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Permalink

https://escholarship.org/uc/item/50k2372b

Journal

Osteoarthritis and Cartilage, 24(12)

ISSN

1063-4584

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Publication Date

2016-12-01

DOI

10.1016/j.joca.2016.07.004

Peer reviewed

Accepted Manuscript

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Please cite this article as: Goldman LH, Tang K, Facchetti L, Heilmeier U, Joseph GB, Nevitt MC, McCulloch CE, Souza RB, Link TM, Role of thigh muscle cross-sectional area and strength in progression of knee cartilage degeneration over 48 months – Data from the Osteoarthritis Initiative, *Osteoarthritis and Cartilage* (2016), doi: 10.1016/j.joca.2016.07.004.
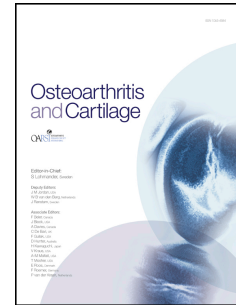
Manuscript Title: Role of thigh muscle cross-sectional area and strength in progression of knee cartilage degeneration over 48 months – Data from the Osteoarthritis Initiative

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Manuscript Type: Original Research

Objective: To determine in a 48-month longitudinal study the association of thigh muscle cross-sectional area (CSA) and strength on progression of morphologic knee cartilage degeneration using 3T magnetic resonance imaging (MRI).

Design: Seventy Osteoarthritis Initiative (OAI) subjects aged 50-60 years, with no radiographic evidence of osteoarthritis (OA) and constant muscle strength over 48 months as measured by isometric knee extension testing were included. Baseline right thigh muscle CSAs were assessed on axial T1-weighted MR images, and extensor to flexor CSA ratios were calculated. Degenerative knee abnormalities at baseline and 48-months were graded on right knee 3T MRIs using a modified whole organ MRI score (WORMS). Statistical analysis employed Student's t-tests and multivariable regression models adjusted for age, body mass index and gender.

Results: Extension strength was significantly and positively correlated with baseline thigh muscle CSA (r=0.65, p<0.001). Greater baseline total thigh muscle CSA was significant associated with increase of cartilage WORMS scores over 48 months in patellar (p=0.027) and trochlear (p=0.038) compartments, but not in other knee compartments. Among specific muscle groups, CSA of extensors (p=0.021) and vastus medialis (VM) (p=0.047) were associated with patellar cartilage increase in WORMS. Baseline E/F ratio had a significant positive association with patellar WORMS cartilage score increase over 48 months, p=0.0015. There were no other significant associations between muscle CSA/ratios and increase in WORMS scores.

Conclusion: Maintenance of proper extensor to flexor muscle balance about the knee through decreased E/F ratios may slow patellofemoral cartilage deterioration, while higher extensor and VM CSA may increase patellofemoral cartilage loss.

1 **Introduction**

2 Conservative treatment modalities for knee osteoarthritis (OA) are limited, despite the

3 fact that radiographic knee OA affects nearly 19% of the general population [1]. Invasive

4 treatments such as total knee arthroplasty (TKA), while having successful short- to

5 intermediate-term outcomes, can often be prone to late failure, with reported revision

6 rates of up to 18.9% at 15 years [2]. For this reason, a focus has been placed on OA

7 prevention and identification of modifiable risk factors in the treatment of knee OA.

8 Part of this focus has turned to the role played by knee stability, and specifically

9 static and dynamic stabilizers of the knee. The integrity of static stabilizers (i.e. bones,

10 ligaments) of the knee has been implicated as protective against degenerative disease of

11 the cartilage [3]. Recent literature has turned to the importance of dynamic stabilizers of the

12 knee as well, with studies showing associations of increased muscle strength about the

13 knee joint with both increased risk and a protective effect with respect to knee OA

14 progression [4-10]. However there is currently no firm agreement regarding the basis of

15 these associations, or the definitive recommendations that should be derived from them

16 with regards to the role of muscle strength in prevention of knee OA progression.

17 Previous studies exploring the relationship between thigh muscle and knee OA

18 progression have mostly used strength testing measures, which can be exceedingly

19 limited in terms of reliability and validity as they are prone to patient effort and comfort

20 levels, to characterize muscle strength in study subjects. Muscle cross-sectional area

21 (CSA) can be accurately and objectively quantified using magnetic resonance (MR)

22 imaging, and this has been shown in several studies to have a close correlation with

23 muscle strength measurements [10, 11]. However, few previous studies have used this

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24   technology for characterizing and quantifying muscle strength when evaluating its

25   relationship to osteoarthritis progression [12-14].

26   The purpose of our study was to determine the relationship between baseline

27   muscle CSA and strength with longitudinal progression of degenerative, morphologic

28   abnormalities of the knee joint in individuals with stable muscle strength over four years

29   and no signs of radiographic osteoarthritis in the tibiofemoral joint. An additional focus

30   of our study was to examine the role that imbalance of agonist and antagonist thigh

31   muscle groups potentially plays in the progression of degenerative changes of the knee

32   joint.

33

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34 **Materials and Methods**

35 *Subjects*

36 Seventy individuals from the Osteoarthritis Initiative (OAI) incidence and progression

37 cohorts were included in this study as outlined in Figure 1. All subjects included had risk

38 factors for OA without symptomatic knee OA in at least one knee. Risk factors included

39 previous knee injury or surgery, family history of TKA, Heberden's nodes, or knee

40 symptoms within the past 12 months. All subjects provided informed consent. The study

41 was HIPAA-compliant and approved by the local committees on human research.

42 Inclusion criteria were no radiographic OA defined by a Kellgren-Lawrence (KL) grade

43 of 0 or 1 [15]. To minimize the effect of age as a confounding variable, only subjects age

44 50-60 years were included. Exclusion criteria were those implemented by the OAI and

45 included contraindications to MR imaging, bilateral end-stage OA, inflammatory

46 arthritis, pregnancy, and co-morbidities that could interfere with study participation [16, 17].

