Predictive potentials of 8 muscle strength actions, KOOS-pain, and Örebro-psychosocial difficulties on self-reported activities-of-daily-life function in patients with knee osteoarthritis: an exploratory regression-based cross-sectional study

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Research Article

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Posted Date: December 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-114877/v1>

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**Predictive potentials of 8 muscle strength actions, KOOS-pain, and
Örebro-psychosocial difficulties on self-reported activities-of-daily-life
function in patients with knee osteoarthritis: an exploratory
regression-based cross-sectional study**

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Abstract

Background

The aim of the study was to explore the relative predictive potentials of a discriminative and
comprehensive set of lower-limb muscle strength factors onto self-reported physical-
activities-of-daily-life-function (SR-ADL-function) in patients with knee osteoarthritis

(KOA), when adjusting for prior known strong prospective predictors in a statistical model which covers the functional domains of the International Classification of Function, Disability, and Health (ICF).

Methods

The design was exploratory, patient-only, cross-sectional, and multivariable regression-based, rotating 8 strength-variables onto a hierarchical model. The setting was an Osteoarthritis-school in a secondary-care hospital in Norway. The participants were 28 Caucasian patients with mild-to-moderate symptomatic and radiographic KOA (mean age 61; 64% women) referred by general physicians to an osteoarthritis-school. Excluded patients had trauma to the lower limbs, BMI >35, and age beyond 45 to 70. The dependent/outcome variable was SR-ADL-function (Knee Injury and Osteoarthritis Outcome Score [KOOS-ADL]). The known predictors were prior documented discriminative KOOS-Pain and psychosocial difficulties (Örebro Musculoskeletal Pain Questionnaire), together with 8 candidate predictor lower-limb muscle-strength actions (Biodex and Commander II dynamometer recorded).

Results

Mutually adjusted for pain and psychosocial difficulties ($R^2 = 0.71$), the predicting muscle-strength actions explained the following unique variances in SR-ADL-function: hip external rotation 7.6% ($p < 0.010$), ankle eversion 4.0% ($p = 0.050$), hip internal rotation 3.8% ($p = 0.060$), ankle inversion 3.6% ($p = 0.066$). The remaining 4 muscle-strength actions explained from 2.0% to 1.2% ($p > 0.099$), where knee extensor strength explained the least unique variance. Flipped, the current three best potential prediction models explained the following substantial proportions of variance in SR-ADL-function: 1) KOOS-pain, 66%; 2) KOOS-pain and Örebro psychosocial difficulties, 71%; and 3) KOOS-pain, Örebro psychosocial difficulties, and hip

external rotation strength, 78%.

Conclusions

Adjusted for pain and psychosocial difficulties, hip rotations and ankle eversion-inversion strength indicate substantial cross-sectional potentials for predicting SR-ADL-function for patients with KOA aged 45 to 70 in primary/hospital health-care. Relevant for future prevention and prediction/treatment studies, however, we suggest clinical researchers to consider the current muscle-strength actions together with the even stronger biopsychosocial predictors KOOS-pain and Örebro psychosocial difficulties for future ICF domain-covering models of SR-ADL. Future confirmative studies are needed to refute or generalize these pioneering exploratory conclusions.

Keywords: Osteoarthritis, Knee; Cross-sectional Studies; Muscle Strength Dynamometer; Psychology; Sociology; Activity of Daily Living, Chronic Pain; Multivariable Analysis; Association.

Background

Osteoarthritis (OA) is responsible for substantial health and social costs, directly and indirectly through work impairment and early retirement (3-6). OA is the second most prevalent condition of all musculoskeletal and rheumatic diseases (7, 8). Herein, knee OA (KOA) is reliably diagnosed by the criteria of the European League Against Rheumatism (EULAR) in primary care (9), and by the criteria of the American College of Rheumatology [ACR](10) in hospital care (9). The KOA incidence is high, about 240 per 100 000 person-

years in adults, or more than 2.5 times than of hip OA (11). KOA is the main contributor to activity limitations in persons older than 45 years (7, 8). Self-reported physical activity in daily life functional [SR-ADL-function] limitations (i.e. perceived difficulties) for these patients are related to muscle strength deficits (12).

Strength is defined as the maximum force or torque a muscle or muscle-group can produce given a specific predetermined velocity (13-15). Therein, task-specific conditions, such as the speed and type of contraction and the length of the muscle during contraction, all co-determine the torque generated (14, 16, 17). The American College of Sports Medicine (ACSM) exemplifies strength as a 1 repetition maximum (1RM) squat (16). Moderate to large(18) deficits in muscle strength are frequent in patients with KOA (19, 20). Recent, meta-analyses demonstrate hip rotations and knee extensor muscle strength to be on average 20–40% lower compared with healthy age-matched controls (19, 20). Moreover, meta-analytic evidence documents knee extensor strength deficit to be a risk factor for radiographic progression (21) and the development of KOA (22). Interestingly, knee extensor muscle strengthening alone have demonstrated small to large (18) improvement on pain and SR-ADL-functional limitations compared to wait-and-see controls in meta-analyzed randomized trials [RCTs] (23-25). Even more interesting, subgroup-data of a meta-analysis (26) indicated the largest treatment effects on pain and SR-ADL function of so-called hip abductor and knee extension strength exercising compared to knee extension strength exercising alone in patients with KOA in a potentially mechanism-triggering (2) RCT (27). However, the importance of muscle strength deficits in *various* joint—strength directions between patients and healthy controls shown in a recent meta-analysis (19) has yet to be evaluated in clinical trials. Adding to the strength discrimination knowledge, we just presented the apparently first study (28) to compare a comprehensive list of lower-limb strength actions between patients with KOA and

healthy controls. The most substantive relative strength deficits were indicated for the hip rotator muscles, closely followed by that of the ankle invertor-evertors, and the knee extensor muscles.

Biopsychosocially evaluated, in the same study [i.e., same sample, different data] (29), we quantified the discrimination of 27 KOA measures as between-group differences using a standardized effect size (18). Among the ICF (International Classification of Functioning, Disability and Health) related measures (29), we found the most substantial discrimination on KOA-specific SR-ADL function, KOOS-pain, and psychosocial difficulties. Indeed, the psychosocial difficulties factor has prospectively predicted the prime KOA-outcome SR-ADL function in patients with non-acute musculoskeletal pain (30). In a systematic review of prospective studies (31), the same primary KOA-outcome is found importantly predicted by pain in patients with KOA.

Summed, the evidence above points towards various muscle strength actions as potential predictors for easing SR-ADL function in patients with KOA. That is important as SR-ADL function is *the* most important functional measure, because its activities are *fundamental* to higher level functions (f. ex. Recreation/Sport) and *necessary* for independent living, its construct is *not* highly variable as the more psychology taxing knee-related quality-of-life (KR-QoL), and it is *the* recommended functional measure in a consensus set given by patients, scientists and clinicians (32). Various muscle strengths are important predictors or causes of SR-ADL function according to systematic reviews of RCTs (19, 23). Further, muscle strength is *necessary* for full ADL-performance, whereas even vigorous physical ADL performance is *insufficient* for maintaining proper strength of supportive muscles (33-35). However, according to systematic reviews (21, 36) neither existing cross-sectional relational

nor prospective studies has yet *systematically* explored the predictive potential/cross sectional relationships of *the most discriminative* joint—strength actions (28) towards the primary KOA-outcome SR-ADL function. Especially not so when adjusted for prior known important predictive variables. The current knowledge-gap limits the understanding of which muscle strength actions have the largest potential for predicting SR-ADL function for these patients. This gap needs closing, especially since prognosis-enhancing short and targeted strength programs show better achievability and effectiveness then long-durable and comprehensive ones (26, 37).

Thus, the purpose of the current study was to explore (38) the relative adjusted cross-sectional predictive potential (i.e. independent relations) of known discriminative strength actions on SR-ADL function in patients with KOA. Adjusted; that is, if each strength action is to be regressed on the outcome in a hierarchical model together with prior known strong predictors. The overall purpose was to indicate which joint—strength actions may have the highest cross-sectional potentials for inclusion in multivariable and biopsychosocial ICF-domain covering management models for future confirmative and prospective prediction studies of the SR-ADL-outcome for patients with KOA.

The current study was exploratory because it had several objectives (i.e. to find the *adjusted* relative magnitude of the predictive potentials of *various* muscle-groups); that is, it did not have a single key hypothesis (38, 39). The latter is the case in confirmatory studies. Exploratory studies lay the wide-scoped fundamentals for future confirmatory studies.

147 Methods

148 The current paper presents data from a larger study, Function with knee osteoarthritis
149 [FUNKART] (28, 40).

150

151 Design and recruitment

152 The current study was exploratory, cross-sectional, case-only, and multivariable relational.
153 Based on statistical rules of thumb regarding the number of cases per predictor variable (31,
154 41, 42) and the assumption about no adjustment needed for multiple comparisons in
155 exploratory studies (38, 39, 43-46), we initially aimed for 30 participants (cf. Statistics
156 analysis). We recruited individuals with KOA referred by general physicians (GPs) to private
157 physiotherapy clinics and to an OA-school at a university hospital in Norway from November
158 2016 to December 2017.

159

160 Ethics approval and informed consent

161 This study was approved by the Regional Committees for Medical and Health Research
162 Ethics, Norway (2016/984, the Regional Ethics Committee North) and performed according
163 to the Helsinki Declaration, and Norwegian regulations. All participants received oral and
164 written information and signed an informed consent form before entering the study.

165

166 Data were collected within a period of approximately two weeks through questionnaires and
167 functional tests in the lab. The questionnaires were e-mailed as web-surveys together with the
168 informed consent forms via the Infopad system (47). The main study was extensive as the
169 questionnaires took about 40 minutes and the physical functional test protocol 2.7 hours.

170

Participants eligibility

The inclusion criteria for patients were having KOA in the tibiofemoral joint in one or both knees diagnosed clinically (by GPs) and radiologically [Kellgren-Lawrence grade (K/L-grade) I-IV] (48), main problem of pain and limited physical function related to the knee(s), be symptomatic for >3 months and daily in the last month, understand Norwegian, and be within 45-70 years old. Both genders were included. The upper age-limit was set in a prior case-vs-healthy control comparison study on the same sample [to prevent possible confounding, cf. (28, 40)].

