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SYSTEMATIC REVIEW

The Influence of Running on Lower Limb Cartilage: A Systematic Review and Meta-analysis

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Abstract

Background Running is a popular activity practiced worldwide. It is important to understand how running affects joint health to provide recommendations to sports medicine practitioners and runners.

Objective Our aim was to summarize the influence of running on lower limb cartilage morphology and composition using quantitative magnetic resonance imaging (MRI).

Methods Prospective repeated-measures studies evaluating cartilage using MRI before and after running were included. Data sources included Pubmed, Embase, CINAHL, SportDiscus, Web of Science, and Cochrane Central Registry of Controlled Trials. Qualitative analyses considered the number and methodological quality ratings of studies based on the *QualSyst* tool, and recommendations were based on the strength of evidence (strong, moderate, limited, or very limited). Quantitative analysis involved meta-analyses, for which effect sizes were calculated as Hedge's g standardized mean differences.

Results We included 43 articles, assessing seven outcomes (lesions, volume, thickness, glycosaminoglycan content, and T1ρ, T2, and T2* relaxation times). Nineteen articles were rated as high quality, 24 were rated as moderate quality, and none were rated as low quality. Qualitative analyses suggest that running may cause an immediate reduction in knee cartilage volume, thickness, as well as T1ρ and T2 relaxation times immediately; however, these changes did not persist. Meta-analyses revealed a small and moderate decrease immediately following a single running bout in T2 relaxation time in the medial femur and tibia, respectively. Qualitative analyses indicated that the influence of repeated exposure to running on cartilage morphology and composition was limited. Despite conflicting evidence regarding pre-existing knee cartilage lesions, moderate evidence suggests that running does not lead to the formation of new lesions. Repeated running exposure did not cause changes to foot and ankle cartilage thickness or composition.

Conclusions Changes to lower limb cartilage following running are transient. Immediate changes to cartilage morphology and composition, which likely reflect natural fluid dynamics, do not persist and were generally not significant when pooled statistically. Results suggest that cartilage recovers well from a single running bout and adapts to repeated exposure. Given that moderate evidence indicates that running does not lead to new lesions, future trials should focus on clinical populations, such as those with osteoarthritis.

Trial Registration Not applicable.

1 Introduction

Running is often promoted as a beneficial physical activity to enhance cardiovascular health and general well-being [1]; however, this activity induces considerable amounts of impact loading through the hip, knee, and ankle joints [2–4]. Considering the high incidence of running-related injuries in lower limb joints [5], it may be hypothesized that running could have detrimental long-term effects on cartilage health by contributing to earlier development of osteoarthritis.

Conversely, the current body of literature does not directly support such widespread belief [6], with the exception of elite-level athletes [7]. In fact, recent literature reviews suggest that a history of recreational running is not associated with a greater risk of developing knee osteoarthritis [8, 9]. In contrast with other sports, running has been shown to

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Key Points

Short-term changes to cartilage morphology and composition, when present, generally do not persist.

Cartilage in the knee, ankle and foot recovers from the impact sustained during running, whether it be from a single run or an extended training programme.

Running does not induce the formation of new cartilage lesions in the knee joint.

reduce the probability of developing coxofemoral osteoarthritis, along with a decreased risk of undergoing a total hip replacement [10], Furthermore, joint loading exercise does not appear to be detrimental for knee cartilage in people at risk of, or with, knee osteoarthritis [11]. Together, these findings might be explained by the ability of cartilage to sustain and even adapt to regular loading under controlled conditions [12].

Magnetic resonance imaging (MRI) protocols can provide insight on cartilage properties. While conventional MRI techniques allow one to accurately estimate cartilage morphology, recent advances in imaging techniques also enable the study of cartilage physiology [13]. Indeed, compositional measures enable early detection of changes in cartilage composition, which are likely to be identified before changes in volume or thickness. Specifically, T2 relaxation times give indications on water and collagen content, while delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T1ρ relaxation time protocols can accurately estimate glycosaminoglycan concentration [13, 14]. Together, both morphology and composition variables are likely to provide accurate information on cartilage structure and behaviour, as well as mechanisms for adaptation in response to loading activities in the short- and long-term.

A previous systematic review noted that acute changes to knee cartilage after a single bout of running were consistently related to the timing of the post-run MRI evaluation [15]. In most studies that scanned participants within 1 h following running, T1ρ and T2 relaxation times were significantly decreased, indicative of greater proteoglycan concentration (decreased water content) and collagen anisotropy. In contrast, studies that performed a delayed MRI evaluation (> 1 h post-run) reported either increased or non-significant changes to T1ρ and T2 values. These findings demonstrate that cartilage changes seen on MRI may be fleeting. A more recent systematic review and meta-analysis suggested that knee cartilage oligomeric protein, an osteoarthritis biomarker, was increased at 30 min after running, but there were no significant changes seen in follow-up tests 1 or 2 h later [16]. Unfortunately, these reviews did not specifically inform on the influence of repeated exposure to running, and focused only on knee cartilage. However, not all lower limb cartilage may respond to load in the same fashion, and it is important to consider differences between anatomical regions within the knee joint. In order to provide sound clinical advice, sports medicine practitioners need to understand how a running regimen affects lower limb cartilage. An understanding of the current evidence on the role of running on cartilage properties will provide researchers with important information to better design new studies in this area. Therefore, the objective of this systematic review and meta-analysis was to provide a summary of the literature on MRI findings with regard to the influence of both single bouts and repeated exposure to running on hip, knee, ankle, and foot articular cartilage morphology and composition in adults.

2 Methods

This systematic review conforms to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) methodological guidelines [17].

2.1 Literature Search and Eligibility Criteria

The search strategy is presented in Online Resource 1. Database searches were performed in Pubmed, Embase, CINAHL, SportDiscus, Web of Science, and the Cochrane Central Registry of Controlled Trials from inception to 21 March 2021. The following keywords were used: ('Lower limb' OR 'Lower extremity' OR 'Leg' OR 'Hip' OR 'Coxofemoral' OR 'Knee' OR 'Tibiofemoral' OR 'Patellofemoral' OR 'Ankle' OR 'Talocrural' OR 'Foot') AND ('Run' OR 'Running' OR 'Runner') AND ('Cartilage' OR 'Magnetic resonance imaging' OR 'MRI' OR 'Arthritis' OR 'Osteoarthritis'). Titles and abstracts of each article were independently reviewed by four raters in two pairs (JFE and JOD; MCMK and JMC). Hand searches of retrieved article reference lists were also conducted to identify any articles not identified in the database searches. Included studies had to be full papers published in peer-reviewed journals in either English or French, and they had to report results from prospective experimental (repeated measures) designs in which MRI was used to assess lower limb cartilage morphology (e.g. cartilage volume, thickness, and presence/severity of lesions) or composition (e.g. T1ρ, T2, and T2* relaxation time) before and after running. Selected studies evaluated the effects of a single running bout or repeated exposure to running. Included studies required at least two assessments of cartilage: one assessment before a single running bout or repeated exposure, and a minimum of one assessment

following cessation of the prescribed run(s) or follow-up period. Review articles, abstracts, and studies on animals were excluded.

2.2 Critical Appraisal

The *QualSyst* critical appraisal tool was used to evaluate the methodological quality of each included article [18]. It was designed to assess quantitative studies and consists of 14 items, with each item awarded a score on a 3-point scale (yes = 2, partial = 1, no = 0). A summary score for each article is determined by dividing the sum of all items by the total possible sum. A first meeting among raters took place to standardize the interpretation of items. Raters independently assessed two papers before meeting in pairs for a second time (JFE and JOD; MCMK and JMC) to compare scores and to ensure similar and consistent interpretation of items. Following independent evaluation of all included papers, raters met again to discuss and agree on a consensus score. Another rater (MAH) was available in case of disagreement. Intraclass correlation coefficient (ICC) estimates and their 95% confidence intervals (CIs) for each rater pair were calculated for pre-consensus scores using SPSS statistical package version 23 (IBM Corporation, Armonk, NY, USA) based on a mean-rating ($k = 2$), absolute agreement, two-way random-effects model. Studies obtaining a quality score of between 80 and 100% were considered to be high quality (HQ), those scoring between 50 and 80% were considered to be moderate quality (MQ), and studies scoring below 50% were considered to be low quality (LQ) [19].