47 As part of the clinical data collection for the OAI, maximum extension strength

48 was measured using an isometric force testing chair at each visit. Patients who endorsed

49 being limited in strength measurement due to pain were excluded, as were patients who

50 did not have isometric strength testing performed at both baseline and 48-months. Only

51 patients who demonstrated less than 3% variability in extension strength testing were

52 included, in an effort to eliminate changes in muscle strength over time (and factors that

53 may contribute to these changes) as confounding variables in our relationship

54 assessments. A threshold of 3% variability was used because of previous studies which

55 report that 5% variability in muscle strength reflects significant changes in Western

56 Ontario and McMaster Universities (WOMAC) functional knee scores [18].

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57

58 *MR imaging*

59 MR imaging was obtained using identical 3T MRI systems (Trio, Siemens, Erlangen,

60 Germany). Identical knee coils were used for all studies. Four sequences were used for

61 image analysis: coronal intermediate-weighted (IW) 2D fast spin-echo (FSE) sequence

62 (echo time (TE) 29 ms, repetition time (TR) 3700 ms, slice thickness 3.0 mm, bandwidth

63 352 Hz/pixel), sagittal 2D IW FSE sequence with fat suppression (TE 30 ms, TR 3200

64 ms, slice thickness 3.0 mm, bandwidth 248 Hz/pixel), sagittal 3D dual-echo in steady

65 state (DESS) sequence (TE 4.7 ms, TR 16.3 ms, flip angle 25 degrees, slice thickness 0.7

66 mm, bandwidth 185 Hz/pixel) with axial multiplanar reconstruction. Further details about

67 image acquisition are provided in the OAI MR protocol [19].

68

69 *Semi-quantitative morphological imaging analysis*

70 All images were viewed on PACS workstations (Agfa, Ridgefield Park, NJ, USA).

71 Baseline and 48-month MR images were obtained of the right knee for all seventy

72 patients included in this study as part of the OAI database. Images were reviewed by a

73 radiologist with three years of experience who was blinded to the initial strength

74 measurement of the subjects. Unclear readings were reviewed by a second board-certified

75 musculoskeletal radiologist with 22 years of experience. Images were semi-quantitatively

76 graded based on the modified Whole Organ Magnetic Resonance Imaging Score

77 (WORMS) assessing morphologic lesions of cartilage, menisci, or ligaments, in addition

78 to presence of bone marrow edema pattern, loose bodies, subchondral cysts, effusion, or

79 popliteal cysts. Cartilage lesions were graded on a scale of 1 to 6, with 1 representing an

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80   intracartilaginous signal abnormality, 2 representing a partial thickness defect of the

81   cartilage surface measuring <1 cm, 2.5 representing a full-thickness cartilage defect

82   measuring <1 cm, 3 representing a partial thickness lesion measuring >1 cm but <75% of

83   the region, 4 representing diffuse cartilage thinning involving >75% of the region, 5

84   representing a full thickness lesion >1 cm but <75% of the region, and 6 involving

85   diffuse full thickness cartilage loss involving >75% of the region. The maximum

86   cartilage score was defined as the highest cartilage score from any measured

87   compartment (patella, trochlea, medial or lateral femur, or medial or lateral tibia).

88   Meniscal lesions were graded on a 5-point scale as normal (0), intrasubstance signal

89   abnormality (1), meniscal tear without deformity (2), meniscal tear with deformity (3), or

90   meniscal maceration (4). Ligament/tendon lesions were graded as normal (0), increased

91   surrounding signal abnormality (1), increased signal abnormality within the

92   tendon/ligament (2), partial tear (3), or complete tear (4). Subchondral bone marrow

93   edema pattern was graded as none (0), mild (<5 mm, grade 1), moderate (>5 mm but <20

94   mm, grade 2), or severe (>20 mm, grade 3). Loose bodies were graded as present or

95   absent. Subchondral cysts were graded as none (0), mild (<3 mm, grade 1), moderate (3-5

96   mm, grade 2), or severe (>5 mm, grade 3). Joint effusion was graded as none (0), mild

97   (<33% maximal distention, grade 1), moderate (33-66% maximal distention, grade 2), or

98   severe (>66% maximal distention, grade 3). Popliteal cysts were also graded on a 4-point

99   scale as none, mild, moderate, or severe [20].

100

101   *Baseline thigh muscle CSA measurements*

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102   Each included subject had standing full-length anterior-posterior radiographs of the right

103   femur obtained. The femoral length was measured from the intercondylar notch to the

104   superior femoral head. A T1W axial MR slice corresponding to the distal-middle third

105   junction of the femur based on the measurement obtained in full-length radiographs was

106   localized on the coronal MR scout view. This was considered the index slice for muscle

107   segmentation; two slices proximal were also segmented for a total of three slices. Manual

108   spline-based segmentation was performed using Matlab software (Figure 2). Eight

109   regions of interest were included for segmentation: rectus femoris, vastus medialis, vastus

110   lateralis, vastus intermedialis, biceps femoris (short head), biceps femoris (long head),

111   semitendinosus, and semimembranosus, and their CSAs were calculated as the average of

112   the CSAs in all segmented MR slices. Extensor CSA was calculated as the sum of the

113   individual CSAs of the rectus femoris, vastus medialis, vastus lateralis, and vastus

114   intermedialis. Flexor CSA was similarly calculated as the sum of the biceps femoris (long

115   and short heads), semitendinosus, and semimembranosus CSAs. Extensor flexor ratio

116   (E/F ratio) was calculated as the ratio of extensor to flexor CSA (Figure 3). MR images

117   were graded based on a Goutallier scale by one radiologist with three years of experience

118   as Grade 0 (no fatty streaks), Grade 1 (some fatty streaks), Grade 2 (more muscle than

119   fat), grade 3 (as much fat as muscle) and grade 4 (less muscle than fat) [21, 22]. A Goutallier-

120   derived correction factor was applied to the CSA values to obtain an adjusted value

121   accounting for intramuscular fat (Grade 0=1, Grade 1=0.90, Grade 2=0.85, Grade 3=0.82,

122   Grade 4=0.70, which is analogous to previously-published studies investigating the

123   relationship between Goutallier grade and fat composition [23, 24]).

124

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125   *Baseline patellofemoral alignment*

126   In order to determine the variation among our study population in terms of patellofemoral

127   alignment factors, each patient was assigned a value for patellofemoral alignment factors

128   including presence/absence of patella alta as defined by Insall-Salvati ratio of greater than

129   1.3 [25]. Presence of patellar tilt was defined as lateral facet angle less than 8 degrees.

130   Patellar subluxation was also assessed (determined through measurement of bisect

131   offset), and trochlear dysplasia as defined by sulcus angle greater than 145 degrees or

132   sulcus depth less than 3 mm was recorded [26].

