Published in final edited form as:

Arthritis Rheumatol. 2018 February ; 70(2): 222–229. doi:10.1002/art.40343.

Loss of muscle strength prior to knee replacement: a question of anatomical cross-sectional area or specific-strength?

Adam G Culvenor^{1,2}, Felix C Hamler¹, Jana Kemnitz¹, Wolfgang Wirth^{1,3}, and Felix Eckstein^{1,3}

¹Institute of Anatomy, Paracelsus Medical University Salzburg & Nuremberg, Salzburg, AUSTRIA

²La Trobe Sport & Exercise Medicine Research Centre, School of Allied Health, La Trobe University, Bundoora, AUSTRALIA

³Chondrometrics GmbH, Ainring, GERMANY

Abstract

Objective—To elucidate whether loss in thigh muscle strength prior to knee replacement (KR) is caused by reductions of muscle anatomical cross sectional area (ACSA) or specific-strength.

Methods—All 100 Osteoarthritis Initiative participants who received a KR (cases) and had thigh isometric muscle strength and MRI recorded (58 women, age 65±8 years, BMI 29±5 kg/m²) were matched with a control (no KR) for age, sex, height, BMI, and radiographic severity. Thigh muscle ACSAs were determined from MRI at the visit before KR (T₀), and two years before T₀ (T₋₂). Specific-strength was calculated (strength÷ACSA) and the measures compared by conditional logistic regression (i.e., odds ratio [OR] per standard deviation).

Results—KR cases displayed significantly smaller extensor (but not flexor) ACSA than controls at T₀ (women: pain-adjusted OR [OR_{adj}] 1.89; 95%CI 1.05–3.90; men: OR_{adj} 2.22; 95%CI 1.04–4.76), whereas no significant differences were found at T₋₂. Women with KR (but not men) displayed lower extensor specific-strength at T₀ (OR 1.59 [1.02–2.50]), although this difference did not maintain significance after adjustment for pain (OR_{adj} 1.22 [0.71–2.08]). Female cases lost significantly more extensor specific-strength between T₋₂ and T₀ than controls (OR_{adj} 3.76; 95%CI 1.04–13.60), whereas no significant differences were noted at T₋₂, or in men.

Conclusion—In women, a significant reduction in knee extensor strength prior to KR appears to occur through two mechanisms: one driven by pain (loss in specific-strength) and one independent of pain (loss in muscle ACSA). Men with KR displayed significantly lower extensor ACSA, but not significantly lower strength or specific-strength.

Address for correspondence: Dr Adam G Culvenor, Institute of Anatomy, Paracelsus Medical University, Strubergasse 21, A5020 Salzburg, AUSTRIA, Tel: +43662242080417; Fax: +436624420021249; adam.culvenor@pmu.ac.at.

Potential conflict of interest:

Felix Eckstein is CEO of Chondrometrics GmbH, a company providing MR image analysis services to academic researchers and to industry. He has provided consulting services to Merck Serono, Samumed, and Bioclinica/Synarc, has prepared educational sessions for Medtronic, and has received research support from Pfizer, Eli Lilly, Merck Serono, Novartis, Stryker, Abbvie, Kolon, Synarc, Ampio, BICL, Orthotrophix and Tissue Gene. Wolfgang Wirth has a part time employment with Chondrometrics GmbH and is a co-owner of Chondrometrics GmbH. No other authors declare a conflict of interest.

Keywords

knee; osteoarthritis; joint replacement; muscle mass; specific strength; muscle activation

More than 600,000 total knee replacements (KR) are performed annually in the United States to improve pain and function associated with end-stage knee osteoarthritis (KOA) (1). This number is expected to rise to 3.5 million per year by 2030, driving significant increases in the health and economic burden of KOA (1). This underlines the urgent need to identify strategies by which the risk of KR surgery due to progressive KOA can be modified.