2.3 Data Extraction

One reviewer from each pair (JFE and MCMK) extracted data independently using a standard data collection form, while the second reviewer in each pair (JOD and JMC) checked accuracy. Descriptive information for the study sample (number of participants; means and standard deviations for age, sex, and body mass index [BMI]; training data), MRI parameters, running protocol characteristics (duration and/or distance of run/running programme), time elapsed between running and imaging, and lower limb cartilage outcomes of interest were extracted. When needed, authors of papers were contacted to provide additional data.

We extracted data on morphology or composition of cartilage in any lower limb joint. Given that joint loading during running is non-uniform and specific regions of cartilage within a joint may respond differently [20], we extracted data for all anatomical regions of a joint that were reported. To provide a summary as complete as possible, we considered the smallest anatomical regions reported in the included studies for our analyses. For example, if a study reported results for the femur, as well as the medial and lateral femur separately, we chose to report results for the medial and lateral femur.

Results were classified as 'immediate' if follow-up MRI data were collected within 30 min after running, or 'delayed' if the time was > 30 min. The 'delayed' classification was further divided into three subcategories: (1) 'same day', (2) 'same week', and (3) 'over 1 month'. The influence of multiple runs, or a running programme, were considered 'repeated exposure'.

2.4 Data Analysis

Both qualitative and quantitative results are presented in this review. For qualitative analyses of the evidence, we considered all studies on a given outcome, as well as their methodological quality ratings. Specifically, recommendations based on the level of evidence were formulated according to a modified version of guidelines provided by van Tulder et al. [21, 22]: (1) strong evidence was indicated by consistent findings among multiple studies including at least three HQ studies; (2) moderate evidence was based on consistent findings among multiple studies, including at least three MQ studies, or a total of two HQ studies; (3) limited evidence was defined as consistent findings among at least two LQ or MQ studies, or only one HQ study; and (4) very limited evidence was indicated by findings from one LQ or MQ study. Conflicting evidence was defined as an equal number of studies of equal strength of evidence reporting opposite results (e.g. increase vs. decrease).

Quantitative analysis of the evidence involved statistically pooling data by meta-analysis for any outcome evaluated in a minimum of three studies. Analyses were conducted for each anatomical region within a joint separately, when available. A random-effects model approach was used to account for study samples and designs. Between-study variance was measured by τ^2 using the DerSimonian–Laird estimator [23]. Inconsistency in study results was categorized as follows: low ($I^2 = 0$–40%), moderate ($I^2 = 30$–60%), substantial ($I^2 = 50$–90%), or considerable ($I^2 = 75$–100%), in accordance with the Cochrane handbook [24]. Effect sizes were calculated as Hedge's g standardized mean differences (SMDs) with 95% CIs using R stats (v.3.6.1) and the meta package [25], and were interpreted as small (0.2), medium (0.5), or large (0.8) [26]. The threshold for statistical significance was set at 0.05.

3 Results

3.1 Search Results

Figure 1 describes the flow of the included studies. A total of 5416 titles were retrieved and analysed for appropriateness

based on inclusion and exclusion criteria. After title and abstract screening, 62 unique articles remained for full-text review, of which 19 were excluded after full-text review. As a result, we report data from 43 articles.

3.2 Quality Assessment

Nineteen articles were rated as HQ, 24 were rated as MQ, and none were rated as LQ (Table 1). The highest overall scores were achieved for item 2 (appropriate study design). ICC agreement between rater pairs based on the initial stage of independent evaluations was 0.62 (95% CI 0.12–0.83) [JFE and JOD] and 0.66 (95% CI − 0.11 to 0.90) [MCMK and JMC]. Agreement was reached during consensus meetings on all items for which rater pairs had discrepancies.

3.3 Study Characteristics

Study characteristics are described in Table 2. Of the 43 articles included, 39 studies evaluated the influence of running on cartilage in the knee, three in the ankle, one in the foot, and none at the hip. Included studies involved a total of 716 unique participants (approximately 41% female) who were included in the analyses, and sample sizes were between 6 and 82. Four studies investigated clinical populations, including tibiofemoral osteoarthritis ($n = 10$) [27], anterior cruciate ligament reconstruction ($n = 23$) [28, 29], and lateral knee pain ($n = 2$) [30]. In each study, the influence of running on foot and ankle cartilages and on knee cartilage are presented in Online Resources 2 and 3, respectively. Participants were scanned immediately after a single run in 21

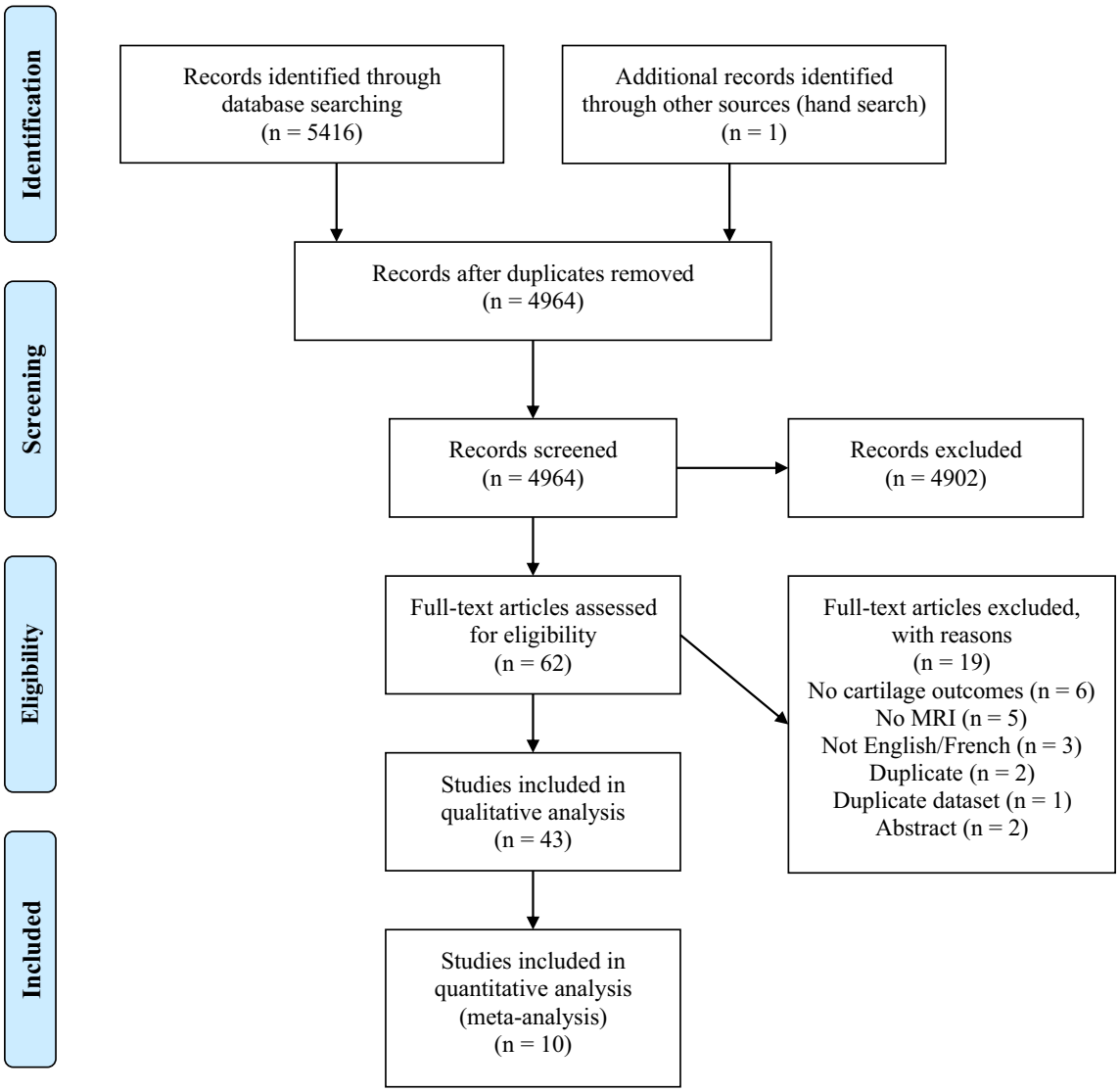

Fig. 1 PRISMA flow diagram of included and excluded studies. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *MRI* magnetic resonance imaging