133

134   *Statistical analyses*

135   Statistical analyses were performed using JMP software version 11 (SAS Institute, Cary,

136   NC, USA). Gender-specific Z-scores were calculated for each muscle CSA

137   compartment/ratio (total, extensors, flexors, VM, and E/F ratio). Multivariable linear

138   regression models adjusted for age, gender, and BMI were used to assess the relationship

139   between gender-specific Z-scores for compartmental muscle CSA/ratios (predictor

140   variables) and subcompartmental cartilage, BMEP, and meniscus WORMS scores

141   (outcome variables), after testing that the appropriate relevant assumptions had been met

142   (specifically regarding normality of variables, which was assessed using Q-Q plots).

143   Analysis of WORMS maximum cartilage score progression and non-progression

144   subgroups (where progression defined as WORMS maximum cartilage score increase $\geq$

145   1) was performed using Student's t-tests. Statistical significance was defined as $p<0.05$.

146   Our group has previously analyzed inter- and intra-reader reproducibility for

147   WORMS measurements in a subset of 15 participants with demonstration of high inter-

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148 observer reliabilities within various WORMS subcategories [19, 27, 28]. Coefficient of

149 variance (CV) for thigh muscle CSA has also been described previously in our group, and

150 was calculated as <2% for all regions of interest measured (vastus medialis, vastus

151 lateralis, vastus intermedialis, rectus femoris, biceps femoris-short head, biceps femoris-

152 long head, semimembranosus, and semitendinosus) [13]. Specifically, CV for total thigh

153 muscle CSA, quadriceps, hamstring, vastus medialis, and vastus lateralis were 0.72%,

154 0.92%, 0.96%, 1.34%, and 1.67%, respectively). Additionally, our group has recently

155 demonstrated high intra- and inter-observer agreement for semi-quantitative grading of

156 fat infiltration using Goutallier's classification (0.83 and 0.81, respectively) [23].

157

158

159 **Results**

160 *Subject characteristics*

161 Baseline demographic variables of the study population are depicted in Table 1. Seventy

162 patients were included, 47.1% of whom were male. Average body mass index was

163 27.5±4.3 kg/m^2. Average maximum right knee extension force among the study cohort

164 was 428.8±148.6 N, with an average speed of extension force of 580±465 N/s.

165 The majority of individuals had Goutallier grade 0 (40.0%, 28/70) or 1 (48.6%,

166 34/70). The remaining eight subjects had Goutallier grade 2. Baseline values for patellar

167 and patellofemoral joint WORMS were compared to previously published data from the

168 OAI normal control cohort, and the incidence of cartilage lesions of various WORMS

169 grades was not found to vary significantly [29].

170

171 *Baseline data*

172 Baseline maximum knee extension strength had a significant positive correlation with

173 both total CSA (r=0.64, 95% CI 0.48, 0.76, p<0.0001), and Goutallier-corrected total

174 CSA (r=0.65, 95% CI 0.49, 0.77, p<0.0001). No significant correlations were found

175 between baseline muscle strength and Goutallier grade, or between baseline PASE

176 (Physical Activity Scale for the Elderly) scores and extensor/flexor ratio.

177 There were no statistically significant relationships between baseline WORMS

178 score for any given cartilage compartment, and baseline muscle CSA for total thigh

179 muscle, extensor compartments, or vastus medialis (VM). However, baseline (and 48-

180 month) trochlear cartilage WORMS scores did have a significant positive association

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181 with E/F ratios (p=0.048 and p=0.031, respectively). Interestingly, CSA had a significant

182 association with meniscal WORMS score at baseline: individuals with lower CSA had

183 higher maximum meniscus WORMS scores for total CSA, flexor CSA, and extensor

184 CSA (p<0.05).

185

186 *Longitudinal data*

187 No significant difference was found regarding demographic and strength measurement

188 variables in groups that experienced increase in WORMS maximum cartilage scores

189 (defined as total 48-month increase $\geq$ 1, n=31) compared to those who had no increase

190 (change in maximum cartilage score equal to <1, n=38). With progression defined as an

191 increase in WORMS cartilage score of at least 1 over the study period, only baseline

192 Goutallier grade and E/F ratio were found to have a significant association with

193 progressive degeneration, with increased values for both being associated with increased

194 progression rate (p < 0.05). No other individual muscle group CSA values were found to

195 have a significant correlation with rate of progression.

196   Tables 2 and 3 summarize the results of a multiple linear regression model

197 adjusted for age, gender, and BMI, to investigate the associations between gender-

198 normalized muscle CSA and compartmental change in WORMS cartilage scores, as well

199 as global maximum cartilage, meniscus, and BMEP WORMS scores. No significant

200 associations were seen with regards to baseline muscle strength measurements and

201 longitudinal change in any WORMS score parameter. However, increase in patellar and

202 trochlear WORMS scores were found to be significantly positively associated with total

203 muscle CSA (p=0.027 and p=0.038, respectively) (Figure 4). Total extensor CSA and

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204 specifically VM CSA were similarly found to be significantly associated with increase in

205 patellar cartilage WORMS (p=0.021 and p=0.038, respectively). No other longitudinal

206 WORMS parameters reached significance. Similarly, vastus intermedialis and vastus

207 lateralis CSA were not found to have significant relationships with 48-month increase in

208 WORMS score. Baseline WOMAC scores were analyzed for correlation with both

209 changes in WORMS scores as well as baseline WORMS values for patellar cartilage and

210 maximum cartilage score, and no significant associations were found.

211 The strongest association demonstrated in our data pertained to the E/F ratio,

212 calculated as the ratio between the sum of the extensor CSA to the sum of the flexor

213 CSA. There was a strong positive association between E/F ratio and increase in patellar

214 WORMS over 48-months follow-up, p=0.0015 (Figures 4D and 5). Specifically,

215 differences between high and low E/F ratio groups demonstrate that the high E/F patients

216 experienced a nearly 1-grade increase in patellar cartilage WORMS scores on average.

217 To determine if our results were potentially influenced by varying Goutallier

218 grades, all analyses were repeated with the exclusion of the eight cases which were

219 classified as Goutallier grade 2 (i.e. only including Grades 0 or 1). The results obtained

220 did not vary significantly regarding associations between gender-normalized muscle CSA

221 and WORMS progression, thus confirming the validity of our analyses. Similarly, to

222 determine if results were influenced by patellar alignment factors (patella alta, patellar

223 tilt, patellar subluxation, or trochlear dysplasia), analyses were repeated with the

224 exclusion of outliers in these categories (one case with patella alta, five cases with

225 patellar tilt, three cases with patellar subluxation, and three cases with trochlear

226 dysplasia), and the results obtained again did not demonstrate significant variation.