Thigh muscle weakness has been identified as a determinant of radiographic and symptomatic KOA incidence and progression (2, 3). In a recent matched case-control study of adults with KOA from the Osteoarthritis Initiative (OAI), we identified thigh muscle weakness as a predictor of KR in women, independent of disease severity and pain (4). However, this relationship was not observed in men (4). Given the modifiable nature of muscle strength, these findings expose a potential therapeutic window by which the risk of women undergoing KR may be modified. However, the mechanisms driving the sex-specific relationship between muscle weakness and KR (and other KOA outcomes) are not known, but are important in directing individualized treatment strategies to counteract deficits in muscle strength. For example, deficits in muscle anatomical cross-sectional area (ACSA) have been reported in symptomatic KOA (5) and may be responsible for loss of muscle strength prior to KR. On the other hand, loss in muscle specific-strength (e.g., strength per ACSA) has recently been identified to play a role in onset of KOA in women (6) and would require different therapeutic approaches (e.g., interventions targeting muscle activation impairments, such as muscle biofeedback or neuromuscular electrical stimulation) as compared with a situation in which reduction in muscle ACSA is the only mechanism that is responsible for muscle strength deficits. In order to elucidate the mechanisms behind thigh muscle weakness and KR risk observed in women (4), the current study aims to elucidate how thigh muscle ACSA and/or specific-strength, or longitudinal changes in these measures, independently impact risk of subsequent KR in men and women.

METHODS

Participants

All OAI participants who were included in our recent analysis of muscle strength prior to KR (4) were eligible for inclusion in the current analysis. Briefly, all OAI participants who reported having a KR at any annual OAI visit between 12- and 60-month follow-up, and who had thigh muscle strength assessed within the two years prior to KR, were eligible as cases (n=136) (4). Only cases with T1-weighted axial spin-echo magnetic resonance imaging (MRI) acquisitions of the thigh at the same time point(s) could be included in the current analysis (one knee per person; n=100). In the OAI, thigh isometric muscle strength measurements and thigh MRIs were obtained biennially (i.e., baseline, 24-, and 48-month visits). In some participants muscle strength and thigh MRIs were obtained at 12- and/or 36-month visits instead of baseline and/or 24-month visits. The time point at which muscle strength and MRI examinations were analyzed as preceding KR (T_0) was within a window

of two years prior to KR (i.e., for a KR detected at the 36-month visit, T_0 was 12- or 24-month measurements, whichever was available, and for a 48-month KR, T_0 was 36- or 24-month measurement). The time point two years prior to T_0 was termed T_{-2} (for details, see Culvenor et al. (4)).

Control knees (one per person) were selected from OAI participants who had not received a KR between baseline and 60-month follow-up in either knee and had muscle strength and MRI assessments at the same time points as KR cases. Cases and controls were matched 1:1 by sex, age (± 5 years), height (± 5 cm), body mass index (BMI) (± 3 kg/m²), KR limb (dominant [preferred kicking leg] versus non-dominant), baseline Kellgren/Lawrence (KL) scores (grades 0, 1, 2, and 3–4) from the central readings, as well as presence and location (i.e., medial/lateral joint space narrowing [JSN]) of baseline compartmental involvement. Due to a lack of thigh MRI at T_0 in three controls from our recent analysis of this cohort (4), we re-matched these ineligible controls with new eligible OAI controls with thigh MRIs. The OAI was approved by local ethics committees and participants gave informed consent for OAI public database inclusion.

Evaluation of muscle strength and ACSAs

Maximal isometric knee extensor and flexor strength had been measured with the Good Strength Chair (Metitur Oy), at 60° knee flexion as previously described (4). Muscle ACSAs of the quadriceps and hamstrings were measured from axial MRI at anatomically consistent locations (33% femoral length; distal-to-proximal) (6) using custom semi-automated software developed at our institution (7). This method has been shown to display reliability and validity in longitudinal studies (7). To account for remaining differences in body size (despite the matching procedure), ACSAs were normalized to femoral size (femur ACSA from same MRI slice). Specific-strength was calculated as strength per unit ACSA (N/cm²) (6). We used strength measurements directly (not moments) to estimate muscle strength, because both the lever arm between the load cell and joint center and that between the muscle tendons and joint center depend on body size and are roughly proportional (8).

Statistical Analysis

After confirming normality, paired t-tests between sex-specific case-control pairs were conducted for extensor and flexor ACSA and specific-strength at T_0 and T_{-2} , and for change between T_{-2} and T_0 . Further, sex-specific case-control conditional logistic regression (case-control odds ratios [OR]) per standard deviation (SD) was performed, for extensor and flexor ACSA and specific-strength at T_0 and T_{-2} , and for longitudinal change between T_{-2} to T_0 . The case-control ORs were additionally adjusted for the effect of pain (4), using standard categories of no pain, infrequent pain and frequent pain (most days of a month in past 12-months). Analysis was performed using SPSS v.23.0. *P*-values <0.05 were considered statistically significant.

