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ORIGINAL REPORT

NONLINEAR RELATIONSHIP BETWEEN ISOKINETIC MUSCLE STRENGTH AND ACTIVITY LIMITATIONS IN PATIENTS WITH KNEE OSTEOARTHRITIS: RESULTS OF THE AMSTERDAM-OSTEOARTHRITIS COHORT

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Objective: **To investigate whether relationships between upper leg muscle strength and activity limitations are non-linear in patients with knee osteoarthritis, and, if so, to determine muscle strength thresholds for limitations in daily activities.**

Design: **Baseline data were used for 562 patients with knee osteoarthritis in the Amsterdam-Osteoarthritis cohort. Upper leg muscle strength (Nm/kg) was measured isokinetically. Activity limitations were measured with the timed Get Up and Go test and timed Stair Climb Test, subdivided into stair-ascent and stair-descent. Linear and non-linear relationships between muscle strength and activity limitations were evaluated, and thresholds were determined.**

Results: **Non-linear models improved model fit compared with linear models. The improvement in percentage variance accounted for was 5.9, 8.2 and 5.2 percentage points for the timed Get Up and Go, stair-ascent and stair-descent times, respectively. Muscle strength thresholds were 0.93 Nm/kg (95% confidence interval (95% CI) 0.82–1.04), 0.89 Nm/kg (95% CI 0.77–1.02) and 0.97 Nm/kg (95% CI 0.85–1.11) for relationships with timed Get Up and Go, stair-ascent and stair-descent times, respectively.**

Conclusion: **In patients with knee osteoarthritis, relationships between muscle strength and activity limitations are non-linear. Patients with muscle strength below the described thresholds might benefit more from muscle strength training to reduce limitations in daily activities than would patients with muscle strength above the thresholds. Further research is needed to assess the clinical value of the thresholds determined.**

Key words: knee osteoarthritis; muscle strength; threshold; activity limitation.

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Osteoarthritis (OA) of the knee joint is a leading cause of activity limitations (1–4), defined as the difficulties an individual may have in executing activities such as rising from a chair, walking and stair climbing (3).

Performing daily activities requires sufficient strength in the quadriceps and hamstrings (1, 4, 5). In a large number of cross-sectional studies, reduced muscle strength was consistently found to be related to activity limitations (1, 5–7). Moreover, emerging evidence from longitudinal studies in patients with knee OA demonstrates that reduced muscle strength is a risk factor for developing activity limitations (4, 8–11).

In previous work in our group (3, 11, 12) and others (13), relationships between muscle strength and activity limitations have been modelled as linear. However, other research groups have found that the ability to perform daily activities is determined by a threshold level of muscular strength: individuals lacking the requisite strength may not be able to perform basic activities of daily living (6, 10, 14). The presence of a threshold suggests non-linearity in the relationship. Although a non-linear relationship between muscle strength and activity limitations has been reported in older adults, in patients with a total knee arthroplasty and in those with hip OA (6, 7, 10, 14–16), non-linearity has never been studied in patients with knee OA. In the study by McAlindon et al. (7) a threshold effect was suggested, but not investigated, in patients with knee OA.

We hypothesized that, in a large sample of patients with knee OA, non-linearities can be observed in the relationship between isokinetically measured upper leg muscle strength and activities that are frequently impaired in patients with knee OA.

At present, there is great demand for information about muscle strength thresholds from health professionals and researchers (17, 18). Knowledge of muscle strength thresholds can help to identify patients who are more likely to benefit from muscle strength training in order to reduce limitations in daily activities (6, 10, 14, 15). We hypothesized that thresholds for upper leg muscle strength are different for the timed Get Up and Go (GUG) test and timed Stair Climb Test (SCT).

The aim of this study was to investigate whether relationships between upper leg muscle strength and activity limitations are non-linear in patients with knee

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OA and, if so, to determine muscle strength thresholds for limitations in daily activities.

