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Effect of Knee Extensor Strength on Incident Radiographic and Symptomatic Knee Osteoarthritis in Individuals with Meniscal Pathology: The MOST Study

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Abstract

Objective—High knee extensor strength may be important to protect against development of knee osteoarthritis (OA) in populations at elevated risk, such as individuals with meniscal pathology. We investigated the extent to which high knee extensor muscle strength was associated

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Ali Guermazi is President of Boston Imaging Core Lab (BICL), LLC and Consultant to MerckSerono, Genzyme, OrthoTrophix and TissueGene. Frank Roemer: CMO, Shareholder BICL, LLC.

with a decreased risk of developing radiographic or symptomatic knee OA in individuals with medial meniscal pathology.

Methods—We studied knees that at the baseline visit of the Multicenter Osteoarthritis (MOST) Study had medial meniscal pathology but did not have radiographic knee OA (373 knees in 373 participants) or symptomatic knee OA (combination of radiographic knee OA and frequent knee symptoms) (531 knees in 531 participants), respectively. Isokinetic knee extensor strength was measured at baseline, and participants were followed for development of incident radiographic knee OA, or incident symptomatic knee OA at 84 months. Separate binomial regression analyses with robust standard errors adjusted for age, history of knee surgery, physical activity level and clinic site were conducted for men and women.

Results—High knee extensor strength (normalized by allometric scaling) was associated with a reduced risk of radiographic knee OA in women (relative risk: 0.52; 95% CI: 0.29 to 0.94) but not in men (0.56; 0.27 to 1.16). High knee extensor strength did not protect against the development of symptomatic knee OA, either in women or in men.

Conclusion—The results only partly confirm the hypothesis that high knee extensor muscle strength protects against later development of knee OA in individuals with medial meniscal pathology.

Introduction

Subjects with knee osteoarthritis (OA) have lower knee extensor muscle strength compared with healthy aged-matched controls (1–4). Consequently, several observational studies have investigated the hypothesis that low knee extensor muscle strength is a risk factor for the development of knee OA. Individual studies have reported low baseline knee extensor strength in women who later developed incident radiographic knee OA (5) and that a reduced knee extensor strength in women is associated with an increased risk of joint space narrowing (6). Furthermore, it has been reported that a high baseline knee extensor strength reduces the risk of self-reported knee and hip OA in women (14 years follow-up) (7) and that a high strength protects against incident symptomatic knee OA in men and women (8). These findings were recently summarized in a systematic review and meta-analysis reporting low knee extensor strength to be a risk factor for the development of knee OA in both men and women regardless of knee OA definition (9). High knee extensor strength for protection against knee OA development may be even more important in populations at elevated risk. Individuals with knee injury or other knee pathology due to degenerative changes constitute such ‘high risk’ populations (10). In particular, high rates of subsequent knee OA have been reported in middle-aged and older individuals with degenerative meniscal lesions that typically are not associated with knee trauma (11), and may or may not have undergone surgical treatment (i.e. partial or total meniscectomy) (12,13). Knee pathology in general is known to be associated with impaired muscle function (14,15); thus individuals with a combination of knee injury or degenerative meniscal tears and low muscle strength may be at particularly high risk for knee OA. Indeed, a recent systematic review and meta-analysis reported middle-aged and older patients who had undergone meniscectomy to have impaired knee extensor strength up to 4 years post surgery (14). However, the importance of this impaired knee extensor strength in the risk for later knee OA has *not* been investigated in individuals with meniscal pathology.

Therefore, the aim of this study was to investigate whether higher knee extensor muscle strength was associated with a lower risk of incident symptomatic and incident radiographic knee OA in individuals with medial meniscal pathology. We focused on subjects with medial meniscal tears and/or extrusions, given the high prevalence of degenerative tears in this compartment (16), as well as the higher incidence of medial compared with lateral compartment knee OA (17).

