

1 **Impact of exercise on articular cartilage in people at risk of, or with**  
2 **established, knee osteoarthritis: a systematic review of Randomized Controlled**  
3 **Trials**

4 A. Bricca<sup>1</sup>, C.B. Juhl<sup>1,2</sup>, M. Steultjens<sup>3</sup>, W. Wirth<sup>4,5</sup>, E.M. Roos<sup>1</sup>

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6 <sup>1</sup>University of Southern Denmark, Odense, Denmark.

7 <sup>2</sup>University of Copenhagen, Herlev and Gentofte Hospital, Copenhagen, Denmark.

8 <sup>3</sup>Glasgow Caledonian University, Glasgow, UK.

9 <sup>4</sup>Paracelsus Medical University (PMU) Salzburg and Nuremberg, Salzburg, Austria.

10 <sup>5</sup>Chondrometrics GmbH - Medical Data Processing, Ainring, Germany.

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12 Corresponding author:

13 Alessio Bricca

14 Research Unit for Musculoskeletal Function and Physiotherapy

15 Department of Sports Science and Clinical Biomechanics

16 University of Southern Denmark

17 Campusvej 55

18 DK-5230 Odense M

19 Denmark.

20 E-mail: abricca@health.sdu.dk

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28 **Abstract**

29 *Objective.* To investigate the impact of knee joint loading exercise on articular  
30 cartilage in people at risk of, or with established, knee osteoarthritis (OA) by  
31 conducting a systematic review of randomized controlled trials (RCT).

32 *Design.* We followed the Preferred Reporting Items for Systematic Reviews and  
33 Meta-analyses guidelines.

34 *Data sources.* We performed a literature search with no restriction on publication  
35 year or language in MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of  
36 Controlled Trials and Web of Science up to September 2017.

37 *Eligibility criteria.* RCTs investigating the impact of exercise on MRI-assessed  
38 articular cartilage in people over 18 years of age.

39 *Results.* We included nine trials, including a total of 14 comparisons of cartilage  
40 morphometry, morphology and composition outcomes, of which two included  
41 participants at increased risk of knee OA and 12 included participants with knee OA.  
42 In participants at increased risk, one study comparison reported no effect on cartilage  
43 defects and one had positive effects on glycosaminoglycans (GAG). In participants  
44 with OA, six study comparisons reported no effect on cartilage thickness, volume or  
45 defects; one reported a negative effect and one no effect on GAG; two reported a  
46 positive effect and two no effect on collagen.

47 *Conclusions.* Knee joint loading exercise seems to not be harmful for articular  
48 cartilage in people at increased risk of, or with, knee OA. However, the quality of  
49 evidence was low, including some interventions studying activities considered  
50 outside the therapeutic loading spectrum to promote cartilage health.

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53 **Keywords:** Exercise, cartilage, humans, collagen and glycosaminoglycans.

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56 **What is already known?**

- 57 • Knee joint loading exercise is a cornerstone in the management of knee OA.
- 58 • Knee joint loading exercise in the form of exercise therapy has a moderate
- 59 effect in reducing pain and improving physical function in knee OA patients.

60 **What are the new findings?**

- 61 • Knee joint loading exercise seems to not be harmful for articular cartilage in
- 62 participants at increased risk of, or with, knee OA.
- 63 • Knee joint loading exercise interventions at a dose sufficient to improve
- 64 cartilage health need to be investigated.

65 INTRODUCTION

66 Knee osteoarthritis (OA) is the most common joint disease and a major cause of  
67 disability and pain.<sup>1</sup> The OA prevalence has doubled since the mid-20<sup>th</sup> Century <sup>2</sup>  
68 with an expected higher incidence in the future.<sup>3</sup> The annual total medical cost per  
69 person suffering from OA is on average €11,100.<sup>4</sup>

70

71 Articular cartilage breakdown is the hallmark of OA, with aggrecan loss being an  
72 early sign of tissue degeneration. Many factors such as age, body mass index (BMI),  
73 knee injury, inflammation, sex and family history independently, and as a result of  
74 their interaction, contribute to its development and progression.<sup>5 6</sup> For example,  
75 approximately every second major knee injury from sports results in OA 10-15 years  
76 later <sup>7-9</sup> and it has been estimated that at least 12% of the total burden of knee OA  
77 originates from knee injury.<sup>10</sup> Hypothetically, interventions targeting younger patients  
78 at increased risk of OA (e.g. following sports injury), or in the early stages of the  
79 disease, increase the chances of slowing down articular cartilage breakdown, since  
80 the integrity of the cartilage may still be intact with little or no aggrecan loss.

81

82 Therapeutic exercise is a first-line treatment in OA: it is safe,<sup>11</sup> and effectively  
83 reduces pain and improves function.<sup>12-14</sup> Less is known about the effects from  
84 therapeutic exercise on knee joint articular cartilage. However, exercise at higher  
85 doses, such as playing sports at elite level, is associated with development of OA,  
86 suggesting not only injury but also load in itself as being a contributing factor.<sup>15 16</sup> The  
87 mechanical loading generated from exercise, in combination with cell biology, and in  
88 some cases inflammatory factors, may alter the function of articular cartilage.<sup>17</sup> While  
89 there are no conclusive studies, it has been suggested that exercise may prevent or  
90 delay OA onset.<sup>18</sup> In support of this, two cohort studies found that a moderate dose of  
91 physical activity could slow down cartilage degeneration in middle-aged individuals at  
92 early OA stages.<sup>19 20</sup> Furthermore, initiating an accelerated and progressive weight-

93 bearing intervention a few hours after cartilage surgery was shown to be safe for the  
94 cartilage and resulted in more favourable clinical outcomes compared to a delayed  
95 knee joint loading exercise intervention.<sup>21</sup> Also, in patients having had meniscectomy,  
96 therapeutic exercise increased cartilage glycosaminoglycan content.<sup>22</sup> However,  
97 patients at risk of, or with, knee OA still often believe that exercise may wear down  
98 their knee joints, creating a barrier to exercise.<sup>25</sup>

99

100 Systematic reviews of randomised controlled trials (RCTs) provide the highest quality  
101 of evidence for assessing effectiveness and harms of treatments. Current knowledge  
102 in this area of interest has not been summarised systematically. Therefore, we aimed  
103 to review the existing evidence regarding the impact of knee joint loading exercise on  
104 articular cartilage.