The exclusion criteria were surgery to a lower extremity < 3 years ago, prior lower limb fractures, generalized pain (49, 50), pain from the spine, hips, or ankles competing with that from the knee, body mass index (BMI) >35 (for reliable optokinematic recordings (51) in the larger study, data not presented here), and medical diagnoses other than KOA with clear negative influence on physical performance and pain.

Measurements

Strength candidate predictors

For a full description of the 12-variable strength-testing procedure, cf. our discriminative strength study (28). Here we present procedures for the 8 strength actions in the current study. Before strength testing, the participants warmed up by several performance tests included in the larger study of the same sample (40). The 6-minute walk test (6MWT), a timed 10-step up-and-down stair-climb test [cf. ref.(40) for results], and a set of 15 repetitions at low-to-moderate load on each specific exercise, were performed. Strength or *concentric* peak torque were recorded at 60°/s by the *isokinetic* mode applying the reliable Biodex® System 4 Dynamometer [Biodex Medical Systems, NY, USA] (52, 53). With the participants sitting,

we sequentially tested strength with the back rest tilted 70° off the horizontal line in the following order: knee flexion and extension, hip internal and external rotation, ankle inversion and eversion, and ankle plantar flexion. These positions and setups were according to the Biodex manual (54), except for the hip rotation tests that were performed according to Baldon et al. (55). Further, with the participants positioned supine on a therapy bench, we tested *isometric* hip abduction strength with the hips in a neutral ab-adducted position, applying a hand-held muscle tester dynamometer (HHD) [type specified below] according to Thorborg et al. (56), except before testing, the pelvis was additionally secured bilaterally against inferior and lateral displacement (57). The supine isometric abduction test was included instead of the side-lying Biodex test because we have experienced that weak patients may be unable to lift the weight of the resistance arm and their leg in the latter (causing floor effects).

We applied five consecutive maximum strength tests by the Biodex system and three repeated trials by the belt-fixed HHD. Oral encouragements were applied according to principles in Thorborg (56). For the knee tests, the Biodex system's "passive isokinetic mode" was chosen, to better accommodate eccentric performance (eccentric data not reported here). Accordingly, fully passive recordings were taken to correct for gravity (see Data processing). The other tests by the Biodex system, we corrected for gravity by its software. The Biodex system was calibrated before each session according to the manual (54). Muscle strength measurements with an isokinetic dynamometer have shown excellent test-retest reliability (ICC 0.93) in patients with KOA (58). The HHD (Commander II Muscle Tester, JTech Medical Industries, USA) is certified by the National Institute of Standards and Technology (NIST) standards. The HHD is self-calibrating and was compared daily to an identical reserve-HHD, and both were weekly compared to traceable Olympic Competition Weights (59) [Eleiko, Halmstad, Sweden]. The team of testers trained about 40 hours to execute the complete strength protocol

within 1.5 hours.

Non-strength candidate predictors, outcome, and characteristics

The chosen outcome variable was KOOS-Activities in Daily Life (ADL) function, from the self-reported (SR) Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire (60-62). The KOOS-ADL was chosen (over the Western Ontario and McMaster Universities Arthritis Index Physical Function [WOMAC-PF]) due to being open access (63), knee specific, electronically available [at non-profit costs in a system (47), or at no-cost (63)], and showing adequate measurement properties (63, 64). The KOOS is scaled 0-100, worst to best, the highest score expressing the best ADL function. KOOS asks for the period “last week”.

The initially considered candidates as non-strength predictor variables (or covariables or adjusting variables) were as follows: KOOS-pain [0-100, worst to best] (60-62), psychosocial difficulties [Örebro Musculoskeletal Pain Screening Questionnaire 10-items (OMSPQ-10), 1-100, best to worst] (65), body mass index (BMI, kg/m^2), average pain last week [Numeric Pain Rating Scale (NPRS), 0-10, best to worst] (66), fear of movement/re-injury [Tampa Scale of Kinesiophobia (TSK-13), 13-52 point, best to worst] (67), age (years), time in activity of moderate intensity (AX3, a 3-axis logging accelerometer, Axivity Ltd, Newcastle, UK, minutes/week) (40, 68, 69), endurance or long-term walking capability [6-minute walk test (6MWT); distance, m] (70), general health quality of life [The European Health Interview Survey-Quality of Life 8-item index (EUROHIS-QoL), 8-40 points, worst to best] (71), and pain duration [number of months] (31).

Note that KOOS-pain (60-62) at its highest score expresses the best KOA-pain-function (least painful), whereas Örebro psychosocial difficulties (65) is scaled in the intuitive direction. Örebro (65) captures work and psychosocial factors, where the original version

identify yellow flags and risk of work disability due to pain (72, 73) and has satisfactory psychometric properties and predictive ability (74). The chosen short version (65) has improved clinical utility and similar psychometric properties in a mixed musculoskeletal pain population.

After the questionnaires, in the laboratory the week thereafter, we registered personal or demographic characteristics, clinical factors, and degree of radiographic KOA [from radiology reports] (48) [cf. Results, Table 1]. In the second half of the lab-session, we measured peak strength. At the end of the lab session, an accelerometer sensor was applied on the anterior left thigh (69, 75) and worn for all hours during one week, before it was returned by conventional mail.

Confounding and sensitivity analysis variables

Based on systematic reviews of prospective predictors in cohort-studies (31), causal variables in therapeutic RCTs (25, 26, 76, 77), and our study of case-vs-control discriminative indications (40), we considered the following variables for a confounding and sensitivity analysis (Cf. Statistics analysis): KOOS-pain, psychosocial difficulties, age, fear of movement/re-injury, time in activity of moderate intensity, and endurance.

Data processing

For concentric knee extensor strength, the passive torques were added to the active ones to correct for the limb's own torque, whereas for knee flexion the passive torques were subtracted. Maximum knee strength at the 30° knee flexed position (0° = straight knee) was reported. The isokinetic mode with software gravity correction was used for the remaining isokinetic tests. In the Biodex-dynamometer tests, the “cushion -function” was set to “hard”

and the signal windowing to 80%. For all tests, strength was taken as “best of” and normalized to body weight (i.e. divided by mass), thus we report Nm/kg.

Statistical analysis

Our sample size calculation assumed that no adjustments for multiple comparisons were needed in the current exploratory study according to several reputative statisticians (38, 39, 43-46). All power analysis was performed in the recognized(41) freeware G*Power version 3.1.9.1 (78-80). Bivariate correlations were performed as part of the statistical analysis, where methods and results and discussion are placed in an e-appendix (to improve readability).

The *a priori* sample size calculation for the multiple regression analysis was performed for a t-test-based linear regression fixed model with a single continuous coefficient per predictor. Therein, the input factors were two tails, effect size f^2 0.35 [i.e. a large effect (81)], α error probability 0.05, power ($1-\beta$ error probability) 0.80, and 3 predictors. The sample required was then 25 cases. Thus, we aimed for 29 participants altogether.

Analytically, case numbers vs. value plots showed no missing data from lab tests or questionnaires. Requirements of independence and representativeness were assumed met due to the design. The inspection of variables, histograms, box plots, Shapiro-Wilk tests, and Normal Q-Q plots, indicated normal distribution, no obvious outliers, and roughly constant variance. Moreover, the assumption of normal distributed residuals was bypassed by the bias-corrected bootstrap inference included in SPSS (IBM, NY, USA, v.25) for both the Pearson’s correlation analysis and the multiple regression analysis (41, 82). Yet further, the bivariate correlation matrix showed moderate correlation [$r < 0.70$] (83) between the chosen non-strength candidate predictor variables (cf. Results in e-appendix). Candidate non-strength

predictors that showed high co-linearity with most candidate strength predictors were excluded before the selecting process assuming they contribute little independent information [e.g. BMI] (84).

Even further, we analyzed the bivariate correlation matrix for patterns, including the variables for a planned multivariable model for the presumed predictors X_1 , X_2 , and X_{3i} and the outcome Y (e-appendix). The standard generic linear multivariable model/equation (Eq. 1) was as follows:

$$\hat{Y} = b_0 + b_1X_1 + b_2X_2 + b_3X_{3i} \quad (\text{Eq. 1})$$

, where $\hat{Y}$ is the estimated (mean) outcome of SR-ADL function, b_0 the intercept or estimated SR-ADL-level when each predictor is zero (nonsensical in this case), b_1 , b_2 , and b_3 the slope of the lines (or weight or effect estimates or regression coefficients) of the predictor or explanatory variables X_1 , X_2 , X_{3i} , where the i denotes the i 'th joint—strength action variable (8 in total).

The selection of the first and second candidate non-strength predictor variables (X_1 , X_2) was based on the following criteria: (i) bivariate current-study findings of candidates (for X_1 and X_2) should have significant moderate-to-high correlation with the outcome variable and low-to-moderate correlation with the strength variables (X_{3i}), (ii) covering the psychosocial aspect of ICF with proven predictive capabilities (31), and (iii) documented clear case-vs-control discrimination in the prior study (40). The strength actions shown to be discriminative (on the most affected leg) in another of our case-vs-healthy control studies (28) on the same sample, were evaluated as X_{3i} (cf. Results, Table 1), but therein we also included hip abduction due to

prior proven causal/trial effects (26, 85). For choosing the first and second candidate predictors, we also considered a confounding analysis (cf. 2nd paragraph below).

After the bivariate analysis (e-appendix), we explored the data in a hierarchical regression analysis for “best” non-strength candidates for X_1 and X_2 . First, candidates were regressed one-by-one (onto SR-ADL) according to their bivariate correlation magnitude, then in various hierarchical orders. The criterium for the “best” two-predictor model was maximum explained variance, R^2 , while including a biopsychosocial construct. Because of the sample size vs number of allowed predictors constraint, we thereafter rotated (as in a Colt-gun magazine) each strength variable onto (and off) the best fitting two-variable model. The results were then rated and tabulated to fulfill the purpose.

