E-appendix (Vårbakken et al. 2021. Predictive potentials…)

The current e-appendix exists due to removing the following text from the original version of the main manuscript: The secondary purpose of exploring bivariate relationships between a comprehensive set of muscle joint-strength directions and the self-reported activities of daily life function, further details of methods (analyses of bivariate correlation, confounding analysis, and sensitivity analysis), results (bivariate relations) and discussion (bivariate relations and potential future clinical use of an assumed valid prediction model). The original manuscript has thus been shorter and hopefully more readable. Still, for the deeply subject-interested reader and the validity of the original manuscript, this e-appendix is offered.

Background

There is limited knowledge on the bivariate relationship between a comprehensive set of muscle joint-strength directions and the self-reported activities of daily life function (SR-ADL) outcome for patients with knee osteoarthritis (KOA).

Methods

Bivariate analyses

For the Pearson's product-moment correlation coefficient analysis, the *a priori* required sample size calculation was based on an exact test of a correlation bivariate normal model with the following factors: Two tails, correlation r $H_1 = 0.5$, α error probability 0.05, power (1-β error probability) 0.80, $H_0 = 0$, where H_1 and H_0 is the alternative and null hypothesis respectively. This resulted in a required sample size of 29 patients. (Additional output parameters were lower and upper critical r -0.37, 0.37, respectively, and actual power 0.81.)

The applied scale for interpreting the strength or importance of the bivariate correlation coefficients ((cf. the E-table 1, in E-results) was as follows: 0.90 to 1.0 for *very high* (correlation) [none found, E-results], 0.70 to 0.90 *high* (color-coded red), 0.50 to 0.70 *moderate* (colored pink = highly significant), 0.30 to 0.50 *low* (yellow = significant, green = not significant), and 0.00 to 0.30 *trivial* [white] (1) These color-codes pertains to each cell. For specific correlation pattern, i.e. more than one cell/rectangles, different line-types were applied. However; having ran out of adequate line-types, light blue and purple color codes were used for specific correlation pattern.

Confounding analysis

Confounding bias is variously defined and operationalized (2-6). According to Williamson et al. (3) the estimated exposure-effect from a model will provide an unbiased estimate of the presumed causal effect (7) of the exposure, given that adjustment for the selected variables is sufficient to remove confounding bias. In causal diagram terms, they (3) explain, removing confounding bias will be the case if the adjustment for these variables closes all non-causal paths from the exposure to the outcome, thereby removing all spurious (non-causal) exposure─outcome relationships under the causal assumptions encoded in the proposed causal diagram. Williamson et al. (3) base their definition on background knowledge (4) about the causal structure of the problem under study, as encoded into a causal diagram.

Sensitivity analysis

A sensitivity analysis is a method to determine the robustness of an assessment by examining the extent to which the results are affected by changes in methods, models, values of unmeasured variables, or assumptions (5).

Results

Bivariate correlations (unadjusted relations)

E-table 1shows interesting bivariate patterns of correlation. First, the correlation between the *outcome* ADL function and all initially considered candidate predictors showed that psychosocial difficulties and KOOS-pain had highly significant *high (8)* correlation with the outcome (cf. red cells, top row). Further, highly significant *moderate* and positive correlations (with the ADL-outcome) were found for general health quality of life, endurance, and hip rotations, ankle eversion, and ankle plantar flexion muscle strength. Moreover, significant similar sized (*moderate*) negative correlation (with ADL) were found for BMI, pain last week, and fear of movement/re-injury (cf. pink cells). Contrastingly, significant *low* positive correlations (with ADL) were found for the strength variables hip abduction and ankle inversion (cf. yellow cells), whereas not significant *low* correlations were observed with the knee extensor and flexor muscles as well as with pain duration, age, and activity-of-moderate-intensity (cf. green cells, top row).

E-TABLE-1-IN-HERE!

The correlations between the *strength* and the *non-strength candidate predictors* also showed noteworthy patterns (E-table 1). The strength variables vs BMI, and the strength variables vs endurance, showed significant mainly *moderate-to-high* correlations (cf. light-blue rectangles). Whereas mainly *trivial-to-low* correlation were found for strength variables vs pain (KOOS-pain and pain last-week), and for strength vs general quality of life (cf. purple rectangles). Even weaker (not significant) correlations were found for the strength variables vs psychosocial difficulties, although negatively directed as expected (cf. the left purple rectangle). Note especially that neither of the correlations between strength variables and KOOS-pain, and strength variables and general health-related quality of life, was high in magnitude (cf. the right purple rectangle). Surprisingly, the weakest correlations were seen between strength variables and fear of motion/re-injury, pain duration, and age, which were of *trivial-to-low* magnitude in positive and negative directions (cf. the long dash dot-dot rectangle). Notably also, age showed "at best" *low* significant correlation with *a single* muscle strength action (cf. E-table 1).