METHODS

Study population

The study was performed with the Amsterdam-Osteoarthritis (AMS-OA) cohort of Reade, Outpatient Center for Rehabilitation and Rheumatology, Amsterdam, the Netherlands. The AMS-OA cohort consists of participants aged 18 years and older with OA of the knee and/or hip according to the clinical criteria of the American College of Rheumatology (ACR) (19, 20). Participants with OA of the knee were included in the present study. Furthermore, muscle strength data from both legs should be available, as well as results from at least one performance-based test. Exclusion criteria were: total knee replacement or any other causes of arthritis (e.g. rheumatoid arthritis, spondylarthropathy, crystal arthropathy or septic arthritis) (19, 20). Participants were assessed by rheumatologists, radiologists and rehabilitation physicians. The measurement protocol contained the assessment of demographic, clinical, radiographic, biomechanical and psychosocial factors related to OA. Medical Ethics Committee approval was obtained from the Slotervaart hospital and Reade, and, informed consent was obtained from participants. For the present study baseline data for participants with knee OA, recruited between 10 October 2008 and 22 May 2014, were used.

Measurements

Measurements were performed by trained assessors from the clinimetric laboratory at Reade.

Muscle strength. Isokinetic muscle strength (in Nm/kg) was measured (EnKnee, Enraf-Nonius, Rotterdam, the Netherlands) at a velocity of 60°/s for the knee extensor and flexor muscles, measured separately for the right and left leg. First, the mean muscle strength of 3 maximal test repetitions was taken for the left and right leg. Subsequently, total upper leg muscle strength was calculated as the sum of the mean muscle strength of the left and right leg and normalized for body weight (Nm/kg). Mean muscle strength of both legs was analysed because, for the daily activities chosen in this study, optimal muscle strength from both legs is required to perform those activities. Also, the correlation between muscle strength of the right and left legs was high ($r=0.81$). Moreover, 405 (72.1%) of the 562 patients included in this study were diagnosed with bilateral knee OA based on the ACR criteria (21). Muscle strength measured with an isokinetic dynamometer has shown excellent test-retest reliability (intercorrelation coefficient (ICC) 0.93) in patients with knee OA (22).

Activity limitations. Two performance-based tests were used to measure activity limitations: the timed GUG test and the timed SCT. Both tests are a good representation of daily activities that pose a problem in patients with knee OA (12, 23, 24).

Get Up and Go test. Patients were sitting in a standard-height chair with armrests (49 cm high). They were instructed to rise from the chair on the command "go" without making use of the armrests and walk a distance of 15.2 m along an unobstructed corridor. The instruction was to walk as fast as possible without a loss of safety and comfort. Patients were not allowed to run. The time required to reach the 15.2-m mark on the floor was measured with a stopwatch. A longer time to complete this test represents greater activity limitations (3, 12). The timed GUG test has been shown to be reliable (23).

Stair Climb Test. The timed SCT was subdivided into stair-ascent and stair-descent. For the timed stair-ascent test, patients started at the bottom of the steps by standing on a line 58 cm from the first step. On the command "go" patients ascended 12 steps, each 16 cm high, and with a step width of 30 cm as fast as possible without a loss of safety and comfort. Patients were not allowed to run. For safety, handrail support was not prohibited, but patients were encouraged not to use the handrail. Time was stopped with a stopwatch when patients reached the top of the stairs with both legs. For the timed stair-descent test, patients started at the top of the stairs. Instructions were the same as for the stair-ascent test, except that the time was stopped when patients reached the bottom of the stairs with both legs. A longer time to complete the test represents greater activity limitations (3). The test has shown good test-retest reliability (22, 24).

Potential confounders

The following potential confounders were considered relevant in the present study: sex, age, unilateral or bilateral knee OA, duration of complaints, radiographic severity, pain and comorbidities. Age was recorded in years. The diagnosis of unilateral or bilateral knee OA was based on the ACR criteria (21). Duration of knee complaints was divided into 7 categories: ≤1 month, 1–3 months, 4–6 months, 7–12 months, 13–24 months, 25–59 months or ≥5 years. Radiographic severity of knee OA was reported using the 5 Kellgren/Lawrence (K/L) score categories: no radiographic symptoms (0), doubtful (1), minimal (2), moderate (3) and severe radiographic symptoms (4) (25). The K/L score for the knee with the highest score was used. Pain scores were obtained with a numeric rating scale (NRS). Patients were asked to specify the amount of knee pain that they had experienced during the last week. The scores range from 0 (no pain) to 10 (most imaginable pain). Comorbidities were assessed with the Cumulative Illness Rating Scale (CIRS). The CIRS consists of questions related to 13 different body systems. Each question can be scored from 0 (none) to 4 (extremely severe) according to the severity of the disease. For the present study, it was calculated whether 1 or more comorbidities were present (dichotomous; "yes" or "no") as well as the total number of comorbidities, calculated as the sum of each body system for which a 2 or higher was scored. Item 10, muscle, bone and skin diseases, was excluded from the scoring because all patients were diagnosed with OA and therefore scored positive on this item.