105 METHODS

106 ***Terminology***

107 As defined by the authors of the original papers, participants at risk of knee OA are  
108 those with risk factors (e.g. knee injury treated with or without surgery, or BMI  
109 (Kg/m<sup>2</sup>) ≥25) associated with the development or progression of the disease, while  
110 participants with OA are those with a clinical diagnosis of OA (i.e. according to the  
111 American College of Rheumatology criteria) with or without radiographic signs of  
112 knee OA (Kellgren-Lawrence (KL) grade >1), in the tibiofemoral and/or patellofemoral  
113 compartments of one or both knees <sup>23</sup>.

114 Articular cartilage outcomes assessed by Magnetic Resonance Imaging (MRI) were  
115 classified into morphometry (i.e. thickness and volume), morphology (i.e. defects) or  
116 composition (i.e. glycosaminoglycans assessed by dGEMRIC and collagen assessed  
117 with T2-mapping in seven comparisons).

118 The term ‘knee joint loading exercise’ refers to “the stimuli applied to the knee joint  
119 from ‘exercise’ or ‘exercise therapy’”. The term ‘exercise’ refers to “*physical activities,*

120 *which are usually done on a regular basis with the intention of improving or*  
121 *maintaining physical fitness or health” and ‘physical activity’ refers to “any bodily*  
122 *movement produced by skeletal muscles that requires energy expenditure”. The term*  
123 *‘exercise therapy’ refers to “a regimen or plan of physical activities designed and*  
124 *prescribed for specific therapeutic goals with the purpose to restore normal*  
125 *musculoskeletal function or to reduce pain caused by diseases or injuries”<sup>24</sup>.*

## 126 **Protocol**

127 This systematic review is reported according to the Preferred Reporting Items for  
128 Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix A). Study  
129 selection, eligibility criteria, data extraction and statistical analysis were performed  
130 according to the Cochrane Collaboration guidelines<sup>25</sup> and published in a protocol in  
131 the PROSPERO database (CRD42016039536).

## 132 **Eligibility criteria**

133 We included RCTs investigating the impact of knee joint loading exercise on articular  
134 cartilage in people over 18 years of age. Studies were excluded when no-full text was  
135 available, and when treatment arms involved interventions other than knee joint  
136 loading exercise that might have impacted on the articular cartilage.

## 137 **Literature search**

138 A systematic literature search was performed with no restriction on publication year  
139 or language in MEDLINE via PubMed, EMBASE via Ovid, CINAHL (including  
140 preCINAHL) via EBSCO, the Cochrane Central Register of Controlled Trials  
141 (CENTRAL) and Web of Science (WoS) up to May 2016. The search was repeated  
142 for the period from May 2016 to September 2017 in these databases to identify  
143 additional studies published before manuscript submission.

144 ***Search methods and study selection***

145 The search was firstly performed in MEDLINE (Appendix B) and then customized for  
146 EMBASE, CENTRAL, WoS and CINAHL. All terms were searched, if possible, both  
147 as keywords [MeSH] and as text words in titles and abstracts [TIAB]. In MEDLINE  
148 and EMBASE, animal studies were identified and removed before screening all the  
149 studies, using a validated animal filter <sup>26 27</sup>. Initially, two reviewers (AB and CJ)  
150 independently screened titles and abstracts and all studies deemed eligible by at  
151 least one of the reviewers was checked independently in full-text by the same two  
152 reviewers. In addition, reference lists from retrieved publications and systematic  
153 reviews published after January 2010 were screened. Disagreements between the  
154 two reviewers in inclusion were discussed until consensus was reached.

155 ***Data collection***

156 A customized data extraction form was developed for each of the articular cartilage  
157 outcome categories: morphometry (i.e. thickness and volume), morphology (i.e.  
158 defects) or composition (i.e. glycosaminoglycans and collagen). These outcomes  
159 were estimated from the combination of different cartilage compartments (i.e. medial  
160 and lateral) when data were available. Otherwise, values from the medial and lateral  
161 values of the tibia, femur and the patella were used. Data were extracted by the first  
162 and second authors (AB and CJ) from tables and graphs of published manuscripts.  
163 The following information was mandatory: authors of the study, year of publication,  
164 design of the trial, intervention characteristics, location of the trial (in the case of  
165 multi-center studies, primary investigator affiliation was applied), number of  
166 participants allocated (to the exercise and control groups respectively), the  
167 participants' average age, average body mass index (BMI (Kg/m<sup>2</sup>)), the duration of  
168 the study (presented in weeks), and the MRI characteristics. When several  
169 intervention groups were included in a study, the between-group difference was  
170 reported for each possible comparison. For example, when a study had two

171 intervention groups (A and B) and one control group (C), we compared A vs. C and B  
172 vs. C, and reported the results as two separate study comparisons. This procedure is  
173 in accordance with the Cochrane handbook.<sup>25</sup>

#### 174 ***Narrative synthesis of results***

##### 175 *Between–group difference*

176 We assessed the effect of knee joint loading exercise as positive ('+') or negative ('-')  
177 when a statistically significant ( $P < 0.05$ ) improvement or decline in the outcome of  
178 interest was reported for the overall cartilage or at least one of the cartilage  
179 compartments assessed in the intervention group compared with the control group. If  
180 none of the compartments showed an increase or a decrease in the outcome of  
181 interest, we reported this finding as no effect ('=').

