: No LTPA, or LTPA of a lesser duration, frequency and/or intensity, or composite score of total volume of LTPA.
Outcome: Adverse health outcomes (especially injury, osteoarthritis, erectile dysfunction, and exposure to pollution)

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Bicycle riding and erectile dysfunction: a review (Sommer et al., 2010) *(96)*									
							Due to **Critically Low** rating on the AMSTAR 2 scale, this systematic review did **NOT** qualify for assessing the GRADE evidence.		HIGH

LTPA = leisure-time physical activity

Exposure to Air Pollution

Population: Adults 18 years of age and older
Exposure: Duration, frequency and/or intensity of LTPA, or a composite score reflecting total volume of LTPA
Comparison: No LTPA, or LTPA of a lesser duration, frequency and/or intensity, or composite score of total volume of LTPA.
Outcome: Adverse health outcomes (especially injury, osteoarthritis, erectile dysfunction, and exposure to air pollution)

Certainty assessment							Summary Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
N/A									
							No Systematic Reviews were found in relation to the Exposure to air Pollution outcome for assessing the GRADE evidence.		LOW

LTPA = leisure-time physical activity