Table 1 Consensus quality scoring of the included studies

Study, year	QualSyst items													Total score, %
	1	2	3	4	5	6	8	9	10	11	12	13	14	(quality)
Crowder et al., 2021 [42]	2	1	1	1	NA	0	2	1	1	2	1	2	2	66.7 (MQ)
Brenneman et al., 2021 [40]	2	2	1	2	NA	0	2	2	2	2	1	2	2	83.3 (HQ)
Zhang et al., 2021 [51]	2	1	1	1	NA	0	1	2	2	2	1	2	1	66.7 (MQ)
Wang et al., 2020 [50]	2	2	1	1	NA	0	1	2	1	2	1	2	2	70.8 (MQ)
Schütz et al., 2020 [60]	2	2	2	2	NA	0	2	1	2	1	1	1	2	75.0 (MQ)
Heckelman et al., 2020 [39]	2	2	1	1	NA	2	2	2	2	2	1	1	2	83.3 (HQ)
Heckelman et al., 2020 [41]	2	2	1	2	NA	0	2	2	2	2	0	1	2	75.0 (MQ)
Horga et al., 2020 [63]	2	2	2	2	NA	0	2	2	1	1	0	1	2	70.8 (MQ)
Horga et al., 2019 [64]	2	2	1	2	NA	1	2	2	2	1	0	1	2	75.0 (MQ)
Qiu et al., 2019 [65]	2	2	2	2	NA	2	2	0	1	2	0	1	1	70.8 (MQ)
Nathani et al., 2019 [55]	2	2	2	2	2	2	2	0	2	2	0	2	1	82.1 (HQ)
Kyung Kim et al., 2019 [53]	2	2	1	2	NA	2	2	2	2	2	2	2	2	95.8 (HQ)
Kyung Kim et al., 2019 [54]	2	2	1	2	NA	0	2	2	2	2	0	2	1	75.0 (MQ)
Esculier et al., 2019 [27]	2	2	2	2	NA	2	2	2	2	2	2	2	2	100.0 (HQ)
Bratke et al., 2019 [43]	2	2	1	2	NA	0	2	2	2	2	1	2	2	83.3 (HQ)
Schütz et al., 2018 [62]	2	2	2	2	NA	0	2	1	2	2	2	2	2	87.5 (HQ)
Karanfil et al., 2018 [44]	2	2	1	0	NA	0	1	1	2	0	2	1	2	58.3 (MQ)
Chen et al., 2017 [45]	1	2	1	2	0	2	1	1	2	1	1	2	2	69.2 (MQ)
Gatti et al., 2017 [46]	2	2	2	2	NA	1	2	2	2	2	2	2	2	95.8 (HQ)
Behzadi et al., 2016 [47]	2	2	2	2	NA	2	2	2	1	1	2	2	2	91.7 (HQ)
Hesper et al., 2015 [56]	2	2	1	1	NA	0	1	1	2	2	1	2	2	70.8 (MQ)
Schütz et al., 2014 [61]	2	2	2	2	NA	0	2	1	2	2	2	2	2	87.5 (HQ)
Lu and Wang, 2014 [66]	2	2	1	2	2	1	2	2	1	2	1	2	1	80.8 (HQ)
Hinterwimmer et al., 2014 [67]	2	1	1	2	NA	0	2	1	2	2	1	2	2	75.0 (MQ)
van Ginckel et al., 2013 [28]	2	2	2	2	NA	2	2	1	2	2	2	1	2	91.7 (HQ)
Subburaj et al., 2012 [48]	2	2	1	2	NA	0	2	2	2	1	2	1	2	79.2 (MQ)
Leiter et al., 2012 [29]	2	2	2	2	NA	2	1	1	2	NA	NA	2	0	80.0 (MQ)
Cha et al., 2012 [49]	2	2	2	1	NA	0	1	1	2	0	2	1	2	66.7 (MQ)
Niehoff et al., 2011 [31]	1	2	1	2	1	1	2	1	2	2	2	2	2	80.8 (HQ)
van Ginckel et al., 2010 [68]	2	2	2	2	0	1	1	2	1	2	2	2	1	76.9 (MQ)
Mosher et al., 2010 [32]	2	2	2	2	NA	0	2	1	1	1	1	1	0	62.5 (MQ)
Luke et al., 2010 [57]	2	1	2	2	NA	2	2	1	1	1	1	2	2	79.2 (MQ)
Boocock et al., 2009 [33]	2	2	1	2	NA	2	2	2	2	2	2	2	2	95.8 (HQ)
Stahl et al., 2008 [72]	2	2	1	1	NA	2	2	1	2	2	1	2	2	83.3 (HQ)
Krampla et al., 2008 [69]	1	2	2	2	NA	2	1	NA	NA	NA	1	2	1	77.8 (MQ)
Kessler et al., 2008 [34]	1	2	2	2	NA	2	2	2	2	0	1	2	2	83.3 (HQ)
Hagemann et al., 2008 [59]	1	2	1	1	NA	2	1	1	2	2	1	1	2	70.8 (MQ)
Schueller-Weidekamm et al., 2006 [30]	2	2	1	2	NA	2	2	2	2	1	1	2	2	87.5 (HQ)
Kessler et al., 2006 [35]	2	2	1	2	0	2	1	2	2	1	2	2	2	80.8 (HQ)
Mosher et al., 2005 [38]	2	2	2	2	NA	0	1	1	2	2	1	1	2	75.0 (MQ)
Kersting et al., 2005 [37]	1	2	2	2	NA	0	2	2	2	2	2	2	2	87.5 (HQ)
Eckstein et al., 2005 [36]	2	2	0	1	NA	1	2	1	1	2	1	1	2	66.7 (MQ)
Krampla et al., 2001 [52]	1	2	0	1	NA	2	1	NA	NA	NA	0	2	0	50.0 (MQ)

Item 1: Description of the objective. Item 2: Appropriate study design for the objective. Item 3: Description of the subject selection strategy. Item 4: Description of subjects' characteristics. Item 5: Random allocation. Item 6: Blinding of investigators. Item 8: Well-defined and robust outcomes. Item 9: Appropriate sample size. Item 10: Appropriate statistical analyses. Item 11: Estimates of variance. Item 12: Controlled for confounding. Item 13: Sufficiently reported results. Item 14: Results support conclusions

HQ high quality, *MQ* moderate quality, *NA* not applicable

studies [27, 28, 31–49], within 1 day in 12 studies [27, 28, 30, 34, 42, 44, 49–54], within 1 week in eight studies [29, 39, 41, 55–59], and at more than 1 month post-running in seven studies [51, 52, 55–59]. The distance for the single bouts of running ranged from 200 m to 42 km. Repeated exposure to running was investigated in 10 studies [60–69], four of which involved a training programme and completion of a marathon [63, 64, 67] or half marathon [65] race. Outcomes included cartilage lesions (13 studies) [29, 30, 52, 54, 55, 57–60, 63–65, 69], volume (13 studies) [28, 31, 33–37, 40, 43, 46, 51, 66, 67], and thickness (13 studies) [31, 32, 38–40, 44, 46, 48, 51, 60–62, 67], as well as T1ρ (six studies) [27, 41, 45, 48, 55, 57], T2 (16 studies) [27, 32, 38, 42, 44–50, 53–55, 57, 65], T2* (six studies) relaxation time [47, 51, 56, 60–62], and dGEMRIC index (1 study) [68]. The majority of studies (40/43) used an MRI scanner ≥ 1 Tesla (Online Resource 4).

3.4 Summary of Results

The results of qualitative analyses (primarily strong, moderate, and limited evidence) are detailed below and summarized in Fig. 2. For conciseness, qualitative results may be presented by joint compartments. Results not detailed below were based on either very limited or conflicting levels of evidence from a low number of studies. Data pooling for quantitative analyses was only possible for the following knee cartilage outcomes (and regions) assessed immediately following a single running bout (thickness volume and T2 relaxation time) and within 1 day (T2 relaxation time) of run cessation.

3.4.1 Single Run: Immediate

All 21 studies investigating the immediate effects of running on lower limb joint cartilage evaluated the knee joint [27, 28, 31–49]. Studies investigated cartilage volume (10 studies) [28, 31, 33–37, 40, 43, 46] and thickness (eight studies) [31, 32, 38–40, 44, 46, 48], as well as T1ρ (three studies) [41, 45, 48], T2 (nine studies) [27, 32, 38, 42, 45–49], or T2* (one study) [47] relaxation times.

Qualitatively, there is strong evidence that a single running bout immediately reduces lateral tibial [28, 31, 33, 37, 43, 46, 70] and patellar [31, 34–36, 43] cartilage volume, as well as strong evidence that medial tibial [28, 33, 37, 40, 43, 46, 71] cartilage volume is reduced or does not change. We found moderate to strong evidence that lateral femoral [28, 31, 33, 43, 46, 70] and medial femoral [28, 31, 33, 37, 43, 46, 70] cartilage volume is reduced or does not change immediately after a single running bout. There is limited and moderate evidence that femoral [37] and tibial [34, 35] cartilage volume, respectively, is reduced immediately following a single running bout. We found strong evidence that a single running bout immediately reduced cartilage thickness of the lateral tibia [40, 46, 71] and patella [41, 43, 71]. There is limited to moderate evidence that a single running bout immediately reduces or does not change cartilage thickness of the lateral [40, 44, 46, 71] and medial femur [40, 44, 46, 71], as well as the medial tibia [40, 46, 71].