Statistical analysis

Baseline characteristics of the study population were calculated. Moreover, data were checked for normality and scatterplots were made to gain insight into the relationships between muscle strength and activity limitations (26).

Non-linearity. First, linear regression analyses ($Y=a + b * x$) were performed to assess the relationships between muscle strength (independent variable) and activity limitations (dependent variables) using the polyfit and polyval functions in Matlab 7.11.0 (R2010b).

Subsequently, an exponential model, a specific type of non-linear model, was fitted to the data using a least-squares fit and it was checked whether this model improved model fit compared with the linear model. The formula for the exponential model was: Y=a + b * exp (–c*x), in which Y is the activity limitation, a, b and c are model parameters and x is muscle strength. Quadratic and cubic models were also considered, but it was decided to focus on comparing linear and exponential type of models, because the exponential model is biologically more plausible and the simplest appropriate model was preferred; i.e. the exponential model had 1 coefficient (free parameter) less than the cubic model and the percentage variance accounted for (%VAF) (%VAF is the same as R-squared) was comparable between the models. Both types of models, the linear and exponential model, were checked to see which model fitted the data best based on the scatterplots, %VAF, residuals, F-ratio change statistic (F_{change}) and the Akaike information criterion (AIC). For the exponential model, unconstrained non-linear optimization (using fminsearch from the Matlab optimization toolbox (Mathworks, Natick, MA, USA) was performed through which the sum of the squared residuals was minimized. Subsequently, the %VAF was calculated by correlating the model predictions with the actual data. To test whether the improvement between models was significant, F_{change} was calculated as: $F_{change} = \left(\frac{R_C^2 - R_S^2}{df_c - df_s}\right) / \left(\frac{1 - R_C^2}{n - df_c - 1}\right)$, where C is the more complex model, S is the simpler model, df is the degrees of freedom and n is the sample size. The %VAF was calculated as the square of the correlation between the model and the data. Moreover, AIC was calculated to represent the relative quality of both models as: $AIC = N * \ln\left(\frac{RSS}{N}\right) + 2 * df$, where RSS in the residual sum of squares. A lower AIC value means that the model fits better considering the complexity of the model as well as its ability to explain the data. Finally, the influence of potential confounders (i.e. age, sex, duration of complaints, pain, unilateral or bilateral knee OA, radiographic severity and comorbidities) was checked, because it may cause non-linearity. If the regression coefficient of muscle strength changed by 10% or more after adding a potential confounder to the model, this variable was considered to be a confounder.

In secondary analyses men and women were analysed separately because it is known that men generally exert greater absolute maximal force and have higher strength per unit of body mass than women, which could influence the results (28, 29). Results were considered statistically significant at $p < 0.05$.

Thresholds of muscle strength. Because the first derivative of an exponential model never reaches zero, this model does not allow objective definition of a threshold. Therefore, a bilinear model was used to calculate thresholds. If the second slope (i.e. after the threshold) of a bilinear model does not significantly differ from zero, a linear plus constant model is a good alternative to a linear plus linear model. It was decided to use a linear plus constant model for calculating thresholds because the residuals were not properly distributed in a linear plus linear model (systematically above zero at the highest muscle forces). Furthermore, we aimed to restrict the number of model parameters. Thus the bilinear model used in the current study consisted of a linear function plus a constant value above the threshold:

$Y = ((a + a_2 x).*H(x < a_3)) + ((a + a_2 * a_3).*H(x \geq a_3))$, in which Y is the activity limitation, x is muscle strength, a(constant), a_2(slope) and a_3(threshold) are coefficients and H denotes the Heaviside function, which yields 1 if the criterion between brackets is met and 0 otherwise. The coefficients that best fit the linear plus constant model were calculated with the least squares method. The threshold was defined as the intersection point of the linear function with the constant value estimated as a_3.

The %VAF values of the linear plus constant and exponential models were compared to determine whether the %VAF of the linear plus constant model approached the %VAF of the exponential model. If they were comparable, it was deemed appropriate to determine thresholds with linear plus constant models.

The reliability of thresholds was assessed by bootstrapping. One thousand bootstrap repetitions were performed, using 560 samples per bootstrap.