Further bivariate, among *the non-strength candidate predictors*, psychosocial difficulties showed significant correlations of *small-to-moderate* magnitudes with 6 of the 9 other non-strength candidate predictors (the exceptions were not significantly weaker correlations with pain duration, age, and activity-of-moderate-intensity) [cf. the dashed rectangle]. Otherwise, the correlations amongst the non-strength candidate predictors were generally weak (cf. the bold triangle); except for endurance, which showed highly significant *moderate* correlations with activity-of-moderate intensity (as expected) and with the unspecific BMI.

Additionally, amongst *the strength variables*, there were some fascinating correlational patterns (cf. the dashed triangle). The antagonist-agonist strength couples of hip internal-external rotators, knee extensor-flexors, and ankle invertor-evertors all showed highly significant *high* positive

correlations between the strength directions within the respective joints. Further, hip internal rotation strength showed highly significant *high* positive correlations with all ankle strength actions. Hip external rotation strength showed a similar sized correlation pattern with ankle strength actions, only slightly weaker in magnitude. Whereas hip abductor strength showed a highly significant *high* positive correlations with ankle eversion and ankle plantar flexion strength, but only *moderately* so with the ankle invertor strength. Contrastingly, knee flexion and extension strength showed the weakest correlations with other joint─strength actions, ranging from *trivial-to-moderate* (E-table 1, the dashed triangle).

Multicollinearity or high correlation between *non-strength candidate predictors* (cf. Eq. 2, main manuscript) was generally not observed (the only exception being for endurance). Correlations between the *strength variables*, however frequent, posed no such (multicollinearity) threat due to the rotation-with-replacement application onto the two-predictor model. According to our criteria, the KOOS-pain and psychosocial difficulties were chosen as the covariables/mutually adjusted candidate predictors (X_1, X_2) applied with each focal predictor strength variable (X_i) in the primary model (Eq. 2).

Discussion

Principle findings

For the bivariate/unadjusted results, the most substantial *strength relationships* with the ADL-outcome were for hip rotations, ankle eversion, and ankle plantar flexion strength. Significant and somewhat less substantially related were ankle inversion and hip abduction strength. Not significant and least related were knee flexion and knee extension strength (of 8 strength predictors). The *non-strength predictors* KOA-specific pain and psychosocial difficulties showed

the most substantial (*high*) such relationships with the ADL-outcome (of 10 such candidate predictors).

Unadjusted cross-sectional and prospective relations in muscle-confined studies

In the current study, we found the unadjusted relations of the muscle strengths hip internal and external rotation, and ankle eversion with the ADL-outcome to be statistically significant, moderate in magnitude (i.e., potentially clinically important), and positively directed. This is seemingly concurrent with the conclusion of the systematic review of cross-sectional and prospective cohort studies by Holla et al. [2014] (9) who stated that there was strong evidence for a relation between muscle weakness and activity limitations. However, therein, the level of evidence was assigned based on a claimed consistency of statistically significant findings whereas the strength of the relation was not considered in their grading. The latter is in sharp contrast to the approach recommended in the Cochrane-anchored GRADE-guidelines (10-12).

Thus, scrutinizing Holla et al.'s (9) extracted but not meta-analyzed unadjusted relations, and the meaning behind their conclusion terms of strength and activity limitation, we found that most of the 40 studies reported significant relations between knee extensor strength and the *performance/capacity* outcomes of particularly knee extensor strength demanding single tasks. Further, these relations mainly proved to be *low* in magnitude according to Hopkins' scale (2002).(8) For knee extensor strength related with the *self-reported* ADL-outcome, however, the review(9) data showed that six cross-sectional studies reported *trivial-to-small* not significant relations [|Pearson's r| range 0.053 to 0.35, N = 24 to 105] (13-18) whereas three studies (19-21) reported significant *trivial-to-moderate*(8) sized relations [|r| 0.27, N 1 344(20); |r| 0.449, N

54(19); |r| 0.528, N 25 (21)]. Particularly interesting, in the cross-sectional study that the review(9) rated highest on methodological quality, Costa et al. [2010] (21) explored all joint─strength actions for the hip and knee and found significant bivariate relations between hip abduction and the Lequesne Index and the WOMAC-PF scale (cf. their unilateral KOA-group). However, even though both these self-report tools were scaled the same way, Costa et al. (21) reported significant relations in *opposite directions* between them, thus indicating a risk of bias in the cross-sectional study and the systematic review (9) due to not highlighting such an important inconsistency for the most examined hip-muscle-group in patients with KOA. Most importantly, the review's (9) conclusion-terms were clearly too broad for the *knee extensor* and *hip abductor* strength actions in relation to *self-rated* physical activity difficulties (i.e., the focus of the current paper).