Limited to moderate evidence suggests that tibiofemoral cartilage T2 relaxation time is reduced or does not change [27, 46–49], and limited evidence suggests that patellofemoral [45, 48] cartilage T2 relaxation time is reduced immediately following a single running bout. Moderate evidence suggests that tibiofemoral and patellar cartilage T1ρ relaxation times are reduced immediately following a single running bout [41, 45, 48], and there is limited evidence that the T1ρ relaxation time of the trochlear cartilage [45, 48] is also reduced. Evidence for a reduction in tibiofemoral and patellar T2* relaxation times is limited [47].

Quantitative analyses revealed significant region-specific changes in T2 relaxation time (Fig. 3). Immediately following a run, T2 relaxation times show a small reduction in cartilage of the medial femur [SMD − 0.37 ms (95% CI − 0.73 to − 0.02); $n = 74$, $p = 0.04$, $I^2 = 13\%$] and moderate reduction in the medial tibia [SMD − 0.59 ms (95% CI − 1.10 to − 0.08); $n = 74$, $p = 0.02$, $I^2 = 55\%$]. Overall, most studies have mean changes showing a reduction in cartilage volume or thickness in all regions of the knee, but when considered together, the pooled effect was not significant ($p \geq 0.18$) [Online Resource 4].

3.4.2 Single Run: Delayed Same Day

Ten studies evaluated changes in knee cartilage [27, 28, 30, 34, 42, 44, 49–52], with outcomes including cartilage lesions (two studies) [30, 52], volume (three studies) [28, 34, 51], or thickness (two studies) [44, 51], as well as T1ρ (one study) [27], T2 (three studies) [27, 42, 49], and T2* (one study) [51] relaxation times.

Qualitatively, there is limited evidence that a single running bout does not lead to the formation of new tibiofemoral lesions [30, 52]. We found limited evidence that there are no same-day changes to cartilage volume of the lateral and medial femur [28, 51], medial tibia [28, 51], tibia [34], and patella [34], and limited evidence that the cartilage volume of the lateral tibia [28] is reduced or does not change. Studies investigating T2 relaxation time included heterogeneous populations (e.g. those with and without tibiofemoral osteoarthritis, and healthy young and older runners [49], although they generally provided limited evidence that there are no same-day cartilage changes to tibiofemoral T2 relaxation time [27, 49]. There is limited evidence that there are no same-day changes to tibiofemoral cartilage T1ρ relaxation time in those with and without tibiofemoral osteoarthritis [27].

Table 2 Characteristics of the included studies

Study	Population	Running protocol	Cartilage outcomes (region)	Category
Crowder et al., 2021 [42]	$N=11$; females, healthy and recreationally active, aged 33.7 ± 4.2 years, BMI 21.4 ± 1.4 kg/m^2, running 16.2 ± 1.5 miles/week	40 min on flat outdoor terrain at a comfortable, sustained effort: MRI before the run, 2 min after the run, and repeated every 5 min for 60 min	T2 relaxation time (TF, P)	Immediate, delayed same day
Brenneman et al., 2021 [40]	$N=15$; females, recreationally active, aged 26.1 ± 3.4 years, BMI 23.1 ± 3.1 kg/m^2	15 min on a treadmill at a self-selected speed (9.8 ± 1.6 km/h): MRI before and 3 min after the run	Cartilage volume and thickness (TF)	Immediate
Zhang et al., 2021 [51]	$N=12$: 7 females, 5 males, amateur marathon runners, age range 21–37 years, BMI range 17.6–27.2 kg/m^2	Marathon: MRI within 24 h before the marathon, within 12 h after the marathon, and after 2 months	Cartilage volume, thickness, T2* relaxation time (TF, PF)	Delayed same day, delayed over 1 month
Wang et al., 2020 [50]	$N=18$: 2 females, 16 males, healthy nonprofessional runners, aged 35.6 ± 6.4 years, height 1.71 ± 0.06 m, weight 65.4 ± 7.4 kg, BMI 22.2 ± 2.2 kg/m^2	Marathon: MRI within 24 h before the race and within 10 h after the race	T2 relaxation time (TF, PF)	Delayed same day
Schütz et al., 2020 [60]	$N=22$ (17 finishers in the analyses): 2 females, 20 males, ultra-marathon runners, aged 50.3 ± 9.6 years	4486 km ultra-marathon, last MRI at 3673 ± 234 km (64 days without a day of rest): first MRI before the race, then three times (t) during the race (distance run since the last MRI: t1 = 1103 ± 106 km; t2 = 1667 ± 223 km, t3 = 890 ± 216 km)	Cartilage thickness, cartilage lesions, T2* relaxation time (PF)	Repeated exposure
Heckelman et al., 2020 [39]	$N=8$; males, healthy runners, aged 31 years (range 27–40), BMI 23 kg/m^2 (range 18–25)	3- and 10-mile runs at a self-selected speed, separated by 21 ± 2 days: MRI before, approximately 10 min after, and 24 h after the run	Cartilage thickness (PF)	Immediate, delayed 1 week
Heckelman et al., 2020 [41]	$N=8$; males, healthy runners, aged 31 years (range 27–40), BMI 23 kg/m^2 (range 18–25)	3- and 10-mile runs at a self-selected speed (9.45 ± 0.19 miles/h), separated by 21 ± 2 days: MRI before, approximately 10 min after, and 24 h after the run	T1ρ relaxation time (TF, P)	Immediate, delayed 1 week

Table 2 (continued)

Study	Population	Running protocol	Cartilage outcomes (region)	Category
Horga et al., 2020 [63]	$N=44$; marathon runners ($n=37$; 24 females, 13 males, aged 46.2 ± 9.3 years, BMI 24.5 ± 3.4 kg/m^2, height 169 ± 8.9 cm, running 2 h/week [range 0–4]), pre-race dropouts ($n=7$; 3 females, 4 males, aged 46.6 ± 4.4 years, BMI 23.2 ± 1.5 kg/m^2, height 177 ± 12.9 cm, running 2 h/week [range 0–4])	Four-month beginner standardized gradual training programme and marathon: MRI 2 months before the start of the programme and 6 months after the marathon	Cartilage lesions (TF, PF)	Repeated exposure
Horga et al., 2019 [64]	$N=82$; marathon runners ($n=71$; 39 females, 32 males, aged 44 ± 8.5 years, BMI 25.2 ± 3.6 kg/m^2, height 171 ± 9.2 cm), non-marathon runners ($n=11$; 6 females, 5 males, aged 44 ± 7.0 years, BMI 24.2 ± 2.2 kg/m^2, height 176 ± 10.7 cm)	Four-month standardized gradual training programme and marathon: MRI 2 months before the start of the programme and half a month after the marathon	Cartilage lesions (TF, P)	Repeated exposure
Qiu et al., 2019 [65]	$N=6$; females, novice half-marathon runners, aged 33.3 years (range 29–41), BMI 22.4 kg/m^2 (range 19.8–29.9)	Half-marathon race: MRI early during training and 6 days (range 2.5–14.0) post-race	T2 relaxation time, cartilage lesions (TF, P)	Delayed 1 week
Nathani et al., 2019 [55]	$N=15$; marathon runners: hyaluronic acid ($n=8$; 6 females, 2 males, aged 31 years [range 23–50]), normal saline ($n=7$; 6 females, 1 male, aged 27 years [range 20–49])	Marathon: MRI within 48 h before the marathon (approximately 5 days after injection) and 48–72 h and 3 months after the marathon	Cartilage morphology, T2 and T1ρ relaxation time (TF, PF)	Delayed 1 week, delayed over 1 month
Kyung Kim et al., 2019 [53]	$N=20$; novice runners ($n=10$; 5 females, 5 males, aged 29 ± 6.8 years, height 1.7 ± 0.1 m, weight 65.5 ± 9.8 kg), experienced runners ($n=10$; 5 females, 5 males, aged 31.2 ± 8.8 years, height 1.73 ± 0.1 m, weight 65.4 ± 9.8 kg)	5-km barefoot running on a treadmill at a self-selected speed after walking for 7 min: MRI on the day before and 3.20 ± 0.97 h after the run	T2 relaxation time (TT)	Delayed same day