Our confounding analysis is explained further in the e-appendix. In short, based on background knowledge of prospective predictors (31), causal (RCT manipulated treatment) variables (37), cross-sectionally case-controlled discriminative variables (1, 20), but also (based) on the size and significance of the bivariate and exploratory multivariable relationships in the current study, we created a causal diagram (directed acyclic graph) applying the DAGitty freeware [DAGitty.net] (86, 87). According to a causal diagram analysis (87-90) the current study’s potential confounders of the total effect of strength came out as KOOS-pain and age (Figure 1). However, in the current chosen primary analysis, in compliance with our selection criteria and current power constraint, we decided to adjust for KOOS-pain and psychosocial difficulties. BMI was not included in the model because the strength results were normalized to body weight (91), BMI showed no discrimination in the prior study (1), and it showed moderate-high correlation with all candidate strength predictors in the current correlation matrix (e-appendix). Figure 1 shows the diagram of the causal modeling of the

total effect of strength on SR-ADL with the influence of the potential confounder variables (arrow-connected pink nodes) and the implied or assumed non-associated variables (unconnected gray nodes).

Figure 1. Modeling the total effect (green arrow) of the assumed focal predictor Strength (green play-button) on the putative outcome Activity of daily life (blue stop-button), together with the potential confounders (pink buttons, C1-C6) with their putative confounding or causal effects on the focal predictor and outcome (pink arrows) to be adjusted for in the multiple regression model. The gray buttons were ruled out of the main model based on case vs control non-discriminative characteristics in prior studies(1, 2) and the inclusion criteria in the current study (C4 skeletal comorbidity).

Finally, having ran the best-fitting models, collinearity diagnostics statistics showed no eigenvalues < 1 nor condition indexes > 15 ; i.e., data met the non-multicollinearity assumption (41). Thus, we inferred that the assumptions of the bivariate correlation and the multiple regression models were met.

Sensitivity analysis

In a sensitivity analysis (92) [e-appendix], we checked the robustness of the models by replacing psychosocial difficulties with age in accordance with the result of the current causal diagram confounder analysis (the sensitivity equation/model is not shown). The sensitivity analysis was compared with that of the generic model (Eq. 1) which was (partially) specified for the main analysis as follows (Eq. 2):

$$\widehat{ADL} = b_0 + b_1 \text{KOOS-pain} + b_2 \text{psychosocial difficulties} + b_3 \text{strength} \quad (\text{Eq. 2})$$

, where $\widehat{ADL}$ is the estimated (mean) outcome of KOOS-SR-ADL function, b_0 the intercept or estimated SR-ADL function when each predictor is zero (not sensical in this case), b_1 , b_2 , and b_3 the slope of the lines/relational weights/beta coefficients of the predictor variables KOOS-pain, psychosocial difficulties, and strength, respectively. We repeated the main analysis for all joint—strength actions rotated into the two-predictor model (Eq. 2).

All bivariate (e-appendix) and multivariable statistical tests were run in SPSS (IBM, NY, USA, v.25). Alpha was set to 0.05 for all tests as no adjustments were assumed needed in an exploratory study (38, 39, 43-46). No multiple imputation was performed for the single drop-out participant.

Results

Flow of patients and centers

At the hospital, we recruited 27 patients out of 36 eligible, where 10 of those invited declined to

participate demotivated by long traveling distances (n=3), not interested (n=4), afraid of strength testing (n=2), and too time-consuming (n=1). One participant answered the questionnaire but withdrew from the study before the lab-test due to a flare-up at home and thus was excluded from the analysis. Two participants were recruited in municipality physiotherapy clinics without information on those who declined. Herein, additional five individuals volunteered but were screened per telephone as to not be qualified for participation due to old age (n=3), BMI (n=1), and an unstable heart (n=1), and were therefore not included. Thus, we included 28 patients.

Patients' characteristics

The patient-group was middle-aged with mainly graduate level of education (n=14, 50%). The group had slightly more females (64%) than men, long-term knee pain (on average 10 years), and mainly small-to-moderate symptomatic and radiographic KOA. Further, it was overweight on average [mean BMI of 28, BMI classifying overweight is 25 to 30 (93, 94)]. Table 1 shows the group's demographic and clinical characteristics.

Table 1. Personal and health characteristics of patients with KOA.

ICF	Variables	Cases (n = 28)
Personal factors	Female, n (%)	18 (64)
	Age, yrs, M (SD)	61.7 (6.4)
	Height, m, M (SD)	1.72 (0.10)
	Weight, kg, M (SD)	82.9 (12.7)
	BMI, kg/m ² , M (SD)	28.0 (4.1)
	Education, n (%)	
	secondary school (10 yrs)	1 (4)
	high school (13 yrs)	6 (21)
	graduate (16 yrs)	14 (50)
	post graduate (18 yrs +)	7 (25)
Patients' clinical factors	Dominant leg (right, left, n)	26, 2
	Yrs since diagnosis, M (SD)	10.2 (8.6)
	Duration knee pain, mo, M (SD)	132.7 (101.6)
	Pain last wk NRS, M (SD)	4.4 (2.3)
	Affected knee (n, %)	
	One	14 (50)
	Both	14 (50)
	Pain medication (n, %)	
	None	15 (54)
	Paracetamol	5 (18)
	NSAIDs	5 (18)
	Opioids	2 (7)
	Others	1 (4)
	X-ray grade (n knees, %)	Inv leg Uninv leg
	No X-rays taken	0 (0) 10 (36)
	KL-grade II	9 (32) 9 (32)
	KL-grade III	17 (61) 8 (29)
	KL-grade IV	2 (7) 1 (4)
	Act mod int, min/wk, M (SD)	286.0 (169.1)
	TSK fear of movement, M (SD)	24.4 (7.6)
	Endurance 6MWT, m, M (SD)	642.5 (94.6)
	KOOS-Symptoms, M (SD)	59.0 (19.1)
	KOOS-Pain, M (SD)	58.8 (18.8)
	KOOS-ADL, M (SD)	68.6 (21.7)
	KOOS-Sport/Rec, M (SD)	31.5 (20.3)
	KOOS-QoL, M (SD)	43.8 (18.6)
	Örebro PsychoSocial, M (SD)	39.0 (12.7)
	EUQOL Gen-H-QoL, M (SD)	32.1 (4.4)

Notes. Case-group = patients with knee osteoarthritis; control-group = individuals without knee complaints; ICF = the International Classification of Function, Disability, and Health of the WHO; M = mean; BMI = body mass index; NSAIDs = Non-Steroid Anti-Inflammatory Drugs; KL = Kellgren-Lawrence osteoarthritis radiographic Grade, Act mod int = Activity level in moderate intensity recorded by acceleromater (in minutes per week),

KOOS = Knee Osteoarthritis Outcome Score, 0 to 100 scale, worst to best; ADL = Activity of daily life (subscale of KOOS); Sport/Rec = Sports and Recreation; QoL = (knee related) Quality of Life; Örebro PsychoSocial = Örebro (psychosocial difficulties) Musculoskeletal Pain Questionnaire 10-item version, 1 to 100 scale, best to worst; M = mean; SD = standard deviation; Inv. leg = involved or most affected leg; Uninv. leg = uninvolved leg or least affected leg.

Adjusted relations

A hierarchical (sequential or “Enter”) multivariable linear regression was employed to explore the extent of unique explained variance of the addition of information about psychosocial difficulties, then various joint—strength directions, improved the prediction of activities of daily life beyond that afforded by information about knee-specific pain. Table 2 indicates the relationship of the simple regression model (cf. Table 2, model 1), meaning that for every 1-point increase (improvement) in KOOS-pain function, the ADL-score is estimated to increase by 0.94 point ($p < 0.001$). That simple/unadjusted model explained about 66% of the variability in activities of daily life (cf. the adjusted R^2). Further, the indicated relationship of that two-predictor model (Table 2, model 2) mean that, when keeping pain fixed/adjusting for pain, every 1-point increase in psychosocial difficulties the ADL-score is estimated to decrease (worsen) by 0.63 point ($p < 0.05$). This two-predictor model explained about 71% of the variance in activity of daily life, an increase of 5% from model 1. Thereafter, the indicated relationship of the best-fitting three-predictor model (cf. Eq. 2, and Eq. 3 cf. e-appendix), when keeping pain and psychosocial difficulties fixed, meant that for every 0.1 Nm/kg increase in hip external rotation strength the ADL-score is estimated to increase by 5.98 points ($p < 0.01$). This “best” model (M3.1, Table 2) explained on average 78% of the total variance in activity of daily life. When its effect estimates were reported in a standardized unit (standardized betas, Table 2), the latter showed that pain, respectively, explained 1.4 times more of the SR-ADL-outcome than psychosocial difficulties and 1.5 times more (of the

outcome) than hip external rotation strength. Table 2's model 3.1 to 3.8 exhibit the top-down rank of the unique explained variance of the joint—strength actions on the SR-ADL-outcome, with the hip external rotation 8%; ankle eversion, hip internal rotation, and ankle inversion each 4%; ankle plantar flexion 3%; hip abduction and knee flexion each 2%, and knee extension strength 1%. The two first relationships were statistically significant or generalizable, the next two borderline-significant, whereas the last four were clearly not significant. In the models of the current main analysis, there were high consistency between the four presented effect magnitude indicators (i.e., adjusted R^2 , unique variance explained, standardized beta, and p-values) [Table 2].

Table 2. Exploratory prediction of activity of daily life by strength while controlling for pain and psychosocial difficulties in a multiple linear regression analysis. Strength models are ranked acc. to avg. of four effect estimates (best-worst, top-down).