Summing up the unadjusted cross-sectional (included our study) and prospective evidence; for knee extensor strength, 7 out of 10 studies (N = 380) showed not significant *trivial-to-low* relation with self-reported ADL-function (13, 15-18, 22), whereas 3 of 10 studies (N = 1 398) support significant *trivial-to-moderate* such relation (19, 20, 23). Further, for hip abduction strength, 4 of 4 studies (N = 102) support a significant *low-to-moderate* (such) relation (14, 24, 25); for hip external rotation strength, 3 of 3 studies (N = 77) support such a relation (17, 21); and for hip internal rotation strength 2 of 2 studies (N = 53) support such a *low-to-moderate* relation (21). For ankle eversion, inversion, and plantar flexion strength, however, we found no proper evidence neither supporting nor negating our significant *small-to-moderate* relations with self-reported ADL-function. Thus, for cross-sectional unadjusted relations between various muscle strength actions of the lower leg and the self-reported ADL-function, there is a need for several comprehensive muscle strength studies before attempting new systematic reviews.

Unadjusted cross-sectional relations in muscle-comprehensive studies

The unadjusted cross-sectional relationships for a comprehensive set of lower limb muscle strength actions vs self-reported ADL-function, are scarcely examined. In patients with bilateral KOA, however, Costa et al. (21) reported a few significant *low* (8) relations between the KOA-specific outcome Lequesne index and the following three strength variables: Concentric isokinetic mode of knee extension at 30°/s ($r = 0.418$, $N = 25$), hip internal rotation at 30°/s ($r = 0.438$), and hip external rotation at 60°/s ($r = 0.484$, all $p < 0.05$). Comparably, their (21) *low* (8) relationships for the two hip rotations strength actions do differ somewhat to the *moderate*(8) relations found in the current study. A difference that may be explained by Costa et al. (21) reporting their relations pinned to strength on the left or right side whereas we pinned ours to the most affected side. Furthermore, in a more recent cross-sectional study, Park et al. (17) [N = 24] explored the relationships of *isometric* strength of hip abduction, hip external rotation, knee flexion, knee extension, and ankle inversion with the outcome KOOS-ADL. Therein, significant but *low* (8) positive relations were found for hip abduction and external rotation strength ($r = 0.418$ and 0.410, respectively) whereas a not significant *trivial* (8) such relation was reported for knee extension strength ($r = 0.204$). For hip abduction strength, however, their (17) significant finding, magnitude, and direction of relationship, as well as the test mode, all agreed with the *low* (8) relation of the current study. However; for hip external rotation strength, their (17) relation magnitude was *low* (8) vs ours *moderate* (8), a distinction that may be explained by their such test was performed *isometrically* in sitting with *90*° hip flexion whereas we tested *concentric and isokinetic* at 60°/s in sitting with *70*° hip flexion. Stringently though, Park et al. (17) did not report strength but force, thus opened up for risk of bias due to unknown moment arms. However, a more serious risk of bias was that for ankle inversion strength where none of their cited references reported the test method. Moreover, in yet another cross-sectional study, Selistre et al.

(26) demonstrated a significant *low* (8) negative relation between *concentric isokinetic* hip abduction strength and WOMAC-PF ($r = -0.49$, $p = 0.01$, $N = 25$), a finding in agreement with that of the *isometric* results in the current study and that of Park et al. (17), and the *concentric isokinetic* ones of Costa et al. (21).