182 Increased T2 values have been associated with deteriorated collagen orientation and  
183 increased hydration<sup>28 29</sup>, which is considered to have a negative impact on the  
184 cartilage. Therefore, we reported increased T2 values as negative ('-') and decreased  
185 T2 values as positive ('+') for the cartilage. A decrease in cartilage thickness/volume  
186 was interpreted as negative for the cartilage. Accordingly, an increase in cartilage  
187 thickness/volume was interpreted as potentially beneficial. However, the proof of a  
188 positive effect on cartilage volume/thickness would need additional information, since  
189 increased cartilage volume/thickness may also be related to the growth of the  
190 subchondral bone for example.

##### 191 *Within–group difference*

192 Additionally, we investigated within-group differences assessing the effect of knee  
193 joint loading exercise as positive ('+') or negative ('-') when an improvement or a  
194 decline in the outcome of interest was reported between pre and post intervention,  
195 and as no effect ('=') if none of the compartments showed an increase or a decrease  
196 in the outcome of interest.

197 ***Overall quality of evidence***

198 *Risk of bias*

199 Study quality was assessed by rating the risk of selection bias, performance bias,  
200 detection bias, attrition bias, reporting bias and other sources of bias. Two reviewers  
201 (AB and CJ) independently assessed whether each of the following domains was  
202 adequate (e.g. low, unclear, or high risk of bias): 'sequence generation', 'allocation  
203 concealment', 'blinding', 'incomplete outcome data addressed', 'selective outcome  
204 reporting' or 'other bias' (e.g. funding) <sup>25</sup>. Disagreements in initial ratings of  
205 methodological quality assessment were discussed between the two reviewers until  
206 consensus was reached.

207 *Knee joint loading exercise quality assessment*

208 Based on a combination of theoretical and clinical considerations, two of the authors  
209 (CJ and EMR) independently assessed the anticipated impact of the knee joint  
210 loading interventions on cartilage (low, moderate or high) and if the dose was  
211 considered adequate to presume positive cartilage modifications were possible. High  
212 impact activities (e.g. jumping) <sup>30</sup> and participation in sports <sup>15</sup> is associated with  
213 cartilage deformation and increased risk of radiographic OA. Similarly, lack of knee  
214 joint loading in the form of knee immobilisation <sup>31</sup> or sedentary behaviour<sup>19 20</sup> is  
215 associated with detrimental cartilage changes. Therefore, interventions including  
216 activities being considered outside the therapeutic loading spectrum were assessed  
217 as inadequate to promote cartilage health. Accordingly, the anticipated impact was  
218 considered to be too high in interventions focusing on jumping and too low in aquatic  
219 exercise.

220 *The GRADE assessment*

221 The overall quality of evidence for the estimates was evaluated using the GRADE  
222 (Grading of Recommendations Assessment, Development and Evaluation) approach.

223 The GRADE is a systematic approach to rate the quality of evidence across studies  
224 for specific outcomes. It is based on five domains that involve the methodological  
225 flaws of the studies (i.e. risk of bias), the heterogeneity of results across studies (i.e.  
226 inconsistency), the generalizability of the findings to the target population (i.e.  
227 indirectness), the precision of the estimates and the risk of publication bias.

228

229 **FIGURE 1.**

230

231 RESULTS

232 ***Study selection and characteristics***

233 The literature search identified a total of 2,868 unique publications, of which 21  
234 individual RCTs were identified as potentially eligible. Ultimately, we included nine  
235 papers, involving 14 study comparisons. MRI-assessed cartilage morphometry was  
236 investigated in four <sup>32-33</sup>, cartilage morphology in three <sup>34-36</sup> and cartilage composition  
237 in seven comparisons <sup>37-40</sup>. One study was reported in two different papers <sup>37 41</sup>.  
238 Multanen et al. <sup>37</sup> reported findings in the tibiofemoral compartment and Koli et al. <sup>41</sup>  
239 in the patellofemoral compartment of the same participants following the same  
240 exercise intervention. We included both papers and counted them as one study with  
241 two study comparisons, as suggested in the Cochrane guidelines <sup>25</sup>.

242 Two study comparisons investigated the effect of knee joint loading exercise in  
243 participants at increased risk of developing OA: one in participants having had  
244 arthroscopic partial meniscectomy <sup>28</sup> and the other in overweight or obese  
245 participants <sup>36 40</sup>. Twelve study comparisons focused on participants with OA <sup>32-35 37-39</sup>  
246 <sup>41</sup>.

247 ***Participant characteristics***

248 The overall number of participants in the included studies was 702, with a mean age  
249 (SD) of 57.7 years (6.5) and a mean BMI (Kg/m<sup>2</sup>) (SD) of 29.5(4.4). The overall  
250 percentage of women was 81.7%, (Table 1).