RESULTS

Of the 136 OAI participants who had a confirmed KR up to the 60-month visit (4), 36 cases could not be included in the current analysis because thigh MRI was not available at T_0 .

Baseline age, sex, BMI, KL grade, or distribution of JSN of the 36 cases who did not have thigh MRI available at T₀ did not differ from that of the 100 cases included in the current analysis ($p>0.05$). Fifty-eight female pairs had MRI and strength data at T₀, and 30 also at T₋₂, while 42 male case/control pairs had these data at T₀, and 25 at T₋₂ (Table 1). Thigh muscle strength differences between cases and controls were of similar magnitude in the current 100 matched-pairs as those observed in the larger sample of 136 matched-pairs previously published (Table 1).

Extensor and flexor ACSA and specific-strength in women

Female cases displayed less extensor ACSA at T₀ compared with matched controls ($P=0.041$ paired-t-test, unadjusted $P[P_{\text{unadj}}]=0.049$, adjusted $P[P_{\text{adj}}]=0.033$), but not at T₋₂ (Table 2). No differences in flexor ACSA were observed between cases and controls at T₀ or T₋₂. Differences in the two-year longitudinal change of extensor ACSA from T₋₂ to T₀ did not reach statistical significance between cases and controls.

Knee extensor specific-strength was significantly lower in case than in control knees at T₀ (paired-t-test, $P=0.032$) in non-adjusted analyses, albeit the difference did not maintain statistical significance after adjustment for pain ($P=0.471$). No significant differences in any of the above measures were observed at T₋₂ (Table 2). Female KR cases lost significantly more extensor specific-strength between T₋₂ and T₀ ($-1.1\pm1.5\text{N/cm}^2$ vs. $0.3\pm1.8\text{N/cm}^2$; $P=0.002$ paired-t-test; $P_{\text{unadj}}=0.011$; $P_{\text{adj}}=0.043$) than their matched non-KR controls. Flexor specific-strength, and its longitudinal change, in contrast, was not significantly associated with KR. Similar results were observed in sensitivity analysis using muscle torque (Nm/cm^2) (Supplementary File).

Extensor and flexor ACSA and specific strength in men

Similar to females, male cases displayed less extensor ACSA at T₀ compared to their matched controls ($P=0.011$ paired-t-test, $P_{\text{unadj}}=0.020$, $P_{\text{adj}}=0.039$), but not at T₋₂ (Table 3). No statistically significant differences in knee flexor ACSA or specific-strength were, however, observed at any time point between male cases and controls, or for the change in knee extensor or flexor ACSA and specific-strength. As a trend, male KR cases displayed somewhat greater (rather than lower) specific-strength than their matched controls at T₀ and T₋₂.

DISCUSSION

To elucidate mechanisms behind thigh muscle weakness and clinical progression of KOA, we explored whether loss in thigh muscle ACSAs or specific-strength increase KR risk. We found that significant deficits in knee extensor ACSA preceded KR in both men and women, independent of age, BMI, disease severity and pain, when measured at a time point within two years prior to surgery (i.e., T₀). Additionally, female KR cases displayed 10% lower knee extensor specific-strength than controls at T₀, but these differences did not remain statistically different after adjustment for pain. Male KR cases, in contrast, displayed slightly higher (5%) muscle specific-strength than matched controls without KR. Interestingly, female KR cases displayed a significantly greater longitudinal loss of knee extensor specific-

strength over a 2-year observational window prior to KR than female control knees, with this loss exceeding that in male KR cases by a factor of 10. Hence, this study is the first to suggest that muscle weakness preceding clinical progression of KOA to KR in women is caused by both deficits in muscle ACSA (independent of pain) and specific-strength (dependent of pain), whereas no deficits in muscle specific-strength were apparent in men prior to KR.