RESULTS

Study population

The study population comprised 562 patients (172 men and 390 women). Table I shows the baseline characteristics of the study population.

Association between upper leg muscle strength and Get Up and Go time

One patient was considered to be an outlier and was excluded from analysis because of morbid obesity and a GUG time of 75.7 s. Another patient was excluded from the analyses because the GUG time was missing. Fig. 1A shows the relationship between muscle

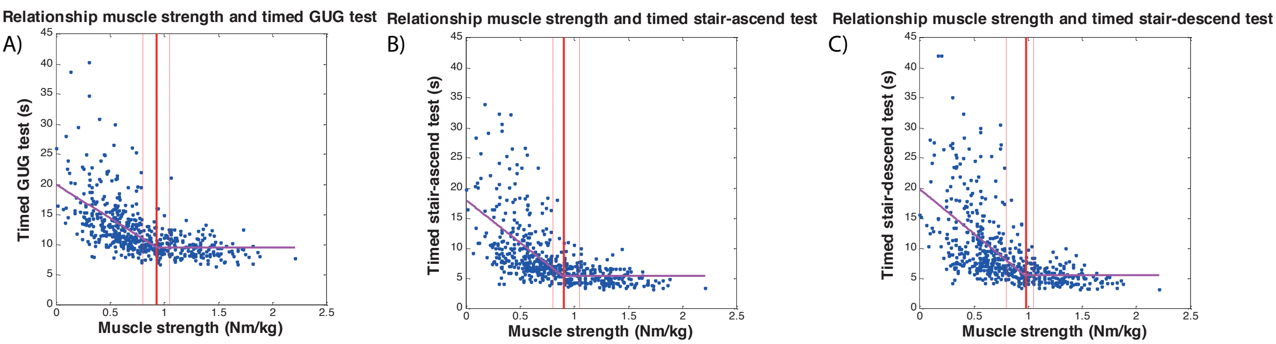

Fig. 1. Relationships between upper leg muscle strength and activity limitations. Solid vertical line: threshold, dashed line: 95% CI, solid line: linear plus constant model. (A) Upper leg muscle strength and timed Get Up and Go (GUG) test, (B) Upper leg muscle strength and timed stair-ascent test. (C) Upper leg muscle strength and timed stair-descent test. More time to perform the test reflects more limitations in daily activities. Therefore, muscle strength below the threshold is related to activity limitations. Note: A strength of 0 Nm/kg means that the patient was not able to move the isokinetic dynamometer at a velocity of 60°/s.

Table I. Baseline characteristics of patients with knee osteoarthritis (OA): total and muscle strength tertiles

Variable	Total (SD) ($n=562$)	Lowest tertile (SD) ($n=187$)	Middle tertile (SD) ($n=187$)	Highest tertile (SD) ($n=188$)
Age, years, mean (SD)	62.1 (8.8)	62.9 (9.8)	62.5 (7.7)	61 (8.6)
Sex, female, %	69.4	93.6	80.9	33.7
BMI, kg/m^2, mean (SD)	30.9 (6.5)	33.8 (7.3)	31.0 (5.4)	28.0 (5.0)
Unilateral/bilateral knee OA[a], %				
Unilateral	27.9	22.5	23.9	37.4
Bilateral	72.1	77.5	76.1	62.6
Duration of complaints, months, %				
≤6 months	8.8	7.5	10.6	8.6
7 months–2 years	21.4	17.1	21.2	25.7
2 years–5 years	18.9	20.9	18.1	17.6
≥5 years	44.3	44.9	42.0	46.0
Missing	6.6	9.6	8.1	2.1
K/L score (0–4), %				
0	5.2	4.8	3.7	7.0
1	29.2	32.1	28.2	27.3
2	26.7	20.9	29.3	29.9
3	20.1	19.3	20.2	20.9
4	15.5	17.6	14.9	13.9
Missing	3.4	5.3	3.7	1.0
NRS pain (0–10), mean (SD)	5.6 (2.2)	6.4 (1.8)	5.5 (2.0)	4.8 (2.2)
Number of comorbidities (CIRS) (0–12), %				
0	51.3	40.6	51.6	64.7
1	25.3	25.7	28.7	21.4
≥2	22.1	32.1	18.7	12.8
Missing	1.2	1.6	1.0	1.1
Isokinetic muscle strength (Nm/kg), mean (SD)	0.79 (0.39)	0.40 (0.14)	0.74 (0.10)	1.24 (0.25)
Isokinetic hamstrings strength (Nm/kg, mean (SD)	0.63 (0.31)	0.32 (0.14)	0.59 (0.11)	0.97 (0.21)
Isokinetic quadriceps strength (Nm/kg), mean (SD)	0.96 (0.49)	0.47 (0.18)	0.89 (0.15)	1.52 (0.34)
Timed GUG test (s), mean (SD)	12.46 (5.28)	15.9 (6.9)	11.5 (2.9)	9.5 (1.9)
Timed stair-ascent test (s), mean (SD)	8.42 (5.25)	12.4 (6.8)	7.6 (2.9)	5.3 (1.5)
Timed stair-descent test (s), mean (SD)	9.41 (6.38)	14.1 (8.0)	8.6 (4.2)	5.6 (1.7)