Table 2 (continued)

Study	Population	Running protocol	Cartilage outcomes (region)	Category
Kyung Kim et al., 2019 [54]	$N=20$; novice runners ($n=10$; 5 females, 5 males, aged 29 ± 6.8 years, height 1.69 ± 0.1 m, weight 65.5 ± 9.8 kg, BMI 22.7 ± 2 kg/m^2, running 5.4 ± 6.9 km/week), experienced runners ($n=10$; 5 females, 5 males, aged 31.2 ± 8.8 years, height 1.73 ± 0.1 m, weight 65.4 ± 9.8 kg, BMI 21.7 ± 1.5 kg/m^2, running 31.4 ± 26.1 km/week)	5-km barefoot running on a treadmill at a self-selected pace: MRI on the day before the run and 3.20 ± 0.97 h after the run	Cartilage lesions, T2 relaxation time (TT)	Delayed same day
Esculier et al., 2019 [27]	$N=20$ females; tibiofemoral osteoarthritis ($n=10$; aged 52.6 ± 7.6 years, running 20.2 ± 9.9 km/week, BMI 23.0 ± 3.4 kg/m^2), healthy controls ($n=10$; aged 52.5 ± 7.8 years, running 25.3 ± 2.5 km/week, BMI 23.5 ± 2.5 kg/m^2)	30 min on the treadmill; tibiofemoral osteoarthritis 7.5 ± 0.9 km/h, healthy controls 7.8 ± 1.2 km/h; for most symptomatic (tibiofemoral osteoarthritis) or randomly chosen knee (healthy controls): MRI before and immediately after the run (sequences ranged from approximately 19–91 min post-run)	T2 and T1ρ relaxation time (TF)	Immediate, delayed same day
Bratke et al., 2019 [43]	$N=12$; 5 females, 7 males, recreationally active, aged 29 ± 4 years, height 1.77 ± 0.08 m, body mass 70.6 ± 7.5 kg	75 min on a treadmill at a self-selected speed (2.78 ± 0.38 m/s): MRI before and < 1 min after the run	Cartilage volume (TF, P, total knee)	Immediate
Schütz et al., 2018 [62]	$N=22$ (13 finishers in the analyses); 1 female, 12 males, ultra-marathon runners, aged 45.4 ± 10.7 years, BMI 23.4 ± 2.5 kg/m^2	4486 km ultra-marathon (64 days without a day of rest): first MRI 4 days before the race, then every 900 ± 211 km and again at the end of the race	Cartilage thickness, T2* relaxation time (TC, TN, CC)	Repeated exposure
Karanfil et al., 2018 [44]	$N=22$; males, physically active, aged 26.2 ± 4.0 years, height 1.77 ± 0.04 m, weight 74.0 kg, BMI 23.6 ± 1.5 kg/m^2	30 min on a treadmill at 80% heart rate after 10 min of warm-up: MRI before for both knees, within 3 min after the run for the right knee and 30 min after the run for the left knee	Cartilage thickness, T2 signal intensity (TF, PF)	Immediate, delayed same day
Chen et al., 2017 [45]	$N=30$ (23 included in the analyses); 12 females, 11 males, healthy, aged 25 years (range 23–30), BMI 20.3 kg/m^2 (range 16.0–24.8)	30 min on a treadmill at a mean speed of 10.4 km/h (range 8.4–11.6): MRI before and immediately after the run	T2 and T1ρ relaxation time (TF, PF)	Immediate

Table 2 (continued)

Study	Population	Running protocol	Cartilage outcomes (region)	Category
Gatti et al., 2017 [46]	$N=15$ (14 included in the analyses); males, healthy, aged 25.8 ± 4.2 years, BMI 23.7 ± 2.6 kg/m^2	15 min on a treadmill at a self-selected speed (7.9–13.2 km/h): MRI before and 3 min after the run	Cartilage thickness, volume, T2 relaxation time (TF)	Immediate
Behzadi et al., 2016 [47]	$N=30$; males, amateur sports participants, aged 27.9 years, BMI 22.5 km/m^2	45 min on a treadmill at a fixed speed = 6.0 miles/h (2.7 m/s): MRI before and 4 min after the run	T2 and T2* relaxation time (TF, PF)	Immediate
Hesper et al., 2015 [56]	$N=10$; 7 females, 3 males, non-professional marathon runners, aged 28.7 ± 3.4 years	Marathon: MRI within 48 h before, within 48 h after, and 4 weeks after the marathon	T2* mapping (TF, PF)	Delayed same week, delayed over 1 month
Schutz et al., 2014 [61]	$N=22$ (13 finishers in the analyses); 12 males, 1 female, ultra-marathon runners, aged 45.4 ± 10.7 years, BMI 23.4 ± 2.5 kg/m^2	4486 km ultra-marathon (64 days without a day of rest): first MRI 4 days before the race, then every 900 ± 211 km and again at the end of the race	Cartilage thickness, T2* relaxation time (TT)	Repeated exposure
Lu and Wang, 2014 [66]	$N=24$; sex not specified, sedentary, aged 19.5 ± 1.1 years, BMI 21.0 ± 1.0 kg/m^2	Randomized to running, cycling, swimming, power-striding, or control for 12 weeks. Assigned activity for 50 min, 5 days/week: MRI before and after the programme	Cartilage volume (TF, PF)	Repeated exposure
Hinterwimmer et al., 2014 [67]	$N=10$; 5 females, 5 males, marathon beginners, aged 39.9 ± 3.8 years, BMI 25.9 ± 5.3 kg/m^2	Six-month training including a marathon at the end: MRI before training and 1 day after the marathon	Cartilage volume and thickness (TF, PF)	Repeated exposure
van Ginckel et al., 2013 [28]	$N=30$; anterior cruciate ligament reconstruction ($n=15$; 7 females, 8 males, median age 26.75 years [95% CI 23.37–31.70], median BMI 25.06 kg/m^2 [95% CI 23.05–25.53]), controls ($n=15$; 7 females, 8 males, median age 27.32 years [95% CI 22.10–33.30], median BMI 23.48 kg/m^2 [95% CI 21.91–25.62])	30 min on a treadmill at a self-selected speed (median speed 10 km/h, distance 4.82 km): MRI 2 min after exercise cessation and repeated in 15-min intervals up to 45 min after exercise	Cartilage volume, thickness, T2 and T2* mapping (TF)	Immediate, delayed same day
Subburaj et al., 2012 [48]	$N=20$; 10 females, 10 males, healthy, aged 28.8 years, BMI 22.7 kg/m^2	30 min on a treadmill at a mean speed of 6.7 miles/h (3.0 m/s): MRI before and < 1 min after the run	T2 and T1ρ mapping (TF, PF)	Immediate
Leiter et al., 2012 [29]	$N=8$; 4 females, 4 males, recreational runners with previous anterior cruciate ligament repair, aged 37.4 ± 2.4 years, BMI 24.9 ± 1.3 kg/m^2	Half-marathon: MRI before and within 48 h after the race	Cartilage lesions (TF)	Delayed 1 week

Table 2 (continued)