The results of the current study help to disentangle the sex-specific mechanisms behind the recently observed relationship between clinical measures of muscle strength and OA incidence and progression (4, 6). Specifically, there appear to be two mechanisms contributing to the strength deficits increasing KR risk in women (4) – one that is driven by pain (specific-strength deficit) and one that is independent of pain (ACSA deficit). Specific-strength reflects the availability of contractile tissue per unit area of muscle and/or the ability to activate existing muscle fibers, with the latter potentially being affected by pain through either a reduction in neural activation or a reluctance of participants with pain to maximally contract (9). Muscle ACSA, in contrast, is a structural feature that is potentially less influenced by pain. In contrast to women, deficits in muscle ACSA in male KR cases were accompanied by a somewhat greater specific-strength than their matched controls. Although this apparent compensatory mechanism may be a chance finding given the relatively small number of men, it does potentially help to explain the lack of significant differences in muscle strength between male KR cases and controls we observed previously (4). Similar sex-specific responses of muscle specific-strength have also recently been observed in those at risk of incident KOA, where thigh muscle specific-strength was maintained in men with greater BMI, but not in women (6).

The presence, persistence, and particularly the worsening of disabling pain are key criteria for a decision to undergo KR. The loss of significant relationship between knee extensor specific-strength in women at risk of KR at T_0 after adjustment for pain suggests that the mechanism through which muscle weakness impacts KR risk in women is dependent on pain. Our prior study found muscle weakness in women to be associated with subsequent KR risk independent of pain (4), likely through a mechanism involving greater loss of ACSA prior to KR compared with non-KR controls. Consistent with these findings, ACSA has been shown to be an important driver of muscle deficits that cause incident KOA in older women (10). In the Multicenter Osteoarthritis (MOST) Study, knee extensor specific-strength in women, and not muscle mass, was predictive of worsening JSN, while neither was predictive for worsening JSN in men (11). Importantly, analyses in the MOST study did not adjust for pain, which would likely attenuate the predictive capacity of specific-strength as we observed in the current study, and muscle mass was assessed as total thigh lean mass by dual energy X-ray absorptiometry rather than isolating muscle groups as possible by MRI. Our finding that male KR cases appear to compensate a significant loss of muscle ACSA by somewhat increased specific-strength explains why we did not previously observe a relationship between muscle strength and KR risk in men. The somewhat greater specific-strength in male KR cases may also help to explain why in some reports of radiographic KOA progression, male cases displayed increased knee extensor strength prior to progression (12).

Interestingly, muscle ACSA and specific-strength in male KR cases and controls were relatively stable over the 2–4 year period prior to KR (<3% loss), whereas female KR cases displayed a significantly greater longitudinal loss of knee extensor specific-strength over the same period (up to 18%) compared with female control knees. This longitudinal loss of specific-strength remained a significant predictor of KR, even after adjustment for pain. Importantly, the reports of pain at the start of the observational period (i.e., T₋₂) were used to adjust case-control ORs, consistent with our previous analyses, which may have resulted in lower pain levels being included in the model compared to T₀. Nevertheless, these findings suggest that women have a more dramatic loss of muscle specific-strength prior to KR than men and highlight the importance of addressing muscle specific-strength deficits (i.e., an inability to activate existing muscle tissue or increase in non-contractile tissue) in those with (and at risk of) KOA. Such interventions may need to have a greater focus on addressing fear and confidence, which can influence muscle activation capacity, or at maintaining contractile tissue per muscle unit area. While eccentric strength training may more effectively increase muscle ACSA and neural adaptations than concentric approaches (13), any heavy resistance training is likely to improve neural activation through increasing motor unit firing frequency and recruitment (14). The ability of specific muscle activation interventions, such as muscle biofeedback and neuromuscular electrical stimulation, as well as interventions addressing confidence, fear and motivation, should be a focus of future research.

We only evaluated a limited window of time prior to KR and it may be that changes in thigh muscles prior to this window are also important in predicting future progression to KR. However, the lack of significant findings earlier than 2–4 years prior to KR suggests that muscle characteristics in the immediate years prior to KR are most strongly implicated in progression risk (4). The relatively few eligible participants within the total OAI cohort with a KR limited the number of included cases to 100. The strict matching approach used to select the 100 controls ensured the potential confounding effects of radiographic severity, BMI, age, and sex were addressed. Although we analyzed measures of muscle strength, morphology (ACSA) and quality (specific-strength), the OAI did not include measures of voluntary muscle activation (e.g., electromyography) that may provide additional information on KR risk.