[a]Based on clinical ACR criteria.
SD: standard deviation; BMI: body mass index; K/L: Kellgren & Lawrence; NRS: numeric rating scale; CIRS: Cumulative Illness Rating; GUG: timed Get Up and Go test.

strength and GUG time ($n=560$). Upper leg muscle strength was associated with GUG time (B=–6.45, 95% CI –7.31 to –5.65, $p<0.001$). Visually, a non-linear (exponential) model seemed to fit better than a linear model. The exponential model (%VAF =37.7, AIC=1,404.8) indeed improved the relationship by 5.9 percentage points compared with the linear model (%VAF=31.8, AIC=1,453.1) ($F_{change}=52.2$, $p=0.01$). Sex and age were found to confound the relationship. The adjusted model is reported in Table II, with sex as constant 1 and age as constant 2.

To identify thresholds, a linear plus constant model could be used as the fit of this model (%VAF=37.3) approached that of the exponential model (%VAF=37.7).

Coefficients for the linear, exponential and linear plus constant model are listed in Table II. The mean threshold of muscle strength after bootstrapping was 0.93 Nm/kg (95% CI 0.82 to 1.04) (Fig. 1A). When confounding variables were added to the linear plus constant model, the threshold was 0.99 Nm/kg, which falls within the confidence interval of the unadjusted model.

Association between upper leg muscle strength and stair-ascent time

Four patients were excluded from the analyses, because their stair-ascent time was missing. In Fig. 1B the relationship between muscle strength and stair-ascent time is shown ($n=558$). Upper leg muscle strength was related to stair-ascent time (B=–7.53, 95% CI –8.70 to –6.29, $p<0.001$). Visually, a non-linear (exponential) model seemed to fit better. The %VAF for the linear model was 31.0 (AIC=1,646.3). The exponential model (%VAF=39.2, AIC=1,577.5) improved the relationship by 8.2 percentage points ($F_{change}=74.9$, $p=0.01$). Sex and total number of comorbidities were found to confound the relationship. The adjusted model is reported in Table II, with sex as constant 1 and total number of comorbidities as constant 2.

The linear plus constant model (%VAF=37.2) slightly decreased model fit compared with the exponential model (%VAF=39.2), but still improved model fit by 6.2 percentage points compared with the linear model. Therefore, it was deemed appropriate to deter-

Table II. Relationship between muscle strength (Nm/kg) and activity limitations (s)