Methods

The Multicenter Osteoarthritis Study (MOST) is a longitudinal cohort study of 3026 community-dwelling men and women (age 50–79 years at baseline) with or at elevated risk of knee OA. The enrollment procedures have been described previously (18). In short, participants were recruited through mass mailings and advertisements. Eligibility was screened by a telephone interview discussing known knee OA risk factors, including knee injury or surgery and obesity. Potential participants were excluded if a history of (or a planned) bilateral knee replacement, non-resected cancer (with the exception of non-melanoma skin cancer), history of chemotherapy or radiation therapy, history of rheumatologic disease was present, or the participant had planned to move out of the area within the first 3 years of enrollment.

The study was approved by the investigators' institutional review boards. All participants provided written informed consent using an institutional review board–approved consent process.

For the current study, we included MOST study participants as detailed in Figure 1. Each participant contributed only one knee, as we sampled from the participants selected for the MOST 60-month and 84-month follow-up paired knee MRI readings; these readings were carried out in one knee (randomly chosen) per person. For the study of incident radiographic whole knee OA (Kellgren–Lawrence (KL) grade 2 or higher), patients without tibiofemoral or patellofemoral knee OA (i.e. having KL grade 0 or 1) at baseline were eligible. For the study of incident symptomatic whole knee OA, eligible participants did *not* have the combination of radiographic whole knee OA and frequent knee symptoms at baseline (see below). Further, we excluded knees of participants who reported pain that prevented them from attempting the knee extensor strength test.

Strength measurements

Concentric knee extensor muscle strength was assessed using an isokinetic dynamometer (Cybex 350, Avocent, Huntsville, AL) at a knee angular velocity of 60 degrees/second, according to a protocol previously described in detail (8). In short, participants performed 3 practice trials with 50% effort followed by 4 trials for the knee flexors and extensors to achieve maximal torque (Nm) following instructions from a standardized script. In a validity study conducted concurrently with the MOST, the strength testing protocol had high reliability (intraclass correlation coefficient of 0.94 (0.82–0.99), a coefficient of variation of

8% (6–12%), and a within-subject variation of 6.3 Nm (4.71–9.63)). In this analysis, only strength measures for the knee extensors were used. To account for body size, peak torque (Nm) was normalized using published allometric scaling equations for older adults ($Nm*kg^{-0.74}$) (19).

Meniscal pathology

Baseline medial meniscal pathology was scored in participants with available magnetic resonance image (MRI) scans (1.0T sagittal and axial fat-suppressed fast spin-echo proton density-weighted sequences and coronal STIR). The full details of the MRI pulse sequence protocol have previously been described (20). The images where read by two musculoskeletal radiologists (AG and FWR) blinded to the participants' clinical and radiographic data. Meniscal integrity (i.e. tears and maceration) was scored according to the whole-organ MRI score (WORMS) method (21). Medial and lateral meniscal extrusion was scored as previously described as **0**, none; **1**, <50% extruded; **2**, ≥50% extruded (22).

For analysis purposes, medial meniscal pathology was defined dichotomously (i.e. 'no meniscal pathology' and 'meniscal pathology') combining the constructs 'meniscal integrity' and 'meniscal extrusion' for the medial compartment. Participants were characterized as having medial meniscal pathology if they had a medial meniscal WORMS grade >0 in either segment and/or medial meniscal body extrusion grade >1.

Knee radiograph assessments

Weight-bearing, fixed-flexion posteroanterior (23) and lateral (24) knee radiographs were obtained at baseline and at 84 months according to the MOST radiograph protocol, as previously described (25). Radiographs were taken of the contralateral knee in participants with unilateral knee replacement. Baseline and follow-up radiographs of the participants were paired and scored by 2 independent readers (an experienced academically-based musculoskeletal radiologist and a rheumatologist experienced in study reading) according to the K/L scale (26). The readers were not blinded to radiograph sequence, but they were blinded to the subjects' clinical characteristics including their knee strength and meniscal status. For cases where the 2 readers disagreed on the presence of incident radiographic tibiofemoral or patellofemoral OA, an adjudication panel of 3 experienced readers decided.

Knee symptoms

At both the baseline assessment and at the 84-month follow-up assessment, participants were asked about the presence of frequent knee symptoms twice - during a telephone interview and at a clinic visit. During the telephone interviews, trained and certified interviewers asked participants: "During the past 30 days, have you had pain, aching or stiffness in or around your knee on most days?" Knee symptoms were assessed again at the clinic visit, where the participants were asked the same question again about knee pain, aching, and stiffness. If a participant responded negatively on either the telephone interview or the baseline visit questionnaire, he/she was not considered to have frequent knee symptoms at baseline.