Adjusted analyses and inappropriate reporting

Strangely enough, confounding is defined as "…[when] another factor related to both the prognostic factor and the outcome is likely to *explain* [italics, red.] the effect of the prognostic factor." (27) [p. 283]. That definition is given in the Cochrane-anchored description of refinement and use of the Quality In Prognosis Studies (QUIPS) tool to assess risk of bias in prognostic factor studies. Therein, however, no proper explanation exists with reference to how the QUIPS-item "all important confounders, including treatment, are measured" should be operationalized. Instead, Hayden et al. (28) stated that "…the decision [i.e., of which potential confounders to adjust for, red.] should be based on previous research and a conceptual model." (p. 431). In the PROBAST explanation paper (29), however, confounding is only indirectly referred to [cf. ref. (30)], where the latter reference again links to the seminal paper by Greenland et al. (2), explaining causal diagram as the proper way to analyze for confounding factors (and thus decide which factors to adjust for in the model).

The study limitations of the cross-sectional prediction studies of van der Esch et al. (31) and Sanchez-Ramirez et al. (32) are understandable because it was not until 2015 that the Cochrane Prognosis Method Group (PGM) launched the TRIPOD statement [Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis] (33, 34). Further, the methodological anchors of TRIPOD were first presented in 2019, in the PROBAST publications [Prediction model Risk Of Bias ASsessment Tool] (29, 35). Thereto, just as recently,

the Cochrane-group launched guidelines for meta-analyzing systematic review of prediction model studies (36, 37).

Possible future application of an assumed valid current prediction model

Assuming validity of the model KOOS-ADL function = KOOS-pain + Örebro-psychosocial difficulties + external rotation strength as a potential prediction model for improving the patient's ADL function prognosis might be done the following way (i.e. an explorative/futuristic discussion). Having assessed and agreed upon the biopsychosocial predictive situation and the patients valued activity goals (38) (see the measures and mathematical specifics in the paragraph below), then explaining how pain can be driven by psychosocial difficulties and specific subtle movement compensations due to muscle weakness (biology) through a biopsychosocial framework (39), using the Cognitive Functional Therapy approach to exposing the patient with control for the problematic activities, and supplement the approach by the specific strength exercises of Ashok (2012), including the standing flexed hip-abduction exercise which targets the ankle inversion-eversion and hip internal-external rotator muscles (40). The strength dose per session should thus be as follows: 60 to 75%1RM × 10 to 12 reps × 3 sets / muscle group, implemented for 3 sessions (minimum 48h in between) per week for 12 weeks. The %1RM should be retested once per 2nd week and the pain algorithmically controlled during training, where pain (by the PNRS, 0 to 10, best to worst) between 1 to 3 during exercise and 3 to 5 the same day/evening is allowed (41-44). Importantly, what the model then predicts is that given the pain, psychosocial difficulties, and hip external rotation are properly dealt with in a biopsychosocial ICF systems framework (45) of Cognitive Functional Therapy (39), the effect on the prime outcome self-reported ADL-function probably is *additive* across these key factors for

patients with KOA. Thus, it highlights the potential importance of proper communication about what evidence-based therapeutic strength training entails and what cognitive, behavioral, diet, and lifestyle measures has to be undertaken by the patient in order to maximize the adaption between sessions and realizing a high degree of regularity and completion of health-promoting actions (38, 46-50).

The current paragraph explains how the potential prediction/regression model can be calculated to forecast the self-perceived ADL function. The model for the current study's best prediction model/equation is modelled as follows (E-eq.1):

$$\widehat{ADL} = 42.3 + 0.58\times\text{KPain} - 0.58\times\text{ÖrebroPsySoc} + 5.98\times\text{HipERStrengt} \quad \text{(E-eq. 1)}$$

, where $\widehat{ADL}$ is the estimated (mean) KOOS-ADL, the intercept b_0 is 42.3, and b1, b2, and b3 is 0.58, 0.58, and 5.98, respectively, and KPain is KOOS-pain, ÖrebroPsySoc is psychosocial difficulties, and HipERStrength is hip external rotation strength (cf. also Eq. 2, in the main manuscript). Strength is given in Nm/kg. To give a fictive example for the average predictive ADL-function for a single patient; let's assume the KPain, ÖrebroPsySoc, and HipERStrength are all 1.3 standard deviations worse than mean of the current sample, where the current M (SD) of the sample is 58.8 (18.8), 39.0 (12.7), and 0.25 (0.10), respectively. We then have KPain = 58.8 - (1.3×18.8) = 34.4, ÖrebroPsySoc = 39.0 + (1.3×12.7) = 55.5, HipERStrength = 0.25 - (1.3×0.10) = 0.10. Then, these numbers are plotted in the formula as follows: ADL = 42.3 +