251 **TABLE 1.** Studies included in the qualitative synthesis. ROI= region of interest; TF=tibiofemoral; M=medial; L=lateral; P=patella; ROA= Radiographic knee  
 252 osteoarthritis; OA= osteoarthritis; KL= Kellgren-Lawrence scale; IG= intervention group; CG= control group. ACR= American College of Rheumatology.<sup>42</sup>

STUDY CHARACTERISTICS			PARTICIPANT CHARACTERISTICS			
Author and year	Study location	Inclusion criteria	Participants included (IG/CG)	Women %	Age (year) Mean (SD)	BMI (Kg/m <sup>2</sup> ) Mean (SD)
Armagan et al. 2015	Eskisehir, Turkey	with OA (ACR criteria)	30/40	68%	56 (0.6)	30.9 (0.2)
Dincer et al. 2016	Istanbul, Turkey	with OA (ACR criteria)	19/16	80%	51 (2.4)	28.6 (0.8)
Henriksen et al. 2014	Copenhagen, Denmark	with OA (osteophytes and/or joint space narrowing assessed by a radiologist)	59/63	-	64 (0.8)	37.2 (0.7)
Hunter et al. 2015	North Carolina, USA	with OA (RKOA KL 2 or 3, BMI of 27 to 37 and sedentary (<30 min exercise/week in the past 6 months)	36/33	72%	66 (6)	33,6 (3.7)
Landsmeer et al. 2016	Rotterdam, Holland	Risk of OA (Overweight/obese with no clinical knee OA according to ACR criteria)	87/87	100%	56 (3.2)	32.3 (4.2)
Multanen et al. 2014 and Koli et al. 2015	Jyväskylä, Finland	with OA (Symptomatic and RKOA KL 1 or 2)	40/40	100%	58 (4.2)	26.9
Munukka et al. 2016	Jyväskylä, Finland	with OA (Symptomatic and RKOA KL 1 or 2)	43/44	100%	64 (2)	27 (0.3)
Ochiai et al. 2014	Chiba, Japan	with OA (RKOA KL 1,2,3)	9/11	100%	59 (0.7)	22.7 (1)
Roos and Dahlberg 2005	Malmö, Sweden	Risk of OA (Patients having had meniscectomy)	22/23	33.30%	46 (3.3)	26.6 (3.2)

253

254

255 **TABLE 2.** Exercise therapy and outcome characteristics of included studies. ROI= region of interest; TF=tibiofemoral; M=medial; L=lateral; P=patella; /Week=  
 256 times per week; min= minutes; WB= weight bearing; \*=too little information available; \*\*=No serious adverse events were reported. Adequate/inadequate=the  
 257 anticipated mechanical stimuli to the cartilage generated from the knee joint exercise intervention was considered of adequate (moderate) impact/of too high  
 258 or too low impact to promote beneficial cartilage health.

KNEE JOINT LOADING EXERCISE CHARACTERISTICS					OUTCOMES CHARACTERISTICS		EXERCISE QUALITY		
Study comparisons	Type	Frequency and duration	Exercise sessions attended /scheduled sessions (n and %)	Non-serious adverse events in the intervention group**	ROI	Outcomes	Anticipated impact on cartilage	Adequate/ Inadequate	
Armagan et al. 2015	Home exercise therapy vs. Oral glucosamine sulphate	WB and non-WB (Quadriceps and hamstring strengthening and dynamic stair step exercises)	24 weeks	-	-	TFML	<b>Morphology</b> (Semi-quantitative scoring)	Low to moderate	Undeterminable*
Dincer et al. 2016	Supervised and home exercise, TENS and hot pack vs. TENS and hot-pack	WB (Closed kinetic chain exercises, transcutaneous electrical nerve stimulation (TENS) and hot-pack)	5 T/W 30 min 12 weeks	-	n=2 (Increase knee pain), n=1 (increase blood pressure)	TFML and P	<b>Morphometry</b> (Thickness and volume)	Low to moderate	Inadequate
Henriksen et al. 2014	Supervised and home exercise vs. Non-exposed group	WB (Circuit training)	3 T/W 60 min 16 weeks	n=7/47 15%	-	TFML	<b>Morphology</b> (Semi-quantitative scoring)	Moderate	Adequate
Hunter et al. 2015	Supervised and home exercise & diet vs. Diet only	WB (Aerobic walking, strength training)	3 T/W 60 min 72 weeks	n=142/216 64%	n=1 (muscle strain), n=2 (trips/falls)	TFM	<b>Morphometry</b> (Thickness and volume)	Low to moderate	Adequate

Landsmeer et al. 2016	Supervised Exercise and diet vs. Oral placebo supplementation	WB (Nordic walking, volleyball, bowling, salsa dancing, tai chi, softball, belly dance and modern dance)	1 T/W 60 min 20 weeks	n=7/20 35%	n=2 (side effects non-specified)	TFML and P	<b>Morphology</b> (Semi-quantitative scoring)	Low	Inadequate
Multanen et al. 2014	Supervised exercise therapy vs. Non-exposed group	WB (Aerobic, step aerobics and jumping exercise)	3 T/W 55 min 48 weeks	n=98/144 68%	-	TF anterior posterior central	<b>Composition</b> (GAG via dGEMRIC, Collagen via T2-mapping)	High	Inadequate
Koli et al. 2015	Same as Multanen	Same as Multanen	Same as Multanen	Same as Multanen	Same as Multanen	Patellar	<b>Composition</b> (Collagen via T2-mapping)	Same as Multanen	Same as Multanen
Munukka et al. 2016	Supervised exercise therapy vs. Non-exposed group	Non-WB (aquatic exercise therapy)	3 T/W 60 min 16 weeks	n=42/48 88%	n=2 (bilateral knee pain and dyspnoea)	TF anterior posterior central	<b>Composition</b> (GAG via dGEMRIC, Collagen via T2-mapping)	Low	Inadequate
Ochiai et al. 2014	Home exercise vs. Local heat treatment	Non-WB (2 sets of straight leg raise, abductor training, and adductor training (20 reps per set) in the morning and evening every day)	14 T/W - 12 weeks	-	n=1 (dizziness during exercise therapy)	TFML	<b>Composition</b> (Collagen via T2-mapping)	Low	Inadequate
Roos and Dahlberg 2005	Supervised individually progressed exercise therapy vs. Non-exposed group	WB (Weight-bearing neuromuscular exercises)	1-5/Week 60 min 16 weeks	n=31/54 54%	-	F central/posterior	<b>Composition</b> (GAG via dGEMRIC)	Moderate	Adequate

259

260

261 ***Outcome measures***

262 In the two study comparisons including participants at risk of OA, articular cartilage  
263 was assessed as cartilage morphology using the semi-quantitative MRI Osteoarthritis  
264 Knee Score (MOAKS) scoring system <sup>36</sup>, and cartilage composition as GAG via  
265 dGEMRIC index <sup>40</sup>.