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227   Of note, several longitudinal WORMS variables (48-month change in WORMS

228   scores) were found to be significantly correlated with baseline WORMS values,

229   specifically for maximum cartilage score (r=-0.263, p=0.029), meniscus (r=-0.266,

230   p=0.027), and BMEP (r=-0.419, p<0.001). For these variables, separate analyses were

231   performed in order to adjust for baseline WORMS values in addition to age, gender and

232   BMI. This additional adjustment did not result in a significant change with regards to

233   data provided in Tables 2 and 3.

234

235

236

237 **Discussion**

238 This study explores the longitudinal effects of muscle strength on changes in knee

239 cartilage degeneration in individuals with OA risk factors, but without preexisting

240 radiographic evidence of OA. Our study used objectively-assessed muscle CSA by 3T

241 MRI and objective maximal muscle force testing to find that individuals with no

242 radiographic knee OA but high extensor CSA have an increased rate of progression of

243 patellofemoral joint cartilage degeneration. Also notable is the role of increased extensor

244 CSA in relation to flexor CSA (E/F ratio), as this had the most significant association

245 with increased patellar cartilage deterioration over 48 months and could potentially

246 provide a target for management of individuals with increased risk for OA.

247 Our study found an association between increased total CSA of thigh musculature

248 with increase in WORMS scores over 48 months in trochlear and patellar regions. This is

249 especially interesting in light of the previously published literature, which is often

250 conflicting regarding the role of total thigh muscle strength in prevention or mitigation of

251 OA. Global muscle weakness has previously been shown to have a close association with

252 the development of OA in other load-bearing joints [30]. However, a recent study by

253 Ruhdorfer et al. failed to demonstrate a significant relationship between thigh muscle

254 CSA between knees with and without radiographic OA [12]. Some studies have suggested

255 that both knee flexion and extension strength weakness can themselves be associated with

256 knee OA [31, 32]. A recent study by Mikesky et al. in which patients without radiographic

257 knee OA underwent strength training of both hamstrings and quadriceps, demonstrated a

258 greater incident joint space narrowing in the strength training group, suggesting an

259 opposite effect of global muscle strength about the knee joint [33]. Another study by Visser

260   et al. supported this finding in demonstrating a positive correlation between skeletal

261   muscle mass and severity of knee OA [34]. Our study sheds light on the role that muscle

262   strength plays in OA because it examines individuals prior to the development of OA

263   symptoms, and shows that in this population, increased total thigh muscle CSA may

264   actually be associated with longitudinal worsening of trochlear and patellar cartilage

265   abnormalities.

266   A primary focus of this study concerned the specific role of extensor strength in

267   the development of knee OA. A detailed regression analysis yielded information

268   regarding the significant association between extensors as a group, and specifically the

269   vastus medialis, in worsening cartilage lesions of the patella. Previous literature related to

270   this topic is conflicting. Palmieri-Smith et al. have suggested that women with early OA

271   had *decreased* quadriceps strength compared to a non-OA cohort, and similarly, Amin et

272   al. have previously demonstrated a protective role of increased quadriceps strength as it

273   relates to cartilage loss of the lateral patella [6, 35]. Another recent study specific to patients

274   with malalignment of the knee demonstrated a detrimental effect of increased quadriceps

275   strength with respect to tibiofemoral OA progression risk [36]. Studies that used quantitative

276   MR imaging modalities such as muscle CSA and cartilage T2 quantification have also

277   demonstrated that the effect of improved extension strength is not necessarily beneficial.

278   In 2012, Pan et al. described increased vastus lateralis/vastus medialis CSA ratios as

279   being inversely related to T2 values of knee cartilage, suggesting that *decreased* vastus

280   medialis CSA (relative to vastus lateralis CSA) may actually be chondroprotective; this is

281   consistent with the results of our study [13].

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282   The strongest association demonstrated in our study involved increased E/F ratio

283   and patellar cartilage degeneration. This finding raises the concept of hamstring strength

284   possibly playing a protective role for knee cartilage, particularly in patients with

285   increased quadriceps strength. The hamstrings-quadriceps ratio has been the focus of

286   previous studies, especially as it relates to patients at risk for ACL injuries (which in turn

287   can give rise to progressive knee OA) [37]. From a biomechanical standpoint, increased E/F

288   ratio has been implicated in anterolateral tibial subluxation, and it has been posited that a

289   higher E/F ratio is itself a risk factor for ACL injury [38, 39]. Though much literature focuses

290   on the role of knee extension strength in knee OA, there has been little focus on the

291   potential role of hamstring strengthening, even though studies have shown a beneficial

292   effect of improvement of hamstring strength for pain reduction in patients with knee OA

293   [31]. Our study in many ways confirms what has been hinted at in previous literature,

294   showing that the most important aspect of thigh musculature governing knee OA, relates

295   to the intrinsic balance between the extensors and flexors (that is, an unbalanced decrease

296   in hamstring strength relative to quadriceps strength, can potentially have detrimental

297   long-term effects on the patellofemoral cartilage). Though we have only demonstrated a

298   possible protective effect of flexor CSA with regards to meniscus health, we see that the

299   role of flexor strength becomes much more important as it relates to balancing against

300   high extensor strength.

301   It is important to note that our study set out to clarify the role of muscle CSA with

302   overall knee cartilage health, including tibiofemoral cartilage. None of our muscle CSA

303   parameters reached significance with regards to the longitudinal effect on the

304   tibiofemoral joint. One possible interpretation which has been described previously, is

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305   that patellofemoral cartilage anomalies are actually a precursor for further cartilage

306   deterioration of the tibiofemoral joint [40]. Previous studies have suggested that structural

307   changes in the patellofemoral joint provide better explanation for knee pain than those in

308   the tibiofemoral joint, and this is also an important consideration as potential

309   relationships between pain and muscle strength/CSA may contribute to our findings [41, 42].

310   Our study shows a potential direct association between E/F ratio and patellar

311   cartilage degeneration. Confounding factors such as level of physical activity and sports

312   participation may have played a role in this relationship, however we did not find a

313   significant correlation between baseline PASE scores and extensor/flexor ratio to suggest

314   that the level to which physical activity confounded these results was significant. Certain

315   variables such as involvement in high-impact sport activities which may preferentially

316   increase extensor muscle bulk, may also be direct contributors to patellar cartilage

317   deterioration, and future studies on this topic may be able to shed light on whether such

318   factors could play a role in this relationship.