Study	Population	Running protocol	Cartilage outcomes (region)	Category
Cha et al., 2012 [49]	$N=20$ males; older runners ($n=10$, aged 51 years, running experience = 5–9 years), younger soccer players ($n=10$, aged 17 years, playing experience = 4–5.5 years)	30 min (3.5 miles; 3.1 m/s): MRI before, 10 min after and 2 h after the run	T2 relaxation time (TF)	Immediate, delayed same day
Niehoff et al., 2011 [31]	$N=14$; 7 females, 7 males, sedentary, aged 23.1 ± 2.1 years, BMI 22.5 ± 1.8 kg/m^2	30 min (4.0 km; 2.2 m/s): MRI before and immediately after the run	Cartilage volume and thickness (TF, PF)	Immediate
van Ginckel et al., 2010 [68]	$N=19$ females (18 in the analyses); novice runners ($n=9$; 8 in the analyses), sedentary controls ($n=10$), aged 22–34 years, BMI 22.2 kg/m^2	10-week start-to-run programme: MRI before and after training	Glycosaminoglycans content using dGEMRIC (TF)	Repeated exposure
Mosher et al., 2010 [32]	$N=37$; young controls ($n=10$; 5 females, 5 males, aged 28.4 ± 6.3 years), young marathoners ($n=12$; 5 females, aged 25.8 ± 5.0 years, running 19 ± 6 miles/week), older controls ($n=5$; 4 females, 1 male, aged 54.0 ± 5.2 years), older marathoners ($n=10$; 2 females, 8 males, aged 52.6 ± 4.8 years, running 28 ± 14 miles/week), BMI 24.4 kg/m^2	30 min at a comfortable pace on asphalt: MRI before and < 15 min after the run	Cartilage thickness and T2 profile (TF)	Immediate
Luke et al., 2010 [57]	$N=20$; recreational runners ($n=10$; 6 females, 4 males, aged 31.4 ± 5.4 years, BMI 23.7 ± 2.7 kg/m^2), controls ($n=10$; 6 females, 4 males, aged 30.0 ± 5.4 years, BMI 23.1 ± 2.2 kg/m^2)	Marathon: MRI within 2 weeks before, within 48 h after and 3 months after the marathon	Cartilage lesions, T2 and T1ρ profiles (TF, PF)	Delayed same week, delayed over 1 month
Boocock et al., 2009 [33]	$N=20$; 10 females, 10 males, recreational runners, aged 32.6 ± 9.4 years, BMI 22.8 ± 2.2 kg/m^2	5000 steps: MRI before and 2 min after the run	Cartilage volume (TF)	Immediate
Stahl et al., 2008 [72]	$N=22$; recreational marathoners ($n=10$; 6 females, 4 males, aged 31.1 ± 5.6 years, weight 68.6 ± 10.0 kg), recreationally active controls ($n=12$; 4 females, 8 males, aged 36.9 ± 11.2 years, weight 75.8 ± 12.6 kg)	Marathon: MRI 2–3 days before, 2–3 days after ($n=10$) and 10–12 weeks after the marathon ($n=4$)	Cartilage lesions (TF, PF)	Delayed same week, delayed over 1 month

Table 2 (continued)

Study	Population	Running protocol	Cartilage outcomes (region)	Category
Krampla et al., 2008 [69]	$N=8$; males, aged 37–55 years, 7/8 runners maintained running over a 10-year follow-up	10 years of training, including running	Cartilage lesions (TF, PF)	Repeated exposure
Kessler et al., 2008 [34]	$N=10$ (20 knees); males, athlete runners, aged 26.5 ± 3.0 years, BMI 22.8 ± 1.5 kg/m^2	20 km: MRI before, 3 min after and 1 h after the run	Cartilage volume (TF, PF)	Immediate, delayed same day
Hagemann et al., 2008 [59]	$N=10$; 3 females, 7 males, marathon runners, aged 37.3 years	90 km: MRI 48 h before, 24–48 h after and 4–6 weeks after the marathon	Cartilage lesions (TF, PF)	Delayed same week, delayed over 1 month
Schueller-Weidekamm et al., 2006 [30]	$N=22$; 6 females, 16 males, non-professional marathon runners, aged 32 ± 5.3 years, BMI 20.5 ± 0.1 kg/m^2. Two subjects complained of lateral knee pain	Marathon: MRI 24 h before and within 1–4 h after the marathon	Cartilage lesions (TF)	Delayed same day
Kessler et al., 2006 [35]	$N=30$ (48 knees; 10 runners per distance); males, athletes, aged 38 ± 14 years, BMI 22.6 ± 1.6 kg/m^2	Either 5, 10, or 20 km: MRI before and 3 min after the run	Cartilage volume (TF, PF)	Immediate
Mosher et al., 2005 [38]	$N=7$; males, sedentary, aged 23–27 years, BMI 24.3 kg/m^2	30 min at comfortable pace on asphalt: MRI before and within 10 min after the run	Cartilage thickness and T2 profile (TF)	Immediate
Kersting et al., 2005 [37]	$N=18$; 7 females, 11 males, trained endurance runners, aged 31.6 ± 7.8 years, BMI 22.9 ± 2.8 kg/m^2	1 h at maximum speed sustainable over that period: MRI before and < 1:20 min after the run	Cartilage volume (TF, PF)	Immediate
Eckstein et al., 2005 [36]	$N=12$; 6 females, 6 males, healthy, aged 23–30 years	200 m, including 54 stairs: MRI before and 90 s after the run	Cartilage volume (P)	Immediate
Krampla et al., 2001 [52]	$N=8$; males, recreational long-distance runners, aged 37 years (range 27–46)	Marathon: MRI 10–14 days before the marathon, within 1 day after running (range 3–21 h) and 6–8 weeks later	Cartilage lesions (TF, PF)	Delayed same day, delayed over 1 month

BMI body mass index, *MRI* magnetic resonance imaging, *TF* tibiofemoral, *PF* patellofemoral, *P* patella, *TT* tibiotalar joint, *TC* talocalcaneal, *TN* talonavicular, *CC* calcaneocuboid, *CI* confidence interval

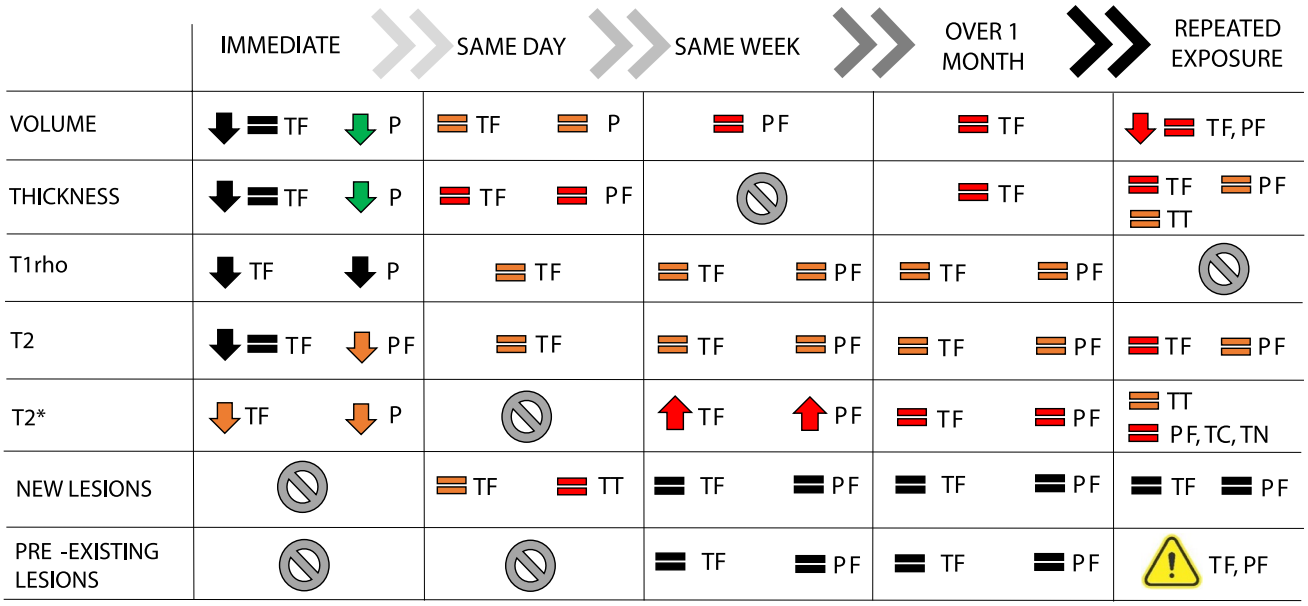

Fig. 2 Summary of qualitative results. Colours represent the levels of evidence: green, strong; black, moderate; orange, limited; red, very limited. The 'Caution' symbol indicates conflicting evidence, and the 'No' symbol indicates no information available. The upwards arrow indicates an increase from baseline, whereas the downwards arrow indicates a decrease from baseline and the equal symbol indicates no change from baseline. Note that when there were different levels of evidence for different regions of a given joint, the colour represents the lowest of these levels. *TF* tibiofemoral joint, *PF* patellofemoral joint, *P* patella, *TT* tibiotalar joint, *TC* talocalcaneal joint, *TN* talonavicular joint

Quantitative analyses did not indicate significant region-specific changes in T2 relaxation time ($p \geq 0.281$) [Online Resource 5]; however, most studies have mean changes showing an increase in T2 relaxation times in cartilage of the lateral femur, medial femur, lateral tibia, and medial tibia. Due to insufficient data, statistical pooling was not available for other cartilage outcomes.

3.4.3 Single Run: Delayed Same Week

Eight studies reported cartilage data at the knee joint [29, 39, 41, 55–57, 59, 72], with outcomes including cartilage lesions (five studies) [29, 55, 57, 59, 72] and thickness (one study) [39], as well as T1ρ (three studies) [41, 55, 57], T2 (two studies) [55, 57], or T2* (one study) [56] relaxation times.