266 In the 12 study comparisons focusing on participants with established OA, articular  
267 cartilage was assessed using cartilage morphometry in four <sup>32</sup> and morphology with  
268 semi-quantitative scoring systems in three <sup>33-35</sup>. Cartilage composition was assessed  
269 in seven comparisons as GAG via dGEMRIC <sup>37 38</sup> or collagen via T2–mapping <sup>37-39 43</sup>.

270 Detailed characteristics of participants and outcome measure characteristics are  
271 reported in Table 2.

272 ***Knee joint loading exercise interventions***

273 Knee joint loading exercise interventions differ substantially among studies. All but  
274 one of the included trials tested the effect of a therapeutic exercise program. One  
275 trial tested the effect from a general physical activity program in which participants  
276 were encouraged to take part in physical activity classes, for example, Nordic-  
277 walking, volleyball or modern dance".<sup>36</sup> Furthermore, all the included studies  
278 compared a knee joint loading exercise intervention to a non-exercising control group  
279 treatment such as local heat or oral glucosamine. Detailed characteristics of knee  
280 joint loading exercise interventions are reported in Table 2.

281

282 ***Narrative synthesis of results***

283 Meta-analysis was not considered appropriate because of the substantial  
284 heterogeneity between study interventions, patient characteristics and outcome  
285 variables.<sup>44</sup> Instead, we summarised the results of these studies narratively, to  
286 provide a clear critical appraisal of the evidence, as recommended by the guidelines  
287 on the conduct of narrative synthesis in systematic reviews.<sup>45</sup>

288 *Between-group difference in participants at risk of OA*

289 In the participants at risk of OA, one study comparison in overweight women with a  
290 mean age of 56 years reported no effect on cartilage defects (MOAKS) <sup>36</sup> and one in  
291 mostly men with a mean age of 46 years, having had arthroscopic partial  
292 meniscectomy, reported positive cartilage composition changes on GAG as  
293 assessed from dGEMRIC <sup>40</sup>.

294 *Between-group difference in participants with established OA*

295 In participants with established OA, six study comparisons found no effect of knee  
296 joint loading exercise on cartilage thickness, volume or defects <sup>32-35</sup>, one study  
297 comparison reported no effect <sup>37</sup> on GAG and one reported a negative effect on the  
298 cartilage composition of the medial condyle of the femur, both assessing GAG via  
299 dGEMRIC <sup>38</sup>. On the contrary, the same knee joint loading exercise intervention that  
300 reported negative effects on GAG also reported a positive effect on collagen  
301 assessed using T2-mapping in the cartilage of the posterior medial femoral condyle  
302 and central medial tibial condyle <sup>38</sup>. Two publications from the same RCT reported a  
303 positive effect on collagen T2-mapping in the patellar cartilage <sup>41</sup> and no effect on  
304 the cartilage of the medial condyle of the femur <sup>37</sup>. Lastly, one study comparison  
305 reported no effect <sup>37 39</sup> on collagen T2-mapping <sup>39</sup> (Table 3).

306



313 *Within-group difference*

314 The within-group differences analysis investigating articular cartilage changes pre to  
315 post intervention (within-group findings), showed that knee joint loading exercise  
316 increased cartilage volume <sup>32</sup>, and had a positive effect on cartilage defects (SPRG)  
317 in the medial femoral condyle <sup>34</sup> and on GAG in the medial and lateral compartment  
318 of the femur and lateral compartment of the tibia <sup>37 40</sup>. Furthermore, positive effects  
319 were also reported on the patellar cartilage <sup>41</sup> and on the posterior medial femoral  
320 condyle and central medial tibial condyle <sup>38</sup>. There was only one negative within-  
321 group finding out of 14 comparisons.

322 *Sub-group analysis on cartilage compartment*

323 Three out of nine studies, assessed the effect of knee joint loading exercise on the  
324 patellar compartment in addition to the tibiofemoral compartment.<sup>32 36 43</sup> In one  
325 study,<sup>36</sup> the patellar and tibiofemoral compartment were combined for the  
326 assessment of exercise on cartilage health, not allowing for comparisons of different  
327 cartilage compartments. In contrast, two studies <sup>32 43</sup> analysed the patellar and  
328 tibiofemoral compartments separately. One study reported a beneficial effect on the  
329 collagen matrix in the patellar but not in the tibiofemoral compartment, <sup>43</sup> and another  
330 study reported no effect in cartilage volume or thickness for the patellar and  
331 tibiofemoral compartment.<sup>32</sup>

332 *Impact of sex on cartilage health*

333 We found no indication of difference in the effect of exercise on cartilage health  
334 between the sexes. Four studies, seven study comparisons, included only women, of  
335 which two study comparisons reported a positive effect on collagen,<sup>38 43</sup> one reported  
336 a negative effect on glycosaminoglycans <sup>38</sup> and four reported no effect of knee joint  
337 loading exercise on cartilage health.<sup>36 37 39</sup>

338 Five studies, seven study comparisons, included both men and women, of which one  
339 reported a beneficial effect on glycosaminoglycans <sup>40</sup> and six reported no effect of  
340 knee joint loading exercise on cartilage health (Table 3).<sup>32 34 35</sup>

#### 341 **Quality of evidence**

##### 342 *Risk of bias*

343 Overall, the majority of the studies applied proper randomization, allocation and  
344 blinding of the outcome assessment. In contrast, all the studies failed to clearly  
345 report, or inadequately addressed, dropouts of participants in the analyses (attrition  
346 bias, Table 3).