At the 84-month telephone screen and clinic visit, participants were asked again the same question regarding pain, aching, and stiffness in their knee on most of the past 30 days. Incident knee symptoms were defined by an affirmative response on both the telephone interview and the clinic visit at 84 months when both had not been affirmative at baseline.

Physical activity

At baseline, participants completed the validated Physical Activity Scale for the Elderly (PASE) questionnaire for calculation of physical activity level (27).

Incident radiographic whole knee OA definition

Knees met the criteria for incident radiographic knee OA if they had no radiographic knee OA in either the tibiofemoral or patellofemoral joints at baseline, and had radiographic tibiofemoral OA (KL grade ≥ 2) and/or patellofemoral OA on the 84-month visit radiographs. Due to the focus on medial meniscal pathology, and thus incident medial compartment knee OA in the present study, we excluded those with incident lateral compartment knee OA. This was done by excluding those participants with a lateral tibiofemoral joint space narrowing grade at 84 months that was higher than the medial tibiofemoral joint space narrowing grade based on the OARSI atlas.

Incident symptomatic whole knee OA definition

Knees met criteria for incident symptomatic whole knee OA at 84-month follow-up if: 1) at baseline they had no radiographic knee OA regardless of symptoms, but at the 84-month follow-up had the combination of radiographic knee OA and knee symptoms on both the screen and clinic visit (i.e. positive x-ray and frequent symptoms); or 2) at baseline had radiographic knee OA (x-ray positive) but did not have symptoms on both the screen and clinic visit (symptoms positive/negative or symptoms negative/negative), but at the 84-month follow-up had knee symptoms both times when asked (symptoms positive/positive); or 3) they had no radiographic knee OA or symptoms at baseline (x-ray negative and symptoms negative) and underwent knee arthroplasty between baseline and follow-up as treatment for OA.

Statistical analysis

Participant characteristics were summarized as means and frequencies. Maximal isokinetic knee extensor strength normalized using allometric scaling ($Nm*kg^{-0.74}$) at baseline was categorized into sex-specific tertiles (low, middle and high). We tested the association of the different categories of knee extensor strength in participants with medial meniscal pathology at baseline with incident radiographic and symptomatic whole knee OA using binomial regression with robust standard errors. Separate analyses were conducted for men and women, including known correlates with knee extensor strength or knee OA (i.e., age, history of knee surgery and PASE) as well as clinic site in the multivariable models. Risk ratios were estimated for each of the muscle strength tertiles using the lowest tertile as reference. The corresponding analyses were originally also planned in the subset of participants *without* meniscal pathology to examine whether the effects of strength on incident OA differed based upon presence or absence of meniscal pathology. However, this was not feasible due to the low number of knees developing radiographic OA (42 of 327) and symptomatic whole knee OA (19 of 394), respectively, in this subset. We considered a two-tailed p-value <0.05 to be statistically significant.

Results

The study sample sizes for incident radiographic and incident symptomatic whole knee OA, respectively were 373 and 531 participants (one study knee per participant) (Figure 1). Their mean age was about 62 years, mean BMI 29 and about 54% were women in both sub-cohorts (Table 1).

In the analysis of incident radiographic knee OA, 42 of 173 men (24%) and 57 of 200 women (29%) developed radiographic whole knee OA by the 84-month visit in the study knee. In men with medial meniscal pathology, we observed no statistically significant association between baseline knee extensor strength and incident radiographic whole knee OA. However, in women with medial meniscal pathology, higher knee extensor muscle strength at baseline was associated with reduced risk of incident radiographic whole knee OA compared to those with lower knee extensor strength (Table 2).

In the analysis of incident symptomatic radiographic knee OA, 29 of 240 men (12%) and 36 of 291 women (12%) developed symptomatic whole knee OA in the study knee by 84-month follow-up. The proportion in each strength tertile that developed incident symptomatic OA was small. We observed no statistically significant associations between knee extensor muscle strength and risk of symptomatic whole knee OA in either men or women (Table 3).