(0.58×34.4) – (0.58×55.5) + (5.98×0.10), thus giving one the predicted ADL = 30.8 points. As the M (SD) score for the sample on KOOS-ADL was 68.6 (21.7), we find the relative difference between these means by 30.8/68.6 = 0.449, 1 - 0.449 = 0.551, and 0.551×100 = 55.1%. It means that the predicted ADL thus is 55.1% below the sample mean. Clearly this should not be seen as a positive prospect for the patient's future ADL-function. However, what then if the clinician convinced the patient to take an anti-inflammatory pill to decrease her pain by 35%? As pain is the strongest predictor in the equation, this would certainly make an impact. However, what if the patient is offered a treatment that has proven to improve pain by 25%, psychosocial difficulties by 20%, *and* strengthen the muscle-group by 35%? Does this treatment really exist? Based on recent guidelines (49) and systematic review (51), one may conclude yes and herein we name it Pain-adjusted Psychosocial Strength Training for KOA. It may start out by administrating the free online calculators of KOOS and Örebro (52) and tests the hip external rotator muscle-strength by a dynamometer (53). It then follows the clinical path described in the first paragraph in the current section. Note, the assumption of validity of the possible prediction model is not confirmatively tested. Thus this explorative discussion is hypothesis based and dependent on future confirmative studies.

E-TABLE-1-IN-HERE (see below)!

E-table 2. Bivariate Pearson's correlation r and 95% CI between ADL, 8 strength variables, and 10 biopsycosocial variables spanning the International Classification of Function, Disability, and Health spectrum (WHO). Point estimates of r are above the gray diagonal and confidence intervals below the diagonal.

Cat.	Row no.	Col. no. → / Variables	1 ADL	2 H-IrStr	3 H-ErStr	4 H-AbStr	5 K-ExStr	6 K-FlStr	7 A-InvStr	8 A-EvStr	9 A-PfStr	10 PsPsoc	11 BMI	12 PainWk	13 TSK	14 PainDuMo	15 Age	16 ActMoWk	17 Endur	18 K-Pain	19 EU-QoL
OV	1	ADL	1	.64**	.52**	.43*	.32	.36	.47*	.56**	.62**	-.75**	-.59**	-.58**	-.56**	-.34	-.33	.31	.51**	.81**	.68**
Strength variables	2	H-IrStr	.40, .82	1	.78**	.64**	.65**	.54**	.74**	.80**	.78**	-.45*	-.62**	-.51**	-.32	-.30	-.38*	.50**	.77**	.57**	.60**
	3	H-ErStr	.28, .71	.62, 83	1	.65**	.69**	.54**	.67**	.71**	.68**	-.26	-.66**	-.49**	-.28	-.32	-.22	.50**	.71**	.29	.41*
	4	H-AbStr	.09, .71	.33, 86	.42, .83	1	.65**	.57**	.63**	.78**	.72**	-.22	-.66**	-.41*	.01	-.03	-.15	.20	.66**	.39*	.48*
	5	K-ExStr	-.01, .64	.35, .87	.45, .85	.45, .81	1	.75**	.53**	.59**	.54**	-.16	-.45*	-.26	-.13	.02	-.12	.09	.59**	.28	.28
	6	K-FlStr	-.001, .69	.12, .90	.16, .84	.27, .81	.51, .92	1	.19	.45*	.40*	-.21	-.53**	-.34	-.18	.10	-.13	-.04	.49**	.27	.35
	7	A-InvStr	.20, .68	.58, .88	.42, .83	.40, .82	.22, .83	-.33, .81	1	.78**	.80**	-.20	-.49**	-.37	-.12	-.20	-.23	.56**	.65**	.40*	.47*
	8	A-EvStr	.32, .74	.62, .92	.57, .87	.55, .91	.27, .81	.002, .81	.68, .89	1	.88**	-.39*	-.61**	-.48*	-.30	-.06	-.34	.41*	.64**	.43*	.46*
	9	A-PfStr	.36, .81	.57, .91	.45, .86	.50, .87	.25, .81	-.12, 81	.51, .92	.78, .95	1	-.43*	-.61**	-.50**	-.23	-.06	-.35	.40*	.61**	.58**	.50**
BioPsySoc ICF non-strength variables	10	PsPsoc	-0.88, -.53	-.70, -.12	-.56, .11	-.52, .16	-.49, .22	-.55, .17	-.46, .15	-.62, .03	-.67, -.12	1	.43*	.51**	.60**	.24	.43*	-.20	-.24	-.68**	-.65**
	11	BMI	-0.81, -.36	-.79, -.44	-.80, -52	-.83, -.42	-.69, -.18	-.79, .21	-.68, -.24	-.76, -.40	-.77, -.39	-.11, .48	1	.27	.20	.09	.04	-.30	-.62**	-.44*	-.47*
	12	PainWk	-0.84, -.30	-.72, -23	-.73, -21	-.67, -.09	-.57, .06	-.61, -.05	-.58, -.14	-.69, -.20	-.72, -.20	.25, .76	-.08, .62	1	.24	.34	.28	-.27	-.28	-.46*	-.33
	13	TSK	-0.79, -.21	-67, .16	-.60, .11	-.36, .43	-.50, .28	-.53, .24	-.42, .20	-.58, .12	-.56, .18	.13, .82	-.23, .58	-.08, .55	1	.25	.40*	-.23	-.14	-.30	-.41*
	14	PainDuMo	-0.65, .09	-.59, .16	-.58, .02	-.39, .34	-.36, .38	-.25, .40	-.50, .15	-.39, .34	-.47, .36	-.16, .57	-.19, .39	-.09, .80	-.12, .59	1	.40*	-.26	-0.17	-.26	-.15
	15	Age	-.64, .09	-.73, .10	-.62, .19	-.59, .37	-.54, .38	-.56, .32	-.65, .26	-.73, .23	-.77, .21	.13, .66	-.41, .52	-.10, .62	.06, .66	.10, .61	1	-.46*	-.33	-.23	-.16
	16	ActMoWk	-.01, .56	.22, .74	.21, .74	-.10, .50	-.28, .49	-.42, .52	.19, .81	.11, .75	.04, .71	-.46, .11	-.57, .006	-.56, .11	-.47, .05	-.54, .12	-.67, -.24	1	.60**	.13	.24
	17	Endur	0.27, 0.71	.69, .88	.50, .85	.49, .81	.38, .80	.16, .81	.50, .80	.49, .84	.45, .77	-.57, .10	-.76, -.44	-.61, .03	-.43, .13	-.46, .14	-.64, .02	.35, .76	1	.38*	.40*
	18	K-Pain	.69, .89	.27, .76	-.12, .63	.04, .66	-.11, 62	-.18, .64	-.05, 69	.02, 68	.23, .79	-.83, -.53	-.68, -.13	-.85, -.05	-.61, .13	-.14, .64	-.64, .20	-.29, .52	.04, .69	1	-.59**
	19	EU-QoL	.45, .85	.33, .80	.10, .67	.12, .72	-.01, 55	-.08, .70	.22, .64	.15, .69	.18, .72	-.85, -.38	-.72, -.15	-.67, .02	-.76, .04	-.51, .32	-.55, .32	-.06, .48	.14, .66	.34, .77	1