##### 347 *Knee joint loading exercise quality*

348 When evaluated and rated independently by two of the co-authors (CJ and EMR),  
349 some of the exercise interventions were assessed as including activities being  
350 considered outside the therapeutic loading spectrum and therefore not necessarily  
351 adequate to promote positive articular cartilage (Table 2). This classification was  
352 purely done for descriptive purposes, and the number of studies did not allow for  
353 subgroup analyses.

##### 354 *The GRADE assessment*

355 The inadequacy of some knee joint loading interventions, the small number of  
356 studies and the few participants involved limits the generalizability of our findings.  
357 Therefore, due to this indirectness and imprecision, the overall quality of evidence  
358 was deemed low. (Appendix C).

359

360

361 **DISCUSSION**

362 Our findings suggest that knee joint loading exercise seems not to be harmful for  
363 articular cartilage in people at increased risk of, or with, knee OA. However, the  
364 quality of evidence was low.

365 ***Articular cartilage morphometry and morphology***

366 The inconclusive findings about knee joint loading and the impact on cartilage  
367 thickness, volume and defects may relate to the heterogeneity of the populations, the  
368 interventions studied, or the outcomes used. In fact, when evaluated and rated  
369 independently by two of the co-authors (CJ and EMR), not all the exercise  
370 interventions were assessed as adequate to promote positive articular cartilage  
371 changes. In some cases, the dose was considered too low and in one case, the type  
372 of exercise (jumps) was considered excessive for the cartilage of older women who  
373 had mild OA. Additionally, the compliance with the exercise interventions  
374 investigating cartilage morphometry or morphology was generally poor. The resulting  
375 inadequate mechanical stimuli could potentially be at least partly responsible for the  
376 lack of effect. On the other hand, MRI-based cartilage assessments have been  
377 shown to be sensitive enough to detect between-group morphometry and  
378 morphology changes in previous randomised studies using quantitative and semi-  
379 quantitative methods <sup>46</sup>. Nevertheless, in our review, the studies assessing cartilage  
380 with both quantitative and semi-quantitative methods failed to report a change for  
381 either method, suggesting the lack of positive effect was not due to poor  
382 responsiveness of the evaluation methods.

383 ***Articular cartilage composition***

384 It is well known that alterations in articular cartilage composition is a marker of early  
385 OA changes <sup>47</sup>. Negative changes in cartilage composition may therefore be  
386 expected to occur prior to changes in morphometry and morphology cartilage  
387 parameters <sup>48</sup>. None of the studies included in our review allowed for a comparison of

388 treatment effects on both structural and compositional changes of the cartilage.  
389 However, GAG and collagen assessed as dGEMRIC and T-2 mapping, respectively,  
390 were the only outcomes that showed a response to the treatment interventions,  
391 supporting the theory that these early OA markers are sufficiently sensitive to detect  
392 treatment effects in individuals with early or established OA. Nevertheless, six out of  
393 seven study comparisons found no effect or beneficial effect or beneficial effect on  
394 cartilage composition, highlighting that knee joint loading exercise seems to be at  
395 least safe in patients at increased risk of, or with, knee OA.

### 396 ***Limitations***

397 This study has some limitations. The heterogeneity of the interventions, patient  
398 characteristics and outcome variables did not support the use of a meta-analysis.  
399 Instead, in accordance with the Cochrane Handbook, we described our findings  
400 narratively.<sup>25</sup> Although, from a statistical point of view, there is no restriction on study  
401 number or similarity, it is important to consider the conceptual diversity of the  
402 included studies, for the meta-analysis to be meaningful for researchers, clinicians  
403 and patients.<sup>44</sup> Furthermore, the low compliance with the exercise interventions in  
404 studies investigating articular cartilage morphology and morphometry, limits the  
405 possibility of concluding whether exercise had a positive or negative impact on these  
406 outcome measures. Additionally, the included studies did not allow for comparison of  
407 different exercise programs and/or comparisons of specific cartilage compartments,  
408 since all studies included a non-exercising control arm and only two studies reported  
409 the patellofemoral compartment separately. Thus, our findings are restricted to the  
410 effect of increased knee joint loading from therapeutic exercise compared to no  
411 change in knee joint loading, particularly in the tibiofemoral compartment. As no  
412 meta-analysis was performed, precision, inconsistency and publication bias were  
413 based on the narrative synthesis of results. Finally, one trial included the control  
414 treatment of glucosamine<sup>34</sup> and another trial included a control of local heat

415 treatment.<sup>39</sup> Recent systematic reviews conclude that glucosamine does not impact  
416 cartilage health <sup>49 50</sup> and there is no evidence to suggest an effect of local heat  
417 treatment on articular cartilage.

#### 418 ***Implications for researchers and clinicians***

419 More high quality RCTs are needed to further investigate the impact of knee joint  
420 loading exercise on articular cartilage in patients at increased risk of, or with, knee  
421 OA. To increase the possibility of finding positive effects, available results suggest  
422 future studies need to focus on interventions in the form of supervised weight-bearing  
423 exercise therapy of sufficient dose in younger subjects at risk or in early stages of the  
424 disease, allowing for evaluation of cartilage composition with measures such as  
425 dGEMRIC and T2-mapping.

#### 426 **CONCLUSION**

427 We narratively summarized the impact of knee joint loading exercise on knee joint  
428 articular cartilage in the participants at risk of, or with, knee OA included in  
429 randomized controlled trials of exercise. Knee joint loading exercise seems not to  
430 harm articular cartilage in participants at increased risk of, or with, knee OA.  
431 However, the quality of evidence was low, including some interventions studying  
432 activities considered outside the therapeutic loading spectrum to promote cartilage  
433 health.