Model	a (95% CI)	b[a] (95% CI)	c[b] (95% CI)	Constant 1[c]	Constant 2[d]	VAF	VAF change[e]
Association muscle strength and timed GUG test (n = 560)							
Linear[f]	−6.45 (−7.31;−5.65)	17.32 (16.45;18.24)				0.32	0
Exponential[g]	7.77 (6.78;8.70)	14.97 (12.78;17.97)	−1.80 (−2.40;−1.26)			0.38	0.06
Adjusted exp. model	5.51 (2.36;8.10)	16.80 (13.64;20.09)	−1.60 (−2.32;−0.95)	−1.78 (−2.64;−0.82) [Sex]	0.06 (0.03;0.10) [Age]	0.43	0.11
Lin + con[h]	19.96 (18.21;21.79)	−11.24 (−14.07;−8.65)	0.93 (0.81;1.06)			0.37	0.05
Association muscle strength and timed stair-ascent test (n = 558)							
Linear	−7.53 (−8.70;−6.29)	14.40 (13.09;15.64)				0.31	0
Exponential	4.19 (2.70;5.49)	18.62 (14.02;24.26)	−2.28 (−3.41;−1.23)			0.39	0.08
Adjusted exp. model	5.09 (3.54;6.14)	18.82 (12.03;26.76)	−2.47 (−4.38;−0.72)	−0.73 (−1.75;0.33) [Sex]	0.71 (0.33;1.12) [Total number of comorbidities]	0.45	0.14
Lin + con	17.95 (15.56;20.40)	−14.12 (−18.35;−10.04)	0.89 (0.78;1.01)			0.37	0.06
Association muscle strength and timed stair-descent test (n = 558)							
Linear	16.58 (15.41;17.55)	−9.02 (−9.96;−7.90)				0.30	0
Exponential	3.09 (0.83;5.19)	20.61 (16.97;25.92)	−1.74 (−2.63;−0.99)			0.35	0.05
Adjusted exp. model	−1.25 (−5.66;2.57)	21.53 (17.65;27.40)	−1.78 (−3.05;−0.65)	−1.19 (−2.61;0.17) [Sex]	0.10 (0.03;0.16) [Age]	0.39	0.09
Lin + con	19.78 (17.43;22.45)	−14.75 (−18.97;−10.95)	0.97 (0.86;1.10)			0.35	0.05

Lin + con = linear plus constant model. [a]$b=a_2$ for the linear plus constant model. [b]$c=a_3$ for the linear plus constant model. [c/d]Constant 1 and 2 are used in the adjusted model: Y=a + b * exp(-c*x) + constant 1 * confounder 1 + constant 2 * confounder 2. [e]The VAF change is calculated with respect to the linear model. [f]Formula linear model: Y=a + b * x. [g]Formula exponential model: Y=a + b * exp(−c*x). Formula linear plus constant model: $Y = ((a+a_2x).*H(x<a_3)) + ((a+a_2*a_3).*H(x \geq a_3))$

mine the threshold with a linear plus constant model. However, a linear plus linear model would be preferred, instead of the linear plus constant model, because the slope of the second line deviated significantly from zero and therefore could not be interpreted as a constant line. Coefficients for the linear, exponential and linear plus constant models are listed in Table II. Bootstrapping yielded a mean threshold of muscle strength of 0.89 Nm/kg (95% CI 0.77 to 1.02) (Fig. 1B). When confounding variables were added to the linear plus constant model, the threshold was 0.89 Nm/kg, which is equal to that of the unadjusted model.

Association between upper leg muscle strength and stair-descent time

Four patients were excluded from the analyses, because stair-descent time was missing. In Fig. 1C the relationship between muscle strength and stair-descent time is shown ($n=558$). Upper leg muscle strength was associated with stair-descent time (B = –9.02, 95% CI –9.96 to –7.90, $p<0.001$). Visually, a non-linear (exponential) model seemed to fit better. The linear model explained 30.1% of the variance (AIC = 1,871.5). Thus, the exponential model (%VAF = 35.3, AIC = 1,830.4) improved the relationship by 5.2 percentage points ($F_{change}=44.5$, $p=0.01$). Sex and age were found to confound the relationship. The adjusted model is reported in Table II, with sex as constant 1 and age as constant 2.

It was appropriate to use a linear plus constant model to calculate thresholds. The fit of the linear plus constant model (%VAF = 34.6) approached that of the exponential model (%VAF = 35.3). Coefficients for the linear, exponential and linear plus constant model are listed in Table II. Bootstrapping resulted in a mean threshold of muscle strength of 0.97 Nm/kg (95% CI 0.85 to 1.11) (Fig. 1C). When confounding variables were added to the linear plus constant model, the threshold was 1.00 Nm/kg, which falls within the confidence interval of the unadjusted model.

Separate analyses for men and women

For the association with GUG time, the exponential model improved the relationship by 20.9 percentage points for men ($F_{change}=91.3$, $p=0.01$) and 3 percentage points for women ($F_{change}=17.5$, p = 0.01). In men and women, 23.3% and 85.6%, respectively, had muscle strength below the threshold. In Table III the thresholds and 95% CI for the different activities for men and women are shown separately.