In conclusion, the current study is the first to suggest that muscle strength deficits preceding clinical progression of KOA to KR in women appears to occur through two mechanisms: one driven by pain (loss in specific-strength) and one independent of pain (loss in ACSA), whereas men with KR displayed lower extensor ACSA, but not strength or specific-strength. These findings uncover potential specific targets for treatment of muscle impairments in men, and particularly in women, with KOA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Data acquisition of part of this study was funded by the Osteoarthritis Initiative, a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the Osteoarthritis Initiative study Investigators. Private funding partners of the OAI include Merck Research Laboratories, Novartis Pharmaceuticals Corporation, GlaxoSmithKline, and Pfizer, Inc. Private sector funding for the Osteoarthritis Initiative is managed by the Foundation for the National Institutes of Health. This research has also received funding from the European Union Seventh Framework Programme (FP7-PEOPLE-2013-ITN; KNEEMO) under grant agreement number 607510. Adam Culvenor is a recipient of a National Health and Medical Research Council (NHMRC) of Australia Early Career Fellowship (Neil Hamilton Fairley Clinical Fellowship, No. 1121173). The sponsors were not involved in the design and conduct of this particular study, in the analysis and interpretation of the data, and in the preparation, review, or approval of the manuscript.

We would like to thank the OAI participants, OAI investigators and OAI Clinical Center's staff for generating this publicly available image data set. The study and image acquisition was supported by the Osteoarthritis Initiative (OAI). The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Pfizer, Inc.; Novartis Pharmaceuticals Corporation; Merck Research Laboratories; and GlaxoSmithKline. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This research has also received funding from the European Union Seventh Framework Programme (FP7-PEOPLE-2013-ITN; KNEEMO) under grant agreement number 607510. Adam Culvenor is a recipient of a National Health and Medical Research Council (NHMRC) of Australia Early Career Fellowship (Neil Hamilton Fairley Clinical Fellowship, No. 1121173).

References

1. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg.* 2007; 89A:780–5.
2. Culvenor AG, Ruhdorfer A, Juhl C, Eckstein F, Oiestad BE. Knee extensor strength and risk of structural, symptomatic and functional decline in knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Care Res.* 2017; 69:649–58.
3. Oiestad BE, Juhl CB, Eitzen I, Thorlund JB. Knee extensor muscle weakness increases the risk of knee osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis Cartilage.* 2015; 23:171–7. [PubMed: 25450853]
4. Culvenor AG, Wirth W, Ruhdorfer A, Eckstein F. Thigh muscle strength predicts knee replacement risk independent of radiographic disease and pain in women - data from the Osteoarthritis Initiative. *Arthritis Rheum.* 2016; 68:1145–55.
5. Sattler M, Dannhauer T, Hudelmaier M, Wirth W, Sanger AM, Kwok CK, et al. Side differences of thigh muscle cross-sectional areas and maximal isometric muscle force in bilateral knees with the same radiographic disease stage, but unilateral frequent pain - data from the osteoarthritis initiative. *Osteoarthritis Cartilage.* 2012; 20:532–40. [PubMed: 22395037]
6. Culvenor AG, Felson DT, Niu J, Wirth W, Sattler M, Dannhauer T, et al. Thigh muscle specific strength and the risk of incident knee osteoarthritis: the influence of sex and greater body mass index. *Arthritis Care Res.* 2017; 69:1266–70.
7. Kemnitz J, Eckstein F, Culvenor AG, Ruhdorfer A, Dannhauer T, Ring-Dimitriou S, et al. Validation of an active shape model-based semi-automated segmentation algorithm for the analysis of thigh muscle and adipose tissue cross-sectional areas. *Magn Reson Mater Phys.* 2017; Epub ahead of print. doi: 10.1007/s10334-017-0622-3
8. Tsaopoulos DE, Maganaris CN, Baltzopoulos V. Can the patellar tendon moment arm be predicted from anthropometric measures? *J Biomech.* 2007; 40:645–51. [PubMed: 16542664]
9. Salomoni S, Tucker K, Hug F, McPhee M, Hodges P. Reduced maximal force during acute anterior knee pain is associated with deficits in voluntary muscle activation. *PLoS ONE.* 2016; 11:e0161487. [PubMed: 27559737]
10. Ikeda S, Tsumura H, Torisu T. Age-related quadriceps-dominant muscle atrophy and incident radiographic knee osteoarthritis. *J Orthop Sci.* 2005; 10:121–6. [PubMed: 15815857]

11. Segal NA, Findlay C, Wang K, Torner JC, Nevitt MC. The longitudinal relationship between thigh muscle mass and the development of knee osteoarthritis. *Osteoarthritis Cartilage*. 2012; 20:1534–40. [PubMed: 22954456]
12. Culvenor AG, Wirth W, Roth M, Hunter DJ, Eckstein F. Predictive capacity of thigh muscle strength in symptomatic and/or radiographic knee osteoarthritis progression: data from the Foundation for the National Institutes of Health osteoarthritis biomarkers consortium. *Am J Phys Med Rehab*. 2016; 95:931–8.
13. Higby EJ, Cureton KJ, Warren GL, Prior BM. Effects of concentric and eccentric training on muscle strength, cross-sectional area, and neural activation. *J App Physiol*. 1996; 81:2173–81.
14. Sale DG. Neural adaptation to resistance training. *MedcSci Sports Exerc*. 1988; 20:S135–45.