434

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439 *Figure legends*

440 **Figure 1.** Flow chart of the included studies in the systematic reviews.

## REFERENCES

1. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Annals of the rheumatic diseases* 2014;73(7):1323-30. doi: 10.1136/annrheumdis-2013-204763 [published Online First: 2014/02/21]
2. Wallace IJ, Worthington S, Felson DT, et al. Knee osteoarthritis has doubled in prevalence since the mid-20th century. *Proc Natl Acad Sci U S A* 2017;114(35):9332-36. doi: 10.1073/pnas.1703856114 [published Online First: 2017/08/16]
3. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;380(9859):2163-96. doi: 10.1016/S0140-6736(12)61729-2 [published Online First: 2012/12/19]
4. Salmon JH, Rat AC, Sellam J, et al. Economic impact of lower-limb osteoarthritis worldwide: a systematic review of cost-of-illness studies. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2016;24(9):1500-8. doi: 10.1016/j.joca.2016.03.012 [published Online First: 2016/04/02]
5. Felson DT. Osteoarthritis as a disease of mechanics. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2013;21(1):10-5. doi: 10.1016/j.joca.2012.09.012 [published Online First: 2012/10/09]
6. Robinson WH, Lepus CM, Wang Q, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. *Nature Reviews Rheumatology* 2016;12(10):580-92. doi: 10.1038/nrrheum.2016.136
7. Buckwalter JA. Sports, joint injury, and posttraumatic osteoarthritis. *J Orthop Sport Phys* 2003;33(10):578-88. doi: DOI 10.2519/jospt.2003.33.10.578
8. Muthuri SG, McWilliams DF, Doherty M, et al. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2011;19(11):1286-93. doi: 10.1016/j.joca.2011.07.015 [published Online First: 2011/09/03]
9. Lohmander LS, Ostenberg A, Englund M, et al. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis and rheumatism* 2004;50(10):3145-52. doi: 10.1002/art.20589 [published Online First: 2004/10/12]
10. Brown TD, Johnston RC, Saltzman CL, et al. Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. *J Orthop Trauma* 2006;20(10):739-44. doi: 10.1097/01.bot.0000246468.80635.ef [published Online First: 2006/11/16]
11. Quicke JG, Foster NE, Thomas MJ, et al. Is long-term physical activity safe for older adults with knee pain?: a systematic review. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2015;23(9):1445-56. doi: 10.1016/j.joca.2015.05.002 [published Online First: 2015/05/25]
12. Juhl C, Christensen R, Roos EM, et al. Impact of exercise type and dose on pain and disability in knee osteoarthritis: a systematic review and meta-

- regression analysis of randomized controlled trials. *Arthritis & rheumatology (Hoboken, NJ)* 2014;66(3):622-36. doi: 10.1002/art.38290 [published Online First: 2014/02/28]
13. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2014;22(3):363-88. doi: 10.1016/j.joca.2014.01.003 [published Online First: 2014/01/28]
  14. Roos EM, Juhl CB. Osteoarthritis 2012 year in review: rehabilitation and outcomes. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2012;20(12):1477-83. doi: 10.1016/j.joca.2012.08.028 [published Online First: 2012/09/11]
  15. Fernandes GS, Parekh SM, Moses J, et al. Prevalence of knee pain, radiographic osteoarthritis and arthroplasty in retired professional footballers compared with men in the general population: a cross-sectional study. *Br J Sports Med* 2017 doi: 10.1136/bjsports-2017-097503 [published Online First: 2017/11/05]
  16. Tveit M, Rosengren BE, Nilsson JA, et al. Former Male Elite Athletes Have a Higher Prevalence of Osteoarthritis and Arthroplasty in the Hip and Knee Than Expected. *Am J Sport Med* 2012;40(3):527-33. doi: 10.1177/0363546511429278
  17. Jorgensen AE, Kjaer M, Heinemeier KM. The Effect of Aging and Mechanical Loading on the Metabolism of Articular Cartilage. *J Rheumatol* 2017;44(4):410-17. doi: 10.3899/jrheum.160226
  18. Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. *Nature Reviews Rheumatology* 2016;12(2):92-101. doi: 10.1038/nrrheum.2015.135
  19. Munukka M, Waller B, Hakkinen A, et al. Physical Activity Is Related with Cartilage Quality in Women with Knee Osteoarthritis. *Med Sci Sport Exer* 2017;49(7):1319-26. doi: 10.1249/Mss.0000000000001238
  20. Lin W, Alizai H, Joseph GB, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2013;21(10):1558-66. doi: 10.1016/j.joca.2013.06.022 [published Online First: 2013/07/09]
  21. Wondrasch B, Risberg MA, Zak L, et al. Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle: a prospective, randomized controlled study presenting MRI-based and clinical outcomes after 5 years. *The American journal of sports medicine* 2015;43(1):146-53. doi: 10.1177/0363546514554910 [published Online First: 2014/11/08]
  22. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage - A four-month, randomized controlled trial in patients at risk of osteoarthritis. *Arthritis and rheumatism* 2005;52(11):3507-14. doi: 10.1002/art.21415
  23. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Annals of the rheumatic diseases* 1957;16(4):494-502. [published Online First: 1957/12/01]
  24. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.