319   Our study has several limitations which should also be discussed. We used the KL

320   scale for subject selection and only included those with KL Grade 0 or 1. The KL grade

321   solely pertains to radiographic OA of the tibiofemoral joint [43]. However, the main

322   findings in our study related to the effect of thigh muscle strength and CSA on the

323   patellar and trochlear cartilage. It is therefore possible that our KL grade selection may

324   have allowed for selection of patients who already had evidence of patellofemoral OA.

325   However, a comparison of our MR data with a previous study by Pan et al. showed no

326   significant difference in frequency of baseline patellar or patellofemoral joint cartilage

327   lesions in our study cohort compared to a normal reference population from the OAI

328   database [29]. Secondly, a complicating limitation of our study pertains to our finding that

329   baseline meniscal WORMS scores differed significantly between patients with low and

330   high thigh muscle CSA, though longitudinal values did not differ significantly between

331   these groups. Though the significance of this finding is unclear, it is possible that this

332   may reflect an underlying protective effect of increased thigh muscle CSA as pertains to

333   meniscal, and, by deduction, tibiofemoral cartilage health. The precise implications of

334   this are beyond the scope of this study, and future investigation is warranted to further

335   clarify this result.

336   Our study demonstrates potentially clinically significant findings regarding

337   patellar cartilage deterioration in relation to muscle strength; however, the findings

338   regarding tibiofemoral cartilage were less robust. One possible explanation may be

339   related to the relatively lesser longitudinal changes seen in these cartilage compartments

340   compared to those of the tibiofemoral joint amongst all included patients, unrelated to

341   muscle CSA. Thus, a potential limiting factor of our study is that the deterioration seen in

342   the tibiofemoral compartment over the 48 month time frame was not sufficient to allow

343   adequate assessment of the relationship with muscle CSA. In that case, additional studies

344   investigating longer periods of time would be needed to assess muscle strength effects on

345   the tibiofemoral joint in particular.

346   Similarly, our study did not find significant associations between total muscle

347   CSA values or WORMS scores and baseline or longitudinal change in WOMAC scores,

348   which is not unexpected as previous studies have reported similar limited correlations

349   between WORMS scores/muscle CSA values and WOMAC scores [13, 44]. This may be

350   explained by the fact that WOMAC scores report only knee functionality over the past

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351 seven days, and they may also have limitations in assessing pain/symptoms in this

352 relatively young cohort (aged 50-60) with KL grades of 0 and 1.

353   In summary, our study shows increased total CSA of thigh muscle, and especially

354 increased extensor to flexor CSA ratio, are significantly associated with worsening

355 patellofemoral cartilage WORMS scores over 48 months. In light of our findings, more

356 effort should be made to ensure that patients with purely patellofemoral OA maintain

357 relatively low E/F ratios through specific exercises designed to increase hamstrings and

358 quadriceps in the appropriate proportions. Additionally, more studies with increased

359 numbers of patients would likely be necessary to investigate more thoroughly the exact

360 role of flexion strength in knee OA prevention. Such knowledge would shed light on how

361 targeted strengthening exercises for various lower extremity muscle groups might

362 ultimately guide conservative management of knee OA.

363

364

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Author contributions

Drs. Lauren H. Goldman and Thomas M. Link both had full access to all of the study data and assume responsibility for its integrity and the accuracy of the data analysis.

Conception and design: Link TM, Heilmeier U, Joseph GB.

Analysis and interpretation of the data: Goldman LH, Tang K, Nevitt MC, McCulloch CE, Joseph GB.

Drafting of the article: Goldman LH.

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387   Critical revision of the article for important intellectual content: Souza RB, Heilmeier U,

388   Nevitt MC, McCulloch CE, Link TM.

389   Final approval of the article: all authors.

390   Statistical expertise: Joseph GB, Nevitt MC, McCulloch CE.

391   Collection and assembly of data: Goldman LH, Facchetti L and Tang K.

392

393   **Role of funding source**

394   This manuscript was prepared using an OAI public use data set and does not necessarily

395   reflect the opinions or views of the OAI investigators, the NIH, or the private funding

396   partners.

397

398   **Competing interests**

399   Nothing to declare. There is no conflict of interest and the paper has not been submitted

400   elsewhere.

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530

531   **Figure legend**

532   **Figure 1:** Flowsheet demonstrating patient exclusion criteria.

533   **Figure 2**: Full-length femur radiograph (A) demonstrates method of obtaining slice

534   selection in uniform manner that accounted for individual height/body size differences.

535   The length of the femur from the superior aspect of the femoral head to the intercondylar

536   notch was first measured, and the obtained measurement was divided by three to obtain

537   the location of the distal-middle third junction of the femur. This length (18.335 cm) was

538   then correlated with the appropriate axial MR slice (B).

539   **Figure 3**: Axial T1-weighted thigh MRIs at the distal one-third junction in patient (A)

540   demonstrates extensor compartment (highlighted in red) and flexor compartment

541   (highlighted in blue) with an E/F ratio of 1.01, in contrast to an axial image in a different

542   patient (B) showing a much larger E/F ratio of 2.17.

543   **Figure 4**: Graphical depiction of relationships between various muscle strength (A) and

544   CSA parameters– including total CSA (B), flexor CSA (C), extensor CSA (D), VM CSA

545   (E), and E/F ratio (F)-- and the corresponding mean increase in subcompartmental

546   cartilage WORMS scores associated with each group. Statistical significance was defined

547   as $p < 0.05$ (asterisk). MF=medial femur; LF=lateral femur; MT=medial tibia; LT=lateral

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548   tibia; Pat=patella; Tr=trochlea; Max=maximum cartilage score (any compartment);

549   Men=meniscus; BMEP=bone marrow edema pattern.

550   **Figure 5:** Baseline sagittal DESS image (A) demonstrating patellar cartilage with small

551   partial-thickness defect (bracket) in patient with high extensor-flexor ratio. 48-month

552   follow-up MRI (B) demonstrates clear progression of the patellar cartilage lesion which

553   is now a large full-thickness defect (arrows).