Notes: ** = p < .01 highly significant; * = p < .05 significant.; Cat. = categories of variables; OV = outcome variable; ADL = Knee Osteoarthtis Outcome Score [KOOS] Activities of Daily Life,H-IrStr = hip internal rotation strength, H-ErStr = hip external rotation strength, H-AbStr = hip abduction strength, K-ExStr = knee extension strength, K-FlStr = knee flexion strength, A-InvStr = ankle inversion strength, A-EvStr = ankle eversion strength, A-PfStr = ankle plantar flexion strength, PsPsoc = psychososial difficulties, BMI = body mass index, PainWk = pain on average last week (the Numeric rating scale), TSK = Tampa Scale of Kinesiophobia, PainDuMo = pain duration in months since debut (Numeric Rating Scale), Age = age in years, ActMoWk = activity of moderate intensity in minutes per week as registered with accelerometer, Endur = endurance or meter walked during the 6 minutes walk test, K-Pain = KOOS-pain, EU-QoL = generic health quality of life (The European Health Interview Survey-Quality of Life 8-item index [EUROHIS-QoL]), red cell = large correlation effect magnitude and highly significant, pink cell = moderate corr. magnitude and highly significant, yellow cell = low to moderate effect mangnitude and significant, green cell = low to moderate correlation but not significant, white cell = trivial to low correlation magnitude and not significant. The codes of color and lines for the squares and triangles, are explained in the running or main text.