- Public health reports (Washington, DC : 1974)* 1985;100(2):126-31. [published Online First: 1985/03/01]
25. Higgins JPea. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). *The Cochrane Collaboration; 2011* 2011
  26. de Vries RB, Hooijmans CR, Tillema A, et al. Updated version of the Embase search filter for animal studies. *Lab Anim* 2014;48(1):88. doi: 10.1177/0023677213494374
  27. Hooijmans CR TA, Leenaars M, Ritskes-Hoitinga M. Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. *Lab Anim* 2010; 44: 170-175 2010
  28. Lammentausta E, Kiviranta P, Nissi MJ, et al. T2 relaxation time and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) of human patellar cartilage at 1.5 T and 9.4 T: Relationships with tissue mechanical properties. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* 2006;24(3):366-74. doi: 10.1002/jor.20041 [published Online First: 2006/02/16]
  29. Nieminen MT, Rieppo J, Toyras J, et al. T2 relaxation reveals spatial collagen architecture in articular cartilage: a comparative quantitative MRI and polarized light microscopic study. *Magnetic resonance in medicine* 2001;46(3):487-93. [published Online First: 2001/09/11]
  30. Eckstein F, Lemberger B, Gratzke C, et al. In vivo cartilage deformation after different types of activity and its dependence on physical training status. *Annals of the rheumatic diseases* 2005;64(2):291-95. doi: 10.1136/ard.2004.022400
  31. Mutsuzaki H, Nakajima H, Wadano Y, et al. Influence of Knee Immobilization on Chondrocyte Apoptosis and Histological Features of the Anterior Cruciate Ligament Insertion and Articular Cartilage in Rabbits. *Int J Mol Sci* 2017;18(2) doi: 10.3390/ijms18020253 [published Online First: 2017/01/31]
  32. Dincer U, Ariba S, Saygin H, et al. The effects of closed kinetic chain exercise on articular cartilage morphology: Myth or reality? A randomized controlled clinical trial. *Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi* 2016;62(1):28-36. doi: <http://dx.doi.org/10.5606/tftrd.2016.93899>
  33. Hunter DJ, Beavers DP, Eckstein F, et al. The Intensive Diet and Exercise for Arthritis (IDEA) trial: 18-month radiographic and MRI outcomes. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2015;23(7):1090-8. doi: 10.1016/j.joca.2015.03.034 [published Online First: 2015/04/19]
  34. Armagan O, Yilmazer S, Calisir C, et al. Comparison of the symptomatic and chondroprotective effects of glucosamine sulphate and exercise treatments in patients with knee osteoarthritis. *Journal of Back & Musculoskeletal Rehabilitation* 2015;28(2):287-93 7p. doi: 10.3233/BMR-140516
  35. Henriksen M, Christensen R, Hunter DJ, et al. Structural changes in the knee during weight loss maintenance after a significant weight loss in obese patients with osteoarthritis: a report of secondary outcome analyses from a randomized controlled trial. *Osteoarthritis and cartilage / OARS,*

- Osteoarthritis Research Society* 2014;22(5):639-46. doi: 10.1016/j.joca.2014.03.003 [published Online First: 2014/03/19]
36. Landsmeer ML, Runhaar J, van der Plas P, et al. Reducing progression of knee OA features assessed by MRI in overweight and obese women: secondary outcomes of a preventive RCT. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2016;24(6):982-90. doi: 10.1016/j.joca.2015.12.016 [published Online First: 2016/01/10]
  37. Multanen J, Nieminen MT, Häkkinen A, et al. Effects of high-impact training on bone and articular cartilage: 12-month randomized controlled quantitative MRI study. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 2014; 29(1).
  38. Munukka M, Waller B, Rantalainen T, et al. Efficacy of progressive aquatic resistance training for tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis: a randomised controlled trial. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2016 doi: 10.1016/j.joca.2016.05.007 [published Online First: 2016/05/24]
  39. Ochiai S, Watanabe A, Oda H, et al. Effectiveness of thermotherapy using a heat and steam generating sheet for cartilage in knee osteoarthritis. *Journal of physical therapy science* 2014;26(2):281-4. doi: 10.1589/jpts.26.281 [published Online First: 2014/03/22]
  40. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis and rheumatism* 2005;52(11):3507-14. doi: 10.1002/art.21415 [published Online First: 2005/11/01]
  41. Koli J, Multanen J, Kujala UM, et al. Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. [Article]. *Medicine & Science in Sports & Exercise* September 2015;47(9):1767-74.
  42. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and rheumatism* 1986;29(8):1039-49. [published Online First: 1986/08/01]
  43. Koli J, Multanen J, Kujala UM, et al. Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. *Medicine and science in sports and exercise* 2015;47(9):1767-74. doi: 10.1249/mss.0000000000000629 [published Online First: 2015/02/11]
  44. Matthias Egger GDS, Douglas G Altman. Systematic Reviews in Health Care: Meta-Analysis in Context, Second Edition. *BMJ Publishing Group* 2008
  45. Popay J RH, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. a product from the ESRC methods programme. *ESRC* 2006
  46. Lohmander LS, Hellot S, Dreher D, et al. Intraarticular sprifermin (recombinant human fibroblast growth factor 18) in knee osteoarthritis: a randomized, double-blind, placebo-controlled trial. *Arthritis & rheumatology (Hoboken, NJ)* 2014;66(7):1820-31. doi: 10.1002/art.38614 [published Online First: 2014/04/18]

47. Migliore A, Massafra U. Towards the identification of early stage osteoarthritis. *Clinical cases in mineral and bone metabolism : the official journal of the Italian Society of Osteoporosis, Mineral Metabolism, and Skeletal Diseases* 2014;11(2):114-6. [published Online First: 2014/10/07]
48. Guermazi A, Alizai H, Crema MD, et al. Compositional MRI techniques for evaluation of cartilage degeneration in osteoarthritis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2015;23(10):1639-53. doi: 10.1016/j.joca.2015.05.026 [published Online First: 2015/06/09]
49. Wandel S, Juni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 2010;341:c4675. doi: 10.1136/bmj.c4675 [published Online First: 2010/09/18]
50. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis - art. no. CD002946.pub2. *Cochrane Db Syst Rev* 2005(2) doi: ARTN CD002946  
10.1002/14651858.CD002946.pub2