Mod no	Intercept and predictors	Adj R ²	F	P of model	FΔ	Uniq var or ΔR ²	P of FΔ	Coefficients			95% CI for b		t	P of coeff	R Md
								Unstd b	SE	Std B	LL	UL			
1	Constant	0,659	50,22	1,6E-07	50,22	0,659	1,6E-07	13,27	8,17	1,62	-3,53	30,08	1,62	0,1165	
	KOOS-pain							0,94	0,13	0,81	0,67	1,21	7,09	1,6E-07	
2	Constant	0,711	34,14	7,1E-08	6,82	0,073	0,015	55,13	17,65		18,79	91,48	3,12	0,0045	
	KOOS-pain							0,65	0,16	0,56	0,31	0,99	3,96	5,5E-04	
3.1	Psychosoc diff							-0,63	0,24	-0,37	-1,13	-0,13	-2,61	0,015	
	Constant	0,784	33,62	9,3E-09	9,46	0,076	0,0052	42,27	15,82		9,63	74,91	2,67	0,013	
	KOOS-pain							0,58	0,14	0,50	0,28	0,97	4,02	5,1E-04	
	Psychosoc diff							-0,58	0,21	-0,34	-1,01	-0,14	-2,74	0,011	
	Hip ext rot str							59,84	19,46	0,29	19,68	100,00	3,08	0,0052	
	Rank	1				1				1				1	1
3.2	Constant	0,744	27,15	6,9E-08	4,26	0,040	0,050	45,95	17,18		10,48	81,42	2,67	0,013	
	KOOS-pain							0,57	0,16	0,49	0,24	0,90	3,59	0,0015	
	Psychosoc diff							-0,56	0,23	-0,33	-1,04	-0,09	-2,44	0,022	
	Ankle ever str							57,64	27,94	0,22	-0,03	115,31	2,06	0,050	
	Rank	2				2				3				2	2
3.3	Constant	0,741	26,72	8,0E-08	3,92	0,038	0,059	47,04	17,19		11,56	82,53	2,74	0,012	
	KOOS-pain							0,52	0,17	0,45	0,17	0,86	3,05	0,0055	
	Psychosoc diff							-0,58	0,23	-0,34	-1,06	-0,11	-2,53	0,018	
	Hip int rot str							18,98	9,59	0,24	-1,06	-0,11	1,98	0,059	
	Rank	3				3				2				3	3
3.4	Constant	0,739	26,48	8,7E-08	3,72	0,036	0,066	53,01	16,79		18,35	87,67	3,16	0,0043	
	KOOS-pain							0,53	0,17	0,46	0,19	0,88	3,18	0,0040	
	Psychosoc diff							-0,68	0,23	-0,40	-1,16	-0,20	-2,94	0,0072	
	Ankle inv str							44,77	23,21	0,21	-3,15	92,68	1,93	0,066	
	Rank	4				4				4				4	4
3.5	Constant	0,731			2,95	0,029	0,099	51,29	17,14		15,91	86,67	2,99	0,0063	
	KOOS-pain							0,52	0,18	0,45	0,16	0,88	2,96	0,0069	
	Psychosoc diff							-0,61	0,23	-0,36	-1,09	-0,13	-2,60	0,016	
	Ankle pl fix str							18,94	11,03	0,21	-3,83	41,71	1,72	0,099	
	Rank	5				5				4				5	5
3.6	Constant	0,722	24,40	1,8E-07	2,04	0,021	0,166	52,18	17,41		16,24	88,11	3,00	0,0063	
	KOOS-pain							0,57	0,17	0,49	0,21	0,92	3,31	0,0029	
	Psychosoc diff							-0,66	0,24	-0,38	-1,15	-0,17	-2,76	0,011	
	Hip abd str							9,79	6,84	0,16	-4,34	23,91	1,43	0,166	
	Rank	6				6				6				6	6
3.7	Constant	0,718	23,96	2,1E-07	1,69	0,018	0,206	48,83	18,07		11,54	86,12	2,70	0,012	
	KOOS-pain							0,61	0,16	0,53	0,27	0,95	3,72	0,0011	
	Psychosoc diff							-0,62	0,24	-0,36	-1,12	-0,13	-2,60	0,016	
	Knee flex str							6,84	5,26	0,14	-4,01	17,69	1,30	0,206	
	Rank	7				7				7				7	7
3.8	Constant	0,712	23,25	2,8E-07	1,12	0,012	0,300	52,16	17,83		15,37	88,95	2,93	0,0074	
	KOOS-pain							0,61	0,17	0,52	0,26	0,95	3,61	0,0014	
	Psychosoc diff							-0,65	0,24	-0,38	-1,15	-0,15	-2,66	0,014	
	Knee ext str							4,82	4,54	0,11	-4,56	14,20	1,06	0,300	
	Rank	8				8				8				8	8

Notes: The outcome is self-reported function in activity of daily life from the Knee Injury and Osteoarthritis Outcome Score (KOOS). The colored cells highlights the four effect estimates. Mod no = the linear regression model numbers; Adj R² = Adjusted total explained variance, where 1 is maximum and 0 minimum; F = F-ratio, a test statistics with a known probability distribution; P = probability (or significance) value for observing the result given the null-hypothesis is true; FΔ = Change in F-ratio by the last variable added to the model; ΔR² change in R-squared or change in coefficient of multiple determination or the unique variance explained by the model by the last added factor (cf. strength); Unstd b = unstandardized beta, the slope of the line, an effect measure of relationship; SE = Standard error; Std B = the standardized coefficient Beta, an effect estimate of relationship, standardized by its SE; CI = confidence interval; LL = lower limit; UL = upper limit, t = t-value or test statistics with a known probability distribution; coeff = coefficient; Ro rank of the original model; Rs rank of the sensitivity model; Psychosoc diff = psychosocial difficulties, a predictor variable or a covariate or control variable in the linear regression model or equation; str = strength.

Sensitivity of the model

With age in the two-candidate predictor model S2 (cf. Table 3, model 2), keeping KOOS-pain fixed, the relationship estimated that a year increase in age reduced SR-ADL function by 0.48 point, but the relationship was not significant. Specifically, age added only 1.9% uniquely explained variance to the KOOS-pain-only model (in contrast to the 7.6% for psychosocial difficulties). In the three-predictor sensitivity-model, age was even weaker related to SR-ADL. Therein, the two strength actions with the highest unique explained variance were still hip external rotation and ankle eversion strength which explained about the same unique variance as before, but only the first was clearly significant (Table 3). There was, however, a marked change in rank for knee flexion strength, going from the seventh (in the original model) to the third rank, although its relationship was still not significant. Other changes in rank were negligible.

Table-3-in-here

Table 3. Exploratory prediction of activity of daily life by strength while controlling for pain and age via multiple linear regression sensitivity analysis. Strength variables are ranked according to the average of four effect estimates (best-worst, top-down).

Mod no	Intercept and predictors	Adj R ²	F	P of model	FΔ	Uniq var, ΔR ²	P of FΔ	Coefficients			95% CI for b		t	P of coeff	R ₀ v R _s Median
								Unstd b	SE	Std B	LL	UL			
1	Constant	0,646	50,22	1,6E-07	50,22	0,659	1,6E-07	13,27	8,17	1,62	-3,53	30,08	1,62	0,1165	
	KOOS-pain							0,94	0,13	0,81	0,67	1,21	7,09	1,6E-07	
2	Constant	0,652	26,33	7,0E-07	1,49	0,019	0,233	45,35	27,48		-11,23	101,94	1,65	0,1113	
	KOOS-pain							0,90	0,14	0,78	0,62	1,18	6,67	5,5E-07	
	Age							-0,48	0,40	-0,14	-1,13	-0,13	-1,22	0,233	
3.1	Constant	0,725	24,75	1,6E-07	7,63	0,078	0,011	25,25	25,49		-27,36	77,85	2,67	0,332	
	KOOS-pain							0,81	0,12	0,70	0,56	1,07	6,56	8,8E-07	
	Age							-0,32	0,36	-0,09	-1,04	1,07	-0,90	0,376	
	Hip ext rot str							61,19	22,15	0,30	15,4694	106,91	2,76	0,011	=
	Rank	1				1				1				1	1
3.2	Constant	0,687	20,75	7,5E-07	3,76	0,044	0,064	26,84	27,76		-30,47	84,14	0,97	0,34	
	KOOS-pain							0,80	0,14	0,69	0,51	1,08	5,76	6,0E-06	
	Age							-0,28	0,39	-0,08	-1,06	-0,11	-0,71	0,484	
	Ankle ever str							61,59	31,75	0,24	-3,95	127,13	1,94	0,064	=
	Rank	2				2				2				2	2
3.7	Constant	0,682	20,28	9,1E-07	3,31	0,039	0,081	37,40	26,65		-17,59	92,40	0,17	0,157	
	KOOS-pain							0,79	0,14	0,68	0,49	1,08	5,49	1,E-05	
	Age							-0,41	0,38	-0,12	-1,19	0,38	-1,07	0,297	
	Knee flex str							15,89	8,73	0,22	-2,13	33,91	1,82	0,081	7→3
	Rank	3				3				4				3	3
3.3	Constant	0,678	19,95	1,0E-06	2,99	0,036	0,0966	26,57	28,59		-32,43	85,57	0,929294	0,36	
	KOOS-pain							0,76	0,14	0,50	0,28	0,87	4,95	4,7E-05	
	Age							-0,27	0,40	-0,34	-1,10	0,55	-2,74	0,469	
	Hip int rot str							19,28	11,15	0,24	-3,73	42,30	1,73	0,0966	3→4
	Rank	4				4				2				4	4
3.5	Constant	0,665	18,87	0,000002	1,95	0,024	0,176	33,02	28,38		-25,55	91,60	1,16	0,2560	
	KOOS-pain							0,78	0,16	0,67	0,45	1,11	4,92	0,0001	
	Age							-0,33	0,40	-0,10	-1,16	0,50	-0,82	0,423	
	Ankle pl fix str							17,84	12,79	0,20	-8,55	44,24	1,40	0,176	=
	Rank	5				5				5				5	5
3.4	Constant	0,660	18,47	2,0E-06	1,57	0,020	0,223	36,38	28,10		-21,61	94,38	1,29	0,2077	
	KOOS-pain							0,84	0,14	0,72	0,54	1,13	5,84	5,0E-06	
	Age							-0,41	0,40	-0,12	-1,22	0,41	-1,03	0,3144	
	Ankle inv str							33,36	26,67	0,15	-3,15	92,68	1,25	0,223	4→6
	Rank	6				6				6				6	6
3.6	Constant	0,646	17,96	2,0E-06	50,22	0,014	0,311	40,05	27,91		-17,55	97,65	1,44	0,164	
	KOOS-pain							0,85	0,15	0,73	0,54	1,15	5,81	5,0E-06	
	Age							-0,46	0,40	-0,14	-1,27487	0,36	-1,16	0,257	
	Hip abd str							7,91	7,64	0,13	-7,86	23,67	1,04	0,311	6→7
	Rank	8				7				7				7	7
3.8	Constant	0,647	17,49	3,0E-06	0,621	0,008	0,647	41,17	28,19		-17,01	99,35	1,46	0,0074	
	KOOS-pain							0,87	0,14	0,75	0,58	1,16	6,19	2,0E-06	
	Age							-0,47	0,40	-0,14	-1,29	0,36	-1,17	0,254	
	Knee ext str							3,97	5,03	0,09	-6,42	14,35601	0,79	0,438	=
	Rank	7				8				8				8	8

Notes: The outcome is self-reported function in activity of daily life from the Knee Injury and Osteoarthritis Outcome Score (KOOS). The rightmost column shows the differences in rank between original and sensitivity models. The colored cells highlights the four effect estimates. Mod no = the linear regression model numbers; Adj R² = Adjusted total explained variance, where 1 is maximum and 0 minimum; F = F-ratio, a test statistics with a known probability distribution; P = probability (or significance) value for observing the result given the null-hypothesis is true; FΔ = Change in F-ratio by the last variable added to the model; ΔR² change in R-squared or change in coefficient of multiple determination or the unique variance explained by the model by the last added factor (cf. strength); Unstd b = unstandardized beta, the slope of the line, an effect measure of relationship; SE = Standard error; Std B = the standardized coefficient Beta, an effect estimate of relationship, standardized by its SE; CI = confidence interval; LL = lower limit; UL = upper limit, t = t-value or test statistics with a known probability distribution; coeff = coefficient; R₀ rank of the original model; R_s rank of the sensitivity model; Psychosoc diffc = psychosocial difficulties, a predictor variable or a covariate or control variable in the linear regression model or equation; str = strength.