Reference list

1. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi medical journal : the journal of Medical Association of Malawi. 2012;24(3):69-71.
2. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10(1):37-48.
3. Williamson EJ, Aitken Z, Lawrie J, Dharmage SC, Burgess JA, Forbes AB. Introduction to causal diagrams for confounder selection. Respirology. 2014;19(3):303-11.
4. Hernan MA, Hernandez-Diaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol. 2002;155(2):176-84.
5. Porta MS. A Dictionary of Epidemiology. Oxford: Oxford University Press; 2014.
6. Hayes AF. Introduction to mediation, moderation, and conditional process analysis Little TD, editor. New York: The Guilford Press; 2018. 692 p.
7. Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? Proceedings of the Royal Society of Medicine. 1965;58:295-300.
8. Hopkins WG. A Scale of Magnitudes for Effect Statistics 2002 [Available from: http://www.sportsci.org/resource/stats/effectmag.html
9. Holla JF, Sanchez-Ramirez DC, van der Leeden M, Ket JC, Roorda LD, Lems WF, et al. The avoidance model in knee and hip osteoarthritis: a systematic review of the evidence. Journal of behavioral medicine. 2014;37(6):1226-41.
10. Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. Journal of clinical epidemiology. 2011;64(12):1311-6.
11. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology. 2011;64(4):380-2.
12. Huguet A, Hayden JA, Stinson J, McGrath PJ, Chambers CT, Tougas ME, et al. Judging the quality of evidence in reviews of prognostic factor research: adapting the GRADE framework. Syst Rev. 2013;2:71.
13. Fitzgerald GK, Piva SR, Irrgang JJ, Bouzubar F, Starz TW. Quadriceps activation failure as a moderator of the relationship between quadriceps strength and physical function in individuals with knee osteoarthritis. Arthritis and rheumatism. 2004;51(1):40-8.
14. Piva SR, Teixeira PE, Almeida GJ, Gil AB, DiGioia AM, 3rd, Levison TJ, et al. Contribution of hip abductor strength to physical function in patients with total knee arthroplasty. Phys Ther. 2011;91(2):225-33.
15. McAlindon TE, Cooper C, Kirwan JR, Dieppe PA. Determinants of disability in osteoarthritis of the knee. Annals of the rheumatic diseases. 1993;52(4):258-62.
16. Maly MR, Costigan PA, Olney SJ. Determinants of self-report outcome measures in people with knee osteoarthritis. Archives of physical medicine and rehabilitation. 2006;87(1):96-104.
17. Park SK, Kobsar D, Ferber R. Relationship between lower limb muscle strength, self-reported pain and function, and frontal plane gait kinematics in knee osteoarthritis. Clinical biomechanics (Bristol, Avon). 2016;38:68-74.
18. Tevald MA, Murray AM, Luc B, Lai K, Sohn D, Pietrosimone B. The contribution of leg press and knee extension strength and power to physical function in people with knee osteoarthritis: A cross-sectional study. The Knee. 2016;23(6):942-9.
19. Liikavainio T, Lyytinen T, Tyrvainen E, Sipila S, Arokoski JP. Physical function and properties of quadriceps femoris muscle in men with knee osteoarthritis. Archives of physical medicine and rehabilitation. 2008;89(11):2185-94.

20. Riddle DL, Stratford PW. Impact of pain reported during isometric quadriceps muscle strength testing in people with knee pain: data from the osteoarthritis initiative. Phys Ther. 2011;91(10):1478-89.
21. Costa RA, Oliveira LM, Watanabe SH, Jones A, Natour J. Isokinetic assessment of the hip muscles in patients with osteoarthritis of the knee. Clinics (Sao Paulo, Brazil). 2010;65(12):1253-9.
22. Alnahdi AH. Outcome measures capturing ICF domains in patient with total knee arthroplasty. Int J Rehabil Res. 2014;37(4):281-9.
23. Gkrilias P, Tsepis E, Kokkalis Z, Panagiotopoulos E, Megas P. The relationship between isokinetic strength and functional performance tests in patients with knee osteoarthritis. Journal of physical therapy science. 2018;30(6):888-91.
24. Alnahdi AH, Zeni JA, Snyder-Mackler L. Hip abductor strength reliability and association with physical function after unilateral total knee arthroplasty: a cross-sectional study. Phys Ther. 2014;94(8):1154-62.
25. Tevald MA, Murray A, Luc BA, Lai K, Sohn D, Pietrosimone B. Hip abductor strength in people with knee osteoarthritis: A cross-sectional study of reliability and association with function. The Knee. 2016;23(1):57-62.
26. Selistre LFA, Goncalves GH, Nakagawa TH, Petrella M, Jones RK, Mattiello SM. The role of hip abductor strength on the frontal plane of gait in subjects with medial knee osteoarthritis. Physiotherapy research international : the journal for researchers and clinicians in physical therapy. 2019:e1779.
27. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. Annals of internal medicine. 2013;158(4):280-6.
28. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Annals of internal medicine. 2006;144(6):427-37.
29. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Annals of internal medicine. 2019;170(1):W1-w33.
30. Greenland S, Robins JM, Pearl J. Confounding and Collapsibility in Causal Inference. Stat Sci. 1999;14(1):29-46.
31. van der Esch M, Knoop J, van der Leeden M, Voorneman R, Gerritsen M, Reiding D, et al. Self-reported knee instability and activity limitations in patients with knee osteoarthritis: results of the Amsterdam osteoarthritis cohort. Clinical rheumatology. 2012;31(10):1505-10.
32. Sanchez-Ramirez DC, van der Leeden M, Knol DL, van der Esch M, Roorda LD, Verschueren S, et al. Association of postural control with muscle strength, proprioception, self-reported knee instability and activity limitations in patients with knee osteoarthritis. Journal of rehabilitation medicine. 2013;45(2):192-7.
33. Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Annals of internal medicine. 2015;162(1):W1-73.
34. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Annals of internal medicine. 2015;162(1):55-63.
35. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. Annals of internal medicine. 2019;170(1):51-8.
36. Riley RD, Moons KGM, Snell KIE, Ensor J, Hooft L, Altman DG, et al. A guide to systematic review and meta-analysis of prognostic factor studies. Bmj. 2019;364:k4597.
37. Debray TP, Damen JA, Riley RD, Snell K, Reitsma JB, Hooft L, et al. A framework for meta-analysis of prediction model studies with binary and time-to-event outcomes. Stat Methods Med Res. 2019;28(9):2768-86.