Discussion

In the present study, we investigated the importance of knee extensor muscle strength as a risk factor for the development of radiographic or symptomatic knee OA, in participants known to be at elevated risk for knee OA due to medial meniscal pathology (13). We found higher knee extensor strength to be associated with reduced risk of radiographic knee OA in women but not in men. However, higher knee extensor strength did not significantly protect against the development of symptomatic knee OA in either women or men.

Knee extensor muscle weakness is reported to be a risk factor for knee OA (9). We hypothesized that high knee extensor strength may be particularly important to delay or prevent knee OA development in participants already at higher risk of knee OA, such as those with medial meniscal pathology. Indeed, a recent systematic review and meta-analysis revealed that thighs of middle-aged and older individuals undergoing meniscal surgery show reduced knee extensor muscle strength both prior to surgery and up to 48 months after surgery (14). The results of the present study only partially confirm our hypothesis, as we observed a protective effect of high knee extensor muscle strength only for incident radiographic knee OA in women. However, it needs to be acknowledged that the proportion of participants developing symptomatic knee OA was small and there was insufficient statistical power to detect an association between knee extensor strength and development of symptomatic OA.

The reason for only finding a protective effect of knee extensor strength on radiographic knee OA in women compared to men is not known but have been observed in several individual reports (5,8). However, one potential explanation may be that, regardless of gender, a certain amount of absolute strength may be necessary to protect the knee joint. To this end, women in the lowest tertile may be too weak to achieve this, which may lead to the observed association in women only.

Meniscal pathology is one of the strongest risk factors for the development of cartilage loss and knee OA (13,28). However, to determine risk factors in complex causal pathways that are not fully understood, there is always a risk of introducing bias in the sample selection and analyses. For example, in the present analysis, based on knees with meniscal pathology at baseline, meniscal pathology may be a common effect of the exposure being studied (i.e. muscle weakness) and the OA process itself, i.e. a collider. Although we have required all study participants to be free of radiographic OA at baseline (defined by KL grade 0 or 1), we cannot exclude the possibility of inducing spurious associations due to collider-stratification bias. In this instance the bias may go in different directions depending on the underlying assumptions. However, it is not likely to be strong enough to explain an OR of 0.5. Further, enrichment of the MOST cohort with other OA risk factors as well as the inclusion of the subset of MOST participants with MRI images that were read at the baseline exam (Figure 1) make interpretation of risk challenging. Additionally, knees that developed KL grade 4 OA or had a joint replacement before the 84 months follow-up were not included in this analysis. A sensitivity analysis using a different selection approach was performed and did not change the interpretation of the data. Another important limitation to the present study is that we originally planned to conduct similar analyses in those MOST participants *without* medial meniscal pathology at baseline for comparison with the analyses on those *with* meniscal pathology. However, the multivariable models did not converge due to the low number of participants developing OA in this subgroup, leaving no results for comparison, highlighting the importance of meniscal integrity to maintain a healthy knee. Finally, it is not possible for us to know if the participants with lower knee extensor strength already had lower strength prior to development of their meniscal pathology (i.e., meniscal pathology is an intermediate in the causal chain of events from low muscle strength to knee OA) or if lower knee extensor strength developed as a consequence thereof. Such information may have implications for the interpretation of the results. Future studies should investigate if knee extensor muscle weakness precedes or is a consequence of meniscal pathology.

In conclusion, we found lower risk of incident radiographic knee OA in women with medial meniscal pathology having higher knee extensor muscle strength than in those having lower strength, but this was not observed for men. In contrast, knee extensor strength was not significantly associated with incident symptomatic knee OA.

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Significance and innovations

- A high baseline knee extensor strength was associated with reduced risk of developing radiographic knee osteoarthritis in women with medial meniscal pathology.
- A high baseline knee extensor strength did not protect against later onset of radiographic knee osteoarthritis in men with medial meniscal pathology.
- A high baseline knee extensor strength did not protect against later development of symptomatic radiographic knee osteoarthritis.