Table 1

Baseline characteristics of the knee replacement cases and the non-knee replacement controls, according to sex *

Characteristic	Women		Men	
	Cases (n = 58)	Controls (n = 58)	Cases (n = 42)	Controls (n = 42)
Age, mean $\pm$ SD years	64 $\pm$ 8	65 $\pm$ 8	66 $\pm$ 9	66 $\pm$ 9
Body mass index, mean $\pm$ SD kg/m ²	28.8 $\pm$ 4.6	28.5 $\pm$ 4.4	29.1 $\pm$ 3.8	29.0 $\pm$ 3.2
Height, mean $\pm$ SD meters	1.61 $\pm$ 0.05	1.61 $\pm$ 0.05	1.77 $\pm$ 0.05	1.77 $\pm$ 0.05
Weight, mean $\pm$ SD kg	74.6 $\pm$ 13.3	74.2 $\pm$ 12.5	91.3 $\pm$ 13.3	90.1 $\pm$ 11.5
Knee replacement in dominant leg [§]	34 (59)	NA	16 (38)	NA
Kellgren/Lawrence grade				
0	5 (9)	5 (9)	2 (5)	2 (5)
1	0 (0)	0 (0)	2 (5)	2 (5)
2	11 (19)	11 (19)	4 (10)	4 (10)
3 – 4	42 (72)	42 (72)	34 (81)	34 (81)
Medial joint space narrowing	41 (71)	41 (71)	37 (88)	37 (88)
Lateral joint space narrowing	9 (15)	9 (15)	4 (10)	4 (10)
T ₀ to KR duration, mean $\pm$ SD months [#]	12 $\pm$ 6	NA	11 $\pm$ 7	NA
T ₀ knee extensor strength, mean $\pm$ SD, Newtons	215 $\pm$ 75	260 $\pm$ 80	384 $\pm$ 130	383 $\pm$ 94
T ₀ knee flexor strength, mean $\pm$ SD, Newtons	87 $\pm$ 35	101 $\pm$ 42	163 $\pm$ 70	147 $\pm$ 52

* Except where indicated otherwise, values are number (%); NA = not applicable; KR, knee replacement.

[§] Dominant leg is the leg participants would kick a ball with.

[#] T₀ defined as OAI clinical visit prior to knee replacement.

If a case participant had a KR in both knees, the one that had been replaced earlier was included. However, if they were both replaced at the same time point, the knee with the lower Kellgren/Lawrence grade at baseline was analyzed.

Table 2

Female: ACSA (cm²) and specific-strength (Newton/cm²) in the KR cases and matched non-KR controls*

	No. matched pairs analyzed	ACSA		Case-control OR (95% CI)	Case-control OR _{pain} (95% CI) †	Specific-strength		Case-control OR (95% CI)	Case-control OR _{pain} (95% CI) †
		Mean ± SD, cm ²	Controls			Mean ± SD, N/cm ²	Controls		
		Cases	Controls			Cases	Controls		
Knee extensors									
T ₀	58	6.5±1.4	7.1±1.7	1.59 (1.00–2.51) ‡	1.89 (1.05–3.90) ‡	6.2±2.1	6.9±2.3	1.59 (1.02–2.50) ‡	1.22 (0.71–2.08)
T ₋₂	30	6.8±1.5	7.3±1.6	1.55 (0.85–2.82)	1.48 (0.78–2.81)	6.9±2.2	6.8±2.2	0.90 (0.52–1.56)	0.81 (0.41–1.64)
Knee flexors									
T ₀	57#	4.9±1.1	5.0±1.0	1.14 (0.74–1.75)	1.07 (0.64–1.79)	4.0±1.3	3.8±1.6	1.45 (0.94–2.22)	1.23 (0.75–2.04)
T ₋₂	29#	5.1±1.2	5.0±1.0	0.97 (0.59–1.61)	0.98 (0.58–1.66)	4.0±1.4	3.7±1.7	0.84 (0.43–1.64)	1.01 (0.39–2.63)
Knee extensors, longitudinal (2 year) change									
T ₋₂ to T ₀	30	−0.2±0.9	−0.2±1.0	1.00 (0.57–1.78)	1.17 (0.62–2.20)	−1.1±1.5	0.3±1.8	3.34 (1.32–8.48) ‡	3.76 (1.04–13.60) ‡
Knee flexors, longitudinal (2 year) change									
T ₋₂ to T ₀	29#	0.0±0.5	−0.1±0.6	0.90 (0.51–1.58)	0.95 (0.53–1.72)	−0.7±1.3	0.0±1.3	2.01 (0.96–4.22)	1.75 (0.73–4.23)