554

Table 1: Demographics in relation to total CSA group

	All	Low Total CSA*	High Total CSA*	P-value^
Number	70	35	35	
Males (%, number)	47.1 (33)	22.9 (8)	71.4 (25)	**<0.0001**
Age (years)	55.3±3.1	55.1±3.3	55.4±2.9	0.648
Height (mm)	1708.6±100.2	1664.8±69.4	1752.4±107.7	**<0.001**
BMI (kg/m^2)	27.5±4.3	26.5±4.0	28.5±4.4	**0.046**
Right knee maximum extension (N)	428.8±148.6	376.6±95.1	481.1±173.6	**0.003**
Maximum extension speed (N/s)	579.8±465.1	589.5±465.1	570.8±472.1	0.874

^ Calculated using student's t-test, with statistical significance defined as $p < 0.05$.
* Groups determined using cut-off value of 10,000 mm^2, which separated upper and lower 50 percentile for corrected total muscle CSA

Table 2: Relationship of muscle CSA parameters to WORMS cartilage scores

	Time-point	Baseline MS*		Total CSA*		Flexor CSA*		Extensor CSA*		VM CSA*		E/F ratio*	
		Low^	High^	Low	High	Low	High	Low	High	Low	High	Low	High
Patella	Baseline	1.66±1.64	1.91±1.54	1.91±1.77	1.66±1.39	1.77±1.55	1.8±1.64	1.97±1.77	1.6±1.38	1.63±1.82	1.94±1.33	2.11±1.84	1.46±1.22
	48-mo	2.19±1.87	2.73±1.73	2.46±1.94	2.46±1.70	2.36±1.81	2.56±1.83	2.51±1.92	2.4±1.72	2.18±1.90	2.73±1.70	2.50±1.91	2.41±1.73
	Change	0.53±0.67	0.76±0.92	**0.49±0.68**	**0.80±0.90**	0.59±0.75	0.71±0.87	**0.49±0.68**	**0.80±0.90**	**0.50±0.79**	**0.79±0.82**	**0.32±0.59**	**0.96±0.88**
Troch-lea	Baseline	1.43±1.63	0.91±1.04	1.00±1.33	1.34±1.43	1.29±1.43	1.06±1.35	1.14±1.48	1.20±1.30	0.94±1.21	1.40±1.52	**0.86±1.19**	**1.49±1.50**
	48-mo	1.77±1.88	1.38±1.23	1.32±1.63	1.83±1.54	1.57±1.65	1.59±1.56	1.47±1.73	1.69±1.47	1.29±1.40	1.86±1.73	**1.21±1.47**	**1.94±1.64**
	Change	0.34±0.68	0.44±0.79	**0.29±0.72**	**0.49±0.74**	0.29±0.71	0.50±0.75	0.29±0.72	0.49±0.74	0.32±0.68	0.46±0.78	0.32±0.68	0.46±0.78

* Groups were defined according to assigned gender-specific Z-scores for the study population. Goutallier-adjusted values were used where appropriate.
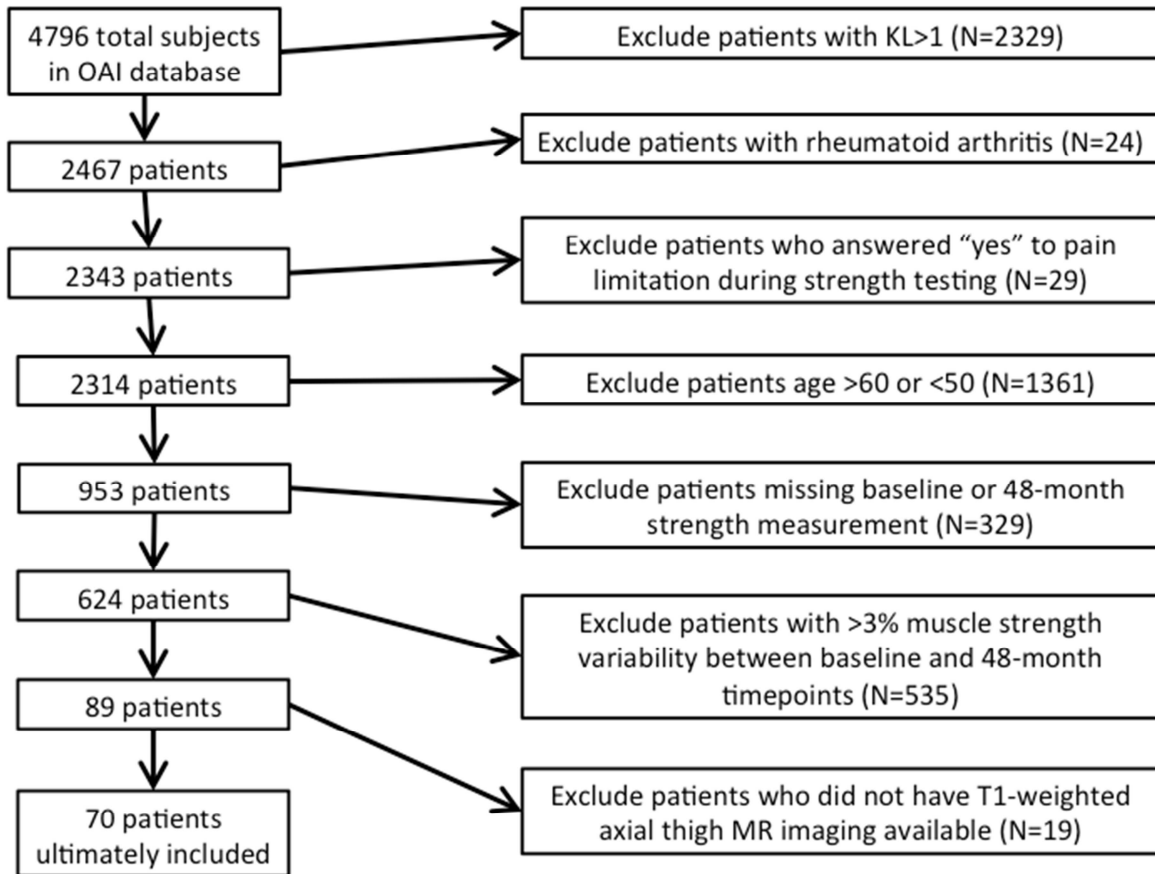
^ All analyses were performed using a multiple regression model adjusted for age, BMI, and gender. Significance was defined as $p < 0.05$, and statistically significant values are depicted in red.
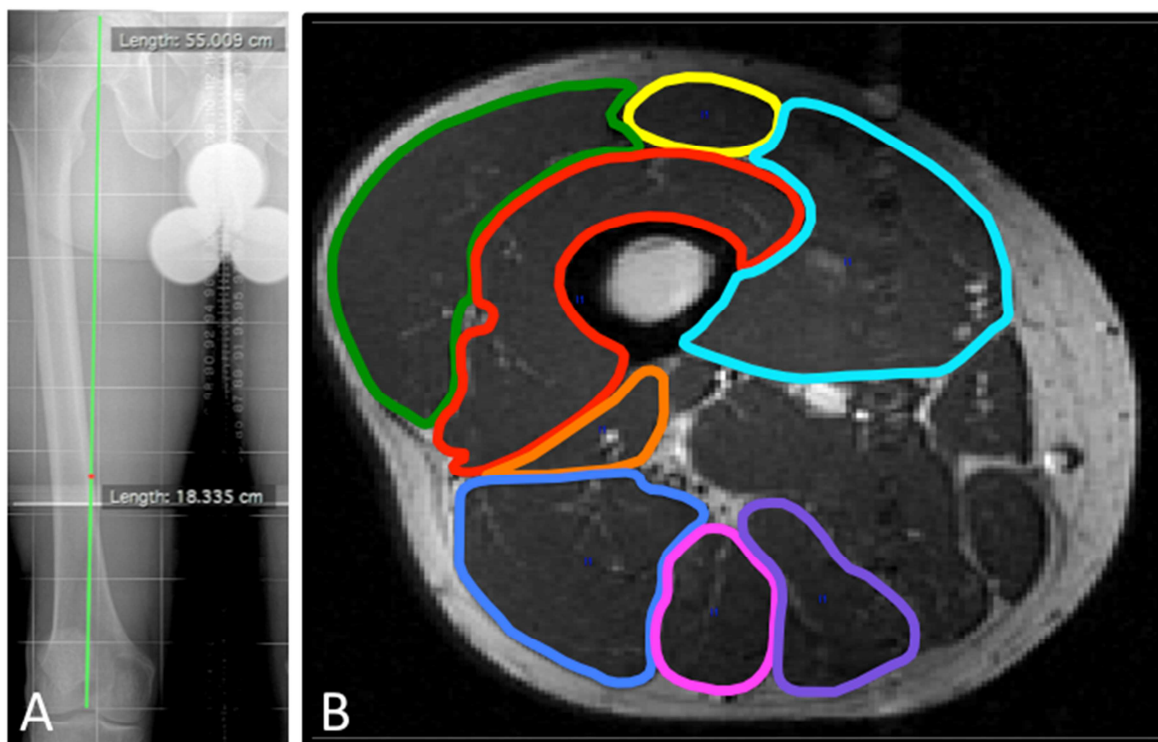
Table 3: Relationship of muscle CSA parameters to WORMS maximum cartilage, meniscus, and BMEP scores