For the relationship with stair-ascent time, the exponential model improved the relationship by 15.9 percentage points for men ($F_{change}=60.5$, $p=0.01$) and 5.1 percentage points for women ($F_{change}=27.7$, $p=0.01$). In men and women, 34.3% and 83.2%, respectively, had muscle strength below the threshold (Table III). Finally, for the relationship with stair-descent time, the exponential model improved the relationship by 13.5 percentage points for men ($F_{change}=49.0$, $p=0.01$) and

Table III. Results from separate analyses for men and women

Activity (s)	Threshold men (95% CI)	Threshold women (95% CI)
Timed GUG test	0.97 (0.73;1.21)	0.96 (0.78;1.15)
Timed stair-ascent test	0.99 (0.74;1.23)	0.96 (0.50;1.43)
Timed stair-descent test	1.03 (0.88;1.18)	1.00 (0.58;1.42)

95% CI: 95% confidence interval; GUG: GUG: timed Get Up and Go test.

3 percentage points for women ($F_{change}=15.7$, $p=0.01$). Muscle strength was below the threshold in 37.4% of men and 85.2% of women.

DISCUSSION

The aim of the present study was to investigate whether relationships between upper leg muscle strength and activity limitations are non-linear in patients with knee OA, and, if so, to determine muscle strength thresholds for limitations in daily activities. Non-linear (exponential) relationships may imply that patients with muscle strength below a certain threshold benefit more from muscle strength training to reduce activity limitations than patients above the threshold who may show only minor or no benefit.

The results of this study in a relatively large cohort of patients with knee OA showed that non-linear (exponential) relationships, compared with linear relationships, improved model fit of the relationships by 5.9, 8.2 and 5.2 percentage points for, respectively, GUG, stair-ascent and stair-descent time. Previous studies found linear relationships between muscle strength and activity limitations, but included smaller groups of patients with knee OA and may therefore have lacked resolution to find non-linearity (11–13). It should be emphasized that, in those previous studies, the assumptions on linearity were properly checked: we do not want to imply that the previous statistical analyses were not appropriate. The results of our present study are consistent with those reported by Buchner et al. (6). In their study, a quadratic model (another type of non-linear model) explained significantly more variance in the relationship between leg strength and gait speed in healthy elderly subjects than a linear model (22% vs 17%). Their improvement of 5 percentage points is comparable with improvements found in the current study, except for the relationship with stair-ascent time, which showed a larger improvement in our study. A quadratic model was also investigated in the current study, but showed no further improvements compared with the exponential model (data not shown). Moreover, our results are in line with the results by Pua et al. (16), who found that muscle strength was non-linearly associated with self-selected and fast-pace timed stair tests in adults with radiographically confirmed hip OA. The small sample size ($n=100$) was a limitation in their study, but our study confirmed their results in a larger sample size ($n=562$) although patients with knee OA instead of hip OA were measured. Furthermore, our results are in agreement with those found by Ferruci et al. (15), who found a departure from linearity in the relationship between muscle strength and lower extremity performance, measured with walking speed, chair stands and standing balance, in a population-based sample of older women affected by chronic disease and functional limitations.

Sex and age influenced the relationship between muscle strength and activity limitations in our study, but non-linearity remained. However, several other non-studied factors may explain the non-linearity found in our study. These factors, such as proprioception, flexibility, heart rate reserve or VO_2max, may contribute to the non-linearity and thresholds in the relationships found in our study (6, 12, 14, 29).

We were able to determine muscle strength thresholds for limitations in daily activities. For example, muscle strength above 0.97 Nm/kg (95% CI 0.86–1.09) did not lead to a significantly better performance on stair-descent time. If we look more closely at the obtained thresholds and their 95% CI, it is notable that the thresholds of different activities were comparable. Clinically, this means that there is no significant difference in the amount of strength a patient requires to perform the different daily activities that were assessed.

A limited amount of previous studies has determined upper leg muscle strength thresholds for limitations in daily activities. In one study, a threshold effect was suggested in patients with knee OA, but thresholds were not reported (7). Thresholds for muscle strength for different physical activities were found in several studies, but we cannot compare previously found thresholds with ours because muscle strength was measured in a different way, without correction for body weight, measured in a different study population, or related to different activities (6, 10, 14, 15). We are aware that we must be careful when interpreting the results. To our knowledge, this is the first study that has defined thresholds in this way. Further research is needed to confirm these muscle strength thresholds. Furthermore, interpretation of the thresholds determined at the level of the individual patient requires caution since the observed non-linear associations represent a mean, and individual variation will exist. Finally, it is important to note the difference in thresholds for quadriceps and hamstrings strength (see Table SI). In our study, muscle strength of both muscle groups was required to perform the daily activities. Therefore, we analysed the mean muscle strength of both muscle groups. However, different thresholds were found for both muscle groups, which can be useful, for example, for strength training decisions. Further research is needed to confirm these thresholds.