Qualitatively, there is moderate evidence that a single running bout does not lead to the formation of new tibiofemoral or patellofemoral lesions or induce changes to pre-existing knee cartilage lesions [29, 55, 57, 58, 73]. Limited evidence suggests that there are no same-week changes to cartilage T2 or T1ρ relaxation times of the lateral femur, lateral tibia, medial femur, medial tibia, patella, or trochlea [39, 55, 57]. No quantitative analyses were conducted, since the criteria for data pooling were not met for studies that assessed cartilage within 1 week following running.

3.4.4 Single Run: Delayed Over 1 Month

Seven studies conducted a second follow-up at over 1-month post-run [51, 52, 56–59, 72], with outcomes including cartilage lesions (five studies) [52, 55, 57, 59, 72], volume (one study) [51] and thickness (one study) [51], as well as T1ρ (two studies) [55, 57], T2 (two studies) [55, 57], or T2* (2 studies) [51, 56] relaxation times.

Qualitatively, moderate evidence suggests a single bout of running does not lead to the formation of new tibiofemoral or patellofemoral cartilage lesions or induce changes to pre-existing knee lesions [52, 55, 57, 59, 72]. We found limited evidence that after 1 month, there were no changes to tibiofemoral or patellofemoral cartilage T2 or T1ρ relaxation times in non-runners [57] and those who received either saline or hyaluronic acid knee injections [55]. The criteria for data pooling were not met for studies assessing cartilage over 1 month following running.

3.4.5 Repeated Exposure

Eight studies investigated the influence of repeated exposure to running on knee cartilage [28, 60, 63–67, 69]. Studies investigated cartilage lesions (five studies) [60, 63–65, 69], volume (two studies) [66, 67] and thickness (four studies) [60–62, 67], as well as T2 (one study) [65] or T2* (three studies) [60–62] relaxation time and dGEMRIC index (one study) [68].

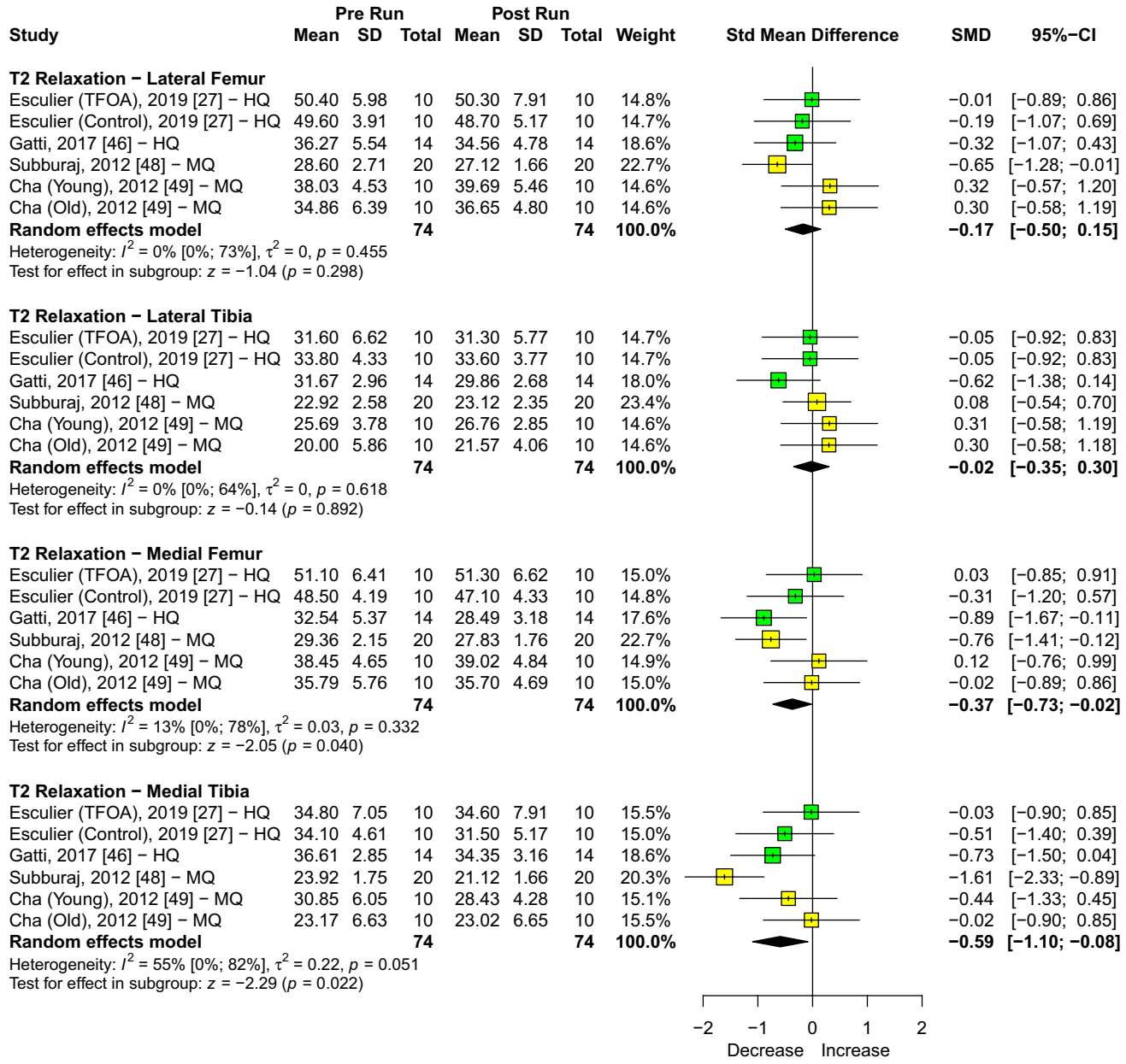

Fig. 3 Forest plot of data for pooling T2 relaxation values immediately following running. Squares represent Hedge's g SMD and are colour-coded to represent the quality of the studies: green, high; yellow, moderate. 'Total' indicates the number of participants included in the analyses and 'Weight' indicates the influence an individual study has on the pooled result. *SMD* standardized mean difference, *SD* standard deviation, *CI* confidence interval, *TFOA* tibiofemoral osteoarthritis, *HQ* high quality, *MQ* medium quality

Based on qualitative analyses, there is moderate evidence that repeated exposure to running does not lead to the formation of new tibiofemoral or patellofemoral cartilage lesions [28, 60, 63–67, 69]. Evidence regarding whether pre-existing knee cartilage lesions improved, deteriorated or remained unchanged following repeated running exposure was conflicting. There is limited evidence that repeated running exposure does not change patellofemoral cartilage thickness [60, 67]. No quantitative analyses were conducted since the criteria for data pooling were not met for studies assessing repeated exposure to running.

3.4.6 Ankle, Single Run: Delayed Same Day

Two studies investigated changes in ankle cartilage between 30 min and 24 h following run cessation [53, 54]. Studies

investigated cartilage lesions [54] and T2 relaxation time [53, 54]. Qualitatively, there is limited evidence that a single running bout increases T2 relaxation time in the tibiotalar cartilage of novice runners; however, no changes were observed in marathon runners [53, 54].

3.4.7 Ankle, Repeated Exposure

One study investigated changes in ankle cartilage following repeated exposure to running and evaluated cartilage thickness and T2* relaxation time [61. There is limited evidence that running a multistage ultramarathon does not change cartilage thickness of the tibial plafond or talar dome. We found limited evidence that tibiotalar T2* relaxation time increases during the first half of the same ultra-marathon; however, the initial increase was followed by a significant decrease [61].

3.4.8 Foot, Repeated Exposure

One study investigated changes to cartilage in the foot following repeated exposure to running, and evaluated cartilage thickness and T2* relaxation time [62]. There is very limited evidence that running a multistage ultramarathon does not change cartilage thickness of the tibiotalar, talonavicular, talocalcaneal, or calcaneocuboid joints. As in the ankle, we found very limited evidence that the T2* relaxation times of cartilage in the foot increases during the first half of a multistage ultramarathon, followed by a secondary reduction for the remainder of the race [62].

4 Discussion

Based on our aggregate findings, the current literature suggests that the influence of running on lower limb cartilage properties seen on MRI is often transient, and that immediate changes are related to normal fluid exchange within the cartilage. Overall, this review suggests that repetitive joint loading from a single run or a running programme is well tolerated and not detrimental to lower limb cartilage. Our results are consistent with previous systematic reviews [15, 16] that assessed changes in knee cartilage after a single run, although we included more articles and considered their methodological quality to formulate recommendations. Our review provides a more comprehensive report for clinicians because it analyses the influence of exposure to a running programme, summarizes research in all lower limb joints, and offers details on different compartments within the knee.