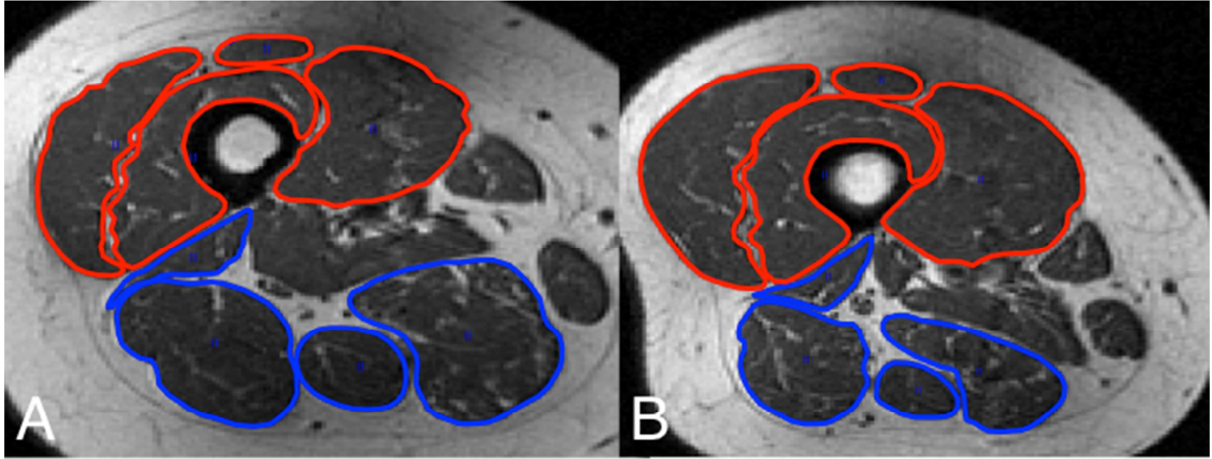|	Time-point	Baseline MS		Total CSA*		Flexor CSA*		Extensor CSA*		VM CSA*		E/F ratio	
		Low^	High^	Low	High	Low	High	Low	High	Low	High	Low	High
Global max cartilage score	Baseline	2.81±1.47	2.29±1.38	2.74±1.48	2.36±1.39	2.54±1.36	2.56±1.54	2.86±1.50	2.24±1.33	2.57±1.50	2.53±1.40	2.69±1.64	2.41±1.22
	48-mo	3.34±1.41	3.06±1.48	3.32±1.43	3.09±1.46	3.20±1.35	3.21±1.55	3.41±1.43	3.00±1.43	3.03±1.38	3.37±1.50	3.09±1.56	3.31±1.32
	Change	0.53±0.70	0.74±0.83	0.53±0.71	0.73±0.82	0.66±0.80	0.60±0.74	0.50±0.71	0.76±0.81	**0.41±0.66**	**0.84±0.81**	**0.35±0.60**	**0.90±0.82**
Meniscus	Baseline	1.20±1.21	0.71±1.10	**1.26±1.29**	**0.66±0.97**	**1.17±1.34**	**0.74±0.95**	**1.26±1.29**	**0.66±0.97**	1.06±1.26	0.86±1.09	0.86±1.14	1.06±1.21
	48-mo	1.46±1.31	1.38±1.28	1.68±1.39	1.17±1.15	1.69±1.32	1.15±1.21	1.62±1.41	1.23±1.14	1.56±1.31	1.29±1.27	1.24±1.26	1.60±1.31
	Change	0.26±0.92	0.68±0.88	0.41±0.86	0.51±0.98	0.51±0.85	0.41±0.99	0.35±0.95	0.57±0.88	0.50±0.86	0.43±0.98	0.38±0.99	0.54±0.85
Bone marrow edema pattern	Baseline	1.06±0.87	1.20±0.96	1.11±0.87	1.14±0.97	1.20±0.83	1.06±1.00	1.14±0.88	1.11±0.96	1.11±0.93	1.14±0.91	1.00±0.84	1.26±0.98
	48-mo	1.23±0.88	1.35±1.01	1.18±0.97	1.40±0.91	1.26±0.92	1.32±0.98	1.21±0.98	1.37±0.91	1.09±0.97	1.49±0.89	0.97±0.97	1.60±0.81
	Change	0.17±0.82	0.15±0.82	0.06±0.81	0.26±0.82	0.06±0.80	0.26±0.83	0.06±0.81	0.26±0.82	**-0.03±0.80**	**0.34±0.80**	-0.03±0.72	0.34±0.87

* Groups were defined according to assigned gender-specific Z-scores for the study population. Goutallier-adjusted values were used where appropriate.