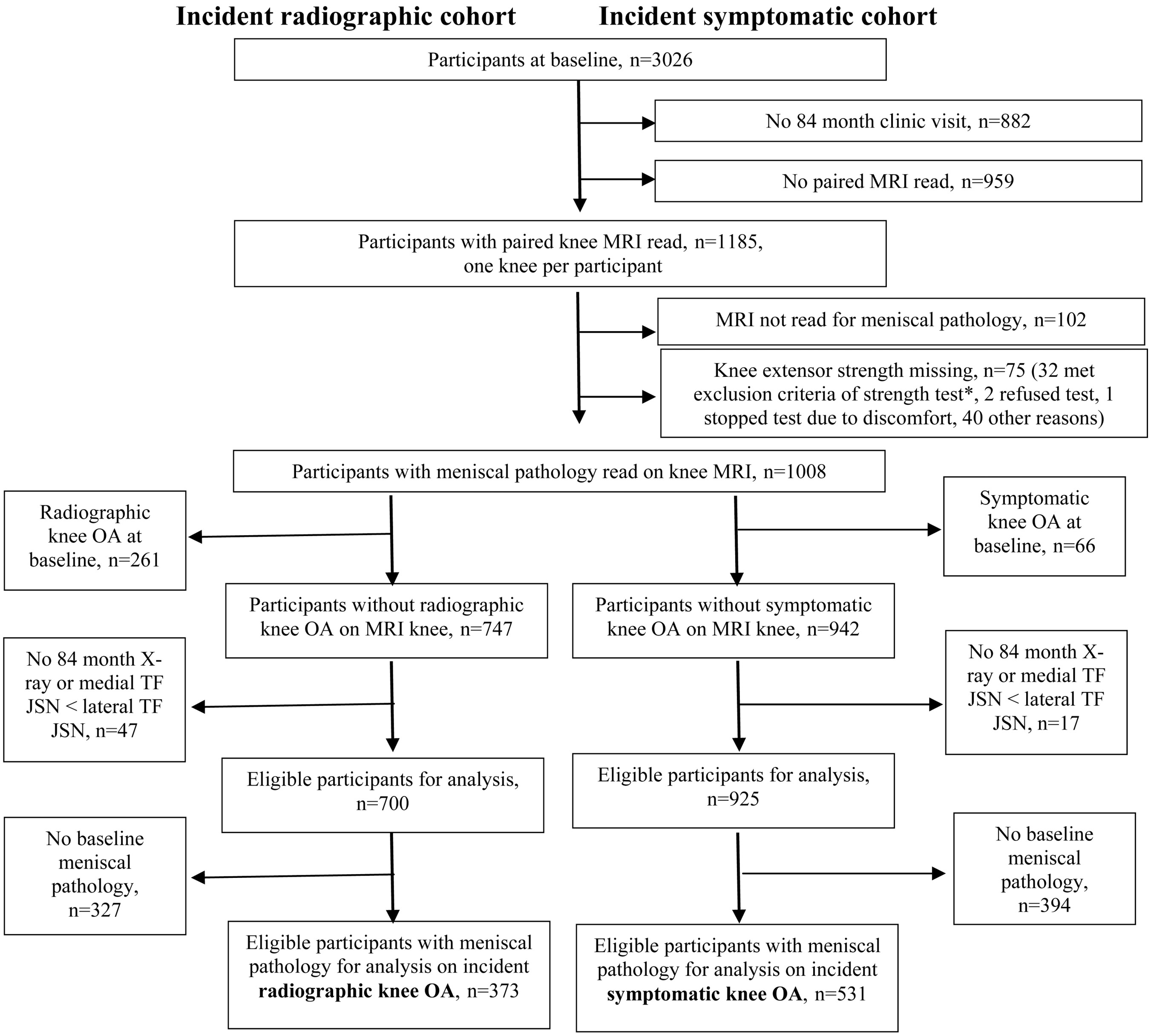

Figure 1.

Participant inclusion flow chart.

*The exclusion criteria included having blood pressure >199 mmHg (systolic) or greater than 109 mmHg (diastolic), an aneurysm in the brain, cerebral hemorrhage in the last six month, knee or hip replacement in the past 3 months, back surgery, heart attack in the past six weeks, hernia in the groin that has not been operated on.