4.1 Immediate Changes are Indicative of Fluid Exchange Within Articular Cartilage

In order to mitigate the high forces experienced by cartilage during running, intrachondral water is exuded from regions experiencing loading, thereby decreasing cartilage matrix volume and compressing proteoglycan molecules [74]. A reduction in free water content and an increase in proteoglycan concentration shortens T1ρ and T2 relaxation times [75], thus changes to cartilage morphology and composition immediately following running are expected. While qualitative analyses in the present review suggest cartilage volume and thickness may be reduced immediately following running, our quantitative analyses included studies with large uncertainty in their effects, such that the summary effect was not significant. Thus, running may cause immediate changes to lower limb morphology, although it is not clear from our analyses. Possible explanations for conflicting results between qualitative and quantitative results may include lack of statistical power from small sample sizes and large CIs surrounding effect sizes leading to low precision, or the fact that the meta-analyses did not include all studies considered in the qualitative analyses due to incomplete datasets.

4.2 Cartilage Recovers After Running

The extracellular matrix of joint cartilage is porous and permeable; thus, when load is removed, water naturally migrates back into the tissue [76]. Our qualitative analyses indicate that knee cartilage morphology and composition are generally restored as the time between the cessation of running and MRI evaluation increases, likely a result of the restoration of intrachondral water content and concomitant decrease in proteoglycan concentration. Furthermore, we report that the recovery of cartilage properties is rapid, often returning to baseline values within 24 h [27, 28, 34, 44, 49]. A fast return to normal fluid dynamics in joint cartilage suggests that immediate alterations to joint cartilage have no detrimental, long-term effects on cartilage morphology or composition, with the exception of one study that reported that compositional measures remained elevated in medial tibiofemoral and patellofemoral cartilage at 3 months post-marathon [57]; however, a subsequent similar study failed to identify such changes [55]. The fact that knee cartilage can recover its structural and functional properties after exposure to running-related loading implies that it can be ready to sustain more load and withstand repeated stimulation following a short period of rest. However, it is important to note that most studies in our review investigated the knee joint. Although it is possible that cartilage of other joints in the lower limb recover in a similar fashion, evidence is lacking at this point.

4.3 Regional Differences in Cartilage Properties

Considering that load distribution within the knee joint is non-uniform during ambulation, it is reasonable to expect larger variations in the medial knee compartment since it experiences higher loads than the lateral compartment [20]. In agreement with our qualitative analyses, data pooling from quantitative analyses in this review revealed significant reductions in T2 relaxation time of the medial knee compartment only, immediately following a single running bout. As such, we agree with previous authors who suggest that compositional analysis may be more sensitive than morphological (i.e. volume and thickness) outcomes in detecting cartilage changes immediately after running [51, 77, 78], and thus we recommend using these measures. It is also important to note that there was large variability between studies with regard to the anatomical regions of interest within a joint that were evaluated. For instance, while earlier papers evaluated femoral cartilage as a whole, more recent studies have further divided this area into much smaller subregions as sensitivity of MRI improves. However, this heterogeneity made results difficult to pool in the present review. While reliability values are generally high across compositional MRI techniques, poorer intraobserver ICC agreements are seen in studies that conduct smaller subregional or laminar analyses. We suggest a consensus should be reached regarding the appropriate cartilage segmentation to achieve standardization among investigations.

Qualitative evidence suggests that our results regarding foot and ankle cartilage are limited. Kyung Kim et al. [53, 54] detected increases in tibiotalar cartilage T2 relaxation times of novice runners at 3 h following a 5 km barefoot run; however, no significant changes from baseline were found in marathon runners, suggestive of adaptations to training. Ankle cartilage is stiffer than knee cartilage, a characteristic that is attributed to a higher glycosaminoglycan content and less introchondral water [79]. It has been speculated that increased glycosaminoglycan content is an adaptation to withstand higher mechanical demands, as suggested by the difference in glycosaminoglycan content reported between a group of sedentary individuals who took part in a 10-week start-to-run programme and those who maintained a sedentary lifestyle [68].

4.4 Clinical Implications

Assurance that load is beneficial for articular cartilage, and recreational running is a safe activity for lower limb joints, is important, as recent survey data suggest that runners, non-runners and healthcare practitioners alike are unsure about the relationship between moderate-to-high loading activities, such as running, and cartilage health [80]. Short-term changes to cartilage volume and thickness in response to running are minimal and transient [60–62, 66, 67], and running, even for 10 years, does not lead to new cartilage lesions [69]. It is important to note that the effects of repeated running exposure on pre-existing knee cartilage lesions are conflicting and it is unclear if pre-existing lesions were a result of running participation or other previous joint trauma. More work is needed to understand how injured or compromised cartilage responds to running in the short and long term. Cartilage composition properties return to baseline when allowed to rest following a run [55–57], and can even do so during a multistage ultra-marathon in well-trained runners [61, 62]. In fact, repeated exposure to mechanical loading within a safe physiological range that cartilage can tolerate may trigger a positive adaptation response. A recent theoretical modelling study further supports the necessity of adaptation to occur to prevent cartilage failure, especially in the knees of runners [12]. Studies demonstrate that individuals who were more physically active at a baseline timepoint showed less changes in cartilage T1ρ and T2 relaxation times following running compared with their less-active counterparts [46, 48, 53, 54]. Our results are consistent with previous systematic reviews that suggest that recreational running is associated with lower rates of hip and knee osteoarthritis, and lower odds of undergoing surgery for osteoarthritis, in comparison with a sedentary lifestyle (underload) or running at the elite level (overload) [9, 81]. As our results did not indicate any adverse effects to continual running training, given the potential protective effects of running, clinicians should consider recommending recreational running, as tolerated, to maintain healthy cartilage.

4.5 Limitations and Considerations

The protocol for this review was not preregistered. Quantitative analyses were only possible for studies that investigated outcomes immediately after running, thus we were unable to provide pooled data for other subgroups or repeated exposure to running. For studies that did not conduct follow-up scans immediately following running cessation, it is unclear whether subjects ran or participated in other strenuous activities that may have loaded their lower limbs in the meantime. Therefore, we cannot be certain if the observed changes in cartilage outcomes were due to running alone. There was significant variation among studies with regard to MRI machines and sequencing parameters: higher field strength machines could have detected smaller variations in cartilage outcomes. Confounders such as participant characteristics (age, sex, history of injury, activity levels) and the distance/duration of runs were not explored in our analyses and most studies investigated young, healthy people who can be categorized as ‘recreational runners’. The findings of a

collection of studies evaluated cartilage response in highly trained runners during a multistage ultramarathon [60–62], thus these specific results may not be generalizable to other populations. The present review considered healthy and clinical populations together; however, recommendations may be different in people with a previous joint injury or those diagnosed with osteoarthritis [27, 28]. There is a clear need for more research investigating the effects of running in clinical populations; however, current evidence suggests that running and impact exercise are not detrimental in those at risk of, or with established, osteoarthritis [8, 11, 82]. Finally, the majority of our findings are restricted to the knee joint; more HQ studies are needed to further investigate the impact of running on cartilage in the foot, ankle, and hip, for which no studies were identified by this review.

5 Conclusion

This review highlights the resiliency of lower limb cartilage in response to the repetitive impacts of running. We report immediate natural and transient dynamics of cartilage fluid exchange and deformation assessed via quantitative imaging within the lower limb joints. While a single bout of running induces immediate changes to lower limb cartilage morphology and composition, these changes are generally not sustained beyond 24-h post-run. As such, the cartilage outcomes we included seem to recover from running relatively quickly, and the cartilage is conditioned to withstand regular training. Given that running has a myriad of health benefits and that loading within a safe physiological range is healthy for cartilage, our results support recommendations in favour of running as a healthy form of physical activity. Future research should investigate clinical populations and further evaluate if findings at the knee can be extrapolated to other lower limb joints.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40279-021-01533-7.

Declarations

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Conflict of interests Michaela Khan, James O'Donovan, Jesse Charlton, Jean-Sébastien Roy, Michael Hunt, and Jean-Francois Esculier declare they have no competing interests.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Author contributions JSR and JFE designed the study. MCMK, JOD, JMC, JSR and JFE performed the literature search, critical appraisal, and data extraction, and MCMK, JMC, MAH and JFE performed the data analyses. The first draft was prepared by MCMK, JMC, MAH and JFE. All co-authors provided feedback and approved the final manuscript.

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