Discussion

Principle findings

The principle findings, mutually adjusted for KOOS-pain and psychosocial difficulties, showed that the most substantial muscle strength potential predictions on the outcome SR-ADL were inferred for hip external rotation and ankle eversion strength, somewhat less substantial and borderline significant (were such) for hip internal rotation and ankle inversion strength, and least and not significant relations for the ankle plantar flexion, hip abduction, knee flexion and knee extension strength. Of potential biopsychosocial clinical importance, on average the current 3 best prediction models explained the following substantial proportions of variance in the SR-ADL-outcome: 1) KOOS-pain alone, 66%; 2) KOOS-pain and psychosocial difficulties, 71%; and 3) KOOS-pain, psychosocial difficulties, and hip external rotation strength, 78%. Apparently, this is the first study to comprehensively report biopsychosocially adjusted cross-sectional predictive potentials of muscle strength on the prime outcome SR-ADL function for patients with KOA. (The e-appendix reports such findings for the bivariate analyses.)

Internal validity

There are several strengths of this study. The current statistical model and the sample size were adjusted to each other in order to detect *substantial* relationships as statistically significant. Further, our current overview of background knowledge allowed us to consider several candidate prediction variables (31) that have documented prospective relationships and important therapeutic effects (24, 25, 76, 77) on the SR-ADL-outcome. Yet further, our choice of candidate predictors incorporated knowledge of the most discriminative variables in two prior case-vs-healthy control exploratory studies on the same sample (28, 40). Moreover,

the KOOS-SR-ADL outcome is highly recommended by reputable health profession guidelines (95-97), research organization guidelines (62, 98, 99), and patient associations (99) [in contrast to the KOOS-Recreation/Sport and -KR-QoL functions]. Even further, the measurement instrument subscales KOOS-ADL and KOOS-pain were both knee and OA specific [in contrast to WOMAC-PF and Pain-VAS] (64). Additionally, the relationship between a comprehensive set of single muscle strength actions and the outcome were adjusted for variables estimated to explain a *substantial* part of the variability in the outcome. Furthermore, the current strength measurement tools are traceable to measurement standards, reliable without manual influence (52, 53, 56), and were applied by a 3 person team (cf. Acknowledgement) led by a trained clinical researcher (KV). Yet additionally, the current confounder analysis was based on proper background knowledge (88, 90) and applied algorithmic-based software for closing potential non-causal paths (86, 87). Finally, the main results were supported by a sensitivity analysis which indicated relatively robust primary findings.

Still, there are several internal validity limitations of the current study. *Firstly*, we did not formally examine the intra- and inter-reliability for the strength tests of the current test team on the current sample. On the other hand, most laboratories still trust their strength equipment and approaches although most teams have never formally tested each team's such specific performances. Thereto, of ethical and resource reasons we chose not to burden our participants with yet another set of our extensive strength measures. *Secondly*, the killing threat to the internal validity of true causality is the current cross-sectional design (100). However, we believe true causality requires a well-performed RCT where increased strength of these key muscles may prove clinical important prediction. *Third*, notwithstanding the current multivariable “best” model, the current study only examined the *total* or *independent* relationship between each explanatory/predictor variable and the outcome. “Only”, because

there might be *indirect* relationships hidden by the current conventional regression model, effects that can be detected by mediation analysis allowing for inter-relationships between predictive variables (101, 102). For example, there might be such serial-coupled relationships between the various muscle strength variables, but also between pain and strength variables, awaiting revelation. However, in order to explore such mediation effects, the sample size of the current study had had to be larger, or we would have had to increase the risks of bias by (i) the small-study effect (103, 104) or (ii) overfitting the prediction model (105). Relatedly so, we may have introduced overadjustment bias (106, 107) or committed mutual adjustment fallacies (108) when adjusting for KOOS-pain and psychosocial factors as we evaluated the strength relations. A related concern is that smaller potential prediction studies are generally at higher risk of bias than larger studies due to including fewer adjustment factors or co-predictors (103). However; for any observational estimates, the validity of analyses depends on assumptions about confounding and selection bias that *cannot* be empirically verified (109). *Forth*, there may be important linear regression interactions between the various muscle joint-strength directions. In sum, according to the sample adjusted purpose and approach, we infer adequate internal validity of the current study.

External validity

On the one hand, the generalizability or external validity of the current findings is substantial considering that both sexes, all GPs' definitions of KOA, all relevant radiological grades, a broad age-range, a broad pain-range, all educational levels, and an upper BMI-range with obesity grade I, were all allowed in order to qualify participants into the study. On the other hand, generalizability is constrained for patients with severe obesity, KOA due to trauma, age outside 45 to 70 years, comorbidities with contraindications for physical activities (36, 110), and physical activity limitations disallowing stair negotiation without walking aids. Yet

further, due to limited sample size, we performed no analyses stratified by gender. Most importantly, perhaps, we downgrade the external validity due to the risk of chance findings because of the overall moderate sample size (111) and the less generalizability inferred through the sensitivity analysis. Altogether, we infer low-to-moderate external validity of the current study.

Results discussion

Adjusted cross-sectional relations

The adjusted *cross-sectional* relations found in current study, indicate that hip external rotation and ankle eversion strength have generalizable *independent* relations with the outcome SR-ADL function. Similar sized relations are also suggested for hip internal rotation and ankle inversion strength, notwithstanding the borderline significance. But no significant relations are indicated for the knee muscles. So, how does the existing multivariable evidence relate to these findings?

Two large regression-based cross-sectional prediction studies (58, 112) [N = 248, 284] could have illuminated that question, but only for the knee muscles. That is, if they had reported the unique explained variance of the predictor knee muscle strength on WOMAC-PF and all the accompanying regression coefficients of their model. Unfortunately, they did not. Instead, van der Esch et al. (112) restricted their report to include the adjusted relationship weight only for their focal candidate predictor, self-reported knee instability, thus, inappropriately left out (of the model/result table) the co-predictors pain and muscle strength. Interestingly though, they (112) wrote the following in their Discussion section:

“The contribution of self-reported knee instability to the variance in activity limitations over knee pain and muscle strength was small. The most important

contributors to the variance in activity limitations are knee pain and muscle strength.”

[p. 1509 (112)]

Specifically, their (112) predictive model included pain-VAS and muscle strength as the mean of isokinetic concentric knee flexion and extension peak torques at 60°/s (Nm/kg). Compared to the current study, which applied the KOA-specific predictor KOOS-pain (which explained 66% alone) and the KOOS-ADL-outcome, their full “best” model explained only 47% of the total variance in WOMAC-PF, where self-reported knee instability explained 4%, thus left 43% to be explained by pain-VAS and knee muscle strength which is substantially less than the KOOS-pain alone in the current study. The difference in choice of measures might explain the pain predictors’ difference in explained variances. Because of their (112) inappropriate reporting of the proportion of explained variance of knee muscle-strength on SR-ADL, their results are unfortunately not comparable to ours not significant findings on knee strength (112).

In the second large cross-sectional prediction-model study, Sanchez-Ramirez et al.’s (58) model included two predictors, the one-leg stance-test (0=cannot stand for 30s, 1=can so) and knee muscle strength [combined, cf. (112)], onto the WOMAC-PF-outcome. Their independent relationship of the one-leg stand test was not significant ($p=0.09$) and the relationship weight (“effect” magnitudes) for muscle strength similarly unreported, as were standardized betas, the various unique R^2 , and the p-value of the model. Thus, the latter study is similarly incomparable to ours on knee strength.

Clearly, the limitations in reporting in the above-cited cross-sectional prediction model studies should be understood in light of the reporting and evaluation standards for such studies were underdeveloped in medical research until recently (103, 105, 113-115) compared to common bivariate analyzed RCTs and systematic reviews. Importantly, both studies above (58, 112) applied the data-driven decision rule that if a potential confounder change the

regression coefficient of the modeled candidate predictors (i.e. self-reported knee instability, knee pain, or muscle strength) by more than 10%, then this variable is classified as a confounder (116). Thus, because the WOMAC-PF predicting model of knee instability, pain, and knee muscle strength in the van der Esch et al. study (112) did not report confounders, we can infer that neither joint proprioception, joint varus–valgus laxity, age, sex, BMI, duration of complaints, nor radiographic severity had an important impact on these relations. Although van der Esch et al. (112) reported to have performed a causal diagram analysis, they still chose to keep those factors out of the model (or result table) due to a data-driven rule. Apparently, further methodological research and PROBAST papers (113, 115) need a clearer definition of confounding as well as criteria for selection, adjustment, and reporting of such factors. Hopefully, the importance of our confounding discussion will be clearer to the non-research reader after the result discussion below.