38. Mitchell T, Beales D, Slater H, O'Sullivan P. Musculoskeletal Clinical Translation Framework - From Knowing to Doing [PDF-file]. Curtin, Australia: The Musculoskeletal Framework Group; 2018 [cited 2020. Available from: https://www.musculoskeletalframework.net/.
39. O'Sullivan PB, Caneiro JP, O'Keeffe M, Smith A, Dankaerts W, Fersum K, et al. Cognitive Functional Therapy: An Integrated Behavioral Approach for the Targeted Management of Disabling Low Back Pain. Phys Ther. 2018;98(5):408-23.
40. Ashok C. Effects of hip abductor muscle strengthening exercises in patients with osteoarthritic knee joints. Indian Journal of Physiotherapy & Occupational Therapy. 2012;6:32-7.
41. Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patients with severe hip or knee OA: the individualized goal-based NEMEX-TJR training program. BMC musculoskeletal disorders. 2010;11:126.
42. Skou ST, Roos EM. Good Life with osteoArthritis in Denmark (GLA:D): evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. BMC musculoskeletal disorders. 2017;18(1):72.
43. Sandal LF, Roos EM, Bogesvang SJ, Thorlund JB. Pain trajectory and exercise-induced pain flares during 8 weeks of neuromuscular exercise in individuals with knee and hip pain. Osteoarthritis Cartilage. 2016;24(4):589-92.
44. @ewa_roos. Keeping physically active is important for good health. Here is some advice on how to exercise safely with painful knee joints. 2020.
45. WHO. ICF - International classification of functioning, disability and health. Geneva, Switzerland: World Health Organization; 2001.
46. Mueller MJ, Maluf KS. Tissue adaptation to physical stress: a proposed "Physical Stress Theory" to guide physical therapist practice, education, and research. Phys Ther. 2002;82(4):383-403.
47. McGill S. Ultimate back fitness and performance2017.
48. van Wingerden BAM. Connective tissue in rehabilitation. Liechtenstein: Scipro Verlag-Vaduz; 1995 1995.
49. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-89.
50. Berenbaum F, Wallace IJ, Lieberman DE, Felson DT. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nature reviews Rheumatology. 2018;14(11):674-81.
51. Hislop AC, Collins NJ, Tucker K, Deasy M, Semciw AI. Does adding hip exercises to quadriceps exercises result in superior outcomes in pain, function and quality of life for people with knee osteoarthritis? A systematic review and meta-analysis. British journal of sports medicine. 2020;54(5):263-71.
52. OrthoToolKit. Welcome to OrthoToolKit! 2019 [Available from: https://www.orthotoolkit.com/.
53. Thorborg K, Bandholm T, Holmich P. Hip- and knee-strength assessments using a hand-held dynamometer with external belt-fixation are inter-tester reliable. KneeSurgSports TraumatolArthrosc. 2013;21(3):550-5.