Separate analyses showed that the improvement in model fit between a linear and non-linear model is greater for men than women for all daily activities. The range of muscle strength was higher in men (0.13–2.21

[1]http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2252

Nm/kg), which means that men are more distributed over the whole exponential curve. In contrast, muscle strength of women (0–1.68 Nm/kg) was especially located in the part where a linear relationship fits well. Apart from the scatterplot, thresholds between men and women did not show large differences. The 95% CI of the thresholds for women showed a broad range for stair-ascent time and stair-descent time and are therefore less reliable. In addition, there was a remarkable difference in performance between men and women: among women, 85.6%, 83.2% and 85.2% did not reach the muscle strength thresholds for, respectively, GUG, stair-ascent and stair-descent times, whereas among men only 23.3%, 34.3% and 37.4% did not reach the thresholds. Our findings are in line with the fact that, in general, men can exert a greater absolute maximal force, have lower fat percentage than women and thus higher strength per unit body mass (28, 29). In accordance with our findings, previous research showed that women are more adversely affected than men by knee OA in performing daily activities (30).

A strength of our study is the large sample size of 562 patients, representing a heterogeneous clinical study population. Simultaneously, because of the diverse characteristics of the patients within the study population, future studies should stratify their study population based on factors such as age or body mass index (BMI), to be able to draw conclusions about possible subgroups of patients.

Several limitations of the present study need to be considered. First, we analysed our data cross-sectionally. Therefore, we cannot draw conclusions about possible longitudinal trends in our data. Secondly, for the GUG and stair-descent time linear plus constant models were a good alternative to determine thresholds. For the stair-ascent time, however, the linear plus constant model yielded an inferior fit. Data suggest that this was caused by a negative slope above the threshold instead of a constant value. Hence, patients with muscle strength above the threshold can probably still improve performance on the assessed daily activities somewhat by increasing muscle strength, although the chosen model does not suggest that this is the case. This was also the case for all analyses performed for men only. Finally, a possible ceiling effect in measuring activity limitations needs to be considered (3). At a certain performance level, patients may not have been able to perform any faster, because they were instructed not to run. Nevertheless, for all activities a finite amount of time would be required, making linear models biologically less plausible. The thresholds determined here apply to low-intensity daily activities. It is possible that more demanding activities, like running up a flight of stairs, or moving the body from other positions (for example kneeling, squatting or rising from the floor) have a higher muscle strength threshold.

The results from the current study may have some important implications. Considering the exponential relationships, increasing strength by, for example, muscle strength training may be more effective in reducing activity limitations in patients with low baseline muscle strength compared with patients with high baseline muscle strength. In this study, it was found that 67.5, 63.3 and 71.3% of the patients had a muscle strength below the threshold for, respectively, the relationship with GUG, stair-ascent and stair-descent time. For these patients, muscle strength training may be more effective to reduce limitations in daily activities.

This is in line with the results of Buchner et al. (6), who found that strength training increased both strength and gait speed in frail adults. However, among stronger adults, higher strength was not associated with higher gait speed. Thus, our results may explain why strength training is not equally effective in all patients. Recently, Chmelo et al. (31) found a mean improvement of 8.1% in knee extensor strength after 5 months of resistance training in older adults, but 30% of the participants did not improve physical function. Several other studies also found no improvement in physical functioning in patients with knee OA after an increase in muscle strength (17). Therefore, it may be suggested that training factors other than muscle strength, such as flexibility, proprioception, aerobic capacity or specific tasks, might be more effective in reducing activity limitations when patients have muscle strength above the thresholds reported here. Future longitudinal research, using data from a strength training trial, should focus on differences in effect of strength training for patients below and above the threshold.

In conclusion, non-linear (exponential) models, compared with linear models, improved model fit of the relationships between muscle strength and activity limitations in patients with knee OA. Furthermore, thresholds were determined by using linear plus constant models, which approached the fit of the non-linear (exponential) models. These results suggest that muscle strength training to reduce activity limitations might be more effective in patients with muscle strength below the thresholds. Further research is needed to assess the clinical value of the thresholds determined.

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