Adjusted prospective knee extension strength relations

Adjusted prospectively, in a recent systematically reviewed and meta-analysis, Culvenor et al. (21) documented a *trivial* (18) and *heterogeneous* increased risk of WOMAC-PF worsening (incline) with lower knee extension strength in patients with, or at high risk of, KOA (OR 1.4 95% CI 1.0–1.9; $I^2=88.4\%$; $p<0.001$). The methodological evaluation of the 4 included studies (117–120) [N >6 500, 42% women, mean age 62–69 years, specialist care centers] showed 3 (117, 118, 120) of 4 studies to be of high-quality. However, altogether these adjusted for 30 confounders where table 4 shows that only 8 of these (28%) were reported by more than one study. Thus, due to high statistically heterogeneity, Culvenor et al. (21) concluded that 3 high-quality studies showed *conflicting evidence* for the trivial relationship between lower knee extension strength and SR-ADL function. Further, the diversity and volume of confounders in their reviewed studies seem troublesome indeed. In sum, the

conflicting prospective evidence of trivial knee extensor strength and SR-ADL supports the
not significant findings for knee strength found in the current study.

Table 4. Factors adjusted for in prognostic studies of ADL-function for patients with KOA in the systematic review of Culvenor et al. (2017).

No CV	Confounding variables (CV)	Colbert (2012)	Sharma (2003)	White (2010)	Thomas (2008)	No of studies
1	Age (years)	✓	✓	✓		3
2	Body mass index (kg/m ²)	✓	✓	✓		3
3	Comorbidity score	✓	✓			2
4	Depression (yes/no)	✓		✓		2
5	Pain, foot (yes/no)	✓		✓		2
6	Pain, hip (yes/no)	✓		✓		2
7	Race (caucasian, other)	✓		✓		2
8	Sex (male/female)	✓		✓		2
9	Activity, physical	✓				1
10	Aerobic exercise		✓			1
11	Alcohol intake	✓				1
12	Comorbidity (none, ≥1)			✓		1
13	Disease severity		✓			1
14	Falls (no.)	✓				1
15	Joint space grade 1 [vs 0]	✓				1
16	Joint space grade 2 [vs 0]	✓				1
17	Knee confidence*	✓				1
18	Knee injury (yes/no)	✓				1
19	Knee laxity		✓			1
20	Knee surgery (yes/no)	✓				1
21	Mental health		✓			1
22	Pain intensity, knee (scale)		✓			1
23	Pain, ankle (yes/no)	✓				1
24	Pain, bilateral knee (yes/no)				✓	1
25	Pain, low back (yes/no)			✓		1
26	Pain, WOMAC score	✓				1
27	Proprioceptive acuity (° error)		✓			1
28	Self-efficacy (scale)		✓			1
29	Stiffness after resting				✓	1
30	Stiffness, duration of morning				✓	1
Sum of confounders per study		17	11	9	3	

Notes. Sorted for 1th) no. of studies 2nd) Confounders alphabetically. * = a subquestion of the KOOS-quality of life subscale, # = Center for Epidemiological Studies Depression, CES-D, score ≥16, yes/no.

Adjusted prospective hip strength relations

The *prospective* adjusted relations between the predictor *hip* muscle strength and the self-reported ADL-outcome in patients with KOA, is sparse. In a systematic review of prognostic factors for progression of clinical KOA, Bastick et al. (36) reported two studies (121, 122) with only *knee extension* strength data. None showed a significant association with WOMAC-PF [one high-quality (121), one low-quality (122); N=502]. Thus, no such studies including hip muscle strength data was found (36). More recently, a prospective cohort study by Chang et al. (91) documented significant relation of *trivial* magnitude (18) between baseline hip abductor strength with baseline-to-5-year poor outcomes on SR-ADL (RR 0.94, 95%CI 0.88 to 0.99, N=187). The authors' wrote that theirs' was the first long-term study reporting a protective effect of hip abductor strength on poor SR-ADL function in patients with knee OA. The *trivial* effect magnitude, however, is concurrent with the low unique variance explained (2%) of such ADL function by hip abductor strength in the current study, indicating low importance of hip abduction strength on SR-ADL.

Therapeutic RCT-findings vs mechanisms vs the current results

What is the link between the current study's strength potentials vs the findings in a recent systematic review of RCTs regarding the effect of strengthening therapy on SR-ADL for patients with KOA? Hislop et al. (123) meta-analyzed 5 trials indicating that adding *hip* to knee extension strengthening as compared to knee extension strengthening alone *moderately* (18) improve SR-ADL function, although the effect was borderline significant (SMD -0.74, 95%CI -1.56 to 0.08). The quality was high in two studies (124, 125) [PEDro score >6] and low in three (27, 126, 127). Highly potentially important, a sub-analysis of these data showed that *the* single study with *the* highest effect-size [*high* (18)] on both pain and SR-ADL, was found for the high intensity-resistance (10RM) strength exercise program of Ashok (27). The

latter program potentially strengthens all the muscles found potential predictive in the current study. But *why* that is probable, must be thoroughly explained in order to be believed:

Ashok's experimental program (27) consisted of concentric-eccentric hip and *knee abductor* strengthening in side-lying (ankle weight-cuff) and standing (a rubber-band around the ankles) as well as knee extension strengthening in sitting (ankle cuffs) [dose: 10RM resistance $\times$ 10 reps $\times$ 3 series/muscle group], followed by a standing isometric 90° flexed-hip so-called hip-abduction exercise against the wall (dose: maximum effort $\times$ 10 sec $\times$ 10 reps $\times$ 3 series/an host of muscle groups). According to clinical-biomechanical analyses (128, 129), the corresponding author's self-training experience, and EMG from non-human primates (130), the *flexed-hip wall-abduction-exercise* probably *highly activates* the abductors of the flexed hip [the gluteus maximus (128, 131) and the quadriceps coxa (129)] in a force-length advantaged position (17, 129, 132) on the non-stance-leg, thus inducing a forceful rotational stimuli onto the stance-leg, which then co-activates its *hip external and internal rotators* (including gluteus maximus), hip abductors, *knee abductors*, and *ankle invertor-evertor muscles* in a gait-important near-anatomical-zero-position. Performed bilaterally, Ashok's (27) simple and feasible *program* thus potentially improve muscle strength in the *mechanism-triggering* directions needed for stabilizing and strengthen the lower-limb kinetic chain in the transverse, frontal, and sagittal plane. Thus, counteracting knee instability (133), imbalanced muscle activation (134), weakness in hip-rotator muscles (28, 135), knee extensors (20), ankle invertor-evertors (28), knee abductors (136), and the so-often left out, regularly moderate-intensity cyclic mechanical stress and rest [i.e., training (137)] of the knee connective-tissue converting DNA-replicating adaptive proliferation and remodeling signals [i.e., mechanotransduction (138-140) repair/strengthening]. Or, put shortly, targeted the plausible *biomechanical* mechanisms for KOA.

Similarly mechanism-important and -supportive of the current study's potential predictive strength-findings, is the strengthening trial of Snyder et al. (141). Our claim again demands a *proper* explanation. It is well known that several hip abduction strengthening programs have failed to reduce the external knee adduction moment (EKADM) during gait in patients with KOA, although it is proven to be related to increased medial tibiofemoral disease progression [although not causally] (142). Promising is a high quality one-group before-and-after strength and kinetic-kinematic analysis study (141) [Snyder et al.] which findings concur with those of the current study regarding the potential importance of proper hip rotator and ankle inversion-eversion muscle strength. Because, in healthy moderately active females, it (141) documented a significant moderate (18) decrease in rearfoot inversion moment (Cohen's d 0.8, 81% within-group difference [WGD]) and a significant small (18) decrease in the EKADM (Cohen's d 0.5, 10% WGD, $p=0.05$) during *running* after 6 weeks with three large range-of-motion (17) hip strengthening exercises. Importantly, what might have been the potential key differences between the strengthening exercises offered by Snyder et al. (141), reducing the EKADM during *running*, and for example Bennell et al. (143), who, in a high methodological quality RCT, showed no change in EKADM during *gait*?

We suggest that the Snyder et al.'s (141) program properly strength-exercised *all* the muscle-actions found potentially predictive in the current study. The exercises targeted the hip rotators eccentric-and-concentrically in single-leg stance. Thus, it must also have strengthened the ankle invertor-evertor muscles during single-leg-stance rotations. (Of course also the hip abductors, but that is *not* the main point here.) In contrast, Bennell et al.'s (143, 144) program apparently only loaded the hip abductors and adductor muscles in the frontal plane. Moreover, Snyder et al. (141) confined their strength dose onto *each muscle group* via *one* targeting exercise, only *once* per session (although via 3 sets). Specifically, the program induced an objective strength-dose per muscle-group of 60% of 1RM resistance $\times$ 10 to 30 repetitions $\times$ 3

720 sets, one-to-one supervised by an in-clinic instructor. The instructor retested 1RM every 2nd
 721 week. Each session was performed 3 times per week, thus the program allowed adequate
 722 restitution time between sessions (>48h). In 6 weeks, this led to moderate strength increase in
 723 hip abduction (Cohen's d 0.7, 15% WG, $p = 0.009$) but a more substantial increase in external
 724 rotation strength (Cohen's d 1.0, 23% WG, $p < 0.0005$). Unfortunately, Snyder et al. (141) did
 725 not test for increased hip *internal* rotation strength, probably because they were unaware that
 726 their “AWAY exercise” exercised that muscle-group (not the hip external rotation muscles).
 727 In contrast, Bennell et al. (143) strength-dosed [resistance×repetitions×sets/muscle group (13,
 728 16, 145)] the hip abductors more than 6 *times* higher that of Snyder et al. (141), while
 729 obtaining only 13% within-group strength improvement after twice as long intervention
 730 period (12 vs 6 weeks). [For ref. (143) we assumed 10RM is ~80% of 1RM(146, 147) and 4
 731 hip-abductor-exercises 5 times-a-week.) Bennell et al.’s (143) between-group difference on
 732 hip abductor strength was *small* (18) [SMD 0.33, 95%CI -0.08 to 0.75]. Although they (143)
 733 also applied the same isometric single-stance *flexed-hip wall abduction exercise* as Ashok
 734 (27), their (143) much larger than optimal weekly abductor muscle training dose (145, 148-
 735 151) likely also unintentionally induced an inappropriately high strength dosage on the hip
 736 rotators and ankle inversion-eversion muscles due to synergistic actions [i.e., tipped towards
 737 overtraining (23, 145)]. In support of such a view, the sub-data of a systematic review of
 738 interventions for knee-pain (152) demonstrate that a simple 2-exercise only program [by
 739 Khayambashi et al. (153): bilaterally; 1 hip abduction exercise, 1 hip external rotation
 740 exercise, 30 min exercise session] with 3 sessions per week for 8 weeks (session dose: 20 to
 741 25RM resistance×20 to 25 repetitions×3 sets/muscle group), resulted in a *large*(18) effect on
 742 hip abduction strength compared to an inactive control group (SMD 1.5, 95%CI 0.7 to 2.4).
 743 Within Khayambashi et al.’s (153) intervention group, we found a 28% increase on the
 744 right/dominant side vs a 35% increase on the left/non-dominant side. Further supportive, a