* A case-control conditional logistic regression odds ratio (case-control OR) of >1 represents greater odds of a KR in the presence of less ACSA or specific-strength, or greater loss of these parameters over time. ORs are based on standardized measures (per SD of ACSA and specific-strength at each interval).

ACSA, anatomical cross-sectional area; 95% CI=95% confidence interval; T₀=examination prior to occurrence of KR (2 years); T₋₂=examination 2 years prior to T₀. ACSA is adjusted for individual femur size.

† Case-control OR after adjustment for the effects of pain at the start of each interval.

‡ P<0.05 versus controls by paired t-test.

One participant had flexor strength values of <10N at T₀ and T₋₂, with extensor strength within normal range, suggesting the measurement of flexor strength was inaccurate. Hence this participant's flexor result was not included in this analysis.

Table 3

Male: ACSA (cm²) and specific-strength (Newton/cm²) in the KR cases and matched non-KR controls *

	No. matched pairs analyzed	ACSA		Case-control OR (95% CI)	Case-control OR _{pain} (95% CI) ‡	Specific-strength		Case-control OR (95% CI)	Case-control OR _{pain} (95% CI) ‡
		Mean ± SD, cm ²				Mean ± SD, N/m ²			
		Cases	Controls			Cases	Controls		
Knee extensors									
T ₀	42	7.2±1.5	8.1±1.8	2.06 (1.12–3.77) ‡	2.22 (1.04–4.76) ‡	7.1±1.8	6.7±1.7	0.79 (0.51–1.25)	0.59 (0.30–1.15)
T ₋₂	25	7.6±1.6	8.1±1.8	1.59 (0.75–3.40)	1.24 (0.52–2.93)	7.2±1.6	6.7±1.6	0.71 (0.40–1.27)	0.64 (0.29–1.41)
Knee flexors									
T ₀	42	5.1±1.0	5.4±1.2	1.35 (0.83–2.18)	1.33 (0.74–2.38)	4.3±1.5	3.8±1.4	0.78 (0.51–1.18)	0.75 (0.44–1.25)
T ₋₂	25	5.4±1.1	5.5±0.9	1.20 (0.56–2.56)	1.18 (0.45–3.07)	4.5±1.6	3.7±1.6	0.68 (0.38–1.20)	0.63 (0.30–1.30)
Knee extensors, change									
T ₋₂ to T ₀	25	-0.2±0.7	-0.1±0.8	1.12 (0.63–2.00)	1.33 (0.64–2.78)	-0.1±1.4	-0.2±1.3	0.94 (0.45–1.96)	0.66 (0.26–1.72)
Knee flexors, change									
T ₋₂ to T ₀	25	-0.2±0.5	-0.1±0.7	1.26 (0.66–2.39)	1.37 (0.62–3.02)	-0.1±1.4	-0.1±1.2	0.95 (0.46–1.95)	0.87 (0.36–2.12)

* A case-control conditional logistic regression odds ratio (case-control OR) of >1 represents greater odds of a KR in the presence of less ACSA or specific -strength, or greater loss of these parameters over time. ORs are based on standardized measures (per SD of ACSA and specific strength at each interval).

ACSA, anatomical cross-sectional area, 95% CI=95% confidence interval; T₀=examination prior to occurrence of KR (2 years); T₋₂=examination 2 years prior to T₀. ACSA is adjusted for individual femur size.

† Case-control OR after adjustment for the effects of pain at the start of each interval.

‡ P<0.05 versus controls by paired t-test.