^ All analyses were performed using a multiple regression model adjusted for age, BMI, and gender. Significance was defined as $p < 0.05$, and statistically significant values are depicted in red.
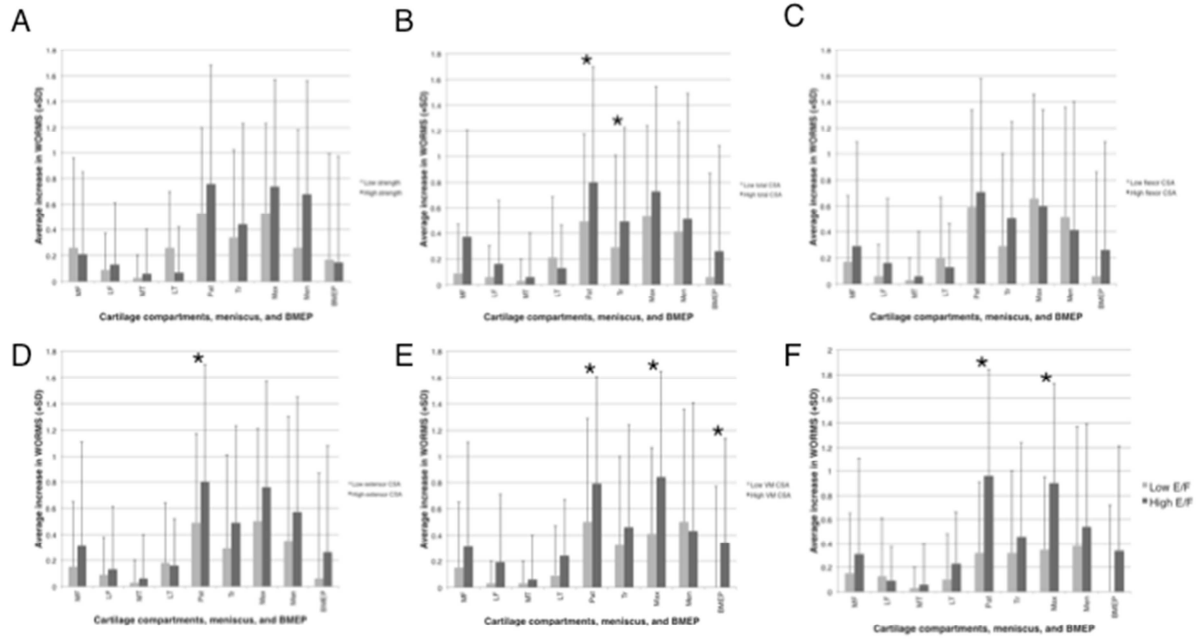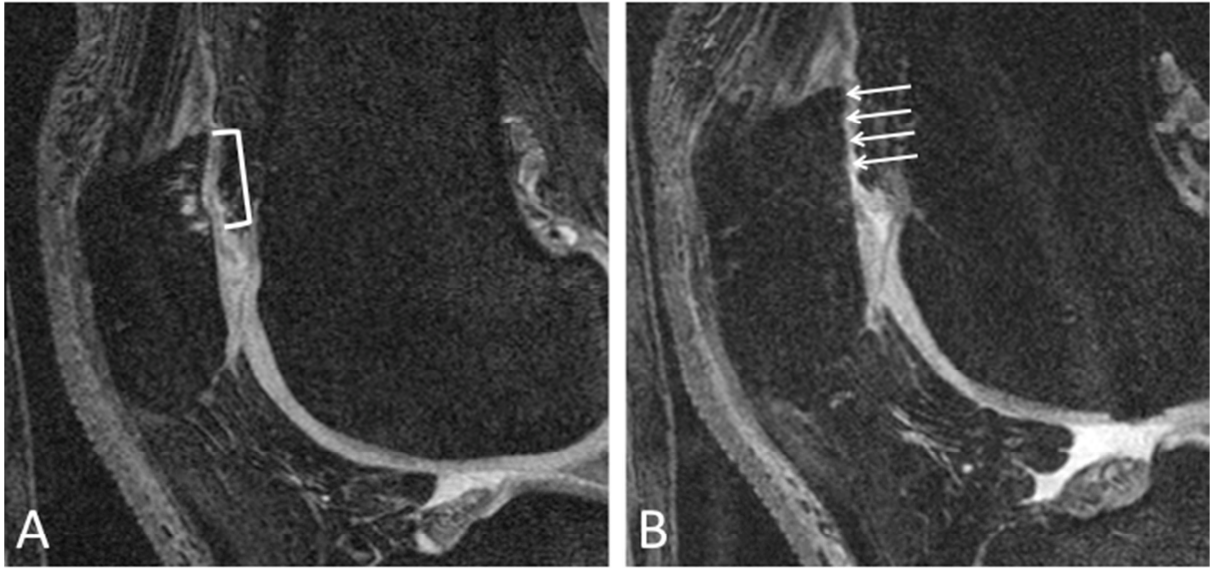
4796 total subjects in OAI database → Exclude patients with KL>1 (N=2329)

2467 patients → Exclude patients with rheumatoid arthritis (N=24)

2343 patients → Exclude patients who answered "yes" to pain limitation during strength testing (N=29)

2314 patients → Exclude patients age >60 or <50 (N=1361)

953 patients → Exclude patients missing baseline or 48-month strength measurement (N=329)

624 patients → Exclude patients with >3% muscle strength variability between baseline and 48-month timepoints (N=535)

89 patients → Exclude patients who did not have T1-weighted axial thigh MR imaging available (N=19)

70 patients ultimately included