meta-regression of RCTs (23) proved that 35% to 40% knee extensor improvement in KOA-
painful knees is achievable within 12 weeks with *focused* (per muscle-group confined)
strength exercise dosage of 60%-75% of 1RM resistance×10 to 12 repetitions×3 sets×3
sessions per week. Potentially highly important, in sum there seems to be a realistic potential
of reducing the EKADM in patients with medial KOA if one *properly* strength-dose (23) the
hip and knee abductors, internal rotators, and external rotators, with *one exercise per muscle-*
group (145) in standing positions that also adequately strength-dose the synergists of the
lower limb. That is, with an eccentric-concentric exercise of ambulation-relevant muscle-
lengthening and -shortening. This paragraph-conclusion supports the potential importance of
the current study's muscle findings. However, it may also indirectly support the importance of
strengthening the *knee abductor muscles* through a single-leg standing hip abduction exercise.

Further dose-mechanistically, relevant to future studies aiming to confirmatively challenge the
findings of the current study, Bartholdy et al. (23) missed the important message of the
ACSM referring publications (148, 149, 154, 155) and the dose-response systematic reviews'
(13, 145, 150, 156) that a session's dose of strength (training/loading) is defined as
resistance×reps×sets/*muscle group*. Pinning strength-dose to a specific muscle group is utterly
important. Important is also the impact of range-of-motion on muscle-strengthening and –
performance (17). Unfortunately, evidence of the length-tension vs. muscle-performance
relationship is barely mentioned in the ACSM publications and not properly explained in
papers of reporting checklists as Template for Intervention Description and Replication
[TIDieR] (157), Consensus on Exercise Reporting Template [CERT] (158), or that of
Bartholdy et al. (159). Highly relevant to the current study, given models of
prognosis/prediction/treatment of SR-ADL function by any strength factors are to be properly
evaluated, multivariable prediction models must at least incorporate the factors of highest

importance for improving muscle strength. Indeed, *the* most important factors for properly predicting future strength of a muscle-group is strength dose per session and the number of such strength doses per week — both pinned down to *a specific muscle-group* (145, 148, 160). In a recent systematic review and meta-regression analysis(159) of 100 primary studies of 6 926 patients with KOA from 10 clinical guidelines, Bartholdy et al.(159) indicated that poorer exercise-program reporting was associated with greater effects on pain and no association with effects on disability/SR-ADL. However, to help reveal any strength intervention mechanism, the above checklists are in need of evidence from systematic review and meta-analysis of its factors' effects on strength performance. Only with the most important strength predicting factors on the list, researchers should take the effort of repeating the otherwise impressive meta-regressions of exercise interventions by Bartholdy et al. (23, 159) onto proper strength exercise interventions. The relevance of such a checklist to the current strength findings seems obvious because only properly dosed strength exercise therapy on the current muscles should be included in future multivariable prediction model studies and treatment trials on the SR-ADL-outcome.

For predictive model studies of SR-ADL function in patients with KOA, researchers should consider the evidence of the underlying mechanism via studies of biomechanics (133-135, 161, 162), discrimination (28, 163), cross-sectional prediction (164), prognosis (21), and systematic review and meta-analysis of randomized trials (26, 85, 152), which we believe underpins the potential importance of including strength of these hip rotators and ankle inversion-eversion muscle-groups in future multivariable SR-ADL-models for people with symptomatic KOA.

794 Possible mechanisms for hip and ankle muscle strength vs SR-ADL relationship

795 What might be the *detailed* potential biomechanical mechanisms behind the relations between
 796 hip rotator and the ankle invertor-evertor strength and SR-ADL function that were seen in the
 797 current study? We may speculate that the relation signify an “effect” of such muscle strength
 798 via the lower limb and knee’s *instability* (133) and *muscle recruitment imbalance* (134)
 799 mechanisms in the frontal plane on the patients SR-ADL function. That is, because these
 800 latter concepts are validly documented as potential mechanisms, probably leading to overload
 801 of the knee joint due to *repetitive stress* while walking downhill (133) and flat (134). How
 802 these *ankle muscles* add to frontal plane motor control is easily fathomable (although the
 803 muscles are small). But how the *hip rotator muscle strength* can affect the frontal plane motor
 804 control is much harder to grasp. We know from cadaver studies that most of the hip external
 805 rotators change their line of action and moment arms with deeper hip flexed positions (129,
 806 165) and that four of the external rotators most likely acts like *an* abductor above 90° of hip
 807 flexion [the quadriceps coxa] (129). However, this does *not* explain much hip rotator frontal-
 808 control actions during downhill and flat walking because of the confined hip flexion range-of-
 809 motion during such weight-bearing phases. And if achieving excessive frontal plane strength
 810 was the obvious remedy, RCTs with hip abduction strengthening only as the addition to knee
 811 exercises would probably show the highest effect sizes on SR-ADL function (and pain) [as
 812 compared to quadriceps strengthening exercises only] whereas, as earlier explained, they do
 813 not (cf. the rotator-strengthening Ashok trial). Thus, shifting our focus to the *transverse*
 814 *plane*, we know that ankle invertor-evertor muscles act to control the *rotation* of the shank, as
 815 do the hip rotators to the femur (166). Collectively, we suspect that these muscles mainly
 816 control the rotation of the lower limb during walking. In support of such’s relevance, muscle
 817 simulation studies tell us that the human gait pattern is the least robust to muscle weakness of
 818 the hip external rotators [as compared to other muscle-groups] (135). Further, during the

loaded phases of walking, the knee-spanning muscles probably control little rotation of the lower limb and even little such of the knee itself. That is due to the much vertical line of action of these muscles during the normal gait's loaded knee range-of-motion. We thus speculate that proper transverse plane leg strength (hip rotators and ankle invertor-evertors) is *necessary* (35) for the proper *ease* of frontal plane knee stability mainly offered by the knee-spanning muscles (167). (Cf. the *ease* of SR-ADL function.) It is well known that an *excess magnitude of* (synergist-antagonist-balanced) *strength* is needed across *joints* in order to properly (i.e. with ease) stabilize *a joint* within a limb with multi-jointed degrees of freedom (168). Further, we know that the muscle-groups cooperate with only partly overlapping action-lines to control the various degrees of freedom in all planes simultaneously in functional tasks (168). What we do not know, is *how* much individuals are allowed to weaken these ankle and hip muscles before they underperform their knee-supportive role, and thus probably induce *compensations* (168) as increased knee muscle co-contraction (136) and thus micro instability, cartilage degeneration, low-grade inflammation, pain, and decreased SR-ADL function [as the output of the belief, context, and personal factor dependent neuro-endocrine-immune-motor body system] (169). Hopefully, single weight-bearing rotational strength exercising of the lower limb in a gait-relevant hip range of motion (141, 170) can prove to be a valuable mechanistic adjunct for improving SR-ADL function in patients with KOA, perhaps through reducing the rotational load on the knee-spanning muscles. Beware though, that knee abduction strength, induced by standing hip abduction resistance, may be a potential co-mechanism.

On the other hand, one might hypothesize that poor SR-ADL function leads to reduced muscle strength through pain and inactivity (164). That is, that the causal direction is the other way around; that the patients' SR-ADL function is the chicken (the independent variable) and

strength is the egg (the dependent variable). Regarding pain, however, note that the current study *did* control for the relationship of KOOS-pain vs SR-ADL function before it reported the *independent* relationship between strength and SR-ADL function. Similarly non-supportive, regarding inactivity, the current patient-sample registered a mean level of accelerometer-recorded moderate intensity physical ADL way above the American recommended weekly average guidance (171) [cf. our study (40)]. The factor vigorous intensity physical ADL-level, on the other hand, was seldom performed by the current patients, thus it was not explored as a factor in the current study. Opposing the importance of the latter, we know from sports that even vigorous regular physical activities are not *sufficient* (35) for maintaining proper muscle strength in supportive muscles (33, 34). The most likely causal factor for maintaining strong muscles is appropriate doses of strength stimuli vs rest per muscle group per week. Thus, currently most injury-prevention programs of the lower limb for athletes acknowledge the need for *regular vaccinating* targeted muscle strengthening exercises in order to keep strong, injury-free, and healthy (33, 34, 172). Thus, there seem to be more support of muscle-strength predicting SR-ADL function than the reverse pattern. Nevertheless, as for patellofemoral pain (172), the pathophysiology of KOA is complex with multiple interactive pathways suggested to contribute to its onset and persistence (173). No doubt *long-term* strong pain and inactivity, especially given no compensating strength-loading, will lead to limited muscle-strength *and* SR-ADL function.

Potential clinical research implications

The evidence supporting the current potential prediction model is cross-sectional and explorative and thus confirmative prospective studies of observation and treatment are needed for its validation. However, for now, let's assume the model is valid. What then? How may it possibly be applied?

869

870 For prevention and treatment, most obviously, clinician researchers could test people at risk
 871 of, or with, KOA (referred from the GPs) on *strength* on the potential important joint-
 872 directions, and, if relevant, put them on a strength exercise programs [e.g. ref. (141, 170)].
 873 Preferably, including regular controls or boosting sessions. However, regarding “if relevant”,
 874 clinical researchers need first to develop reliable, valid, and inexpensive diagnostic isometric
 875 strength measurement approaches for the ankle inversion-eversion muscles. For the hip and
 876 knee muscles, however, the currently existing isometric dynamometer approaches seems to
 877 function adequately [intra-rater reliability, ICC_{2,2} 0.84 to 0.97 and coefficient of variation
 878 (CV) <9.8% (174); ICC_{2,2} 0.86-0.95 (175); and inter-tester reliability ICC_{2,1} 0.76 to 0.95 and
 879 SEM 5% to 11 % (56)]. Linked to the dynamometers, however, clinicians urgently need
 880 electronically data systems offering instant individual standardized differences on strength/kg
 881 vs normative values of age and activity-level matched healthy groups. How else may
 882 clinicians say if the strength outputs are relevant?