Table 1

Baseline characteristics of participants *with* medial meniscal pathology

	No baseline radiographic knee OA (n=373)	No baseline symptomatic knee OA (n=531)
Age, years	61.3 (7.5)	62.2 (7.7)
Women, n	200 (53.6%)	291 (54.8%)
BMI, kg/m^2	29.0 (4.4)	29.2 (4.4)
PASE score	186.3 (84.9)	183.0 (83.0)
Knee alignment, n *		
Varus (<179°)	163 (44.1%)	248 (47.1%)
Neutral (179°–181°)	162 (43.8%)	215 (40.5%)
Valgus (>181°)	45 (12.2%)	64 (12.1%)
Kellgren Lawrence grade, n		
0	261 (70.0%)	274 (52.0%)
1	112 (30.0%)	127 (23.9%)
2		76 (14.3%)
3		53 (10.0%)
4		1 (0.2%)
Previous knee surgery, n	21 (5.6%)	45 (8.5%)
Quadriceps torque (Nm)		
Women	73.7 (25.4)	72.5 (24.9)
Men	129.4 (43.8)	128.1 (42.8)
Allometry scaled quadriceps torque (Nm*kg$^{-0.74}$)		
Women	3.0 (1.0)	2.9 (1.0)
Men	4.5 (1.5)	4.4 (1.5)

BMI = Body Mass Index, PASE = Physical Activity Scale for the Elderly, Nm = Newton meter.

* Hip-Knee-Ankle angle was missing for 3 and 4 participants in the incident radgiographic and symptomatic cohort, respectively.

Table 2

Association between knee extensor strength and incident *radiographic* whole knee osteoarthritis in participants with medial meniscal pathology.

Men	Cases/n	RR (95% CI)*	RR (95% CI)**
Lowest tertile, 0.45–3.82 $Nm*kg^{-0.74}$	15/53	1.0	1.0
Middle tertile, 3.83–5.18 $Nm*kg^{-0.74}$	16/60	0.91 (0.50–1.67)	0.90 (0.49–1.63)
Highest tertile, 5.19–8.53 $Nm*kg^{-0.74}$	11/60	0.61 (0.30–1.25)	0.56 (0.27–1.16)
Test for linear trend, *P*		0.1765	0.1159
Women			
Lowest tertile, 0.33–2.52 $Nm*kg^{-0.74}$	26/64	1.0	1.0
Middle tertile, 2.53–3.37 $Nm*kg^{-0.74}$	18/69	0.68 (0.41–1.13)	0.70 (0.43–1.15)
Highest tertile, 3.38–5.48 $Nm*kg^{-0.74}$	13/67	0.53 (0.30–0.96)	0.52 (0.29–0.94)
Test for linear trend, *P*		0.0269	0.0223

RR = relative risk, 95% CI = 95% confidence intervals

*Model adjusted for age and clinic site

**Model adjusted for age, clinic site, history of knee surgery and Physical Activity Scale for the Elderly

Table 3

Association between knee extensor strength and incident *symptomatic* whole knee osteoarthritis in participants with medial meniscal pathology.

Men	Cases/n	RR (95% CI)*	RR (95% CI)**
Lowest tertile, 0.45–3.82 $Nm*kg^{-0.74}$	10/81	1.0	1.0
Middle tertile, 3.83–5.18 $Nm*kg^{-0.74}$	11/80	1.00 (0.44–2.25)	1.04 (0.47–2.30)
Highest tertile, 5.19–8.53 $Nm*kg^{-0.74}$	8/79	0.63 (0.25–1.61)	0.68 (0.27–1.68)
Test for linear trend, *P*		0.3354	0.4107
Women			
Lowest tertile, 0.33–2.52 $Nm*kg^{-0.74}$	15/94	1.0	1.0
Middle tertile, 2.53–3.37 $Nm*kg^{-0.74}$	12/100	0.88 (0.44–1.75)	0.90 (0.45–1.79)
Highest tertile, 3.38–5.48 $Nm*kg^{-0.74}$	9/97	0.73 (0.34–1.56)	0.74 (0.35–1.55)
Test for linear trend, *P*		0.4112	0.4223

RR = relative risk, 95% CI = 95% confidence intervals

* Model adjusted for age and clinic site

** Model adjusted for age, clinic site, history of knee surgery and Physical Activity Scale for the Elderly