883

884 For *psychosocial variables* (and questionnaire data in general) such normative systems
 885 fortunately already exist (47, 176). Where to evidence-based help towards self-management
 886 can be offered according to a recent systematic review (177). For example, for patients with
 887 KOA, clinician-based coping skill training has proven moderately effective on the outcome of
 888 self-efficacy (178). Whereas internet-based cognitive behavior therapy has proven moderately
 889 effective on depression and on psychological distress [in a trial (179) given high methodology
 890 and reporting quality (177)]. Both RCTs applied treatment-as-usual as control.

891

892 For *pain*, through Cognitive functional therapy (CFT) (173, 180) clinician researchers may
 893 target the *pain experience* (cf. KOOS-pain and Örebro). Firstly, by helping clients make sense

of pain as something caused by multidimensional biopsychosocial factors that should be remedied by thereto adapted self-management. Therein, pain can be addressed cognitively by clinicians offering hope by a positive evidence-based alternative belief (181) to the currently held misbelief about KOA being an incurable disease of a progressive nature linked to specific causal factors (182). Specifically, based on a huge longitudinal cohort (N >1 800 participant), White et al. (2010) offer evidence that clinically important *improvement* is frequent in people with, or at high risk of, KOA (181). Further, pain-reliving hope can be conveyed by the fact that simple and inexpensive *endurance exercises* have documented the highest standardized effect size on pain (*high*) compared to wait and see controls seen relative to other exercise modes (183). Moreover, as mentioned above, strengthening exercises of hip and knee muscles has documented large effects on walking performance compared to already known effective quadriceps strengthening control therapy (26). In the same systematic review (26) the latter comparison also proved moderately effective on SR-ADL function.

For active goal-targeted rehabilitation, the *KOOS-pain questions* could be used as a starting point for clinical examination and therapy. Where the *non-painful activities* can be emphasized to build confidence for and increase their everyday volume. Whereas the *painful activities* can be used as rehabilitation targets to induce new movement strategies into, and or progress them as loading activities in a frame of training, that challenges how clients think about, physically perform, and emotionally-and-physiological respond to them, followed by educating individuals to de-dramatize the act of loading with *some* pain (184-186), explaining the discordance between radiological KOA findings and pain (187-189), reinforcing loading beliefs with evidence that such does not damage the cartilage (190), teaching relaxed state-of-mind, respiration, and muscle activation, as well as extinction of safety behavior during such activities (173, 180), and further add KOA biomechanical mechanism-targeting strengthening

exercises (141, 170) based on the current model's strength tests. All this would also be in line with the CFT approach (173, 180). But of course, for the individual patient, the wider scope of CFT and KOA in particular (191-193) should be considered, because the individual's main problem(s) might likely be hidden in personal, environmental, or other biopsychosocial ICF factors not covered by the KOOS-pain, Örebro questionnaire, nor muscle-strength.

What seems obvious from that above, is that there are no clear boundaries between prevention, diagnosis, prognosis and treatment (194). These approaches are all about management and thus in need of a proper biopsychosocial multidimensional clinical model. In light of the total KOA evidence, the current one may be a valuable stepping-stone for new confirmative studies in these areas. Another alternative may be to run more and larger similar, but more statistically advanced, exploratory studies.

[The interested clinical researcher will find further exploratory discussion on potential applications of the current latent clinical prediction model in the e-appendix. Further, relevant research hypotheses are suggested in an hopefully upcoming PhD thesis (193)].

Conclusions

In conclusion, the current cross-sectional study indicates potential important potential predictions (i.e. independent relations) of hip rotator and ankle invertor-evertor muscle strength, in addition to such of KOOS-pain and Örebro psychosocial difficulties, on self-reported ADL function. That is, for patients aged 45 to 70 with small-to-moderate symptomatic and radiographic KOA in primary/secondary care. The current muscle-strength factors, when modelled individually with KOOS-pain and Örebro psychosocial difficulties to

cover important domains of the biopsychosocial ICF-model, potentially explain a substantial proportion of the variance in SR-ADL function (74% to 78%). Future confirmative multivariable prediction model (observational) studies of biopsychosocial mechanisms and management are needed to challenge these exploratory findings. RCTs are suggested to add earlier promising strength exercise programs (141, 170), which likely targets the current muscles (by proper doses per muscle-group, session, and week) and trigger key biomechanical mechanisms, onto a holistic multivariable approach that targets at least pain-and-disability and psychosocial factors, e.g. Cognitive functional therapy (173, 180).

List of abbreviations

ACR = American College of Rheumatology; ACSM = The American College of Sports Medicine; AX3 = An three axis accelerometer or sensor for measuring activity levels; BMI = Body mass index; CFT = Cognitive functional therapy; EKADM = external knee adduction moment; EULAR = the European League Against Rheumatism; EUROHIS-QoL = The European Health Interview Survey-Quality of Life 8-item index, a questionnaire; FUNKART = Function with knee osteoarthritis study; GPs = General physicians; HHD = Hand-Held muscle tester Dynamometer; ICC = Intra-class correlation coefficient, a measure of reliability; ICF = International Classification of Function, Disability, and Health (WHO's system-based clinical framework for classification of human function); K/L-grade = Kellgren-Lawrence grade of radiographic osteoarthritis; KOA = Knee osteoarthritis; KOOS = Knee Injury and Osteoarthritis Outcome Score, a questionnaire or standardized measurement instrument; NIST = the National Institute of Standards and Technology; NPRS = Numeric Pain Rating Scale; OA = Osteoarthritis; OMSPQ-10 = Örebro Musculoskeletal Pain Screening Questionnaire 10-

items; p = the p -value is the probability value in null hypothesis significance testing, i.e., the probability of obtaining test results at least as extreme as the results actually observed, under the assumption that the null hypothesis is true; PROAST = Prediction model Risk Of Bias ASsessment Tool; R^2 = Statistical measure that represents the proportion of the variance for a dependent variable that's explained by an independent variable or variables in a regression model; RCTs = Randomized controlled trials (most often of therapeutic interventions versus active therapy, placebo therapy, or a wait-and-see control condition); RM = Repetition maximum, the maximum number of exercise repetitions one can execute with a certain weight and or body mass; SR-ADL = Self-reported activities of daily life function, a subscale of KOOS; TSK-13 = Tampa Scale of Kinesiophobia, a questionnaire about fear of movement/re-injury; WOMAC-PF = the Western Ontario and McMaster Universities Arthritis Index Physical Function, a subscale of the WOMAC questionnaire or measurement tool; Örebro = Örebro Musculoskeletal Pain Questionnaire; $\sim$ the symbol means approximate or circa; 10StUpDwSCT = 10-step up-and-down stair-climb test; 1RM = 1 repetition maximum in a strength test; 6MWT = The 6-minute walk test, a physical capability test often executed in physical therapy clinics.

Declarations

Acknowledgements

We thank our participants for time and effort, our scientific-assistants, Erik Borg Kolsung and Anja Liljegren, for co-developing and implementing the Biodex protocol and test-assistance, our student-assistant Tina Marlen Bråten Mella for the latter, our training- and testing-expert Dale Reese for Biodex training, and Professor Karin Roeleveld for support with analysis of

Biodex data. We also thank the primary care physiotherapists Anita Bones and Bjørg Vada for critics on the project proposal.

Authors' contributions

All authors substantially revised the manuscript versions for clinical and scientific content and approved the submitted version in the present form (as well as the versions leading up to it).

Further, all authors have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately

investigated, resolved, and the resolution publicly documented. KV, AKS, and KGN have

substantially contributed to the conception and design of the work. I.e., AKS secured funding

for the project, KV wrote the research proposal update, ethical application, and protocol, and

KGN substantially revised these documents together with AKS. KV and ME extensively

recruited participants and collected data. KV and HL substantially analyzed and interpreted

data. KV drafted and redrafted all manuscript versions before and between rounds of

revisions. KV is the guarantor of the manuscript's authenticity.

Funding

This work was supported by the former Sor-Trondelag University College. The funding was

granted to A. K. Stensdotter, the head of the PhD-project entitled "Mechanisms for improved

physical function with knee osteoarthritis". There exists no grant number. The funders had no

role in study design, data collection and analysis, decision to publish, or in writing the

manuscript.

1014 [Ethics approval and consent to participate](#)

1015 The FUNKART study was approved by a Regional Ethics Committee for Medical and Health
1016 Research (the Regional Ethics Committee North, REC-north 2016/984 [In Norwegian REK-nord])
1017 and conducted according to the Helsinki declaration and Norwegian laws. The participants
1018 signed the approved written consent before participation.

1019

1020 [Consent for publication](#)

1021 Not applicable.

1022

1023 [Availability of data and material](#)

1024 The dataset generated and analyzed during the current study are available on reasonable
1025 request from the head of the project AKS or from the Department of Neuroscience and
1026 Movement Science, Faculty of Medicine and Health Science, Norwegian University of
1027 Science and Technology.

1028

1029 [Competing interests](#)

1030 The authors declare that they have no competing interests regarding the present study.

1031

1032 [Trial registration](#)

1033 Not applicable.

1034

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Figures

Figure 1

Modeling the total effect (green arrow) of the assumed focal predictor Strength (green play-button) on the putative outcome Activity of daily life (blue stop-button), together with the potential confounders (pink buttons, C1-C6) with their putative confounding or causal effects on the focal predictor and outcome (pink arrows) to be adjusted for in the multiple regression model. The gray buttons were ruled out of the main model based on case vs control non-discriminative characteristics in prior studies(1, 2) and the inclusion criteria in the current study (C4 skeletal comorbidity).

Supplementary Files

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- [EappendixBMCKV25.11.2020kl1428VAN.pdf](#)
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